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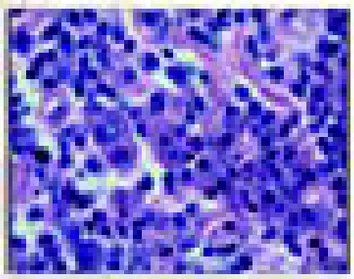

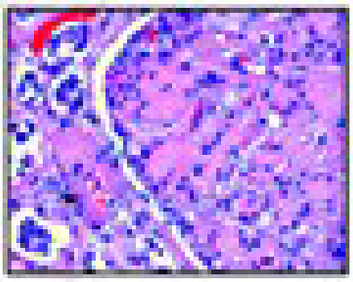

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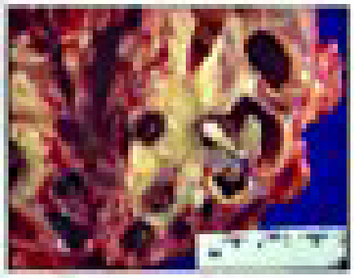

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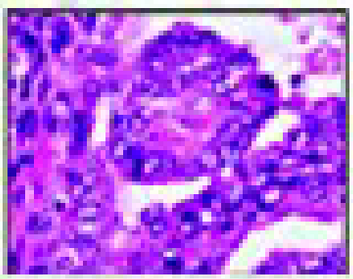

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Contents

IMPORTANT NOTES OF NEW CHAPTER ADDED IN ROBBINS 9TH EDITION

CELL AS A UNIT OF HEALTH AND DISEASE

- **Virchow** coined the term 'cellular pathology'
- **The human genome** contains roughly **3.2 billion DNA base pairs** and only about 2% is used for coding of proteins.
- **80% of the human genome either binds proteins,** implying it is involved in regulating gene expression, or can be assigned some functional activity, mostly related to the regulation of gene expression, often in a cell-type specific fashion.
- The **two most common forms** of **DNA variation** in the **huxvixvman genome** are ***single-nucleotide polymorphisms (SNPs) and copy number variations (CNVs).***
- **SNPs** are variants at single nucleotide positions and are almost always biallelic (i.e., only two choices exist at a given site within the population, such as A or T).
- **CNVs** are a more recently identified form of genetic variation consisting of different numbers of large contiguous stretches of DNA from 1000 base pairs to millions of base pairs.
- Epigenetics is defined as heritable changes in gene expression that are not caused by alterations in DNA sequence.
- Nuclear chromatin exists in two basic forms:

1. Cytochemically dense and transcriptionally inactive heterochromatin and
2. Cytochemically dispersed and transcriptionally active euchromatin

- Different histone modifications are generically called as *marks*. The modifications include methylation, acetylation, or phosphorylation of specific amino acid residues on the histones.

Gene regulation can also be done through noncoding RNAs which can be of the following subtypes:

a. ***MicroRNAs*** (miRNA): The miRNAs are small RNA molecules 22 nucleotides in length which do not encode proteins. They function primarily to modulate the translation of target mRNAs into their corresponding proteins.

b. ***Long noncoding RNAs*** (lncRNA): RNAs are >200 nucleotides in length. Its example includes **XIST**, which is transcribed from the X chromosome and plays an essential role in ***physiologic X chromosome inactivation.***

MiRNA associated with cancers are called oncomiRs. They act by increasing the number of cancer causing genes and suppress the tumor suppressor genes.

The non coding RNAs fall into several classes:

- **Piwi-interacting RNAs** (piRNAs), the most common type of small noncoding RNA, which (like miRs) are believed to have a role in post-transcriptional gene silencing;
- **Sno RNAs**, which are important in maturation of rRNA and the assembly of ribosomes; and
- **Long intervening noncoding RNAs (lincRNAs)**, some of which regulate the activity of chromatin "writers," the factors that modify histones and thereby control gene expression

CELLULAR HOUSEKEEPING (as per 9th edition of Robbins)

Organelles	Key points
Mitochondria	Oxidative phosphorylation Intermediates for heme synthesis Intrinsic pathway of Apoptosis (programmed cell death)
Smooth endoplasmic reticulum (SER)	Abundant in gonads and liver Used for lipoprotein and steroid hormone synthesis, Required for converting the hydrophobic compounds like drugs into water-soluble molecules Sequestration of calcium
Proteasomes	Required for selectively chewing of denatured proteins using ubiquitin. Also needed for presentation of peptides in context of the class I major histocompatibility molecules
Peroxisomes	Breakdown of fatty acids

Contd...

Contd...

Organelles	Key points
Plasma membrane proteins	Phosphatidylinositol serves as scaffold for intracellular proteins as well as for the generation of intracellular second signals like diacylglycerol and inositol trisphosphate. Phosphatidylserine is required for apoptosis (programmed cell death) and on platelets, it serves as a cofactor in the clotting of blood. Glycolipids are important in cell-cell and cell-matrix interactions, including inflammatory cell recruitment and sperm-egg interactions.
Lysosomes	Most cytosolic enzymes prefer to work at pH 7.4 whereas lysosomal enzymes function best at pH 5 or less.
Golgi apparatus	Mannose 6 phosphateQ is the marker

- ***Channel proteins*** create hydrophilic pores, which, when open, permit ***rapid movement*** of solutes (usually restricted by size and charge)
- *Carrier proteins* bind their specific solute and undergo a series of conformational changes to transfer the ligand across the membrane; their transport is relatively *slow*.

- Exocytosis is the process by which large molecules are exported from cells. In this process, proteins synthesized and packaged within the RER and Golgi apparatus are concentrated in secretory vesicles, which then fuse with the plasma membrane and expel their contents.
- Transcytosis is the movement of endocytosed vesicles between the apical and basolateral compartments of cells. It is a mechanism for transferring large amounts of intact proteins across epithelial barriers.
- Potocytosis is literally "cellular sipping." whereas ***pinocytosis*** is "***cellular drinking***"
- Endocytosis is the uptake of fluids or macromolecules by the cell. It could be of the following types:

1. *Caveolae-mediated endocytosis:* **Caveolin**Q *is the major structural protein of caveole.* Internalization of caveolae with any bound molecules and associated extracellular fluid is sometimes called potocytosis—literally "cellular sipping."
2. *Pinocytosis and receptor mediated endocytosis: Pinocytosis* ("cellular drinking") describes a fluid-phase process during which the plasma membrane invaginates and is pinched off to form a cytoplasmic vesicle. ***Receptor-mediated endocytosis*** is the major uptake mechanism for certain macromolecules like **transferrin** and **low-density lipoprotein** (LDL).

- *Most cytosolic enzymes prefer to work at pH 7.4* whereas **lysosomal enzymes** function best at **pH 5 or less**.

Cytoskeleton

The ability of cells to adopt a particular shape, maintain polarity, organize the relationship of intracellular organelles, and move about depends on the intracellular scaffolding of proteins called the cytoskeleton. The three major classes of cytoskeletal proteins are:

i. ***Actin microfilaments*** are 5- to 9-nm diameter fibrils formed from the **g**lobular protein actin (**G**-actin), the most abundant cytosolic protein in cells.

ii. ***Intermediate filaments*** are 10-nm diameter fibrils that impart tensile strength and allow cells to bear mechanical stress. The examples include:

- *Lamin A, B, and C:* nuclear lamina of all cells
- *Vimentin:* mesenchymal cells (fibroblasts, endothelium)
- *Desmin:* muscle cells, forming the scaffold on which actin and myosin contract
- *Neurofilaments:* axons of neurons, imparting strength and rigidity
- *Glial fibrillary acidic protein:* glial cells around neurons
- *Cytokeratins: 30* different types are present, hence can be used as cell markers

Clinical significance!

Since they have characteristic tissue-specific patterns of expression, they are useful for assigning a cell of origin for poorly differentiated tumors.

iii. ***Microtubules***: these are 25-nm-thick fibrils composed of non-covalently polymerized dimers of α- and β-tubulin arrayed in constantly elongating or shrinking hollow tubes with a defined polarity. Within cells, microtubules are required to move vesicles, organelles, or other molecules around cells along microtubules. There are two varieties of these motor proteins: kinesins (for anterograde transport) and dyneins (for retrograde transport).

Mitochondrial function: key points

- *Intermembrane space* in the mitochondria is the ***chief site of ATP synthesis.***
- *Thermogenin* is an inner membrane protein which is used to generate heat by uncoupling electron transport chain with ATP generation. It is present in high concentration in brown fat and is useful to generate heat by ***non-shivering thermogenesis***.
- **Warburg effect:** it is the phenomenon in which rapidly growing cells (both benign and malignant) upregulate **glucose and glutamine uptake** and decrease their production of ATP per glucose molecule. This is responsible for providing metabolic intermediates which are useful for cellular growth and maintenance.

Receptors

Cell-surface receptors are generally transmembrane proteins with extra cellular domains that bind soluble secreted ligands. They can be of the following types:

1. **Ion channels** (typically at the synapse between electrically excitable cells)
2. ***G protein coupled receptors***: activate an associated GTP-binding regulatory protein
3. **Enzymatic receptors**: activate an associated enzyme usually tyrosine kinase
4. Receptors which trigger a proteolytic event or a change in protein binding or stability that activates a latent transcription factor. Examples include Notch, Wnt, and Hedgehog receptors which regulate normal development.

Transcription factors

- **MYC** and **JUN** are the transcription factors that regulate the expression of genes that are needed for **growth.**
- **p53** is a transcription factor that triggers the expression of genes that lead to **growth arrest**.

Summary of growth factors and the receptors

The major role of growth factors is to stimulate the activity of genes that are required for cell growth and cell division. They are also involved in the non-growth activities, including migration, differentiation, and synthetic capacity. Some important examples include:

a. **Epidermal Growth Factor and Transforming Growth Factor-α.**

The "EGF receptor family" includes four membrane receptors with intrinsic tyrosine kinase activity. The examples include ***EGFR1 involved in lung cancer, head and neck, breast*** etc. and the ERBB2 receptor (also known as HER2) ***involved in breast cancer***

b. **Hepatocyte Growth Factor** (also known as **scatter factor**)

HGF acts as a morphogen in embryonic development, promotes cell migration and enhances hepatocyte survival. MET is the receptor for HGF, it has intrinsic tyrosine kinase activity and is frequently over-expressed or mutated in tumors, particularly ***renal and thyroid papillary carcinomas***.

c. *Platelet-Derived Growth Factor*

PDGF is stored in platelet granules and is released on platelet activation.

d. *Vascular Endothelial Growth Factor*

- *VEGF-A* is the **major *angiogenic* factor** (inducing blood vessel development) after injury and in tumors.
- VEGF-B and PlGF (placental growth factor) are involved in embryonic vessel development, and VEGF-C and -D stimulate both angiogenesis and lymphatic development (lymphangiogenesis).
- In adults, VEGFs are also involved in the maintenance of normal adult endothelium and not involved in angiogenesis.
- ***Hypoxia is the most important inducer of VEGF production***.
- **VEGFR-2** is highly expressed in **endothelium** and is the **most important for angiogenesis.**
- Anti-VEGF antibodies are being used for a number of ophthalmic diseases including "wet" age-related macular degeneration, the angiogenesis associated with retinopathy of prematurity; and diabetic macular edema.

e. *Fibroblast Growth Factor* (FGF-7)

- *FGF-7* is also referred to as *keratinocyte growth factor* (KGF).

f. *Transforming Growth Factor-β*

TGF-β has multiple and often opposing effects depending on the tissue and concurrent signals. Agents with such multiplicity of effects are called pleiotropic.

- ***TGF-β*** is involved in ***scar formation after injury***. It also drives fibrosis in lung, liver, and kidneys in conditions of chronic inflammation.
- ***TGF-β*** is an ***anti-inflammatory cytokine*** that serves to limit and terminate inflammatory responses.

Extracellular matrix

- ***Laminin*** is the most abundant glycoprotein in ***basement membrane***
- The major constituents of basement membrane are amorphous **nonfibrillar type IV collagen** and **laminin.**
- **Collagens** are typically composed of three separate polypeptide chains braided into a ropelike **triple helixQ**.

CHAPTER 1

Cell Injury

Golden Points

- ***Hypoxia*** is the most common cause of cell injury.
- ***Neurons*** are the most sensitive cell to hypoxic injury in the brain.
- ***Coagulative necrosis*** is associated with ***"tombstone appearance"***. It is seen with ischemic injury to all tissues ***except central nervous system***.
- **Caseous necrosis** is caused by: **TB** (most common), syphilis, fungus (Histoplasmosis, Coccidiodomycosis).
- Best example of coexistence of hypertrophy and hyperplasia is ***uterus during pregnancy*** **(gravid uterus)**.
- Most common metaplasia is ***squamous metaplasia*** in the lungs of **smokers**.
- Sign of reversible cell injury in alcoholic liver disease: Cytoplasmic lipid vacuole.
- **CD 95** plays a role in apoptosis (extrinsic pathway).
- **Mitochondria** plays a pivotal role on apoptosis.
- Marker for apoptosis *(programmed cell death)* is **annexin V.**
- Most important **stimulatory gene for apoptosis is p53 gene** and most important *inhibitory gene* for apoptosis is *bcl family* (bcl-2) of genes.
- Keywords associated with apoptosis: caspases, cytochrome C and embryogenesis.
- '**Chromatin condensation**' is the **hallmark feature** of apoptosis.
- *"Step ladder pattern"* on gel electrophoresis is a feature of apoptosis. Stepladder fever is seen in typhoid/enteric fever.
- **Intranucleosomal cleavage of DNA** is characteristic of Apoptosis.
- Anticancer drugs (chemotherapeutic agents) can cause: Both necrosis and apoptosis.
- Important example of apoptotic bodies: ***Councilman bodies, civatte bodies, kamino bodies, Tangible bodies***.
- Mitochondrial abnormality is seen in Oncocytoma.
- Steatosis means Fatty change due to accumulation of triglyceride.
- Caspases are involved in: Apoptosis (organogenesis/morphogenesis).
- ***Lipofuscin*** is also known by several other names like ***'lipochrome', 'wear and tear' pigment, pigment of aging*** and ***"indicator of free radical injury"***. It gets deposited mostly in heart and liver.
- The ***endogenous brown-black pigments*** include ***melanin*** (present in skin) and **homogentisic acid** (the black pigment in patients with *alkaptonuria*).
- ***Dystrophic calcification: normal*** serum calcium levels and in ***dead tissues*** (areas of necrosis).
- ***Metastatic calcification:*** **increased** serum calcium levels and in **living** tissues.
- Suprasellar calcification is *always* a pathological calcification.
- Oncocytes are seen in: Salivary glands, thyroid, parathyroid, kidney, lung, pituitary, and pancreas.
- **"Lungs"** are the commonest site for *metastatic calcification*. Other sites include stomach, pulmonary vein, systemic artery and kidneys.
- ***Psammoma bodies:*** meningioma, papillary thyroid carcinoma, prolactinoma, glucagonoma and serous cystadenoma of the ovary.
- **Gandy gamma body** is seen in **congestive splenomegaly.** It contains hemosiderin and calcium.
- *Oncocytes* are formed with modified *mitochondria.*
- Germ cells have the capacity for self renewal because of telomerase activation.
- **Cancer cells** have the phenomenon of **'telomerase reactivation'**.
- Germ cells have the maximum telomerase activity amongst all the cells of the body.
- **'Not'** seen in cell aging: Increased free radical injury, increased somatic mutation, decreased number of mitochondria & cells, cross-linkage of collagen shortening of telomeres, glycosylation of proteins.
- *Cell cannibalization* required for self survival is called ***autophagy***. In ***Alzheimer disease, formation of autophagosomes is accelerated*** and in *Huntington disease, mutant huntingtin impairs autophagy.*
- **Necroptosis** is a ***caspase independent process*** which resembles necrosis morphologically and apoptosis mechanistically as a form of programmed cell death. It is also called **"programmed necrosis"**.
- **Pyroptosis** is a programmed cell death is accompanied by the release of fever inducing cytokine IL-1. It also involves **caspases 1 and 11**.
- Commonest *fixative used for light microscopic* examination: ***10% buffered neutral formalin.***
- Commonest fixative used for *electron microscopic* examination: **glutaraldehyde.**
- **Fenton's reaction** leads to free radical generation when: **Iron** *is converted from* **ferrous to ferric form.**
- **Haber-Weiss reaction** is: *Generation of free radical from* H_2O_2.
- Enzymes that protect against free radical damage: Superoxide dismutase (SOD), catalase, glutathione peroxidase.

Pathology is a science dealing with the study of diseases. Four important components of pathology are *etiology* (causative factors), *pathogenesis* (mechanism or process by which disease develops), *morphology* (appearance of cells, tissues or organs) and *clinical features*.

CELL INJURY

Disease occurs due to alteration of the functions of tissues or cells at the microscopic level. The various causes of cell injury include:

1. **Hypoxia:** It is the **most common cause of cell injury**. It results due to decrease in oxygen supply to the cells. Hypoxia may be caused by
   a. ***Ischemia:*** Results due to decrease in blood supply. It is the *most common cause of hypoxia*[Q]
   b. ***Anemia:*** Results due to decrease in oxygen carrying capacity of blood
   c. ***Cardio-respiratory disease:*** Results from decreased oxygenation of blood due to cardiac or respiratory disease.

Recent Exam Question

Neurons are the most sensitive cells in the body. They are most commonly damaged due to global hypoxia.

2. **Physical Agents:** Cell injury may occur due to radiation exposure, pressure, burns, frost bite etc.
3. **Chemical Agents:** Many drugs, poisons and chemicals can result in cell injury.
4. **Infections:** Various infectious agents like bacteria, virus, fungus and parasites etc can cause cell injury.
5. **Immunological reactions:** These include hypersensitivity reactions and autoimmune diseases.
6. **Genetic causes:** Cell injury can also result due to derangement of the genes.
7. **Nutritional imbalance:** Cell injury can result due to deficiency of vitamins, minerals etc.

Concept

At a the cellular level, the protective effect in mammalian cells against hypoxic injury is induction of a transcription factor called hypoxia inducible factor 1 which promotes blood vessel formation, stimulates cell survival pathways and enhances anaerobic glycolysis. The only reliable clinical strategy to decrease ischemic brain and spinal cord injury is transient reduction of core body temperature to 92°F.

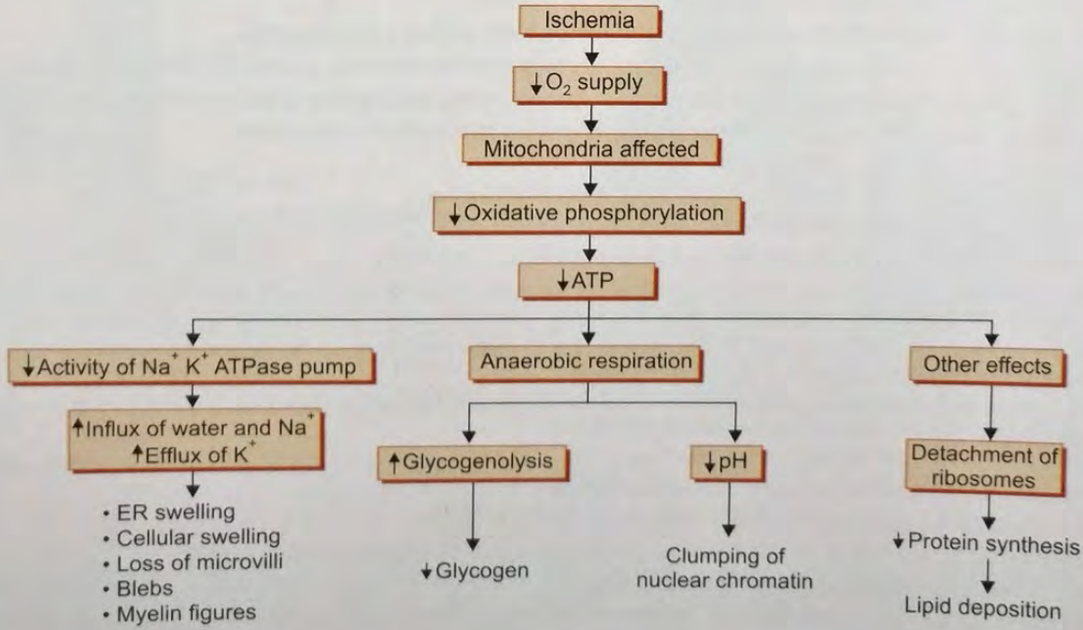
In response to injury, a cell/tissue can have following consequences:

- *Adaptation*: The cell changes its physiological functions in response to an injurious stimulus.
- *Reversible cell injury*
- *Irreversible cell injury.*

1. **REVERSIBLE CELL INJURY:** As already discussed, hypoxia is the most common cause of cell injury. Oxygen is an important requirement of mitochondria for the formation of ATP; therefore, hypoxia will result in **earliest involvement of mitochondria**[Q] resulting in decreased formation of ATP. All cellular processes requiring ATP for normal functioning will be affected. Important organelles affected are *cell membranes* (require ATP for functioning of Na^+ - K^+ pump), *endoplasmic reticulum* (require ATP for protein synthesis) *and nucleus.*

Recent Exam Questions

- **Mitochondria** is the *earliest organelle* affected in cell injury.
- **Myelin figures** are made up of **phospholipids**



- *Swelling of organelles* like endoplasmic reticulum results in decreased protein synthesis
- *Bleb formation* results due to outpouching from the cell membrane to accommodate more water.
- *Loss of microvilli*
- Formation of *myelin figures* due to breakdown of membranes of cellular organelles like endoplasmic reticulum. These are composed of *phospholipids*[Q]. Myelin figures are intracellular whorls of laminated lipid material (resembling myelin of nerves). When these are present in membrane bound structures containing lysosomal enzymes, these are known as *myeloid bodies or myelinoid bodies.*

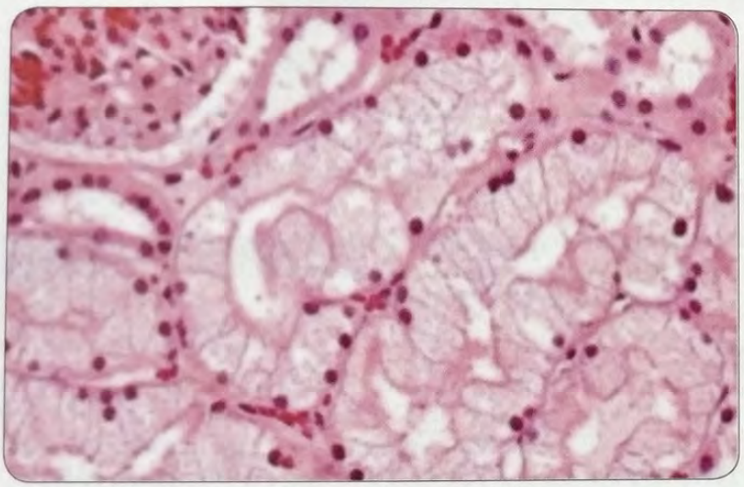


Fig. 1: Hydropic change in kidney.

Key Point

Hydropic change or swelling of the cell due to increased water entry is the *earliest change* seen in reversible cell injury (see Figure 1).

All the features discussed above are of reversible cell injury because if the injurious agent is removed at this point, cell can recover back to its normal state of functioning. However, if the stimulus continues, then irreversible cell injury ensues.

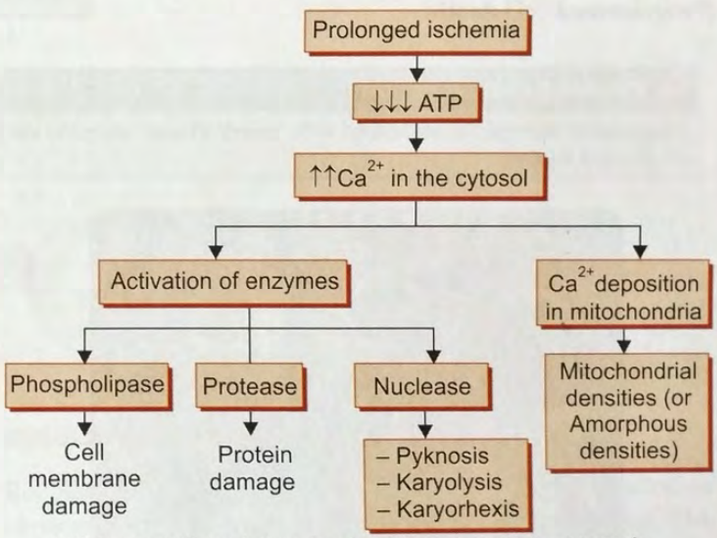
2. **IRREVERSIBLE CELL INJURY:** Features of irreversible cell injury include
   - **Damage to cell membrane:** It results due to continued influx of water, loss of membrane phospholipids and loss of protective amino acids (like glycine). Damage to cell membranes result in massive influx of calcium.
   - **Calcium influx:** Massive influx of Ca^{2+} results in the formation of *large flocculent mitochondrial densities* and activation of enzymes.
   - **Nuclear changes:** These are the most specific microscopic features of irreversible cell injury. These include: ***Pyknosis** (nuclear condensation), ***Karyorrhexis** (fragmentation of the nucleus) and ***Karyolysis** (nuclear dissolution).

Key Point

Inability to reverse mitochondrial dysfunction and development of profound **disturbances in the membrane function** characterize irreversibility.

Recent Exam Question

Increased calcium, reactive oxygen species and oxygen deprivation causes damage of **mitochondria.**



* All the mentioned changes lead to cell death by necrosis

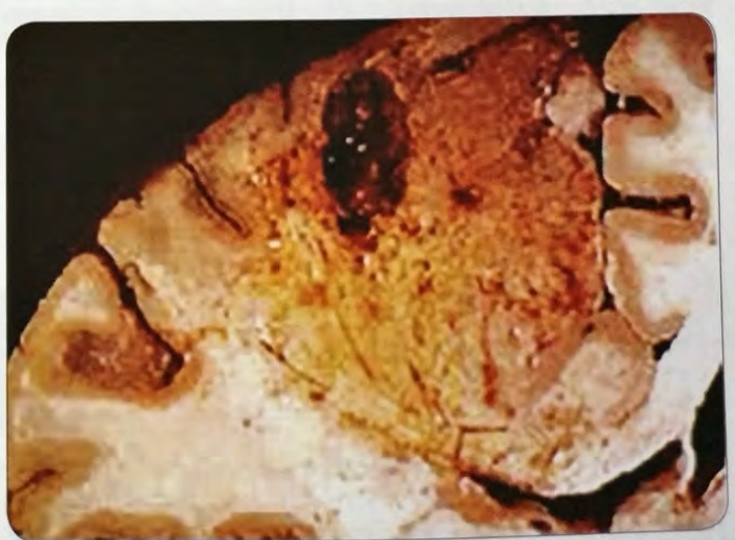


Fig. 2: Liquefactive necrosis in CNS. ...**(All India Image)**

Type of necrosis

Coagulative necrosis	Liquefactive necrosis	Caseous necrosis	Fat necrosis	Fibrinoid necrosis	Gangrenous necrosis
– Most common[Q] type of necrosis – Loss of nucleus with the cellular outline being preserved – Associated with ischemia – Seen in most organs (heart, liver, kidney etc.) **except BRAIN[Q]**.	– Enzymatic destruction of cells – Abscess formation – Pancreatitis – Seen in **brain** (see Figure 2)	– Combination of coagulative and liquefactive necrosis – Cheese like appearance of the necrotic material. – Characteristic of **TB[Q]** – Also seen in syphilis, histoplasmosis and coccidioidomycosis	– Action of lipases on fatty tissue – Seen in breast, omentum and pancreatitis[Q] (see Figure 3)	– Complexes of antigens and antibodies are deposited in vessel wall with leakage of fibrinogen out of vessels – Seen in PAN[Q] Aschoff bodies[Q] (in rheumatic heart disease) and malignant hypertension[Q].	(Surgically used term; necrosis of tissue with superadded putrefaction) – Dry gangrene is similar to coagulative necrosis – Wet gangrene is similar to liquefactive necrosis and is due to secondary infection – Noma is gangrenous lesion of vulva or mouth (cancrum oris) – Fournier's gangrene is seen in scrotum

Irreversible cell injury may be necrosis or apoptosis (Programmed cell death)

Recent Exam Question

Coagulative necrosis is associated with **'tomb stone'** appearance of affected tissue

Fig. 3: Fat necrosis with saponification.

APOPTOSIS

Apoptosis or programmed cell death can be induced by intrinsic or extrinsic pathway. Normally, growth factors bind to their receptors in the cells and prevent the release of *cytochrome C and SMAC*. So, withdrawal or absence of growth factors can result in release of these mediators and initiate the intrinsic pathway.

Key Point

Mitochondrion must be recognized not only as an organelle with vital roles in intermediary metabolism and oxidative phosphorylation, but also as a central regulatory structure of apoptosis.

Intrinsic pathway: It is initiated by the release of *cytochrome C and SMAC* (second mitochondrial activator of caspases) from the *mitochondrial inter-membrane* space. Cytoplasmic cytochrome C stimulates APAF-1 (apoptosis activating factor -1) leading to sequential activation of caspase-9 and effector caspases {Caspases- 3 and -7}. On the other hand, the released SMAC binds and blocks the function of caspases inhibitor IAPs (Inhibitor of Apoptosis Proteins).

Recent Exam Questions

- **Cytosolic cyt "C"-apoptosis**
- *Mitochondrial cyt "C"-electron transport chain.*

Extrinsic pathway: It is activated by *binding of Fas ligand to CD95* (Fas; member of TNF receptor family) *or binding of TRAIL* (TNF related apoptosis inducing ligand) *to* death receptors *DR4 and DR5*. This induces the *association of FADD* (Fas- associated death domain) *and procaspase-8 to death domain motifs* of the receptors resulting in *activation of caspase 8 (in humans caspase 10)* which finally activates **caspases- 3 and 7** that **are final effector caspases.** A cellular proteins called FLIP, binds to procaspase-8 but can not activate it. This is important because some viruses produce homologues of FLIP and protect themselves from Fas mediated apoptosis.

Recent Exam Questions

- Initiator Caspase: caspase 8, 9 and 10
- Executioner caspase: **caspase 3** and 6

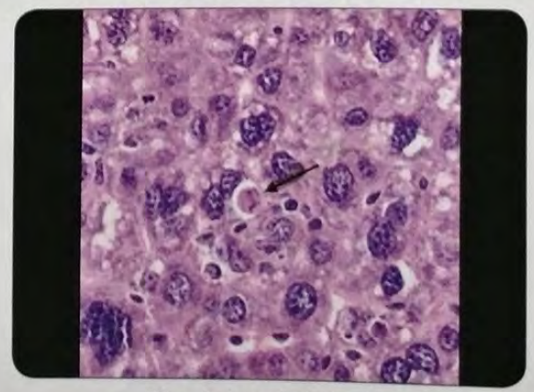
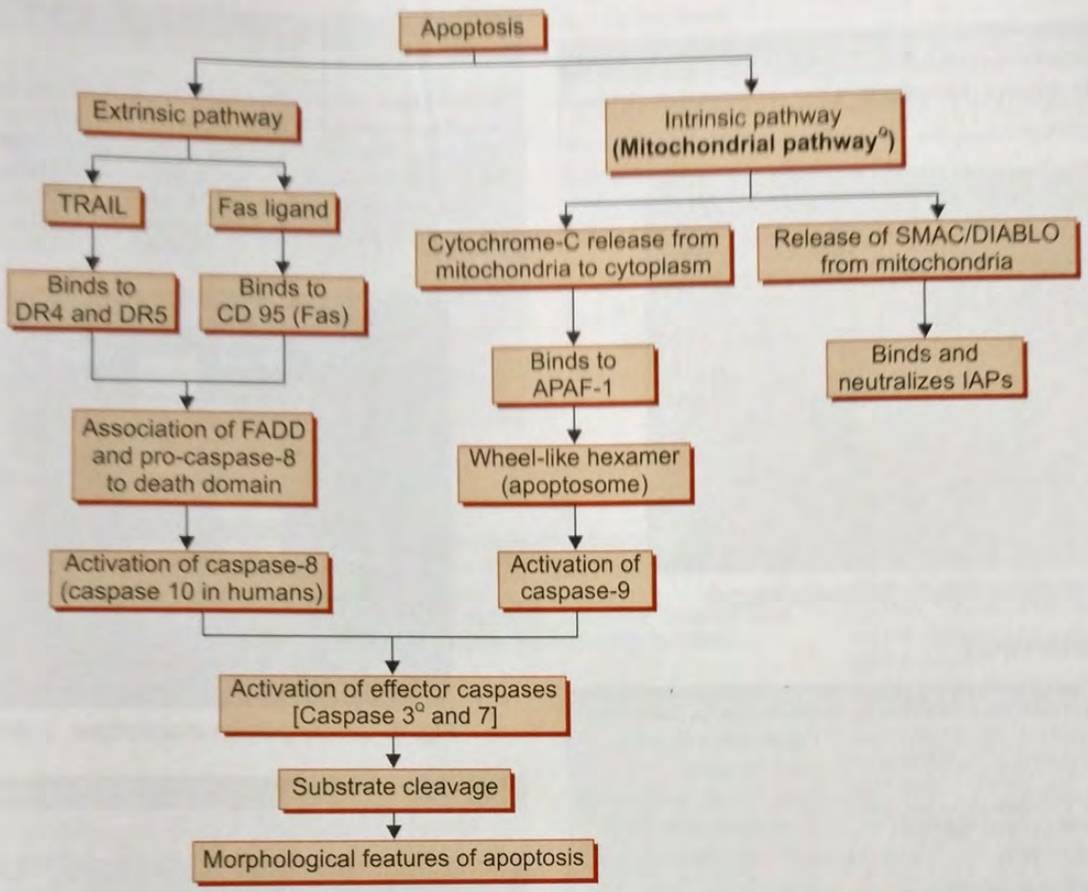


Fig. 4: Apoptotic body.



Key Point

Condensation of nuclear chromatin is the **most characteristic** feature of apoptosis

Recent Exam Question

- **Caspase independent programmed cell death** is called **necroptosis**

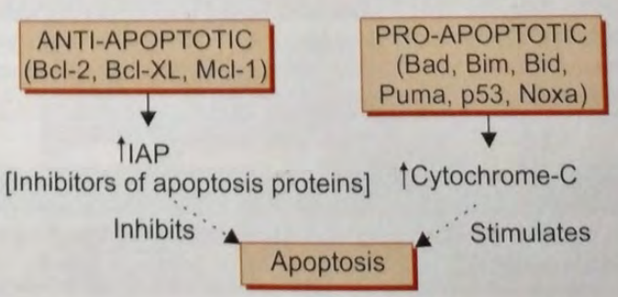
Mnemonic: Short Story to understand the pathogenesis of apoptosis.

Suppose, a person is working in some institution. If he leaves his job, this will be equivalent to apoptosis. There are two reasons due to which that person can leave the work. 1. This person is fired from work (equivalent to extrinsic pathway through death receptors). 2. Person is not given pay for long time, so that the person himself gives resignation (equivalent to intrinsic pathway, due to absence of growth factors). In latter case, before giving resignation, the person will talk to his colleagues, whether he should leave or not. Some of them will suggest him to leave (equivalent to pro-apoptotic gene products like bak, bid etc.) and some of them will stop him and suggest to wait (equivalent to anti-apoptotic factors like bcl-2, bcl-xL etc.) This regulation has been discussed below.

REGULATION OF APOPTOSIS

Regulation is primarily by **bcl-2 family** of genes ***located on chromosome 18***. Some members of this family like bak, bid, bin, bcl-x**S** (to remember, S for **s**timulate apoptosis) stimulate apoptosis whereas others like bcl-2, bcl-xL (to remember, L for lower apoptosis) etc inhibit apoptosis.

Normal cells have bcl-2 and bcl-xL present in the mitochondrial membrane. They inhibit apoptosis because their protein products prevent the leakage of mitochondrial cyt 'c' into the cytoplasm. When there is absence of growth factors or hormones, bcl-2 and bcl-xL are replaced by bax, bin etc. resulting in increased permeability of mitochondrial membrane. This result in stimulation of intrinsic pathway of apoptosis (described above in flowchart).



Recent Exam Question

Glucocorticoids induce apoptosis while *sex steroids* **inhibit** apoptosis

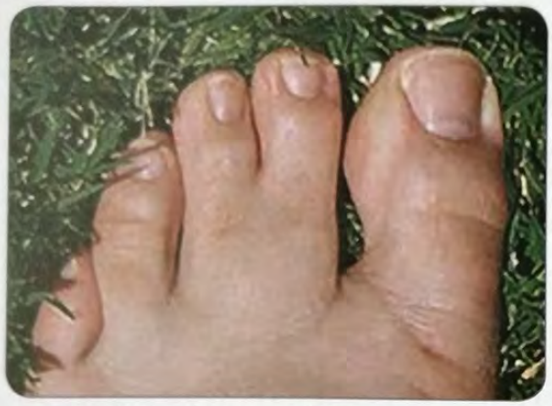


Fig. 5: Syndactyly. **...(All India Image)**

EXAMPLES OF APOPTOSIS

Physiological conditions	Pathological conditions
1. Endometrial cells (Menstruation)	1. Councilman bodies: Viral hepatitis
2. Cell removal during **embryogenesis** (see Figure 5)	2. Gland atrophy following duct obliteration as in cystic fibrosis
3. Virus infected cells and Neoplastic cells by cytotoxic T cells	3. Graft versus host disease (GVHD)

Diagnosis of apoptosis: ***Special topics for PG***

1. **Chromatin condensation** seen by hematoxylin, Feulgen and acridine orange staining.
2. Estimation of cytochrome 'c'
3. Estimation of activated caspase
4. **Estimation of Annexin V** (apoptotic cells express *phosphatidylserine* on the outer layer of plasma membrane because of which these cells are recognized by the dye *Annexin V*[Q]. Some cells also express high concentration of *thrombospondin*).
5. **DNA breakdown at specific sites can be detected by 'step ladder pattern' on gel electrophoresis or TUNEL** (TdT mediated d-UTP Nick End Labelling) **technique**.

Key Point

Apoptosis affects only single cells or small group of cells

Key Point

Apoptotic cells express molecules facilitating their uptake by adjacent cells/macrophages. This leads to **absence of inflammatory response** in apoptosis.

Recent Exam Question

On agarose gel electrophoresis, **ladder pattern**[Q] see Figure 6 is seen in **apoptosis** (in necrosis, smeared pattern is seen).

Clinical Significance of apoptosis in cancers

Mutated cells are cleared normally in the body by apoptosis but in cancers, apoptosis is decreased. Commonly it could be due to mutation in p53 gene or increased expression of genes like bcl-2. The bcl-2 over expression is seen with translocation (14;18) preventing the apoptosis of abnormal B lymphocytes which proliferate then and result in the development of B cell follicular lymphoma.

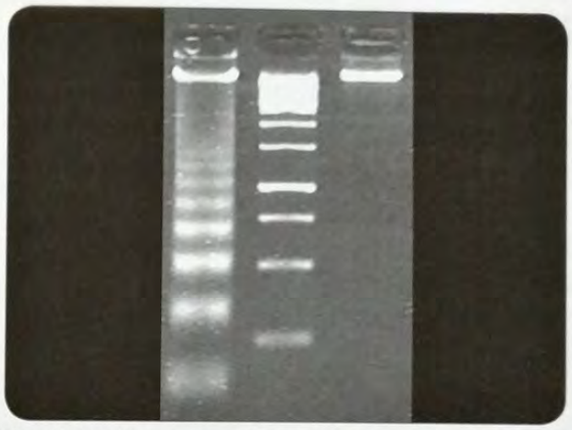


Fig. 6: Ladder pattern in apoptosis. ...(AIIMS Image)

Necrosis	Apoptosis
• Always pathological	• May be **physiological** or **pathological**
• Associated with disruption of cellular homeostasis (e.g. ischemia, hypoxia & poisoning)	• Important for development, homeostasis & elimination of pathogens & tumor cells
• Affects contiguous (adjacent) group of cells	• Affect single cells
• Cell size is increased	• Cell size is **shrunken**
• Passive	• **Active**
• Causes inflammatory reaction	• **No inflammatory** reaction
• Plasma membrane is disrupted	• Plasma membrane is **intact**
• 'Smear pattern' on electrophoresis	• **Step ladder pattern** is seen

Mnemonic: Apoptosis can be considered as suicide whereas necrosis as murder. Like

- Murder is always done by someone else (i.e. pathological) whereas suicide can be committed by oneself (physiological) or due to undue pressure (pathological).
- A person can murder many people (affects group of cells) whereas suicide can be committed only by oneself (affect single cells).
- The person who is being killed doesn't need to plan or do anything (passive) whereas for suicide, lot of planning and effort has to be made (active process).
- When a person is being killed, he will make a lot of efforts to save himself and thus may lead to accumulation of other people or police (equivalent to inflammatory mediators coming there) whereas in suicide no help is called for (no-inflammation).

Other patterns of irreversible cell injury are Necroptosis and Pyroptosis

1. Necroptosis

- Necroptosis resembles necrosis morphologically and apoptosis mechanistically as a form of **programmed cell death**. It is triggered by ligation of TNFR1, and viral proteins of RNA and DNA viruses.
- Necroptosis is **caspase-independent** but dependent on signaling by the RIP1 and RIP3 complex.
- RIP1-RIP3 signaling reduces mitochondrial ATP generation, causes production of ROS, and permeabilizes lysosomal membranes, thereby causing cellular swelling and membrane damage as occurs in necrosis.
- The release of cellular contents evokes an inflammatory reaction as in necrosis.

2. Pyroptosis

Pyroptosis occurs in cells infected by **microbes**. It involves activation of **caspase-1** which cleaves the precursor form of **IL-1** to generate biologically active IL-1. Caspase-1 along with closely related caspase-11 also lead to death of the infected cell.

3. **ADAPTATION:** Cells may show adaptation to injury by various processes like atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia etc.

Atrophy

- Reduced size of an organ or tissue resulting from a decrease in cell size and number.
- Caused by ischemia, ageing, malnutrition, etc.
- May result due to chronic absence of stimulus (disuse atrophy).

Hypertrophy

- Increase in size and function of cells.
- Results due to increase in growth factors or trophic stimuli.
- Includes puberty, lactating breasts and skeletal muscle fibers (in body-builders).

Hyperplasia

- Increase in number of cells in tissues/organ.
- Results due to increase in growth factors, increased expression of growth-promoting genes and increased DNA synthesis.
- It persists so long as the stimulus is present.
- E.g. **breast development at puberty, endometrial hyperplasia,** benign hyperplasia of prostate, hyperplasia of liver cells after partial hepatectomy.

Metaplasia	Dysplasia
• **Reversible change** in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type. • Results from "reprogramming" of stem cells that are known to exist in normal tissues, or of undifferentiated mesenchymal cells in connective tissue.	• Abnormal multiplication of cells characterized by change in size, shape and loss of cellular organization • The **basement membrane is intact**[Q] • Can progress to cancer

Key Point

- **Epithelial metaplasia**: Barret's esophagus (squamous to intestinal columnar epithelium).
- **Connective tissue metaplasia**: myositis ossificans (bone formation in muscle after trauma)

INTRACELLULAR ACCUMULATIONS

Various substances like proteins, lipids, pigments, calcium etc. can accumulate in cells.

1. **Proteins:** Proteins are synthesized as polypeptides on ribosomes. These are then re-arranged into α-helix or β sheets and folded. **Chaperones** *help in protein folding* and transportation across endoplasmic reticulum and golgi apparatus. Chaperones thus can be induced by stress (like heat shock proteins; hsp 70 and hsp 90). They also prevent 'misfolding' of proteins. However, if misfolding occurs, chaperones facilitate degradation of damaged protein via ubiquitin-proteasome complex.

Disorders with protein defects

Defect in transport and secretion of proteins	Misfolded/unfolded proteins
Accumulation of proteins inside cells	Initially increase chaperone concentration, Later, these induce apoptosis by activating caspases
• α_1 – Antitrypsin deficiency [Q] • Cystic fibrosis [Q]	• Alzheimer's Disease[Q] • Huntington's Disease • Parkinson's Disease

2. **Lipids:**
   - *Triglycerides:* Fatty change in liver, heart and kidney (stained with Sudan IV or Oil Red O).
   - *Cholesterol:* Atherosclerosis, xanthoma
   - *Complex lipids:* Sphingolipidosis

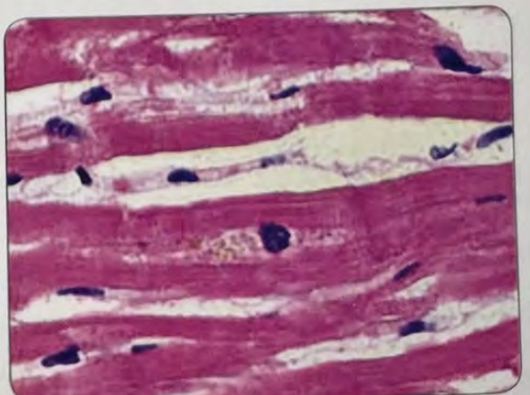


Fig. 7: Lipofuscin (wear and tear pigment).

3. **Endogenous Pigments:**

Lipofuscin	Melanin	Hemosiderin
- Perinuclear, brown coloured pigment - Responsible for *brown atrophy*[Q] of liver and heart - It is derived through lipid peroxidation of membrane lipids. - Seen in aging, **protein energy malnutrition** and **cancer cachexia**.	- Only naturally occurring endogenous black pigment derived from tyrosine[Q] - Responsible for pigmentation of skin and hair	- Golden yellow pigment - Seen at sites of hemorrhage or bruise[Q] - Also seen in hemochromatosis[Q] (Iron overload)

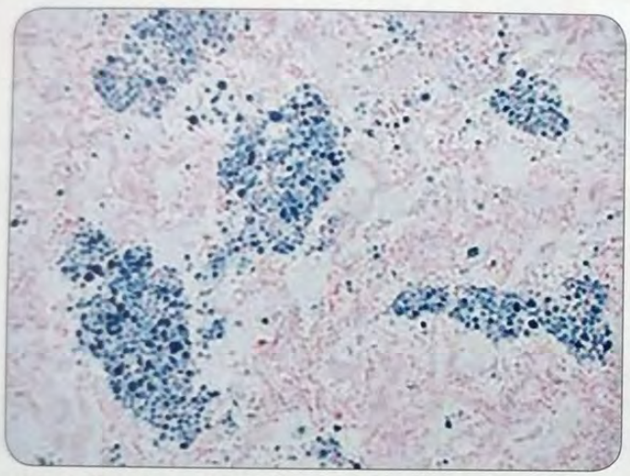


Fig. 8: Pearl reaction of hemosiderin. ...(AIIMS Image)

4. **Hyaline change:** It is any intracellular or extracellular accumulation that has pink homogenous appearance.

Intracellular	Extracellular
- Mallory alcoholic hyaline - Russell bodies (seen in multiple myeloma) - Zenker's hyaline change	- Hyaline membrane in newborns - Hyaline arteriosclerosis - Corpora amylacea in prostate, brain, spinal cord in elderly, old lung infarct

INFO: The deposition of such hyaline like material and the associated sclerosis is important in diseases affecting the kidneys (glomerulopathies).

Concept

Zenker's degeneration is a true necrosis **(coagulative necrosis)** affecting skeletal muscles (more commonly) and cardiac muscles (less commonly) during acute infections like **typhoid**. Rectus and the diaphragm are the usual muscles affected.

5. **Calcification:** Pathologic calcification is the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral salts. It can be of the following two types:

Dystrophic	Metastatic
- Seen in **dead** tissues[Q] - Serum **calcium is normal**[Q] - Seen at sites of **necrosis**[Q] - Often causes organ dysfunction - Examples include: **R** – **R**heumatic heart disease (in cardiac valves) **A** – **A**theromatous plaque **T** – **T**ubercular lymph node Tumors (**MOST** for **PG**) • **M** – **M**eningioma, **M**esothelioma • **O** – Papillary carcinoma of **O**vary (serous ovarian cystadenoma) • **S** – Papillary carcinoma of Salivary gland • **T** – Papillary carcinoma of Thyroid • **P**rolactinoma • **G**lucagonoma	- Seen in **living tissues** also - Association with **elevated serum** Ca^{2+} - Does not cause clinical dysfunction - Seen in • *Hyperparathyroidism*[Q] • *Renal failure*[Q] • *Vitamin D intoxication*[Q] • *Sarcoidosis*[Q] • *Milk alkali syndrome*[Q] • *Multiple myeloma*[Q] • *Metastatic tumors to bone*[Q] - Found in organs which loose acid and have alkaline environment inside them [like **lungs (most commonly)**, kidneys, stomach, systemic artery, pulmonary veins etc]

Note: *Hypercalemia normally is responsible for metastatic calcification but it also accentuates dystrophic calcification.

Mnemonic

D for **Dead** and **D** for **Dystrophic**. So, at sites of necrosis or death of cells, we have dystrophic calcification

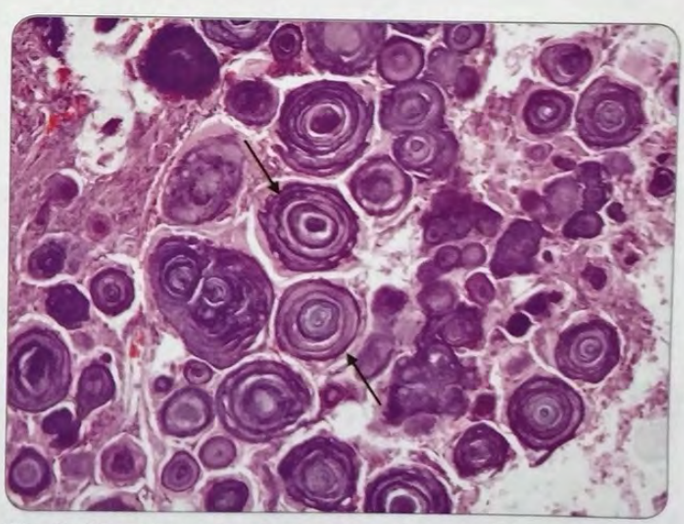


Fig. 9: Psammoma bodies in meningioma. ...(All India Image)

Recent Exam Questions

- **Calcification begins in mitochondria** of all organs *except* kidney (begin in basement membrane)
- **Lungs** are the **commonest site for metastatic calcification**

REPERFUSION INJURY

It is seen with cerebral or myocardial injury. On re-establishment of blood flow, there is increased recruitment of white blood cells which cause inflammation as well as generation of more free radicals.

Key Point

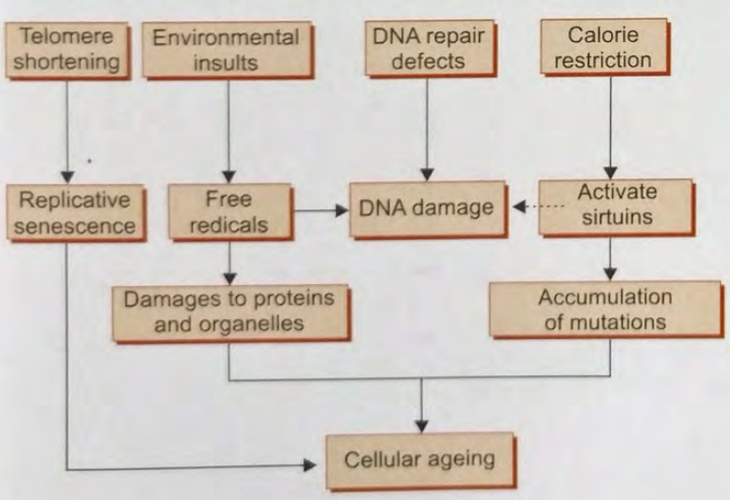
Reperfusion injury is characteristically seen in cardiac cells appearing as **contraction bands after myocardial infarction.**

Cellular Ageing

Features of ageing include decreased oxidative phosphorylation, decreased synthesis of nucleic acids and proteins, deposition of lipofuscin, accumulation of glycosylation products and abnormally folded proteins. The most effective way to prolong life is calories restriction because of a family of proteins called **SIRTUINS**. The latter have histone deacetylase activity and promote expression of genes whose products increase longevity.

The best-studied mammalian sirtuin is Sirt-1[Q] which has been shown to improve glucose tolerance and enhance β cell insulin secretion. It is implicated in diabetes[Q].

- Ends of the chromosomes are known as telomeres. Enzyme *telomerase* helps in keeping the length of telomere constant. *Decreased activity* of this enzyme is *associated with ageing* whereas excessive activity is associated with cancers.



Recent Exam Questions

- A defect in DNA helicase enzyme (required for DNA replication and repair) results in premature ageing **(WERNER SYNDROME)**
- Decreased activity of **telome-rase** is associated with ageing whereas its **excessive activity** is associated with **cancers**.

FREE RADICAL INJURY

Free radical injury is caused by the following mechanisms:

1. Oxidative stress/reactive oxygen species (O_2^-, H_2O_2, OH)
2. Radiation exposure
3. Drugs (carbon tetrachloride, paracetamol)
4. Metals (iron, copper):

Key Point

Fenton reaction: $H_2O_2 + Fe^{2+} \rightarrow Fe^{2+} + OH^- + OH\cdot$

Nitric oxide (NO), an important chemical mediator generated by endothelial cells, macrophages, neurons, and other cell types can act as a free radical and can also be converted to highly reactive peroxynitrite anion ($ONOO^-$) as well as NO_2 and NO_3.

Recent Exam Question

Free radicals in reperfusion injury are produced by **neutrophils**

Mechanism of Free Radical Injury

It can result in lipid peroxidation, DNA breaks and fragmentation of the proteins. This is associated with formation of more free radicals thereby making free radical induced injury as an autocatalytic reaction.

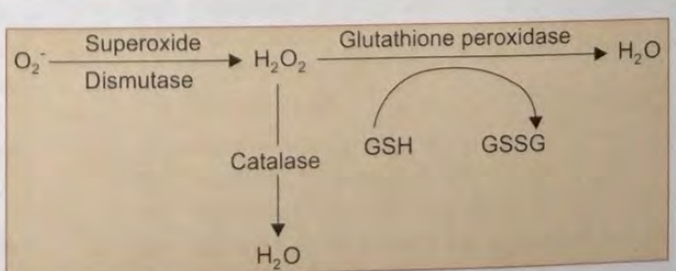
Antioxidants

Antioxidants may act by inhibiting the generation of free radials or scavenging the already present free radicals. These may be divided into enzymatic and non-enzymatic.

Concept

The intracellular ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) is a reflection of the oxidative state of the cell and is an important aspect of the cell's ability to detoxify reactive oxygen species.

Enzymatic	Non-enzymatic
a. Superoxide dismutase	a. Vitamin E
b. Catalase	b. Sulfhydryl containing compounds: cysteine and glutathione
c. Glutathione peroxidase	c. Serum proteins: Albumin, Ceruloplasmin and Transferrin



Recent Exam Questions

- H_2O_2 is **produced** as well as **destroyed** in **peroxisomes**
- *Lysosomes only produce* H_2O_2 but ***dont*** destroy it.

- Catalase is present in peroxisomes and decomposes H_2O_2 into O_2 and H_2O. ($2\ H_2O_2 \rightarrow O_2 + 2\ H_2O$).
- Superoxide dismutase is found in many cell types and converts superoxide ions to H_2O_2. ($2\ O_2^- + 2\ H \rightarrow H_2O_2 + O_2$).This group includes both manganese-superoxide dismutase, which is localized in mitochondria, and copper-zinc-superoxide. dismutase, which is found in the cytosol.
- Glutathione peroxidase also protects against injury by catalyzing free radical breakdown. ($H_2O_2 + 2\ GSH \rightarrow$ GSSG [glutathione homodimer] + $2\ H_2O$, or $2\ OH + 2\ GSH \rightarrow GSSG + 2\ H_2O$).

Concept

Deficiency of SOD 1 gene may result in motor neuron disorder. This finding strengthens the view that SOD protects brain from free radical injury.

Recent Exam Questions

- The most common fixative for **light microscopy** is **10% neutral buffered formalin** (4% formaldehyde in phosphate buffered saline).
- For **electron microscopy**, the most commonly used fixative is **glutaraldehyde** (2.5% solution in phosphate buffered saline).

CHEMICAL FIXATIVES

- Chemical fixatives are used to preserve tissue from degradation, and to maintain the structure of the cell and of sub-cellular components such as cell organelles (e.g., nucleus, endoplasmic reticulum, mitochondria).
- These fixatives preserve tissues or cells mainly by irreversibly cross-linking proteins.
- Frozen section is a rapid way to fix and mount histology sections. It is used in surgical removal of tumors, and allow rapid determination of margin (that the tumor has been completely removed). It is done using a refrigeration device called a cryostat. The frozen tissue is sliced using a microtome, and the frozen slices are mounted on a glass slide and stained the same way as other methods.

Commonly Used Stains

Substance	Stain
Glycogen	Carmine (best), PAS with diastase sensitivity
Lipids	Sudan black, Oil Red 'O'
Amyloid	Congo Red, Thioflavin T (for JG apparatus of kidney) and S
Calcium	Von Kossa, Alzarine Red
Hemosiderin	Perl's stain (see Figure 8)
Trichrome	Collagen^Q appears blue, while smooth muscle^Q appears red.

Multiple Choice Questions

CELL INJURY, NECROSIS, APOPTOSIS

1. **CD 95 is a marker of:** *(AIIMS Nov 2012)*
   (a) Intrinsic pathway of apoptosis
   (b) Extrinsic pathway of apoptosis
   (c) Necrosis of cell
   (d) Cellular adaption

2. **Which of the following is the characteristic of irreversible injury on electron microscopy?**
   (a) Disruption of ribosomes *(AIIMS May 2012)*
   (b) Amorphous densities in mitochondria
   (c) Swelling of endoplasmic reticulum
   (d) Cell swelling

3. **Caspases are associated with which of the following?**
   (a) Hydopic degeneration *(AIIMS May 2010)*
   (b) Collagen hyalinization
   (c) Embryogenesis
   (d) Fatty degeneration

4. **Caspases are seen in which of the following?**
   (a) Cell division (b) Apoptosis *(AI 2010)*
   (c) Necrosis (d) Inflammation

5. **Light microscopic characteristic feature of apoptosis is:**
   (a) Intact cell membrane *(AI 2010)*
   (b) Eosinophilic cytoplasm
   (c) Nuclear moulding
   (d) Condensation of the nucleus

6. **Coagulative necrosis is found in which infection?**
   (a) TB *(AI 2009, AIIMS May' 10)*
   (b) Sarcoidosis
   (c) Gangrene
   (d) Fungal infection

7. **Organelle which plays a pivotal role in apoptosis is:**
   (a) Cytoplasm *(AI 2011, 09, AIIMS May 2010)*
   (b) Golgi complex
   (c) Mitochondria
   (d) Nucleus

8. **All of the following statements are true regarding reversible cell injury, except:** *(AI 2005)*
   (a) Formation of amorphous densities in the mitochondrial matrix
   (b) Diminished generation of adenosine triphosphate (ATP).
   (c) Formation of blebs in the plasma membrane.
   (d) Detachment of ribosomes from the granular endoplasmic reticulum.

9. **Fibrinoid necrosis may be observed in all of the following, except:** *(AI 2005)*
   (a) Malignant hypertension
   (b) Polyarteritis nodosa
   (c) Diabetic glomerulosclerosis
   (d) Aschoff's nodule

10. **In apoptosis, Apaf-I is activated by release of which of the following substances from the mitochondria?**
    (a) Bcl-2 (b) Bax *(AI 2005)*
    (c) Bcl-XL (d) Cytochrome C

11. **Which of the following is an anti-apoptotic gene?**
    (a) C-myc (b) p 53 *(AI 2004)*
    (c) Bcl-2 (d) Bax

12. **Annexin V on non-permeable cell is indicative of:**
    (a) Apoptosis *(AIIMS May 2009)*
    (b) Necrosis
    (c) Cell entering replication phase
    (d) Cell cycle arrest

13. **Ultra-structural finding of irreversible injury:**
    (a) Ribosomal detachment from endoplasmic reticulum
    (b) Amorphous densities in mitochondria
    (c) Formation of phagolysosomes *(AIIMS Nov 2007)*
    (d) Cell swelling

14. **Caspases are involved in:** *(AIIMS Nov 2007)*
    (a) Necrosis (b) Apoptosis
    (c) Atherosclerosis (d) Inflammation

15. **True about Apoptosis are all except:**
    (a) Inflammation is present *(AIIMS May 2007)*
    (b) Chromosomal breakage
    (c) Clumping of chromatin
    (d) Cell shrinkage

16. **The following is an antiapoptotic gene:**
    (a) Bax (b) Bad *(AIIMS Nov 2006)*
    (c) Bcl-X (d) Bim

17. **Cytosolic cytochrome C plays an important function in:**
    (a) Apoptosis *(AIIMS Nov 2006)*
    (b) Cell necrosis
    (c) Electron transport chain
    (d) Cell division

18. **Most pathognomic sign of irreversible cell injury:**
    (a) Amorphous densities in mitochondria
    (b) Swelling of the cell membrane *(AIIMS Nov 2006)*
    (c) Ribosomes detached from endoplasmic reticulum
    (d) Clumping of nuclear chromatin

19. **Internucleosomal cleavage of DNA is characteristic of:** *(AIIMS Nov 2005)*
(a) Reversible cell injury
(b) Irreversible cell injury
(c) Necrosis
(d) Apoptosis

20. **Programmed cell death is known as:**
(a) Cytolysis (b) Apoptosis *(AIIMS Nov 2005)*
(c) Necrosis (d) Proptosis

21. **Ladder pattern of DNA electrophoresis in apoptosis is caused by the action of the following enzyme:** *(AIIMS Nov 2004)*
(a) Endonuclease
(b) Transglutaminase
(c) DNAse
(d) Caspase

22. **Which finding on electron microscopy indicates irreversible cell injury?** *(AIIMS Nov 2002)*
(a) Dilatation of endoplasmic reticulum
(b) Dissociation of ribosomes from rough endoplasmic reticulum
(c) Flocculent densities in the mitochondria
(d) Myelin figures

23. **True about apoptosis is all, except:** *(AIIMS Nov 2001)*
(a) Considerable apoptosis may occur in a tissue before it becomes apparent in histology
(b) Apoptotic cells appear round mass of the intensely eosinophilic cytoplasm with dense nuclear chromatin fragments
(c) Apoptosis of cells induces inflammatory reaction
(d) Macrophages phagocytose the apoptotic cells and degrade them

24. **Morphological changes of apoptosis include:** *(PGI Dec 01)*
(a) Cytoplasmic blebs
(b) Inflammation
(c) Nuclear fragmentation
(d) Spindle formation
(e) Cell swelling

25. **True about apoptosis:** *(PGI June 2003)*
(a) Migration of Leukocytes
(b) End products are phagocytosed by macrophage
(c) Intranuclear fragmentation of DNA
(d) Activation of caspases
(e) Annexin V is a marker of apoptotic cell

MOST RECENT QUESTIONS

26. **Which of the following is the hallmark of programmed cell death?**
(a) Apoptosis
(b) Coagulation necrosis
(c) Fibrinoid necrosis
(d) Liquefaction necrosis

27. **Inhibitor of apoptosis is:**
(a) p53 (b) Ras
(c) Myc (d) Bcl-2

28. **Apoptosis is associated with all of the following features except:**
(a) Cell shrinkage
(b) Intact cellular contents
(c) Inflammation
(d) Nucleosome size fragmentation of nucleus

29. **All of the following are morphological features of apoptosis except:**
(a) Cell shrinkage
(b) Chromatin condensation
(c) Inflammation
(d) Apoptotic bodies

30. **Irreversible injury in cell is:**
(a) Deposition of Ca++ in mitochondria
(b) Swelling
(c) Mitotic figure
(d) Ribosomal detachment

31. **Apoptosis is:**
(a) Cell degeneration
(b) Type of cell injury
(c) Cell regeneration
(d) Cell activation

32. **Pyogenic infection and brain infarction are associated with:**
(a) Coagulative necrosis
(b) Liquefactive necrosis
(c) Caseous necrosis
(d) Fat necrosis

33. **In apoptosis initiation:**
(a) The death receptors induce apoptosis when they get engaged by *fas* ligand system
(b) Cytochrome C inhibits Apoptosis Activating (Apaf-1) Factor – 1
(c) Apoptosis may be initiated by caspase activation
(d) Apoptosis mediated through DNA damage

34. **Apoptosis is alternatively called:**
(a) Ischemic cell death
(b) Programmed cell death
(c) Post traumtic cell death
(d) All

35. **First cellular change in hypoxia:**
(a) Decreased oxidative phosphorylation in mitochondria
(b) Cellular swelling
(c) Alteration in cellular membrane permeability
(d) Clumping of nuclear chromatin

36. **About apoptosis, true statement is:**
(a) Injury due to hypoxia
(b) Inflammatory reaction is present
(c) Councilman bodies are associated with apoptosis
(d) Cell membrane is damaged

37. Fournier's gangrene is seen in:
(a) Nose (b) Scrotal skin
(c) Oral cavity (d) All are true

38. Coagulative necrosis is seen in:
(a) Brain (b) Breast
(c) Liver (d) All

39. In cell death, myelin figures are derived from:
(a) Nucleus (b) Cell membrane
(c) Cytoplasm (d) Mitochondria

40. Irreversible cell injury is characterised by which of the following?
(a) Mitochondrial densities
(b) Cellular swelling
(c) Blebs
(d) Myelin figures

41. Coagulative necrosis as a primary event is most often seen in all except:
(a) Kidneys (b) CNS
(c) Spleen (d) Liver

42. Organelle that plays a pivotal role in apoptosis:
(a) Endoplasmic reticulum
(b) Golgi complex
(c) Mitochondria
(d) Nucleus

43. Liquefactive necrosis is seen in:
(a) Heart (b) Brain
(c) Lung (d) Spleen

44. In apoptosis, cytochrome C acts through:
(a) Apaf 1 (b) Bcl-2
(c) FADD (d) TNF

45. Cells most sensitive to hypoxia are:
(a) Myocardial cells
(b) Neurons
(c) Hepatocytes
(d) Renal tubular epithelial cells

46. Intracellular calcification begins in which of the following organelles?
(a) Mitochondria (b) Golgi body
(c) Lysososme (d) Endoplasmic reticulum

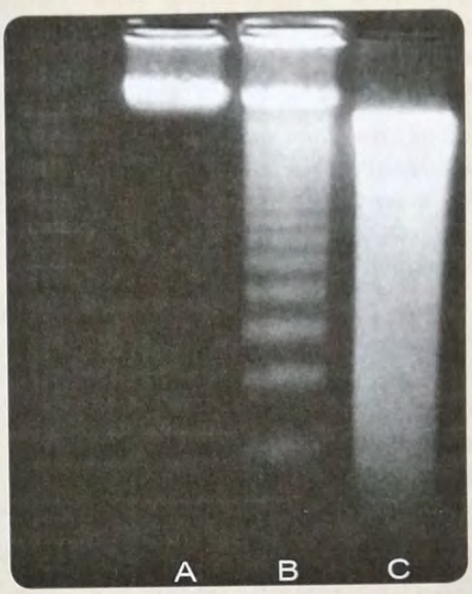
47. Which of the following induces apoptosis in a cell? *(AIIMS Nov 2013)*
(a) Oleic acid
(b) Isoprenoids
(c) Myristic acid
(d) Glucocorticoids

48. Which of the following is not seen is apoptosis? *(AIIMS Nov 2013)*
(a) Chromatin condensation
(b) DNA fragmentation
(c) Inflammation
(d) Cell membrane shrinkage

49. Following gene when mutated protects tumor cells from Apoptosis:
(a) BCL – 2 (b) BRCA
(c) RB (d) TGF – β

50. Following is seen in both apoptosis and necrosis:
(a) Both may be physiological
(b) Both may be pathological
(c) Inflammation
(d) Intact cell membrane

51. Agarose gel electrophoresis from DNA of a population of cells as seen under ultraviolet light is shown below. What is the correct explanation for the finding is seen in the band labelled as "C"? *(AIIMS May 2016)*



(a) Predominantly necrotic cells
(b) Apoptotic cells
(c) Mixed population of normal and apoptotic cells
(d) A population of viable cells

52. What is the common change in cell death associated with both apoptosis and necrosis?
(a) Cell shrinkage
(b) Bleb formation
(c) Chromatin condensation
(d) Presence of inflammation

53. Example/s of physiological atrophy is:
(a) Senile atrophy
(b) Disuse atrophy
(c) Post-pregnancy uterine atrophy
(d) All of the above

54. Caseous necrosis is seen in which of the following:
(a) CMV infection
(b) Staphylococcal infection
(c) Treponemal infection
(d) HSV infection

55. Apoptotic bodies are:
(a) Clumped chromatin bodies
(b) Pyknotic nucleus without organelles
(c) Cell membrane bound with organelles
(d) No nucleus with organells

56. Neutrophilic infiltration with fibrinoid necrosis in walls of vessels is seen in:
(a) Giant cell arteritis
(b) Takayasu arteritis
(c) Churg strauss syndrome
(d) Polyarteritis nodosa

57. Myelin figures are derived from:
(a) Nucleus (b) Cell membrane
(c) Cytoplasm (d) Mitochondria

58. Diabetic foot is associated with following type gangrene:
(a) Dry gangrene (b) Wet gangrene
(c) Gas gangrene (d) Fourniers gangrene

59. Spread of infection causes?
(a) Fibrinoid necrosis
(b) Fat necrosis
(c) Liquefactive necrosis
(d) Coagulative necrosis

60. Unfolded protein metabolism is associated with:
(a) Nucleus (b) Endoplasmic reticulum
(c) Golgi apparatus (d) Mitochondria

61. Anti-apoptotic gene:
(a) BIM (b) P53
(c) BAX (d) FLIP

62. Not a apoptotic gene:
(a) P53 (b) bax
(c) Mcl-1 (d) n-myc

CELLULAR ADAPTATION, INTRACELLULAR ACCUMULATION

63. Psammoma bodies are seen in all *except:* *(AI 2011,09)*
(a) Follicular carcinoma of thyroid
(b) Papillary carcinoma of thyroid
(c) Serous cystadenoma of ovary
(d) Meningioma

64. True about metastatic calcification is: *(AIIMS May 2009)*
(a) Calcium level is normal
(b) Occur in dead and dying tissue
(c) Occur in damaged heart valve
(d) Mitochondria involved earliest

65. Both hyperplasia and hypertrophy are seen in?
(a) Breast enlargement during lactation
(b) Uterus during pregnancy *(AIIMS May 2009)*
(c) Skeletal muscle enlargement during exercise
(d) Left ventricular hypertrophy during heart failure

66. Which of the following is not a common site for metastatic calcification? *(AIIMS Nov 2005)*
(a) Gastric mucosa (b) Kidney
(c) Parathyroid (d) Lung

67. Calcification of soft tissues without any disturbance of calcium metabolism is called: *(AIIMS Nov 2004)*
(a) Inotrophic calcification
(b) Monotrophic calcification
(c) Dystrophic calcification
(d) Calcium induced calcification

68. The light brown perinuclear pigment seen on H & E staining of the cardiac muscle fibres in the grossly normal appearing heart of an 83 year old man at autopsy is due to deposition as: *(AIIMS May 2003)*
(a) Hemosiderin
(b) Lipochrome
(c) Cholesterol metabolite
(d) Anthracotic pigment

69. Dystrophic calcification is seen in: *(AIIMS Nov 2002)*
(a) Rickets
(b) Hyperparathyroidism
(c) Atheromatous plaque
(d) Vitamin A intoxication

70. The Fenton reaction leads to free radical generation when: *(AIIMS Nov 2002)*
(a) Radiant energy is absorbed by water
(b) Hydrogen peroxide is formed by Myeloperoxidase
(c) Ferrous ions are converted to ferric ions
(d) Nitric oxide is converted to peroxynitrite anion

71. Mallory hyaline is seen in: *(PGI Dec 2000)*
(a) Alcoholic liver disease
(b) Hepatocellular carcinoma
(c) Wilson's disease
(d) I.C.C. (Indian childhood cirrhosis)
(e) Biliary cirrhosis

72. Heterotopic calcification occurs in: *(PGI Dec 2000)*
(a) Ankylosing spondylitis
(b) Reiter's syndrome
(c) Forrestier's disease
(d) Rheumatoid arthritis
(e) Gouty arthritis

73. Pigmentation in the liver is caused by all except: *(PGI Dec 01)*
(a) Lipofuscin
(b) Pseudomelanin
(c) Wilson's disease
(d) Malarial pigment
(e) Bile pigment

74. Wear and tear pigment in the body refers to: *(Karnataka 2006)*
(a) Lipochrome
(b) Melanin
(c) Anthracotic pigment
(d) Hemosiderin

75. Mallory hyaline bodies are seen all except: *(AI 97) (UP 2004)*
(a) Indian childhood cirrhosis
(b) Wilson's disease
(c) Alcoholic hepatitis
(d) Crigler-Najjar syndrome

76. "Russell's body" are accumulations of: *(UP 2006)*
(a) Cholesterol (b) Immunoglobulins
(c) Lipoproteins (d) Phospholipids

MOST RECENT QUESTIONS

77. Dystrophic calcification is seen in:
(a) Atheroma
(b) Paget's disease
(c) Renal osteodystrophy
(d) Milk-alkali syndrome

78. Brown atrophy is due to:
(a) Fatty necrosis (b) Hemosiderin
(c) Lipofuscin (d) Ceruloplasmin

79. Psammoma bodies are typically associated with all of the following neoplasms except:
(a) Medulloblastoma
(b) Meningioma
(c) Papillary carcinoma of the thyroid
(d) Papillary serous cystadenocarcinoma of the ovary

80. Transformation of one epithelium to other epithelium is known as:
(a) Dysplasia (b) Hyperplasia
(c) Neoplasia (d) Metaplasia

81. All are true about metaplasia except:
(a) Slow growth
(b) Reverse back to normal with appropriate treatment
(c) Irreversible
(d) If persistent may induce cancer transformation

82. About hyperplasia, which of the following statement is false?
(a) ↑ no of cells
(b) ↑ size of the affected cell
(c) Endometrial response to estrogen is an example
(d) All

83. Example of hypertrophy is:
(a) Breast in puberty
(b) Uterus during pregnancy
(c) Ovary after menopause
(d) Liver after resection

84. Metastatic calcification occurs in all except:
(a) Kidney
(b) Atheroma
(c) Fundus of stomach
(d) Pulmonary veins

85. An old man Muthoot has difficulty in urination associated with increased urge and frequency. He has to get up several times in night to relieve himself. There is no history of any burning micturition and lower back pain. On rectal examination, he has enlarged prostate. Which of the following represents the most likely change in the bladder of this patient?
(a) Hyperplasia (b) Atrophy
(c) Hypertrophy (d) Metaplasia

86. An increase in the size of a cell in response to stress is called hypertrophy. Which of the following does not represent the example of smooth muscle hypertrophy as an adaptive response to the relevant situation?
(a) Urinary bladder in urine outflow obstruction
(b) Small intestine in intestinal obstruction
(c) Triceps in body-builders
(d) None of the above

87. Metastatic calcification is most often seen in:
(a) Lymph nodes (b) Lungs
(c) Kidney (d) Liver

88. True about psammoma bodies are all except:
(a) Seen in meningioma
(b) Concentric whorled appearance
(c) Contains calcium deposits
(d) Seen in teratoma

89. Russell bodies are seen in:
(a) Lymphocytes (b) Neutrophils
(c) Macrophages (d) Plasma cells

90. Psammoma bodies show which type of calcification:
(a) Metastatic (b) Dystrophic
(c) Secondary (d) Any of the above

91. Oncocytes are modified form of which of the following:
(a) Lysososmes (b) Endoplasmic reticulum
(c) Mitochondria (d) None of the above

92. Gamma Gandy bodies contain hemosiderin and:
(a) Na+ (b) Ca++
(c) Mg++ (d) K+

MISCELLANEOUS: FREE RADICAL INJURY: STAINS

93. Which of the following is the most common fixative used in electron microscopy? *(AIIMS Nov 2012)*
(a) Glutaraldehyde (b) Formalin
(c) Picric acid (d) Absolute Alcohol

94. The fixative used in histopathology: *(AIIMS May 2012)*
(a) 10% buffered neutral formalin
(b) Bouins fixative
(c) Glutaraldehyde
(d) Ethyl alcohol

95. Which is the most commonly used fixative in histopathological specimens? *(AI 2011)*
(a) Glutaraldehyde (b) Formaldehyde
(c) Alcohol (d) Picric acid

96. Lipid in the tissue is detected by: *(AIIMS Nov 2009)*
(a) PAS (b) Myeloperoxidase
(c) Oil Red O (d) Mucicarmine

97. The most abundant glycoprotein present in basement membrane is: *(AI 2004)*
(a) Laminin (b) Fibronectin
(c) Collagen type 4 (d) Heparan sulphate

98. Enzyme that protects the brain from free radical injury is: *(AI 2001)*
(a) Myeloperoxidase (b) Superoxide dismutase
(c) MAO (d) Hydroxylase

99. Increased incidence of cancer in old age is due to:
(a) Telomerase reactivation *(AIIMS May 2009)*
(b) Telomerase deactivation
(c) Inactivation of protooncogene
(d) Increase in apoptosis

100. Stain not used for lipid: *(AIIMS Nov 2007)*
(a) Oil red O (b) Congo red
(c) Sudan III (d) Sudan black

101. Acridine orange is a fluorescent dye used to bind: *(AIIMS Nov 2007)*
(a) DNA and RNA (b) Protein
(c) Lipid (d) Carbohydrates

102. PAS stains the following except: *(AIIMS Nov 2007)*
(a) Glycogen
(b) Lipids
(c) Fungal cell wall
(d) Basement membrane of bacteria

103. All are components of basement membrane except:
(a) Nidogen (b) Laminin *(AIIMS Nov 2007)*
(c) Entactin (d) Rhodopsin

104. Which of the following pigments are involved in free radical injury? *(AIIMS Nov 2006)*
(a) Lipofuscin (b) Melanin
(c) Bilirubin (d) Hematin

105. True about cell ageing: *(AIIMS Nov 2001)*
(a) Free radicals injury
(b) Mitochondria are increased
(c) Lipofuscin accumulation in the cell
(d) Size of cell increased

106. Neutrophil secretes: *(PGI Dec 2002)*
(a) Superoxide dismutase
(b) Myeloperoxidase
(c) Lysosomal enzyme
(d) Catalase
(e) Cathepsin G

MOST RECENT QUESTIONS

107. Which of the following is a peroxisomal free radical scavenger?
(a) Superoxide dismutase
(b) Glutathione peroxidase
(c) Catalase
(d) All of the above

108. Crooke's hyaline body is present in:
(a) Yellow fever
(b) Basophil cells of the pituitary gland in Cushing's syndrome
(c) Parkinsonism
(d) Huntington's disease

109. Stain used for melanin is:
(a) Oil red
(b) Gomori methamine silver stain
(c) Masson fontana stain
(d) PAS stain

110. Which of the following statements about Telomerase is true?
(a) Has RNA polymerase activity
(b) Causes carcinogenesis
(c) Present in somatic cells
(d) Absent in germ cells

111. Which of the following is a negative stain?
(a) Fontana (b) ZN stain
(c) Nigrosin (d) Albert stain

112. Oil red O staining is used for:
(a) Frozen section
(b) Glutaraldehyde fixed specimen
(c) Alcohol fixed specimen
(d) Formalin fixed specimen

113. The surgical registrar successfully performs a testicular biopsy and hands over the specimen to the attending nurse. The sister asks you how to send the specimen to the pathologist. What fluid will you tell the sister to put the specimen in: *(AIIMS May 2016)*
(a) 95% Ethanol (b) 10% formalin
(c) Bouin's solution (d) Zenker's solution

114. Most reactive free radical is: *(AIIMS May 2016)*
(a) Superoxide (b) Hydroxyl
(c) Peroxide (d) Carboxyl

115. Stain useful for identifying premalignant lesions of the lip is: *(AIIMS Nov 2016)*
(a) Hematoxylin and eosin
(b) Toluidine blue
(c) Giemsa
(d) Alizarin red

116. Resolving power of a light microscope is not affected by: *(AIIMS Nov 2016)*
(a) Sample thickness
(b) Focal length of objective lens
(c) Numerical aperture of the lens
(d) Wavelength of light

117. All are sources of free radicals except:
(a) Fentons reaction (b) Glutathione
(c) Myeloperoxidase (d) Nitric oxide

118. Lipschutz bodies are seen in:
(a) Hodgkin's disease (b) Viral hepatitis
(c) Herpes (d) Yellow fever

119. Which of the following is detected by Prussian blue stain?
(a) Ferric ions (b) Glycogen
(c) Lipids (d) Ferrous ions

Explanations

1. **Ans. (b) Extrinsic pathway of apoptosis**

(Ref: Robbins 8/e p29-30, 9/e p56)

In the activation of Extrinsic pathway of apoptosis, *binding of Fas ligand* takes place to *CD95* (Fas; member of TNF receptor family) *or binding of TRAIL* (TNF related apoptosis inducing ligand) attaches *to* death receptors *DR4 and DR5*. This induces the *association of FADD* (Fas-associated death domain) *and procaspase-8 to death domain motifs* of the receptors resulting in *activation of caspase 8 (in humans caspase 10)* which finally activates **caspases- 3 and 7** that **are final effector caspases**

2. **Ans. (b) Amorphous densities in mitochondria**

(Ref: Robbins 8/e p14-19, 9/e p42,50)

Two phenomena consistently characterize irreversibility:

1. The first is the ***inability to reverse mitochondrial dysfunction*** (lack of oxidative phosphorylation and ATP generation) even after resolution of the original injury.
2. The second is the development of ***profound disturbances in membrane function.***

So, the answer for the given question is 'Amorphous densities in mitochondria'.

However, please remember friends that the Robbins in its 8th edition pg 14 mentions small amorphous densities to be present in reversible cell injury also. Therefore, the best answer for characterizing irreversibility of an injury is '*profound disturbances in membrane function*'.

3. **Ans. (c) Embryogenesis** *(Ref: Robbins 8/e p25, 9/e p52)*

Caspases are cysteine proteases and are critical for the process of apoptosis. It is required at the time of different processes in embryogenesis like implantation, organogenesis, developmental involution and metamorphosis.

4. **Ans. (b) Apoptosis** *(Ref: Robbins 8/e p27, 9/e p53)*

5. **Ans. (d) Condensation of the nucleus**

(Ref: Robbins 8/e p14-15, 26-27, 9/e p53)

The morphologic features characteristic of apoptosis includes

- **Cell shrinkage**: The cell is smaller in size having dense cytoplasm and the organelles are tightly packed.
- **Chromatin condensation:** This is the *most characteristic feature* of apoptosis.
- **Formation of cytoplasmic blebs and apoptotic bodies**

Regarding option 'a'...'Plasma membranes are thought to remain intact till late stage of apoptosis, as well as is a normal cell.

Regarding option "b", eosinophilic cytoplasm, it is a common feature of necrosis and apoptosis.

***Regarding option "c"*, nuclear moulding** is defined as the "The shape of one nucleus conforming around the shape of an adjacent nucleus". It is a ***characteristic* of malignant cells**.

6. **Ans. (a) TB > (c) Gangrene** *(Ref: Robbins 8/e p16, 9/e p43)*

In the 7th edition of Robbins it was clearly stated that... "***Caseous necrosis**, a distinctive form of coagulative necrosis, is encountered most often in foci of tuberculous infection. The term caseous is derived from the cheesy white gross appearance of the area of necrosis."*

Regarding the option gangrene, it is not specified the type of gangrene and therefore, we go with the better option as tuberculosis in the given question. Moreover, according to Robbins, gangrenous necrosis is not a specific pattern of necrosis but is a term used in clinical practice.

Dry gangrene has coagulative necrosis whereas wet gangrene has liquefactive necrosis.

7. **Ans. (c) Mitochondria** *(Ref: Harrison 18/e p681, 9/e p53)*

8. **Ans. (a) Formation of amorphous densities in mitochondrial matrix** *(Ref: Robbins 7/e p19, 9/e p42)*

Formation of amorphous densities in the mitochondrial matrix is a feature of irreversible injury (more commonly) and left commonly can be seen in reversible injury.

9. **Ans. (c) Diabetic glomerulosclerosis**

(Ref: Robbins 7/e p214, 594, 1008, 9/e p44) ...see text for details

10. **Ans. (d) Cytochrome C** *(Ref: Harrison 17/e p506, 9/e p55)*

Apoptosis or programmed cell death can be induced by intrinsic or extrinsic pathway. As can be seen in the intrinsic pathway; cyt c gets associated with APAF-1 which activates caspase and cause cell death.For detail see text.

11. **Ans. (c) Bcl-2** *(Ref: Harrison 17/e p506)*

12. **Ans. (a) Apoptosis** *(Ref: Robbins 8/e p27, 9/e p56)*

Apoptotic cells express phosphatidylserine in the outer layers of their plasma membranes. This phospholipid moves out from the inner layers where it is recognized by a number of receptors on the phagocytes. These lipids are also detected by binding of a protein called Annexin V. So, **Annexin V** staining is used to identify the apoptotic cells.

13. **Ans. (b) Amorphous densities in mitochondria**

(Ref: Robbins 7/e p12, 9/e p42) ...See earlier explanation.

14. **Ans. (b) Apoptosis** *(Ref: Robbins 7/e p28, 9/e p53)*
Caspases are present in *normal cells as inactive proenzymes* and when they are activated they *cleave proteins and induce apoptosis*. These are cysteine proteases.

15. **Ans. (a) Inflammation is present** *(Ref: Robbins 9/e p56)*
In *Apoptosis* the dead cell is rapidly cleared, before its contents have leaked out, and therefore cell death by this pathway **does not elicit an inflammatory reaction**[Q] in the host.

16. **Ans. (c) Bcl-X** *(Ref: Robbins 7/e p29, 9/e p55)*

17. **Ans. (a) Apoptosis** *(Ref: Robbins 7/e p26, 9/e p55)*

- **Cytosolic cytochrome C** and **Apaf-1** are involved in **intrinsic pathway of apoptosis**[Q].
- **Mitochondrial cyt 'c'** and not cytosolic cyt'c' is involved in **aerobic respiration**[Q].

18. **Ans. (a) Amorphous densities in mitochondria** *(Ref: Robbin's 7/e p12, 9/e p50)*

19. **Ans. (d) Apoptosis** *(Ref: Robbin's 8/e p27, 9/e p52)*
The inter-nucleosomal cleavage of DNA into oligonucleosomes (in multiples of 180-200 base pairs) is brought about by Ca^{2+} and Mg^{2+} dependent **endonucleases** and is characteristic of apoptosis.

20. **Ans. (b) Apoptosis** *(Ref: Robbins 7/e p26, 27, 9/e p52)*

21. **Ans. (a) Endonuclease** *(Ref: Robbins 8/e pg28)*
- **Endonucleases** are enzymes which cause **internucleosomal cleavage** of DNA into oligonucleosomes, the latter being visualized by *agarose gel electrophoresis* **as DNA ladders.**
- **In necrosis, smeared pattern is commonly seen**

22. **Ans. (c) Flocculent densities in mitochondria** *(Ref: Robbins's 7/e p12, 9/e p50)*

23. **Ans. (c) Apoptosis of cells induces inflammatory reaction** *(Ref: Robbins 7/e p27, 9/e p56)*
Remember important features of apoptosis

- Formation of **cytoplasmic blebs and apoptotic bodies**[Q]
- **Cell Shrinkage**[Q]: The cells are smaller in size and the cytoplasm is dense.
- **Chromatin condensation**[Q]: This is the **most characteristic features of apoptosis**.
- Absence of inflammation[Q]
- **Gel Electrophoresis** of DNA shows **'Step ladder'**[Q] **Pattern**.

24. **Ans. (a) Cytoplasmic blebs; (c) Nuclear fragmentation** *(Ref: Robbins 7/e p26, 9/e p53)*
Apoptosis is a programmed cell death.
During apoptosis, cells destined to die activate enzymes that degrade the cell's own nuclear DNA and nuclear and cytoplasmic proteins. There is no inflammatory reaction elicited by host.
- **Spindle formation** is found in cell division in **mitosis.**
- During necrosis, cell swelling is seen.

25. **Ans. (b) End products are phagocytosed by macrophage; (c) Intranuclear fragmentation of DNA; (d) Activation of caspases; (e) Annexin V is a marker of apoptotic cell** *(Ref: Robbins 7/e p25-31, 9/e p53)*

26. **Ans. (a) Apoptosis** *(Ref: Robbins 8/e p25, 9/e p52)*

27. **Ans. (d) Bcl-2** *(Ref: Robbins 7/e p29, 31, 32, 9/e p55)*

28. **Ans. (c) Inflammation** *(Ref: Robbins 7/e p26, 9/e p53)*

29. **Ans. (c) Inflammation** *(Ref: Robbin 7/e p27, 9/e p56)*

30. **Ans. (a) Deposition of Ca^{++} in mitochondria** *(Ref: Robbins 8/e p13-14; 7/e p11, 9/e p47)*

31. **Ans. (b) Type of cell injury** *(Ref: Robbins 9/e p52)*

32. **Ans. (b) Liquefactive necrosis** *(Ref: Robbins 9/e p43)*

33. **Ans. (a) The death receptors induce apoptosis when they get engaged by *fas* ligand system** *(Ref: Robbins 9/e p56)*

34. **Ans. (b) Programmed cell death** *(Ref: Robbins 9/e p52)*

35. **Ans. (a) Decreased oxidative phosphorylation in mitochondria** *(Ref: Robbins 8/e p18-19, 7/e p15, 9/e p45)*

36. **Ans. (c) Councilman bodies are associated with apoptosis** *(Ref: Robbins 8/e p25; 7/e 26, 9/e p823)*

37. **Ans. (b) Scrotal skin**

38. **Ans. (c) Liver** *(Ref: Robbins 7/e p21, 8/e p15; 9/e p43)*

39. **Ans. (b) Cell membrane** *(Ref: Robbins 9/e p50-51)*

40. **Ans. (a) Mitochondrial densities** *(Ref: Robbins 9/e p50)*

41. **Ans. (b) CNS** *(Ref: Robbins 8/e p15, 7/e p22, 9/e p43)*

42. **Ans. (c) Mitochondria** *(Ref: Robbins 8/e p28, 9/e p15, 53)*

43. **Ans. (b) Brain** *(Ref: Robbins 8/e p15, 7/e p22, 9/e p43)*

44. **Ans. (a) Apaf 1** *(Ref: Robbins 8/e p29, 9/e p55)*
On being released in the *cytosol*, **cytochrome *c* binds to a protein called Apaf-1** (apoptosis-activating factor-1 which is responsible for formation of a complex called *apoptosome*. This complex binds to caspase-9 which is a critical initiator caspase of the mitochondrial pathway of apoptosis.

NEET POINTS about APOPTOSIS

- **Mitochondrion** is the critical organelle required for apoptosis.
- **Chromatin condensation** is the most characteristic feature.
- Cell shrinkage is seen
- Gel electrophoresis demonstrates "**step ladder pattern**"
- **Annexin V** is the marker for apoptosis.
- **CD 95** is the molecular marker for apoptosis

45. Ans. (b) Neurons *(Ref: Robbins 8/e p11-2)*

Potential future questions!

The most sensitive neurons in the brain are in the **pyramidal cell layer of the hippocampus** (especially area CA1, also referred to as *Sommer sector*), **cerebellar Purkinje cells** and **pyramidal neurons in cerebral cortex.**

46. Ans. (a) Mitochondria *(Ref: Robbins 8/e p19, 9/e p65-66)*
Direct quote.. "Initiation of *intracellular calcification* occurs in the *mitochondria* of dead or dying cells that accumulate calcium".

47. Ans. (d) Glucocorticoids
(Ref: Underwood's Pathology 6/e p80)
Glucocorticoids induce apoptosis while *sex steroids inhibit apoptosis*. ..Underwood Pathology

Inducers of apoptosis	Inhibitors of apoptosis
• Withdrawal of growth factor • Loss of matrix attachment • Glucocorticoids • Free radicals • Some viruses • Ionising radiation • DNA damage	• Growth factors • Extracellular matrix • **Sex steroids** • Some viral proteins

48. Ans. (c) Inflammation *(Ref: Robbin 8/e p26-7)*
Inflammation is **not** seen in apoptosis.
Chromatin condensation is the most characteristic feature of apoptosis. Other findings like cell membrane shrinkage and DNA fragmentation are also associated with apoptosis.

49. Ans (a) BCL-2 *(Ref: Robbin 9th/ 8thed: pg606)*
We need to identify a gene which should be able to inhibit apoptosis. The answer therefore is BCL-2. It is seen to result in the development of follicular lymphoma.

50. Ans (b) Both may be pathological *(Ref: Robbin 9th/40)*

51. Ans. (a) Predominantly necrotic cells *(Ref: Robbins 8th/27)*

- Presence of a smeared pattern on gel electrophoresis is associated with necrosis...(C in figure)
- Presence of a step ladder pattern on electrophoresis is associated with apoptosis (B in figure).

52. Ans (c) Chromatin condensation *(Ref: Robbins 9/e p15)*

53. Ans (c) Post-pregnancy uterine atrophy
(Ref: Robbins 9/e p36)

Physiological atrophy includes:

a. Post-pregnancy uterine atrophy
b. Atrophy of embryonic structures, (like notochord and thyroglossal duct), undergo during fetal development.

54. Ans (c) Treponemal infection *(Ref: Robbins 9/e p381)*
Caseous necrosis is seen with tuberculosis, syphilis and certain fungi (histoplasmosis, cryptococcosis, and coccidioidomycosis).

55. Ans (c) Cell membrane bound with organelles
(Ref: Robbins 9/e p52)

56. Ans (d) Polyarteritis nodosa *(Ref: Robbins 9/e p509)*

57. Ans (b) Cell membrane *(Ref: Robbins 9/e p42)*
Dead cells may be replaced by large, whorled phospholipid masses called myelin figures that are derived from damaged cell membranes.

58. Ans (b) Wet gangrene *(Ref: Robbins 9/e p43)*

59. Ans (c) Liquefactive necrosis *(Ref: Robbins 9/e p43)*

60. Ans (b) Endoplasmic reticulum *(Ref: Robbins 9/e p12)*
Excess accumulation of misfolded proteins, exceeding the capacity of the ER to edit and degrade them, leads to the *ER stress response* (also called the *unfolded protein response or UPR)* that triggers cell death through apoptosis.

61. Ans (d) FLIP *(Ref: Robbins 9/e p56)*

62. Ans (d) n-myc *(Ref: Robbins 9/e p302)*
Anti apoptotic genes include:

- Bcl-2
- Bcl-XL
- MCL-1

63. Ans. (a) Follicular carcinoma of thyroid
Tumors (MOST for PG) *(Ref: Robbins 8/e p38, 9/e p65)*

- **M** – **M**eningioma
- **O** – Papillary carcinoma of **O**vary (serous ovarian cystadenoma)
- **S** – Papillary carcinoma of **S**alivary gland
- **T** – Papillary carcinoma of **T**hyroid
- **P**rolactinoma, **P**apillary type of renal cell carcinoma
- **G**lucagonoma

(Psammoma bodies are seen in papillary thyroid cancer and not follicular thyroid cancer)

64. Ans. (d) Mitochondria involved earliest
(Ref: Robbins 8/e p38, Robbins 7/e p41-42, 9/e p65)

65. Ans. (b) Uterus during pregnancy *(Ref: Robbins 9/e p36)*

- *Hypertrophy refers to an increase in the size of cells, resulting in an increase in the size of the organ.* The increased size of the cells is due the synthesis of more structural components.
- The massive physiologic growth of the uterus during pregnancy is a good example of hormone-induced increase in the size of an organ that results from both hypertrophy and hyperplasia
- Regarding the 'a' choice, Breast enlargement during lactation; it is written in Robbins that prolactin and estrogen cause ***hypertrophy of the breasts*** during ***lactation***. Hormonal *hyperplasia* is best exemplified by the proliferation of the glandular epithelium of the female *breast at puberty and during pregnancy.*

66. Ans. (c) Parathyroid *(Ref: Robbins 7/e p42, 9/e p65)*

- Metastatic calcification may occur widely throughout the body but principally affects:

- Interstitial tissues of gastric mucosa[Q]
- Kidneys[Q]
- Lungs[Q]
- Systemic arteries[Q] and
- Pulmonary veins[Q]

- The common feature of all these sites, which makes them prone to calcification is that **can loose acid** and therefore they have an **internal alkaline component** favorable for metastatic calcification.
- Absence of derangement in calcium metabolism
- Often a cause of organ dysfunction.

67. **Ans. (c) Dystrophic calcification** *(Ref: Robbins 9/e p65)*

68. **Ans. (b) Lipochrome** *(Ref: Robbins 7/e p39, 9/e p64)*

Regarding other options

- Hemosiderin: It is a pigment deposited in conditions of excess iron.
- Anthracotic pigment: It is pigment seen in the lung of coal

69. **Ans. (c) Atheromatous plaque** *(Ref: Robbins 9/e p65)*

- Atheromatous plaque would have dead cells, so, there is presence of dystrophic calcification.

Mnemonic: D for **D**ead and **D** for **D**ystrophic.

70. **Ans. (c) Ferrous ions are converted to ferric ions** *(Ref: Robbins' 7/e p16, 9/e p48)*

- Free radicals are generated through **Fenton's reaction** which is ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^+ + OH^-$)
- In this reaction iron is converted from its ferrous to ferric form and a radical is generated.
- The other options are also examples of free radical injury but the questions specifically about Fenton reaction.
- The effects of these reactive species relevant to cell injury include: **Lipid peroxidation of membranes, oxidative modification of proteins and lesions in DNA.**

71. **Ans. (a) Alcoholic liver disease; (b) Hepatocellular carcinoma; (c) Wilson's disease; (d) I.C.C. (Indian childhood cirrhosis); (e) Biliary cirrhosis** *(Ref: Robbins' 7/e p905)*

Mallory bodies: Scattered hepatocytes accumulate tangled skeins of cytokeratin intermediate filaments and other proteins, visible as eosinophilic cytoplasmic inclusions in degenerating hepatocytes. See details in chapter on 'Liver'.

72. **Ans. (a) Ankylosing spondylitis; (c) Forrestier's disease** *(Ref: Robbins' 7/e p41-2; Harrison17/e p1952)*

Pathologic calcification (Heterotopic calcification) is the abnormal tissue deposition of calcium salts together with small amounts of iron, manganese and other mineral salts. It may be of **two types: Dystrophic calcification** or **Metastatic calcification**

*In **ankylosing spondylitis** - There is calcification and ossification usually most prominent in anterior spinal ligament that gives **"Flowing wax" appearance**[Q] on the anterior bodies of vertebrae.

***Diffuse idiopathic skeletal hyperostosis (Forrestier's disease**[Q], ankylosing hyperostosis) affects spine and extra-spinal locations. It is an enthesopathy, causing bony overgrowths and ligamentous ossification and is characterized by flowing calcification over the anterolateral aspects of vertebrae.

73. **Ans. None** *(Ref: Robbins 7/e p39, 910, 914)*

Pigmentation in liver is caused by:

- **Lipofuscin:** It is an insoluble pigment known as lipochrome and 'wear and tear' pigment. It is seen in cells undergoing low, regressive changes and is particularly prominent in liver and heart of ageing patient or patients with severe malnutrition and cancer cachexia.
- **Pseudomelanin:** After death, a dark greenish or blackish discoloration of the surface of the abdominal viscera results from the action of sulfated hydrogen upon the iron of disintegrated hemoglobin. Liver is also pigmented.
- **Wilson's disease:** Copper is usually deposited in periportal hepatocytes in the form of reddish granules in cytoplasm or reddish cytoplasmic coloration stained by rubeanic acid or rhodamine stain for copper or orcein stain for copper associated protein. Copper also gets deposited in chronic obstructive cholestasis.
- **Malarial pigment:** Liver colour varies from dark chocolate red to slate-grey even black depending upon the stage of congestion.
- **In biliary cirrhosis** liver is enlarged and greenish-yellow in colour due to cholestasis. So liver is pigmented due to bile.

74. **Ans. (a) Lipochrome** *(Ref: Robbins 7/e p39, 9/e p64)*

75. **Ans. (d) Crigler-Najjar syndrome** *(Ref: Robbins 7/e p905)*

76. **Ans. (b) Immunoglobulins** *(Ref: Robbins 9/e p63)*

77. **Ans. (a) Atheroma** *(Ref: Robbins 8/e p38, 9/e p65)*

78. **Ans. (c) Lipofuscin** *(Ref: Robbins 8/e p10,532; 7/e 10, 9/e p64)*

79. **Ans. (a) Medulloblastoma** *(Ref: Robbins 9/e p65)*

80. **Ans. (d) Metaplasia** *(Ref: Robbins 8/e p10,11; 9/e p37)*

81. **Ans. (c) Irreversible** *(Ref: Robbins 8/e p265; 9/e p37-38*

82. **Ans. (b) ↑ size of the affected cell** *(Ref: Robbins 9/e p35)*

83. **Ans. (b) Uterus during pregnancy** *(Ref: Robbins 8/e p6, 7/e p7-8 , 9/e p34-36)*

Breast at Puberty	**Hyperplasia**
Breast during lactation	Hypertrophy
Uterus after resection	**Hyperplasia**
Uterus during pregnancy	Hyperplasia + Hypertrophy

84. **Ans. (b) Atheroma** *(Ref: Robbins 8/e p38; 7/e p41, 9/e p65)*

85. **Ans. (c) Hypertrophy** *(Ref: Robbins 8/e p6-7, 9/e p36)*

The patient is most likely suffering from benign hyperplasia of the prostate. The question however asks about the change in bladder which would be hypertrophy. This is secondary to the obstruction in the urine outflow following which the smooth muscle in the bladder undergoes hypertrophy.

Benign prostatic hyperplasia is due to action of the hormone **dihydrotestosterone** and not testosterone.

86. **Ans. (c) Triceps in body-builders** *(Ref: Robbins 9/e p34)*

The enlargement of the triceps is an example of **skeletal muscle hypertrophy (not smooth muscle hypertrophy)**.

87. **Ans. (b) Lungs**
(Ref: Dail and Hammar's Pulmonary Pathology: Non-neoplastic lung disease, Springer 3/e p777)
Direct quote...'Lung are the most frequent involved of all organs.'
Ours is the only and the first book to give you an authentic reference for this one friends. This is in **sharp contrast to all our competitors who give name and page number of books where this info is just not there. Try that yourself. You would find many such questions and answers in other chapters of this edition. Happy reading!**

88. **Ans. (d) Seen in teratoma** *(Ref: Robbins 8/e p38, 9/e p65)*
The progressive acquisition of outer layers may create lamellated configurations, called **psammoma bodies** because of their resemblance to grains of sand. Some common cancers associated with psammoma bodies are:
- M – Meningioma, Mesothelioma
- O – Papillary carcinoma of Ovary (serous ovarian cystadenoma)
- S – Papillary carcinoma of Salivary gland
- T – Papillary carcinoma of Thyroid
- Prolactinoma
- Glucagonoma

89. **Ans. (d) Plasma cells** *(Ref: Robbins 8/e p35, 9/e p63)*
Russell bodies are homogenous eosinophilic inclusions that result from hugely distended endoplasmic reticulum.

90. **Ans. (b) Dystrophic** *(Ref: Robbins 8/e p38, 9/e p65)*
Direct quote... "On occasion single necrotic cells may constitute seed crystals that become encrusted by the mineral deposits. The progressive acquisition of outer layers may create lamellated configurations, called **psammoma bodies**."

91. **Ans. (c) Mitochondria** *(Ref: Robbins 8/e p35, 9/e p53)*
Oncocytes are epithelial cells stuffed with **mitochondria**, which impart the granular appearance to the cytoplasm.

92. **Ans. (b) Ca++** *(Ref: Robbins 7/e p705)*
In chronic venous congestion of spleen, some of the hemorrhages overlying fibrous tissue get deposits of **hemosiderin and calcium**, these are called **Gamma Gandy bodies** or **siderofibrotic nodules**.

93. **Ans. (a) Glutaraldehyde** *(Ref: Ackerman 9th/27)*

- Commonest fixative used for ***light microscopic examination***: **10% buffered neutral formalin**
- Commonest fixative used for ***electron microscopic examination***: **Glutaraldehyde**

94. **Ans. (a) 10% buffered neutral formalin**
(Ref: Bancroft 6/e p53, Ackerman 9th/27) ...see above answer.

95. **Ans. (b) Formaldehyde** *(Ref: Bancroft 6/e p53)*

96. **Ans. (c) Oil Red O** *(Ref: Bancroft histology 6/e p53)*

97. **Ans. (a) Laminin** *(Ref: Robbins Harrison 17/e p2462)*
Laminin is the most abundant glycoprotein in basement membranes. Type IV collagen, laminin and nidogen are present in basement membranes.

Tendons and ligaments consist primarily of collagen type I whereas cartilage is mainly consisted of Type II collagen.

98. **Ans. (b) Superoxide dismutase**
(Ref: Robbins 7/e p17, Harrison's 17/e p2572 , 9/e p48)

99. **Ans. (a) Telomerase reactivation** *(Ref: Robbins 9/e p67)*

- After a fixed number of divisions, normal cells become arrested in a terminally non-dividing state known as **replicative senescence**. With each cell division there is some shortening of specialized structures, called telomeres, at the ends of chromosomes. Once the telomeres are shortened beyond a certain point, the loss of telomere function leads to activation of p53-dependent cell-cycle checkpoints, causing proliferative arrest or apoptosis. Thus, telomere shortening functions as a clock that counts cell divisions.
- In **germ cells**, telomere shortening is prevented by the sustained **function of the enzyme telomerase**, thus explaining the ability of these cells to **self-replicate extensively**. This enzyme is **absent in most somatic cells**, and hence they suffer progressive loss of telomeres.
- **Cancer cells** prevent telomere shortening by the reactivation of telomerase activity. Telomerase activity has been detected in more than 90% of human tumors. Telomerase activity and maintenance of telomere length are essential for the maintenance of replicative potential in cancer cells.

100. **Ans. (b) Congo red** *(Ref: Bancroft's histopathology 5th/204)*
Congo red is used for staining amyloid and not lipids

Stains for Lipids

• Oil red O	• Sudan black	• Sudan III and IV
• Filipin	• Schultz	• Nile blue sulfate

101. **Ans. (a) DNA and RNA** *(Ref: Bancroft 5th/236, 237, 238)*
- **Acridine orange** is a nucleic acid selective fluorescent cationic dye useful for cell cycle determination.
- It is cell-permeable, and interacts with DNA and RNA by intercalation or electrostatic attractions respectively and emits green and red right respectively.
- **Acridine orange can be used in conjunction with ethidium bromide to differentiate between live and apoptotic cells.**

102. **Ans. (b) Lipids** *(Ref: Bancroft's histopathology 5th/204)*
PAS (periodic acid-Schiff) stain is versatile and has been used to stain many structures including glycogen, mucin, mucoprotein, glycoprotein, as well as fungi. PAS is useful for outlining tissue structures, basement membranes, glomeruli, blood vessels and glycogen in the liver.

*Lipids are stained by oil red O and Sudan stains. (See explanation above)
*PAS can also stain glycolipids but here it is used for staining carbohydrate moiety of these compounds and not lipid portion.

103. Ans. (d) Rhodopsin *(Ref: Robbins 7/e p103, 9/e p24)*

Basement membrane is Periodic Acid Schiff (PAS) positive amorphous structures that lie underneath epithelia of different organs and endothelial cells. It consists of

• **Laminin**	• *Fibronectin*	• *Tenascin*
• **Proteoglycans**	• **Entactin (Nidogen)**	• *Perlecan* (heparin sulphate)
• Collagen type IV		

104. Ans. (a) Lipofuscin *(Ref: Robbins 7/e p39 , 9/e p64)*

Important points about Lipochrome or Lipofuscin.

*Also called '**wear and tear pigment**'[Q] or '**pigment of ageing**'[Q]
*Perinuclear in location
*Derived through **lipid peroxidation**[Q]
*Indicative of **free radical injury to the cell**
*Prominent in ageing[Q], severe malnutrition[Q] and cancer cachexia[Q]

105. Ans. (c) Lipofuscin accumulation in the cell *(Ref: Robbins 9/e p64)*

106. Ans. (b) Myeloperoxidase; (e) Cathepsin G *(Ref: Robbins 7/e p73)*

107. Ans. (d) All of the above *(Ref: Robbins 9/e p48) ...see text*

108. Ans. (b) Basophil cells of the pituitary gland in Cushing's syndrome *(Ref: Robbins 8/e p1149)*

In Cushing's syndrome, the normal granular, basophilic cytoplasm of the ACTH producing cells in the anterior pituitary becomes paler and homogenous. This is due to **accumulation** of intermediate **keratin filaments** [Q] in the cytoplasm.

109. Ans. (c) Masson fontana stain *(Ref: Histopathology p150)*

Stain	Substance
Masson Fontana	Melanin
Oil red O	Neutral lipids and fatty acids
PAS	Glycogen, mucin, mucoprotein, glycoprotein and fungi
Gomori methamine silver stain	Fungi (like Cryptococcus, Coccidiodes and Pneumocystis jiroveci (carinii)

- Other stains for melanin are Schmorl's method and enzyme histochemical method called **DOPA-oxidase (most specific method)**.

110. Ans. (b) Causes carcinogenesis *(Ref: Robbins 9/e p67)*

- Telomerase is a specialized RNA-protein complex that uses its own RNA as a template for adding nucleotides to the ends of chromosomes.
- Regulatory protein sense the telomere length and they restrict the activity of telomerase to prevent unnecessary elongation.
- **Telomerase activity** is **highest** in **germ cells** and present at lower levels in stem cells, but it is usually undetectable in most somatic tissues

Decreased activity of **telomerase** is associated with ageing whereas its **excessive activity** is associated with **cancers**.

111. Ans. (c) Nigrosin

- **Negative staining** is a technique in which the background is stained, leaving the actual specimen untouched, and thus visible. In contrast, with 'positive staining', the actual specimen is stained.
- Examples of negative stains include **nigrosin** and **India Ink.**
- **India ink** is used to make a diagnosis of **cryotococcal infection** by making its **capsule prominent.**

112. Ans. (a) Frozen section *(Ref: Bancroft Histology 7th/83)*

Fresh cryostat sections must be used for oil red O stains

113. Ans. (b) 10% formalin

(Ref: Bancroft Histological techniques..page 70)

114. Ans. (b) Hydroxyl *(Ref: Robbins 9th/47)*

Hydroxyl radical is the most reactive free radical.

115. Ans. (b) Toluidine blue

Premalignant lesions have abnormal cells containing ***high DNA/RNA*** thereby making these cells hyperchromatic. The same can be *detected grossly* with the help of stains like ***toluidine blue***.

It is important to know that for detection of these lesions under the microscope, we either use H&E (hemaotxylin and eosin) and toluidine blue.

116. Ans (b) Focal length of objective lens

(Ref: Bancroft Histological techniques..page 45-47)

Resolving power of a light microscope is NOT affected by Focal length of objective lens. Rest all mentioned options do affect the resolving power.

117. Ans (b) Glutathione *(Ref: Robbins 9/e p47-48)*

118. Ans (c) Herpes *(Ref: Robbins 9/e p336)*

Lipschutz bodies are seen in herpes.

119. Ans (a) Ferric ions *(Ref: Robbins 9/e p650)*

CHAPTER 2

Inflammation

Golden Points

- **Celsus** was the frost person to describe the **four cardinal signs of inflammation**: *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). These signs are hallmarks of acute inflammation.
- **Rudolf Virchow** added the fifth clinical sign '**loss of function**' *(function laesa).*
- **Elie Metchnikoff** discovered the process of ***phagocytosis*** by observing the ingestion of rose thorns by amebocytes of starfish larvae and of bacteria by mammalian leukocytes.
- **Sir Thomas Lewis** established the concept that *chemical substances, such as* ***histamine*** *(produced locally in response to injury), mediate the vascular changes of inflammation.*
- **Increased vascular permeability** is the hallmark feature of acute inflammation.
- **Endothelial cell contraction** is the most common mechanism of increased vascular permeability.
- "**Selectins**" are responsible for '**rolling**' whereas "*integrins*" are required for "*adhesion*".
- Hallmark of acute *cytokine mediated* acute inflammation: Endothelial expression of E-selectin. Selectin family includes E-selectin, L-selectin and P-selectin (not A-selectin).
- Transmigration (also called **diapedesis**) requires PECAM molecule or **CD31**.
- Chemotaxis: single direction targeted movement of WBCs like neutrophils caused by exogenous molecule (bacterial products) or endogenous molecules (C5a, LTB4 or IL-8).
- Opsonisation requires special chemicals called opsonins (complement proteins like C3b, lectins and antibodies).
- ***Phagocytic receptors*** include **mannose receptors, scavenger receptors and receptors for various opsonins.**
- ***Scavenger receptors*** were originally defined as molecules that bind and mediate endocytosis of oxidized or acetylated low-density lipoprotein (LDL) particles that can **no longer** interact with the conventional LDL receptor.
- The **H_2O_2-MPO-halide system** is the most efficient bactericidal system of **neutrophils**.
- **Nitroblue tetrazolium** test is used for monitoring the functioning of phagocytes and is useful in patients suffering from ***chronic granulomatous disease***.
- **N**eutrophil extracellular **t**raps **(NETs)** are **extracellular fibrillar networks** which provide a high concentration of antimicrobial substances at sites of infection. They are produced **by neutrophils** in response to chemicals mainly **interferons**. NET formation is dependent on ***platelet activation*** and it is associated with the pathogenesis of autoimmune conditions like **SLE.**
- In the ***absence of effective TH17 responses***, individuals are susceptible to fungal and bacterial infections, and the skin abscesses that develop are "**cold abscesses**," lacking the classic features of acute inflammation, such as warmth and redness.
- **Histamine** is the most important chemical mediator of *acute inflammation.*
- *Arachidonic acid is derived from* the conversion of essential fatty acid **linoleic acid**.
- The **prostaglandins** are involved in the pathogenesis of *pain* and *fever* in inflammation. Also know that **PGE2** is *hyperalgesic.*
- ***Lipoxins*** are also generated from AA by the **lipoxygenase pathway.** They **suppress inflammation** by inhibiting the recruitment of leukocytes**.** Formation of lipoxins requires two cell populations (**leucocytes and platelets**) for the biosynthesis.
- 'C' in CRP stands for: Carbohydrate antigen of pneumococcus.
- Complement proteins constitute **5-10%** of plasma proteins.
- **Eculizumab** prevents the conversion of C5 to C5a. This inhibitor not only reduces the hemolysis and attendant transfusion requirements in patients of **paroxysmal nocturnal hemoglobinuria** (PNH), but also lowers the risk of thrombosis by up to 90%.
- **Catarrhal inflammation** is the commonest type of acute inflammation.
- **Adiponectin, IL-10, IL-6, IL-4** and **TGF beta** are **anti-inflammatory** cytokines
- Stable tissues have a limited capacity to regenerate after injury the ***only exception*** being **liver**.
- **Not** seen in acute inflammation: **Granuloma formation**.
- Not an immune granuloma: Silicosis (it causes non-immune granuloma).
- Important causes of necrotizing granuloma: TB syphilis, histoplasma, Cat's scratch disease, Wegner's granulomatosis, RA, Hodkins disease, Byssinosis. Please revise that **Leprosy** is ***not*** a cause of necrotizing granuloma.
- Important macrophages: ***Histiocytes, Kupffer cells, osteoclasts, mesangial cells, Hoffbouer cells, Littoral cells, type A synoviocytes.***
- Components of basement membrane: Laminin Collagen IV, fibronectin, tenascin, enatactin, proteoglycons perlecan. Not a component of basement membrane is **Rhodopsin**.
- Most abundant glycoprotein in basement membrane: Laminin.
- Degradation of basement membrane is caused by: *Metalloproteinases.*
- Collagen in hyaline articular cartilage: **Type II.**
- Characteristic of protective epithelium is Regeneration. 'Regeneration' is replacement of lost tissue by Living tissue of similar kind.
- Granulation tissue is formed by: Budding of new capillaries (neovascularization). Angiogenesis is formation of new blood vessels.
- Sequence of appearance of cells in wound healing: ***Platelets-neutrophils-macrophages-fibroblasts***. Fibrosis is due to: TGF-β.

Response of the blood vessels and cells to an injurious stimulus is called inflammation. It can be:

- *Acute inflammation:* It is of shorter duration (seconds, minutes, few hours)
- *Chronic inflammation:* It is of longer duration (weeks, months and years)

The changes seen in inflammation can be in the blood vessels (called vascular changes) and in the cells (called cellular changes).

I. Vascular Changes

1. *Vasoconstriction*: It is the *first*[Q] change in the blood vessels which is transient in nature. Clinically it is responsible for the blanching seen immediately after injury.
2. *Vasodilation*: Second change in the blood vessels lasting for a longer duration is vasodilation. It results in increased blood flow leading to redness (*rubor*) and the sensation of warmth (*color*).
3. *Increased permeability*: It is the *hallmark of acute inflammation*[Q] caused by separation of the endothelial cells resulting in movement of fluid, cells and proteins out of the blood vessels (collectively called *exudate*). The *exudate* is a protein rich fluid which is responsible for the swelling (*tumor*) associated with an injury. It is *maximally seen in the venules*. The various mechanisms of increased vascular permeability are explained below:
4. The loss of fluid results in concentration of red cells in small vessels and increased viscosity of the blood leading to slower blood flow and is called *stasis*.

Recent Exam Questions

- **Increased vascular permeability** is the **hallmark of acute inflammation**
- Formation of endothelial gaps (**Immediate transient response**) is the **commonest mechanism for increased permeability**.

II. Cellular Changes

The sequence of events in the journey of leukocytes from the vessel lumen to the interstitial tissue, called *extravasation*, can be divided into the following steps:

1. *Margination*: Movement of the leukocytes which are normally moving in the centre of the blood vessel towards the periphery of the blood vessel is called margination.

Mechanisms of Increased Vascular Permeability

Mechanism	Caused by	Affected blood vessels	Properties of response
1. Formation of endothelial gaps (***Immediate transient response***[Q])	Vasoactive mediators like histamine, leukotrienes, bradykinin and contraction of endothelial cell cytoskeleton	Venules	Rapid; Reversible; short lived (15 to 30 minutes)

Contd...

Contd...

Mechanism	Caused by	Affected blood vessels	Properties of response
2. Direct endothelial injury (***immediate sustained response***[Q])	Toxins, infections, burns, chemicals causing endothelial cell necrosis and detachment	Venules, capillaries and arterioles	Fast and may be long lived
3. Cytoskeletal reorganisation **(Endothelial cell retraction**[Q]**)**	Due to cytokines and hypoxia	Mostly venules[Q]; capillaries may be also involved	***Reversible, delayed and prolonged***
4. Delayed prolonged leakage	Thermal and radiation injury induced endothelial cell damage	Venules and capillaries	Delayed and long lived
5. Leukocyte mediated endothelial injury	Activated leukocytes causing endothelial injury or detachment	Venules (mostly); pulmonary and glomerular capillaries	Late and long lived
6. Increased transcytosis	Formation of vesiculo-vacuolar organelles near inter cellular junctions by histamine and VEGF	Venules	
7. Leakage from new blood vessel	Mostly by vascular endothelial growth factor (VEGF) and less commonly by histamine and substance P	Sites of angiogenesis	

2. *Rolling*: It is the process of transient adhesion of leukocytes with the endothelial cells. *Selectins* are the most important molecules responsible for it. They interact with the complementary molecules resulting in transient adhesion. The selectins can be either.

Recent Exam Question

Selectins are responsible for **"rolling" of neutrophils**.

E selectin (CD 62E) – Present on cytokine-activated *endothelial cells* and interacts with sialyl lewis X receptor on the leukocyte.
L selectin (CD 62L) – Present on *leukocytes* and interacts with glycoprotein adhesion molecules (GlyCAM-1), Mad CAM-1 and CD34 on endothelial cells.
P selectin (CD 62P) – Present on *platelets and endothelial cells* and interacts with sialyl lewis X receptor on leukocytes.

Key Point

Endothelial cell expression of **E-selectin** is a hallmark of acute **cytokine mediated inflammation**.

3. *Adhesion*: It is firm attachment of the leukocytes to the endothelial cells. *Integrins* are the most important molecules promoting cell-cell or cell-matrix interactions by interacting with vascular cell adhesion molecule (VCAM) or intercellular adhesion molecule (ICAM). These can be of two types:

β_1-containing integrins: These are also called VLA molecules and interact with VCAM-1 on endothelial cells.

β_2-containing integrins: These are also called LFA-1 or Mac-1 and interact with ICAM-1 on endothelial cells.

Key Point

β_2-Integrins are neutrophil adhesion molecules.

Concept

Clinical importance of adhesion molecules

- **Leukocyte adhesion deficiency type 1 (LAD1)** is caused *by a defect in the CD 18 molecule required for biosynthesis of the β_2 chain shared by the LFA-1 and Mac-1 integrins.*
- **Leukocyte adhesion deficiency type 2 (LAD2)** is caused by the absence of *sialyl-Lewis X, the fucose-containing ligand for E-selectin, owing to a defect in the enzyme fucosyl transferase* responsible for binding fucose moieties to protein backbones.
- Both LAD1 and LAD2 are autosomal recessive conditions.

Recent Exam Question

LAD1: ***Integrin*** defects; recurrent *infections* and **delayed separation of umbilical cord stump**

Recent Exam Question

LAD2: ***Selectin*** defects; recurrent *infections*, **Bombay blood group** and *mental retardation.*

4. *Transmigration:* The step in the process of the migration of **the leukocytes**[Q] through the endothelium is called transmigration or *diapedesis.* Neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours, then are replaced by monocytes in 24 to 48 hours *(except in Pseudomonas infection in which neutrophils predominate over 2 to 4 days).*

Recent Exam Question

CD31 or PECAM-1: Responsible for ***diapedesis***.

Key Point

Leukocyte diapedesis, similar to increased vascular permeability, occurs predominantly in the **venules** (*except* in the *lungs*, where it also occurs in *capillaries*).

5. *Chemotaxis*: It is **unidirectional movement**[Q] of the leukocytes towards antigens/bacteria in response to certain chemicals. These chemicals are called chemotactic stimuli. They can be:

a. *Exogenous:* Bacterial products[Q]
b. *Endogenous products:* C5a, LTB 4, IL-8

All the chemotactic agents mentioned above bind to G-protein coupled receptors (GPCRs) on the surface of leukocytes to cause actin polymerization and all movements. Other actin-regulating proteins like *filamin, gelsolin, profilin,* and *calmodulin* also interact with actin and myosin to produce contraction and cellular movement. The leukocytes degranulate to release lysosomal enzymes, cytokines and produce arachidonic acid metabolites. The leukocyte activation takes place due to GPCRs, cytokine receptors and Toll-like receptors (TLRs).

Recent Exam Question

Example of **Opsonins** include **antibodies, complement proteins and lectins.**

6. *Opsonisation*: Coating of the bacteria so that they are easily phagocytosed by the white blood cells is known as opsonisation.

Mnemonic

*Mnemonic corollary – friends, I believe all of you have had water-balls or golgappe at some point of time in your life, you can have them both with and without water but in which condition do you think they are tastier? Well majority would answer the latter option i.e. 'with water'. The function of water is to make the golgappa tastier. Similarly, opsonins make the bacteria tastier for the leukocytes. Please remember that the WBCs can kill bacteria without opsonins also but opsonised bacteria are preferentially killed.

Chemicals causing opsonisation are called **opsonins**. These are:

- **C3b**[Q]
- Fc fragment of antibody or **IgG**[Q].
- Some serum proteins (like **fibrinogen**[Q], mannose binding **lectin**[Q] and **C reactive protein**[Q])

Recent Exam Question

IgG is produced by activated B cells called plasma cells. Bruton's disease is a defect in maturation of the B cells in which there is absence of immunoglobulin. So, ***Bruton's disease*** is characterized by ***defective opsonisation***.

7. *Phagocytosis*: It is the process by which bacteria are killed/eaten up by the white blood cells. Lysosomes are important organelles required for phagocytosis.

Phagocytosis: It is characterized by 3 steps

a. **Recognition and attachment**: The particles to be ingested by leukocytes (microbes and dead cells) are

recognized by receptors present on the surface of WBCs. These receptors are.

i. *Scavenger receptors:* These bind microbes and oxidized or acetylated LDL particles.
ii. *Mac-1 integrins:* These are present on the surface of macrophages.
iii. *Mannose receptors:* These bind to mannose and fucose residues of glycoproteins in microbial cell wall. The presence of an additional terminal sialic acid or N-acetyl galactosamine in human cells prevents their destruction by WBCs.

b. **Engulfment**: There is formation of phagolysosome (due to fusion of the lysosomes and the phagosome containing the microbe) inside the leukocytes. This is followed by degranulation of leukocytes.

Recent Exam Question

Phagocytosis (cell eating) requires **polymerization of actin** filaments whereas in contrast, *pinocytosis* (cell drinking) and *receptor mediated endocytosis* require *clathrin* coated pits.

Key Point

The leukocytes in **Chediak-Higashi syndrome** have **giant granules** seen in peripheral blood smear which are due to aberrant organelle fusion.

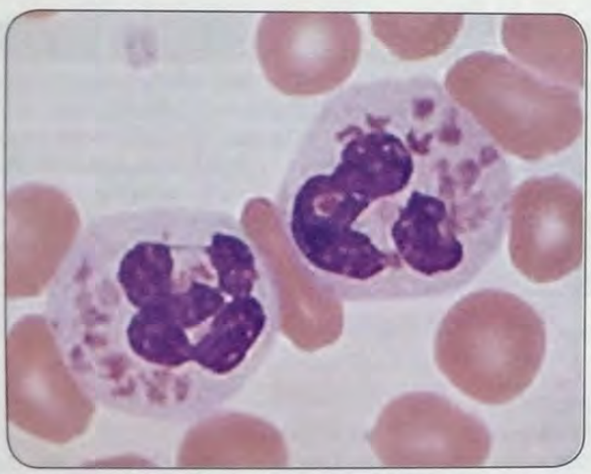


Fig. 1: Chediak-Higashi syndrome: giant granules in leukocytes.

Concept

The clinical significance of phagolysosome formation is appreciated in an autosomal recessive disorder known as Chediak-Higashi syndrome. It is characterized by LYST protein defect leading to *reduced transfer of lysosomal enzymes to phagocytic vacuoles* in phagocytes, defective degranulation, and delayed microbial killing causing increased susceptibility to infections. The *polymorphs also exhibit defective random movements and have* ***defective chemotaxis***.

Clinical features: It includes neutropenia, albinism, nerve defects, nystagmus and bleeding disorders. These patients also have reduced NK cell responsiveness.

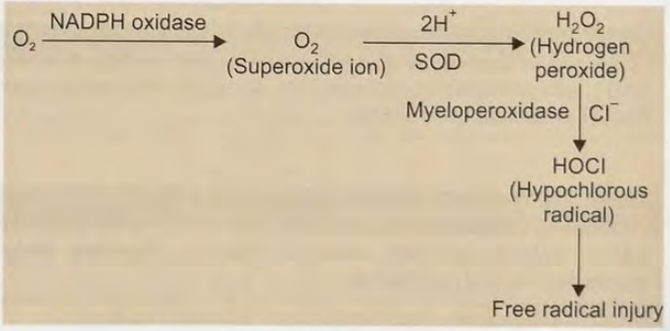
The secretion of granule proteins by cytotoxic T cells is also affected which also contributes to the immunodeficiency.

c. **Killing and degradation:** Final step in phagocytosis is the killing of infectious organism within the leukocytes. It can be accomplished by

i. **Oxygen dependent killing mechanism**
There is production of microbicidal reactive oxygen species within phagocytic vesicles by the following mechanism:
The final step in the microbial killing is due to reactive oxygen species called as '**respiratory burst**'.
Phagocytes (i.e., neutrophils, monocytes, and macrophages) require an enzyme to produce reactive oxygen species to destroy bacteria after they ingest the bacteria in a process called phagocytosis. This enzyme is termed "phagocyte NADPH oxidase" (*PHOX*). The initial step in this process involves the one-electron reduction of molecular oxygen to produce superoxide free radical. Superoxide then undergoes a further series of reactions to produce products such as peroxide, hydroxyl radical and hypochlorite. The reactive oxygen species thus produced are toxic to bacteria and help the phagocyte kill them once they are ingested.

Recent Exam Questions

- **O_2-dependent MPO** system is most potent microbicidal system.
- **NADPH oxidase** is also called by the name of **respiratory burst oxidase.**



Chronic granulomatous disease (CGD) has a defective NADPH oxidase activity with recurrent infection and granuloma formation affecting gastrointestinal or genitourinary tract. CGD can be diagnosed with the following tests:

1. **Nitroblue-tetrazolium (NBT) test:** It is negative in chronic granulomatous disease and positive in normal individuals. This test depends upon the direct reduction of NBT by superoxide free radical to form an insoluble formazan.
2. **Dihydrorhodamine (DHR) test**
3. **Cytochrome C reduction assay**.

Key Point

Chronic granulomatous disease (CGD) is a disease caused due to a defect in NADPH oxidase activity and respiratory burst. It is characterised by repeated infections by **catalase positive organisms**; (bacterial infections mostly due to **Staph. aureus** and fungal due to **Candida**).

Recent Exam Question

Nitroblue-tetrazolium test is the most widely known test for chronic granulomatous disease. **NBT** is a **qualitative** test whereas ***Cytochrome C reduction assay*** is a ***quantitative*** test for superoxide radicals.

Concept

Difference between Myeloperoxidase deficiency and Chronic Granulomatous Disease (CGD).

In CGD, some phagocytosed organisms (catalase negative organisms like steptococci) can be killed because these organisms produce their own hydrogen peroxide which is used by neutrophilic myeloperoxidase to produce free radicals and kill them.

In myeloperoxidase deficiency, the enzyme myeloperoxidase is absent, so both catalase positive and catalase-negative organisms will survive within phagocytes and cause infections.

Enzymes involved in respiratory burst

- NADPH oxidase is chiefly responsible for the formation of hydrogen peroxide which plays the most important role in microbial killing.
- Catalase degrades hydrogen peroxide into water and oxygen.
- Superoxide dismutase (SOD) causes conversion of superoxide ion into hydrogen peroxide.
- Glutathione peroxidase causes conversion of reduced glutathione to its homodimer.

$$2OH^- + 2GSH \rightarrow 2H_2O + GSSG$$

Note: H_2O_2 – MPO – halide system is the most efficient way of killing the bacteria[Q].

ii. **Oxygen independent killing mechanism**

It can be done by various enzymes and proteins like

Lysozyme: Causes hydrolysis of bacterial glycopeptide coat

- *Lactoferrin:* It is an iron binding protein.
- Bacterial permeability increasing protein.
- ***Major basic protein***[Q] (MBP).
- *Defensins*: These are arginine rich peptides toxic to the microbes.
- *Cathelicidins*: These are antimicrobial proteins in the neutrophils and other cells They are highly effective against M. tuberculosis.

Key Point

Major basic protein is present in **Eosinophils** and is ***toxic to parasites***.

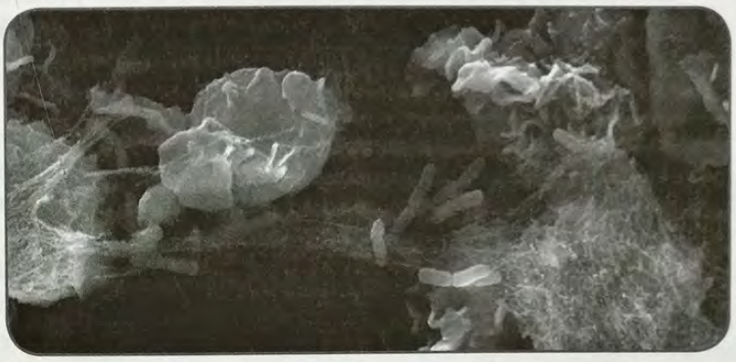


Fig. 2: Neutrophil extracellular traps.

Neutrophil extracellular traps (NETs)

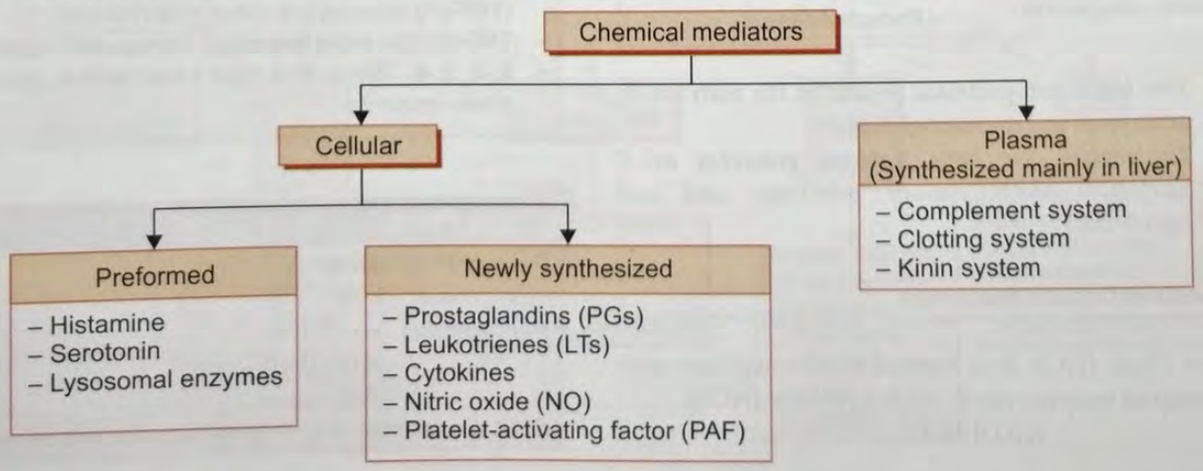
- **NETs** are **extracellular fibrillar networks** which provide a high concentration of antimicrobial substances at sites of infection. They are produced **by neutrophils** in response to chemicals mainly **interferons**. NET formation is dependent on **platelet activation** and it is associated with the pathogenesis of autoimmune conditions like **SLE.**

Recent Exam Question

Conversion of **arginine** residues **to citrulline** in the **histones** is an essential step in the formation of neutrophil extracellular traps.

IMPORTANT CHEMICAL MEDIATORS

Chemical mediators of inflammation may be present in cells (cellular) or in the plasma.



Concept

The synthesis of antimicrobial protein cathelicidin is stimulated by 1, 25 dihyroxyvitamin D. The importance of this non skeletal effect of vitamin D is that vitamin D deficiency can increase the chances of tubercular infections

Preformed Cellular Mediators

a. *Histamine*: It is formed from the amino acid 'histidine'. **Mast cells** are the richest source of histamine. It is also present in platelets and basophils. It causes **vasodilation (but vasoconstriction of large arteries)**, increased permeability (*immediate transient response*) and bronchoconstriction.

b. *Serotonin* (5-HT): Richest source of serotonin (5-hydroxytryptamine; 5- HT) is **platelets**. It has actions similar to histamine. It is also present in **enterochromaffin cells**.

c. *Lysosomal Enzymes*: These are present in the lysosomes of neutrophils and monocytes. Lysosomes contain two types of granules; Primary (azurophilic) and secondary (specific) granules.

Recent Exam Questions

- **Lewis Triple response** is associated with **histamine.**
- Histamine is the most important chemical mediator of acute inflammation.

Lysosomal granules

Primary (azurophilic) granules	Secondary (specific) granules
– Require high level of agnonist to be released extracellularly – Postentially more destructive – Secrete – Myeloperoxidase (MPO) – Acid hydrolase – Elastase – Defensin – Phospholipase A_2 – Non-soecific collagenase	Secreted at lower concentration of agonists – Secrete extracellularly more readily – Secrete – Lysozyme – Lactoferrin – Alkaline phosphatase – Type IV collagenase – Phospholipase A_2

- Two major anti-proteases present in the body are α_1 antitrypsin and α_2 macroglobulin
- *Neutrophils also have **tertiary granules or C particles** which contain gelatinase and acid hydrolases.*

Newly Synthesized Cellular Mediators

a. *Nitric Oxide* (NO): It is formed from l-arginine with the help of enzyme nitric oxide synthase (NOS).

$$\text{L-Arginine} \xrightarrow[\text{NOS}]{\text{NADPH} + O_2} \text{L-Citrulline} + \text{NO}$$

Three isoforms of NOS are present in the body:

i. **e** NOS (Present in **e**ndothelium)
ii. **n** NOS (Present in **n**eurons)
iii. **i** NOS (**i**nducible form)

eNOS and nNOS are constitutively expressed whereas i NOS production is induced by cytokines like TNF α and IFN-γ.

Important Actions of NO

- Potent vasodilator
- Reduction of platelet aggregation
- Endogenous regulator of leucocyte recruitment
- Also possess microbicidal action: NO acts as a free radical and can also be converted to highly reactive peroxynitrite anion ($ONOO^-$) as well as NO_2 and NO_3.

b. *Cytokines:* These are small proteinaceous molecules secreted by the inflammatory cells. These include interleukins, interferons and tumor necrosis factor-alpha (TNF-α). These can produce local and systemic effects. Most important cytokine responsible for systemic effects of inflammation are interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α).

IL-1, TNF-α		
Acute phase reaction - Fever - Increased sleep - Decreased appetite - Neutrophilia	Endothelial and fibroblast effects • ↑ PGI_2 formation • ↑ Procoagulant • ↑ Fibroblast • ↑ Collagen	WBC effects • ↑ Secretion of IL-1 and IL-6

Recent Exam Questions

- **IL-1^Q** is the **most important cyto-kine** responsible for the **systemic effects** of inflammation
- **IL-10^Q**, **IL-4^Q**, **IL-6^Q** and transforming growth factor – beta **(TGF-β^Q)** possess anti-inflammatory action.
- **TGF-β** is the **most important fibrogenic^Q** agent
- **IL-1, IL-6, TNF-α and type I interferons** contribute to acute phase response.

Key Point

Pyrogenic cytokines

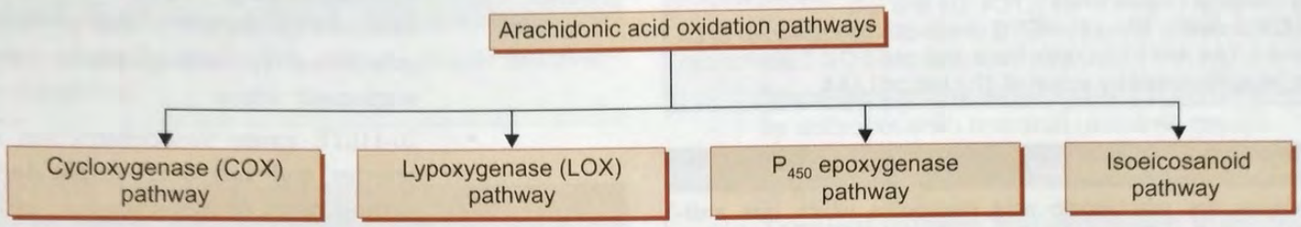
- Exogenous : LPS
- Endogenous : IL-1/TNFα
  IFNα/CNTF
  IL-6

IL-18 is a member of IL-1 family but does **not** cause **fever**.

Concept

Resolvins and protectins are anti inflammatory lipid mediators derived from polyunsaturated fatty acids which along with IL-10, TGF-β and lipoxins help in the termination of acute inflammatory response.

c. *Arachidonic acid metabolites* : Arachidonic acid (AA) is a 20-C fatty acid containing four double bonds. It must be released/mobilized from membrane phospholipids (PL) for oxygenation to various compounds.



i. **COX pathway:** Two type of COX-enzymes (also known as PGH synthase); COX-1 and COX-2 convert AA to PGG_2 first and then to PGH_2 [both are called cyclic endoperoxides]. Further fate of PGH_2 depend upon the enzyme present in a particular cell e.g. endothelium contain PGI_2 synthase and thus forms PGI_2 whereas platelets contain TXA_2 synthase and therefore synthesize TXA_2.

Recent Exam Questions

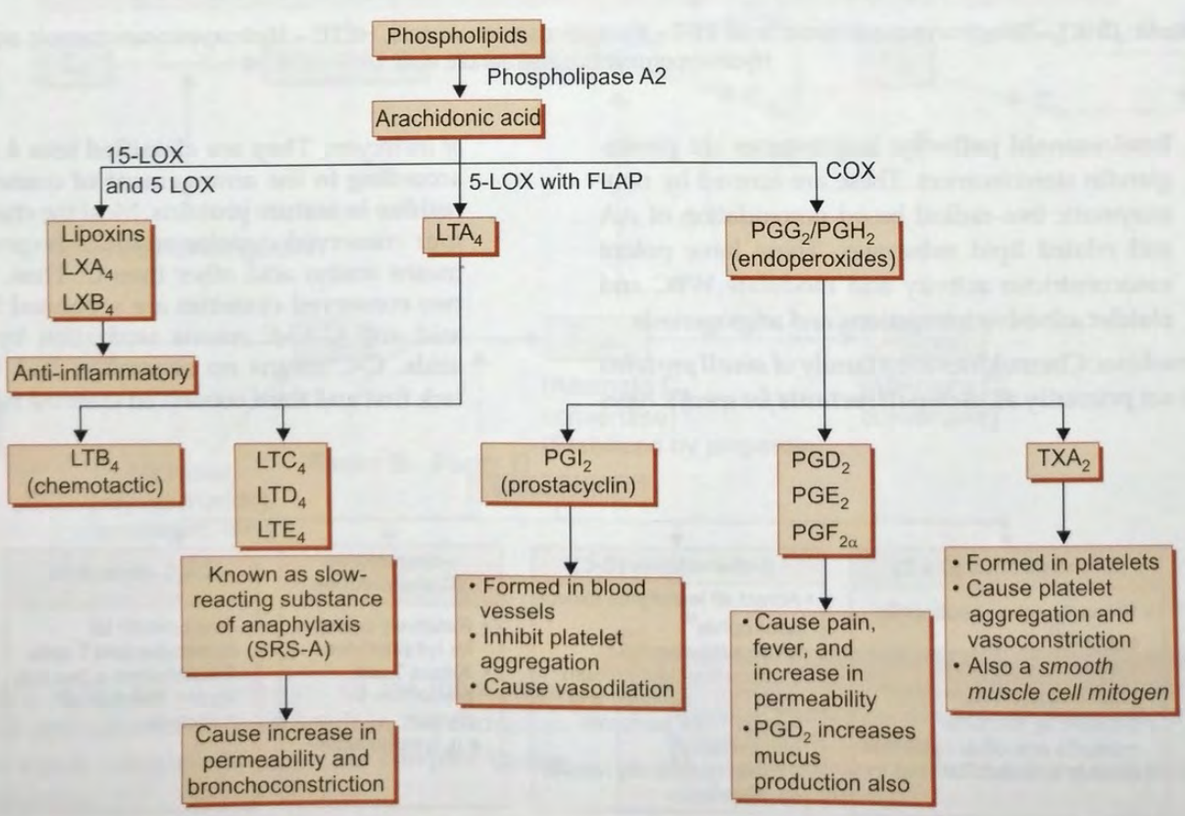
- $PGF_{2\alpha}$ [Q] is a **vasoconstrictor** whereas PGD_2 and PGE_2 are vasodilators.
- **PGE_2** is the most important chemical for development of **fever**.

Key Point

COX-1 is mostly **constitutive** (house-keeping) whereas ***COX-2*** is ***inducible***. However, in endothelium, kidney and CNS, even COX-2 is constitutively present.

Mnemonic

PGI_2 cause inhibition of platelet aggregation (**I** stands for **I**nhibition) and $TX\mathbf{A}_2$ cause platelet aggregation (**A** for **a**ggregation)



FLAP- Five Lipoxygenase Activating Protein

ii. **LOX-pathway:** AA can be acted upon different types of LOX enzymes.

1. 5-LOX (present in leukocytes, mast cells and dendritic cells) acts in the presence of FLAP [5-LOX activating protein] to convert AA to LTA4. This product can be converted either to LTB4 or to cysteinyl Leukotrienes (LTC4, D4 and E4).
2. 15-LOX converts AA to 15-HETE which can be converted to Lipoxins (LXA4 and LXB4) with the action of 5-LOX. Lipoxins can also be synthesized by action of 12-LOX on LTA4.

Recent Exam Question

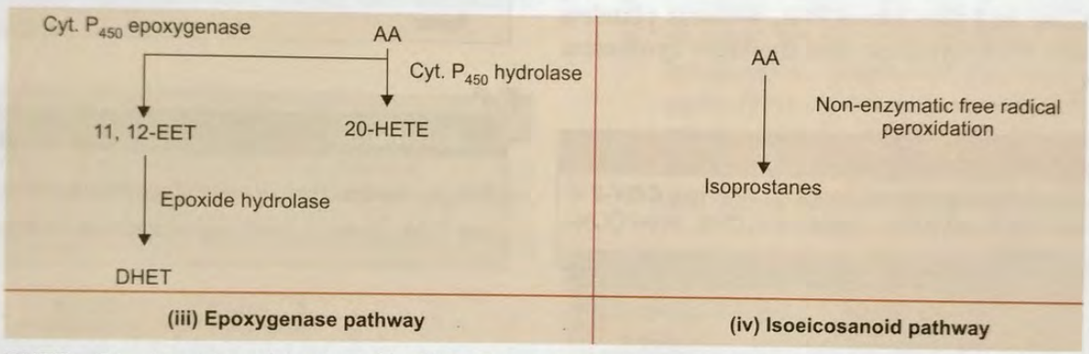
- **Lipoxins** are arachidonic acid metabolite which has **anti-inflammatory action**.

Key Point

LTC_4^Q and **LTC_4^Q** [primary components of **slow reacting substance of anaphylaxis; SRS-A^Q]** are powerful bronchoconstrictors, increase permeability and mucus secretion in airways.

iii. **Epoxygenase pathway:** Cytochrome P450 may convert AA to 20-HETE or EET. Biological effects of EET are reduced by metabolism to less active DHET with the help of epoxide hydrolases.

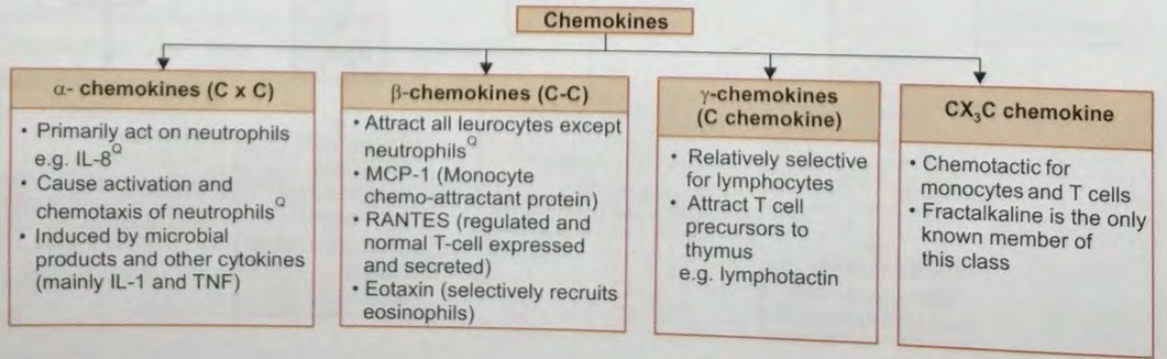
- EET may function as endothelium derived hyperpolarizing factor particularly in coronary circulation. It also possesses anti-inflammatory, anti-apoptotic and pro-angiogenic action.
- 20-HETE cause vasoconstriction of renal arteries and has been implicated in the pathogenesis of hypertension. In contrast, EET possess antihypertensive properties via its vasodilating and natriuretic actions. Inhibitors of epoxide hydrolase [results in elevated levels of EET] are being developed as antihypertensive drugs.



Abbreviations: DHET – Dihydroxyeicosatrienoic acid, EET – Epoxyeicosatrienoic acid, HETE – Hydroxyeicosatetraenoic acid, HPETE – Hydroxyperoxyeicosatetraenoic acid.

iv. **Isoeicosanoid pathway:** Isoprostanes are prostaglandin stereoisomers. These are formed by non-enzymatic free-radical based peroxidation of AA and related lipid substrates. These have potent vasoconstrictor activity and modulate WBC and platelet adhesive interactions and angiogenesis.

d. *Chemokines:* Chemokines are a family of ***small proteins*** that act primarily as ***chemoattractants*** *for specific types of leukocytes.* **They are classified into 4 major groups according to the arrangement of conserved cysteine residue in mature proteins.** Most the chemokines have four conserved cysteine residues (expressed as C). X means amino acid other than C. Thus, C-X-C means two conserved cysteines are separated by one amino acid and C-X3-C means separation by three amino acids. C-C means no separation and C-chemokines lack first and third conserved cysteine residues.



Note: Chemokines mediate their actions through chemokine receptors (CXCR or CCR). Certain receptors (CXCR4; CCR5) act as co-receptors for binding and entry of HIV into CD4 cells.

Recent Exam Question

IL-8 is chemotactic for **neutrophils** whereas *Eotaxin selectively recruits eosinophils.*

Key Point

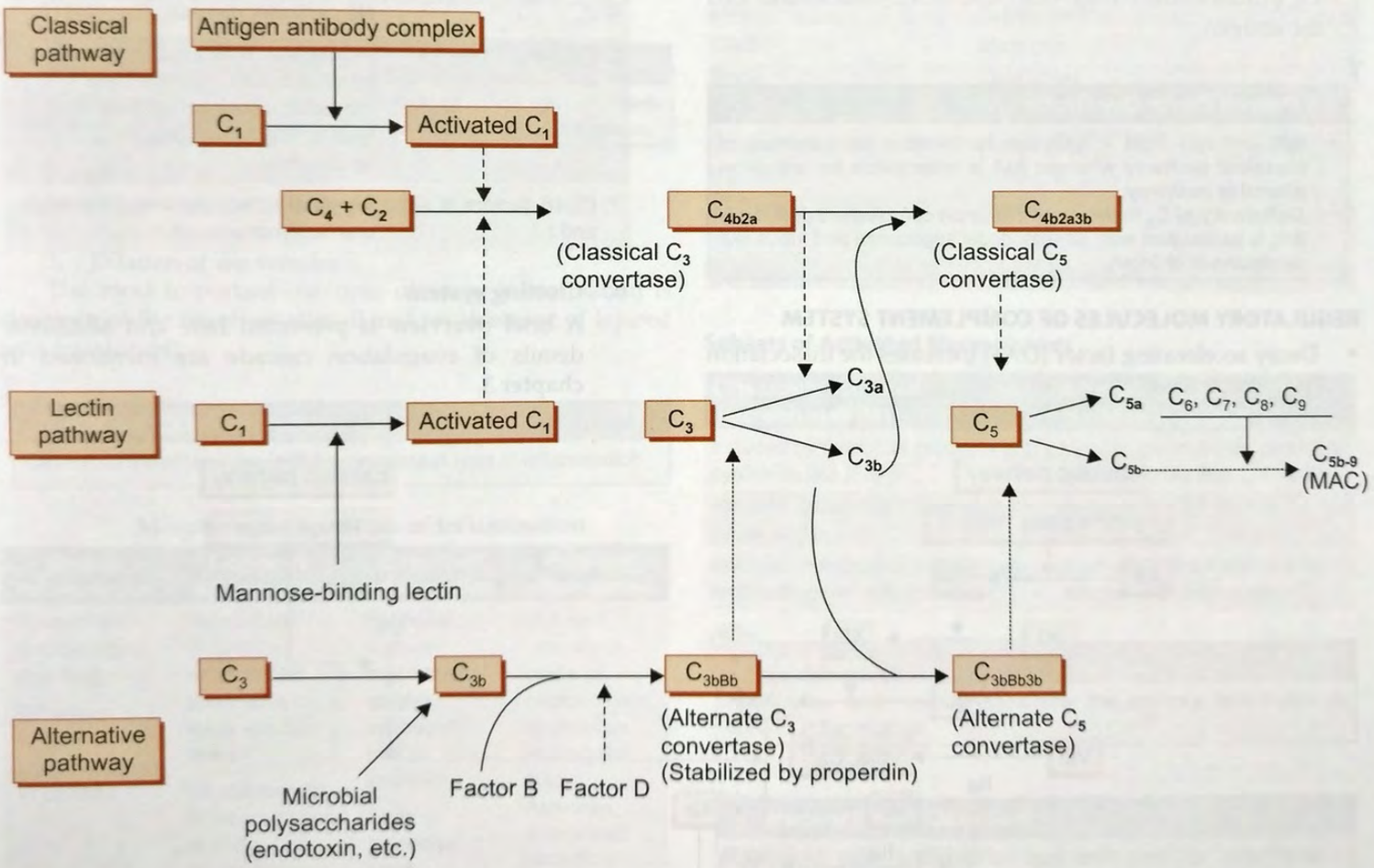
Critical step in the functioning of the complement system is the **activation of C_3** (most abundant component).

Mediators Present in Plasma

a. **Complement system**

It consists of 20 complement proteins (and their breakdown products) present in the plasma. They constitute **5-10%** of plasma proteins. These are numbered C_1 to C_9. The complement system has the following four pathways:

- **Classic** activation pathway activated by antigen/antibody immune complexes,
- **Mannose binding lectin** activation pathway activated by microbes with terminal mannose groups
- **Alternative** activation pathway activated by microbes or tumor cells
- **Terminal** pathway that is common to the first three pathways and leads to the membrane attack complex that lyses cells.



Irrespective of the initial pathway, all the three cause break down of activation of C_3 and result in the formation of membrane attack complex (MAC). This complex causes antigenic destruction.

Key Point

- **Classical Pathway activation:** ***decreased*** C_1, C_2, C_4, C_3; *with normal factor B.*
- **Alternative pathway activation:** ***decreased factor B,*** C_3; *with normal* C_1, C_2 *and* C_4.

Recent Exam Questions

Hereditary angioneurotic edema

- **Autosomal dominant**[Q] clinical condition
- *Deficiency of C_1 inhibitor*
- **Non pitting edema**[Q] of the skin, subcutaneous, GIT and larynges.
- More common in **females**[Q].
- Levels of complement proteins **C1is normal** but levels of **C2 and C4 are depleted**.
- **Danazol**[Q] is the drug for treatment.

FUNCTIONS OF IMPORTANT INDIVIDUAL COMPLEMENT PROTEINS

- C_{3a} and C_{5a} are also called **anaphylatoxins** which are chemicals causing release of histamine from mast cells. So, they cause vasodilation and increased vascular permeability.
- C_{3b} and inactive C_3 (C_{3i}) used for opsonisation.
- C_{5a} also has important role in chemotaxis.
- $C_{5b\text{-}9}$ (Membrane Attack Complex; MAC) attacks and kills the antigen.

Recent Exam Questions

- **IgM** and IgG (**IgM** > IgG) are responsible for activation of **classical pathway** whereas ***IgA*** is responsible for activation ***alternate pathway***.
- ***Deficiency of C_2 is the most common*** complement deficiency and is associated with Streptococcal septicemia and lupus like syndrome in children.

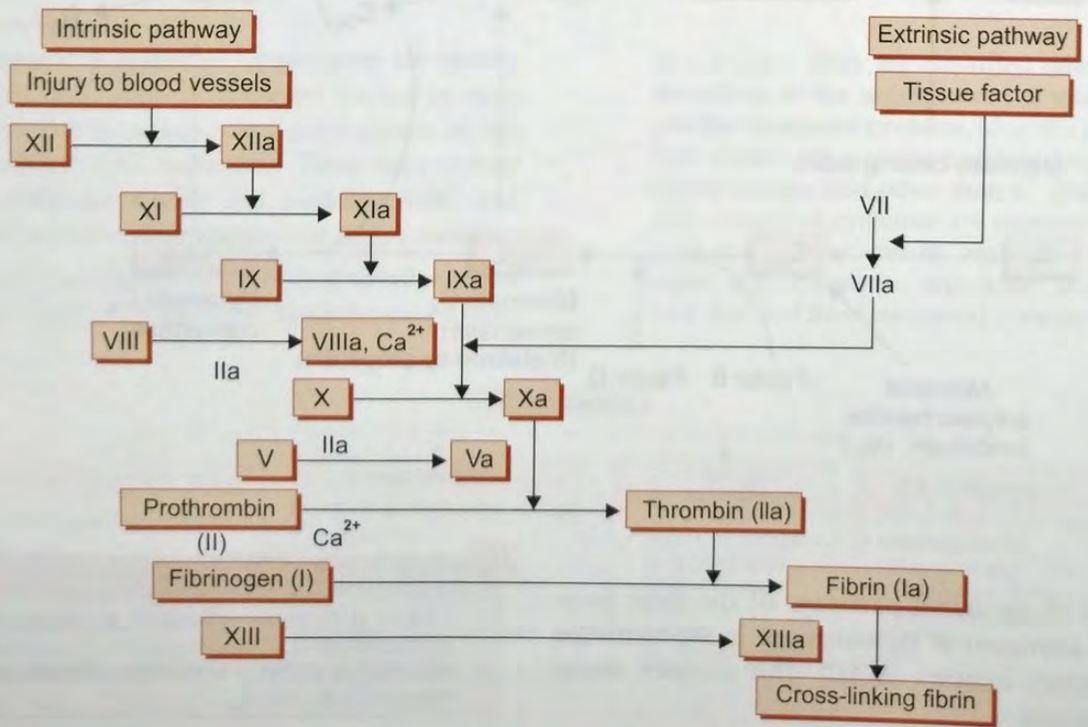
REGULATORY MOLECULES OF COMPLEMENT SYSTEM

- Decay accelerating factor (DAF) increases the dissociation of C_3 convertase.
- Factor I proteolytically cleaves C_{3b}.
- CD59 (Membrane inhibitor of reactive lysis) inhibits formation of MAC.
- Factor H, factor I and CD46 prevent exessive alternate pathway activation.

Deficiency of complement component	Disease/Syndrome
1. C_1 esterase Inhibitor	Hereditary angioneurotic edema (subcutaneous edema because of excessive complement activation)
2. Early complement proteins C_1, C_2, C_4	SLE and collagen vascular disorders
3. C_{3b} and C_{3b} inactivator	Recurrent pyogenic infections
4. C_5 to C_8	Bacterial infections with Neisseria and Toxoplasmosis
5. C_9	No particular disease
6. DAF and CD59	Paroxysmal nocturnal hemoglobinuria (complement mediated increased intravascular lysis of RBCs, platelets and neutrophils)
7. CD46, factors H and I	**Atypical** or 'non epidemic' hemolytic uremic syndrome (HUS)

b. **Clotting system**

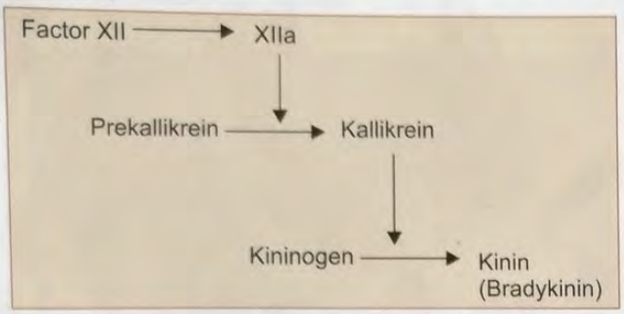
A brief overview is presented here and additional details of coagulation cascade are mentioned in **chapter 3**.



The most important function of clotting system activation is formation blood clot that helps to prevent excessive blood loss. Some of the components of the clotting system also play other roles e.g. fibrinogen is used for opsonisation and thrombin causes chemotaxis.

c. **Kinin System**

It is initiated by activated factor XII (Hageman's factor)



Kallikrein can also activate plasminogen into plasmin and cause activation of complement protein C5a.

Key Point

Activated factor XII can cause activation of **kinin system, clotting system, fibrinolytic system** and the **complement system.**

Functions of Bradykinin:

1. Contraction of smooth muscles
2. Pain
3. Dilation of the venules

The most important outcome of acute inflammation is clearance of the injurious stimuli and replacement of injured cells (resolution).

Recent Exam Question

Catarrhal inflammation is the **commonest** type of inflammation

Morphological patterns of inflammation

Serous inflammation	Fibrinous inflammation	Catarrhal inflammation	Purulent inflammation
*Presence of outpouring of thin fluid ***Effusion** is fluid accumulation in cavities	*Deposition of fibrin in extracellular space due to large vascular leaks *Characteristic of inflammation in body cavity linings (meninges, pericardium)	*Epithelial surface inflammation causes increased mucus secretion *Seen in ***common cold***	*Purulent exudate is made of necrotic cells, neutrophils and edema fluid ***Abscess** is localized collection of purulent inflammatory tissue

CHRONIC INFLAMMATION

Chronic inflammation is characterized by infiltration with mononuclear cells (including macrophages, lymphocytes, and plasma cells), tissue destruction and healing by replacement of damaged tissue via angiogenesis and fibrosis. Macrophage is the dominant cell in chronic inflammation. It accumulates inside the tissue because of recruitment from circulation; local proliferation in tissue and immobilization at the site of inflammation. *Tissue destruction is the hallmark of chronic inflammation.*

Key Point

Infection are the *most common cause of chronic inflammation.*

Stem cell (Bone marrow) → Gives rise to monoblast → Monocyte (Present in blood) → Macrophage (Present in tissues)

Macrophages have a life span ranging from months to years and they are given different names in different tissues e.g.

Liver	-	Kupffer cell
CNS	-	Microglia
Bone	-	Osteoclast
Lung	-	Alveolar macrophage or 'Dust cells'
Connective tissue	-	Histiocyte
Placenta	-	Hoffbauer cells
Spleen	-	Littoral cells
Kidney	-	Mesangial cells
Synovium	-	Type A lining cells

Subsets of Activated Macrophages

Classically activated macrophages (M1)	Alternatively activated macrophages (M2)
Induced by microbial products and cytokines like IFN-γ^{Q}.	Induced by microbial products and cytokines like IL-4, IL-5^{Q}
Release lysosomal enzymes, nitric oxide, IL-1and IL-12	Release IL-10^{Q}, TGF-β^{Q}
Involved in microbicidal activities and pathogenic inflammation^{Q}	Involved in anti-inflammatory actions and wound repair^{Q}

Key Point

Monocytes and macrophages are the primary leukocytes in chronic inflammation.

Recent Exam Question

Epithelioid cells are macrophages activated by **interferon** γ released from CD4 T cells. Epithelioid cells have **only secretory** (***not*** phagocytic) function.

GRANULOMATOUS INFLAMMATION

It is a type of chronic inflammation characterized by formation of granuloma. Granuloma is an *aggregation of macrophages surrounded by a collar of mononuclear cells* principally

lymphocytes. Macrophages may get activated to form epithelioid cells (epithelium like cells). Some of the cells may fuse together to form a bigger cell called a **giant cell**. The giant cells can be primarily of the following types:

1. *Langhans giant cell:* The nuclei in this giant cell are present in the periphery and in a horse shoe pattern. It is seen is **tuberculosis.**

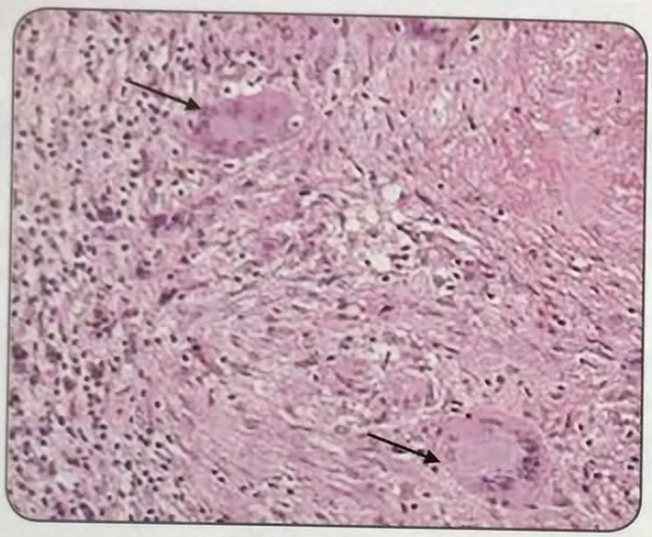


Fig. 3: Langhans giant cell.

2. *Foreign body giant cell:* The nuclei are arranged randomly or haphazardly here. It is seen in granuloma formed by *foreign bodies* like sutures, talc etc.
3. *Touton giant cells* are seen in *xanthomas, fat necrosis, xanthogranulomatous inflammtion and dermatofibroma.* They are formed by fusion of epithelioid cells and contain a ring of nuclei surrounded by foamy cytoplasm.

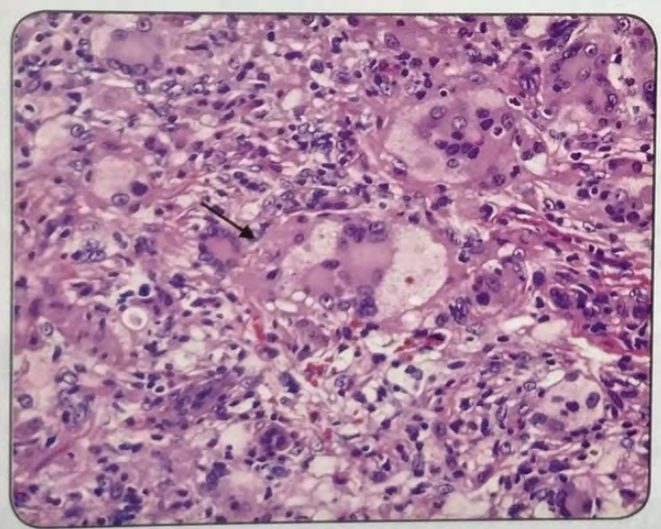


Fig. 4: Touton giant cells.

4. *Physiological giant cells* are seen in *osteoclasts, syncytiotrophoblasts and megakaryocytes.*

Key Point

Warthin-Finkeldey giant cells are seen in **measles**.

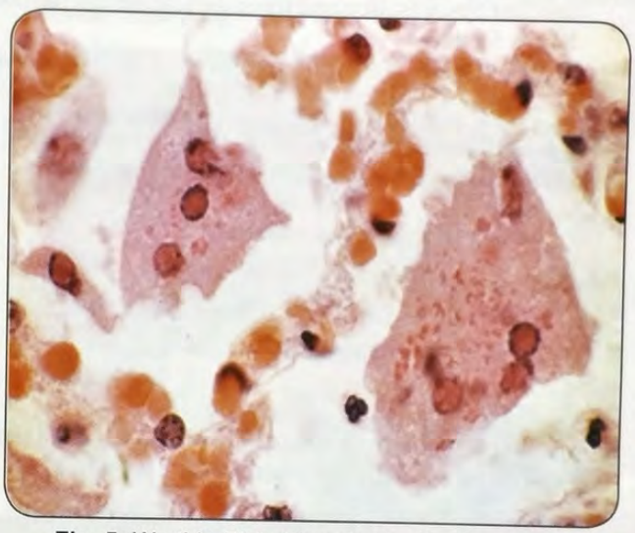


Fig. 5: Warthin-Finkeldey giant cells of measles.

Key Point

Tumor giant cells like **Reed-Sternberg cells** are seen in **Hodgkin's lymphoma**

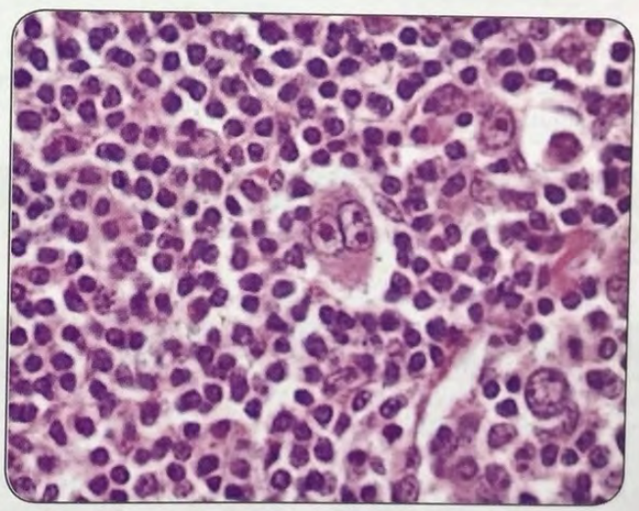


Fig. 6: Reed-Sternberg cells of Hodgkin's lymphoma.

Common conditions resulting in granuloma formation with important features

- Tuberculosis
- Sarcoidosis (**Non caseating granuloma**^{Q})
- Brucellosis
- Syphilis (**Gumma**^{Q})
- Lymphogranuloma inguinale
- Leprosy
- Inflammatory bowel disease (IBD)

The formation of a granuloma is discussed later in the chapter of 'immunity'.

Recent Exam Questions

- **Amongst IBD, Granuloma formation** is associated with **only Crohn's disease**; it is *not* seen in *ulcerative colitis*.
- **Durck granuloma** is seen in **cerebral malaria**.
- **Doughnut granuloma** is seen in **Q fever.**
- Cat scratch disease has **Stellate**[Q] shaped or **round granuloma**

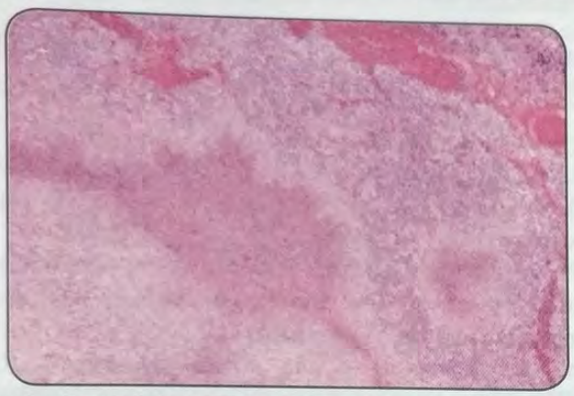


Fig. 7: Stellate granuloma in cat scratch disease.

Definition

- **Regeneration** is proliferation of cells and tissues to replace lost structures.
- **Repair** consists of a combination of regeneration and scar formation by the deposition of collagen

Types of Cells

Depending on the regenerative capacity, cells can be divided into 3 categories:

1. Permanent cells	Cells of the body which **never divide** e.g. neurons, skeletal muscle fibres and cardiac myocytes.
2. Stable cells	They have a low rate of multiplication and are usually present is the **G_0 phase**. When given a stimulus, they enter the G1 phase and multiply e.g. Cells of proximal tubule of kidney, hepatocytes, pancreatic cells, fibroblasts etc.
3. Labile cells	These cells can regenerate throughout life e.g. hematopoietic cells, cells of skin, gastrointestinal mucosa etc.

WOUND HEALING

It is characterized by the process of regeneration of the damaged tissue by cells of the same type and replacement of the lost tissue with connective tissue. Regeneration results in complete restitution of lost or damaged tissue.

Repair consists of a combination of regeneration and scar formation by the deposition of collagen. It may restore some original structures but can cause structural derangements.

Healing by Primary Intention

The healing of a clean uninfected wound is called healing by **first intention** or **primary union**. It involves the following changes.

Day	Features of wound
Day 0 (when the wound has formed)	Presence of blood clot in the incision
Day 1 (within 24 hours)	Neutrophilic infiltration + blood clot
Day 2 (24 to 48 hours)	Neutrophils + blood clot + continuous thin epithelial layer[Q]
Day 3	Macrophages replace neutrophils, Appearance of granulation tissue, type III collagen deposition begins but do not bridge the incision
Day 5	Abundant granulation tissue - Collagen fibrils bridge the incision - *Neovascularisation is maximum*[Q] - Full epithelial thickness with surface keratinization
End of 2nd week	Accumulation of collagen; fibroblast proliferation
1 month	Replacement of collagen type III with collagen type I (has greater tensile strength) due to action of collagenase enzyme

Vitamin C is required for the conversion of tropocollagen to collagen due to hydroxylation of lysine and proline residues providing stability to collagen molecules.

Recent Exam Questions

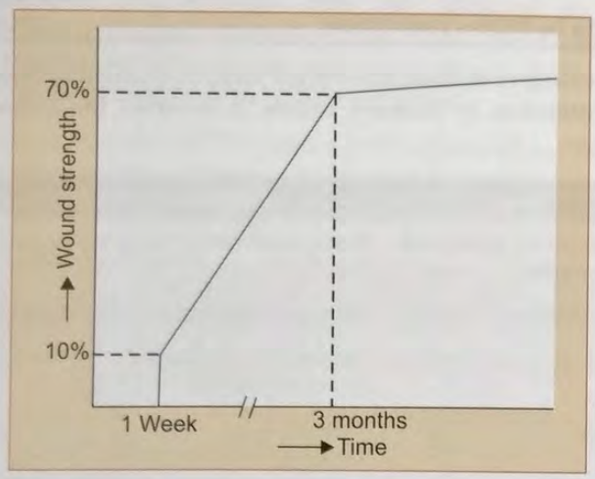
- **Granulation tissue** is fibroblasts + small blood vessel + chronic inflammatory cells (macrophage and lymphocytes)
- **Neo vascularisation is maximum on day 5.**
- **Granulation tissue** is the hall-mark of the **fibrogenic repair.**
- The chief cell responsible for **scar contraction** is **myofibroblast.**

Healing by Secondary Intention

During healing by **secondary intention** or **secondary union**; inflammatory reaction being more intense, granulation tissue is abundant and a large scar is formed. The scar decreases in size after sometime; this is called **scar contraction.**

Wound strength is 10% after 1 week[Q]; it increases rapidly during next 4 weeksQ and becomes 70% at the end of 3rd month[Q]. The tensile strength of the wound keeps on increasing as time progresses.

The predominant collagen in adult skin is type I[Q] whereas in early granulation tissue, it is type III and I[Q].



Recent Exam Questions

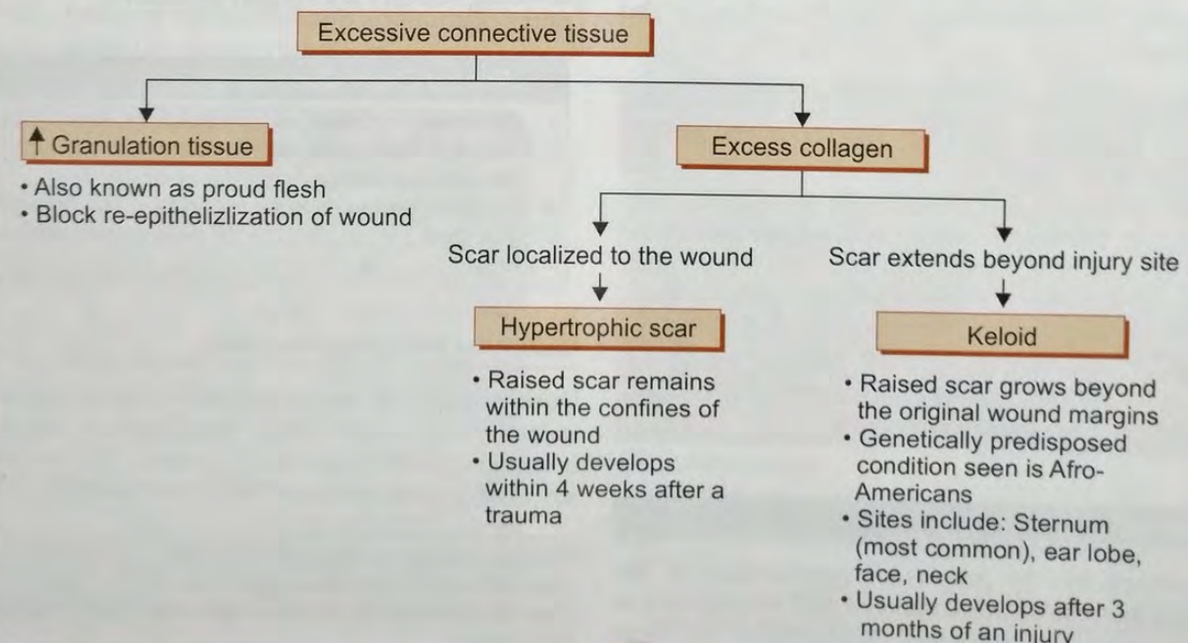
Wound strength
- After **1 week: 10%**
- After *12 weeks: 70%*
- Will **never** reach 100%.

The balance between extracellular matrix (ECM) synthesis and degradation results in *remodeling* of the connective tissue framework which is an important feature of chronic inflammation and wound repair. The collagen degradation is done by zinc dependent matrix metalloproteinases (MMP). Collagen degradation is important for tissue remodeling, angiogenesis and cancer metastasis. That is why ***zinc deficiency is associated with impaired wound healing***. MMPs are synthesized by several cells like fibroblasts, macrophages, neutrophils, synovial cells, and some epithelial cells. Activated collagenases (a type of MMP) are rapidly inhibited by specific *tissue inhibitors of metalloproteinases (TIMPs)*, which are produced by most mesenchymal cells, thus preventing uncontrolled action of these proteases. The regulated activity is required for proper wound healing.

Key Point
- **Zinc** is a cofactor in **collagenase**
- **Infections** are the most common cause of impaired wound healing.

During wound healing, **complications** can arise from:

1. *Delayed wound healing*: Due to foreign body, ischemia, diabetes, malnutrition, hormones (glucocorticoids), infection or scurvy.
2. *Deficient scar formation*: Dehiscence or rupture of a wound is most common after abdominal surgery and is due to increased abdominal pressure.
3. *Excessive formation of the repair components*: Certain conditions may arise because of increased granulation tissue or excessive collagen leading to keloid, hypertrophic scar and 'proud flesh'.
   Incisional scars or traumatic injuries may be followed by exuberant proliferation of fibroblasts and other connective tissue elements called *desmoids* or *aggressive fibromatoses*. These recur frequently after excision.
4. *Formation of contractures*: Contractures are particularly prone to develop on the palms, the soles, and the anterior aspect of the thorax. These are commonly seen after serious burns.



Key Point

Sternum is commonest site for **keloid formation**

Key Point

Intralesional steroids (triamcinolone) are the usual drugs for the managment of keloid.

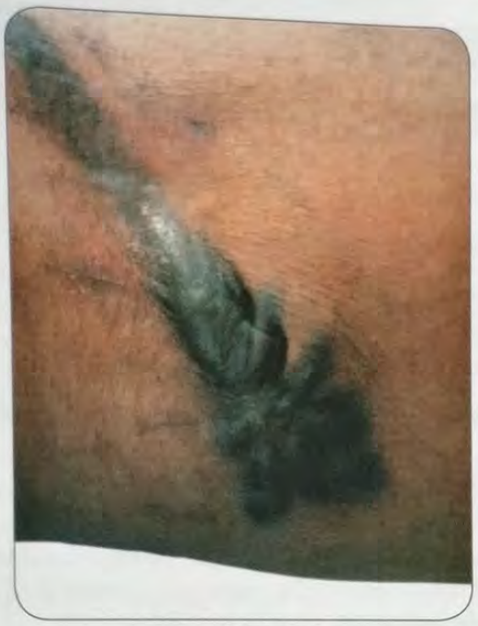


Fig. 8: Keloid.

STEM CELLS

Definition: The most widely accepted stem cell definition is a cell with a unique capacity to produce unaltered daughter cells (*self-renewal*) and to generate specialized cell types (*potency*).

1. **Self-renewal** can be achieved in two ways:

Asymmetric cell division	Symmetric cell division
• Produces one daughter cell that is identical to the parental cell and one daughter cell that is different from the parental cell and is a progenitor or differentiated cell • Asymmetric cell division does not increase the number of stem cells.	• Produces two identical daughter cells

For stem cells to proliferate *in vitro*, they must divide symmetrically. Self-renewal alone cannot define stem cells, because any established cell line, e.g., HeLa cells proliferate by symmetric cell division.

2. **Potency** is used to indicate a cell's ability to differentiate into specialized cell types. This can be classified as:

Totipotent cells	Multipotent cells	Oligopotent cells	Uni/Monopotent cells
Can form an entire organism autonomously.	Can form multiple cell lineages but cannot form all of the body's cell lineages.	Can form more than one cell lineage but are more restricted than multipotent cells.	Can form a single differentiated cell lineage.
Only zygote[Q] (fertilized egg) has this feature.	Hematopoietic[Q] stem cells	**Neuron**[Q] stem cells	Spermatogonial[Q] stem cells

Terminally differentiated cells, such as fibroblast cells, also have a capacity to proliferate (which may be called self-renewal) but maintain the same cell type (e.g., no potency to form another cell type) and are not, therefore, considered unipotent cells.

Embryonic stem cells are pluripotent, that is, they are capable of forming all the tissues of the body

Adult stem cells are usually only able to differentiate into a particular tissue.

- Stem cells are located in special sites called **niches**.

Name of the cell	Location	Function
Oval cells[Q]	Canals of Herring of the liver	Forming hepatocytes and biliary cells
Satellite cells[Q]	Basal lamina of myotubules	Differentiate into myocytes after injury
Limbus cells[Q]	Canals of Schlemm[Q]	Stem cells for the cornea[Q]
Ito cells[Q]	Subendothelial space of Disse[Q]	Store vitamin A[Q]
Paneth cells	Bottom of crypts	Host defense against microorganisms

Other sites for stem cells are the base of the crypts of the colon and the dentate gyrus of the hippocampus.

Other Important Concepts in Stem Cell Biology

- Development naturally progresses from totipotent fertilized eggs to pluripotent epiblast cells, to multipotent cells, and finally to terminally differentiated cells.
- **Nuclear reprogramming:** The reversal of the terminally differentiated cells to totipotent or pluripotent cells (called *nuclear reprogramming*) has been achieved using *nuclear transplantation*, or *nuclear transfer* (NT), procedures (often called "cloning"), where the nucleus of a differentiated cell is transferred into an enucleated oocyte.
- **Stem cell plasticity or trans-differentiation:** The prevailing standard in develop-mental biology is that once cells are differentiated, their phenotypes are stable. However, a number of reports have shown that tissue stem cells, which are thought to be lineage-committed multipotent cells, possess the capacity to differentiate into cell types outside their lineage restrictions (called *trans-differentiation*). For example, hematopoietic stem cells may be converted into neurons as well as germ cells.

Key Point

In human embryo in about 3rd week of development stem cells appear in yolk sac.

Recent Exam Question

In adults, most of the stem cells are found in the bone marrow, but a subset normally circulates in peripheral blood.

Concept

Stem cells are used in bone marrow transplantation in treatment of various types of leukemia and lymphoma.

Multiple Choice Questions

ACUTE INFLAMMATION, VASCULAR AND CELLULAR CHANGES

1. **In acute inflammation endothelial retraction leads to:** *(AIIMS Nov 2011)*
   (a) Delayed transient increase in permeability
   (b) Immediate transient increase in permeability
   (c) Delayed prolonged increase in permeability
   (d) Immediate transient decrease in permeability

2. **After binding of complement and antibody on the surface of encapsulated bacteria, the process of phagocytosis by polymorphonuclear leukocytes involves which of the following?** *(AIIMS Nov 2011)*
   (a) Fc and C3b
   (b) Receptor-mediated endocytosis
   (c) Respiratory burst
   (d) Pseudopod extension

3. **Free radicals are generated by all except:** *(AI 2011)*
   (a) Superoxide dismutase
   (b) NADPH Oxidase
   (c) Myeloperoxidase
   (d) NO synthase

4. **Which among the following is the hallmark of acute inflammation?** *(AI 2011, AIIMS May 2010)*
   (a) Vasoconstriction
   (b) Stasis
   (c) Vasodilation and increase in permeability
   (d) Leukocyte margination

5. **Main feature of chemotaxis is:** *(AIIMS May 2010)*
   (a) Increased random movement of neutrophils
   (b) Increase adhesiveness to intima
   (c) Increased phagocytosis
   (d) Unidirectional locomotion of the neutrophils

6. **Characteristic of acute inflammation is:** *(AI 2009)*
   (a) Vasodilation and increased vascular permeability
   (b) Vasoconstriction
   (c) Platelet aggregation
   (d) Infiltration by neutrophils

7. **Which of the following helps in generating reactive O_2 intermediates in the neutrophils?**
   (a) NADPH oxidase *(AI '11, 08, AIIMS Nov 2008)*
   (b) SOD (superoxide dismutase)
   (c) Catalase
   (d) Glutathione peroxidase

8. **Basement membrane degeneration is mediated by:**
   (a) Metalloproteinases *(AI 2008)*
   (b) Oxidases
   (c) Elastases
   (d) Hydroxylases

9. **Delayed prolonged bleeding is caused by:** *(AI 2008)*
   (a) Histamine
   (b) Endothelial retraction
   (c) IL-1
   (d) Direct injury to endothelial cells

10. **Earliest transient change following tissue injury will be:** *(AI 2007)*
    (a) Neutropenia (b) Neutrophilia
    (c) Monocytosis (d) Lymphocytosis

11. **All of the following vascular changes are observed in acute inflammation, except:** *(AI 2005)*
    (a) Vasodilation
    (b) Stasis of blood
    (c) Increased vascular permeability
    (d) Decreased hydrostatic pressure

12. **The following host tissue responses can be seen in acute infection, except:** *(AI 2002)*
    (a) Exudation (b) Vasodilation
    (c) Margination (d) Granuloma formation

13. **Oxygen dependent killing is done through** *(AI 2007)*
    (a) NADPH oxidase
    (b) Superoxide dismutase
    (c) Catalase
    (d) Glutathione peroxidase

14. **Which of the following is not true?** *(AIIMS May 2009)*
    (a) NADPH oxidase generate superoxide ion
    (b) MPO kills by OCl^-
    (c) Chediak-Higashi syndrome is due to defective phagolysosome formation
    (d) In Bruton's disease there is normal opsonization

15. **Nitroblue tetrazolium test is used for?** *(AIIMS Nov 2008)*
    (a) Phagocytes (b) Complement
    (c) T cell (d) B cell

16. **In acute inflammation due to the contraction of endothelial cell cytoskeleton, which of the following results?** *(AIIMS Nov 2006)*
    (a) Delayed transient increase in permeability
    (b) Early transient increase
    (c) Delayed permanent increase
    (d) Early permanent increase

17. **Diapedesis is:** *(AIIMS Nov 2001)*
    (a) Immigration of leukocytes through the basement membrane
    (b) Immigration of the leukocytes through the vessel wall to the site of inflammation
    (c) Aggregation of platelets at the site of bleeding
    (d) Auto digestion of the cells

18. **Endothelium leukocyte interaction during inflammation is mediated by/due to** *(PGI, Dec 2003)*
(a) Selectins (b) Integrins
(c) Defensins (d) Endothelin

MOST RECENT QUESTIONS

19. **In genetic deficiency of MPO the increased susceptibility to infection is due to:**
(a) Defective production of prostaglandins
(b) Defective rolling of neutrophils
(c) Inability to produce hydroxyl-halide radicals
(d) Inability to produce hydrogen peroxide

20. **After extravasation, leukocytes emigrate in the tissue towards the site of injury. It is called as:**
(a) Margination (b) Chemotaxis
(c) Diapedesis (d) Pavementing

21. **The complex process of leukocyte movements through the blood vessels are all except?**
(a) Rolling (b) Adhesion
(c) Migration (d) Phagocytosis

22. **All are true about exudate except:**
(a) More protein
(b) Less protein
(c) More specific gravity
(d) All

23. **All of the following are signs of inflammation except:**
(a) Pain
(b) Swelling
(c) Redness
(d) Absence of functional loss

24. **Endogenous chemoattractant is:**
(a) C5a
(b) Bacterial products
(c) Lipopolysaccharide A
(d) C8

25. **Most important for diapedesis?**
(a) PECAM (b) Selectin
(c) Integrin (d) Mucin like glycoprotein

26. **All of the following are a family of selectin except:**
(a) P selectin (b) L selectin
(c) A selectin (d) E selectin

27. **In acute inflammation the tissue response consists of all except:**
(a) Vasodilatation
(b) Exudation
(c) Neutrophilic response
(d) Granuloma formation

28. **Which of the following regarding cellular events in acute inflammation is not correct?**
(a) PECAM/CD31 is responsible for neutrophil activation
(b) Components of complement can assist in chemotaxis
(c) Neutrophil margination is assisted by selectins
(d) ICAM-1/VCAM-1 is responsible for neutrophil adhesion

29. **The function common to neutrophils, monocytes, and macrophages is:**
(a) Immune response is reduced
(b) Phagocytosis
(c) Liberation of histamine
(d) Destruction of old erythrocytes

30. **Correct sequence of events in acute inflammation is?**
(a) Rolling, adhesion, margination, transmigration
(b) Margination, rolling, adhesions, transmigration
(c) Adhesion, rolling, transmigration, margination
(d) Margination, adhesion, rolling, transmigration

31. **Most important amino acid for formation Neutrophilic extracellular trap (NET) is?**
(a) Leucine (b) Methionine
(c) Citrulline (d) Valine

CHEMICAL MEDIATORS OF INFLAMMATION

32. **The role of bradykinin in process of inflammation is:**
(a) Vasoconstriction *(AIIMS May 2012)*
(b) Bronchodilation
(c) Pain
(d) Increased vascular permeability

33. **Which of the following is not a pyrogenic cytokine?**
(a) IL - 1 (b) TNF *(AI 2012)*
(c) IFN - α (d) IL - 18

34. **All of the following are true in respect of angioneurotic edema except?** *(AI 2012)*
(a) It is caused by deficiency of complement proteins
(b) It is more common in females
(c) It manifests as pitting edema
(d) It is an autosomal dominant disorder

35. **Which of the following complement component can be activated is both common as well as alternative pathways?** *(AI 2011)*
(a) C1 (b) C2
(c) C3 (d) C4

36. **Which of the following is not an inflammatory mediator?** *(AIIMS Nov 2010)*
(a) Tumor Necrosis Factor
(b) Myeloperoxidase
(c) Interferons
(d) Interleukin

37. **Nephrocalcinosis in a systemic granulomatous disease is due to:** *(AIIMS Nov 2010)*
(a) Overproduction of 1,25 dihydroxy vitamin D
(b) Dystrophic calcification
(c) Mutation in calcium sensing receptors
(d) Increased reabsorption of calcium

38. Bradykinin is for: *(AI 2010)*
(a) Pain
(b) Vasodilatation
(c) Vasoconstriction
(d) Increase vascular permeability

39. Most important bactericidal agent is: *(AI 2009)*
(a) Cationic basic protein
(b) Lactoferrin
(c) Lysozyme
(d) Reactive O_2 species

40. Bradykinin causes: *(AI 2008)*
(a) Vasoconstriction
(b) Pain at the site of inflammation
(c) Bronchodilation
(d) Decreased vascular permeability

41. Lewis triple response is caused due to: *(AI 2008)*
(a) Histamine
(b) Axon reflex
(c) Injury to endothelium
(d) Increased permeability

42. Factor present in the final common terminal complement pathway is: *(AI 2007)*
(a) C4 (b) C3
(c) C5 (d) Protein B

43. To which of the following family of chemical mediators of inflammation, the Lipoxins belong? *(AI 2004)*
(a) Kinin system
(b) Cytokines
(c) Chemokines
(d) Arachidonic acid metabolites

44. Both antibody dependent and independent complement pathway converge on which complement component?
(a) C3 *(AIIMS Nov 2008) (DNB 2008)*
(b) C5
(c) C1q
(d) C8

45. C-C beta chemokines includes: *(AIIMS Nov 2006)*
(a) IL-8 (b) Eotaxin
(c) Lymphotactin (d) Fractalkine

46. All of the following are mediators of acute inflammation except: *(AIIMS Nov 2005)*
(a) Angiotensin (b) Prostaglandin E2
(c) Kallikrein (d) C3a

47. All of the following are mediators of inflammation except: *(AIIMS May 2005)*
(a) Tumour necrosis factor-α (TNF-α)
(b) Interleukin-1
(c) Myeloperoxidase
(d) Prostaglandins

48. Interleukin secreted by macrophages, stimulating lymphocytes is: *(AIIMS May 2001)*
(a) IFN alpha (b) TNF alpha
(c) IL-1 (d) IL-6

49. Cytokines are secreted in sepsis and Systemic Inflammatory Response Syndrome (SIRS) by: *(PGI Dec 01)*
(a) Neutrophils (b) Adrenal
(c) Platelets (d) Collecting duct
(e) Renal cortex

50. Febrile response in CNS is mediated by *(PGI Dec 2003)*
(a) Bacterial toxin
(b) IL-l
(c) IL-6
(d) Interferon
(e) Tumor necrosis factor (TNF)

51. Cytokines: *(PGI Dec 2005)*
(a) Includes interleukins
(b) Produced only in sepsis
(c) Are polypeptide (complex proteins)
(d) Have highly specific action

52. Conversion of prothrombin to thrombin requires:
(a) V only (b) V and Ca^{++} *(Delhi PG-2008)*
(c) XII (d) X and Ca^{++}

53. Which complement fragments are called 'anaphylatoxins'?
(a) C3a and C3b (b) C3b and C5b *(Delhi PG-2006)*
(c) C5a and C3b (d) C3a and C5a

54. Cryoprecipitate is rich in which of the following clotting factors: *(Delhi PG-2005)*
(a) Factor II (b) Factor V
(c) Factor VII (d) Factor VIII

55. Most important mediator of chemotaxis is:
(a) C3b (b) C5a *(Delhi PG-2005)*
(c) C5-7 (d) C2

56. Histamine causes: *(Delhi PG-2004)*
(a) Hypertension (b) Vasoconstriction
(c) Vasodilation (d) Tachycardia

57. Which of the following is found in secondary granules of neutrophils? *(UP 2000)*
(a) Catalase (b) Proteolytic enzyme
(c) Gangliosidase (d) Lactoferrin

58. All are mediators of neutrophils except:
(a) Elastase (b) Cathepsin *(UP 2004)*
(c) Nitric oxide (d) Leukotrienes

59. Ultra-structurally, endothelial cells contain:
(a) Weibel-Palade bodies *(UP 2004)*
(b) Langerhan's granules
(c) Abundant glycogen
(d) Kallikrein

60. Partial thromboplastin time correlates with: *(UP 2006)*
(a) Intrinsic and common pathway
(b) Extrinsic and common pathway
(c) Vessel wall integrity and intrinsic pathway
(d) Platelet functions and common pathway

61. Bleeding time assesses: *(UP 2006)*
(a) Extrinsic clotting pathway
(b) Intrinsic clotting pathway
(c) Fibrinogen level
(d) Function of platelets

62. **The estimation of the prothrombin level is useful in the following clotting factor deficiency, except:** *(UP 2006)*
(a) II (b) V
(c) VII (d) IX

63. **Which of the following is secondary mediator of the anaphylaxis is?** *(UP 2006)*
(a) Histamine
(b) Proteases
(c) Eosinophilic chemotactic factor
(d) Leukotriene B_4

64. **Birbeck's granules in the cytoplasm are seen in:**
(a) Langerhans cells (b) Mast cells *(UP 2006)*
(c) Myelocytes (d) Thrombocytes

65. **The Eosinophils secrete all except:** *(UP 2005) (UP 2007)*
(a) Major basic protein
(b) Hydrolytic enzyme
(c) Reactive form of O_2
(d) Eosinophilic chemotactic factor

66. **In Lipooxygenase pathway of the arachidonic acid metabolism, which of the following products helps to promote the platelet aggregation and vasoconstriction?**
(a) C5a (b) Thromboxane A_2 *(UP 2008)*
(c) Leukotriene B_4 (d) C1 activators

67. **Chemotactic complement components are:** *(RJ 2001)*
(a) C3a (b) C5a
(c) Both (d) C3b

68. **In inflammatory process, the prostaglandin E1and E2 cause:** *(AP 2000)*
(a) Vasodilatation
(b) Increased gastric output
(c) Decreased body temperature
(d) Vasoconstriction

MOST RECENT QUESTIONS

69. **Opsonins are:**
(a) C3a
(b) IgM
(c) Carbohydrate-binding proteins
(d) Selectins

70. **Inflammatory mediator of generalized systemic inflammation is:**
(a) IL-1 (b) IL-2
(c) Interferon alpha (d) TNF

71. **All are cytokines except:**
(a) Monoclonal antibody
(b) Interleukin
(c) Chemokine
(d) TNF

72. **Cell-matrix adhesions are mediated by?**
(a) Cadherins (b) Integrins
(c) Selectins (d) Calmodulin

73. **Pro inflammatory Cytokines include all of the following except:**
(a) Interleukin 1 (b) Interleukin-10
(c) Interleukin 6 (d) TNF- Alpha

74. **Fever occurs due to:**
(a) IL-1 (b) Endorphin
(c) Enkephalin (d) Histamine

75. **E cadherin gene deficiency is seen in:**
(a) Gastric cancer (b) Intestinal cancer
(c) Thyroid cancer (d) Pancreatic cancer

76. **The most important source of histamine:**
(a) Mast cells (b) Eosinophil
(c) Neutrophil (d) Macrophages

77. **Following injury to a blood vessel, immediate haemostasis is achieved by which of the following?**
(a) Fibrin deposition
(b) Vasoconstriction
(c) Platelet adhesion
(d) Thrombosis

78. **Platelet activating factor causes all except:**
(a) Bronchoconstriction
(b) Vasoconstriction
(c) Decreased vascular permeability
(d) Vasodilation

79. **Both antibody dependent and independent complement pathway converge on which complement component?**
(a) C3 (b) C5
(c) C1q (d) C8

80. **Cryoprecipitate is rich in which of the following clotting factors?**
(a) Factor II (b) Factor V
(c) Factor VII (d) Factor VIII

81. **Prostaglandins are synthesized from:**
(a) Linoleic acid
(b) Linolenic acid
(c) Arachidonic acid
(d) Butyric acid

82. **Eosinophils are activated by:**
(a) IL-1 (b) IL-5
(c) IL-4 (d) IL-6

83. **Which chemical mediator is an arachidonic acid metabolite produced by cyclo-oxygenase pathway?**
(a) LXA4 (b) LXB4
(c) 5HETE (d) PGH2

84. **Which of the following factors is morphogenic as well as mitogenic?**
(a) Fibroblast growth factor
(b) Platelet derived growth factor
(c) Bone morphogenetic protein
(d) Insulin-like growth factor

85. **Procalcitonin is used as marker of:**
(a) Cardiac dysfunction in acute coronary syndrome
(b) Menstrual periodicity
(c) Pituitary function
(d) Sepsis

86. Complement complex that attacks cell membrane is:
(a) C12345 (b) C23456 *(AIIMS May 2016)*
(c) C34567 (d) C56789

87. Systemic inflammatory response syndrome, false is:
(a) Leucopenia (b) Fever
(c) Leukocytosis (d) Hypoglycemia

88. What is true about interferon?
(a) Are specific for individual viruses
(b) Are protective against only viruses
(c) Reduce protein synthesis in the target cell
(d) Are divided into 5 subtypes

89. Which of the following helps in movement and adhesion?
(a) MCP1 (b) PGE2
(c) LTB4 (d) CD31

90. C3 complement is cleared by:
(a) CD 59 (b) CD 55
(c) Factor D (d) Factor E

91. Which of the following is true for macrophage chemotactic factor?
(a) Heat labile
(b) High molecular weight
(c) Chymotrypsin sensitive
(d) Are antigenically similar to C3

92. Phagocytosis was discovered by:
(a) Elie Metchinkoff
(b) Aulus Cornelius Celsus
(c) Rudolf Virchow
(d) Emil Adolf von Behring

93. To which of the following family of chemical mediators of inflammation do the lipoxins belong?
(a) Kinin system
(b) Cytokines
(c) Chemokines
(d) Arachidonic acid metabolites

94. Anti-inflammatory cytokines are all except:
(a) Interleukin 10 (b) Interleukin 4
(c) Interleukin 6 (d) TNF-alpha

95. Which of the following is derived from fibroblast cell?
(a) TGF-beta (b) Collagen
(c) MMP2 (d) Angiopoietin

96. Slow mediators of inflammation are:
(a) Leukotrienes
(b) Prostaglandins
(c) Interleukins
(d) Vasoactive amines

97. Complement proteins constitute what percentage of serum proteins?
(a) <1 (b) 1-5
(c) 5-10% (d) >10%

98. Which of the following is not a cachexia gene?
(a) APEH (b) MC4R
(c) Smad7 (d) Smad3

99. Negative acute phase reactant is:
(a) C-reactive protein
(b) Alpha-1 antitrypsin
(c) Transferrin
(d) Serum amyloid protein

100. Complement mediated lysis is mediated by which of the following antibodies?
(a) IgE
(b) IgG
(c) IgM
(d) IgD

101. Deficiency of complement proteins C5 to C8 leads to increased infection by which of the following?
(a) Streptococcus
(b) Neisseria
(c) Pseudomonas
(d) Staphylococcus

102. Which of the following increased in acute phase response?
(a) Alpha2 microglobulin
(b) Transferrin
(c) Albumin
(d) Retinal binding protein

CHRONIC INFLAMMATION; GRANULOMATOUS INFLAMMATION

103. The epithelioid cell and multinucleated giant cells of Granulomatous inflammation are derived from:
(a) Basophils *(AI 2002)*
(b) Eosinophils
(c) CD4-T lymphocytes
(d) Monocytes-Macrophages

104. Granuloma is pathological feature of all, except:
(a) Giant cell arteritis *(AIIMS Nov 2001)*
(b) Microscopic polyangiitis
(c) Wegener's granulomatosis
(d) Churg Strauss disease

105. Granulomatous inflammatory reaction is caused by all, except: *(AIIMS Nov 2001)*
(a) M. tuberculosis (b) M. leprae
(c) Yersinia pestis (d) Mycoplasma

106. Non-caseating granulomas are seen in all of the following except: *(AIIMS May 2001)*
(a) Byssinosis
(b) Hodgkin's lymphoma
(c) Metastatic carcinoma of lung
(d) Tuberculosis

107. Epithelioid granuloma is caused by: *(PGI Dec 2002)*
(a) Neutrophil
(b) Cytotoxic T-cells
(c) Helper T-cells
(d) NK cells

108. Caseous necrosis in granuloma are not found in: *(PGI June 2006)*
(a) Tuberculosis (b) Leprosy
(c) Histoplasmosis (d) CMV
(e) Wegener's granulomatosis

MOST RECENT QUESTIONS

109. The most important function of epithelioid cells in tuberculosis is:
(a) Phagocytosis (b) Secretory
(c) Antigenic (d) Healing

110. Necrotizing epithelioid cell granulomas are seen in all, except:
(a) Tuberculosis
(b) Wegener's granulomatosis
(c) Cat Scratch disease
(d) Leprosy

111. Epithelioid granulomatous lesions are found in all of the following diseases, except:
(a) Tuberculosis (b) Sarcoidosis
(c) Berylliosis (d) Pneumocystis carinii

112. Caseous granuloma is seen in:
(a) Histoplasmosis (b) Silicosis
(c) Sarcoidosis (d) Foreign body

113. Non-caseating granuloma is characteristically seen in:
(a) Syphilis (b) Sarcoidosis
(c) Tuberculosis (d) Histoplasmosis

114. All are granulomatous diseases except:
(a) Syphilis (b) Sarcoidosis
(c) Schistosomiasis (d) P. carinii

115. Which of the following is the most characteristic of granuloma:
(a) Epithelioid cell (b) Giant cell
(c) Fibroblasts (d) Endothelial cell

116. Caseating granuloma are seen in: *(Bihar 2003)*
(a) Histoplasmosis
(b) Sarcoidosis
(c) Coccidiodomycosis
(d) All

117. In a lymph node showing non necrotizing and non-caseating granuloma which of the following is suspected?
(a) Toxoplasmosis
(b) Lymphogranuloma venereum
(c) Cat scratch disease
(d) Kikuchis lymphadenitis

118. Which of these is not a granulomatous disease?
(a) Leprosy (b) Tuberculosis
(c) Sarcoidosis (d) Amebiasis

119. In a granuloma, epithelioid cells and giant cells and derived from:
(a) T - lymphocytes
(b) Monocyte - macrophages
(c) B - lymphocytes
(d) Mast cells

WOUND HEALING; STEM CELL BIOLOGY

120. Which one of the following statements is not correct regarding 'Stem cell'? *(DPG 2011)*
(a) Developmental elasticity
(b) Transdifferentiation
(c) Can be harvested from embryo
(d) "Knockout mice" made possible because of it

121. An adult old man gets burn injury to his hands. Over few weeks, the burned skin heals without the need for skin grafting. The most critical factor responsible for the rapid healing in this case is: *(AIIMS May 2003)*
(a) Remnant skin appendages
(b) Underlying connective tissues
(c) Minimal edema and erythema
(d) Granulation tissue

122. Absolute lymphocytosis is seen in:
(a) SLE (b) TB
(c) CLL (d) Brucellosis

123. Which of the following is absolutely essential for wound healing? *(Karnataka 2009)*
(a) Vitamin D (b) Carbohydrates
(c) Vitamin C (d) Balanced diet

124. Chronic granulomatous disease is: *(Karnataka 2009)*
(a) Associated with formation of multiple granulomas
(b) A benign neoplastic process
(c) A parasitic disease
(d) Acquired leukocyte function defect

125. In regeneration: *(UP 2002)*
(a) Granulation tissue
(b) Repairing by same type of tissue
(c) Repairing by different type of tissue
(d) Cellular proliferation is largely regulated by biochemical factors

126. Wound contraction is mediated by: *(Jharkhand 2005)*
(a) Epithelial cells (b) Myofibroblasts
(c) Collagen (d) Elastin

MOST RECENT QUESTIONS

127. When a cell transforms itself into different lineage the ability us know as?
(a) De-differentiation
(b) Re-differentiation
(c) Trans-differentiation
(d) Sub-differentiation

128. Prion disease is caused by:
(a) Misfolding of protein
(b) Denaturation of proteins
(c) Reduced formation of proteins
(d) Exces formation of proteins

129. Which of the following adhesion molecules is involved in morphogenesis?
(a) Osteopontin
(b) Osteonectin SPARC
(c) Tenascin
(d) Thrombospondins

130. Maximum collagen in wound healing is seen at which stage of healing?
(a) End of first week
(b) End of second week
(c) End of third week
(d) End of 2 months

131. First sign of wound injury is:
(a) Epithelialization
(b) Dilatation of capillaries
(c) Leukocytic infiltration
(d) Localized edema

132. "Oval cells" are seen in the stem cells of which of the following tissues?
(a) Skin (b) Cornea
(c) Liver (d) Bone

133. Which of the following is the source of hepatic stem cells?
(a) Limbus cells (b) Ito cell
(c) Oval cell (d) Paneth cell

134. Tensile strength of wound after laparoscopic cholecystectomy in a 30 year old woman depends upon:
(a) Replacement of type 3 collagen
(b) Extensive cross-linking of tropocollagen
(c) Macrophage activity
(d) Granulation tissue

135. One of the following statements about hematopoietic stem cell is false?
(a) Stem cells have self renewal property
(b) Subset of stem cells normally circulate in peripheral blood
(c) Marrow derived stem cells can seed other tissues and develop into non hematopoietic cells as well
(d) Stem cells resemble lymphoblasts morphologically

136. Vitamin used for post translational modification of glutamic acid to gamma carboxy glutamate is:
(a) A (b) D
(c) E (d) K

137. After an incised wound, new collagen fibrils are seen along with a thick layer of growing epithelium. The approximate age of the wound is:
(a) 4–5 days (b) About 1 week
(c) 12–24 hours (d) 24 –72 hours

138. True about hypertrophic scar?
(a) No genetic predisposition
(b) More common in blood group A
(c) No HLA association
(d) Predominantly collagen type 4

139. Which of the following is a totipotent cell?
(a) Hematopoietic stem cell
(b) Embryonic stem cell
(c) Tissue stem cell
(d) Adult stem cell

Explanations

1. **Ans. (c) Delayed prolonged increase in permeability** *(Ref: Robbins 8th/45, 9/e p74)*

2. **Ans. (d) Pseudopod extension** *(Ref: Robbins 9/e p78)*
Typically the phagocytosis of microbes and dead cells is initiated by recognition of the particles by leukocyte receptors like ***mannose receptors and scavenger receptors.*** During engulfment, **extensions of the cytoplasm (pseudopods) flow around the particle to be engulfed**, eventually resulting in complete enclosure of the particle within a phagosome created by the plasma membrane of the cell
   - Option 'a' Both Fc fragment of IgG and C3b are required in opsonisation. It takes place before phagocytosis.
   - Option 'c' respiratory burst occurs after the formation of the phagolysosome.

3. **Ans. (a) Superoxide dismutase** *(Ref: Robbins 9/e p48)*
Superoxide dismutase (SOD) is an anti oxidant enzyme
Some clarification regarding option 'd'.... 'Nitric oxide (NO), an important chemical mediator generated by endothelial cells, macrophages, neurons, and other cell types can act as a free radical and can also be converted to highly reactive peroxynitrite anion (ONOO-) as well as NO_2 and NO_3^-.

4. **Ans. (c) Vasodilation and increase in permeability** *(Ref: Robbins 8th/46-47 9/e p74)*
Direct quote "a hallmark of acute inflammation is increased vascular permeability leading to the escape of protein-rich exudate into the extravascular tissue, causing edema".

5. **Ans. (d) Unidirectional locomotion of the neutrophils** *(Ref: Robbins 8th/50 9/e p77)*

6. **Ans. (a) Vasodilation and increased vascular permeability** *(Ref: Robbins 8th/45 9/e p74)*

7. **Ans. (a) NADPH oxidase** *(Ref: Robbins 9/e p79)*
Within the phagocytes, the following reaction takes place:
The initiating enzyme for this process is NADPH oxidase (also called **respiratory burst oxidase**).
Glutathione peroxidase, glutathione reductase and superoxide dismutase are examples of anti-oxidants. They reduce free radical formation.

8. **Ans. (a) Metalloproteinases** *(Ref: Robbins, 9/e p105)*
   - Extracellular Matrix (ECM) comprises of interstitial matrix and basement membrane. The degradation of collagen and other ECM proteins is achieved by a family of matrix metalloproteinases (MMPs) which are dependent on zinc ions for their activity.
   - MMP8 and MMP2 are collagenases which cleave type IV collagen of basement membranes.
   - MMPs also have a role in tumour cell invasion.

9. **Ans. (d) Direct injury to endothelial cells**... *For details see text* *(Ref: Robbins 9/e p74)*

10. **Ans. (b) Neutrophilia** *(Ref: Robbins 7th/56)*

11. **Ans. (d) Decreased hydrostatic pressure** *(Ref: Robbins 7th/50-51 9/e p73-74)*
With acute inflammation, ***hydrostatic pressure is increased*** (due to increased blood flow from vasodilation) and at the same time ***osmotic pressure is reduced*** because of protein leakage (due to increased permeability)

12. **Ans. (d) Granuloma formation** *(Ref: Robbins 9/e p97)*
   - **Granuloma formation is characteristic of chronic granulomatous inflammation** and is not seen in acute inflammation.

13. **Ans. (a) NADPH oxidase** *(Ref: Robbins 9/e p48)*

14. **Ans. (d) In Bruton's disease there is normal opsonization** *(Ref: Robbins 8th/231-232,55 9/e p240-241)*

15. **Ans. (a) Phagocytes** *(Ref: Harrison 17th/384)*
The **nitroblue-tetrazolium (NBT) test** is the original and most widely known **test for chronic granulomatous disease**. It is negative in chronic granulomatous disease and positive in normal individuals. It is used for detecting the production of reactive oxygen species in the phagocytes. The basis of the test has been discussed in the text.

16. **Ans. (b) Early transient increase** *(Ref: Robbin's 9/e p74)*

Name of Mechanism	Involved Mechanism
Early transient increase	Endothelial cell contraction
Delayed transient increase in permeability	Direct endothelial injury
Delayed permanent increase	Endothelial cell retraction, endothelial cell damage

17. **Ans. (b) Immigration of the leukocytes through the vessel wall to the site of inflammation** *(Ref: Robbins 9/e p76)*

18. **Ans. (a) Selectins; (b) Integrins** *(Ref: Robbins 9/e p76)*
   - Endothelium and WBC interact through the molecules like Immunoglobulins (family molecules e.g. ICAM-I, VCAM-I), Integrins, Mucin-like glycoprotein and selectins.

Molecule	Function	Deficiency disease
Integrin	Firm adhesion	LAD I
Selectin	Rolling and loose adhesion	LAD II

- **Defensins** are cationic arginine rich peptides having broad antimicrobial activity found in **Azurophil granules** of neutrophils.
- **Endothelin** is a potent endothelial derived **vasoconstrictor**

19. **Ans. (c) Inability to produce hydroxyl-halide radicals** *(Ref: Robbins 8th/53, 56, 9/e p79)*

20. **Ans. (b) Chemotaxis** *(Ref: Robbins 9/e p77)*

21. **Ans. (d) Phagocytosis** *(Ref: Robbins 9/e p75)*

22. **Ans. (b) Less protein** *(Ref: Robbins 9/e p73)*

23. **Ans. (d) Absence of functional loss** *(Ref: Robbins 8th/44; 7th/79, 9/e p71)*

24. **Ans. (a) C5a** *(Ref: Robbins 8th/66; 7th/56, 9/e p77)*

25. **Ans. (a) PECAM** *(Ref: Robbins 8/e p50, 9/e p77)*

26. **Ans. (c) A selectin** *(Ref: Robbins 8/e p49, 9/e p76)*

Selectins are a family of proteins that are involved in the cellular process of rolling interactions. They are of three types: E selectin, L selectin and P selectin. For details see text.

27. **Ans. (d) Granuloma formation** *(Ref: Robbins 9/e p97)*

28. **Ans. (a) PECAM/CD31 is responsible for neutrophil activation** *(Robbins 9/e p76-7)*

29. **Ans. (b) Phagocytosis**

30. **Ans (b) Margination, rolling, adhesions, transmigration** *(Ref: Robbins 9/e p75)*

31. **Ans (c) Citrulline**
(Robbins 9th/82, NETosis 2: The Excitement Continues pg 205)
Conversion of ***arginine*** *residues* to ***citrulline*** in the ***histones*** is an essential step in the formation of neutrophil extracellular traps.

32. **Ans. (d) Increased vascular permeability > (c) Pain** *(Ref: Robbins 8th/65-6, 9/e p89)*
Functions of Bradykinin:
1. Increases vascular permeability
2. Contraction of smooth muscles
3. Dilation of the blood vessels
4. Pain when injected into the skin

- Out of these actions of bradykinin, the increase in vessel permeability is a better answer as it is the hallmark of acute inflammation.

33. **Ans. (d) IL - 18** *(Ref: Harrison 18th/144 , 9/e p99)*
Pyrogens are substances which cause fever. These can be either exogenous or endogenous. The **endogenous pyrogens (**also called the **pyrogenic cytokines)** include:
- IL-1[Q]
- IL-6[Q]
- Tumor necrosis factor[Q] (TNF)
- Ciliary neurotopic factor[Q] (CNTF)
- IFN-α[Q] (alpha)

Harrison clearly mentions that the **IL-18[Q]** which is a *member of IL-1 family* **does not** appear to be a pyrogenic cytokine.

Important points about regulation of body temperature

PGE_2[Q] is the final mediator responsible for causing elevation of the thermoregulatory set point by increasing the concentration of cAMP.
Exogenous pyrogens include **endotoxin[Q]** produced by gram negative bacteria. Body temperature is regulated at the level of the hypothalamus. Most individuals with **hypothalamic damage** have **subnormal** and not supranormal body temperature.

34. **Ans. (c) It manifests as pitting edema** *(Ref: Harrison 17th/2066, 18th/2711-3)*

35. **Ans. (c) C3** *(Ref: Robbins 8th/63-64 , 9/e p88)*
The complement proteins can be activated by 3 pathways; classical, lectin and alternate pathways. Terminal pathway is common to the first three pathways and is present at the level of post activation stage of C3. It eventually leads to the membrane attack complex that lyses cells.

36. **Ans. (b) Myeloperoxidase** *(Ref: Robbins 9/e p83)*
Myeloperoxidase (MPO) is an enzyme present in primary (or azurophilic) granules of the neutrophils. In the presence of a halide such as Cl-, MPO converts H_2O_2 to HOCl• (hypochlorous radical) during the process of respiratory burst.

37. **Ans. (a) Overproduction of 1, 25 dihydroxy vitamin D** *(Ref: Robbins 8th/433-6, Heptinstall's pathology of the kidney, LWW, Volume 1; 6th/1051, Interstitial Lung Disease by Schwarz 5th/458-9)*
Nephrocalcinosis is defined as calcification of the renal interstitium and tubules. It is associated with hypercalcemia. In chronic granulomatous inflammation, the important cells involved are macrophages and lymphocytes.
Direct quote Heptinstall's ... '**Sarcoidosis and other granulomatous diseases can be cause of hypercalcemia and hypercalciuria owing to exces vitamin D from extra renal conversion of 1,25 $(OH)_2D_3$.** Nephrocalcinosis was found to be associated with 22% patients with chronic sarcoidosis'.
In other granulomatous conditions (like **Sarcoidosis**), there is presence of **metastatic calcification due to activation** of **vitamin D precursor by macrophages**..... **Robbins**

38. **Ans. (a, b, d)** *(Ref: Robbins 8th/65, 7th/45, 9/e p89)*
Friends, in our opinion the question should have been asked with an "except" because bradykinin **has the following effects**:
- Increases vascular permeability
- Arteriolar dilation
- Bronchial smooth muscle contraction
- Pain at the site of injections/inflammation

Since ***increased vascular permeability*** is the most ***characteristic feature of acute inflammation***, some people were of the opinion that this could be single best option to be marked presuming the stem of question was correct.

39. **Ans. (d) Reactive O_2 species** *(Ref: Robbins 9/e p79)*
H_2O_2- MPO- halide system is the most efficient bactericidal system of neutrophils.

40. **Ans. (b) Pain at the site of inflammation**
(Ref: Robbin 7th/e 45, 9/e p89)

41. **Ans. (a) Histamine** *(Ref: Goodman & Gilman 10th/650)*
When histamine is injected intradermally it causes the **triple response** consisting of:

- **Red spot:** Due to capillary dilatation
- **Wheal:** Due to exudation of fluid from capillaries and venules
- **Flare:** Redness in the surrounding area due to arteriolar dilation mediated by axon reflex.

42. **Ans. (c) C5** *(Ref: Harrison 17th/2030-2032)*
- The terminal pathway that is common to all pathways of the complement system leads to the membrane attack complex and consists of factors C5, C6, C7, C8 and C9 (C_{5b6789}).

43. **Ans. (d) Arachidonic acid metabolites**
(Ref: Robbins 7th/69; Katzung 11th/314-323, 9/e p85)
Lipoxins are a recent addition to the family of bioactive products generated from arachidonic acid. They have anti-inflammatory activity (explained in text).

44. **Ans. (a) C3** *(Ref: Harrison 17th/2030, 9/e p88)*

45. **Ans. (b) Eotaxin** *(Ref: Robbins 8th/62-63; 7th/71, 9/e p87)*

46. **Ans. (a) Angiotensin** *(Ref: Robbin's 9/e p83)*
Kallikreins like bradykinin, PGs and *complement components are mediators of acute inflammation.*

47. **Ans. (c) Myeloperoxidase** *(Ref: Robbins 9/e p83)*

48. **Ans. (c) IL-1 > (d) IL-6** *(Ref: Javetz, 22nd/1291)*
- Macrophages release IL – 1 which stimulates the T – helper cells.
- The T – cells in response proliferate and release IL – 2 which in turn further stimulates T – cell proliferation and B cell proliferation and differentiation into plasma cells.
- Please note that even IL-6 (produced by macrophages) acts on late stages of B cell differentiation enhancing antibody formation. Still, IL-1 being the most important cytokine having systemic effects of inflammation has been chosen as the answer here in preference to IL-6.

49. **Ans. (a) Neutrophils; (c) Platelets**
(Ref: Harrison' 18th/2223-5, Robbins 7th/202)
Cytokines are peptide mediators or intercellular messengers which regulate immunological, inflammatory and reparative host responses. They are produced by widely distributed cells like macrophage, monocytes, lymphocytes, platelets, fibroblast, endothelium, stromal cells etc.

50. **Ans. (a) Bacterial toxin; (b) IL-1; (d) Interferon; (e) TNF**
(Ref: Harrison 18th/143-5)
Fever is produced in response to substances called pyrogens that act by stimulating prostaglandin synthesis in the vascular and perivascular cells of hypothalamus. They can be classified as:

- **Exogenous pyrogens** - endotoxin of gram '-' bacteria, superantigens (gram '+' bacteria)
- **Endogenous pyrogens** - IL-1, TNF-a, IL-6, Ciliary neurotropic factor and IFN-a.

51. **Ans. (a) Includes interleukins; (c) Are polypeptide (complex protein)**
(Ref: Ananthanarayan 7th/143; Harrison 16th/1915, Robbins 7th/202)
Cytokines are peptide mediators or intracellular messengers produced by wide variety of haemopoietic and non- haemopoietic type of cells in response to immuno, inflammatory or infectious disease states. Most of the lymphokines exhibit multiple biological effects and same effect may be caused by different lymphokines.

Classification of cytokines

1.	Cytokines that mediate innate immunity - IL-1, TNF, IFN, IL-6. IL-12
	• Are involved in both innate and adaptive immunity.
2.	Cytokines regulating lymphocyte growth, activation and differentiation (IL-2, IL-4, IL-12, IL-15, TGF-β)
	• IL-2 is a growth factor for T-cells.
	• IL-4 stimulates differentiation to TH2 pathway.
	• IL-12 stimulates differentiation to T H1 pathway.
	• IL-15 stimulates the growth and activity of NK cells.
	• IL-10 and TGF-β down regulate immune responses.
3.	Cytokines that activate inflammatory cells:
	• IL-5 activates eosinophils.
	• TNF induces acute inflammation by acting on neutrophils and endothelial cells.
4.	Cytokines that affect movement of WBCs (chemotaxis).
5.	Cytokines that stimulate hematopoiesis e.g. GM-CSF, G-CSF, stem cell factor.

- Same cytokine can be produced by different cells. This called **Redundancy**
- Same cytokine can have multiple actions (**pleiotropic** in nature).

52. **Ans. (d) X and Ca^{++}** *(Ref: Robbins 9/e p118)*

53. **Ans. (d) C3a and C5a** *(Ref: Robbins 9/e p89)*

54. **Ans. (d) Factor VIII** *(Ref: Robbins 7th/664)*

55. **Ans. (b) C5a** *(Ref: Robbins 7th/56, 9/e p77)*

56. **Ans. (c) Vasodilation** *(Ref: Robbins 7th/64, 9/e p73)*

57. **Ans. (d) Lactoferrin** *(Ref: Robbins 8th/54; 7th/61, 9/e p80)*

58. **Ans. None** *(Ref: Robbins 8th/53-54; 7th/69, 9/e p80)*

Cathepsin G is a serine protease secreted by activated neutrophils that play a role in the inflammatory response.

59. **Ans. (a) Weibel-Palade bodies** *(Ref: Robbins 9/e p76)*

60. **Ans. (a) Intrinsic and common pathway** *(Ref: Robbins 8th/120,666; 7th/469, 9/e p118)*

61. **Ans. (d) Function of platelets** *(Ref: Robbins 8th/666)*

62. **Ans. (d) IX** *(Ref: Robbins 8th/119, 7th/128, 9/e p119)*

63. **Ans. (d) Leukotriene B_4** *(Ref: Robbins 9/e p203)*

64. **Ans. (a) Langerhans cells** *(Ref: Robbins 9/e p622)*

> *Birbeck granules* are rod shaped/***Tennis-racket shaped*** cytoplasmic organelles with a central linear density and a striated appearance. They are diagnostic microscopic feature in ***Langerhans cell histiocytosis (Histiocytosis X)***

65. **Ans. (b) Hydrolytic enzyme** *(Ref: Robbins 8th/54)*

66. **Ans. (b) Thromboxane A_2** *(Ref: Robbins 9/e p84)*

67. **Ans. (b) C5a** *(Ref: Robbins 8th/64, 7th/56, 9/e p77)*

68. **Ans. (a) Vasodilatation** *(Ref: Robbins 9/e p85)*

69. **Ans. (c) Carbohydrate-binding proteins** *(Ref: Robbins 8th/51-53; 7th/59, 9/e p78)*

70. **Ans. (a) IL-1** *(Ref: Robbins 8th/57, 61, 7th/71, 9/e p86)*

71. **Ans. (a) Monoclonal antibody** *(Ref: Robbins 9/e p86)*

72. **Ans. (b) Integrins** *(Ref: Robbins 8/e p96, 9/e p24)*

The cell adhesion molecules (CAMs) are classified into four main families:

- Immunoglobulin family CAMs
- *Cadherins*

> *Integrins*: Fibronectin, laminin, and osteopontin provid a connection between cells and extracellular matrix (ECM) proteins).

- *Selectins*
  - *Cadherins and integrins link the cell surface with the cytoskeleton through binding to actin and intermediate filaments.*
  - *Laminin* is the most abundant glycoprotein in the basement membrane and has binding domains for both ECM and cell surface receptors.

73. **Ans. (b) Interleukin-10**
(Ref: Robbins 8/e p56; Cytokines and Pain/pg 3, 9/e p86)

> The following are the anti inflammatory cytokines: IL-10, TGF-β, IL-4, IL-13).

74. **Ans. (a) IL-1** *(Ref: Robbins 8/e p61,66 , 9/e p83, 90)*

75. **Ans. (a) Gastric cancer** *(Ref: Robbins 8/e p96, 9/e p297)*

Cadherin is derived from the "calcium-dependent adherence protein." It participates in interactions between cells of the same type. The linkage of cadherins with the cytoskeleton occurs through the catenins. The cell -to-cell interactions mediated by cadherin and catenins play a major role in regulating cell motility, proliferation, and differentiation and account for the inhibition of cell proliferation that occurs when cultured normal cells contact each other ("**contact inhibition**").

> - Reduced function of **E-cadherin** is associated with certain types of **breast and gastric cancer.**

76. **Ans. (a) Mast cells** *(Ref: Robbins 8/e p57, 9/e p83)*

77. **Ans. (b) Vasoconstriction**
(Ref: Robbins 8/e p115 ... Not given in 8/9 edition of Robbins)

78. **Ans. (c) Decreased vascular permeability** *(Ref: Robbins 8/e p60, 9/e p73)*

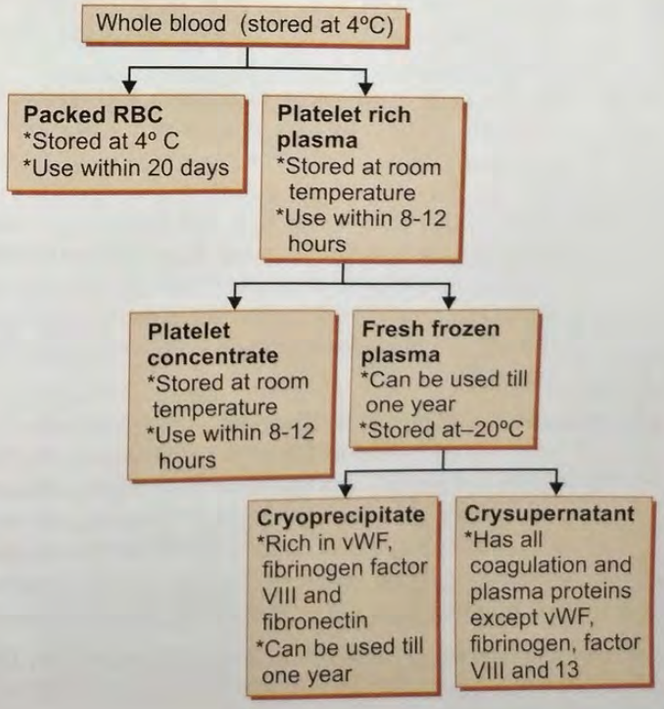
PAF is another phospholipid-derived mediator having the following inflammatory effects:

- Platelet aggregation
- Vasoconstriction
- Bronchoconstriction
- ***At extremely low concentration, it may cause vasodilation and increased venular permeability***

79. **Ans. (a) C3** *(Ref: Robbins 9/e p88)*

80. **Ans. (d) Factor VIII** *(Ref: Robbins 7/e p664)*

Cryoprecipitate is a **rich source of Factor VIII.** Have a glance at the flowchart given below.



81. Ans. (c) Arachidonic acid *(Ref: Robbins 9/e p84)*

Arachidonic acid is an essential fatty acid which is acted on by the enzyme **cyclo-oxygenase**[Q] (COX) leading to the formation of the prostaglandins.

Also know:

- **Linoleic, linolenic and arachidonic acid** are examples of polyunsaturated **essential fatty acids**[Q] **(PUFA)** which means they cannot be synthesized in the human body.
- **Docosahexaenoic acid**[Q] is an ***essential fatty acid*** present in **breast milk** which is required for **myelination of nerves**[Q].
- **Richest source** of PUFA is **safflower oil**[Q]
- **Coconut oil**[Q] is the **poorest source** of PUFA.

82. Ans. (b) IL-5 *(Ref: Robbins 8/e p200)*

IL-5 is required for the development and maturation of the eosinophil.

83. Ans. (d) PGH2 *(Ref: Robbins 9/e p84)*

84. Ans. (a) Fibroblast growth factor

(Robbins 9th/ 19-20; 8th/87-88, Fetal and Neonatal Physiology 4th/867-8)

Fibroblast growth factor (FGF) contributes to wound healing responses, hematopoiesis, and development. They can be belonging to

- Acidic FGF (aFGF, or FGF-1)
- Basic FGF (bFGF, or FGF-2): necessary for angiogenesis
- FGF-7 is also referred to as keratinocyte growth factor (KGF)

Growth Factor	Source	Functions
Epidermal growth factor (EGF)	Activated marcophages, selivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates karatinocytes migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated marcophages, keratinocytes, many other cells types	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) scater factor	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility.
Vascular endothelial growth factor (VEGF)	Messenchymal cells	Stimulates proliferation of endothelial cells; increases vascular parmeability
PLatelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells, activates and stimulates proleferation of fibroblasts, endothelial, and other cells, stimulates ECM protein synthesis

Contd...

Contd...

Growth Factor	Source	Functions
Fibroblast growth factor (FGFs), including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates anglogenesis and ECM protein synthesis.
Transforming growth factor β-(TGF-β)	Platelets, T lymphovcytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblast	Stimulates keratinocyte migration, proliferation, and differentiation.
ECM, EXtracellular membrane		

85. Ans. (d) Sepsis *(Ref: Harrison 18th/3419)*

Procalcitonin is an acute phase reactant which is now useful for being a **marker of sepsis**. It is in fact utilized for differentiating the bacterial and aseptic meningitis.

86. Ans. (d) C56789 *(Ref: Robbins 9th/88)*

The complement complex attacking the cell membrane is membrane attack complex having a composition of C56789. Action of this complex leads to entry of fluid and ions inside the cells leading to cell lysis.

87. Ans (d) Hypoglycemia

(Ref: CMDT 2018/ 502, Robbins 9/e p131)

Systemic inflammatory response syndrome is diagnosed when 2 or more of the following criteria are met:

- Core temperature <36° or >38°C
- Heart rate >90 beats/min
- Respirations >20/min or PCO_2 <32 mmHg
- White blood cell count >12,000/μL, <4000/μL, or 10% bands

88. Ans (c) Reduce protein synthesis in the target cell

(Ref: Robbins 9/e p188)

Interferons act by reducing the protein synthesis in the target cell.

89. Ans (d) CD31 *(Ref: Robbins 9/e p77)*

CD31 is responsible for transmigration.

90. Ans (b) CD 55 *(Ref: Robbins 9/e p642)*

- **CD55** is decay accelerating factor. It is responsible for **breakdown of C3**.
- **CD59** is ***membrane inhibitor of reactive lysis***. It is a potent inhibitor of C3 convertase that prevents the spontaneous activation of the alternative complement pathway.

91. Ans (c) Chymotrypsin sensitive *(Ref: Immunology 278)*

Macrophage chemotactic factor is a **heat stable** low molecular weight protein. It is **chymotrypsin sensitive** and is *resistant to treatment by RNase and neuraminidase*. It is different from C3 and C5.

92. **Ans (a) Elie Metchinkoff** *(Ref: Robbins 9/e p71)*
Elie Metchnikoff discovered the process of *phagocytosis* by observing the ingestion of rose thorns by amebocytes of starfish larvae and of bacteria by mammalian leukocytes.

93. **Ans (d) Arachidonic acid metabolites** *(Ref: Robbins 9/e p85)*

94. **Ans (d) TNF-alpha** *(Harrison 19/e p1753)*

- **Adiponectin, IL-10, IL-6, IL-4** and **TGF beta** are **anti-inflammatory cytokines...Harrison/19th.**

95. **Ans (b) Collagen** *(Ref: Robbins 9/e p19,21)*
- Interstitial matrix is produced by mesenchymal cells like fibroblasts and is mainly composed of fibrillar and non-fibrillar collagen.
- TGF-beta is chemotactic for leukocytes and fibroblasts. It induces proliferation of fibroblasts.

96. **Ans (a) Leukotrienes** *(Ref: Robbins 9/e p85)*
Slow-reacting substance of anaphylaxis consists of **leukotrienes** C4, D4, and E4.

97. **Ans (c) 5-10%** *(Ref: Hepatic plasma proteins 78)*
Complement proteins are accounting for **5-10%** of the total plasma proteins in the human body.

98. **Ans (c) Smad7** *(Ref: AIIMS Faculty)*
Smad 7 is associated with reduction in cachexia.

99. **Ans (c) Transferrin**

100. **Ans (c) IgM** *(Ref: Robbins 9/e p88)*

101. **Ans (b) Neisseria** *(Ref: Robbins 9/e p89)*

102. **Ans (a) alpha2 microglobulin** *(Ref: Robbins 9/e p702, Anderson 10/e p411)*

103. **Ans. (d) Monocytes-Macrophages** *(Ref: Robbins 9/e p97)*
Delayed type hypersensitivity (as seen in TB) results from accumulation of mononuclear cells around small veins and venules, producing a perivascular cuffing. Monocytes transform into macrophages which undergo morphological changes to produce epithelioid cells.

104. **Ans. (b) Microscopic polyangiitis** *(Ref: Robbins Illustrated 7th/540)*
- **Microscopic polyangiitis** is a small vessel vasculitis showing the presence of necrotizing inflammation of the affected vessels without the presence of granuloma.

Systemic vasculitis causing granulomas	Systemic vasculitis causing necrotizing inflammation
• Giant cell arteritis	• Polyarteritis nodosa (PAN)
• Takayasu's disease	• Microscopic polyangiitis
• Wegener's granulomatosis	• Wegener's granulomatosis
• Churg-Strauss syndrome	• Churg-Strauss syndrome

105. **Ans. (d) Mycoplasma** *(Ref: Robbins 8th/802 9/e p97)*
- **Granulomatous inflammation** is a distinctive pattern of chronic inflammatory reaction characterized by focal accumulations of activated macrophages, which often develop an epithelial-like (epithelioid) appearance.
- **Tuberculosis** is the prototype of the granulomatous diseases, but **sarcoidosis, Crohn's disease, cat-scratch disease, lymphogranuloma inguinale, leprosy, brucellosis, syphilis, some mycotic infections, berylliosis, and reactions of irritant lipids** are also included.
- In Robbins (8th ed, page 802), *Yersinia* has also been mentioned to be associated with granulomatous inflammation. So, the answer of exclusion is Mycoplasma.

106. **Ans. (c) Metastatic carcinoma of the lung** *(see below)*
Friends, remember that fungal and mycobacterial granulomas are usually associated with central necrosis but all large caseating granulomas come from small non-caseating granulomas. Granuloma can be seen in both Byssinosis and Hodgkin's lymphomas.
- Granulomas are also seen in Hodgkin's disease (Dorland's, 28/p 716)
- So, metastatic carcinoma of lung is the answer of exclusion.

107. **Ans. (c) Helper T-cells** *(Ref: Robbins 7th/83*
CD 4 Helper T-cells are involved in granuloma formation as it secretes IFN-γ, IL-2 and IL-12.

108. **Ans. (b) Leprosy; (d) CMV; (e) Wegener's granulomatosis** *(Ref: Robbins 7th/83,8th/73, 9/e p98)*
Caseous necrosis is characteristic of tubercular granuloma, rare in others type of granulomatous disease. TB granuloma is a prototype of immune granuloma. These are caused by insoluble particles; typically microbes that are capable of inducing a cell mediated immune response. Granulomatous lesions may develop in liver in CMV infection.

109. **Ans. (b) Secretory** *(Ref: Harsh Mohan 9/e p97)*

110. **Ans. (d) Leprosy** *(Ref: Robbins 8th/73, 9/e p98)*

111. **Ans. (d) Pneumocystis carinii** *(Ref: Robbins 9/e p98)*

112. **Ans. (a) Histoplasmosis** *(Ref: Robbins 8th/718)*

113. **Ans. (b) Sarcoidosis** *(Ref: Robbins 8th/701, 9/e p98)*

114. **Ans. (d) *P. carinii*** *(Ref: Robbins 8th/246, 9/e p98)*

115. **Ans. (a) Epithelioid cell** *(Ref: Robbins 9/e p97-98)*

116. **Ans. (a) Histoplasmosis** *(Ref: Robbins 8th/717-718)*

117. **Ans. (a) Toxoplasmosis**
This is a characteristic feature of toxoplasmosis.
Also know
- Toxoplasmosis is transmitted by ***cat*^Q *(definitive host)***. *Man is the intermediate host*^Q.
- It is diagnosed by **Sabin Feldman dye test**^Q.
- **Chorioretinitis**^Q is the commonest manifestation of this disease when **transmitted congenitally**. In the *acquired disease, there is usually absence of symptoms.*
- ***Drug of choice*** for toxoplasmosis is **combination of pyrimethamine and sulfadiazine**^Q.
- **Drug of choice** for toxoplasmosis in **pregnancy** is **spiramycin**^Q.

118. Ans. (d) Amebiasis *(Ref: Robbins 9/e p98)*

119. Ans. (b) Monocyte – macrophages *(Ref: Robbins 9/e p97)*

120. Ans. (a) Developmental elasticity
(Ref: Robbins 8th/82-5; Harrison 17th/426... Not in 9/Edition of Robbins)
Stem cells show the property of developmental plasticity (Not developmental elasticity) which is also known as transdifferentiation.

> A change in stem cell differentiation from one cell type to another is called **transdifferentiation**, and the multiplicity of stem cell differentiation options is known as **developmental plasticity**. ...Robbins 8th/85.

121. Ans. (a) Remnant skin appendages *(Ref: Love & Bailey 23rd/189)*

- Skin consists of two layers. Epidermis which is the most superficial layer of the skin constantly replaced from the basal layer and the dermis which is thicker than epidermis and contains adnexal structures. The importance of these adnexal structures is that they contain epithelial cells can proliferate and can heal a partial thickness wound by epithelialization.

122. Ans. (b) TB; (c) CLL; (d) Brucellosis *(Ref: P.J. Mehta 14th – 374)*

Absolute lymphocytosis	Relative lymphocytosis
1. Bacterial infections like tuberculosis, brucellosis, syphilis, pertussis, and toxoplasmosis. 2. Viral infections like mumps, rubella, and infectious mononucleosis. 3. Leukemia (chronic lymphocytic). 4. Thyrotoxicosis	1. All causes of neutropenia. 2. Infective hepatitis 3. Convalescence from acute injection. 4. Infant with infections, malnutrition and avitaminosis.

123. Ans. (c) Vitamin C *(Ref: Robbins 7th/114, 9/e p106)*
Healing is modified by a number of influences (including both *systemic and local host factors*) frequently impairing the quality and adequacy of both inflammation and repair.

> **Ascorbic acid deficiency** causes **reduced cross linking of tropocollagen to collagen**[Q]
> So, the patient has increased bleeding tendencies and poor wound healing.

124. Ans. (a) Associated with formation of multiple granulomas *(Ref: Harrison 18th/387)*
It is a congenital and not acquired leucocyte function defect.

125. Ans. (b) Repairing by same type of tissue *(Ref: Robbins 8th/92-94, 7th/88, 9/e p101)*

126. Ans. (b) Myofibroblasts *(Ref: Robbins 9/e p105)*

127. Ans. (c) Trans-differentiation *(Ref: Robbins 9/e p26-27)*
Tissue stem cells which are thought to be lineage-committed multipotent cells, possess the capacity to differentiate into cell types outside their lineage restrictions (called *trans-differentiation*). For example, hematopoietic stem cells may be converted into neurons as well as germ cells.

128. Ans. (a) Misfolding of protein *(Ref: Robbins, 9/e p1281)*
Prions are abnormal forms of a cellular protein that cause transmissible neurodegenerative disorders. This group of disorders includes:

> - Creutzfeldt-Jakob disease[Q] (CJD),
> - Gerstmann-Sträussler-Scheinker syndrome[Q] (GSS),
> - Fatal familial insomnia[Q], and
> - Kuru[Q] in humans;
> - Scrapie in sheep and goats; mink-transmissible encephalopathy; chronic wasting disease of deer and elk; and ***bovine spongiform encephalopathy***[Q]

- The *prion protein* (PrP) is both **infectious**[Q] and **transmissible**[Q].
- These disorders are predominantly characterized by **"spongiform change"** caused by intracellular vacuoles in neurons and glia.
- In pathogenesis, the disease occurs when the PrP undergoes a conformational change from its normal α-helix-containing isoform (PrP^c) to an abnormal β-pleated sheet isoform, usually termed PrP^{sc} (for scrapie). It is associated with resistance to the digestive action of proteases.

129. Ans. (c) Tenascin *(Ref: Robbins 8/e p96)*

Name of adhesion molecule	Function
Osteonectin (SPARC)	Tissue remodeling in response to injury, Angiogenesis inhibitor
Thrombospondins	Inhibit angiogenesis
Osteopontin	Regulates calcification Mediator of leukocyte migration in inflammation, Vascular remodeling Fibrosis in various organs
Tenascin **family**	Morphogenesis Cell adhesion

SPARC is secreted protein acidic and rich in cysteine.

130. Ans. (c) End of third week *(Ref: Robbins 9/e p106-108)*
Measurements in Wound Healing: Science and Practice Springer 2012 pg 112-3
Measurements in Wound Healing... *"maximum collagen production occurs at 20 days"*. The remodeling of the collagen continues beyond this duration.

Also know for future NEET questions

> - *TGF-β is the most important fibrogenic agent*
> - Wound strength is **10% after 1 week**[Q]; it increases rapidly during **next 4 weeks**[Q]and becomes **70% at the end of 3rd month**[Q].
> - The tensile strength of the wound keeps on increasing as time progresses.
> - Collagen is the most abundant protein in the body
> - ***Type I collagen*** is the ***major component*** of extracellular matrix in skin.
> - **Type III collagen** which is also normally present in skin, becomes **more prominent and important during the repair process**.

131. Ans. (b) Dilatation of capillaries....
(Ref: Robbins 8/e p46, 102, 7/e p107, 9/e p106)

Direct quote.. "the cutaneous wound healing is divided into the three phases: inflammation proliferation and maturation."

One of the earliest manifestations of inflammation is dilation of the capillaries.

132. Ans. (c) Liver *(Ref: Robbins 8/e p85-6, 9/e p28)*

133. Ans. (c) Oval cell....discussed in detail in a different question *(Ref: Robbins 8/e p83, 7/e p91, 9/e p28)*

134. Ans. (b) Extensive cross-linking of tropocollagen
(Ref: Robbin 8/e p 105-6)

Fibrillar collagens (mostly type I collagen) form a major portion of the connective tissue in repair sites and are essential for the development of strength in healing wounds.

Net collagen accumulation, however, depends not only on increased collagen synthesis but also on decreased degradation.

The ***recovery of tensile strength*** results from the excess of collagen synthesis over collagen degradation during the first 2 months of healing, and, at later times, from *structural modifications of collagen fibers* (***cross-linking, increased fiber size***) after collagen synthesis ceases.

135. Ans. (b) Subset of stem cells normally circulate in peripheral blood *(Ref: Robbin 9/e p 581)*

Hematopoietic stem cells have two essential properties that are required for the maintenance of hematopoiesis: pluripotency and the capacity for self-renewal. Pluripotency refers to the ability of a single HSC to generate all mature blood cells. When an HSC divides, at least one daughter cell must self renew to avoid stem cell depletion. Self-renewing divisions occur within a specialized marrow niche, in which stromal cells and secreted factors nurture and protect the HSCs. During stress, HSCs are mobilized from the bone marrow and appear in the peripheral blood.

Remember HSC resemble blasts morphologically.

136. Ans. (d) K *(Ref: Robbins 9/e p442, 119)*

137. Ans. (a) 4–5 days *(Ref: Robbins 9th/106)*

As directly mentioned in the book..... "By day 3, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Collagen fibers are now evident at the incision margins. Epithelial cell proliferation continues, forming a covering approaching the normal thickness of the epidermis.

138. Ans. (b) More common in blood group A
(Ref: Robbins 9/e p702, Plastic Surgery Secrets Plus 120)

139. Ans. (b) Embryonic stem cell *(Ref: Robbins 9/e p27)*

ANNEXURE

Table 1: Endothelial Leukocyte adhesion molecules and their functions

Endothelial molecule	*WBC receptor*	*Major role*
P-selectin	Sialyl- Lewis X	Rolling
E-selectin	Sialyl- Lewis X	Rolling, adhesion to activated endothelium
ICAM-1	CD 11/CD 18 (Integrins)	Adhesion, arrest, transmigration
VCAM-1	VLA 4, LPAM-1	Adhesion
Glycam-1	L-selectin	Lymphocytes homing to high endothelial venules
CD 31(PECAM)	CD 31	WBC migration through endothelium.

Table 2: Role of different mediators in inflammation

Increased vascular permeability	**Chemotaxis, leukocyte recruitment and activation**
(a) C3a and C5a	(a) C5a
(b) Vasoactive amines	(b) Leukotriene B_4
(c) Leukotriene C_4, D_4, E_4	(c) Chemokines
(d) PAF	(d) IL-8
(e) Substance P	(e) Bacterial products
(f) Bradykinin	(f) TNF
Fever	**Vasodilatation**
(a) **IL-1**	(a) NO
(b) TNF	(b) Histamine
(c) Prostaglandins (**PGE_2**)	(c) Prostaglandins
Tissue damage	**Pain**
(a) Neutrophil/macrophage lysosomal enzymes	(a) Prostaglandin
(b) NO and reactive oxygen species	(b) Bradykinin

CHAPTER 3

Hemodynamics

Golden Points

- Increased blood volume in a tissue can be due to Hyperemia (due to increased flow) or congestion (due to impaired venous return).
- Blood in blood vessels normally does not clot because Endothelium is smooth and coated with glycocalyx.
- Vitamin K dependent clotting factors are ***factors 2,7,9,10*** as well as anti clotting factors like ***protein C*** and ***protein S***.
- Thrombin is a procoagulant but ***thrombin-thrombomodulin complex is an anticoagulant***.
- **Virchow's triad** of thrombosis include: Vascular (endothelial) injury; abnormal blood flow (stasis or turbulence); hypercoagulability.
- Cancers causing migratory thrombophlebitis are Pancreas (most commonly), lung (2nd), prostate, stomach, brain, breast, ovary, lymphomas and AML-M3.
- **SLE** is most commonly associated with secondary anti phospholipid antibody syndrome and formation of **anti beta 2 glycoprotein antibody**.
- **Leiden mutation (factor V mutation)** is a **missense mutation** the most common ***inheritable cause*** of hypercoagulability.
- Important laboratory findings of fat embolism: Thrombocytopenia, fat microglobulinemia, fat globules in urine, anemia, hypocalcemia and hypoalbuminemia.
- Most common site of DVT is Calf veins whereas most common source of pulmonary embolism: DVT of proximal veins of lower limb (above knee), i.e. popliteal femoral or iliac veins.
- **White infarct** occurs with arterial occlusions in solid organs with end-arterial circulation (e.g., heart, spleen, and kidney).
- **Red infarcts** occur in venous occlusions (e.g., testis), in loose tissues (e.g., lung), in organs with dual circulations (e.g.,lung and small intestine).
- **Lines of Zahn** are seen in antemortem clots.
- **"Chicken fat" appearance** is seen in *post mortem* clots.
- Characteristic feature of shock: Poor tissue perfusion.
- Endotoxic shock is initiated by **Cytokine action**. (most important cytokine is TNF-α followed by IL-1.
- *Disseminated intravascular coagulation, hypotensive shock*, and metabolic disturbances (including insulin resistance and hyperglycemia) are referred to as the ***clinical triad of septic shock***.

Criteria for **S**ystemic **I**nflammatory **R**esponse **S**yndrome (2 or more of the following conditions)

- **Fever**[Q] (oral temperature >38°C) or **hypothermia**[Q] (<36°C)
- **Tachypnea**[Q] (>24 breaths/minute)
- **Tachycardia** [Q] (>90 beats/minute)
- **Leukocytosis**[Q] (>12,000/μl), **leucopenia**[Q] (<4,000/μl), or **>10%**[Q] **bands**

HEMODYNAMICS

In a normal blood vessel like capillary, there are two forces (Starling forces) acting on the fluid in the circulation. The **hydrostatic pressure** causes fluid movement from inside the vessel to outside and the **colloid osmotic pressure** (mostly due to proteins) is responsible for the reverse movement of fluid from outside the vessel to the inside. The capillary hydrostatic and osmotic forces are normally balanced so that there is no *net* loss or gain of fluid across the capillary bed. However, *increased* hydrostatic pressure or *diminished* plasma osmotic pressure leads to a net accumulation of extravascular fluid *(edema)*.

In edema, the excessive interstitial fluid can be either an exudate or a transudate.

Key Point

Transudate is **protein-poor** and cell-poor fluid.

Key Point

Exudate is **protein-rich** and **cell-rich fluid**.

A transudate is a fluid with low protein content (most of which is albumin) and a specific gravity of less than 1.012. It is essentially an ultrafiltrate of blood plasma that results from osmotic or hydrostatic imbalance across the vessel wall without an increase in vascular permeability.

An exudate is an inflammatory extravascular fluid that has a high protein concentration, cellular debris, and a specific gravity above 1.020. It is formed mainly due to alteration in the normal permeability of small blood vessels in the area of injury.

Recent Exam Question

Breast lymphedema (inflammatory carcinoma) is due to blockage of *subcutaneous lymphatics* by malignant cells. It is called as **Peau d' orange appearance** of the breast.

Causes and conditions associated with edema

↑ Hydrostatic pressure	↓ Plasma osmotic pressure	Lymphatic obstruction (Lymphedema)	Sodium retention	Inflammation
• CHF • Ascites (Cirrhosis) • Venous obstruction due to thrombosis of physical inactivity • Arteriolar dilation	• Liver cirrhosis • Malnutrition • Protein-losing gastro-enteropathy	• After surgery or irradiation • Neoplasia • Inflammatory	• ↑ Salt intake • ↓ Renal perfusion • ↑ RAAS activity	• Acute and chronic inflammation

When edema is influenced by gravity, it is called *dependent edema* and it is a characteristic feature of congestive heart failure (particularly the right ventricle).

- Edema due to a renal cause (as in Nephrotic syndrome) is more severe and affects all parts of body equally. However, it is initially appreciated in tissue with loose tissue matrix such as around eyes and is called periorbital edema.

Definition

Severe generalized edema is called **anasarca**.

Key Point

Heart failure cells are present in the **lungs** and *NOT* in the heart. These are **hemosiderin laden macrophages**.

Hyperemia	Congestion
• **Active** process due to arteriolar dilation	• **Passive** process due to impaired venous outflow
• **Edema** is **absent**	• Edema is present
• **Red color** of the tissues	• **Blue red color** of the tissue (due to deoxyhemoglobin)
• Seen in **Inflammation**	• Seen in *Right heart failure*, portal venous obstruction in *cirrhosis*.

In chronic passive congestion, there is chronic hypoxia and capillary rupture leading to hemorrhage foci. Phagocytosis of red cells results in hemosiderin-laden macrophages.

Pulmonary Congestion

In acute pulmonary congestion there is presence of engorged alveolar capillaries and focal intra-alveolar hemorrhage.

In chronic pulmonary congestion there is presence of thickened and fibrotic septa and alveoli contain hemosiderin laden macrophages (heart failure cells).

Hepatic Congestion

Acute hepatic congestion manifest as central vein and sinusoidal distension with degeneration of central hepatocytes.

In chronic hepatic congestion, central region of lobule shows loss of cells and have red brown color which is accentuated against surrounding normal liver (called **nutmeg liver**). Initially there is centrilobular necrosis and presence of hemosiderin laden macrophages. In long standing congestion (as in heart failure), there is presence of hepatic fibrosis called **cardiac cirrhosis**.

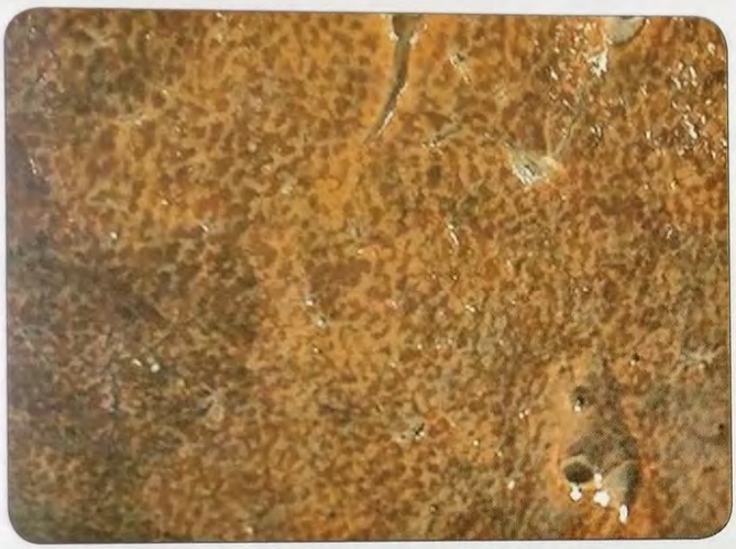


Fig. 1: Nutmeg liver. **...(AIIMS Image)**

Key Point

Fibrosis associated with Chronic passive congestion of the liver (in heart failure) is called as **cardiac cirrhosis.**

HEMOSTASIS

It is defined as a sequence of events leading to cessation of bleeding by the formation of a stable fibrin-platelet hemostatic plug. The process involves the vascular endothelium, platelets and the coagulation system.

1. **Vascular Endothelium**
   After an injury, there is *transient vasoconstriction* of the vessel *due to endothelin*. This is followed by the activation of thrombogenic factors which include:
   a. *Alteration in the blood flow* resulting in turbulence and stasis favoring the clot formation.
   b. There is release of tissue factor from the injured cells activating the factor VII (extrinsic pathway) and exposure to subendothelial collagen causing activating of factor XII (intrinsic pathway). The endothelial cells also release von Willebrand factor (vWF) which binds to exposed collagen and facilitates platelet adhesion.
   c. There is also release of inhibitors of plasminogen activator (PAIs) which inhibit fibrinolysis.

2. **Platelets**
   Initially vWF binds with the collagen followed by the binding of the platelets with vWF through the glycoprotein Ib factor. The platelets then undergo a shape change and their degranulation occurs. The granules in the platelets can be *Alpha granules* or *delta granules*. The release of granule mediators result in release of calcium (required in the coagulation cascade), ADP (potent mediator of platelet aggregation) and the surface expression of *phospholipid complexes*, which provide the platform for the coagulation cascade. The platelets also synthesize thromboxane A_2 (TXA_2) which is a potent vasoconstrictor and is also responsible for platelet aggregation. The platelets bind to each other by binding to fibrinogen using Gp IIb-IIIa.

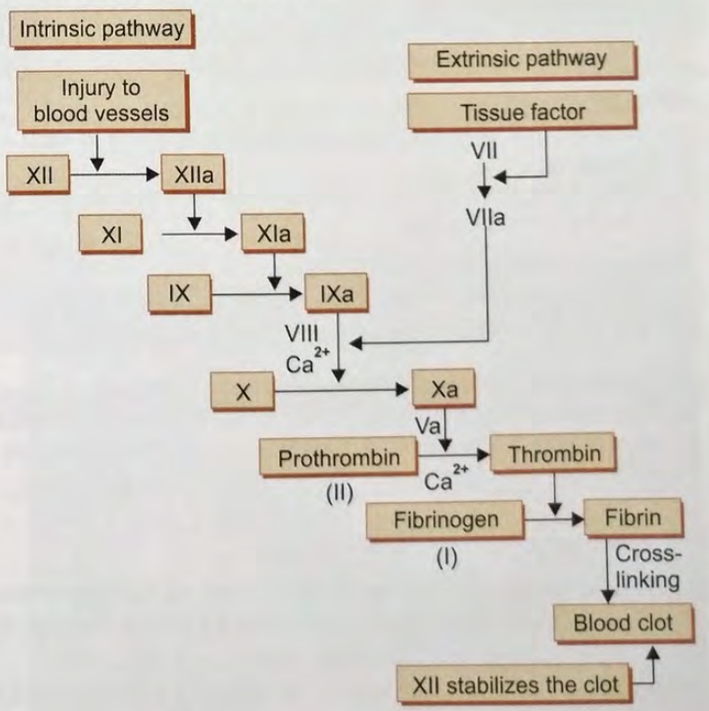
Recent Exam Question

Delta granules of platelets have
A – **A**DP / **A**TP
C – **C**alcium
E – **E**pinephrine
S – **S**erotonin

Concept

A defect in the glycoprotein **Ib** factor results in defective platelet adhesion known as **Bernard Soulier syndrome** whereas deficiency of *Gp IIb/IIIa* lead to *Glanzmann thrombasthenia*, a disorder having defective platelet aggregation.

3. **The Coagulation System**



The clotting system can be activated by intrinsic (through factor XII) or the extrinsic pathway (through factor VII). The intrinsic pathway is activated by exposing factor XII to thrombogenic surfaces (like glass and other negatively

charged surfaces) whereas extrinsic pathway requires exogenous trigger (provided originally by tissue extracts). The division is artifact because extrinsic pathway is physiologically relevant for after vascular damage whereas intrinsic pathway is of relevance in vitro.

Recent Exam Questions

- **PT** is prolonged by **deficiency** of **VII, X, V,** prothrombin **(II)** and fibrinogen **(I)** and oral anticoagulants like **warfarin**.
- **aPTT** is prolonged by **deficiency** of factors **XII, XI, IX, III, X, V, prothrombin and fibrinogen** and drugs like **heparin**.
- **BT** is elevated in **quantitative** *(thrombocytopenia)*and **qualitative** *(thrombasthenia)* platelet defects.

Prothrombin time (PT)
- It is used to monitor the functioning of the **extrinsic and the common** coagulation pathways.
- Normal PT is **12-16 seconds**.

Activated partial thromboplastin time (aPTT)
- It is used to monitor the functioning of the intrinsic and the common coagulation pathways.
- Normal aPTT is 26-34 seconds.
- A relatively rare cause of prolonged aPTT is presence of antibodies against coagulation plasma proteins called inhibitors. It can be seen due to the following reasons:

Hemophilia A and B patients receiving clotting factors to control their bleeding episodes, Pregnancy, Autoimmune diseases, Malignancies (lymphoma, prostate cancer) and Dermatologic conditions This has been dealt extensively in chapter-8 of this book.

Thrombin time (TT)
- It is used for testing the conversion of fibrinogen into fibrin and depends on adequate fibrinogen levels.

Bleeding time (BT)
- It is the time taken for a standardized skin puncture to stop bleeding
- It tests the ability of blood vessels to constrict and platelets to form a hemostatic plug.

Fibrin degradation products (FDPs)
- They are used to assess the fibrinolytic activity and they are increased in disseminated intravascular coagulation (DIC).

Key Point

Thrombin time is elevated in afibrinogenemia, dysfibrinogenemia, heparin like inhibitors and DIC.

Important anticoagulant substances are:

1. ***Antithrombin III*** – It inhibits activity of thrombin and other factors like XIIa, XIa, Xa and IXa. It is activated by binding to heparin- Like molecules.
2. ***Proteins C and S*** – Vitamin K dependent proteins which inactivate Va and VIIIa.
3. Endothelial prostacyclin *(PGI_2)* and nitric oxide *(NO)* are potent vasodilators and inhibitors of platelet aggregation.
4. ***Tissue factor pathway inhibitor*** – Derived from endothelium and inhibits tissue factor VIIa and Xa molecules.
5. ***Thrombomodulin*** binds to thrombin and this complex activates protein C (in the presence protein S), which finally inactivates factor V and VIII. This action result in anticoagulant effect.

The binding of clotting factors II, VII, IX and X to calcium depends on the addition of γ **carboxylation of glutamic acid**[Q] residues on these proteins using vitamin K as a cofactor. These clotting proteins are prothrombotic. ***Proteins C and S*** are two other vitamin K-dependent proteins which can inactivate factors Va and VIIIa. These are anticlotting factors.

Recent Exam Questions

- *Thrombin is a procoagulant* but the **thrombin-thrombomodulin complex is an anticoagulant.**
- **Thrombomodulin** is produced by all endothelial cells *except those* ***in the cerebral microcirculation***[Q].

THROMBOSIS

It is defined as the pathologic formation of intravascular fibrin-platelet thrombus.

Virchow's triad is required for thrombus formation. Its components are:

1. *Endothelial injury:* It can be due to the factors like vasculitis, hypertension, turbulent flow, bacterial endotoxins, homocystinuria, hypercholesterolemia, radiation, etc. It is particularly important for thrombus formation occurring in the heart or in the arterial circulation.
2. *Alterations in the normal blood flow:* Both turbulence and stasis contribute to the development of thrombosis. Turbulence causes arterial whereas stasis causes venous thrombosis. It can also be seen with hyperviscosity syndromes like polycythemia and with deformed red cells as in sickle cell anemia.
3. *Blood hypercoagulability:* It can be either primary or secondary hypercoagulable state.

Key Point

Virchow's triad = Endothelial injury + Alterations in the normal blood flow + Blood hypercoagulability

Hypercoagulable states

Primary (Genetics)	Secondary (Acquired)
• Mutations in factor V (Most common) • Antithrombin III deficiency • Protein C or S deficiency • Fibrinolysis defects • Homocysteinemia • Allelic variations in prothrombin levels • Mutations in the methyl tetra hydro folate (MTHF) gene	• Prolonged bed rest or immobilization • Homocysteinemia • Tissue damage (Surgery, fracture, burns) • Cancer • MI, Prosthetic cardiac valves • DIC (Disseminated intravascular coagulation) • Heparin induced thrombocytopenia • Antiphospholipid antibody syndrome

Relationship between coagulation defect and site of thrombosis *(updated from Harrison18th/462)*

- *Factor V mutation (also called Leiden mutation) is the most common inherited cause of hypercoagulability* in which normal arginine is replaced by glutamine at position 506 making it resistant to degradation by protein C. This causes unchecked coagulation and it manifest with recurrent deep venous thrombosis.
- Antithrombin III, Protein C or Protein S deficiency are other genetic causes of hypercoagulability manifesting typically as venous thrombosis and recurrent thromboembolism in adolescence or early adult life.
- All conditions mentioned above would have presence of venous thrombosis except for the following:

Conditions with both arterial and venous thrombi

- Homocysteinuria[Q]
- Antiphospholipid antibody[Q]
- Hyperhomocysteinemia[Q]
- Disseminated intravascular coagulation[Q]
- Heparin induced thrombocytopenia[Q]
- Essential thrombocythemia[Q]
- Cancer[Q]
- PNH[Q]
- Polycythemia vera[Q]
- Dysfibrinogenemia[Q]

Recent Exam Questions

- **Factor V mutation** (also called **Leiden mutation**) is the most common inherited cause of hyper-coagulability
- **Hyperhomocystenemia** is the only mixed disorder **(inherited as well as acquired)** which can cause **both venous and arterial thrombosis**

Arterial and Venous Thrombi

- An area of attachment to the underlying vessel or heart wall, frequently firmest at the point of origin, is characteristic of all thromboses. **Venous thrombi are called as stasis thrombi because they are formed in the sluggish venous circulation. These are also known as red thrombi as they contain more enmeshed red cells and relatively few platelets. Arterial thrombus contains more platelets and relatively less fibrin.**

Definition

Arterial thrombi arising in heart chambers or in the aortic lumen usually adhere to the wall of the underlying structure and are termed **mural thrombi.**

Key Point

Lines of Zahn which are produced by the alternating pale layers of platelets mixed with some fibrin and darker layers containing more red cells.

Feature	Arterial thrombus	Venous thrombus
Pathogenesis	Endothelial injury or site of turbulence	Stasis of blood
Blood flow	Associated with **active** blood flow	Associated with sluggish blood flow
Sites	Coronary, cerebral and femoral arteries	Superficial and deep leg veins, ovarian/ periuterine veins
Propagation	Grows in a **retrograde manner** from point of attachment	Grows in an antegrade manner from point of attachment
Gross	Lines of Zahn **present**	Lines of Zahn absent
Microscopic	Pale platelet layer alternating with dark red cell layer so also called as **white thrombi**	Red cells mixed with relatively less platelets, so also called as red thrombi
Occlusion	**Incomplete** lumen occlusion	Complete vessel occlusion
Complications	Ischemia and infarction of organs	Embolism, edema and ulceration

Postmortem clots are gelatinous with a dark red dependent portion where red cells have settled by gravity and a yellow *chicken fat* supernatant resembling melted and clotted chicken fat. These are usually not attached to the underlying wall whereas as discussed above, an area of attachment is characteristic of all thrombosis. Thrombi may form on heart valves as seen in **infective endocarditis; nonbacterial thrombotic endocarditis and verrucous (Libman-Sacks) endocarditis**.

EMBOLISM

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried downstream from its site of origin. It is most commonly composed of thromboembolism. The emboli may also be composed of other types like atheroemboli, fat emboli (most commonly with skeletal injuries), air emboli, amniotic fluid emboli and tumor emboli.

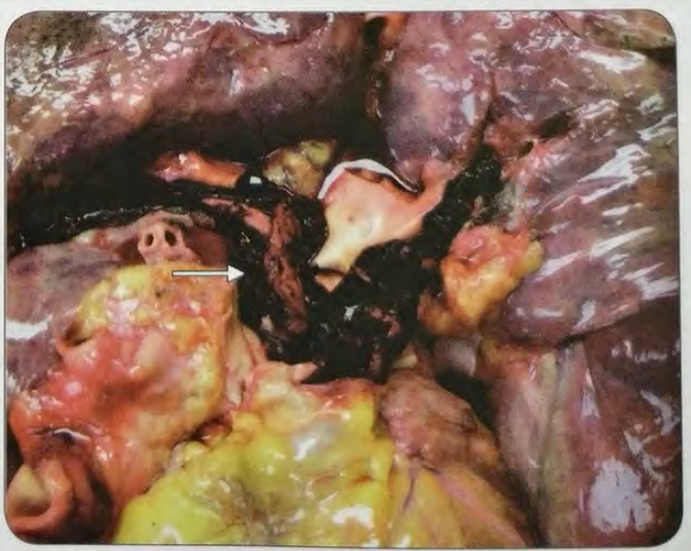


Fig. 2: Pulmonary embolus. **...(All India Image)**

Pulmonary Emboli

Most of the pulmonary emboli arise in the ***deep leg veins above the level of the knee***. *Paradoxical embolus* is a rare embolus that can pass through an inter-atrial or inter-ventricular defect, thereby entering the systemic circulation. Most ***pulmonary emboli (60% to 80%) are clinically silent*** because they are small. They ***rarely may cause pulmonary infarction*** (because lungs have dual blood supply from pulmonary and bronchial vessels) manifesting clinically as breathlessness, pleuritic pain, hemoptysis and pleural effusion. Sudden death may occur if >60% of the pulmonary circulation is obstructed. Recurrent pulmonary emboli may also cause pulmonary hypertension which may lead to cor pulmonale.

Systemic Thromboembolism

Most of them arise in the heart and *the major sites of arterial embolization are the lower extremities* (75%), the brain (10%) and less commonly, the intestines, kidneys, spleen, and upper extremities.

Fat Embolism

Fat embolism syndrome is characterized by ***pulmonary insufficiency, neurologic symptoms*** (irritability, restlessness and even coma), ***anemia, and thrombocytopenia*** (manifesting as diffuse petechial rash). It is seen after fractures of long bones (which contain fatty marrow) or after soft-tissue trauma. It is ***fatal only in 10%*** of cases. The pathogenesis involves both mechanical obstruction and free fatty acids causing local toxic injury to endothelium.

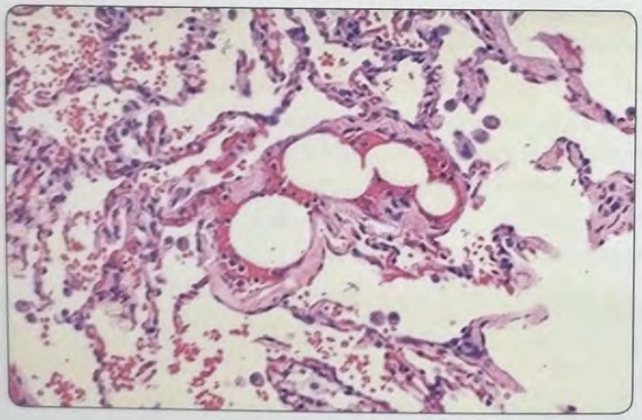


Fig. 3: Fat embolism. **...(AIIMS Image)**

Recent Exam Questions

- Most common site for **venous thrombosis** is the deep leg veins in **below** the knee.
- Most of the **pulmonary emboli**arise in the deep leg veins **above (femoral veins)** the level of the knee.

Recent Exam Question

Fat embolism is seen after fractures of long bones and is **fatal only in 10%** of cases.

Infarct

It is an area of necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue. Nearly 99% of all infarcts result from thrombotic or embolic events, and almost all result from arterial occlusion. Venous thrombosis usually causes venous obstruction and congestion but can cause infarction (more in organs with a single venous outflow like testis and ovary). The infarcts may be either red (hemorrhagic) or white (anemic) and may be either septic or bland.

Fig. 4: White infarct

Concept

All **infarcts** tend to be **wedge shaped** with the occluded vessel at the apex and the periphery of the organ forming the base. The infarct microscopically has features of **ischemic coagulative necrosis.**

Feature	Red infarcts	White infarcts
Cause	• **Arterial occlusion** in **loose tissues** or organs having dual **blood supply** • **Venous occlusion** (in ovarian torsion)	• Arterial occlusions in solid organs with end arterial circulation
Affected organs	Lung and small intestine	Solid organs (heart, spleen, kidney)
Properties	**Ill define hemorrhagic margins** which change in color to brown	Well defined margins and progressively paler with time
Edema	Usually present	Usually absent

Disseminated Intravascular Coagulation (DIC)/Consumption Coagulopathy

DIC is an acute, subacute, or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases. It is characterized by activation of the coagulation sequence that leads to the formation of microthrombi throughout the microcirculation of the body. *As a consequence of the thrombotic diathesis, there is consumption of platelets, fibrin, and coagulation factors and, secondarily, activation of fibrinolytic mechanisms.*

Causes of DIC				
Obstetrics complications	**Infections**	**Neoplasm**	**Massive tissue injury**	**Miscellaneous**
- Abruptio placenta - Retained dead fetus - Septic abortion - Amniotic fluid embolism - Toxemia	- Gram negative sepsis - Meningococcemia - Histoplasmosis - Aspergillosis - Malaria - Toxemia	- Ca pancreas - Ca prostate - Ca lung - Ca stomach - Acute promyelocytic leukemia	- Traumatic - Burns - Extensive surgery	- Acute intravascular hemolysis - Snake bite - Shock - Heat stroke - Vasculitis - Aortic aneurysm - Liver disease

Recent Exam Question

D-dimer is a fibrin split product whose levels **increase** in **deep vein thrombosis** and **pulmonary embolism**.

Laboratory investigations in DIC reveal that

- Platelet count is decreased
- Prolonged PT/TT
- Decreased fibrinogen
- Elevated fibrin split products (D-dimers)

The management is to treat the underlying disorder.

Recent Exam Question

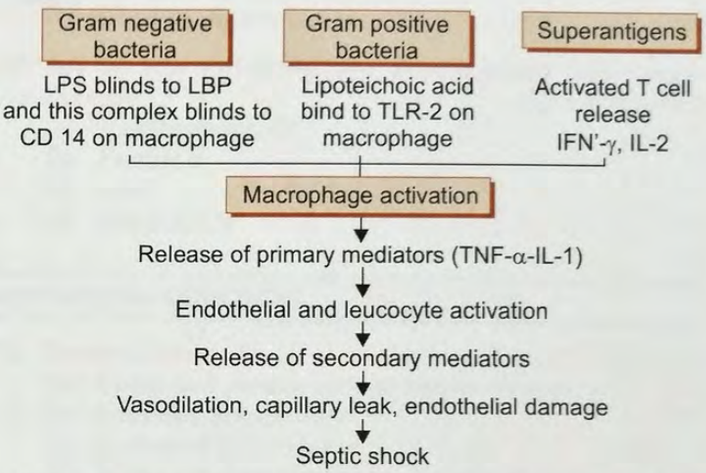
Procalcitonin is an acute phase reactant which is now useful for being a **marker of sepsis**.

SHOCK

It is defined as *systemic hypoperfusion* caused by reduction either in cardiac output or in the effective circulating blood volume.

Causes of Shock

- *Cardiogenic shock*: Presence of cardiac pump failure as seen with myocardial infarction, cardiac arrhythmia, cardiac tamponade and pulmonary embolism.
- *Hypovolemic shock*: Caused by reduction of blood volume due to hemorrhage, severe burns and severe dehydration.
- *Neurogenic shock*: Presence of generalized vasodilation due to anesthesia and CNS injury.
- *Anaphylactic shock*: Presence of generalized vasodilation due to type I hypersensitivity reaction
- *Septic shock*: It is due to release of endotoxins or bacterial cell wall lipopolysaccharides (gram negative infections) resulting in production of cytokines like TNF-alpha, IL-1 and IL-6, vasodilation and hypotension, acute respiratory distress syndrome and multiple organ dysfunction syndrome. Pathogenesis of septic shock is explained in the flowchart below:



LPS: Lipopolysaccharide **LBP:** LPS Binding Protein **TLR:** Toll Like Receptor

Concept

Most common cause of septic shock is gram positive bacteria now; so, the earlier term of endotoxic shock is not used now.

Recent Exam Question

Triad of septic shock is ***DIC***, ***hypotensive shock*** and ***metabolic disturbances***.

STAGES OF SHOCK

Stage I: ***Stage of compensation*** in which perfusion to the vital organs is maintained by mechanisms like increased sympathetic tone, catecholamine release and activation of renin-angiotensin system.

Stage II: ***Stage of decompensation*** in which there is tissue hypoperfusion and other features like development of metabolic acidosis, electrolyte disturbances and renal insufficiency.

Stage III: ***Irreversible stage*** having irreversible tissue injury and multiple organ failure which is not even corrected by the removal of the underlying cause or correction of the hemodynamic disturbance.

FEATURES OF SHOCK

Brain	Ischemic encephalopathy
Heart	Coagulative necrosis or contraction band necrosis
Liver	Fatty change with hemorrhagic central necrosis; 'shock liver'
Kidneys	Extensive tubular ischemic injury (Acute tubular necrosis) leading to oliguria and electrolyte disturbances.
Adrenal	Cortical cell lipid depletion.

Contd...

Contd...

GIT	Hemorrhagic enteropathy.
Lungs are uncommonly affected but may show features of **diffuse alveolar damage** or **shock lung**.	

Clinical Features

In hypovolemic and cardiogenic shock, the patient presents with hypotension; a weak, rapid pulse; tachypnea; and cool, clammy, cyanotic skin. In septic shock, however, the skin may initially be warm and flushed because of peripheral vasodilation. Then, patients develop a second phase dominated by renal insufficiency and marked by a progressive fall in urine output as well as severe fluid and electrolyte imbalances.

Multiple Choice Questions

HEMODYNAMICS AND HEMOSTASIS

1. **All are true about blood coagulation except?** *(AI 2011)*
   (a) Factor X is a part of both intrinsic and extrinsic pathway.
   (b) Extrinsic pathway is activated by contact of plasma with negatively charged surfaces.
   (c) Calcium is very important for coagulation.
   (d) Intrinsic pathway can be activated in vitro.

2. **Vitamin K is responsible for the carboxylation of which amino acid in the clotting factors?** *(AI 2011)*
   (a) Aspartate (b) Glutamate
   (c) Proline (d) Lysine

3. **Edema in nephrotic syndrome occurs due to**
   (a) Na^+ and water restriction *(AIIMS Nov. 2010)*
   (b) Increased venous pressure
   (c) Decreased serum albumin
   (d) Decreased fibrinogen

4. **Thrombomodulin thrombin complex prevents clotting because:** *(DPG 2011)*
   (a) Thrombomodulin inhibits prothrombin activator
   (b) The complex activates antithrombin III
   (c) Thrombomodulin-thrombin complex activates heparin
   (d) The complex removes thrombin and also activates protein C which inactivates the activated factors V and VIII

5. **Vitamin K associated clotting factors are:**
   (a) IX, X (b) I, V *(AI 2010)*
   (c) VII, VIII (d) I, VIII

6. **All endothelial cells produce thrombomodulin except those found in:** *(AI 2005)*
   (a) Hepatic circulation
   (b) Cutaneous circulation
   (c) Cerebral microcirculation
   (d) Renal circulation

7. **Which of the following is a procoagulation protein?** *(AI 2004)*
   (a) Thrombomodulin (b) Protein C
   (c) Protein S (d) Thrombin

8. **All of the following are correct about Thromboxane A2 except:** *(AI 2001)*
   (a) Low dose aspirin inhibits its synthesis
   (b) Causes vasoconstriction in blood vessels
   (c) Causes bronchoconstriction
   (d) Secreted by WBC

9. **Coagulation defects associated with increased coagulation are seen in:** *(PGI Dec 2006)*
   (a) Increased protein C
   (b) Increased protein S
   (c) Increased anti-thrombin III
   (d) Protein C resistance
   (e) Dysfibrinogenemia

10. **All of the following are anticoagulant substances except:** *(Karnataka 2006)*
    (a) Antithrombin III
    (b) Protein S
    (c) vWF
    (d) Nitric oxide

MOST RECENT QUESTIONS

11. **Cause of edema is:**
    (a) Decreased plasma protein concentration
    (b) Increased lymph flow
    (c) Increased ECF volume
    (d) Increased plasma protein concentration

12. **Endothelium derived relaxing factor (EDRF) is associated with:**
    (a) Ras (b) C-myc
    (c) Bcl (d) nNOS

13. **Which is not involved in local hemostasis?**
    (a) Fibrinogen (b) Calcium
    (c) Vitamin K (d) Collagen

14. **Which is the following not synthesized in the liver?**
    (a) Factor II (b) Factor VII
    (c) Factor IX (d) Factor VIII

15. **A 54-year-old chronic alcoholic Adhiya Kumar is brought by his son as he has developed progressively increasing abdominal distension from past 3 months. The physician aspirates the abdominal fluid which is straw-colored and clear and is found to have protein content (mainly albumin) of 2.3 g/dl. Which of the following is a major contributor to the fluid accumulation in this patient?**
    (a) Blockage of lymphatics
    (b) Decreased oncotic pressure
    (c) Decreased capillary permeability
    (d) Inflammatory exudation

16. **Gandy gamma body is typically seen in chronic venous congestion of which of the following?**
    (a) Lung (b) Kidney
    (c) Spleen (d) Liver

17. **Extrinsic pathway of clotting factors is measured by?**
(a) Prothromin time
(b) Activated partial thromboplastin time
(c) Bleeding time
(d) Clotting time

18. **Tissue thromboplastin activates:**
(a) Factor VII (b) Factor IV
(c) Factor VI (d) Factor XII

19. **Platelet adhesion to collagen is mediated by which of the following?**
(a) Factor VIII
(b) Factor IX
(c) Von Willebrand factor
(d) Fibronectin

20. **Adhesion of platelets to collagen is due to:**
(a) Factor IX
(b) Fibrinogen
(c) Von Willebrand factor
(d) Fibronectin

21. **The clot formed after coagulation cascade is not stable unless extensive cross-linking occurs. This is done by:**
(a) Plasmin
(b) Thrombin
(c) Factor XII
(d) High molecular weight kininogen

THROMBOSIS: EMBOLISM: INFARCT

22. **Histologic sections of lung tissue from 66-year-old woman, Sheena with congestive heart failure and progressive breathing problems reveal numerous hemosiderin-laden cells within the alveoli. Which of the following is the cell of origin of these "heart failure cells"?**
(a) Endothelial cells
(b) Pneumocytes
(c) Lymphocytes
(d) Macrophages

23. **At autopsy, the spleen of a patient is noted to have a thickened capsule and many small, scarred areas. Microscopic examination of the scarred areas reveals fibrosis with hemosiderin and calcium deposition. This type of spleen is usually seen in conjunction with which of the following disorders?**
(a) Hepatic cirrhosis
(b) Hodgkin's disease
(c) Rheumatoid arthritis
(d) Sickle cell anemia

24. **Antiphospholipid syndrome is associated with all except:** *(AI 2012)*
(a) Recurrent abortion
(b) Venous thrombosis
(c) Pancytopenia
(d) Antibody to lupus

25. **Pale infarct is seen in all except:** *(AIIMS Nov 2010)*
(a) Lungs (b) Spleen
(c) Kidney (d) Heart

26. **Congenital hypercoagulability states are all of the followings except:**
(a) Protein C deficiency *(AIIMS Nov 2010)*
(b) Protein S deficiency
(c) Anti-phospholipid antibody syndrome
(d) MTHFR gene mutation

27. **Fat embolism is commonly seen in:** *(DPG 2011)*
(a) Head injuries
(b) Long bone fractures
(c) Drowning
(d) Hanging

28. **Virchow's triad includes all except:**
(a) Injury to vein
(b) Venous thrombosis
(c) Venous stasis
(d) Hypercoagulability of blood

29. **Hypercoagulability due to defective factor V gene is called:** *(AIIMS Nov 2003)*
(a) Lisbon mutation
(b) Leiden mutation
(c) Antiphospholipid syndrome
(d) Inducible thrombocytopenia syndrome

30. **Arterial thrombosis is seen in:** *(PGI June 2003)*
(a) Homocysteinemia
(b) Antiphospholipid syndrome
(c) Protein S deficiency
(d) Protein C deficiency
(e) Antithrombin III deficiency

31. **Hemorrhagic infarction is seen in:** *(PGI Dec 2002)*
(a) Venous thrombosis
(b) Thrombosis
(c) Septicemia
(d) Embolism
(e) Central venous thrombosis

32. **Hyperviscosity is seen in:** *(PGI Dec 2003, 04)*
(a) Cryoglobulinemia
(b) Multiple myeloma
(c) MGUS
(d) Lymphoma
(e) Macroglobulinemia

33. **Predisposing factor for venous thrombosis:**
(a) AT III deficiency
(b) Protein S deficiency
(c) Protein C deficiency
(d) Dysfibrinogenemia

34. **Inherited coagulation disorders are:** *(PGI Dec 2005)*
(a) Protein C deficiency
(b) Protein S deficiency
(c) Leiden factor mutation
(d) Lupus anticoagulant
(e) Anti-cardiolipin

35. **Which of the following statements about pulmonary emboli is not correct?** *(Delhi PG 2009 RP)*
(a) 60-80% pulmonary emboli are clinically silent
(b) In more than 95% cases venous emboli originate from deep leg veins
(c) Embolic obstruction of pulmonary vessels almost always cause pulmonary infarction
(d) Embolic obstruction of medium sized arteries may result in pulmonary infarction

MOST RECENT QUESTIONS

36. **Which one of the following inherited disorders produces arterial thrombosis?**
(a) Factor V Leiden mutation
(b) Antithrombin deficiency
(c) Homocysteinemia
(d) Protein S deficiency

37. **Heart failure cells are seen in:**
(a) Chronic venous congestion of liver
(b) Chronic venous congestion of lung
(c) Acute venous congestion of lung
(d) Acute venous congestion of liver

38. **Necrosis with putrefaction is called as:**
(a) Desiccation
(b) Gangrene
(c) Liquefaction
(d) Coagulative necrosis

39. **Lines of Zahn are found in:**
(a) Thrombus
(b) Infarct tissue
(c) Postmortem clot
(d) All

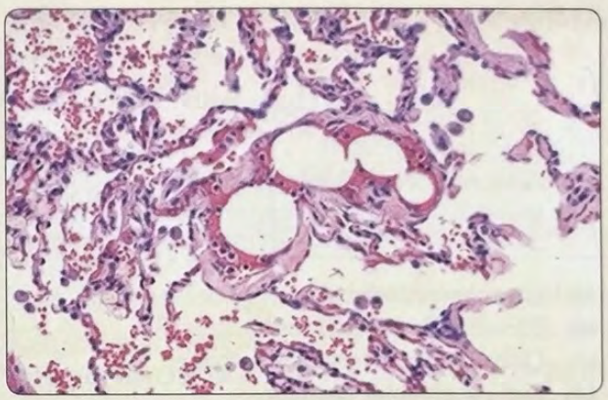
40. **Chicken fat clot is:**
(a) Postmortem clot
(b) Thrombus
(c) Infarct
(d) All

41. **Lines of Zahn occur in which of the following?**
(a) Postmortem clot
(b) Infarct
(c) Embolus
(d) Coralline thrombus

42. **White infarcts are seen in the following *except:***
(a) Liver
(b) Kidney
(c) Spleen
(d) Heart

43. **White infarct is seen in:**
(a) Lung
(b) Intestine
(c) Heart
(d) Ovary

44. **A 58-year-old man suffered road traffic accident and came to the hospital. He had multiple fractures in his lower limbs, ribs and lung contusion. Ultimately he succumbed to his injuries. At autopsy, a biopsy from the lung showed the following appearance. What is the likely cause of his death?** *(AIIMS Nov 2016)*



(a) Fat embolism
(b) Emphysema
(c) Pulmonary embolism
(d) Congestive heart failure

45. **Leiden mutation is an example of which of the following mutations:**
(a) Non sense mutation
(b) Mis-sense mutation
(c) Frameshift mutation
(d) Trinucleotide repeat mutation

46. **Lines of Zahn are seen in:**
(a) Heart
(b) Liver
(c) Lungs
(d) Kidneys

SHOCK, DIC AND MISCELLANEOUS

47. **All of the following are true about DIC except?** *(AI 2012)*
(a) Increased fibrinogen
(b) Increased activated partial thromboplastin time
(c) Decreased prothrombin time
(d) Increased fibrin degradation products

48. **The initiating mechanism in endotoxic shock is**
(a) Peripheral vasodilatation *(AIIMS Nov 2010)*
(b) Endothelial injury
(c) Increased vascular permeability
(d) Reduced cardiac output

49. **Reverse transcriptase is a RNA dependent DNA polymerase. Which of these viruses has it?**
(a) Hepatitis A virus
(b) Hepatitis B virus
(c) Hepatitis E virus
(d) Hepatitis C virus

50. The initiating mechanism in endotoxic shock is: *(AIIMS Nov 2010)*

(a) Peripheral vasodilatation
(b) Endothelial injury
(c) Increased vascular permeability
(d) Cytokine release

51. D-Dimer is the most sensitive diagnostic test for: *(DPG 2011)*

(a) Pulmonary embolism
(b) Acute pulmonary oedema
(c) Cardiac tamponade
(d) Acute myocardial infarction

52. Shock lung is characterized by: *(AIIMS May 2008; Nov 2007)*

(a) Alveolar proteinosis
(b) Bronchiolitis obliterans
(c) Diffuse pulmonary hemorrhage
(d) Diffuse alveolar damage

53. The histological features of shock includes:

(a) ATN
(b) Pulmonary congestion
(c) Depletion of lipids in adrenal cortex
(d) Hepatic necrosis
(e) Depletion of lymphocytes

54. Conditions associated with incoagulable state are:

(a) Abruption placentae *(PGI Dec 2003, 2004)*
(b) Acute promyelocytic leukemia
(c) Severe falciparum malaria
(d) Snake envenomation
(e) Heparin overdose

55. Which of the following is a feature of Disseminated Intravascular Coagulation (DIC)? *(Karnataka 2006)*

(a) Normal prothrombin time
(b) Reduced plasma fibrinogen
(c) Normal platelet count
(d) Normal clotting time

Explanations

1. **Ans. (b) Extrinsic pathway is activated by contact of plasma with negatively charged surfaces**
(Ref: Robbins 8th/119, 9/e 118)
Contact of plasma with negative charged surface activates intrinsic and not extrinsic pathways.

2. **Ans. (b) Glutamate** *(Ref: Robbins 8th/119, 9/e p119)*
The binding of clotting factors II, VII, IX and X to calcium depends on the addition of γ carboxylation of glutamic acid residues on these proteins. This step requires vitamin K as a cofactor.

Vitamin K dependent factors

Increasing clotting	Inhibiting clotting
• Clotting factors **II, VII, IX and X**	• Protein **C** and protein **S**

Proteins C and S are two other vitamin K-dependent proteins which can inactivate factors Va and VIIIa. These are anticlotting factors.

3. **Ans. (c) Decreased serum albumin**
(Ref: Robbins 8th/922, 9/e p115)
Na^+ and water retention is now the more important cause of edema in nephrotic syndrome. For details see the Chapter on Kidney.

> Receptor Na^+ and water retention is not to be confused with option (a) Na^+ and water restriction.

4. **Ans. (d) The complex removes thrombin and also activates protein C which inactivates the activated factors V and VIII**
(Ref: Harrison 17th/364-5, Robbins 8th/116, 9/e p121)

5. **Ans. (a) IX, X** *(Ref:Robbins 8th/118-119 9/e p119)*

6. **Ans. (c) Cerebral microcirculation**
(Ref: Ganong 21st/546, Robbins 7th/85, Robbins 8th/116, Harrison 17th/365, 9/e p121)
*'All endothelial cells **except** those in the **cerebral microcirculation** produce thrombomodulin, a thrombin protein, and express it on their surface'.*

7. **Ans. (d) Thrombin**
(Ref: Robbins 7th/127, Harrison 17th/364, 9/e p120-121)

8. **Ans. (d) Secreted by WBC** *(Ref: Robbins 9/e p118)*
Thromboxane A2 (TXA2) is synthesized and released from activated platelets (Not WBCs)
- TXA_2 is also a powerful vasoconstrictor and bronchoconstrictor.
- Low does aspirin (50-325 mg) is used as antiplatelet drug because it inhibits COX irreversibly and decreases formation of TXA_2 by platelets.

9. **Ans. (d) Protein C resistance; (e) Dysfibrinogenemia** *(Ref: Harrison 16th/149l, 9/e p123)*

10. **Ans. (c) Von Willebrand factor (vWF)**
(Ref: Robbins 7th/125-126/129-130, 9/e p121,118)

> VWF (von Willebrand Factor) is produced by endothelial cells and it is required for platelet binding to collagen and other substances. So, it is a procoagulant factor.

11. **Ans. (a) Decreased plasma protein concentration**
(Ref: Robbins 8th/112; 7th/120-121, 9/e p114)

12. **Ans. (d) nNOS** *(Ref: Robbins 8th/60, 7th/72-73, 9/e p80)*

13. **Ans. (c) Vitamin K** *(Ref: Robbins 9/e p118-119)*

14. **Ans. (d) Factor VIII** *(Ref: Robbins 9/e p47-118)*

15. **Ans. (b) Decreased oncotic pressure**
(Ref: Robbins 8th/112, 9/e p114)
The patient in the stem of the question is most likely having liver cirrhosis secondary to chronic alcoholism. An important manifestation of this disease is reduced hepatic synthesis of albumin which is the most important contributor to plasma oncotic pressure. Also, ascites is associated with increased sodium and water retention because of stimulation of the renin-angiotensin aldosterone system (RAAS). A minor contribution is also because of hydrostatic forces (due to intra-hepatic scarring and partial obstruction of the portal venous return) resulting in fluid transudation and increased secretion of hepatic lymph.

16. **Ans. (c) Spleen** *(Ref: Harsh Mohan 6th/52)*
Gamna-Gandy bodies in chronic venous congestion (CVC) of the spleen is characterized by calcific deposits admixed with haemosiderin on fibrous tissue.

17. **Ans. (a) Prothromin time** *(Ref: Robbin 9/e p119)*

Prothrombin time	*Extrinsic pathway*	**Factor 5/7**
Activated partial thromboplastin time	*Intrinsic pathway*	**Factor 8**
Bleeding time	*Platelet function and platelet count*	**Platelet function and count**

18. **Ans. (a) Factor VII** *(Ref: Robbins 9/e p118)*
The extrinsic pathway is activated by tissue factor (thromboplastin) causing activation of factor VIIa. For details, refer to text.

19. Ans. (c) Von Willebrand factor *(Ref: Robbin 8/e p116-8)*
Direct lines.. *"Von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (Gp Ib) platelet receptor. Aggregation is accomplished by fibrinogen bridging GpIIb-IIIa receptors on different platelets."*

20. Ans. (c) Von Willebrand factor *(Ref: Robbins 9th/117)*
Direct quote .... "Platelet adhesion is mediated largely via interactions with vWF, which acts as a bridge between the platelet surface receptor glycoprotein Ib (GpIb) and exposed collagen."

21. Ans. (b) Thrombin *(Ref: Robbins 9th/119)*
Thrombin also stabilizes the secondary hemostatic plug by activating factor XIII, which covalently cross-links fibrin.

22. Ans. (d) Macrophages *(Ref: Robbins 9/e p116)*
- Example of tissue macrophages are Kupffer cells (liver), alveolar macrophages (lung), osteoclasts (bone), Langerhan's cells (skin), microglial cells (central nervous system)
- In the lung, alveolar macrophages can phagocytose the red blood cells that accumulate in alveoli in individuals with congestive heart failure. These cells contain hemosiderin and are referred to as "heart failure cells."

23. Ans. (a) Hepatic cirrhosis *(Ref: Robbins 9/e p530)*
The spleen shows the changes of chronic congestive splenomegaly, typically associated with hepatic cirrhosis. The described small scars are called Gandy-Gamma nodules which are due to the result of organization of old hemorrhages.

- ***Hodgkin's disease*** (choice B) produces large ***splenic nodules*** in which ***Reed-Sternberg cells*** can be found surrounded by mature lymphocytes, eosinophils, and neutrophils.
- ***Rheumatoid arthritis*** (choice C) and many other chronic inflammatory disorders induce reactive hyperplasia of the spleen with formation of many ***large germinal centers in the splenic follicles***.
- ***Sickle cell anemia*** (choice D) produces many ***small (often triangularly shaped) infarctions*** in the spleen.

24. Ans. (c) Pancytopenia
(Ref: Harrison 17th/1795, Robbins 8th/123,215, 7th/133, 229, 9/e p124-125)

Antiphospholipid antibody syndrome is characterized by antibodies against plasma proteins in complex with phospholipid. In **primary antiphospholipd antibody syndrome** there is hypercoagulable state without evidence of autoimmune disorders. In association with SLE or lupus, the name given is **secondary antiphospholipd antibody syndrome.** There is formation of antibody against **phospholipid beta– 2-glycoprotein 1 complex**Q. It also binds to cardiolipin antigen and lead to **false positive test for syphilis**Q. It also interferes with in vitro clotting time and so, called as lupus anticoagulant. In vivo, these patients have hypercoagulable state resulting in **arterial and venous thrombosis** resulting **spontaneous recurrent miscarriage** and focal or cerebral ischemia.

25. Ans. (a) Lungs *(Ref: Robbins 8th/128, 9/e p129)*
The Lungs have dual blood supply and so, they exhibit red infarct. The infarcts may be either red (hemorrhagic) or white (anemic) and may be either septic or bland.

All infarcts tend to be wedge shaped with the occluded vessel at the apex and the periphery of the organ forming the base. The infarct microscopically has features of **ischemic coagulative necrosis.**

26. Ans. (c) Anti-phospholipid antibody syndrome
(Ref: Robbins 8th/123, 9/e p123)
Anti-phospholipid antibody syndrome is an acquired causes of hypercoagulability

Hypercoagulable states

Primary (Genetics)	Secondary (Acquired)
• Mutations in factor V (Most common) • Antithrombin III deficiency • Protein C or S deficiency • Fibrinolysis defects • Homocysteinemia • Allelic variations in prothrombin levels • Mutations in the methyl tetra hydro folate (MTHF) gene	• Prolonged bed rest or immobilization • Homocysteinemia • Tissue damage (Surgery, fracture, burns) • Cancer • MI, Prosthetic cardiac valves • DIC (Disseminated intravascular coagulation) • Heparin induced thrombocytopenia • Antiphospholipid antibody syndrome

27. Ans. (b) Long bone fractures
(Ref: Robbins 8th/126, 9/e p128)

28. Ans. (b) Venous thrombosis
(Ref: Anderson 10th/387, Robbin's 7th/130, 9/e p122)
The factors that predispose to venous thrombosis were initially described by Virchow in 1856 and are known as **Virchow's triad**. These include:
• Stasis^{Q} • Vascular damage^{Q} • Hypercoagulability^{Q}

29. Ans. (b) Leiden mutation
(Ref: Robbins 7th/p131, Robbins 8th/122, 9/e p123)
- Mutation in factor V gene is caused by the substitution of glutamine for the normal arginine residue at position 506. It is known as **Leiden mutation and it is the most common inherited cause of hypercoagulability.**

Note: Lisbon mutation is associated with a mutation in **thyroid peroxidase gene**Q.

30. Ans. (a) Homocysteinemia; (b) Antiphospholipid syndrome *(Ref: Harrison 18th/462, 9/e p123)*

31. Ans. (a) Venous thrombosis; (b) Thrombosis; (d) Embolism *(Ref: Anderson's10th/2707)*
Hemorrhagic infarction is seen in:
- Hypercoagulable states (OCP use, pregnancy, polycythemia vera, malignancy, etc.)

- Embolism - Infarct is attributed to lysis of clot exposing infarct tissue and its permeable capillary bed to recirculating blood.
- Venous thrombosis.

32. Ans. (a) Cryoglobulinemia; (b) Multiple myeloma; (d) Lymphoma; (e) Macroglobulinemia
(Ref: William's Hematology 6/1268)

Hyperviscosity is seen in
- Multiple myeloma
- Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)
- Cryoglobulinemia
- Myeloproliferative disorders

MGUS (Monoclonal Gammopathy of uncertain significance): Here, M Protein can be identified in the serum of 1% of healthy individual >50 years of age and 3% in older than 70 yrs. It is the most common form of monoclonal gammopathy. In MGUS less than 3g/dL of monoclonal protein is present in serum and there is no Bence Jones proteinuria.

Normal viscosity of blood is 1.8

33. Ans. All. *(Ref: Harrison 16th- 686, Robbin's 7th/132)*
Dysfibrinogenemia produces hypercoagulable state and leads to thrombus formation in some patients. Other causes have already been discussed.

34. Ans. (a) Protein C deficiency; (b) Protein S deficiency; (c) Leiden factor mutation
(Ref: Harrison 16th/685; de Gruchy's 5th/420, Robbins 9/e p123)

Congenital coagulation disorders

- Hemophilia A and B
- von Willebrand's disease
- Fibrinogen absence or deficiency.
- Prothrombin absence or deficiency.
- Factor V deficiency.
- Factor VII deficiency.
- Factor X (Stuart) deficiency.
- Factor XII, XI deficiency.
- Factor XIII deficiency.
- Fitzgerald factor (HMWK) deficiency.

35. Ans. (c) Embolic obstruction of pulmonary vessels almost always cause pulmonary infarction *(Ref: Robbins 8th/126)*
As discussed is text, most pulmonary emboli (60% to 80%) are clinically silent because they are small. With time, they undergo organization and are incorporated into the vascular wall. Embolic obstruction of medium-sized arteries may result in pulmonary hemorrhage but usually does not cause pulmonary infarction because of the dual blood flow into the area from the bronchial circulation.

36. Ans. (c) Homocysteinemia
(Ref: Robbins 7th/131, 8th/122, Harrison 18th/462, 9/e p123)

Hyperhomocystenemia♀ is a mixed disorder (inherited as well as acquired♀) which can cause both venous and arterial thrombosis♀.

37. Ans. (b) Chronic venous congestion of lung
(Ref: Robbins 8th/535, 7th/122, 9/e p116)

38. Ans. (b) Gangrene *(Ref: Robbins 9/e p43, 129)*

39. Ans. (a) Thrombus *(Ref: Robbins 9/e p125)*

40. Ans. (a) Postmortem clot *(Ref: Robbins 9/e p125)*

41. Ans. (d) Coralline thrombus *(Ref: Robbins 9/e p125)*
Thrombi often have grossly and microscopically apparent laminations called **lines of Zahn**; these represent pale platelet and fibrin deposits alternating with darker red cell-rich layers. Such laminations signify that a thrombus has formed in flowing blood; their presence can therefore distinguish antemortem thrombosis from the bland non laminated clots occurring in postmortem clots.
In veins thrombi form coral-like system with framework of platelets, fibrin and trapped white blood cells; this is a coralline thrombus.

42. Ans. (a) Liver.....see explanation of earlier question....
(Ref: Robbins 8/e p128, 7/e p138)

43. Ans. (c) Heart *(Ref: Robbins 8/e p128, 9/e p129-130)*

44. Ans. (a) Fat embolism *(Ref: Robbins 9th/128)*
Presence of empty cells in the slide is consistent with the presence of fat in the slide. A patient who has met with a road traffic accident with fat cells in the lung histopathology is highly suggestive of fat embolism.

45. Ans (b) Mis-sense mutation *(Ref: Robbins 9/e p124)*
Factor V Leiden mutation is a **mis-sense mutation** resulting in glutamine to arginine substitution at amino acid residue 506 that renders factor V resistant to cleavage and inactivation by protein C.

46. Ans (a) Heart *(Ref: Robbins 9/e p125)*
Lines of Zahn are seen in thrombi and used for differentiating it from postmortem clots. Thrombi occurring in heart chambers or in the aortic lumen are designated **mural thrombi**. So, the best answer in the given question.

47. Ans. (c) Decreased prothrombin time
(Ref: Robbins 8th/674, 9/e p134, 664-665)

48. Ans. (b) Endothelial injury *(Ref: Robbins 9/e p131-132)*
The principle mechanisms for septic shock include:
- Peripheral vasodilation and pooling of blood
- Endothelial activation/injury
- Leukocyte-induced damage
- Disseminated intravascular coagulation
- Activation of cytokine cascades

If the question talks about the initiating mechanism, it should be preferably answered as cytokin release. If this option is not given then endothelial injury is the next best answer.
1. Thrombosis
2. Increase in vascular permeability
3. Vasodilation

The other three options are following this primary event of endothelial injury due to cytokine release.

49. **Ans. (b) Hepatitis B virus** *(Ref: Robbins 9th/832)*
Hepatitis B virus contains the pol gene. This exhibits both DNA polymerase activity and reverse transcriptase activity. Replication of the viral genome occurs via an intermediate RNA template, through a unique replication cycle: DNA → RNA → DNA.

50. **Ans. (d) Cytokines release** *(Ref: Robbins 9/e p132-133)*

51. **Ans. (a) Pulmonary embolism** *(Ref: Robbins 9/e p127)*
D-dimer is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two crosslinked D fragments of the fibrinogen protein. D-dimer concentration may be determined by a blood test to help diagnose thrombosis. D-dimer testing is of clinical use when there is a suspicion of **deep venous thrombosis** (DVT) or **pulmonary embolism** (PE). In patients suspected of disseminated intravascular coagulation (DIC), D-dimers may aid in the diagnosis.

52. **Ans. (d) Diffuse alveolar damage**
(Ref: Harrison 17th/1680-1681; Robbin's 7th/715, 9/e p134)

> *Shock lung is also known as acute respiratory distress syndrome, diffuse alveolar damage, acute alveolar injury and acute lung injury.*

53. **Ans. (a) ATN; (b) Pulmonary congestion; (c) Depletion of lipid in adrenal cortex and (d) Hepatic necrosis**
(Ref: Robbins 7th/141, 142, 9/e p134)
Shock is characterized by failure of multiple organ systems due to systemic hypoperfusion caused by reduction either in cardiac output or in effective circulating blood volume.

Liver → Fatty changes with hemorrhagic central necrosis.
Kidneys → Extensive tubular ischemic injury (Acute tubular necrosis).
Lungs → Pulmonary congestion with diffuse alveolar damage.
Adrenal → Cortical cell lipid depletion.
Brain → Ischemic encephalopathy.
Heart → Coagulation necrosis or contraction band necrosis.
GIT → Hemorrhagic enteropathy.

54. **Ans. (a) Abruptio placentae; (b) Acute promyelocytic leukemia; (c) Severe falciparum malaria (d) Snake envenomation; (e) Heparin overdose.**
(Ref: Robbins 7th/657, KDT 5th/562, 9/e p664-665)

55. **Ans. (b) Reduced plasma fibrinogen level**
(Ref: Robbins 7th/656-658, 9/e p664-665)

CHAPTER 4

Genetics

Golden Points

- *Approximate number of genes in human genome is* **30,000**.
- Coding DNA constitutes **only 2%** of the entire genome.
- Watson and Crick are associated with Double helical DNA model.
- **Fuelgen reaction** is for DNA.
- *Multifactorial inheritance is known for*: **cleft lip**, hypertension, *gout*, Cardiac septal defects, diabetes mellitus and coronary artery disease.
- Inheritance of *ABO blood group and HLA antigens* is **Codominance**
- **Autosomal dominant disorders** are characterized by expression in heterozygous state; they affect males and females equally, and both sexes can transmit the disorder. It affects receptors and **structural proteins**.
- **Autosomal recessive diseases** occur when both copies of a gene are mutated; **enzyme proteins** are frequently involved. Males and females are affected equally.
- **X-linked disorders** are transmitted by heterozygous **females to their sons**, who manifest the disease.
- **DiGeorge syndrome** (thymic hypoplasia with diminished T-cell immunity and parathyroid hypoplasia with hypocalcemia) and **Velocardiofacial** syndrome (congenital heart disease involving outflow tracts, facial dysmorphism, and developmental delay)
- *Down syndrome* is due to: Trisomy 21; it is *most commonly* caused by *:* Maternal non-disjunction in meiosis-I .
- *Patau syndrome karyotype*: Trisomy 13 (47 XX, + 13).
- *Edward syndrome karyotype*: Trisomy 18 (47 XX, + 18).
- *Increasing severity of mental retardation of male members over generations is due to* Triple repeat mutations (anticipation or dynamic mutation).
- ***Barr body** is **not** seen in females in the condition of* **Turner syndrome**.
- Gene regulate normal morphogenesis: Homeobox. This gene mutation is not cause ventricular septal defect.
- Defective DNA repair syndromes: Bloom syndrome, Fanconi anemia, Ataxia telangiectasia and Xeroderma pigmentosum.
- Genes involved in RETT syndrome: MECP2 (most common), FOXG1, CDKL5.
- Normal parents transmitting autosomal dominant disorders is usually due to: *Germ line (gonadal) mosaicism.* Seen with tuberous sclerosis and osteogenesis imperfecta.
- *Mother transmitting the disease to all children*: *Mitochondrial disorders.*
- **Genomic Imprinting:** The disorders associated with imprinting are also called as the ***parent-of-origin*** gene disorders. Examples include Prader Willi syndrome and Angelman syndrome.
- In **Prader- Willi syndrome:** deletion of **p**aternal chromosome 15 occurs with imprinting of maternal chromosome 15. Patients have mental retardation, short stature, hypotonia, hyperphagia, small hands and feet, and hypogonadism.
- In **Angelman syndrome:** deletion of maternal chromosome with imprinting of paternal chromosome 15. Affected patients have mental retardation, ataxia, seizures, and inappropriate laughter.
- Inheritance of both chromosomes of a pair from one parent is called ***uniparental disomy***. Angelman syndrome can also result from uniparental disomy of paternal chromosome 15.
- **Microarray'** is used for study of **multiple genes**.
- In-situ DNA nick end labelling can quantitate the fraction of cells in apoptotic pathway.
- **Comparative genomic hybridization** is for comparing **cancer cells and normal cells.**

Genetics is the study of the genes. Genes are a part of chromosome and they code for a trait or character. The position of gene on a chromosome is called as a **locus**. Out of a total number of 46 chromosome, 22 pairs of chromosomes are homologous and are called ***autosomes***. The 23rd pair is alike only in the females (have 2 similar X chromosomes) whereas in a male there is one X chromosome and one Y chromosome. The X and Y are therefore referred to as ***sex chromosomes***.

Key Point

The amount of the purine is equal with the corresponding pyrimidine which is called **Chargaff's rule.**

The genetic makeup of an individual is called genotype whereas the manifested physical feature is called as phenotype.

Key Point

The part of the DNA which is **ex**pressed is called **ex**on and the **int**ervening region is called **int**ron.

The Gene are made up of nucleic acids like ribonucleic acid; RNA or deoxyribonucleic acid; DNA. RNA is present only in the nucleus whereas DNA is present in both the nucleus and mitochondria of a cell. These nucleic acids are made up of nucleotides whose composition includes nitrogenous base, a sugar (deoxyribose in DNA and ribose in RNA) and a phosphate group. The nitrogenous base can be either a purine (adenine, guanine) or pyrimidine (thymine, cytosine, uracil). The purines bind with the pyrimidines complementarily.

Recent Exam Question

Human genome has nearly **20,000 protein** coding genes comprising about **1.5%** of the genome.

Alternate form of gene coding for different forms of a character is called allele. A normal gene has 2 alleles. When these code for same trait, it is known as homozygous state whereas if the alleles code for different traits, it is called heterozygous state.

If an allele manifests itself in a heterozygous state, it is called as dominant. The alternate allele which is unable to manifest itself in the heterozygous state is called as a recessive allele.

Key Point

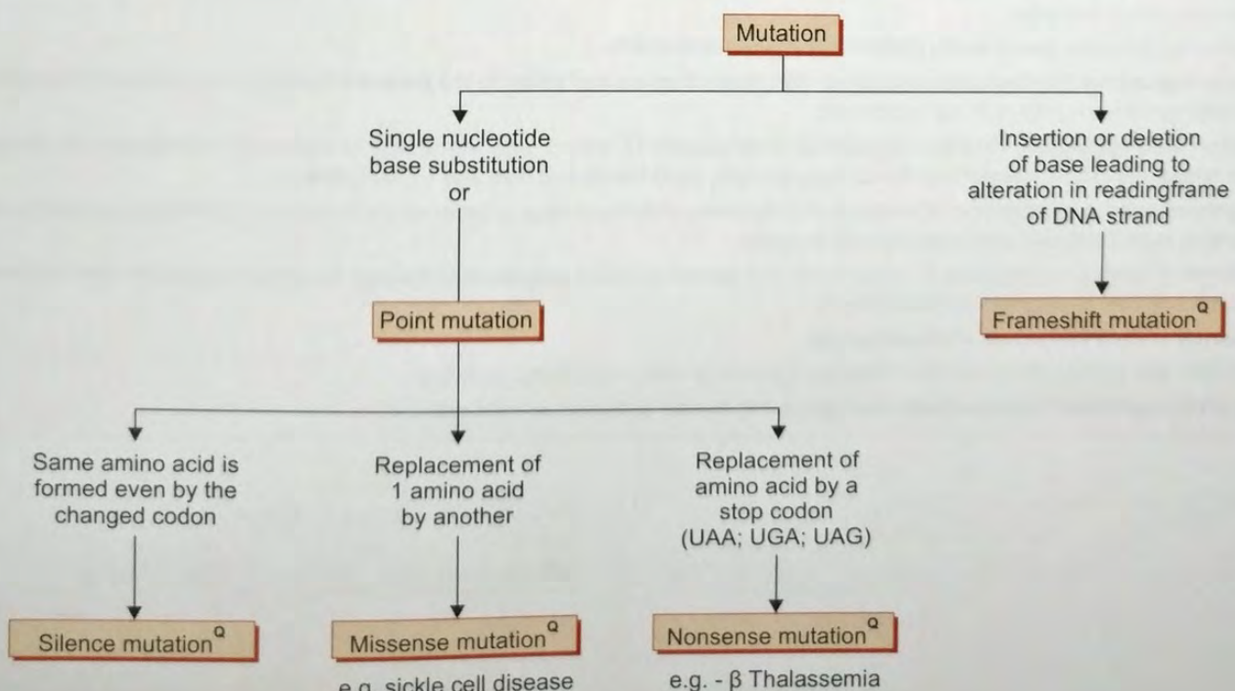
Mutation is a ***permanent*** change in the DNA. The types of the mutations are given alongside.

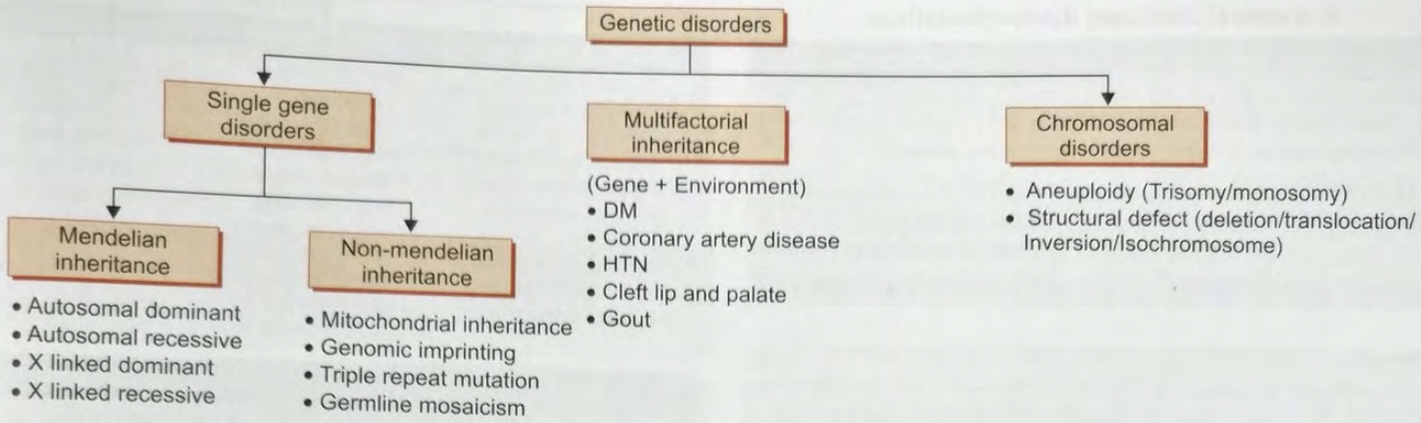
Recent Exam Question

Stop codons: ***(UAA; UGA and UAG)***

Gene	AA (homozygous state)	aa (homozygous state)	Aa (heterozygous state)
Net expression	A	a	A

(So, 'A' is Dominant and 'a' is Recessive)





Key Point

Blood group and histocompatibility antigens **(HLA)**are examples of ***co-dominant*** antigens.

SINGLE GENE DISORDERS WITH MENDELIAN/CLASSICAL INHERITANCE

a. Autosomal Dominant (AD) Inheritance Diseases

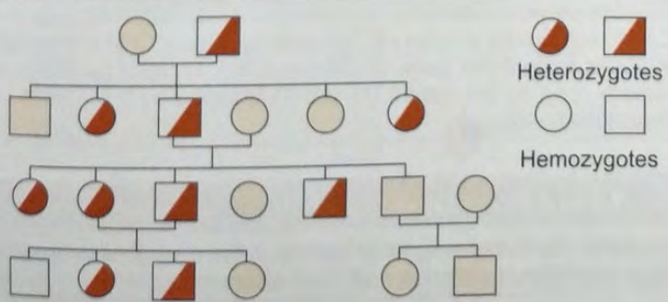
- Mutated genes can express themselves in *heterozygous state*.
- Usually cause defect in the synthesis of ***structural***[Q] **or non-enzyme** proteins.
- These have *variable onset* (so, onset may be into adulthood).
- These are characterized by **reduced penetrance**[Q] (individuals inherit the gene but can be phenotypically normal) and **variable expressibility**[Q] (the trait is seen in the individuals carrying the mutant gene but is expressed differently among individuals, e.g. patients of neurofibromatosis have variant from brownish skin spots to multiple skin tumors in different patients).

Key Point

In AD inheritance, heterozygotes with dominant mutant gene express disease.

Key Point

Homozygous individual for the dominant mutant gene usually die prenatally.



Recent Exam Questions

Autosomal dominant disorders

- Variable age of onset
- Reduced penetrance[Q]
- Variable expressibility[Q]

Examples of autosomal dominant disorders

Mnemonic

Vo Familial Hypercholesterolemia Autosomal DOMINANT Hai

Vo	**V**on Willebrand Disease[Q]
Familial	**F**amilial Adenomatous Polyposis[Q]
Hypercholesterolemia	Hypercholesterolemia (Familial)
Autosomal	**A**dult polycystic kidney[Q]
D	**D**ystrophia myotonica[Q]
O	**O**steogenesis imperfecta[Q]
M	**M**arfan syndrome[Q]
I	**I**ntermittent porphyria[Q]
N	**N**eurofibromatosis-1[Q]
A	**A**chondroplasia[Q]
N	**N**eurofibromatosis – 2[Q]
T	**T**uberous sclerosis[Q]
Hai	**H**untington's disease[Q]; ***H***ereditary spherocytosis[Q]

Key Point

Dominant negative mutant allele is associated with the more common **"loss of function"** mutation. Its clinical examples includes ***Osteogenesis imperfecta***, ***Ehler Danlos syndrome*** and ***Marfan's syndrome***.

There are the following types of autosomal dominant gene mutations:

Autosomal dominant disease mutations

Gain of function	Loss of function
Protein product of the mutant allele has properties not normally associated with the natural/wild-type protein	Leads to the reduced production of a gene product or give rise to an inactive protein
Less common	More common
Affects normal proteins with toxic properties	Affects regulatory proteins & subunits of multimeric proteins
e.g. ***Huntington's disease***	e.g. ***Osteogenesis imperfecta***

Concept

Dominant negative mutant allele is associated with the more common **"loss of function"** mutation. This type of mutation leads to not only reduced production of a gene product but the inactive polypeptide interferes with the functioning of a normall allele in a heterozygote. This usually affects structural proteins. At times, the inactive protein is a part of multiunit protein complex and it interferes with the normal functioning of other units of the same complex.

Example: **Osteogenesis imperfecta**

The collagen molecule is made up of triple helical molecule made up of three collagen chains arranged in a helical configuration. Each collagen chains in the helix must be normal for the normal assembly and stability of the collagen molecule. If there is a single mutant collagen chain, normal collagen trimers cannot be formed, and hence there is a marked deficiency of collagen.

Concept

In **Huntington's disease**, the protein formed ***huntingtin*** is different from normal protein by the fact that it is toxic to the neurons. So, **"gain of function"** mutation increases the amount of the toxic protein and hence, neurological features in the affected patients

SOME IMPORTANT AUTOSOMAL DOMINANT DISEASES

Marfan Syndrome

It is an autosomal dominant disease having mutation in the *fibrillin gene*[Q] on the chromosome 15q21. Fibrillin behaves as a scaffolding protein for the alignment of elastic fibers. So, any defect affects the following systems:

Key Point

Features of Marfan Syndrome

M	-	**M**itral Valve Prolapse
A	-	**A**ortic Aneurysm
R	-	**R**etinal Detachment
F	-	**F**reely movable joints (hyperextensible joints), **F**ibrillin protein defect.
A	-	**A**rachnodactyly
N	-	**N**ine feet height (very tall person)
Disease	-	**D**islocation of lens (Ectopia lentis)

Skeletal defects	CVS changes	Ocular changes
• Tall and thin built[Q] • Long and slender fingers and hands **(Arachnodactyly)**[Q] • **Hyperextensible joints** (especially thumb[Q]) • Inward depressed stemum **(Pigeon breast deformity**[Q]**)**	• Mitral valve prolapse causing **mitral regurgitaiton**[Q] • **Medial** degeneration causing dissecting aortic aneurysm and **aortic regurgitation**[Q].	• Bilateral dislocation or subluxation of the lens (know as **Ectopia lentis**[Q])

Recent Exam Question

Cause of death in **Marfan syndrome** is **Aortic dissection**. So, hypertension should be treated at the earliest in these patients.

Neurofibromatosis

Neurofibromatosis

NF-1 (von Recklinghausen Disease[Q])	NF-2 (Bilateral acoustic neurofibromatosis[Q])
• More common, seen in 90% patients[Q] • Presence of neural tumors of neurofibromas in the body which can be cutaneous, subcutaneous or plexiform • 6 or more pigmented skin lesions called 'cafe au lait' spots • Pigmented iris hamartoma called **Lisch Nodules**[Q] • Associated skeletal muscle defects like scoliosis, bone cysts or tibial pseudoarthrosis • Risk of development of meningioma, pheochromocytomas and Wilm's tumor[Q]	• Less common, seen in 10% patients • **Bilateral acoustic neuromas**[Q] • **Multiple meningioma**[Q] • Cafe au lait spot are present but **Lisch nodules are absent**[Q]

Note:

- *NF1 gene* is present on *chromosome 17*[Q] and its product called **neurofibromin** is a tumor suppressor gene which normally causes decreased activity of p21 ras oncoprotein.
- *NF2 gene* is present on *chromosome 22*[Q] and it normally produces **merlin** which is a protein causing contact inhibition of proliferation of Schwann cells.
- So, any mutation in NF1 or NF2 causes increased chances of tumor formation.

Mnemonic

Count the number of letters in 'neurofibromatosis'. It is 17, so, NF1 is due to mutation in gene on chromosome 17. NF2 gene can be remembered as two letters (N and F) followed by 2 (of NF2) i.e. chromosome 22.

Recent Exam Question

Juvenile myelomonocytic leukemia is the commonest leukemia seen in **children** suffering from **neurofibromatosis-1**

Ehler Danlos Syndrome (EDS)

It is an inherited tissue disease due to defect in collagen structure or synthesis. The clinical features include presence of hyperextensible skin (*cigarette paper skin*[Q]) which can be easily injured as it is fragile. There is also presence of *hyperextensible joints*. There are different variants of EDS having different modes of inheritance.

Key Point

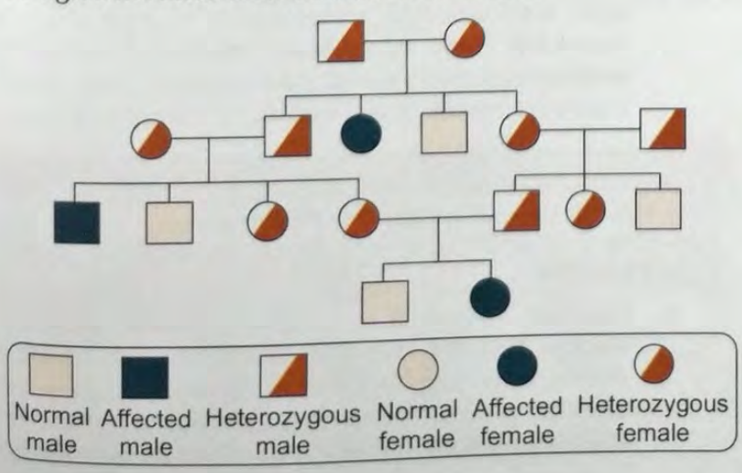
- **EDS type 3** is most **common** type
- **EDS type 4** is most **dangerous** type

EDS type 3 (Hypermobility type)	AD inheritance; presence of joint hypermobility; pain and dislocation
EDS type 4 (Vascular type)	AD inheritance; defect in collagen type III; presence of thin skin; easy bruising; arterial and uterine rupture, small joint hyperextensibility
EDS type 6 (Kyphoscoliosis type)	AR inheritance, mutation in the enzyme lysyl hydroxylase resulting in formation of unstable collagen; there is presence of hypotonia, joint laxity, congenital scoliosis and ocular fragility.

b. **Autosomal Recessive (AR) Inheritance Diseases**

- Mutant genes express themselves *only in Homozygous state.*[Q]
- Usually cause defect in the synthesis of an *enzyme protein.*[Q]
- These have an *early* uniform *onset*[Q] (usually in childhood).
- There is *complete penetrance*[Q] (persons having defective gene in homozygous state will have disease as well).
- *"Inborn errors of metabolism"* are usually inherited as autosomal recessive disorders.[Q]
- *If one parent is carrier and the other one is normal,* autosomal recessive disorders usually donot manifest but if an *affected baby* is born to such a couple, **Uniparental disomy (UPD)** should be suspected. UPD occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent.

Pedigree in Autosomal Recessive Disorders



Recent Exam Question

Autosomal Recessive is the *most common* **Mendelian** mode of inheritance.

Key Point

- In AR inheritance, both parents must have mutant gene.
- Most AR disorders involve enzyme deficiencies.

Concept

Uniparental disomy UPD should be suspected in an individual manifesting a recessive disorder, where only one parent is a carrier.

Mnemonic

- Examples of Autosomal Recessive Diseases
- Fried Poori aur Garam CHAWAL MAST Hai

Fried	**F**riedrich's ataxia[Q]
Poori aur	**P**henylketonuria[Q]
Garam	**G**alactosemia[Q]
C	**C**ystic fibrosis[Q]
H	**H**emochromatosis[Q]
A	α_1 – Antitrypsin deficiency[Q]
W	**W**ilson's disease[Q]
A	**A**lkaptonuria[Q]
L	**L**ysosomal and glycogen storage diseases[Q]
M	**M**uscular atrophy (both spinal as well as neurogenic)
A	**A**drenal hyperplasia[Q] (congenital)
S	**S**ickle cell disease[Q]
T	**T**halassemia[Q]
Hai	**H**omocystinuria[Q]

Some Important Autosomal Recessive Diseases

1. **Phenylketonuria (PKU):** It is caused by the deficiency of *enzyme phenylanine hydroxylase* resulting in inability to convert phenylalanine to tyrosine and resultant hyperphenylalaninemia. The clinical presentation is a child normal at birth but developing profound mental retardation by 6 months of age. The absence of tyrosine results in light-colored skin and hair. There is also presence of a *mousy or musty odor* to the sweat and urine *due to* secondary accumulation of a metabolite called *phenylacetate.*

Recent Exam Question

Phenylketonuria

- Phenylanine hydroxylase deficiency
- Mousy or musty odor of urine
- ↑ Increased urinary phenylacetate

The management is done by the dietary restriction of phenylalanine.

Key Point

Tyrosine becomes an ***essential*** amino acid in ***Phenylketonuria***

2. **Alkaptonuria (Ochronosis):** It is caused by the *deficiency of homogentistic acid oxidase* resulting in the accumulation of homogentistic acid. The latter has an affinity for connective tissues (especially cartilage), resulting in a black discoloration **(ochronosis)**. The clinical features include the passage of normal coloured urine (which turn black on exposure to air), black cartilage, discoloration of the nose and ears and early onset of degenerative arthritis.

Key Point

Vitamin C/ascorbic acid provide partial relief in alkaptonuria

3. **Glycogen Storage Diseases:** These are a group of rare diseases that have in common a deficiency in an enzyme necessary for the metabolism of glycogen, which results in the accumulation of glycogen in the liver, heart, and skeletal muscle. Some salient types include:

Type	Name of disorder	Enzyme deficiency
Type I	Von Gierke's disease	Glucose-6-phosphatase
Type II	Pompe's disease	Acid maltase
Type III	Cori's disease	Debranching enzyme
Type IV	Anderson's disease	Branching enzyme
Type V	McArdle's disease	Muscle phosphorylase
Type VI	Her's disease	Hepatic phosphorylase
Type VII	Tarui's disease	Phosphofructokinase 1 (PFK-1)

Mnemonic

Vo **P**hysics **C**hemistry **A**ur **M**aths mein **H**oshiyaar **T**ha is for different types of glycogen storage diseases in the exact order; For the enzymes see the first letter and remember the alphabets A→B (Anderson with Branching) and C→D (Cori with Debranching)

4. **Lysosomal Storage Diseases**

Disease	Enzyme deficiency	Accumulating substance
Tay-Sachs disease	Hexosaminidase A	GM2 ganglioside
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin
Gaucher disease	Glucocerebrosidase	Glucocerebroside
Fabry disease	α-Galactosidase A	Ceramide trihexoside
Metachromatic leukodystrophy	Aryl sulfatase A	Sulfatide
Hurler syndrome	α-1-Iduronidase	Dermatan sulfate Heparan sulfate
Hunter syndrome	L-Iduronosulfate sulfatase	Dermatan sulfate Heparan sulfate

Mnemonic

[Tarun Has Nine Shirts; Most Are Saffron, Few Are Green]

Disease		Deficiency	
Tarun	– Tay Sachs	Has	– Hexosaminidase
Nine	– Neimann Pick	Shirts	– Sphingomyelinase
Most	– Metachromatic leukodystrophy	Are Saffron	– Aryl Sulfatase
Few	– Fabry	Are Green	– Alpha Galactosidase

a. **Tay-Sachs Disease:** It is caused by the deficiency of the enzyme *hexosaminidase A* leading to *accumulation of GM2 ganglioside* in the lysosomes of the CNS and retina. It is common in *Ashkenazi Jews. Cherry red spot* is seen in the retina whereas dilated neurons with cytoplasmic vacuoles are seen in the CNS. The clinical presentation includes normal child at birth with onset of symptoms by 6 months. It is associated with progressive mental deterioration and motor incoordination and death by the age of 2-3 years. Electron microscopy shows the presence of distended lysosomes with whorled membranes.

Mnemonic

T **T**ay-Sachs Disease
A **A**utosomal recessive
Y **Y**oung Deaths (< 4 years)
S **S**pot in the macula (Cherry red spot)
A **A**shkenazi Jews (more commonly affected)
C **C**ytoplasmic vacuoles in dilated neurons in CNS
H **H**exosaminidase A deficiency
S **S**torage disease (Lysosomal)

b. **Niemann-Pick Disease:** It is caused by the deficiency of the enzyme *sphingomyelinase* leading to the accumulation of sphingomyelin within the lysosomes of the CNS and reticuloendothelial system. It is also commoner in Ashkenazi Jews. There is presence of a retinal *cherry-red spot* and CNS having distended neurons with a foamy cytoplasmic vacuolization. The clinical presentation includes normal child at birth with onset of symptoms by 6 months. It is associated with progressive *massive splenomegaly, lymphadenopathy, mental deterioration and motor manifestations* resulting in death by the age of 2 years.

Key Point

Electron microscopy in **Niemann-Pick's disease** shows the presence of distended lysosomes containing lamellated figures (**"zebra bodies"**).

c. **Gaucher Disease:** It is the **most common lysosomal storage disorder** caused by the *deficiency of glucocerebrosidase* leading to the accumulation of glucocerebroside predominantly in the lysosomes of the reticuloendothelial system. It is characterized by the

presence of *hepatosplenomegaly, hypersplenism* leading to thrombocytopenia/pancytopenia, *lymphadenopathy and bone marrow involvement* leading to bone pain, deformities, and fractures. A subgroup of patients may also have CNS manifestations.

Key Point

- Microscopically cells show the presence of **Gaucher's cells** which are enlarged macrophages with a fibrillary **(crumpled tissue-paper-like) cytoplasm.**
- **Pseudo Gaucher's cell:** In **bone marrow of CML patients.**

d. **Mucopolysaccharidosis (MPS):** These are a group of lysosomal storage disorders characterized by deficiencies of the lysosomal enzymes required for the degradation of mucopolysaccharides (glycosaminoglycans). The clinical features of the patients include *mental retardation, cloudy cornea, hepatosplenomegaly, skeletal deformities and coarse facial features, joint abnormalities and cardiac lesions.*

Mnemonic

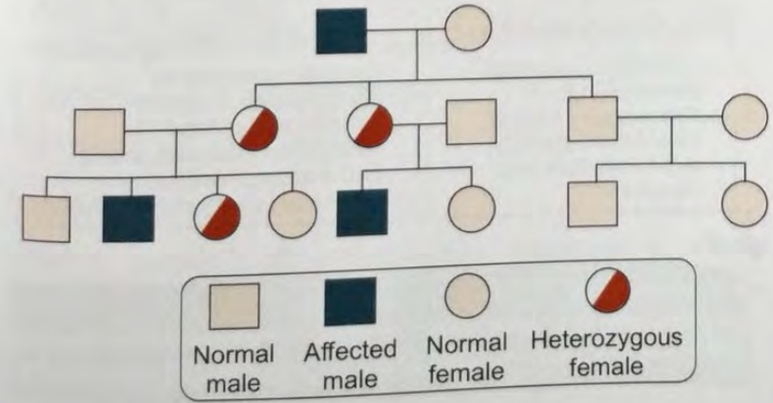
Most of the metabolic disorders have autosomal recessive inheritance *except:*

Her – **H**unter syndrome (X-linked recessive)
Left – **L**esch Nyhan syndrome (X-linked recessive)
Eye – **O**cular albinism (X-linked recessive)
Has – **H**ypercholesterolemia (familial) (Autosomal Dominant)
Five – **F**abry's disease (X-linked recessive)
Pimples – **P**orphyria [Acute intermittent] (Autosomal Dominant)

Remember the hunter has an a**xe**/**X**.

X-LINKED RECESSIVE DISORDER

Males have an X and a Y chromosome. There is no corresponding locus for a mutant allele of the X chromosome on the Y chromosome. The mutant recessive gene on the X chromosome expresses itself in a male child because it is not suppressed by a normal allele whereas in the female, the presence of a normal allele on other X-chromosome prevents the expression of the disease. So, *females only act as carriers.*[Q]



Mnemonic

Examples of X-linked recessive disorder can be remembered by the following line
Less **hCG** is **D**etected **C**linically in **A** **F**ragile **W**oman

Examples of X-linked recessive disorders

Less	**L**esch-Nyhan syndrome[Q]
H	**H**emophilia A and B[Q]; **H**unter syndrome[Q]
C	**C**hronic granulomatous disease[Q]
G is	**G**6PD deficiency[Q]
Detected	**D**uchhene muscular dystrophy[Q], **D**iabetes insipidus[Q]
Clinically in	**C**olor blindness[Q]
A	**A**gammaglobulinemia[Q] (*Bruton's disease*)
Fragile	**F**ragile X syndrome[Q], **F**abry Disease[Q]
Woman	**W**iskott Aldrich syndrome[Q]

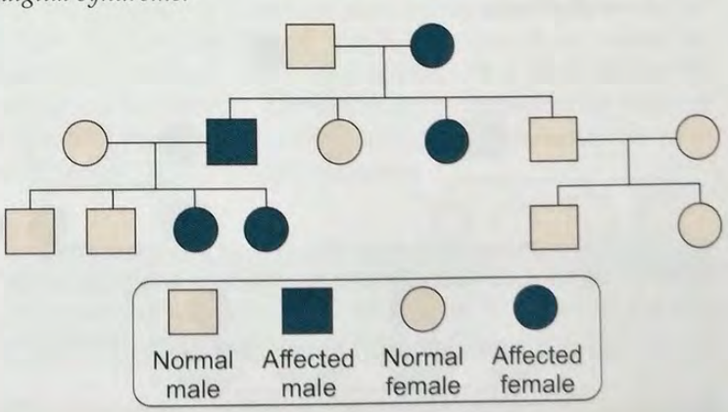
Key Point

In XR inheritance, asymptomatic female carrier transmits mutant gene to 50% of sons.

X-LINKED DOMINANT DISORDERS

These are the conditions in which both heterozygous males and females are affected. All the sons of the affected male are normal and all the daughters are affected. The affected female transmits the disease to half of the sons and daughters.

Examples: *Hypophosphatemic type of vitamin D resistant rickets; Incontinentia pigmenti, Alport Syndrome and oro-facio-digital syndrome.*



SINGLE GENE DISORDERS WITH NON-MENDELIAN INHERITANCE

Non-Mendelian Inheritance can be classified into the following categories:

A. Mitochondrial inheritance
B. Genomic Imprinting
C. Triple Repeat Mutations
D. Germline Mosaicism

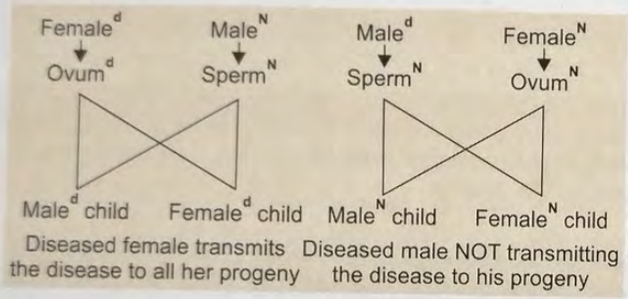
A. MITOCHONDRIAL INHERITANCE

Mutation in the mitochondrial DNA has the characteristic feature of **maternal inheritance**Q because the ovum contains the mitochondria with their abundant cytoplasm whereas sperms contains minimal number of mitochondria. The fertilized oocyte degrades mtDNA carried from the sperm in a complex process involving the ubiquitin proteasome system. So, while mothers transmit their mtDNA to both their sons and daughters, only the daughters are able to transmit the inherited mtDNA to future generations.

Key Point

All offspring of an affected female will be having the disease and all daughters transmits the disease further to their progeny.

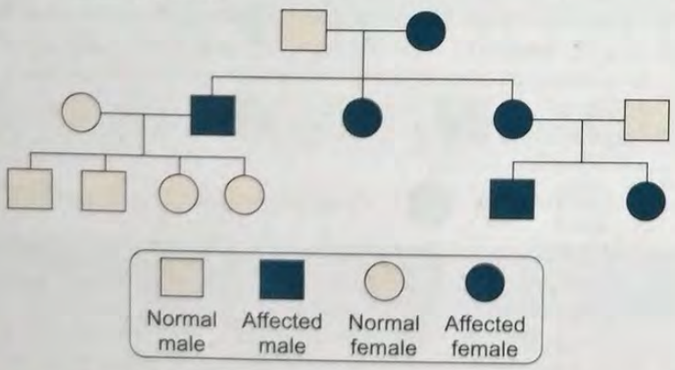
Affected sons **do not** transmit the disease to progeny



Recent Exam Question

Mitochondrial inheritance is governed by **Population genetics principle** and not by Mendelian genetics.

- d denotes diseased whereas N denotes normal individuals.



Recent Exams Questions

Examples of mitochondrial inheritance

- **Leber's optic neuropathy**
- **Leigh's disease**
- **MELAS** (**m**itochondrial **e**ncephalopathy, **l**actic **a**cidosis and **s**troke like syndrome)
- **NARP syndrome** (**N**europathy, **a**taxia, and **r**etinitis **p**igmentosa.)
- Kearns-Sayre syndrome
- Chronic progressive external ophthalmoplegia
- Pearson syndrome.

Salient features of these diseases

- The **organs most commonly affected** in these diseases are the ones having large number of mitochondria inside them. Such organs include **CNS, skeletal muscle, cardiac muscle, liver and kidneys**.
- Tissues may have both normal/wild and mutant mitochondrial DNA.
- ***Sons do not transmit the disease to progeny***Q

B. GENOMIC IMPRINTING

Definition

Genomic imprinting is defined as differential expression of a gene based on chromosomal inheritance from maternal or paternal origin

A person gets two alleles for a character; one from mother and second from father. Normally these two alleles are similar. But, in some cases these alleles are differentially expressed. i.e. either maternal gene become silent (only paternal gene express) or paternal gene become silent (only maternal express). In such a condition, if the chromosome containing the gene which is expressed undergoes deletion, there will be disease, whereas if homologous undergoes deletion, nothing will happen.

Recent Exams Questions

- **Ghrelin** is the ***only gut hormone*** to have **orexigenic** (↑increased food intake) property.
- **Prader-Willi syndrome** patients have **increased** levels of **ghrelin**.

Example of genomic imprinting disorder is microdeletion of chromosome 15q11-13. If microdeletion occurs in maternal chromosome; Angelman syndrome results whereas paternal chromosomal microdeletion may cause Prader-Willi syndrome.

It is also seen in *Beckwith-Wiedmann syndrome* and *Albright's hereditary osteodystrophy*.

Mnemonic

P for **p**aternal and **P**rader Willi whereas **m** for **m**aternal and **m** is present in Angel**m**an

Prader-Willi syndrome Q	Angelman syndrome Q
• Deletion on paternal Q chromosome 15 • Presence of mental retardation, obesity; hypogonadism and hypotonia	• Deletion on maternal Q chromosome 15 • Presence of mental retardation, seizures, ataxia and inappropriate laughter (so, called as 'happy puppets')

Mnemonic

Mom wears **SARI** – it stands for **S**eizures, **A**taxia, **R**etardation and **I**nappropriate laughter

- Molecular studies of cytogenetically normal patients with Prader Willi syndrome reveal that they have two maternal copies of chromosome 15.
- Inheritance of both chromosomes of a pair from one parent is called uniparental disomy. So, Prader Willi Syndrome may be due to UPD of maternal chromosome 15.
- Similarly Angelman syndrome patients might have uniparental disomy of paternal chromosome 15.

Mnemonic

Chromosome 15 has its own **MAP**, so diseases associated with this chromosome are **M**arfan syndrome, **A**ngelman syndrome and **P**rader-Willi syndrome.

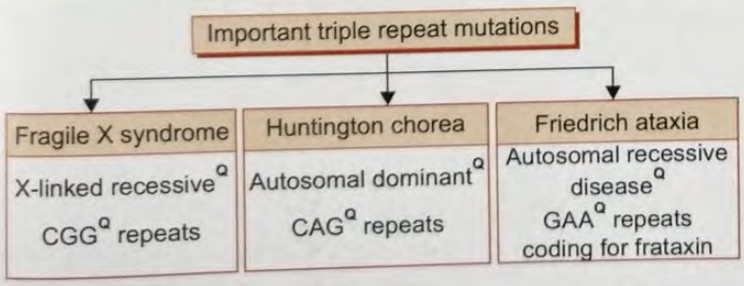
C. TRIPLE REPEAT MUTATIONS

The mutation in this disease group is characterized by a long repeating sequence of three nucleotides. It is characteristically different from other types of mutations because it is **dynamic** in nature. Dynamicity means that the **degree of amplification** of a sequence of three nucleotides **increases during gametogenesis**.

Trinucleotide repeat disorders

Expansions in non-coding regions	Expansions in coding regions
"Loss of function" type mutation	***"Gain of function"*** type mutation
Mutant proteins aggregate as intranuclear inclusions	Mutant proteins interfere with other proteins
Examples: • Fragile X syndrome[Q] • Friedrich's ataxia[Q] • Myotonic dystrophy[Q]	*Examples:* • Huntington's disease[Q] • Spinobulbar muscular atrophy[Q] (Kennedy's disease) • Spinocerebellar ataxia types 1, 2, 3, 6, 7[Q]

The ***trinucleotide repeat expansions*** in the ***non-coding regions*** involve different repeats as ***Fragile X syndrome (CGG[Q])***, ***Friedrich's ataxia (GAA[Q])*** and ***Myotonic dystrophy (CTG[Q])***.



Fragile X Syndrome

There is presence of triplet repeat mutations of **CGG** nucleotides. The mutation affects the *FMR-1 gene* (Familial Mental Retardation – 1 gene) present on the X chromosome. On karyotyping, the chromosome appears as broken (so, called fragile site). It is the *second most common* cause of mental retardation (*Down syndrome is the commonest cause*). The clinical features of patient include *long face with a large mandible, large everted ears and large testicles* (*macro-orchidism*).[Q]

Recent Exam Question

Commonest cause of mental retardation is **Down syndrome** followed by ***Fragile X Syndrome***.

In the normal people, the number of CGG repeats is from 10 to 55. There is amplification of CGG repeat in carrier females to 55-200 CGG repeats which is called *premutation*. In diseased individuals, the CGG repeats range from 200-4000 repeats called *full mutations*. During the process of oogenesis (*Not spermatogenesis*), amplification causes conversion of premutations to full mutations. This is responsible for **Sherman's Paradox**[Q] (the risk of mental retardation is much higher in grandsons than the brothers of transmitting males as the grandsons acquire a premutation from their grandfather which gets amplified to a mutation in their mother ova).

Mnemonic

In Anticipation, additional trinucleotide repeats cause worsening of clinical features with each successive generation.

- Southern blot is useful for genetic counseling (it can differentiate between premutation and mutation prenatally and postnatally).

Key Point

PCR is the method of choice for diagnosis of fragile X syndrome

Huntington's Chorea

There is presence of **CAG** repeats associated with chromosome 4 that are responsible for the production of an abnormal neurotoxic protein called **Huntington**[Q]. It is associated with *caudate nucleus atrophy*. Clinical features include early onset of *progressive dementia* and presence of *choreiform movements* (due to inhibition of GABAergic neurons).

Mnemonic

A Hunter puts an animal in a **CAG** that has **FOUR** sides, four for association with **chromosome 4.**

Concept

It describes the **genetic effect of a single gene on multiple phenotypic traits**. The underlying mechanism is that the gene codes for a product that is used by various cells, or has a signaling function on various targets. A classic example of pleiotropy is the human disease **phenylketonuria**.

Antagonistic pleiotropy refers to the expression of a gene resulting in multiple competing effects, some beneficial but others detrimental to the organism. An example is the p53 gene, which suppresses cancer, but also suppresses stem cells, which replenish worn-out tissue.

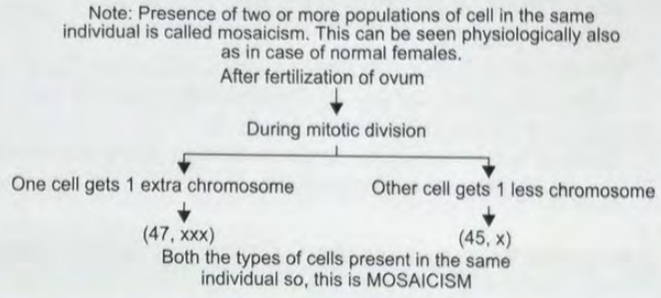
D. GONADAL/GERMLINE MOSAICISM

Normally autosomal dominant disorders have affected parents but in some patients with autosomal dominant disorders, the parents are not affected. In such patients, the disorder results from a new mutation in the egg or the sperm from which they were derived; as such, their siblings are neither affected nor at increased risk of developing the disease.

However, in certain autosomal dominant disorders, exemplified by **osteogenesis imperfecta**[Q] and **tuberous sclerosis**[Q], phenotypically normal parents have more than one affected child. This may appear to clearly violate the laws of Mendelian inheritance but is explained by gonadal mosaicism.

Gonadal mosaicism results from a mutation that occurs postzygotically during early (embryonic) development. If the mutation affects only cells destined to form the gonads, the gametes carry the mutation, but the somatic cells of the individual are completely normal. Such an individual is said to exhibit ***germ line*** **or** ***gonadal mosaicism***. A phenotypically normal parent who has germ line mosaicism can transmit the disease-causing mutation to the offspring through the mutant gamete. Since the progenitor cells of the gametes carry the mutation, there is a definite possibility that more than one child of such a parent would be affected. **Gonadal mosaicism should not be confused with mosaicism (explained below).**

MOSAICISM



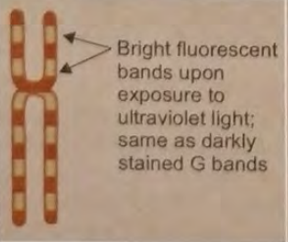
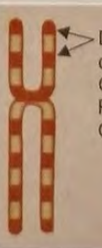
CHROMOSOMAL DISORDERS

Study of chromosomes is called **karyotyping.** It is done in cells like skin fibroblasts, peripheral blood lymphocytes and amniotic cells. The normal number of chromosomes in a somatic cell is diploid and is expressed as 46, XX or 46, XY.

Key Point

A ***karyotype*** is a standard arrangement of a photographed or image stained chromosome pairs in ***metaphase*** stage in *order of decreasing length*.

- Mitosis is arrested in dividing cells in **metaphase stage** by use of colchicine. In this stage, individual chromosomes take the form of two chromatids connected at the centromere. The Short arm of chromosome is called "**p**" (petite) and long arm is reffered to as "**q**".

Banding technique and selected features				
	Q banding	**G banding**	**R (Reverse) banding**	**C banding**
Dye used	Quinacrine mustard	Trypsin followed by Giemsa	Alkaline solution followed by Giemsa	Chemical followed by Giemsa
Microscope used	Fluorescence microscopy	Light microscopy	Light microscopy	Light microscopy
Special features	*Temporary So, not used[Q] for routine cytogenetic analysis	*Permanent ***MC technique[Q] for routine cytogenetic analysis**	*Used for analyzing rearrangements involving the terminal ends[Q] of chromosomes *Gives pattern opposite to G banding	*Used for studying chromosomal translocations involving centromeric regions[Q]
Appearance of chromosomes	 Bright fluorescent bands upon exposure to ultraviolet light; same as darkly stained G bands	 Darly stained G bands	 Darkly stained R bands correspond to light bands in G-banded chromosomes. Pattern is the reverse of G-banding	 Darkly stained C band centromeric region of the corresponds to region of constitutive heterochromatin

Note: Q, G and R banding produce bands along entire length of chromosomes whereas for specific chromosomal structures, other types of banding may be used. Some of these include **T- banding** (for **T**elomeres), **C banding** (for **C**onstitutive heterochromatin) and **NOR-banding** (for **n**ucleolus-**o**rganizing **r**egions).

Sometimes, fluorodeoxyuridine (FUdR)[Q] banding is also done. It is a direct inhibitor of thymidylate synthetase and it can induce folate-sensitive fragile sites in chromosomes. Chromosomal fragile sites can induce mental retardation as is seen in fragile X syndrome[Q].

Recent Exam Question

Chromosomes are visualized with a **light microscope** having **resolution of 5 Mb**.

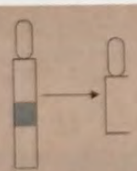
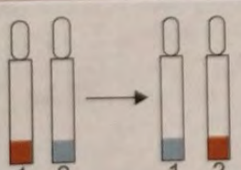
TYPES OF CHROMOSOMES

Metacentric	Centromere is in the center of the chromosome (the chromosome has two equal arms).
Submetacentric	Centromere is away from the center so that the arms are unequal in size (one arm shorter than the other). .
Acrocentric	Centromere is almost at the tip (one end) of the chromosome (one arm is much longer than the other).
Telocentric	Centromere is at the extreme end of the replicating chromosome (chromosome has only one arm). Not seen in humans[Q].

Recent Exam Questions

- **X chromosome** is large **submetacentric**[Q] chromosome
- **Y chromosome** is small **acrocentric**[Q] chromosome

CYTOGENETIC ABNORMALITIES

	Deletion (Loss of genetic material)
	Balanced translocation

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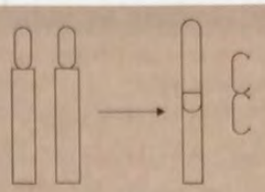
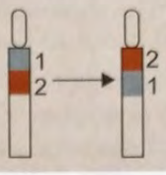
	**Robertsonian translocation** – Translocation between the 2 acrocenteric chromosomes with breakpoint occurring close to the centromeres. So, very large and very small chromosomes are obtained. The ***small chromosomes are usually lost***.
	Inversion

- The gametes contain half the number of chromosomes (haploid) and are represented as (23, X) or (23, Y).

Recent Exam Questions

- **DNA fingerprinting** utilizes identification of **"Banding patterns"**.
- **Colin Pitchfork** was convicted by ***DNA fingerprinting*** technique *discovered* by ***Alec Jeffrey.***

Recent Exam Questions

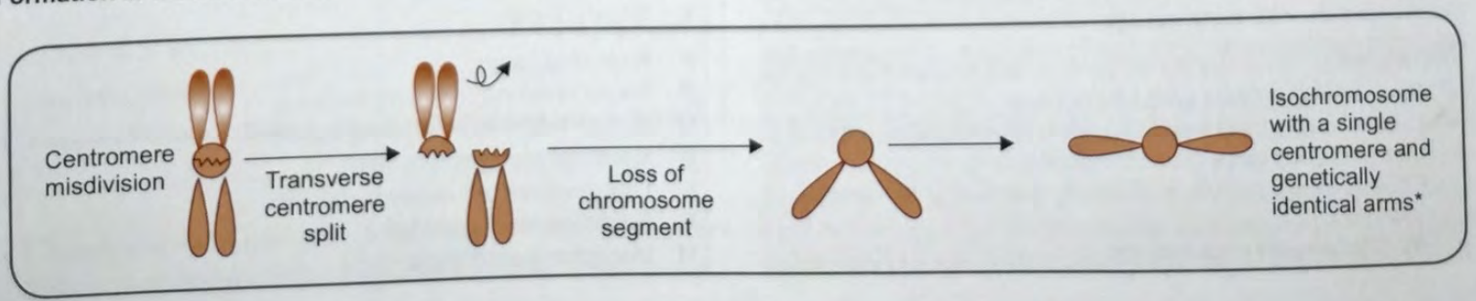
- Insertion, Deletion and Robertsonian translocation are associated with change in genetic material.
- Unlike the above mentioned, **inversion** is **NOT** associated with change in genetic materials

Isochromosome

Isochromosome formation results when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of two short arms only or of two long arms. It has morphologically identical genetic information in both arms.

- The reason for the formation of an isochrome is the centromere misdivision. Instead of ***dividing longitudinally to separate the two sister chromatids, the centromere undergoes a transverse split that separated the two arms from one another.***

Formation of isochromosome

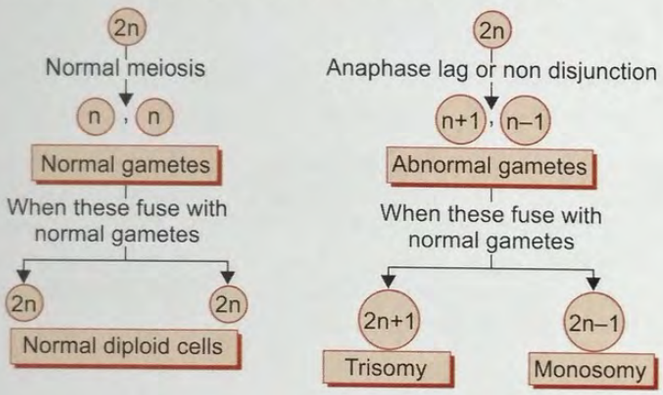


Recent Exam Questions

- **Isochromosome** is formed by division of a chromosome in an ***axis perpendicular to usual axis of division***.
- **Isochromosome 12p** is associated with **testicular germ cell cancer**.

- An exact multiple of haploid chromosomes is called **Euploidy** (2n, 3n, 4n … etc).
- When exact multiple of haploid chromosomes is not present, it is called **Aneuploidy**.

Genome mutations involve loss or gain of whole chromosomes, giving rise to monosomy or trisomy.



DOWN SYNDROME (TRISOMY 21)Q

- It is the most common of the chromosomal disorders[Q] and a major cause of mental retardation.[Q]

Concept

Mitotic non-disjunction is responsible for development of mosaicism.

- Genetics of Down syndrome.

Meiotic nondisjunction of chromosome 21 occuring in the ovum

- Seen in ***95% cases*** with trisomy 21. So, it is the ***commonest cause*** of Down syndrome
- The extra chromosome is of ***maternal origin***.
- ***Strong relation with maternal age***

Robertsonian translocation

- Seen in about ***4% of cases*** of Down syndrome.
- The extra chromosomal material derives from the presence of a robertsonian translocation of the long arm of chromosome 21 to another acrocentric chromosome (e.g., 22 or 14).
- Most cases are frequently (but not always) familial.
- ***No relation with maternal age***

Mosaicism

- Seen in ~1% of Down syndrome patients
- Results from ***mitotic nondisjunction of chromosome 21*** during an early stage of embryogenesis.
- Patients have a mixture of cells with 46 and 47 chromosomes (mosaicism).
- ***No relation with maternal age***.

Recent Exam Question

Most common cause of Down syndrome is **maternal meiotic non-disjunction**.

- **Important signs of the disease include:**
  - Flat facial profile
  - Mental retardation
  - Microgenia (abnormally small chin)
  - Oblique palpebral fissures with epicanthic skin folds (**mongoloid slant**)
  - Muscle **hypotonia** (poor muscle tone)
  - Flat nasal bridge
  - Single palmar fold (**Simian crease**)
  - Curvature of little finger towards other four fingers (**Clinodactyly**)
  - Protruding tongue or macroglossia
  - White spots on the iris known as **Brushfield spots**
  - Excessive joint laxity including atlanto-axial instability
  - Excessive space between large toe and second toe (**Sandle toe**)
  - A single flexion furrow of the fifth finger
  - Higher number of ulnar loop dermatoglyphs

Key Point

- *Advance maternal age* has a strong influence on the incidence of *trisomy 21* whereas it is not related to advanced paternal age.
- Down syndrome associated with ***Robertsonian translocation*** and ***Mosaicism*** has *no relation with maternal age*.

Mnemonic

Features of Down Syndrome

Micro **Mental Retardation/Micrognathia**

C **Congenital heart disease/Cataracts**
H **Hypotonia/Hypothyroidism**
I **Increased gap between 1st and 2nd toe (Sandle toe)**
L **Leukemia risk/Lung problem (↑ risk of Respiratory Infections)**
D **Duodenal atresia**

H **Hirshsprung's disease/Hearing loss**
A **Alzheimer's disease/Atlantoaxial instability**
S **Simian Crease**

P **Protruding tongue**
R **Round face/Rolling eye (nystagmus)**
O **Occiput flat/Oblique palpabrel fissure**
B **Brushfield spot/Brachycephaly**
L **Low nasal bridge/Language problem**
E **Epicanthic fold/Ear folded**
M **Mongolian slant/Myoclonus**

Key Point

Down syndrome patients are having predisposition for **Hirschprung's disease, duodenal atresia, annular pancreas** and **Alzheimer's disease**

Recent Exam Questions

Complications of Down syndrome are

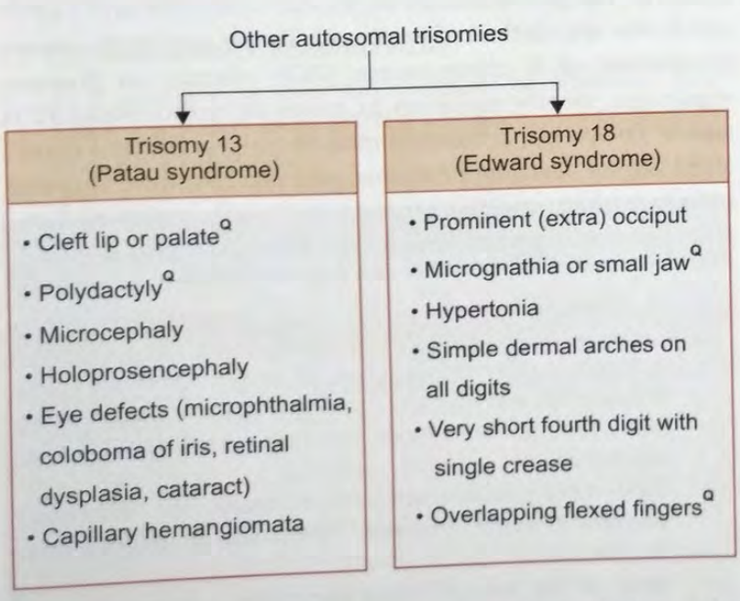
- Congenital cardiac defects (Most common is **ventricular septal defect**)
- Increased risk of leukemia particularly **ALL (more commonly)** and specifically the ***megakaryoblastic form of AML*** (M7-AML)
- Hypothyroidism
- Reduced fertility in females (Males are totally infertile)
- Increased risk of respiratory tract infections

Screening for Down Syndrome

Many standard prenatal screens can discover Down syndrome. Amniocentesis and chorionic villous sampling (CVS) are considered invasive procedures, in that they involve inserting instruments into the uterus, and therefore carry a small risk of causing fetal injury or miscarriage. The risks of miscarriage for CVS and amniocentesis are often quoted as 1% and 0.5% respectively. There are several common non-invasive screens that can indicate a fetus with Down syndrome. These are normally performed in the late first trimester or early second trimester. Due to the nature of screens, each has a significant chance of a false positive, suggesting a fetus with Down syndrome when, in fact, the fetus does not have this genetic abnormality. Screen positives must be verified before a Down syndrome diagnosis is made. Common screening procedures for Down syndrome are given in the table below.

First and second trimester Down syndrome screens

Screen	When performed (weeks gestation)	Detection rate	False positive rate	Description
Triple test	15-20	70%	5%	Maternal serum α-feto protein (Low) + Estriol (Low) + hCG (High)
Quad screen	15–20	81%	5%	Triple test + inhibin-Alpha (High)
First Trimester Combined Test	10–13	85%	5%	Ultrasound to measure: *Nuchal Translucency (Increased) *Ductus venosus flow (reversed) *Nasal bone (hypoplasia) + hCG + Pregnancy associated plasma protein A; PAPPA (Low)
Integrated Test	10-13 and 15–20	95%	5%	Measurements from both the 1st Trimester Combined test and the 2nd trimester Quad test to yield a more accurate screening result.



Common features of both are *mental retardation, rocker bottom feet and congenital heart defects (VSD and PDA).*

Mnemonic

- Ectodermal scalp defects, cleft lip and cleft palate points towards diagnosis of trisomy 13 whereas elongated skull and simple arches on all digits suggest trisomy 18.
- **(Mnemonic: p** for **P**atau and **p**olydactyly as well as **p**alate defects and **e** for **E**dward and **e**xtra occciput).

Key Point

- All three components of triple test i.e. MSAFP, Estriol and hCG are low in Edward syndrome.
- **MSAFP** is ***increased*** in ***neural tube defects*** whereas *reduced* in *Down* and *Edward* syndromes.

TRISOMY 22

Cat Eye Syndrome is a rare condition caused by the **partial trisomy of chromosome 22** (The short arm (p) and a small section of the long arm (q) of Chromosome 22 is present three instead of the usual two times. The term "Cat Eye" syndrome was coined due to the particular appearance of the **vertical colobomas** in the eyes of some patients.

Key Point

Vertical colobomas are seen in the eyes of patient having ***cat eye syndrome***.

Klinefelter Syndrome

- *It is the most common chromosomal disorder of males associated with hypogonadism and infertility.*
- It is due to extra-X-chromosome. Classically, it is **47, XXY**. Other variants can have 48 XXXY, rarely 49 XXXY or mosaics can be there with some cells containing normal 46, XY and others 47, XXY.
- Classically, it results from **meiotic non-disjunction** of sex chromosomes [40% during spermatogenesis and 60% during **oogenesis**]. Mostly, non-disjunction occur during **1st meiotic division**.
- Extra X- chromosomes increase the **female like features,** i.e. feminization [as shown by atrophic testes, lack of secondary sexual characteristics, gynecomastia]. Further, Extra inactive X-chromosome appear as **Barr body**
- Presence of single Y-chromosome is enough for male phenotype. Thus XY, XXY, XXXY all are males.

Key Point

In Klinefelter's syndrome, there is ↓ testosterone and inhibin but ↑ LH and FSH, respectively

Clinical Features of Klinefelter Syndrome

- Male sex
- Hypogonadism
- Loss of secondary sexual characteristics
- **Subnormal IQ**
- Disproportionately long arms and legs
- Gynecomastia
- There is increased risk of breast carcinoma, germ cell tumors (like embryonal cell carcinoma, teratoma and mediastinal germ cell tumors) and autoimmune diseases like SLE.
- Patients can develop cardiovascular problems. **Most commonly associated is mitral valve prolapse** followed by varicose veins.
- Due to less testosterone (hypogonadism), feedback inhibition is less and pituitary produces **more LH and FSH**.

Turner Syndrome

- *Most common cause of sex chromosomal abnormality in the females.*[Q]
- Usually results from complete or partial monosomy of X chromosome and associated with hypogonadism in phenotypic females.[Q] Patients have the (45X) karyotype or may be mosaics.

Recent Exam Question

Autoimmune thyroiditis is not associated with Marfan syndrome. It is seen with *Down syndrome, Turner syndrome* and *Congenital rubella syndrome*

- *Clinical features in infancy* include **edema of dorsum of hands and feet,**[Q] neck webbing or edema of nape of neck (also produces **cystic hygroma**[Q]) and **congenital cardiac defect** (particularly **preductal coarctation of the aorta**[Q] and **bicuspid aortic valve**[Q]).
- *Clinical features in adolescence and adulthood* include short stature, low posterior hairline, webbing of neck, **cubitus valgus** (increased carrying angle),[Q] **streak ovaries**[Q] (contributing to infertility and amenorrhea), **coarctation of the aorta, broad chest and widely spaced nipples, short 4th metacarpal**.

Recent Exam Question

Turner's syndrome is the most important cause of **primary amenorrhea**.
Pregnancy is *overall* the commonest as well as the most important cause of *secondary amenorrhea*

Noonan Syndrome

It is a relatively common autosomal dominant (**chromosome 12** defect) congenital disorder considered to be a type of dwarfism, that affects both males and females equally. It used to be referred to as the male version of Turner's syndrome; however, the genetic causes of Noonan syndrome and Turner syndrome are distinct. Genetics of Turner syndrome shows monosomy of X chromosome (XO) whereas **in Noonan syndrome, mostly mutation in genes on chromosome 12 is noted**. The principal features include congenital heart defect, short stature, learning problems, pectus excavatum, impaired blood clotting, and a characteristic configuration of facial features which is quite similar to Turner syndrome.

Concept

- Autosomal monosomies (loss of one chromosome) are incompatible with fetal development and are not found in live births. Only monosomy compatible with live birth is XO (Turner syndrome).
- Most of the trisomies occur due to meiotic non- disjunction whereas **Trisomy 7, mostly occur due to mitotic non-disjunction.**
- **Most of the meiotic non-disjunctions occur during 1st meiotic division. In Trisomy 18, it is more commonly seen in 2nd meiotic division.**

Recent Exam Questions

Sex chromatin bodies
- **Barr body:** for **females**
- **F body:** for **males.**

LYON'S HYPOTHESIS

- **Only one** of the X chromosome is **genetically active**.
- Other X of the paternal or maternal origin undergoes pyknosis and is rendered inactive.
- Inactivation of either maternal or paternal X occurs at random among all the cells of the blastocyst by **about 16th day of embryonic life.**♀
- Inactivation of the same X chromosome persists in all the cells derived from each precursor cell. Inactivation of X is because of a gene called **Xist** which is causing gene silencing DNA methylation. So, all normal females are actually mosaics.

Definition

The inactive X can be seen in the interphase nucleus as a small mass near the nuclear membrane called as the **Barr Body or X chromatin.**

Mnemonic

Number of Barr bodies = Number of X chromosomes - 1.
So, they are **absent** in **normal males and Turner syndrome** whereas a *normal female has 1 barr body*

1. **Polymerase chain reaction (PCR)**

PCR analysis involves the synthesis of relatively short DNA fragments from a DNA template. It can be of the following subtypes:

Sanger sequencing	Pyrosequencing	Single-base primer extension
*Analysis of **large genes or multiple genes** *"**Gold standard**" for sequence determination	***More sensitive** than Sanger sequencing *Detection of as little as **5% mutated alleles** in a background of normal alleles. *Used to analyze DNA obtained from **cancer biopsies**, in which tumor cells are often "contaminated" with large numbers of admixed stromal cells.	*Useful approach for identifying mutations at a **specific nucleotide position**

Restriction fragment length analysis	Amplicon length analysis	Real-time PCR
*Useful for molecular diagnosis when the **causal mutation always occurs at an invariant nucleotide position**	*Detection of **mutations that affect the length of DNA** (e.g., deletions or expansions)	*Can detect and quantify the **presence of particular nucleic acid sequences in "real time"** (i.e., during the exponential phase of DNA amplification * Also be used to **detect somatic point mutations in oncogenes** such as KRAS and BRAF
		Real-time PCR performed on cDNA is **the method of choice** for monitoring **residual disease** in patients with **CML**

Also know

2. **Fluorescence in Situ Hybridization (FISH)**
   - A technique used when we want to **recognize sequences specific to particular chromosomal regions**.
   - These DNA clones are labeled with fluorescent dyes and labels a specific chromosomal region that can be visualized under a fluorescent microscope.

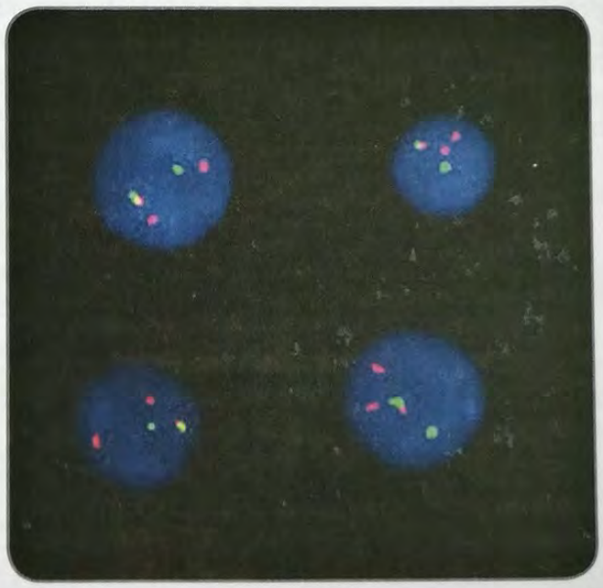


Fig. 1: FISH

Advantages of FISH

a. Does **not require dividing cells** especially when a rapid diagnosis is warranted (e.g., deciding to treat a patient with acute myeloid leukemia with retinoic acid).

b. Can be performed on prenatal samples, peripheral blood cells, touch preparations from cancer biopsies, and even fixed archival tissue sections.
c. FISH is used to detect **aneuploidy; subtle microdeletions or complex translocations that are not demonstrable by routine karyotyping**; and gene amplification (e.g., HER2 in breast cancer or NMYC amplification in neuroblastomas).

Variants of FISH

a. **Chromosome painting:** Extension of FISH whereby probes are prepared that span entire chromosomes. It can *detect limited number of chromosomes simultaneously*.
b. **Spectral karyotyping** (also called **multicolor FISH**): Use of different fluorochromes *permitting visualization of entire human genome*[Q]. Since it is so powerful, it is also called as "spectacular karyotyping."

3. **Multiplex Ligation-Dependent Probe Amplification (MLPA)**

MLPA blends DNA hybridization, DNA ligation, and PCR amplification to detect deletions and duplications of any size, including anomalies that are too large to be detected by PCR and too small to be identified by FISH.

4. **Southern Blotting**

Changes in the structure of specific loci can be detected by Southern blotting. It is useful in the *detection of certain large-trinucleotide-expansion diseases*, including the fragile X syndrome.

5. **Cytogenomic Array Technology**

Genomic abnormalities can also be detected without prior knowledge by using microarray technology to perform a global genomic survey. The techniques include:

I. **Comparative genomic hybridization (CGH)**
It is a method that can be used *only when DNA is available from a specimen of interest*. The entire DNA specimen from the sample of interest is labeled in one color (e.g., red), and the normal control DNA specimen is indicated by another color (e.g., green). These are mixed in equal amounts and hybridized. The red-to-green ratio is analyzed by a computer program with the following interpretation:

a. Red color: gain of genetic material
b. Green color: loss of genetic matrial
c. Yellow color: due to equal mixture of green and red color indicating equal amount of control and test samples. It is currently used for detection of **cancer, mutations in mental retardation and the detection of microdeletions**.

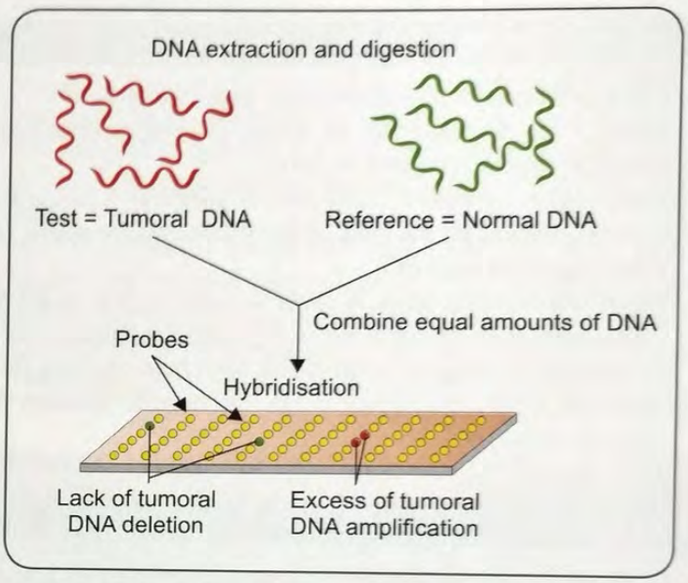
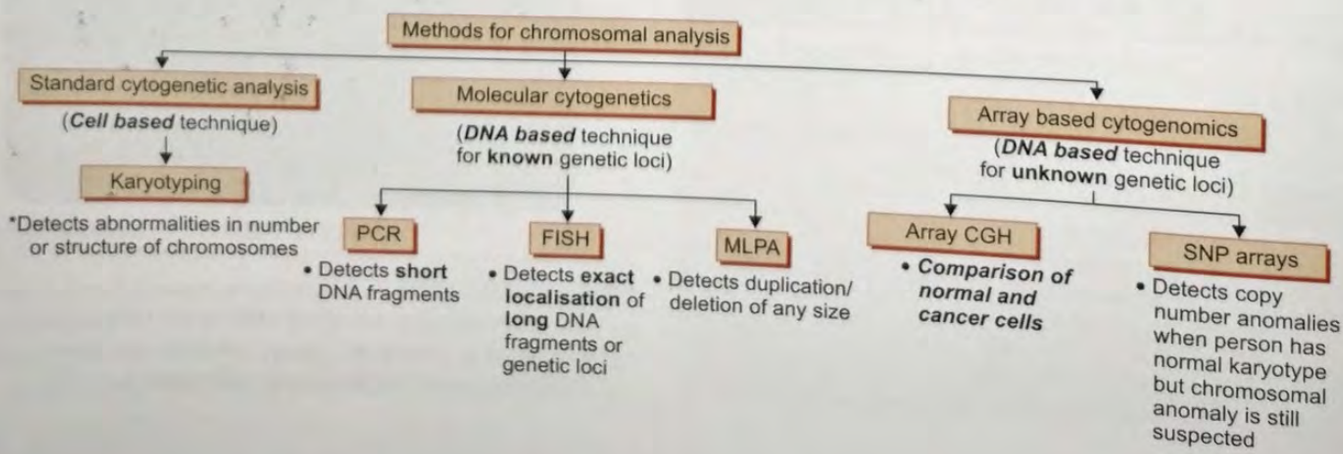


Fig. 2: Comparative genomic hybridization (CGH)

Disadvantage of CGH

- **Cannot** *detect balanced chromosomal abnormalities* such as reciprocal translocations, inversions or ring chromosomes do not affect copy number.

II. **SNP genotyping approaches:**
SNP arrays are routinely used to uncover copy number abnormalities in pediatric patients when the karyotype is normal but a structural chromosomal abnormality is still suspected. It is the ***mainstay of genome wide association studies*** (GWAS). It serves as both a physical landmark within the genome and as a genetic marker whose transmission can be followed from parent to child:



SUMMARY OF CYTOGENTIC TECHNIQUES

- **PCR analysis:** it can detect relatively **short DNA fragments** from a DNA template.
- **FISH:** use of *DNA probes that recognize* ***sequences specific to particular chromosomal regions***
- **Spectral karyotyping** (also called **multicolor FISH**): Use of different fluorochromes **permitting visualization of entire human genome**[Q].
- **M**ultiplex **L**igation-Dependent **P**robe **A**mplification (**MLPA**): to **detect deletions and duplications of *any size***, including anomalies that are too *large to be detected by PCR and too small to be identified by FISH.*
- **C**omparative **g**enomic **h**ybridization **(CGH)**: to detect **unbalanced chromosomes** and to **differentiate normal and cancer cells**.
- **SNP genotyping approaches:** is the mainstay of genome wide association studies

Epigenetic Alterations

It is defined as the study of **heritable chemical modification of DNA or chromatin** that does **not alter the DNA sequence itself** but alters its expression. Examples include:

a. *Methylation of DNA*
b. Methylation of histones
c. Acetylation of histones

DNA methylation can be detected with the treatment of genomic DNA with **sodium bisulfite**

Epigenetic modifications are critical for normal human development including the regulation of tissue-specific gene expression, X chromosome inactivation, genomic imprinting, aging and cancer. Some disease states having this alteration include fragile X syndrome and Prader-Willi and Angelman syndromes.

Polymorphic Markers and Molecular Diagnosis

Linkage is the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome. It is used particularly when the specific gene is not known or if a polygenic condition is being analysed. The two types of genetic polymorphisms most useful for linkage analysis are SNPs and repeat-length polymorphisms known as minisatellite and microsatellite repeats.

Single nucleotide polymorphism (SNPs)	Repeat-length polymorphisms
• ***Most common*** type of DNA polymorphism, occurring every 1000 nucleotides throughout the genome • *Transmission can be followed from parent to child*	• Subdivided microsatellite repeats and minisatellite repeats. • **Microsatellites** are usually < 1 kilobase and are characterized by a repeat size of ***2 to 6 base pairs***. • **Minisatellite** repeats are larger (1 to 3 kilobases), and the repeat motif is usually **15 to 70 base pairs**.

Significance of microsatellite markers

- Are scattered throughout the human genome and have such a high level of polymorphism, they are ideal for differentiating between two individuals and to follow transmission of the marker from parent to child.
- Validated panels of microsatellite marker PCR assays have been routinely used for **determination of relatedness and identity in transplantation, cancer genetics, paternity testing, and forensic medicine.**

Polymorphisms and Genome-Wide Analyses

- In genome wide association studies (GWAS), **large cohorts of patients** with and without a disease (rather than families) are **examined** across the **entire genome** for common **genetic variants or polymorphisms** that are overrepresented in patients with the disease.
- It **identifies** regions of the **genome** that contain a variant gene or genes that **confer disease susceptibility**.
- Important for diseases like **type 2 diabetes, hypertension.**

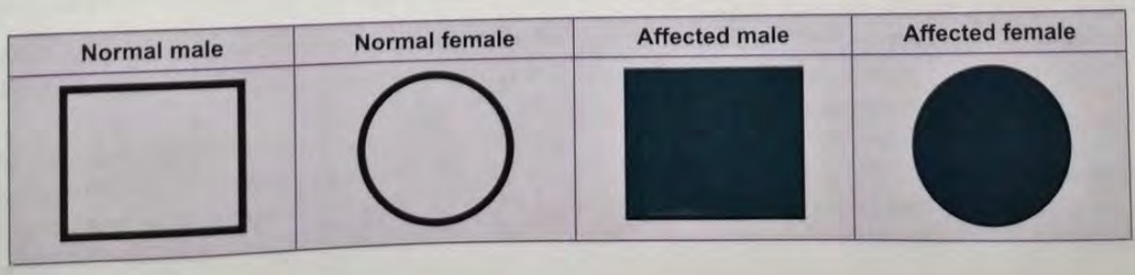
Next-generation sequencing (NGS)

- Next-generation sequencing describes several newer DNA sequencing technologies that are capable of producing large amounts of sequence data in a massively parallel manner.
- In contrast to Sanger sequencing which requires a single, simple, homogenous template DNA (usually either a specific PCR product or prepared plasmid), NGS can use are well suited to heterogeneous DNA samples. It means ***any DNA from almost any source can be used.***
- Sequence reads from NGS instruments are approximately *less than 500 bp.*

PEDIGREE ANALYSIS

Symbols Used

Male is represented as a square and female is represented as a circle. Affected individuals are represented by filling the circle or square by shading.



Two parents are joined by horizontal line and progeny is indicated by a vertical line.

Analysis

Step 1: First of all see whether there is mitochondrial inheritance or not. If female is transmitting the disease to all offsprings (both males and females) and male is not transmitting the disease to any child, it is **mitochondrial** inheritance.

Step 2: If mitochondrial inheritance is not present, now see whether the disease is inherited as dominant or recessive trait. In dominant inheritance, at least one member in all generations will have disease whereas in recessive inheritance, there will be some generations without disease also. Means, if offsprings of both unaffected parents carry the disease/character, it is recessive whereas if both affected parents produce normal offspring, it is dominantly inherited.

Step 3: Now see, whether it is sex-linked or autosomal by looking at the sex-predilection as under

Concept

- If male is transmitting the disease only to daughters (all daughters) and not to the sons whereas female transmit the disease to half daughters and half of sons, it is **X-linked dominant**.
- If only males are affected in a pedigree, it is likely to be **X-linked recessive** disease (females act as carriers; only transmit the disease and themselves remain unaffected).
- If there is no sex-predilection and affected individuals transmit the disease to half of the offsprings, it is **autosomal dominant** disorder.
- If there is no sex-predilection and affected individuals transmit the disease to one fourth of the offsprings, it is likely to be **autosomal recessive** disorder.

Multiple Choice Questions

SINGLE GENE DISORDERS WITH CLASSICAL INHERITANCE

1. Which of the following is an autosomal recessive condition? *(AI 2012)*
(a) Ataxia telangiectasia
(b) Peutz Jeghers syndrome
(c) Neurofibromatosis
(d) Tuberous sclerosis

2. Which of the following is an autosomal dominant metabolic disorder? *(AI 2004)*
(a) Cystic fibrosis
(b) Phenylketonuria
(c) α-1 antitrypsin deficiency
(d) Familial hypercholesterolemia

3. The approximate number of genes contained in the human genome is: *(AIIMS Nov 2002)*
(a) 40,000
(b) 30,000
(c) 80,000
(d) 1,00,000

4. True statements about α-l anti-trypsin deficiency is:
(a) Autosomal dominant disease *(PGI June 2003)*
(b) Emphysema
(c) Fibrosis of portal tract
(d) Diastase resistant positive hepatocytes
(e) Orcein positive granules

5. Autosomal recessive diseases are: *(PGI June 2003)*
(a) Hereditary spherocytosis
(b) Thalassemia
(c) Sickle cell anemia
(d) Cystic fibrosis
(e) Hemophilia A

6. Autosomal dominant disorders are all except:
(a) Hereditary spherocytosis *(PGI Dec 2003)*
(b) Thalassemia
(c) Sickle cell anemia
(d) Cystic fibrosis
(e) Hemophilia

7. Which of the following disorders has been shown to be genetically transmitted by single autosomal dominant genes? *(Delhi PG 2010)*
(a) Catatonic schizophrenia
(b) Phenylketonuria
(c) Creutzfeldt-Jakob's disease
(d) Huntington's disease

8. Duchenne dystrophy is a: *(Delhi PG-2006)*
(a) Autosomal dominant disorder
(b) X-linked dominant disease
(c) Autosomal recessive disease
(d) X-linked recessive disease

9. Catastrophic variant of Ehler Danlos syndrome is:
(a) I (b) II
(c) III (d) IV

10. Sickle cell disease is due to: *(UP 2005)*
(a) Point mutation
(b) Frame shift mutation
(c) Nucleotide receptor blockage
(d) Non-sequence mutation

11. All are autosomal dominant disorders except:
(a) Albinism *(UP 2007)*
(b) Marfan's syndrome
(c) Familial adenomatous polyposis
(d) Von-Hippel Lindau syndrome

12. In Marfan's syndrome there is defect in protein:
(a) Collagen *(RJ 2000)*
(b) Elastin
(c) Fibrillin
(d) All

13. Neurofibromatosis is: *(RJ 2001)*
(a) Autosomal dominant
(b) AR
(c) X-linked recessive
(d) All

14. Blue black pigmentation in alkaptonuria is due to:
(a) Homogentisic acid *(RJ 2002)*
(b) Oxalic acid
(c) Glucouronic acid
(d) All

15. A 26-year-old woman presents because of trouble with her vision. Physical examination reveals a very tall, thin woman with long, thin fingers. Examining her eyes reveals the lens of her left eye to be in the anterior chamber. Her blood levels of methionine and cystathionine are within normal levels. Which of the following is the most likely cause of this patient's signs and symptoms?
(a) Abnormal copper metabolism
(b) Decreased levels of vitamin D
(c) Decreased lysyl hydroxylation of collagen
(d) Defective synthesis of fibrillin
(e) Defective synthesis of type I collagen

MOST RECENT QUESTIONS

16. **Which of the following is the inheritance of Huntington's chorea?**
    (a) Autosomal dominant
    (b) Autosomal recessive
    (c) X-linked
    (d) Mitochondrial

17. **Hemophilia is associated with:**
    (a) X chromosome (b) Y Chromosome
    (c) Chromosome 3 (d) Chromosome 16

18. **Which one of the following is an autosomal dominant disorder.**
    (a) Duchenn's muscular dystrophy
    (b) Fragile X syndrome
    (c) Fanconi's anemia
    (d) Huntington's chorea

19. **Adult polycystic kidney disease is inherited by:**
    (a) Autosomal dominant
    (b) Autosomal recessive
    (c) X-linked
    (d) Mitochondrial

20. **Neurofibroma is having which of the following inheritance?**
    (a) Autosomal dominant
    (b) Autosomal recessive
    (c) X-linked recessive
    (d) X-linked dominat

21. **Which of the following is not X-linked condition:**
    (a) Duchenne muscular dystrophy
    (b) Emery-Dreifuss muscular dystrophy
    (c) Facioscapulohumeral muscular dystrophy
    (d) Becker muscular dystrophy

22. **Which one is not a feature of cystic fibrosis?**
    (a) Autososmal recessive disease
    (b) Abonormal chloride transport
    (c) Affects intestine only
    (d) Increased risk of pulmonary infections

23. **Which of the following is an X-linked dominant disorder?**
    (a) Vitamin D resistant rickets
    (b) Familial hypercholesterolemia
    (c) Red green color blindness
    (d) Achondroplasia

24. **Duchenne muscular dystrophy is inherited as:**
    (a) X-linked
    (b) Autosomal dominant
    (c) Autosomal recessive
    (d) Codominant

25. **Inheritance of Gardner syndrome is:**
    (a) Autosomal recessive
    (b) Autosomal dominant
    (c) X linkeddominant
    (d) X linked recessive

26. **In the entire human genome, coding DNA constitutes:** *(AIIMS May' 14)*
    (a) 2% (b) 1%
    (c) 0.1% (d) 4%

27. **Methylation of cytosine leads to:** *(AIIMS May' 14)*
    (a) Increased expression of gene
    (b) Decreased expression of gene
    (c) No effect on gene expression
    (d) Mutation

28. **ABO blood group inheritance is an example of:**
    (a) Codominance
    (b) Mitochondrial inheritence
    (c) Allelic exclusion
    (d) Sex-linked Inheritance

29. **Which of the following does not show X-linked dominant inheritance?**
    (a) Incontinentia pigmenti
    (b) Duchene muscular dystrophy
    (c) X-linked hypophosphatemic rickets
    (d) Fragile X syndrome

30. **Which is not an autosomal dominant disorder?**
    (a) Gardner's syndrome
    (b) Polycystic kidney
    (c) Ataxia telangiectasia
    (d) Achondroplasia

SINGLE GENE DISORDERS WITH NON CLASSICAL INHERITANCE

31. **In Prader Willi syndrome, which of the following is increased?** *(AI 2012)*
    (a) LH
    (b) FSH
    (c) TSH
    (d) Ghrelin

32. **NARP syndrome is seen in:** *(AI 2011)*
    (a) Mitochondrial diseases
    (b) Glycogen storage diseases
    (c) Lysosomal storage diseases
    (d) Lipid storage diseases

33. **Maternal disomy of chromosome 15 is seen in:**
    (a) Prader-Willi syndrome *(AIIMS Nov 2010)*
    (b) Klinefelter's syndrome
    (c) Angelman syndrome
    (d) Turner's syndrome

34. **Two siblings with osteogenesis imperfecta have normal parents. The mode of inheritance is explained by which of the following?** *(AIIMS May 2010)*
    (a) Anticipation
    (b) Genomic imprinting
    (c) Germline mosaicism
    (d) New mutation

35. **Mitochondrial DNA (mt-DNA) is known for all except:** *(DPG 2011)*
(a) Maternal inheritance
(b) Heteroplasmy
(c) Leber hereditary optic neuropathy is the prototype
(d) Nemaline myopathy results due to mutations in mt-DNA

36. **Preferential expression of the gene depending upon the parent of origin is called:** *(AI 2009)*
(a) Mosaicism (b) Genomic imprinting
(c) Alleles (d) Chimerism

37. **Preferential expression of the gene depending upon the parent of origin is called:** *(AI 2008)*
(a) Anticipation
(b) Germ line mosaicism
(c) Genomic imprinting
(d) Aneuploidy

38. **Differential expression of same gene depending on parent of origin is referred to as:** *(AI 2005)*
(a) Genomic imprinting
(b) Mosaicism
(c) Anticipation
(d) Non-penetrance

39. **A couple has two children affected with tuberous sclerosis. On detailed clinical and laboratory evaluation (including molecular studies) both parents are normal. Which one of the following explains the two affected children in this family?** *(AIIMS May 2006)*
(a) Non penetrance
(b) Uniparental disomy
(c) Genomic imprinting
(d) Germline mosaicism

40. **Genomic imprinting is associated with:** *(PGI Dec 01)*
(a) Silencing of paternal chromosome
(b) Silencing of maternal chromosome
(c) Angelman syndrome
(d) Prader Willi syndrome
(e) Gonadal mosaicism

41. **Dominant negative inheritance is seen in:** *(PGI Dec 2002)*
(a) Ehler-Danlos syndrome
(b) Marfan's syndrome
(c) Hunter syndrome
(d) Osteogenesis imperfecta
(e) Hereditary retinoblastoma

42. **True statements regarding the mitochondrial genes are:** *(PGI Dec 2002)*
(a) Paternal transmission
(b) Maternal transmission
(c) Mendelian inheritance
(d) Mitochondrial myopathy
(e) Horizontal inheritance

43. **Mitochondrial DNA is:** *(PGI June 2003)*
(a) Paternally inherited
(b) Maternally inherited
(c) Horizontal inheritance
(d) Vertical inheritance
(e) Mendelian inheritance

MOST RECENT QUESTIONS

44. **Which of the following is/are an example/examples of non-Mendelian inheritance?**
(a) Genomic imprinting
(b) Uniparental disomy
(c) Mitochondrial inheritance
(d) All of the above

45. **Increasing severity of mental retardation in male members over generations is a result of:**
(a) Mitochondrial DNA mutation
(b) Frameshift mutation
(c) Y-linked disorder
(d) Trinucleotide repeat mutation

46. **All of the following are chromosomal breakage syndromes except:**
(a) Fanconi's anemia
(b) Ehler-Danlos syndrome
(c) Bloom's syndrome
(d) Ataxia telangiectasia

47. **All of the following are characterized by 'trinucleotide repeats' affecting the non-coding regions except:**
(a) Friedrich's ataxia
(b) Fragile X syndrome
(c) Huntington's disease
(d) Myotonic dystrophy

48. **In Huntington chorea the causative mutation in the protein huntingtin is a:**
(a) Point mutation
(b) Gene deletion
(c) Frameshift mutation
(d) Trinucleotide repeat expansion

49. **Which of the following is NOT an example of a syndrome caused by uniparental disomy?** *(AIIMS May' 14)*
(a) Prader-Willi syndrome
(b) Angelman syndrome
(c) Russell-Silver syndrome
(d) Bloom syndrome

50. **Genomic imprinting is seen in:**
(a) Klinefelter's syndrome
(b) Down's syndrome
(c) Angelman syndrome
(d) Hydatidi form mole

51. **Mitochondrial chromosomal abnormality leads to:**
(a) Leber's hereditary optic neuropathy
(b) Angelman syndrome
(c) Prader villi syndrome
(d) Myotonic dystrophy

52. **One of the following disorders is due to maternal disomy:**
(a) Prader-Willi syndrome
(b) Angelman syndrome
(c) Hydatidiform mole
(d) Klinefelter's syndrome

53. **In genomic imprinting, DNA is modified by:**
(a) Acetylation (b) Methylation
(c) Phosphorylation (d) Deamination

54. **A 48-year-old lady presented with bone pains and hepatosplenomegaly. On examination of biopsy specimen from spleen, crumpled tissue paper appearance was seen. Which is the product is likely to have accumulated?**
(a) Glucocerebroside
(b) Sphingomyelin
(c) Sulfatide
(d) Ganglioside

55. **The phenomenon where subsequent generations are at risk of earlier and more severe disease is known as:**
(a) Anticipation (b) Pleiotropy
(c) Imprinting (d) Mosaicism

CHROMOSOMAL DISORDERS AND KARYOTYPING

56. **No change of genetic material occurs in which of the following cytogenetic abnormalities?** *(AIIMS Nov 2012)*
(a) Deletion (b) Insertion
(c) Translocation (d) Inversion

57. **Patient present with skin bullae on sun exposure. There is a defect in which of the following?**
(a) Thymidine dimers *(AIIMS Nov 2012)*
(b) Trinucleotide repeats
(c) Sugar changes
(d) DNA methylation

58. **Which of the following tests is used to differentiate the chromosome of normal and cancer cells?**
(a) PCR *(AIIMS Nov 2012)*
(b) Comparative genomic hybridization
(c) Western blotting
(d) Karyotyping

59. **Down's syndrome is associated with the clinical manifestation of mental retardation. Which of the following is not associated with Down's syndrome?**
(a) Trisomy 21 *(AIIMS Nov 2011)*
(b) Mosaic 21
(c) Translocation t (14,21), t (21,21)
(d) Deletion of 21

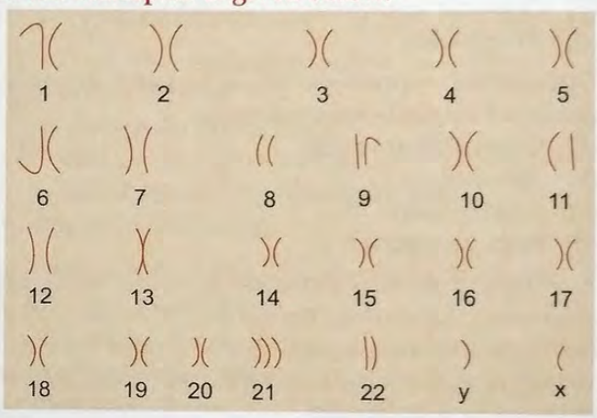
60. **The genetics involved in Down syndrome is:**
(a) Maternal non-disjunction *(AI 2010)*
(b) Paternal non-disjunction
(c) Mosacism
(d) Monosomy

61. **Karyotyping is done for:** *(AI 2009)*
(a) Chromosomal disorders
(b) Autosomal recessive disorders
(c) Autosomal dominant disorders
(d) Linkage disorders

62. **Males who are sexually underdeveloped with rudimentary testes and prostate glands, sparse pubic and facial hair, long arms and legs and large hands and feet are likely to have the chromosome complement of:** *(AI 2004)*
(a) 45, XYY (b) 46, XY
(c) 46, XXY (d) 46, X

63. **Which of the following procedures as routine technique for karyotyping using light microscopy?** *(AI 2003)*
(a) C-banding (b) G-banding
(c) Q-banding (d) Brd V-staining

64. **A married middle aged female gives history of repeated abortions for the past 5 years. The prenatal karyogram of the conceptus is given below:**



This karyogram suggests the following: *(AI 2003)*
(a) Klinefelter's syndrome
(b) Turner's syndrome
(c) Down's syndrome
(d) Patau's syndrome

65. **A 19-year-old female with short stature, wide spread nipples and primary amenorrhea most likely has a karyotype of:** *(AI 2003)*
(a) 47, XX + 18 (b) 46, XXY
(c) 47, XXY (d) 45 X

66. **Karyotyping most commonly done under light microscopy:** *(AIIMS Nov 2009)*
(a) G banding (b) Q banding
(c) C banding (d) R banding

67. **Effective polymerase reaction was repeated for 3 cycles on a DNA molecule. What will be the resulting formation of the copies?** *(AIIMS Nov 2001)*
(a) Double number of copies
(b) Three times the number of DNA molecule
(c) Four times the number of DNA molecule
(d) Eight times

MOST RECENT QUESTIONS

68. **Y-chromosome is:** *(AIIMS May 2007)*
(a) Telocentric (b) Metacentric
(c) Submetacentric (d) Acrocentric

69. **Which of the following is true of Klinefelter's syndrome.** *(PGI Dec 01)*
(a) Chromosome pattern in 47XXY
(b) Mental retardation is present
(c) Hypogonadism occurs
(d) Increased FSH level
(e) Eunuchoid proportions

70. **The classic karyotype of Klinefelter's syndrome is:** *(Karnataka 2009)*
(a) 47XXY
(b) 45XO
(c) 48XXXY
(d) 46XY/47XXY

71. **Chromosomal abnormality in Mongolism is:** *(Karnataka 2005)*
(a) Trisomy 21
(b) Trisomy 22
(c) Trisomy 17
(d) Trisomy 5

72. **Trisomy 13 is identified as:** *(Karnataka 2005)*
(a) Edward's syndrome
(b) Patau's syndrome
(c) Down's syndrome
(d) Klinefelter's syndrome

73. **In Down syndrome, there is non-disjunction of chromosome:**
(a) 13 (b) 15
(c) 18 (d) 21

74. **Barr body is not seen in:**
(a) Klinefelter syndrome
(b) Turner syndrome
(c) Normal female
(d) XXX syndrome

75. **Karyotype is:**
(a) Size, shape and number of chromosome
(b) Gene packing
(c) DNA assay
(d) None

76. **Osteogenesis imperfecta defect in:**
(a) Collagen type I (b) Elastin
(c) Collagen type IV (d) Fibrillin 2

77. **Karyotyping is done in which phase of cell cycle?**
(a) Anaphase (b) Metaphase
(c) Telophase (d) S phase

78. **The number of chromosomes in Turner syndrome is:**
(a) 47 (b) 46
(c) 45 (a) 44

79. **Patau syndrome is due to which of the following?**
(a) Trisomy 21 (b) Trisomy 18
(c) Trisomy 21 (d) Trisomy 13

80. **The number of chromosomes in Klinefelter syndrome is:**
(a) 47 (b) 46
(c) 45 (d) 44

81. **Chromosomes are visualized through light microscope with resolution of:**
(a) 5 Kb
(b) 50 Mb
(c) 5 Kb
(d) 500 Kb

82. **Which of the following techniques can be used to detect exact localisation of a genetic locus?** *(AIIMS May, Nov 2013)*
(a) Chromosome painting
(b) FISH
(c) Comparative genomic hybridization
(d) Western blot

83. **In Marfan syndrome, the defect is in:**
(a) Fibrillin I
(b) Fibrillin II
(c) Collagen
(d) Elastin

84. **If a chromosome divides in an axis perpendicular to usual axis of division it is going to form:**
(a) Ring chromosome
(b) Isochromosome
(c) Acrocentric chromosome
(d) Subtelocentric chromosome

85. **Most lethal combination:**
(a) Autosomal trisomy
(b) Chromosomal monosomy
(c) Autosomal monosomy
(d) Chromosomal trisomy

86. **All of the following are true about the Downs syndrome except:**
(a) Most common cause is trisomy21
(b) Extra chromosome is of maternal origin
(c) Incidence of the Robertsonian translocation is 1:1000
(d) Mosaicism 21 has no association with maternal age

87. **All are true about turner syndrome except:**
(a) Short stature
(b) Webbed neck
(c) Dysgenetic gonads
(d) True hermaphroditism

88. **SnRNA mutation is associated with which syndrome?**
(a) Turner's syndrome
(b) Prader-Willi syndrome
(c) Klinefelter syndrome
(d) Patau syndrome

PEDIGREE ANALYSIS, GENE LOCATION, LYON HYPOTHESIS

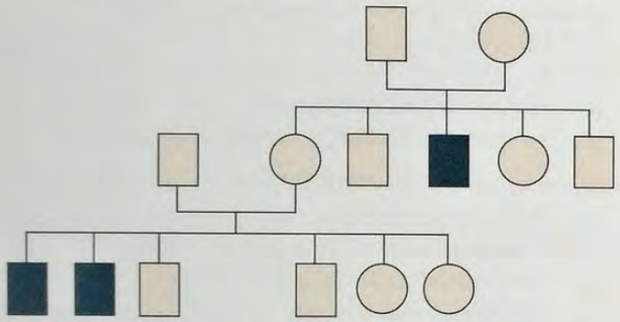
89. **BRCA 1 gene is located on?** *(AIIMS May 2011)*
(a) Chromosome 13
(b) Chromosome 11
(c) Chromosome 17
(d) Chromosome 22

90. Males are more commonly affected than females in which of the following genetic disorders? *(AI 2010)*
(a) Autosomal recessive disorder
(b) Autosomal dominant disorder
(c) X-linked recessive disorder
(d) X-linked dominant disorder

91. In-situ DNA nick end labeling can quantitate:
(a) Fraction of cells in apoptotic pathways
(b) Fraction of cells in S phase *(AI 2005)*
(c) p53 gene product
(d) bcr/abl gene

92. The chances of having an unaffected baby, when both parents have achondroplasia, are: *(AI 2005)*
(a) 0%
(b) 25%
(c) 50%
(d) 100%

93. Study the following carefully: *(AI 2005)*



Read the pedigree. Inheritance pattern of the disease in the family is:
(a) Autosomal recessive type
(b) Autosomal dominant type
(c) X-linked dominant type
(d) X-linked recessive type

94. Kinky hair disease is a disorder where an affected child has peculiar white stubby hair, does not grow, brain degeneration is seen and dies by age of two years. Mrs. A is hesitant about having children because her two sisters had sons who had died from kinky hair disease. Her mother's brother also died of the same condition. Which of the following is the possible mode of inheritance in her family? *(AI 2004)*
(a) X-linked recessive
(b) X-linked dominant
(c) Autosomal recessive
(d) Autosomal dominant

95. An albino girl gets married to a normal boy, what are the chances of their having an affected child and what are the chances of their children being carriers? *(AI 2003)*
(a) None affected, all carriers
(b) All normal
(c) 50% carriers
(d) 50% affected, 50% carriers

96. The mother has sickle cell disease; Father is normal; Chances of children having sickle cell disease and sickle cell trait respectively are: *(AI 2001)*
(a) 0 and 100% (b) 25 and 25%
(c) 50 and 50% (d) 10 and 50%

97. Father has a blood group B; Mother has AB; Children are not likely to have the following blood group: *(AI 2001)*
(a) O (b) A
(c) B (d) AB

98. Gene therapy is used for: *(AIIMS May 2009)*
(a) Cystic fibrosis
(b) Sickle cell anemia
(c) Thalassemia
(d) All of the above

99. Gene for major histocompatibility complex is located on which chromosome? *(AIIMS Nov 2008)*
(a) Chromosome 10
(b) Chromosome 6
(c) X chromosome
(d) Chromosome 13

100. Gene for folate carrier protein is located on chromosome: *(AIIMS Nov 2008, May 2008)*
(a) Chromosome 10
(b) Chromosome 5
(c) Chromosome 21
(d) Chromosome 9

101. Ability of stem cells to cross barrier of differentiation to transform into a cell of another lineage expressing the molecular characteristics of different cell type with the ability to perform the function of the new cell type is referred as: *(AIIMS Nov 2007)*
(a) De differentiation
(b) Re differentiation
(c) Trans-differentiation
(d) Sub differentiation

102. If both husband and wife are suffering with achondroplasia, what are their chances of having a normal child. *(AIIMS May 2004)*
(a) 0% (b) 25%
(c) 50% (d) 100%

103. A one year old boy presented with hepatosplenomegaly and delayed milestones. The liver biopsy and bone marrow biopsy revealed presence of histiocytes with PAS-positive Diastase-resistant material in the cytoplasm. Electron-microscopic examination of these histiocytes is most likely to reveal the presence of: *(AIIMS Nov 2003)*
(a) Birbeck's granules in the cytoplasm
(b) Myelin figures in the cytoplasm
(c) Parallel rays of tubular structures in lysosomes
(d) Electron dense deposit in the mitochondria

104. The gene that regulates normal morphogenesis during development is: *(AIIMS Nov 2002)*
(a) FMR-1 gene (b) Homeobox gene
(c) P-16 (d) PTEN

105. **A baby's blood group was determined as O Rh negative. Select the blood group the baby's mother or father will not have:** *(AIIMS Nov 2002)*
(a) A, Rh positive
(b) B, Rh positive
(c) AB, Rh negative
(d) O, Rh positive

106. **Thalassemia occurs due to which mutation?** *(PGI Dec 2000)*
(a) Missense (b) Splicing
(c) Transition (d) Frame-shift
(e) Truncation

107. **Congenital syndrome associated with lymphoproliferative malignancy is:** *(PGI June 2005)*
(a) Bloom syndrome
(b) Fanconi's anemia
(c) Turner syndrome
(d) Chediak Higashi syndrome
(e) Ataxia telangiectasia

108. **Loss of heterozygosity means:** *(PGI Dec 2005)*
(a) Loss of single arm of chromosome.
(b) Loss of mutant allele in mutant gene
(c) Loss of normal allele in mutant gene
(d) Loss of normal allele in normal gene

MOST RECENT QUESTIONS

109. **Long and short arm of chromosome are called respectively:**
(a) p and q
(b) q and p
(c) m and n
(d) r and s

110. **Cystic fibrosis transmembrane conductance regulator gene is located on chromosome:**
(a) 5
(b) 6
(c) 7
(d) 8

111. **Which one of the following is not a germ cell tumor?**
(a) Dermoid
(b) Granulosa cell tumor
(c) Choriocarcinoma
(d) Gynandroblastoma

112. **The CFTR gene associated what cystic fibrosis is located on chromosome:**
(a) 5 (b) 12
(c) 4 (d) 7

113. **In cystic fibrosis the most frequent pulmonary pathogen is:**
(a) Pseudomonas
(b) Enterococci
(c) Staphylococci
(d) Klebsiella

114. **Male to male transmission is not seen in:**
(a) Autosomal dominant diseases
(b) Autosomal recessive disease
(c) X-linked dominant disease
(d) Genomic imprinting

115. **Microarray is best characterised by:**
(a) Study of multiple genes
(b) Study of disease
(c) Study of organisms
(d) Study of blood group

116. **The technique used for separation and detection of RNA is which one of the following:**
(a) Northern blot
(b) Southern blot
(c) Eastern blot
(d) Western blot

117. **True statement about inheritance of an X-linked recessive trait is:**
(a) 50% of boys of carrier mother are affected
(b) 50% of girls of diseased father are carrier
(c) Father transmits disease to the son
(d) Mother transmits the disease to the daughter

118. **Gene for Wilm's tumor is located on:**
(a) Chromosome 1 (b) Chromosome 10
(c) Chromosome 11 (d) Chromosome 12

119. **Which of the following potentially represents the most dangerous situation?**
(a) Rh+ve mother with 2nd Rh-ve child
(b) Rh-ve mother with 2nd Rh+ve child
(c) Rh+ve mother with 1st Rh-ve child
(d) Rh-ve mother with 1st Rh+ve child

Explanations

1. **Ans. (a) Ataxia telangiectasia**
(Ref: Robbins 8th/302-3, 1323-4, 9/e p242-243)
   - **Ataxia** telangiectasiais an **autosomal recessive condition.**
   - Patients have increased ***sensitivity to X-ray-induced chromosome abnormalities***.
   - Characterized by an ataxic-dyskinetic syndrome beginning in early childhood, caused by neuronal degeneration predominantly in the cerebellum, the subsequent development of telangiectasias in the conjunctiva and skin, and immunodeficiency.
   - The nuclei of cells in many organs (e.g., Schwann cells in dorsal root ganglia and peripheral nerves, endothelial cells as well as pituicytes) show a bizarre enlargement of the cell nucleus and are referred to as **amphicytes**.
   - The *lymph nodes, thymus,* and *gonads* are **hypoplastic**.
   - Clinical features include **recurrent sinopulmonary infections** and **unsteadiness in walking**.
     - Increased risk of development of lymphoid malignant disease (T-cell leukemia and lymphoma

   All other options are autosomal dominant conditions.

2. **Ans. (d) Familial hypercholesterolemia**
(Ref: Robbins 7th/152, 9/e p141)
Most of the metabolic disorders have **autosomal recessive inheritance except**:
Her – Her's disease [Liver phosphorylase deficiency]
Left – Lesch Nyhan syndrome
Eye – Ocular albinism
Has – Hunter syndrome and Hypercholesterolemia (familial)
Five – Fabry's disease
Pimples – Porphyria [Acute intermittent]

   Note: All these exceptions have X-linked recessive inheritance **except** acute intermittent porphyria and familial hypercholesterolemia which are autosomal dominant disorders.

3. **Ans. (b) 30,000 genes** *(Ref: Robbins's 7th/1219, 8th/136)*
Humans have a mere 30,000 genes rather than the 100,000 predicted only recently. Recent Robbins mentions the number of genes to 20,000 to 25,000.

4. **Ans. (b) Emphysema; (c) Fibrosis of portal tact; (d) Diastase resistance positive hepatocytes** *(Ref: Robbins 9/e p850-851)*
   - This is an autosomal recessive disease characterized by deficiency of α_1 - antitrypsin (important protease inhibitor).
   - There is portal tract fibrosis in neonatal hepatitis. About 10 - 20% of newborn with α_1 - antitrypsin deficiency develop neonatal hepatitis and cholestasis.
   - Hepatocellular carcinoma develops in 2-3 % α_1 - antitrypsin deficiency in adults.
   - The treatment and cure, for severe hepatic disease is *orthotropic liver transplantation.*

5. **Ans. (b) Thalassemia; (c) Sickle cell anemia; (d) Cystic fibrosis** *(Ref: Robbins 7th/151, 8th/141-2, 9/e p141)*
   - Hereditary spherocytosis is an autosomal dominant disorder
   - Hemophilia is an X-linked recessive disease.

   A broad generalization is that the physiologic metabolic enzyme deficiencies are all autosomal recessive whereas Structural defects are autosomal dominant.

6. **Ans. (b) Thalassemia; (c) Sickle cell anemia; (d) Cystic fibrosis; (e) Hemophilia** *(Ref: Robbins 8th/652 , 9/e p141)*

7. **Ans. (d) Huntington's disease**
(Ref: Harrison 17th/401 Robbins 7th/1393, 8th/141,168, 9/e p141)

8. **Ans. (d) X-linked recessive disease**
(Ref: Robbins 7th/1336 , 9/e p142)

9. **Ans. (d) IV** *(Ref: Robbins 9/e p146)*

10. **Ans. (a) Point mutation** *(Ref: Robbins 9/e p138)*

11. **Ans. (a) Albinism** *(Ref: Robbins 9/e p141-142)*

12. **Ans. (c) Fibrillin** *(Ref: Robbins 9/e p144)*

13. **Ans. (a) Autosomal dominant** *(Ref: Robbins 9/e p140)*

14. **Ans. (a) Homogentisic acid** *(Ref: Robbins 9/e p64)*

15. **Ans. (d) Defective synthesis of fibrillin**
(Ref: Robbins 7th/104, 154-155 , 9/e p144)
The stem describes a patient of Marfan syndrome which is an autosomal dominant disorder that results from defective synthesis of fibrillin.

16. **Ans. (a) Autosomal dominant...see earlier explanation**
(Ref: Robbins 9/e p141)

17. **Ans. (a) X chromosome...explained earlier**
(Ref: Robbins 8/e p142, 9/e p142)

18. **Ans. (d) Huntington's chorea** *(Ref: Robbins 8/e p141)*

19. **Ans. (a) Autosomal dominant...see earlier explanation**
(Ref: Robbins 9/e p141)

20. **Ans. (a) Autosomal dominant...see earlier explanation**
(Ref: Robbins 9/e p141)

21. Ans. (c) Facioscapulohumeral muscular dystrophy
(Ref: Robbins 8/e p142, 1270)

- Facioscapulohumeral muscular dystrophy is an **autosomal dominant** disorder characterised by ***facial weakness*** (difficulty with eye closure and impaired smile) and ***scapular winging***.

Progressive Muscular Dystrophies

Type	Inheritance	Clinical Features
Duchenne's	XR	Progressive weakness of girdle muscles Unable to walk after age 12 Progressive kyphoscoliosis Respiratory failure in 2d or 3d decade
Becker's	XR	Progressive weakness of girdle muscles Able to walk after age 15 Respiratory failure may develop by 4th decade
Limb-girdle	AD/AR	Slow progressive weakness of shoulder and hip girdle muscles
Emery-Dreifuss	XR/AD	Elbow contractures, humeral and peroneal weakness
Congenital	AR	Hypotonia, contractures, delayed milestones Progression to respiratory failure in some; static course in others
Myotonica (DM1, DM2)	AD	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion Preferential proximal weakness in DM2
Facioscapulo-humeral	**AD**^{Q}	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion
Oculopharyn-geal	AD	Slowly progressive weakness of extraocular, pharyngeal, and limb muscles

22. Ans. (c) Affects intestine only *(Ref: Robbins 9/e 466-471)*

- **Cystic fibrosis** is also known as **salty baby syndrome**^{Q} or **mucoviscidosis**^{Q}. It is an **autosomal recessive**^{Q} **genetic disorder** that affects most critically the lungs, and also the pancreas, liver, and intestine.
- It is characterized by abnormal transport of chloride and sodium across epithelium, leading to thick, viscous secretions
- Affected patients are prone to ***Pseudomonas infections***^{Q} for which a **combination of 3rd generation cephalosporins and aminoglycoside**^{Q} is used.
- The most commonly used form of testing is the sweat test using the drug that stimulates sweating (***pilocarpine iontophoresis***^{Q}).
- Patients require repeated use of antibiotics and lung transplantation (in later stages) to survive.

23. Ans. (a) Vitamin D resistant rickets *(See Below)*

Vitamin D resistant rickets	X-linked dominant due to PHEX gene
Familial hypercholesterolemia	Autosomal recessive
Red green colour blindness	X-linked recessive
Achondroplasia	Autosomal dominant

24. Ans. (a) X-linked
(Ref: Robbins 8/e p142 , 9/e p142) ...see text for details
X-linked recessive disorder can be remembered by the following line: **L**ess **hCG** is **D**etected **C**linically in **A** **F**ragile **W**oman.

25. Ans. (b) Autosomal dominant
(Ref: Robbins 8/e p816 , 9/e p806,809)

- It is a subtype of familial adenomatous polyposis inherited as an **autosomal dominant disorder**.
- **Gardener syndrome**^{Q} Intestinal polyps + epidermal cysts + fibromatosis + osteomas (of the mandible, long bones and skull).

26. Ans. (a) 2% *(Robbins 9th /2)*
*'98.5% of the human genome that **does not** encode proteins'*..... direct quote from Robbins. So, it means that about 1.5% of the genome is used for coding proteins. The best answer therefore is option "a".

27. Ans. (b) Decreased expression of gene *(Robbins 9th/4)*
High levels of ***DNA methylation*** in gene regulatory elements typically result in ***transcriptional silencing.***

28. Ans. (a) Codominance *(Ref: Robbins 9th/140)*
When both of the alleles of a gene pair contribute to the phenotype, this is called as codominance. Good examples of codominant inheritance are:

- Histocompatibility
- Blood group antigens

29. Ans. (b) Duchene muscular dystrophy
(Ref: Robbins 9/e p142)

30. Ans (c) Ataxia telangiectasia *(Ref: Robbins 9/e p141)*

31. Ans. (d) Ghrelin
(Ref: Robbins 8th/441-2, and 9/e 444, Pediatric endocrinology: mechanisms, manifestations, management 1st/26-8)

- **Ghrelin** is a **growth hormone secretagogue** and the ***only gut hormone with orexigenic*** (means increasing food intake) property.
- It is primarily **produced in the stomach**. In children, its value is inversely related with body mass index and insulin values. It is postulated to play an important role in hyperphagia.

Direct quote from Pediatric endocrinology... 'fasting ghrelin levels were obtained in children with Prader Willi syndrome and found to be elevated 3-4 times when compared to children who are obese'.

Pancreatic polypeptide Y (PYY) is normally secreted from endocrine cells of the **ileum and colon**. It reduces energy intake and its reduced levels in the patients of ***Prader Willi syndrome*** may contribute to hyperphagia and obesity.

32. **Ans. (a) Mitochondrial diseases**
(Ref: Harrison 17th/316-317, Robbins 8th/1328)
NARP syndrome (Neuropathy, ataxia, and retinitis pigmentosa), is a condition related to changes in mitochondrial DNA.
For details, see text.

33. **Ans. (a) Prader-Willi syndrome** *(Ref: Robbins 8th/172)*
Prader Willi syndrome could be present because of the following:
a. Deletion of paternal chromosome 15 or
b. Uniparental disomy of maternal chromosome 15.
For details, see text.

34. **Ans. (c) Germline mosaicism** *(Ref: Robbins 8th/173)*
Gonadal mosaicism results from a mutation that occurs postzygotically during early (embryonic) development. If the mutation affects only cells destined to form the gonads, the gametes carry the mutation, but the somatic cells of the individual are **completely normal**. Such an individual is said to exhibit germ line or gonadal mosaicism. A phenotypically normal parent who has germ line mosaicism can transmit the disease-causing mutation to the offspring through the mutant gamete. Since the progenitor cells of the gametes carry the mutation, there is a definite possibility that more than one child of such a parent would be affected. It is seen with tuberous sclerosis and osteogenests imperfecta.

35. **Ans. (d) Nemaline myopathy results due to mutations in mt-DNA** *(Ref: Harrison 17th/2688, Robbins 8th/171)*
Nemaline myopathy is not a mitochondrial disease

Nemaline Myopathy

Nemaline myopathy is a clinically heterogeneous condition and not a mitochondrial disease. Five genes have been associated with this myopathy. All code for thin filament–associated proteins, suggesting disturbed assembly or interplay of these structures as a pivotal mechanism. Mutations of the nebulin (NEB) gene account for most cases, including both severe neonatal and early childhood forms, inherited as autosomal recessive disorders.

36. **Ans. (b) Genomic imprinting** *(Ref: Robbins 9/e 173)*

37. **Ans. (c) Genomic imprinting** *(Ref: Robbin 9/e 173)*

38. **Ans. (a) Genomic imprinting**
(Ref: Harrison's 17th/413, 18th/518; Robbins 7th/186. 8th/171-2 , 9/e 173)
Genomic imprinting is the phenomenon that leads to preferential expression of an allele depending on its, parental origin. It is also seen in (**updated from HARRISON 18th**):

- *Wiedemann syndrome* (have two paternal but no maternal copies of *chromosome 11*).
- *Albright's hereditary* osteodystrophy (short stature, brachydactyly and PTH resistance). There is *mutation in the Gs α subunit*; individuals express the disease only when the mutation is inherited from the mother).

39. **Ans. (d) Germline mosaicism**
(Ref: Robbins 8th/173, 7th/187, Harrison 17th/1800, 9/e 174)
Germline mosaicism is seen with osteogenesis imperfecta and tuberous sclerosis. For details, see text.

40. **Ans. (a) Silencing of paternal chromosome; (b) Silencing of maternal chromosome; (c) Angelman syndrome; (d) Prader-Willi syndrome**
(Ref: Robbins' 7th-1856, 8th/171-3 , 9/e 173)

41. **Ans. (a) Ehler-Danlos syndrome; (b) Marfan's syndrome; (d) Osteogenesis imperfecta**
(Ref: Robbins 7th/151 , 9/e 144-146)
Dominant negative effects occurs when a **mutant polypeptide not only loses its own function but also interferes with the product of normal allele in a heterozygote**, thus causing more severe effects than deletion or non-sense mutations in the same gene. Structural proteins that contribute to multimeric structures are vulnerable to dominant negative effects, e.g. collagen.

Seen in: Osteogenesis imperfecta, Ehler-Danlos syndrome, Marfan's syndrome.

42. **Ans. (b) Maternal transmission; (d) Mitochondrial myopathy**
(Ref: Harrison 18th/501, Robbins 8th/171) ...see text

43. **Ans. (b) Maternally inherited** *(Ref: Robbins 9/e 171)*

44. **Ans. (d) All of the above** *(Ref: Robbins 8th/167 , 9/e 168)*
Non-Mendelian inheritance can be classified into following four categories:

Trinucleotide repeat mutation disorders	Mitochondrial gene mutations	Genomic imprinting	Gonadal Mosaicism
• Fragile- X syndrome • Friedreich's Ataxia • Myotonic dystrophy • Huntington disease • Spinobulbar muscular atrophy (Kennedy disease) • Spinocerebellar ataxias	• Leber Hereditary Optic Neuropathy • Kearns-Sayre syndrome • Chronic progressive external ophthalmoplegia • Pearson syndrome • Neurogenic muscular weakness with ataxia and retinitis pigmentosa (NARP)	• Prader-Willi syndrome (Paternal deletion) • Angelman syndrome (maternal deletion)	• Tuberous sclerosis • Osteogenesis imperfecta

45. **Ans. (d) Trinucleotide repeat mutation**
(Ref:Robbins 8th/169-171 , 9/e 169)

46. **Ans. (b) Ehlers-Danlos syndrome**
(Ref: Robbins 7th/155-6, Table 5.5 174 , 9/e 145-146)
Chromosome breakage syndromes are associated with high level of chromosomal instability. Such conditions include. Fanconi anemia, Bloom syndrome and Ataxia telangiectasia.
Ehlers-Danlos syndrome (EDS)
- Genetic disorder resulting from defective synthesis of fibrillar collagen
- Skin is extraordinary stretchable, extremely fragile and vulnerable to trauma, joints are hypermobile
- Internal complications: rupture of colon, large arteries

47. **Ans. (c) Huntington's disease** *(Ref: Robbins 9/e 168)*
Huntington's disease is characterized by trinucleotide repeats affecting the coding region. Rest all conditions mentioned in the options affects the non-coding regions.

48. **Ans. (d) Trinucleotide repeat expansion**
(Ref: Robbins 9/e p168)
Expansion of trinucleotide repeats is an important genetic cause of human disease, particularly neurodegenerative disorders. There are three key mechanisms by which unstable repeats cause diseases:

- Loss of function of the affected gene occurs in fragile X syndrome. In such cases the repeats are generally in non-coding part of the gene.
- A toxic gain of function by alterations of protein structure as in Huntington disease and spinocerebellar ataxias. In such cases the expansions occur in the coding regions of the genes.
- A toxic gain of function mediated by mRNA as is seen in fragile X tremor-ataxia syndrome. In this condition, the non coding parts of the gene are affected.

49. **Ans. (a) Bloom syndrome** *(Robbins 9th/314-5) ...see text*

50. **Ans. (c) Angelman syndrome** *(Ref: Robbins 9/e 172)*

51. **Ans. (a) Leber's hereditary optic neuropathy**
(Ref: Robbins 8/e p171 , 9/e 172)
Examples of mitochondrial inheritance *are* ***Leber's optic neuropathy, Leigh's disease, MELAS*** (*m*itochondrial *e*n-cephalopathy, *l*actic *a*cidosis and *s*troke like syndrome) NARP syndrome (Neuropathy, ataxia, and retinitis pigmentosa), Kearns-Sayre syndrome, Chronic progressive external ophthalmoplegia and Pearson syndrome.

52. **Ans. (a) Prader-Willi syndrome** *(Ref: Robbins 9/e 173)*
Maternal disomy is associated with disorders like Prader-Willi syndrome and Angelman syndrome. It is also seen in other conditions like molar pregnancy and Beckwith-Wiedemann syndrome.

53. **Ans. (b) Methylation** *(Ref: Robbins 9th/172)*
Imprinting selectively inactivates either the maternal or paternal allele. Thus, maternal imprinting refers to transcriptional silencing of the maternal allele, whereas paternal imprinting implies that the paternal allele is inactivated. Imprinting is associated with differential patterns of DNA methylation at CG nucleotides. Other mechanisms include histone H4 deacetylation and methylation.

54. **Ans. (a) Glucocerebroside** *(Ref: Robbins 9th/153)*

Presence of bone pain and hepatosplenomegaly with a splenic biopsy cell having "crumpled paper" appearance is highly suggestive of Gaucher's disease.

55. **Ans. (a) Anticipation** *(Ref: Robbins 9th/169)*

Anticipation refers to the observation that clinical features of a genetic disease worsen with each successive generation. It is observed in association with Fragile X syndrome and Huntington disease commonly.

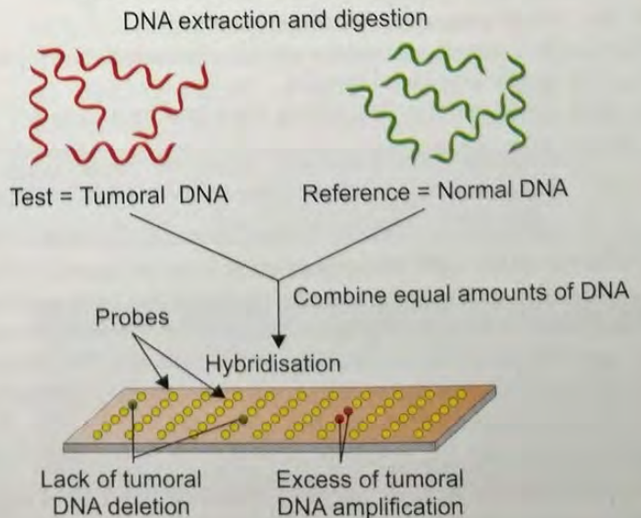
56. **Ans. (d) Inversion** *(Ref: Robbins 8th/138, 160)*

Inversion refers to a rearrangement that involves two breaks within a single chromosome with reincorporation of the inverted, intervening segment. It is ***not associated with change in genetic material.***

57. **Ans. (a) Thymidine dimers** *(Ref: Robbins 8th/275, 302)*
Xeroderma pigmentosum

- **Autosomal recessive**[Q] inherited disorder of *defective DNA repair*[Q].
- Affected individuals are at increased risk for the development of skin cancers particularly following *exposure to the UV light* contained in sun rays.
- UV radiation causes *cross-linking of pyrimidine residues*, preventing normal DNA replication. Such DNA damage is repaired by the **nucleotide excision repair system**[Q].
- Deficiency of enzymes like ***UV specific endonuclease (commonest), DNA polymerase and DNA ligase*** is implicated

58. **Ans. (b) Comparative genomic hybridization**
(Ref: Robbins 8th/179, Harrison 18th/512)
- *Comparative genomic hybridization (CGH) differentiates between cancer and normal cells.*



- Comparative genomic hybridization (CGH) is a method that can be used only when DNA is available from a specimen of interest. The **entire DNA specimen** from the **sample of interest** is **labeled in one color** (e.g., red), and the normal control DNA specimen is indicated by another color (e.g., green). These are mixed in equal amounts and hybridized to normal metaphase chromosomes. The **red-to-green ratio is analyzed** by a computer program that determines where the DNA of interest may have gains or losses of material.

59. **Ans. (d) Deletion of 21** *(Ref: Robbins 8th/161-162)*
Down syndrome is characterized by trisomy 21 **(NOT deletion of chromosome 21).** ***For details see text.***

60. **Ans. (a) Maternal non-disjunction**
(Ref: Robbins 8th/161)

Genetics of Down syndrome

- **Meiotic nondisjunction of chromosome 21 occuring in the ovum is** seen in ***95% cases*** with trisomy 21 and is the so, ***commonest cause*** of Down syndrome. The extra chromosome is of ***maternal origin***.
- ***There is a Strong relation*** with maternal age
- It may also be seen with Robertsonian translocation and mosaicism.

61. **Ans. (a) Chromosomal disorders** *(Ref: Robbins 8th/158)*

- **Karyotyping** is the study of chromosomes
- Chromosomes are arrested in **metaphase** by **Colchicine**
- These are then stained by many stains. **Most commonly** used stain is **Giemsa stain**, so called **G-banding**
- The chromosomes are **arranged in order of decreasing length**
- Any alteration in number or structure of chromosomes can be easily detected by karyotyping

62. **Ans. (c) 46, XXY**
(Ref: Harrison's 17th/2340 – 2341, 411, Robbins 7th/179)
It is a typical case of Klinefelter syndrome. The features pointing towards this diagnosis are:
- Male phenotype
- Hypogonadism [rudimentary testes]
- Decreased secondary sexual characteristics [sparse pubic and facial hairs]
- Disproportionately long arms and legs.

Patients with Klinefelter syndrome have extra X chromosome, so they may be 47,XXY or 46XY/47 XXY mosaics.

None of the options appear correct as an extra X chromosome in the male should increase the total number of chromosomes to 47 and hence 47 XXY should be the most appropriate answer. However an extra X–chromosome is the most essential aspect and hence, within the available options, the best answer is 46 XXY.

63. **Ans. (b) G-Banding**
(Ref: Harsh Mohan 6th/17, Robbins 8th/159, Cancer cytogenetics3rd/2010)
G banding is the most widely used technique for routine cytogenetic analysis.' So, **G** banding is chosen as the answer of choice. For details of different banding techniques, please see text.

64. **Ans. (c) Down's syndrome** *(Ref: Robbins 7/175)*
- The given karyogram shows three chromosomes at 21 instead of a pair. It is called **Trisomy 21.**
- Trisomy 21 is synonymous with **Down's syndrome** and is the most common of the chromosomal disorders. It is a major cause of mental retardation.
- **Other trisomies** are Edward syndrome (Trisomy 18) and Patau syndrome (Trisomy 13)

65. **Ans. (d) 45X** *(Ref: Robbins 7/179-180)*
Given features (*Female, primary amenorrhea, short stature, widely spaced nipples*) suggests the diagnosis of **Turner's syndrome**.

Turner's Syndrome

Turner's syndrome is the *most common sex chromosomal disorder in phenotypic females.*

Turner's syndrome results from complete or partial loss of one X chromosome (45, XO) and is characterized by **hypogonadism in phenotypic females**

66. **Ans. (a) G banding**
(Ref: Harsh Mohan 6th/17, Robbins 8th/159, Cancer cytogenetics 2010/3rd edition)
Refer to the text for detail.

Q banding is easily ruled out because it does not require light microscopy. *Cancer cytogenetics* clearly mentions that 'sequence specific techniques like **T** banding; **C** banding and **NOR** banding have been replaced by in situ hybridization techniques. G banding is the most widely used technique for routine cytogenetic analysis.' So, **G** banding is chosen as the answer of choice.

67. **Ans. (d) Eight times** *(Ref: Harrison 17th/391)*
Friends, the number of copies of the particle after 'n' cycles of polymerase chain reaction is given by the formula 2^n times the original copies. So, the number of copies after 3 cycles would be $2^3 = 8$ times the original copies.
PCR is used to amplify DNA but RT – PCR (reverse transcriptase PCR) can be used for studying mRNA.

68. **Ans. (d) Acrocentric** *(Ref: Nelson 17th/382)*
X chromosome is Submetacentric and Y chromosome is Telocentric.

69. **Ans. (a) Chromosome pattern is 47XXY; (b) Mental retardation is present; (c) Hypogonadism occurs; (d) Increased FSH level; (e) Eunuchoid proportions**
(Ref: Harrison' 16th-2215, 2216, Robbins 7th/179, 8th/165) ...see text

70. **Ans. (a) 47XXY** *(Ref:Robbins 7th/179, 8th/161-2)*

71. **Ans. (a) Trisomy 21** *(Ref: Robbins 7th/179, 8th/165)*

72. **Ans. (b) Patau's syndrome** *(Ref: Robbins 7th/177)*

73. **Ans. (d) 21** *(Ref: Robbins 8th/161, 7th/175-176)*

74. **Ans. (b) Turner syndrome** *(Ref: Robbins 8th/165-167)*

75. **Ans. (a) Size, shape and number of chromosome**
(Ref: Robbins 8th/158-159; 7 th/170)

76. **Ans. (a) Collagen type I** *(Ref: Robbins 8/e p1211-2)*
- ***Osteogenesis imperfecta*** (or ***brittle bone disease***Q) is a phenotypically diverse disorder caused by deficiencies in the synthesis of **type 1 collagen**Q.
- It is the most common inherited disorder of connective tissue.
- It principally affects bone, but also impacts other tissues rich in type 1 collagen (joints, eyes, ears, skin, and teeth). It is characterized by **bone fragility, hearing loss, blue sclera**Q **and dentinogenesis imperfect**.
- Osteogenesis imperfecta usually results from autosomal dominant mutations in the genes that encode theα1 and α2 chains of collagen.

77. **Ans. (b) Metaphase** *(Ref: Robbins 8/e p158)*

Revise NEET info!

- Karyotyping is the study of chromosomes
- Chromosomes are arrested in **metaphase by Colchicine**Q
- These are then stained by many stains. Most commonly used stain is **Giemsa stain**Q, so called **G-banding**Q
- The chromosomes are arranged in **order of decreasing length**Q. Any alteration in number or structure of chromosomes can be easily detected by karyotyping

78. **Ans. (c) 45** *(Ref: Robbins 8/e p165)*
Turner syndrome is the ***most common cause of sex chromosomal abnormality in the females***. It usually results from complete or partial monosomy of X chromosome and associated with hypogonadism in phenotypic females.Q Patients have the (**45X**) karyotype or may be mosaics.

79. **Ans. (d) Trisomy 13** *(Ref: Robbins 8/e p162)*

Trisomy 13 is known as **Patau syndrome** characterized by:
- *Mentalretardation, rocker bottom feet and congenital heart defects (VSD and PDA)*
- *Cleft lip/palate*
- *Polydactyly*
- *Microcephaly*
- *Eye defects* (microphthalmia, iris coloboma, cataract, retinal dysplasia)
- *Capillary hemangiomata*

Mnemonic: useful for AIIMS and NEET questions!

- **p** for **P**atau and **p**olydactyly as well as **p**alate defects: Patau syndrome (trisomy 13)
- **Edward syndrome (trisomy 18): e** for **E**dward and **E**xtra occiput (prominent occiput)

80. **Ans. (a) 47** *(Ref: Robbins 8/e p165)*
Klinefelter syndrome is *the most common chromosomal disorder of males associated with hypogonadism and infertility.* It is due to extra-X-chromosome. Classically, it is **47, XXY**. Other variants can have 48 XXXY, rarely 49 XXXY or mosaics can be there with some cells containing normal 46, XY and others 47, XXY.

81. **Ans. (c) 5 Mb** *(Ref: Encyclopedia of Genetics 3/e p29)*
Karyotype analysis detects both numerical and structural chromosomal aberrations (overall resolution is **5 Mega bases (Mb)**; breakpoint resolution is 5 to 15 Mb).

82. **Ans. (b) FISH** *(Ref: Robbin 8/e p 179)*
FISH uses DNA probes that ***recognize sequences specific to particular chromosomal regions.***

83. **Ans. (a) Fibrillin I** *(Ref: Robbins 8/e p144)*
- Fibrillin occurs in two homologous forms, fibrillin-1 and fibrillin-2, encoded by two separate genes, *FBN1* and *FBN2* mapped on chromosomes 15q21.1 and 5q23.31, respectively.
- Mutations of ***FBN1*** (affecting ***fibrillin-1***Q) underlie Marfan syndrome
- Mutations of the related ***FBN2*** gene (***fibrillin-2***Q) are less common, and are associated with ***congenital contractural arachnodactyly***, an autosomal dominant disorder characterized by skeletal abnormalities.

84. **Ans. (b) Isochromosome**
(Ref: Robbin 8/e p160, The Principles of Clinical Cytogenetics 3/e p157-8)
Isochromosome formation results when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of two short arms only or of two long arms. It has morphologically identical genetic information in both arms.

- The reason for the formation of an isochrome is the centromere misdivision. Instead of ***dividing longitudinally to separate the two sister chromatids, the centromere undergoes a transverse split that separated the two arms from one another***.

85. **Ans. (c) Autosomal monosomy** *(Ref: Robbins 9/e p159)*
Monosomy involving an autosome generally causes ***loss of too much genetic information to permit live birth or even embryogenesis.***

86. **Ans (c) Incidence of the Robertsonian translocation is 1:1000** *(Ref: Robbins 9/e p161)*

87. **Ans (d) True hermaphroditism** *(Ref: Robbins 9/e p166)*

88. **Ans (b) Prader-Willi syndrome** *(Ref: Robbins 9/e p173)*
Prader-Willi syndrome is characterized by interstitial deletion in the long arm of chromosome 15. In all cases the deletion affects the paternally derived chromosome 15. SNORP family of genes encodes small nucleolar RNAs which are involved in modifications of ribosomal RNAs. Loss of SNORP functions is believed to contribute to Prader-Willi syndrome.

89. **Ans. (c) Chromosome 17**
(Ref: Robbins 8th/1078, Harrison 17th/563)

Features	BRCA1	BRCA2
Chromosome	17q21	13q12.3
Function	Tumor suppressor, Transcriptional regulation, Role in DNA repair	Tumor suppressor, Transcriptional regulation, Role in DNA repair

Contd...

Contd...

Features	BRCA1	BRCA2
Age at onset	Younger age (40s to 50s)	50 years
% Single gene hereditary disorders	52%	32%
Risk of other tumors (varies with specific mutation)	Ovarian, Male breast cancer (lower than BRCA2), Prostate, colon, pancreas	Ovarian, ale breast cancer Prostate, pancreas, stomach, melanoma, colon
Pathology of breast cancers	Greater incidence of medullary carcinomas, poorly differentiated carcinomas, ER-, PR-, and *Her2/neu*-negative carcinomas, carcinomas with *p53* mutations	Similar to sporadic breast cancers

90. Ans. (c) X-linked recessive disorder

(Ref: Robbins 8th/142)

Analysis of X-linked recessive disorders

Males have an X and a Y chromosome. There is no corresponding locus for a mutant allele of the X chromosome on the Y chromosome. The mutant recessive gene on the X chromosome expresses itself in a *male child* because it is *not suppressed by a normal allele* whereas in the female, the presence of a normal allele on other X-chromosome prevents the expression of the disease so, *females only act as carriers.*Q

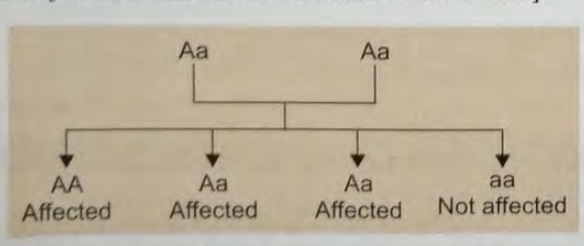
91. Ans. (a) Fraction of cells in apoptotic pathways

(Ref: The journal of Histochemistry & Cytochemistry: Volume 47 (5): 711-717, 1996: Wikipedia)

In situ DNA nick end – labeling *is an in-situ method for detecting areas of DNA which are nicked during apoptosis. Terminal deoxynucleotidyl transferase mediated dUTP–biotin nick end labeling (TUNEL) is a method for detecting apoptotic cells that exhibit DNA fragmentation.*

92. Ans. (b) 25% *(Ref: Harrison's 17th/385)*

Achondroplasia is an **autosomal dominant** condition. Only one mutant allele is enough to cause disease. Thus, AA and Aa will be affected whereas aa will be unaffected. ['A' is mutant allele whereas 'a' is normal].



As is clear from the diagram, 3 out of 4, i.e. 75% of children will be affected and 1 out of 4, i.e. 25% children will be unaffected. However, please note that clinically the baby with AA genotype usually donot survive.

93. Ans. (d) X-linked recessive type *(Ref: Robbins 8th/142)*

Presentation of disease only amongst males identifies the disorder as sex (X) linked. Because carrier mothers are not manifesting the disease, yet their sons do, the disorder can only be recessive. The disorder is thus X– linked recessive.

94. Ans. (a) X –linked recessive *(Ref: Robbins 8th/142)*

The given disease is manifesting only in males, therefore it is sex-linked disease. Females are not affected, so they must be carriers. This is a classical inheritance feature of X-linked recessive disorder.

Remember:

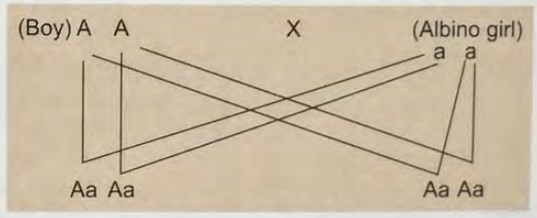
- Male is having XY, i.e. only X-chromosome. So, ***even if one mutant allele is present on X-chromosome, it will manifest*** (whether recessive or dominant).
- Females are XX, so if one gene is mutated in X-chromosome, female will be phenotypically normal and genotypically carrier, ***if inheritance is recessive but female will suffer from disease***, if it is X-linked dominant.
- There is ***no sex predilection in autosomal dominant or recessive disorders***.

95. Ans. (a) None affected, all carriers

(Ref: Harrison 17/2332)

Albinism is an autosomal recessive (AR) disorder

- AR disorders express only in homozygous state, i.e. if both alleles are mutant
- If 'A' is normal allele and 'a' is mutant, then the given cross in the question can be made as

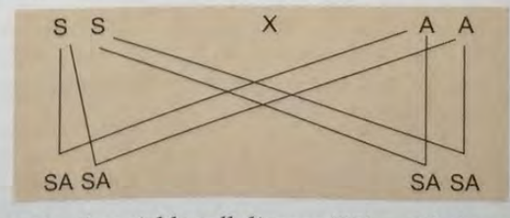


- Thus genotypically all offsprings are carriers and Phenotypically, all of then will be normal.

96. Ans. (a) 0 and 100% *(Ref: Harrison 17th/637)*

Sickle cell anemia is an autosomal recessive disorder.

- Sickle cell disease is the homozygous state of HbS (SS) where S stands for gene coding HbS.
- Sickle cell trait is the heterozygous state of HbS (SA) where A stands for absent gene.
- Normal individual has no gene for HbS (AA)



If the mother has sickle cell disease 'SS' and father is normal 'AA' all the offsprings will be 'SA'. Thus % of sickle

cell disease (SS) will be zero and that of sickle cell trait (SA) will be 100%.

97. **Ans. (a) Blood group O** *(Ref: Harrison 17th/708)*

Major blood group system is ABO system. These are based on the presence of antigen on surface of RBCs Four blood groups according to this system are.

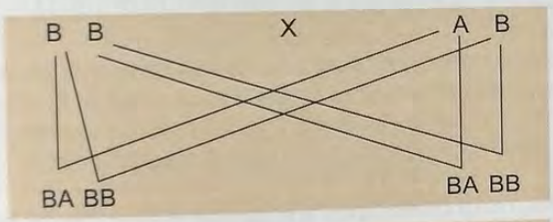
Blood Group	Antigen	Anti body (Isoagglutinins)
A	A	Anti – B
B	B	Anti – A
AB	A and B	None
O	None	Anti – A and Anti – B

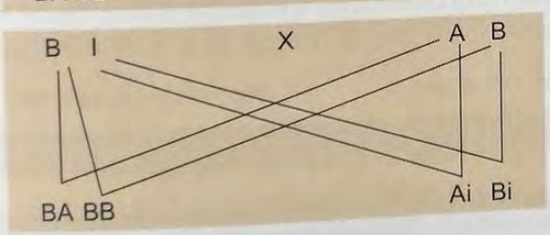
- The genes that determine A and B phenotypes are found on chromosome 9p and are expressed in a Mendelian co-dominant manner.
- AB group is universal recipient (No antibody) and Blood group O is universal donor (No antigen)
- Blood group according to alleles can be

A	AA or Ai
B	BB or Bi
AB	AB
O	ii

[i means allele containing gene for no antigen]

- In the given question, father is blood group B [i.e. BB or Bi] and mother is AB. The cross can be





- Thus, phenotypically blood group can be A (Ai), B (Bi, BB) or AB (AB). Thus, none of the children can have O blood group.

98. **Ans. (d) All of the above** *(Ref: Harrison 18th/547-551)*

Gene transfer is a novel area of therapeutics in which the active agent is a nucleic acid sequence rather than a protein or small molecule. Most gene transfers are carried out using a vector or gene delivery vehicle because delivery of naked DNA or RNA to a cell is an inefficient process. More clear-cut success has been achieved in a gene therapy trial for another form of SCID, adenosine deaminase (ADA) deficiency. Other diseases likely to be amenable to transduction of hemaopietic stem cells (HSCs) include

- Wiskott-Aldrich syndrome
- Chronic granulomatous disease
- Sickle cell disease
- Thalassemia.

Clinical trials using recombinant adeno-associated vectors are now ongoing for muscular dystrophies, alpha-1 antitrypsin deficiency, lipoprotein lipase deficiency, hemophilia B, and a form of congenital blindness called Leber's congenital amaurosis.

99. **Ans. (b) Chromosome 6** *(Ref: Harrison 17th/2045)*

100. **Ans. (c) Chromosome 21** *(Ref: Harrison 17th/644)*

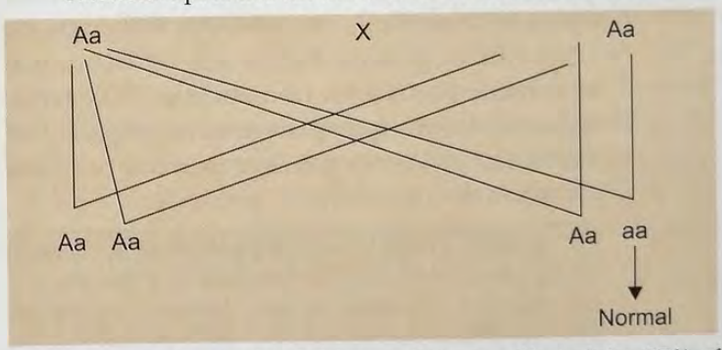
101. **Ans. (c) Trans-differentiation**
(Ref: Robbins 7th/92 & Harrison 17th/426)

Stem cell is defined as a cell with a unique capacity to produce unaltered daughter cells (*self-renewal*) and to generate specialized cell types (*potency*).

The prevailing paradigm in developmental biology is that once cells are differentiated, their phenotypes are stable. However, tissue stem cells, which are thought to be lineage-committed multipotent cells, possess the capacity to differentiate into cell types outside their lineage restrictions (called **trans-differentiation** or **stem cell plasticity**). For example, hematopoietic stem cells may be converted into neurons as well as germ cells.

102. **Ans. (b) 25%** *(Ref: Robbins 8th/141, 7th/151)*

Achondroplasia is an autosomal dominant disease.



So, only 1 out of 4 children will be unaffected, i.e. 25% of children will be normal.

103. **Ans. (c) Parallel rays of tubular structure in lysosomes**
(Ref: Robbin 8th/152-153)

- **PAS stain** is a widely used stain which gives positive reaction with glycogen (primarily) and non glycogen substances like glycoprotein, glycolipids, proteoglycans and neutral mucins.
- Whether the PAS positivity of a particular cell is due to presence of glycogen or due to latter can be differentiated with diastase (glycogen digesting enzyme).
- If the cell is PAS positive due to glycogen, the pretreatment with diastase will make it PAS negative. But if the cell is PAS positive due to non glycogen substances, the cell will retain its PAS positivity even after pretreatment with diastase. So, in the given question, the presence of PAS positive and diastase resistant material indicates presence of non glycogen substances.

- The clinical feature of delayed milestones and hepatosplenomegaly in 1 year old boy is suggestive of some lysosomal storage disorder (like Niemann Picks disease).
- This disease is characterized by the presence of large foam cells in bone marrow, liver and spleen. There is presence of pleomorphic inclusion of lipids in lysosomes enclosed in concentric or parallel lamellae.

104. Ans. (b) Homeobox gene *(Ref: Robbins 8th/452-3)*

Classes of genes known to be important in normal morphogenesis during development include

- **Homeobox genes (HOX):** *The HOX genes have been implicated in the patterning of limbs, vertebrae, and craniofacial structures. HOX* genes possess retinoic acid response elements *(RAREs)*, and that the latter are required for mediating both physiologic and pathologic effects of retinoids during development. Mutations of ***HOXD13*** cause ***synpolydactyly*** (extra digits) in heterozygous individuals and mutations of ***HOXA13*** cause ***hand-foot-genital syndrome***, characterized by distal limb and distal urinary tract malformations.
- **PAX genes:** *PAX* genes are characterized by a 384 base pair sequence — the *paired box*. They code for DNA-binding proteins that are believed to function as transcription factors. In contrast to *HOX* genes, however, their expression patterns suggest that they act singly, rather than in a temporal or spatial combination.

- Mutation in ***PAX3*** causes ***Waardenburg syndrome*** (congenital pigment abnormalities and deafness).
- Mutation in ***PAX6*** causes ***Aniridia*** (congenital absence of the iris)
- **PAX2** mutations cause the "***renal-coloboma***" syndrome (developmental defects of the kidneys, eyes, ears, and brain).
- Translocations involving ***PAX3*** and ***PAX7*** are seen in **alveolar rhabdomyosarcomas**.
- Translocations involving **PAX5** are seen in subsets of ***lymphomas***
- Translocations involving ***PAX8*** are seen in **thyroid cancers**.

Other options

FMR gene: It is involved in fragile X-syndrome.

PTEN gene: located on chromosome 10q is associated with endometrial cancers and glioblastoma. (phosphatase and tensin homologue)

p16 blocks cell cycle and is a tumor suppressor gene.

105. Ans. (c) AB, Rh negative (Too obvious to explain friends)

106. Ans. (b) Splicing; (d) Frame-shift: *(Ref: Harper' 27th/415, Robbins 8th/648-9)*

Important causes of thalassemia are:

β-thalassemia: A wide variety of mutations in β-globin gene may cause this including
- Promoter region mutations
- Chain terminator mutations include frameshift mutations.
- Splicing mutations

β^0-thalassemia, associated with total absence of β-globin chains in the homozygous state. Its commonest cause is chain termination.

β^+-thalassemia, characterized by reduced (but detectable) β-globin synthesis in the homozygous state. Its commonest cause is **splicing mutation**.

α-thalassemia: Mutations in α-globin gene are mainly unequal crossing over and large deletions and less commonly nonsense and Frame-shift mutations.

107. Ans. (a) Bloom syndrome; (b) Fanconi's anemia; (d) Chediak-Higashi syndrome; (e) Ataxia telangiectasia *(Ref: Harrison 16th/643, 631, Robbins 7th/307)*

Bloom's syndrome, Fanconi anemia, Klinefelter syndrome, Ataxia telangiectasia and Kostman syndrome are associated with myeloid leukemia.

108. Ans. (c) Loss of normal allele in mutant gene *(Ref: Robbins 7th/299)*

"A child with inherited mutant RB allele in somatic cells is perfectly normal. Because such a child is a heterozygous at the Rb locus, it implies that heterozygosity for the Rb gene does not affect cell behavior. Cancer develops when the cell becomes homozygous for the mutant allele or in other words when the cell loses heterozygosity for the normal Rb gene (a condition known as LOH loss of heterozygosity)"

Thus, from these lines we interpret that loss of heterozygosity means loss of normal allele in mutant gene.

109. Ans. (b) q and p *(Ref: Robbins 6th/166, 7th/171)*

- Short arm of a chromosome is designated 'p' (for petit) and long arm is referred to as 'q'
- In a banded karyotype, each arm of the chromosome is divided into two or more regions by prominent bands.

- The regions are numbered (e.g. 1, 2, 3) from centromere outwards.
- Each region is further subdivided into bands and sub bands and these are ordered numerically as well.
- Thus, the notation Xp 21.2 refers to a chromosomal segment located on the short arm of the 'x' chromosome, in region 2, band 1 and sub band 2.

110. Ans. (c) 7 *(Ref: Robbins 8th/465; 7th/490)*

111. Ans. (b) Granulosa cell tumor *(Ref: Robbins 8th/1338;)*

112. Ans. (d) 7 *(Ref: Robbins 9/e p466)*

113. Ans. (a) Pseudomonas *(Ref: Robbins 9/e p469)*

Pseudomonas aeruginosa species, in particular, colonize the lower respiratory tract, first intermittently and then chronically.

114. Ans. (c) X-linked dominant disease

(Ref: Robbins 8/e p142)

Since a male transmits only the 'Y' chromosome to his son, so obviously he cannot transmit any X linked disease.

115. Ans. (a) Study of multiple genes *(Ref: Robbins 8/e p174)*

Microarrays are gene chips used to **sequence genes or portions of genes.** In this technique, short sequences of DNA (oligonucleotides) that are complementary to the wild-type sequence and to known mutations are "tiled" adjacent to each other on the gene chip, and the DNA sample to be tested is hybridized to the array. Before hybridization the sample is labeled with fluorescent dyes. The hybridization (and consequently, the fluorescent signal emitted) will be strongest at the oligonucleotide that is complementary to wild-type sequence if no mutations are present, while the presence of a mutation will cause hybridization to occur at the complementary mutant oligonucleotide.

116. Ans. (a) Northern blot

- **N**orthern Blot : **RNA** ⟶ **N**orth : **R**oti
- **S**outhern Blot : **DNA** ⟶ **S**outh : **D**osa
- **W**estern Blot : **Proteins** ⟶ **W**est : **P**oha/**P**izaa

117. Ans. (a) 50% of boys of carrier mother are affected

(Ref: Robbins 8/e p142)

Looking at the statements one by one:

- Carrier mother contributes to the transfer of one of the two boys getting the affected chromosome. So, 50% of boys of carrier mother are affected.
- Option "**b**"...All girls having diseased father are affected as carriers because they get the affected 'X' sperm from their fathers. However, these girls are not going to manifest the disease.
- Option "c"...fathers cannot transmit the disease to their sons as they transmit just the "Y" chromosome to them whereas the disease is "X" linked.
- Option "d"... mothers contribute to just one "X" chromosome and so, 50% of the daughters would become carriers if t other was a carrier.

118. Ans. (c) Chromosome 11 *(Ref: Robbins 8/e p479-80)*

Easiest way to remember that info..... count the number of letters in Wilms tumour..yea it is exactly 11...the location of both genes associated with Wilms tumour ☺

So, the two genes associated with Wilms tumour **WT1** gene (located on **chr 11p13**)and WT2 gene (located on **chr 11p15).**

119. Ans. (b) Rh-ve mother with 2nd Rh+ve child

- Rh-ve mother with 2nd Rh+ve child can result in the development of **hemolytic disease of newborn** or **erythroblastosis fetalis**. So, it is a dangerous condition.
- This condition is a **type II hypersensitivity** reaction.
- *This is Not to be confused with Hemorrhagic disease of the newborn* which is a coagulation disturbance in the newborns due to vitamin K deficiency. As a consequence of vitamin K deficiency there is an impaired production of coagulation factors II, VII, IX, X, C and S by the liver.

ANNEXURE

LOCATION OF IMPORTANT GENES ON CHROMOSOMES

Gene	Chromosome
p73	1p
Folate transporter	**21q**
Neuroblastoma	1p
Rhodopsin	3
VHL	3p
ADPKD-2	4q
ADC	5p
MHC	**6p**
ARPKD	6
Cystic fibrosis	7q

Contd...

Contd...

Gene	Chromosome
MET	7
RET	10
WT-1	11p
vWF	12
Retinoblastoma	**13q**
BRCA-1	**17q**
Fibrillin-1	15
Fibrillin-2	5
BRCA-2	**13q**
NF-1	**17q**
p53	**17p**
NF-2	**22q**

CHAPTER 5

Neoplasia

Golden Points

- **Willis** gave the definition of neoplasm.
- Excessive fibrosis in tumor is called as desmoplasia. It is responsible for linitis plastic appearance of stomach cancer.
- Abnormal differentiation at normal site: Hamartoma. It is now considered as a neoplasm.
- Normal differentiation at abnormal (ectopic) site: Choristoma.
- Replacement of a mature (differentiated) cell type into other mature cell is called Metaplasia. **Squamous metaplasia** in the *lungs of smokers* is the commonest example.
- Lack of differentiation is called Anaplasia. It has irreversible loss of polarity.
- Disordered differentiation is called dysplasia. It has reversible loss of polarity.
- Carcinoma in situ and invasive carcinoma are differentiated by: ***involvement of basement membrane*** (penetration is seen in invasive carcinoma).
- **Most reliable** sign of malignancy is **Metastasis**.
- 2nd most reliable sign of malignancy: Local invasion.
- Sarcomas metastalize usually by hematogenous route whereas carcinomas metastatize usually by lymphatic route.
- Cancer cells derive energy from Aerobic glycolysis (**Warburg effect**).
- Most common target for genetic alteration in human tumor: p53.
- DNA damage by irradiation/UV light causes: Increase in p53 level and cell cycle arrest in G_1 (due to blockade at G_1S transition).
- Mutated form of p53 gene associated with cancer whereas the non-mutated form (wild form) is associated with reduced risk of development of cancer.
- p53 acts through: CDK inhibitor p21 (p53 itself is not a CDK inhibitor).
- p53 acts at: G_1S check point.
- Retinoblastoma (RB) gene regulates: G_1- S transition.
- Important autosomal dominant familial cancers: FAP, Wilms tumor, breast/ovary cancers, retinoblastoma, MEN-1 and 2, Neurofibromatosis 1 and 2.
- ***Defective DNA repair syndromes*** predisposing to cancer: Bloom syndrome, Fanconi anemia, Ataxia telangiectasia and Xeroderma pigmentosa.
- BRCA-1 is located on chromosome I7q whereas BRCA-2 is located on Chromosome 13q
- Retinoblastoma gene is located on: Chromosome 13q14.
- Conditions predisposing to cancer include regeneration, hyerplasia, dysplasia, metaplasia, chronic inflammation and atrophy. Hypertrophy does not cause cancer.
- The detachment of epithelial cells from basement membranes and from cell-cell interactions can lead to a particular form of cell death called ***anoikis***.
- ***COX2 inhibitors*** decrease the incidence of colonic adenomas and are now approved for treatment of patients with ***familial adenomatous polyposis***
- ***All trans-retinoic acid*** is a highly effective therapy is **the first example** of **differentiation therapy**, in which immortal tumor cells are induced to differentiate into their mature progeny, which have limited life spans. It is used for treating patients with **acute promyelocytic leukemia**.
- ***Chromothrypsis*** *is a process in which a chromosome is "shattered" and then re-assembled in a haphazard way. It is seen in is found in up to 25% of* ***osteosarcomas*** *and at a relatively high frequency in* ***gliomas*** *as well.*
- Tumor markers can be used for screening to assess response of therapy/surgery, follow- up (to see recurrence), prognosis and to assess the growth. They cannot be used to confirm diagnosis.
- Marker of testicular tumors: AFP, HCG, placental alkaline phosphatase, placental lactogen, LDH.
- **AFP** (alpha feto-protein) is genetically and structurally related to **Albumin.**
- Important markers for different cancers: CD-99 (Ewing's sarcoma), Placental alkaline phosphatase (Seminoma of testis), Cytokeratin(carcinoma), CD34 (Alveolar soft part sarcoma) Desmin (rhabdomyosarcoma/leiomyosarcoma) and 'BRAF' gene mutation (Melanoma)

- **SYT-SSX1 and SYT-SSX2 genes** are associated with **synovial sarcoma**.
- Mutagenicity test is called as **Ames test.**
- Most important predictor of mesenchymal tumors: Grade.
- Commonest carcinoma in male is carcinoma of Lung. However, the commonest carcinoma in elderly male is Prostate.
- Cachexia in tumor is due to TNF.
- **Migratory thrombophlebitis** is seen in **Pancreas** (most common), lung (2nd common), GIT, Prostate, breast, ovary, brain and lymphomas.
- Most common hormone producing hypercalcemia in tumors: Parathormone related peptide.
- Features of tumor lysis syndrome include: Hypocalcemia, hyperkalemia, hyperuricemia, hyperphosphatemia and lactic acidosis. It does not include hypercalcemia
- Spontaneous regression is seen in the following tumors: Neuroblastoma, malignant melanoma and retinoblastoma.
- Exfoliative cytology is useful in: Cancers of cervix, endometrium, lung (bronchogenic), bladder, prostate and stomach.
- *Intraoperative histopathological analysis* **can not** be used for immediate definite diagnosis of a cancer. It is only useful for detecting positive margins after resection and is used to confirm suspected metastasis.
- **Lewis Thomas** and **Macfarlane Burnet** coined the term ***immune surveillance***, which implies that a normal function of the immune system is to constantly "scan" the body for emerging malignant cells and destroy them.

NEOPLASIA

Neoplasia refers to the process of new growth. The important feature of the growth associated with neoplasms is the fact that it is an uncoordinated growth of the tissue persisting even after the cessation of the stimulus which evoked the change. Oncology is the study of tumors or neoplasms. The tumors are usually composed of the:

Concept

Desmoplasia is a term used for stimulation of abundant collagenous stroma by the parenchymal cells.

1. Parenchyma – Made up of proliferating neoplastic cells
2. Stroma – Made up of connective tissue and blood vessels.

Benign Tumors

These are usually denoted by adding a suffix "- oma" to the cell of origin, so, these may be arising from fibroblastic cells (fibroma); cartilage cells (chondroma) or osteoblasts (osteoma). Adenoma and Papilloma are examples of benign tumors.

Definition

Adenoma – Benign epithelial tumor arising from glands or forming a ***glandular pattern***
Papilloma – Benign tumor with ***finger–like projections***
Polyp – Tumor producing a visible projection above a mucosal surface protruding in the lumen.

MALIGNANT TUMORS

Cancer is a generalized term used for all malignant tumors. These tumors can be of the following types:

1. **Sarcoma** - Arising from mesenchymal tissue.
2. **Carcinoma** – Tumor of epithelial cell origin derived from any germ layer. If this tumor is having a glandular pattern, it is called adenocarcinoma.

The divergent differentiation of parenchymal cells produces mixed tumors or pleomorphic tumors.

In teratoma, parenchymal cells are made up from more than one germ layer e.g. Dermoid cyst.

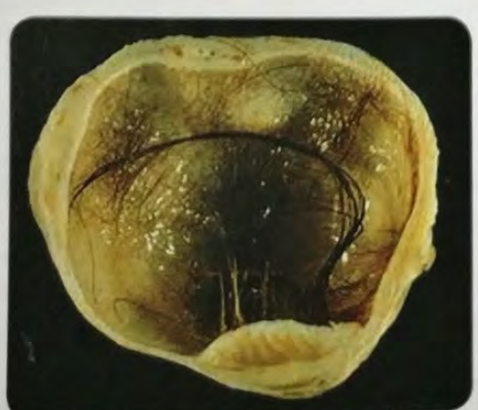
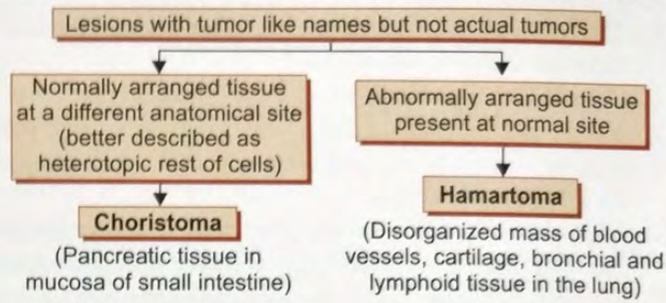


Fig. 1: Dermoid cyst

Key Point

Teratoma is derived from *ectoderm, endoderm* and *mesoderm.*



Concept

Many **hamartoma** have clonal chromosomal aberrations that are acquired through somatic mutations and so, ***now they are considered as neoplasms***.

Characteristics of Neoplasia

I. **Anaplasia**: The extent to which neoplastic cells resemble normal cells both morphologically and functionally is called differentiation. An *absence of differentiation* is called anaplasia.

The features of anaplasia are:

1. *Pleomorphism* – It is the variation in the size and shape of the cells.
2. *Hyperchromasia* – Increased nuclear material or DNA is responsible for dark staining of the cells called hyperchromasia. In normal cells, the nuclear cytoplasmic (or N: C) ratio is 1:4 whereas it becomes 1: 1 in anaplastic cells.
3. *Increased mitosis* gives rise to atypical bizarre mitotic figures.

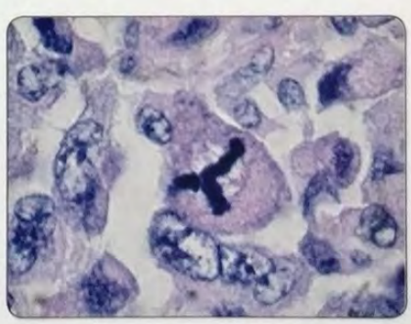


Fig. 2: Tripolar mitotic spindle in anaplasia

4. *Loss of polarity* due to disturbed orientation of anaplastic cells.
5. Presence of tumor giant cells having big hyperchromatic nuclei.

Key Point

Anaplasia is the hallmark of malignant transformation.

Concept

- Dysplasia is characterized by the abnormal proliferation of the cells which also exhibit pleomorphism. It is not cancer but can give rise to cancer as it is a preneoplastic lesion.
- When dysplastic changes involve entire thickness of the epithelium but the lesion remains confined to the normal tissue, it is called ***carcinoma in situ***. When the cancer cells move beyond the normal tissue, it is said to be invasive.

Recent Exam Question

Malignant tumors have upregulation of telomerase activity.

Key Point

Dysplasia is a *partially reversible* condition having **intact basement membrane**.

Key differentiating features between Metaplasia, Dysplasia and Anaplasia

Feature	Metaplasia	Dysplasia	Anaplasia
Definition	Reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type	A change having loss in the uniformity of the individual cells and loss of architectural orientation	An *absence of differentiation* (extent to which neoplastic cells resemble normal cells both morphologically and functionally)
Pleomorphism (variation in the size and shape of cells/nuclei)	Absent	**Present**[Q] in low grade	**Present**[Q] in high grade
Reversibility	Reversible[Q]	**Reversible in early stages** (irreversible if whole epithelium is involved)	Irreversible[Q]
N:C ratio	Normal (1:4)	Increased (↑)	Increased (↑↑↑)
Hyperchromatism	Absent	Present (small degree)	Present (high degree)
Mitotic figures	Absent/minimal at normal places	**Typical mitotic figures**[Q] present at abnormal places	**Atypical mitotic figures**[Q] (multipolar spindles) present at abnormal places
Other features (Tumor giant cells[Q], hemorrhage, necrosis)	Absent	Absent	**Present**[Q]
Example	Barret's esophagus, myositis ossificans	Cervical dysplasia of squamous cells	Carcinoma of the cervix, carcinoma esophagus

II. **Rate of growth**: The growth of a tumor correlates with the level of differentiation. Well-differentiated tumors have a slow proliferation rate. Recently, cancer stem cells or tumor-initiating cells (*T-ICs*) have been identified in breast cancer, glioblastoma multiforme (a brain tumor), and acute myeloid leukemia. These T-ICs are cells that allow a human tumor to grow and maintain itself definitely when transplanted into an immunodeficient mouse.

Key Point

Usually, **10^9 cells** produce a clinically detectable tumor.

III. **Local invasion**: It is the second most reliable feature that differentiates malignant from benign tumors. The benign tumors are slow growing, cohesive, expansile masses that are usually capsulated. The malignant tumors show invasion, infiltration and destruction of the surrounding tissue.

Recent Exam Question

Almost all cancers can metastasize *except* **glioma** (malignancy of central nervous system) and the **rodent ulcer** (or **basal cell cancer** of the skin).

IV. **Metastasis**: It is the *most reliable feature* of a malignant tumor, characterized by the spread of the tumor to other parts because of penetration into blood vessels, lymphatics and the body cavities.

Recent Exam Question

Sentinel lymph node is useful for breast cancer, malignant melanoma, colon cancer and vulval cancer.

Pathways of spread

Direct seeding of body cavities and surfaces	Lymphatic spread	Hematogenous sprad
• Involvement of peritoneal cavity (in ovarian cancer). • Surface of abdominal viscera (mucus secreting appendicle cancer causing pseudomyxoma peritonei).	• Usual for carcinomas • Pattern of lymph node involvement follows natural route of lymphatic drainage. • **Sentinel lymph node** is the first lymph node to receive lymph flow from a primary tumor. • Seen in melanoma, breast and colon cancer.	• Usual for sarcomas • Thinner walls of veins causes preferential venous invasion in comparison to arteries. • **Liver and lungs** are the most commonly affected organs. • Invasion of veins is particularly prominent is hepatocellular cancer and renal cell cancer.

PRECURSOR LESIONS

Precursor lesions are localized morphologic change that are associated with a high risk of cancer. They can be of the following subtypes:

Precursor Lesions

With inflammation
- Barret esophagus due to chronic reflux disease
- Squamous metaplasia of bronchus due to smoking
- Colonic metaplasia in stomach due to pernicious anemia

Without inflammation
- Endometrial hyperplasia
- Leukoplakia of the oral cavity/penis/vulva

Benign tumors with malignant transformation
- Colonic villous adenoma

Cancer-Enabling Inflammation

Inflammatory cells increase the risk of cancers by different mechanisms like:

i. Release of factors that promote proliferation
ii. Removal of growth suppressors,
iii. Enhanced resistance to cell death,
iv. Inducing angiogenesis,
v. Activating invasion and metastasis
vi. Evading immune destruction

Concept

Monoclonality of tumors

- Most of the cancers arise from single clone of the cells (monoclonal in nature) non neoplastic proliferations are coming from multiple cells (polyclonal in nature). Because of *random X inactivation*, **normally all females will be having both isoforms of the enzymes whereas malignant transformation results in a single marker being expressed**.
- ***Monoclonality of tumors*** is assesed by ithe analysis of methylation patterns adjacent to the highly polymorphic locus of the human androgen receptor gene **(HUMARA)**and enzymes like glucose-6-phosphate dehydrogenase **(G6PD)**, *iduronate-2-sulfatase* and *phosphoglycerate kinase*.

Recent Exam Question

Immunoglobulin receptor and *T-cell receptor* gene rearrangements serve as markers of clonality in **B-** and *T-cell* lymphomas, respectively

GENETIC PREDISPOSITION TO CANCER/INHERITED CANCER SYNDROMES

I. **Autosomal dominant cancer syndrome**
- Inheritance of a single mutant gene increases the risk of development of cancer.
- Can be remembered as

Very	- **V**on Hippel Lindau (VHL) syndrome causing renal cell cancer
Rich	- **R**etinoblastoma
Cute and	- **C**owden syndrome (PTEN gene)
Nice	- **N**eurofibromatosis 1, 2; **N**evoid basal cell cancer syndrome
Men	- **M**elanoma: **M**EN (Multiple Endocrine Neoplasia) 1 and 2

Hereditarily	- Hereditary nonpolyposis colon cancer
Like	- Li-Fraumeni syndrome, LKB1 gene in Peutz Jeghers syndrome
Familiar	- Familial adenomatous polyposis
Females	- ovarian and breast tumor (will occur is **females** obviously)

Mnemonic

For **Autosomal dominant** cancer syndrome, just remember the line:
Very Rich, Cute and Nice Men Hereditarily Like Familiar Females

II. **Familial cancers**
- These are cancers occurring at high frequency in families ***without a clear defined pattern of transmission.*** These usually show early age of onset and are present is 2 or more close relatives of the index case.
- Include cancer of colon, ovary, breast, pancreas, etc.

III. **Autosomal recessive cancer syndrome (all of these are caused due to Defective DNA Repair)**

Mnemonic

Big	- **B**loom syndrome
F	- **F**anconi anemia
A	- **A**taxia telangiectasia
X	- **X**eroderma pigmentosum

The seven fundamental changes in cell physiology that together determine the malignant phenotype are:
1. Self-sufficiency in growth signals: Due to oncogene activation
2. Insensitivity to growth-inhibitory signals
3. Evasion of apoptosis: Presence of resistance to apoptosis
4. Limitless replicative potential: Presence of unrestricted proliferative capacity due to telomerase activity
5. Development of sustained angiogenesis
6. Ability to invade and metastasize
7. Genomic instability resulting from defects in DNA repair
8. Aerobic glycolysis (*Warburg effect*).

Recent Exam Questions

- **Warburg effect** or **aerobic glycolysis** is the shifting of glucose metabolism by the cancer cells from the efficient mitochondria to glycolysis.
- It is seen because tumor cells have **M2** isoform of **pyruvate kinase** enzyme
- **PET scanning** requires the injection of **18 fluoro-deoxy-glucose** (18-FDG)

CELL CYCLE AND CONTROL MECHANISMS

- Cell cycle consists of five phases. These include:

G_1	:	Pre-synthetic phase
S	:	Synthetic phase (DNA synthesis)
G_2	:	Post-synthetic pre-mitotic phase
M	:	Mitotic phase: Cells divide and produce new cells, which either directly re-enter next cycle or pass into non- proliferative G_0 phase
G_0	:	Quiescent state: Cells in this state remain quiescent for variable periods, but can be recruited in cell cycle if stimulated later.

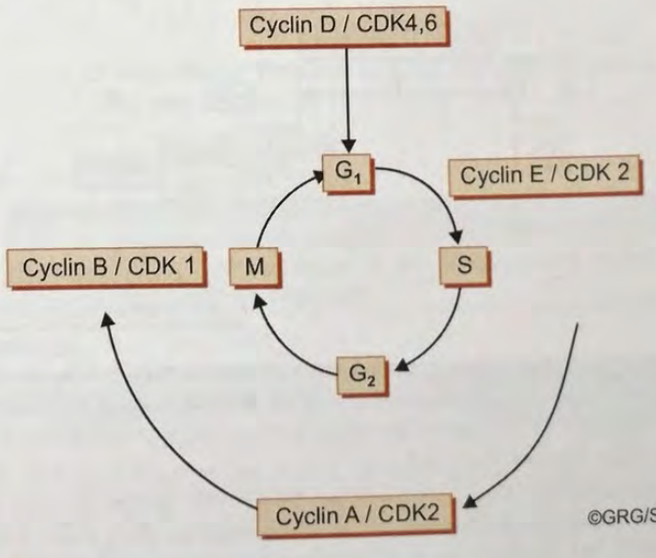
Key Point

S phase is characterized by doubling of the nuclear material. It is a ***point of no return*** in the cell cycle

- Resting (non-dividing) cells are in the G_0 stage of the cell cycle and must enter G_1 stage for replication. *The orderly progression of cells through the various phases of cell cycle is controlled by cyclins and cyclin-dependent kinases (CDKs), and by their inhibitors.*
- CDKs are expressed constitutively during the cell cycle but in an inactive form whereas cyclins are synthesized during specific phases of the cell cycle, and their function is to activate the CDKs.
- Cyclins D, E, A, and B appear sequentially during the cell cycle and bind to one or more CDKs.

Key Point

Cyclin D is the **first cyclin** to increase in the cell cycle.



Key Point

The **initiation of DNA replication** involve the formation of an active complex between **cyclin E** and **CDK2**.

- During the G_1 phase of the cell cycle, cyclin D binds to and activates CDK4, forming a *cyclin D-CDK4 complex*. This complex has a critical role in the cell cycle by phosphorylating the retinoblastoma susceptibility protein (RB). *The phosphorylation of RB is a molecular ON-OFF switch*

for the cell cycle. Phosphorylation of RB results in activation of transcription factor E2F. Activated E2F results in transcription of target genes like cyclin E, DNA polymerases, thymidine kinase, dihydrofolate reductase etc.

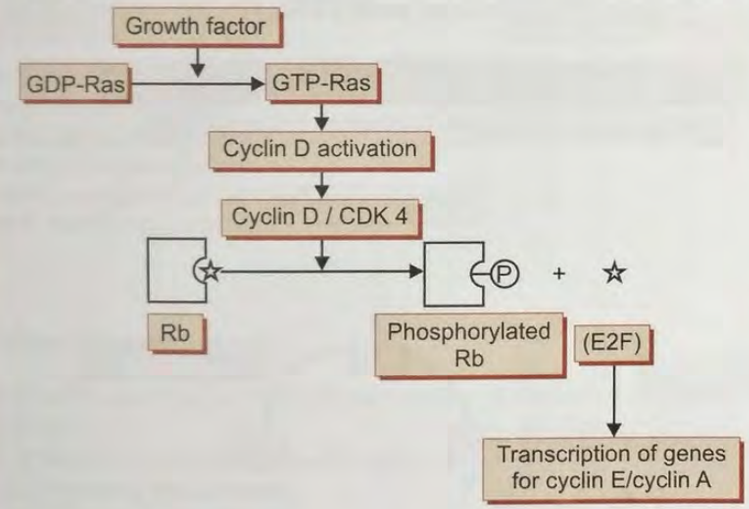
Key Point

The **phosphorylation of** RB is a **molecular ON-OFF switch** for the cell cycle.

- *Further progression through the S phase and the initiation of DNA replication involve the formation of an active complex between cyclin E and CDK2.* The next decision point in the cell cycle is the G_2/M transition. This transition is initiated by the E2F-mediated transcription of cyclin A, which forms the cyclin A-CDK2 complex that regulates events at the mitotic prophase. The main mediator that propels the cell beyond prophase is the cyclin B-CDK1 complex, which is activated by a *protein phosphatase (Cdc 25).* Cyclin B-CDK1 activation causes the breakdown of the nuclear envelope and initiates mitosis.

Key Point

The main mediator that propels the cell **beyond prophase** is the **cyclin B-CDK1 complex**.



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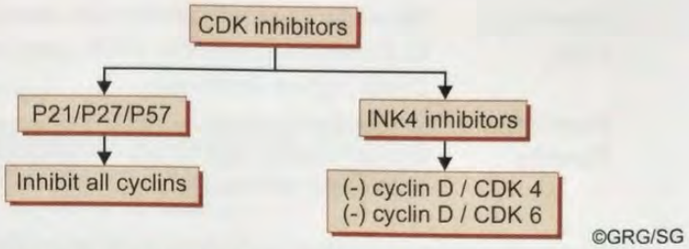
Cell-Cycle Inhibitors

The activity of cyclin-CDK complexes is tightly regulated by inhibitors, called CDK inhibitors. There are two main classes of CDK inhibitors: *the Cip/Kip and the INK4/ARF families.*

- *The Cip/Kip family* has three components, p21, p27, and p57, which bind to and inactivate the complexes formed between cyclins and CDKs. Transcriptional activation of p21 is under the control of *p53*
- The *human INK4a/ARF locus* (a notation for "*in*hibitor of *k*inase 4/*a*lternative *r*eading *f*rame") encodes two proteins, p16INK4a and p14ARF, which block the cell cycle and act as tumor suppressors. p16INK4a competes with cyclin D for binding to CDK4 and inhibits the ability of the cyclin D-CDK4 complex to phosphorylate RB, thus causing cell-cycle arrest at late G_1 whereas p14ARF prevents p53 degradation.



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Cell-Cycle Checkpoints

The cell cycle has its own internal controls, called *checkpoints.* There are two main checkpoints, one at the G_1/S transition and another at G_2/M.

- The S phase is the point of no return in the cell cycle, and before a cell makes the final commitment to replicate, the **G1/S checkpoint** checks for DNA damage. If DNA damage is present, the DNA repair machinery gets activated and arrests the cell cycle. If the damage is not repairable, apoptotic pathways are activated to kill the cell. Thus, the G_1/S checkpoint prevents the replication of cells that have defects in DNA.

Key Point

Cells damaged by **ionizing radiation** activate the **G_2/M checkpoint** and arrest in G_2; defects in this checkpoint give rise to chromosomal abnormalities.

- DNA damaged after its replication can still be repaired as long as the chromatids have not separated. The **G_2/M checkpoint** monitors the completion of DNA replication and checks whether the cell can safely initiate mitosis and separate sister chromatids. This checkpoint is particularly important in cells exposed to ionizing radiation.

Key Point

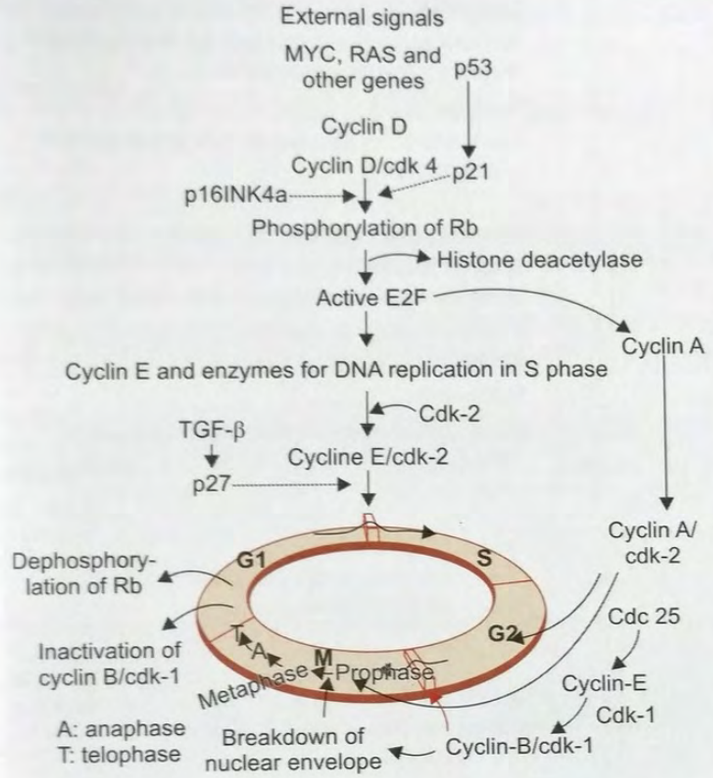
G_1/S check-point is controlled by **p53** whereas ***G_2/M check-point*** has both ***p53 dependent as well independent*** mechanisms.

- To function properly, cell-cycle checkpoints require sensors of DNA damage, signal transducers, and effector molecules. In the G_1/S checkpoint, cell-cycle arrest is mostly mediated through p53, which induces the cell-cycle inhibitor p21. Arrest of the cell cycle by the G_2/M checkpoint involves both p53-dependent (via cyclin A/cdK-2) and independent (via cdc 25) mechanisms.
- *p53 links cell damage with DNA repair, cell-cycle arrest, and apoptosis. In response to DNA damage, it is phosphorylated by genes that sense the damage and are involved in DNA repair. p53 assists in DNA repair by causing G1 arrest and inducing DNA repair genes. A cell with damaged DNA that cannot be repaired is directed by p53 to undergo apoptosis. With homozygous loss of p53, DNA damage goes unrepaired and mutations increase the chances of malignant transformation.*

Key Point

- Proteins of the **RAD** and ataxia telangiectasia mutated **(ATM)** families act as **sensors of DNA damage.**
- Proteins of the **CHK kinase** families act as *transducers.*

Regulation of Cell Cycle



Key Point

p53 is called as "**guardian of the genome.**"

Recent Exam Questions

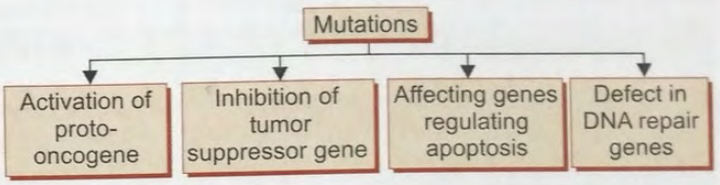
- **Prophase:** The **chromatin is condensing** into chromosomes.
- **Metaphase:** chromosomes **align at the metaphase plate.**
- **Anaphase:** The **chromosomes split** and the kinetochore microtubules shorten.
- **Telophase:** the **decondensing chromosomes** are surrounded by nuclear membranes.

CARCINOGENESIS

It is a multi-step process which requires accumulation of multiple genetic changes either as germline or somatic mutations. The following four are the principal targets of genetic damage:

Key Point

Proto-oncogenes were discovered by **Harold Varmus** and **Michael Bishop**.



I. Proto-Oncogenes

Proto-oncogenes (Normal genes required for cell proliferation and differentiation)

↓

Oncogenes (Genes promoting autonomous cell growth in cancer cells)

↓

Oncoproteins (Proteins lacking regulatory control and responsible for promoting cell growth)

Recent Exam Question

Chromosomal translocation is the ***commonest*** cause of ***activation*** of **proto-oncogenes**.

Selected Oncogenes, their mode of activation and associated human tumors

Category	Proto-oncogenes	Mode of activation	Associated human tumor
Growth factors			
PDGF-β chain	**SIS**	Overexpression	Astrocytoma Osteosarcoma
Fibroblast growth factors	HST-1 INT-2	Overexpression Amplification	Stomach cancer Bladder cancer Breast cancer Melanoma
TGF-α	TGFA	Overexpression	Astrocytomas Hepatocellular carcinomas
HGF	HGF	Overexpression	Thyroid cancer
Growth factor: Receptors			
EGF-receptor family	ERB-B1 **(EGFR)** **ERB-B2**	Overexpression Amplification	Squamous cell carcinomas of lung, gliomas Breast and ovarian cancers

Contd...

Contd...

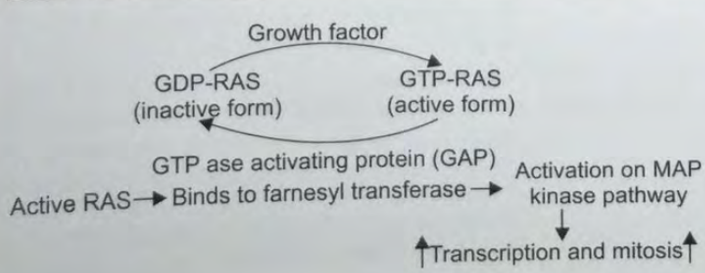
CSF-1 receptor	FMS	Point mutation	Leukemia
Receptor for neurotrophic factors	**RET**	Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptors	PDGF-R	Overexpression	Gliomas
Receptor for stem cell (steel factor)	KIT	Point mutation	Gastrointestinal stromal tumors and other soft tissue tumors
Proteins involved in signal transduction			
GTP-binding	**K-RAS** **H-RAS** **N-RAS**	Point mutation Point mutation Point mutation	Colon, lung and pancreatic tumors Bladder and kidney tumors Melanomas, hematologic malignancies
Non-receptor tyrosine kinase	ABL	Translocation	Chronic myeloid leukemia Acute lymphoblastic leukemia
RAS signal transduction	BRAF	Point mutation	Melanomas
WNT signal transduction	b-catenin	Point mutation Overexpression	Hepatoblastomas, hepatocellular carcinoma
Nuclear regulatory proteins			
Transcriptional activators	**C-MYC** **N-MYC** **L-MYC**	Translocation Amplification Amplification	Burkitt lymphoma Neuroblastoma, small cell carcinoma of lung Small cell carcinoma of lung
Cell-cycle regulators			
Cyclins	CYCLIN D CYCLIN E	Translocation Amplification Overexpression	Mantle cell lymphoma Breast and esophageal cancers Breast cancer
Cyclin dependent kinase	CDK4	Amplification or point mutation	Glioblastoma, melanoma, sarcoma

The Important Oncogenes Include

1. **RAS** – It is an example of signal transducing protein. Normally, inactive RAS binds to GDP and the presence of growth factor causes GDP to be exchanged by GTP causing RAS activation. The activated RAS binds to its farnesyl transferase receptor causing increased activation of MAP kinase and promoting mitogenesis. The activated RAS comes back to its normal inactive state due to the intrinsic GTPase activity which gets augmented due to a group of proteins called GTPase Activating Proteins (or *GAP*). Mutated RAS proteins bind to GAP without augmentation of GTPase activity resulting is uncontrolled mitogenesis and tumor formation.

Key Point

The **point mutation of the RAS family** gene is the single most common abnormality of dominant oncogenes in human tumors.



Key Point

Neurofibromin (protein affected in neurofibromatosis 1) is an example of GAP whose mutation results in neurofibromatosis 1.

The different types of RAS affected in different tumors are:

K – RAS	Colon, lung and pancreatic tumors
N – RAS	Melanoma, blood tumors (AML)
H – RAS	Bladder and kidney tumors

2. **ABL** – It possess ***non-receptor associated tyrosine kinase activity***. C-ABL present on chromosome 9 fuses with BCR gene on chromosome 22 and result in Philadelphia chromosome (t 9;22). The fusion gene possesses uncontrolled tyrosine kinase activity responsible for causing cancer development.

Recent Exam Questions

- In **CML**, the tumor cells are dependent on BCR-ABL fusion gene tyrosine kinase activity. This is called as **ONCOGENE ADDICTION.**
- The non receptor excessive tyrosine kinase activity associated with **CML** is countered by a *specific tyosine kinase inhibitor* drug called **imatinib**. This is an example of ***targeted drug therapy***

3. **MYC** – Normally in the presence of growth factors, increased levels of MYC along with another protein, MAX form a heterodimer and cause activation of transcription.

Uncontrolled nuclear transcription gives rise to development of cancer. In the absence of growth factor, MYC can cause apoptosis. The types of MYC and the tumors associated with their mutation include:

a. *C – MYC* - Burkitt's lymphoma
b. *L- MYC* - Small cell lung cancer [**L**- for **l**ung]
c. *N- MYC* - Neuroblastoma [**N** for **N**euroblastoma]

Recent Exam Questions

- **L**-MYC: **L**ung cancer (small cell)
- **N**-MYC: **N**euroblastoma

- ***Loss of function*** mutations in RET oncogene result in intestinal aganglionosis and Hirschsprung disease
- Gain of function mutations in RET oncogene result in Multiple Endocrine Neoplasia (MEN 2A/2B) syndromes.

Key Point

- **MYC** is the ***most common nuclear transcription regulator*** affected in the human tumors.
- MYC gene is associated with **"Conflict model"** in carcinogenesis

II. Tumor Suppressor Genes

These genes normally regulate cell growth (they do not prevent tumor formation, so the name is actually a misnomer). Any failure of growth regulation causes development of cancer.

Key Point

- ***Breast carcinoma is most common malignancy in females in India.***
- It is associated with mutations in BRCA1 and BRCA2 genes.

Selected Tumor Suppressor Genes involved in Human Neoplasms

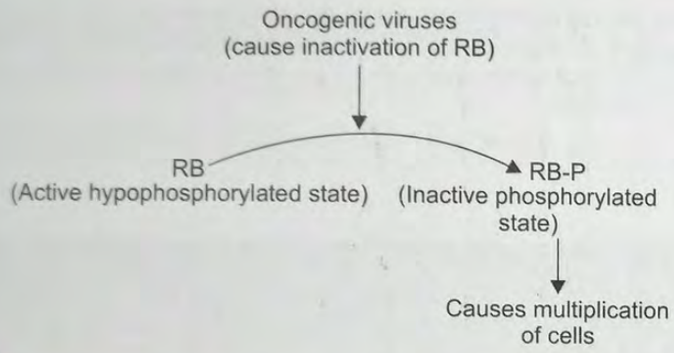
Subcellular Location	*Gene*	*Function*	*Tumors associated with Somatic Mutations*	*Tumors associated with Inherited Mutations*
Cell surface	TGF-β receptor E-cadherin	Growth inhibition Cell adhesion	Carcinoma of colon Carcinoma of stomach	Unknown Familial gastric cancer
Inner aspect of plasma membrane	**NF-1**	Inhibition of RAS signal transduction and of p21 cell-cycle inhibitor	Neuroblastoma	Neurofibromatosis type 1 and sarcomas
Cytoskeleton	**NF-2**	Cytoskeleton stability	Schwannomas and meningiomas	Neurofibromatosis type 2, acoustic schwannomas and meningiomas
Cytosol	**APC/β-catenin** **PTEN** SMAD 2 and SMAD 4	Inhibition of signal transduction PI-3 kinase signal transduction TGF-β signal transduction	Carcinomas of stomach, colon, pancreas; melanoma Endometrial and prostate cancers Colon, pancreas tumors	Familial adenomatous polyposis coli/colon cancer Unknown Unknown
Nucleus	**RB**	Regulation of cell cycle	Retinoblastoma; osteosarcoma, carcinomas of breast, colon, lung	Retinoblastomas, osteosarcoma
	P53	Cell-cycle arrest and apoptosis in response to DNA damage	Most human cancers	Li-Fraumeni syndrome; multiple carcinomas and sarcomas
	WT-1	Nuclear transcription	Wilms tumor	Wilms tumor
	P16 (INK4a)	Regulation of cell cycle by inhibition of cyclin-dependent kinase	Pancreatic, breast and esophageal cancers	Malignant melanoma
	BRCA-1 and **BRCA-2**	DNA repair	Unknown	Carcinoma of female breast and ovary; carcinomas of male breast
	KLF-6	Transcription factor	Prostate	Unknown

Some important tumor suppressor genes include:

1. **RB gene**
   - In the active or hypophosphorylated state, it is present in the non- multiplying cells. The oncogenic viruses cause phosphorylation of RB resulting in its inactivation. The RB inactivation results in cell multiplication by activation of the transcription factor E2F (as discussed eariler under control mechanism of cell cycle).

Key Point

RB gene was the first tumor suppressor gene to be discovered.



Recent Exam Question

The **normal RB gene** is present on **chromosome 13q14.**

Concept of Loss of Heterozygosity (LOH)

Concept

- Retinoblastoma is a prime example of a tumor which is associated with loss of heterozygosity. This term is mostly used in the context of oncogenesis.
- Retinoblastoma develops when both the normal alleles of the Rb gene are inactivated or altered.
- In familial case of retinoblastoma, children are born with *one normal and one defective copy of the Rb gene.*
- Such a child is said to be heterozygous at the Rb locus (*one allele of the gene is normal while the other is a mutant*). So, till the time there is heterozygosity for the Rb gene, the cell behavior is not affected (no chances of cancer development).
- When there is a mutation affecting the second allele, the chances of cancer increases. It means that the cell ***loses heterozygosity for the normal Rb gene (called as loss of heterozygosity)***.
- Loss of heterozygosity is the basis of two hit hypothesis of cancers (Knudson's hypothesis).

Knudson's Two Hit Hypothesis

According to this hypothesis, both the normal alleles should be inactivated for the development of retinoblastoma. Retinoblastoma can be of the following types:

Recent Exam Question

Retinoblastoma is associated with Concept of **Loss of Heterozygosity** as well as **Knudson's Two Hit Hypothesis**

a. **Inherited/Familial Retinoblastoma (40%)**

In hereditary cases of Retinoblastoma one genetic change (first hit) is inherited from the affected parent therefore it is present in all the somatic cells of the body. But one genetic change is not sufficient to produce cancer. The second mutation (second hit) is required to produce cancer. It occurs in the retinal cells (which are carrying the first mutation).

Key Point

Familial Retinoblastoma is also associated with increased risk of **osteosarcomas**.

b. **Sporadic Retinoblastoma (60%)**

In sporadic cases both mutations (hits) occur somatically within a single retinal cell whose progeny then form the tumor.

Key Point

p53 is the *most commonly mutated gene in human cancers.*

2. **p 53 gene**

It is also known as *'molecular policeman'* and *'guardian of the genome'*. The gene is present on chromosome *17p*. The non-mutated p53 gene is also called as the 'wild type' of p53 gene and is associated with reduced risk of development of cancers. Any inactivation of p53 prevents successful DNA repair in a cell leading to the development of a tumor. The p53 gene codes for 53 KDa nuclear phophoprotein.

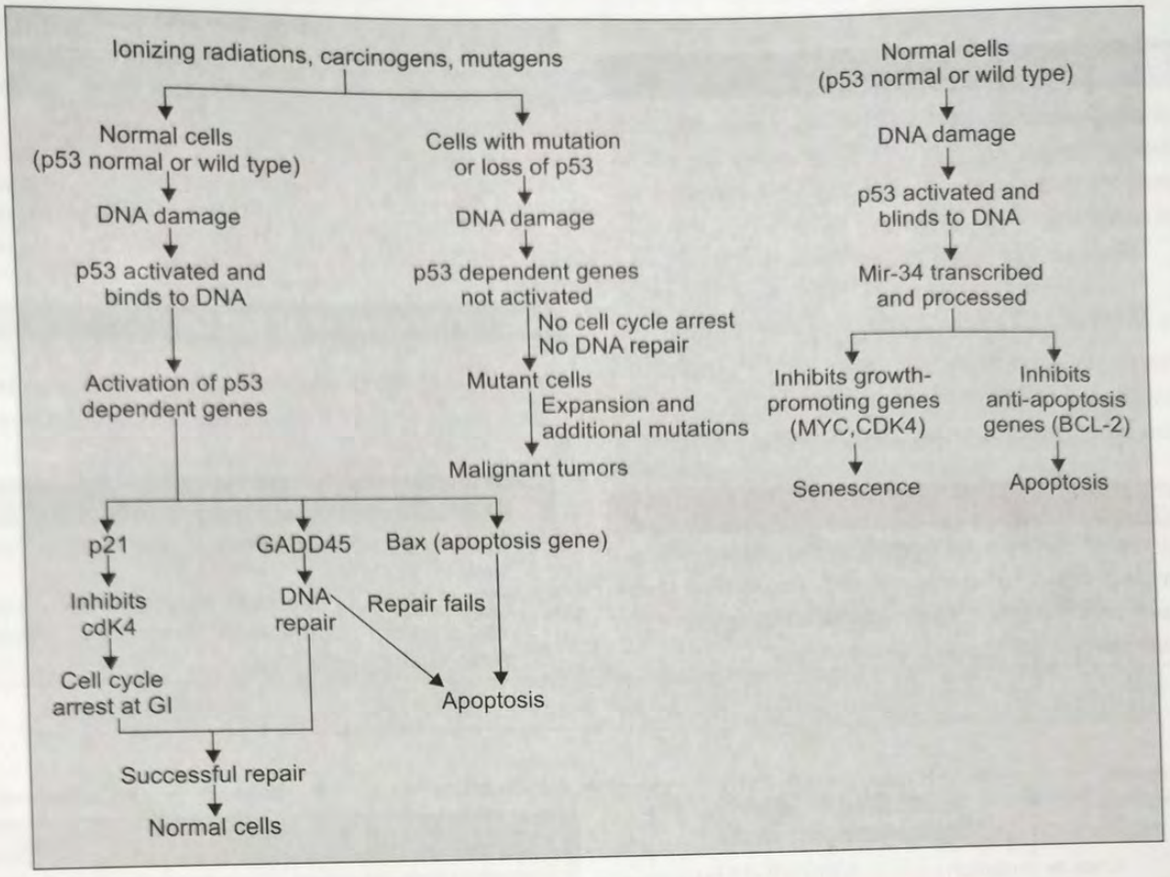
- In most of the cases, the inactivating mutations in both the alleles of p53 are acquired in somatic cells. However, sometimes individual may inherit one mutant p53 allele and the second acquired 'hit' may inactivate the normal p53 allele. This later condition is called **Li-Fraumeni syndrome** associated with development of *sarcoma, breast cancer, leukemia and brain tumors.*
- Human papilloma virus (HPV) causes inactivation of p53 through its E6 protein and so, is responsible for development of cancer of anal and genital region.

Key Point

The **non-mutated p53 gene** is also called as the **'wild type'** of p53 gene and is associated with **reduced risk** of development of **cancers**.

Key Point

Cancers carrying p53 mutations are relatively resistant to chemotherapy and radiotherapy.



Concept

MicroRNAs (miRNAs) are small RNA molecules which inhibit gene expression. They ***DONOT encode proteins***. miRNAs get incorporated into a multiprotein complex called RISC (RNA-induced silencing complex). Then it can either cause target mRNA cleavage or repress its translation.

Mir34 family of miRNAs is **activated by p53 gene.** The targets of mir34 include pro-proliferative genes like cyclins and anti-apoptotic genes like bcl2. This is an important mechanism by which p53 gene is able to repress the function of other genes.

Note: p73 (big brother of p53) and p63 are other members of the family of p53 gene. p63 is esential for the differentiation of stratified squamous epithelia. p73 has pro-apoptotic effects after DNA damage induced by the chemotherapeutic agents.

Key Point

Small interfering RNAs (siRNAs) are similar to miRNA except that siRNA precursors are introduced by investigators into the cell. So, they are now used for **studying gene function.**

3. **NF-1 and NF2 gene**

NF- 1 gene gives rise to **neurofibromin** which is a GTPase activating protein (GAP). NF2 gives rise to neurofibromin 2 or **merlin** protein which inhibits the proliferation of Schwann cells. So, any mutation affecting any of these genes increases the chances of development of cancer.

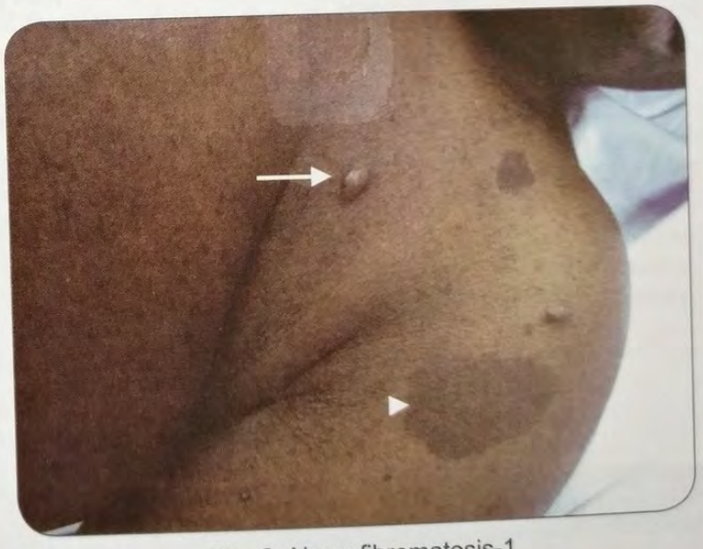


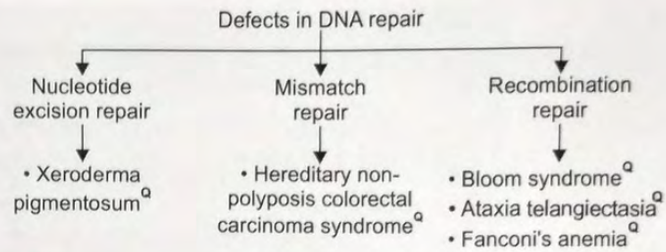
Fig. 3: Neurofibromatosis-1

III. Genes Regulating Apoptosis

Apoptosis (or programmed cell death) is *promoted* by the genes *bax, bad, bcl- Xs and p53* whereas it is inhibited by bcl-2. Understandably, any increase in bcl-2 would cause inhibition of apoptosis and development of cancer. Normally chromosome 14 has immunoglobulin heavy chain gene whereas chromosome 18 has bcl-2 gene. In **follicular lymphoma**, there is presence of translocation **t (14:18)**^{Q} which causes increased expression of bcl-2 thereby preventing apoptosis and inducing the development of cancer.

Recent Exam Question

Hereditary non polyposis colon cancer **(HNPCC)** is an **autosomal dominant** condition caused by ***defective DNA repair*** genes. All others are conditions associated with defective DNA repair genes are autosomal recessive.



IV. Genes Inhibiting DNA Repair

Defective DNA repair increases DNA instability increasing the chances of development of a cancer. This can be of the following three types:

Key Point

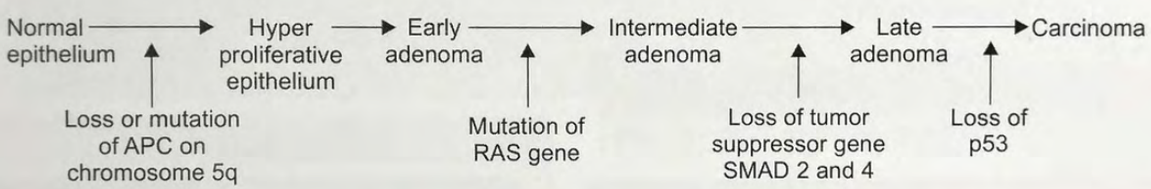
Additional features of diseases with defects in DNA repair by homologous recombination include *bone marrow depression (Fanconi's anemia)*, ***developmental defects (Bloom syndrome)*** and *neural symptoms (Ataxia telangiectasia)*.

MULTI-STEP CARCINOGENESIS

The normal epithelium undergoes sequential mutations in different genes eventually leading to development of carcinoma.

Recent Exam Questions

- **Multistep carcinogenesis** is best seen in cancers like **colon cancer**
- COX2 inhibitors decrease the incidence of colonic adenomas and are now approved for treatment of patients with familial adenomatous polyposis



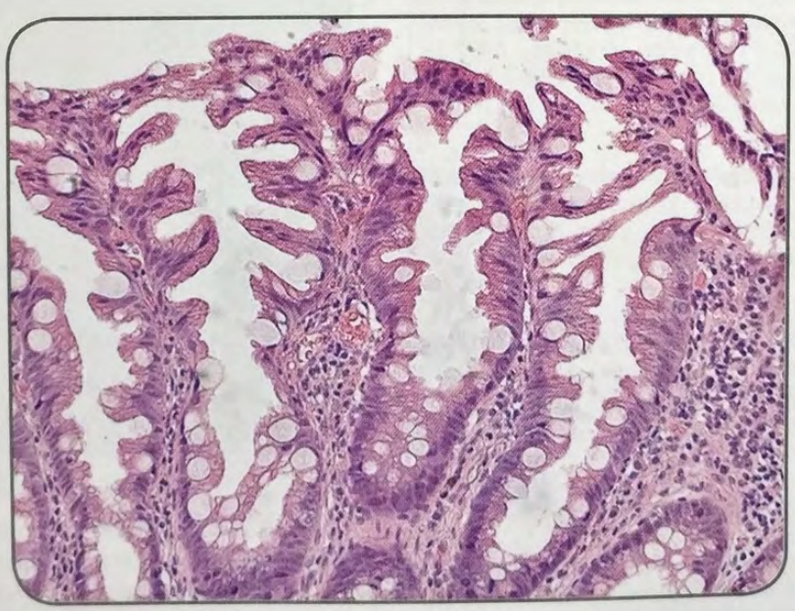
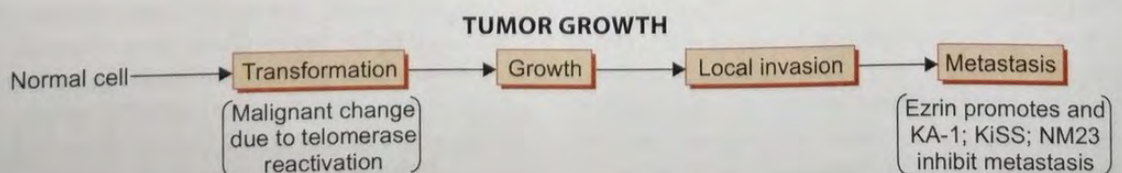
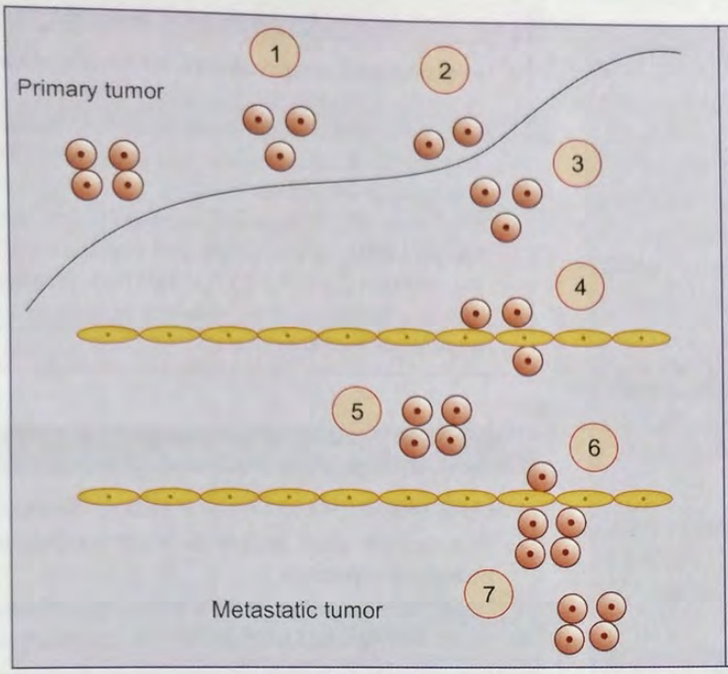


Fig. 4: Hyperproliferative epithelium in polyp



SPREAD OF TUMORS



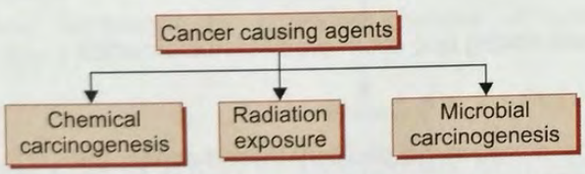
1. Detachment of tumor cells – Due to ↓ E-cadherin and abnormal catenin
2. Attachment to matrix component fibronectin and laminin due to integrins (on cancer cells)
3. Degradation of extracellular matrix by serine, cysteine and matrix metalloproteinases
4. Intravasation
5. Tumor cell embolus
6. Extravasation – CD44 on T cells used by tumor cells for migration in lymphoid tissue
7. Metastatic deposit

Key Point

Genes **promoting** metastasis include **ezrin** (in rhabdomyosarcoma and osteosarcoma)

Genes **inhibiting** metastasis include **NM23, KAI-1** (prostate cancer) and **Ki55** [malignant melanoma]

ETIOLOGY OF CANCERS



Recent Exam Questions

- Tumor can grow **only 1-2 mm without vascularization** or angiogenesis.
- **1 g** ≈ 10^9 cells: **Smallest** clinically detectable mass.
- **1 kg** ≈ 10^{12} cells: **Maximum** mass compatible with life.

I. Chemical Carcinogens

Chemical carcinogenesis has two steps called initiation and proliferation. Initiation can be by two types of agents

Key Point

Sir Percival Pott demonstrated the increased incidence of **scrotal skin cancer** in **chimney workers** exposed to chemical soot.

a. *Direct acting agents* – These are mutagens causing cancer by direct damage or modification of DNA.

b. *Indirect acting agents (also called as procarcinogens)* – These require metabolic conversion to form active carcinogens.

Initiators cause irreversible DNA damage. The proliferation of the tumor cells is done by promoters (chemicals causing multiplication of already mutated cells). The **promoters cause *reversible DNA damage*.** The *carcinogenic potential* of a chemical is tested by *Ames test.*

Concept

Initiators cause **irreversible DNA damage**. The proliferation of the tumor cells is done by promoters (chemicals causing multiplication of already mutated cells). The **promoters** cause **reversible DNA damage**.

Chemical Carcinogens

Alkylating agents	Acute myeloid leukemia, bladder cancer
Androgens	Prostate cancer
Aromatic amines (dyes)	Bladder cancer
Arsenic	Cancer of the lung, skin
Asbestos	Cancer of the lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung cancer
Diethylstilbestrol (prenatal)	Vaginal cancer (clear cell)
Estrogens	Cancer of the endometrium, liver, breast

Contd...

Contd...

Ethyl alcohol	Cancer of the liver, esophagus, head and neck
Immunosuppressive agents (azathioprine, cyclosporine, glucocorticoids)	Non-Hodgkin's lymphoma
Nitrogen mustard gas	Cancer of the lung, head and neck, nasal sinuses
Nickel dust	Cancer of the lung, nasal sinuses
Oral contraceptives	Bladder and cervical cancer
Phenacetin	Cancer of the renal pelvis and bladder
Polycyclic hydrocarbons	Cancer of the lung, skin (especially squamous cell carcinoma of scrotal skin)
Sunlight (ultraviolet)	Skin cancer (squamous cell and melanoma)
Tobacco (including smokeless)	Cancer of the upper aerodigestive tract, bladder
Vinyl chloride	Liver cancer (angiosarcoma)

Concept

- In **Ames test,** a modified bacterium ***Salmonella typhimurium*** is used, which is unable to produce histidine due to absence of histidine synthetase enzyme in it.
- The modified bacteria are first put on a histidine free medium where it cannot grow.
- Then it is put on the same medium but now having additionally the presence of the suspected mutagen. In the second case, the bacteria grow if the chemical has mutagenic potential.
- The in *vitro mutagenic potential correlates well with the carcinogenic potential in vivo.*

Recent Exam Questions

- UV-**B** is **B**ad for humans as it causes cancers.
- **CLL** is the only leukemia **NOT** associated with **ionizing radiation** exposure.
- **Basal cell carcinoma** is the most common cancer due to **excessive UV light** exposure.

Radiation exposure

UV radiation

- It has three subtypes
  UV-A is 320 - 400 nm
  UV-B is 280 - 320 nm
  UV-C is 200 - 280 nm

UVC gets filtered by ozone layer, whereas UV-B^{Q} is the most carcinogenic UV ray to reach the earth

Exposure to UV rays

↓

Pyrimidine dimers in DNA

↓

Mutation in oncogenes and tumor suppressor genes

↓

Incidence of skin cancer

Ionizing radiation

- It includes x-rays, γ rays α and β particles
- Maximum sensitivity is at G2 stage
- Exposure to ionizing radiation

↓

Cross-linking and chain break in nucleic acids

↓

↑ Cancer

- Most common are papillary thyroid cancer and leukemias **(except CLL)**
- Lung cancer is seen in uranium miners
- The cells of skin, bone and GI tract are relatively to radiation induced neoplasms

Infectious Organisms

BACTERIA (H. PYLORI)

H. pylori is the first bacterium classified as a carcinogen. *H. pylori* infection is implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas. The gastric lymphomas are of **B-cell origin**^{Q} and are called MALT lymphomas (marginal zone-associated lymphomas) because the transformed B cells normally reside in the marginal zones of lymphoid follicles. *H. pylori* infection results in the formation of *H. pylori*-reactive T cells, which cause polyclonal B-cell proliferations. The MALT lymphoma is associated with **t(11;18)**^{Q} translocation.

Recent Exam Question

- **H. pylori** is associated with **t(11;18)** translocation and causes **B-cell** origin **MALT lymphomas**.

VIRUSES

Carcinogenic Viruses

RNA viruses	DNA viruses
• Human T cell leukemia virus-1 (HTLV-1) • Hepatitis C virus (HCV)	• Hepatitis B virus (HBV) • Human herpes virus 8 (HHV8) • Human papilloma virus (HPV) • Epstein-Barr virus (EBV)

Pathogenesis

HTLV-1

It is a RNA oncogenic virus which is transmitted by blood products, sexual intercourse or breastfeeding. It has attraction for CD4 T cells (similar to HIV). HTLV-1 has a gene TAX. The **TAX protein**[Q] causes

Recent Exam Questions

- **HHV8** is associated with **Primary effusion lymphoma** and **Multicentric Castleman's disease**
- **HCV** is associated with **Lymphoplasmacytic lymphoma**
- **HTLV1** can cause **T-cell leukemia**/lymphoma and demyelinating disorder called **Tropical spastic paraparesis**..

1. Transcription of host genes involved in proliferation and differentiation of T-cells (e-FOS, IL-2 genes)
2. Genomic instability by inhibiting DNA repair function and by inhibiting cell cycle checkpoints activated by DNA damage

These contribute to increased chances of cancer by HTLV-1.

HCV

Hepatitis C virus (HCV) is also strongly associated with the development of hepatocellular carcinoma. This is associated with its ability to cause chronic liver cell injury and inflammation that is accompanied by liver regeneration. Mitotically active hepatocytes, surrounded by an altered environment, are presumably prone to genetic instability and cancer development.

Recent Exam Question

- **EBV** causes **polyclonal B-cell activation** which also leads to *auto immune diseases.*

EBV

It is a DNA oncogenic virus. It causes infection of epithelial cells of oropharynx and B- cells because of the presence of **CD21 molecule**[Q] on the surface of these cells. **LMP-1 gene**[Q] present in the EBV causes activation of NF-κβ and JAK/STAT signaling pathways thereby promoting B-cell survival and proliferation. (This increases the chances of B- cell lymphoma). Another EBV-encoded gene, *EBNA-2,* transactivates several host genes like cyclin D and the *src* family genes. The EBV genome also contains a viral cytokine, vIL-10 which prevents macrophages and monocytes from activating T cells and is required for EBV-dependent transformation of B cells. EBV acts a polyclonal B-cell mitogen followed by acquisition of **t(8;14)**[Q] translocation which ultimately results in development of Burkitt's lymphoma.

Key Point

EBV is most commonly associated with **'lymphocyte depleted' variant** of Hodgkin's lymphoma

*EBV belongs to the herpes family and can cause the following cancers:

- African form of Burkitt's lymphoma
- B- cell lymphoma in immunosuppressed (post transplant) individuals
- Hodgkin's lymphoma
- 1° CNS diffuse large B-cell lymphoma
- Nasopharyngeal cancer

Key Point

Nasopharyngeal cancer is the **only T cell malignancy** amongst the cancers caused by EBV

HBV

It encodes for HBx protein[Q] which disrupts the normal growth control of infected liver cells by activation of several growth promoting genes. HBx also causes inactivation of the tumor suppressor gene p53. This results in HBV causing hepatocellular cancer.

HPV

It is responsible for development of squamous cell carcinoma of cervix and anogenital lesion and in some cases, oral and laryngeal cancers. The virus gets integrated in the genome of host cells which is essential for the malignant transformation of the affected cells HPV 16 (more commonly) and HPV 18 (less commonly) are particularly important in carcinogenesis as they have viral genes **E6 and E7 which causes Rb and p53 gene inactivation respectively.** Since both p53 and Rb are tumor suppressor genes, so, their inactivation increases the chances of cancer development.

Recent Exam Questions

- **E6 gene** product **inhibits P53** suppressor gene
- **E7 gene** product **inhibits RB** suppressor gene

PARANEOPLASTIC SYNDROMES

Clinical syndromes	Major forms of underlying cancer	Causal mechanism
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	***Small cell carcinoma of lung;*** ***Intracranial neoplasms***	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T-cell leukemia/lymphoma Ovarian carcinoma	Parathyroid hormone-related protein (PTHRP), TGF-α, TNF, IL-1
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Hepatocellular carcinoma	Insulin or insulin-like substance
Carcinoid syndrome	Bronchial adenoma (carcinoid) Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin
Polycythemia	*Renal carcinoma* *Cerebellar hemangioma* *Hepatocellular carcinoma*	Erythropoietin
Nerve and Muscle Syndromes		
Myasthenia	Bronchogenic carcinoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic, breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	***Pancreatic carcinoma*** ***Bronchogenic carcinoma*** Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymic neoplasms	Unknown
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

ACTH, adrenocorticotropic hormone; TGF, transforming growth factor; TNF, tumor necrosis factor; IL, interleukin.

Recent Exam Questions

- **Hypercalcemia** is probably the most common paraneoplastic syndrome.
- **Cushing syndrome** is the most common **endocrinopathy**.
- **Trousseau phenomenon (Migratory thrombophlebitis)** is seen with **pancreatic** and **bronchogenic carcinoma**

Mnemonic

- **Grading** of a cancer is based on the **degree of differentiation** of the tumor cells and the number of mitoses within the tumor as presumed *correlates of the neoplasm's aggressiveness.*
- The **staging** of cancers is based on the **size of the primary lesion, its extent of spread** to regional lymph nodes, and the presence or absence of **distant metastases.**

IMMUNOHISTOCHEMISTERY

It is a method for diagnosis of cancer.

1. **Categorization of undifferentiated malignant tumor:** Sometimes, many tumors like anaplastic carcinoma, lymphoma, melanoma and sarcoma are difficult to distinguish with routine H and E staining because of poor differentiation. So, immunohistochemical stains can help in diagnosis e.g.
   - Presence of cytokeratin points to epithelial origin (carcinoma).
   - Presence of desmin is specific for muscle cell origin.
   - Presence of Leucocyte Common Antigen (LCA) points to lymphoma.

Recent Exam Question

- **Lymph node imprinting** is a technique useful for diagnosis of malignancy

2. **Determination of site of origin of metastatic tumor:** There are markers that point to the origin of tumor (primary) in a biopsy specimen of metastasis. Examples include *PSA (for prostate cancer) and thyroglobulin (for thyroid cancer).*
3. **Prognostic or therapeutic significance:** Estrogen/progesterone receptor detection has therapeutic value in breast carcinomas. Receptor positive breast cancers are susceptible to anti-estrogen therapy. Similarly, over-expression of erb-B2 protein suggests a poor prognosis.

TUMOR MARKERS

Tumor markers are biochemical substances (include cell-surface antigens, cytoplasmic proteins, enzymes, and hormones) which indicate the presence of a tumor.

Concept

hCG is a **placental glycoprotein hormone** composed by α and β subunits. ***Alpha hCG is not used as tumor marker because it is similar to the FSH, LH and TSH.*** The beta subunit of hCG is typically measured as a tumor marker because it has unique sequence that are not shared with other human glycoprotein hormones. So, it is quite specific and there is no cross reactivity between beta subunits of these hormones.

Markers	Associated Cancers
Hormones	
Human chorionic gonadotropin (hCG)	Trophoblastic tumors, non-seminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See above
Oncofetal Antigens	
α-Fetoprotein	Liver cell cancer, non-seminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart

Contd...

Contd...

Isoenzymes	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small cell cancer of lung, neuroblastoma
Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen and prostate-specific membrane antigen	Prostate cancer
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer
New Molecular Markers	
p53, APC, RAS mutations in stool and serum	Colon cancer
p53 and RAS mutations in stool and serum	Pancreatic cancer
p53 and RAS mutations in sputum and serum	Lung cancer
p53 mutations in urine	Bladder cancer

The important antigens for the determination of specific tumor cell origin are:

Epithelial Tumors

- Breast: Alpha lactalbumin, GCDP-15, estrogen/progesterone
- Thyroid: Thyroglobulin, calcitonin
- Liver: AFP (α fetoprotein), HBsAg, keratin
- Prostate: Prostatic acid phosphatase, prostate specific antigen
- Mesothelioma: Keratin, Calretinin, mesothelin

Recent Exam Questions

- **Valproate embryopathy** is due to mutation in **HOX gene^{Q}.**
- **Vitamin A induced embryopathy** is due to mutation in **TGF-β^{Q} signaling pathway.**
- **t(12;15) (p13;q25)** is associated **with congenital infantile fibrosarcoma**

Germ Cell Tumors

- Human chorionic gonadotropin, AFP (α-fetoprotein)

Mesenchymal Tumors

- Endothelial tumors: Factor VIII, CD 34,
- Melanoma: HMB 45, S 100
- Fibrohistiocytic tumors: Lysozyme, HAM 56
- Myogenic tumors: Desmin, smooth muscle specific antigen, myoglobin

Key Point

In malignant melanoma, HMB 45 is more specific whereas *S-100 is more sensitive.*

Neuroendocrine Tumors

- Neuron specific enolase (NSE), chromogranin, synaptophysin
  - Malignant melanoma expresses HMB 45, S-100 and vimentin. **HMB 45** is present in melanosomes and is **more specific**. S-100 is more sensitive but is non-specific (also present in Langerhans' cell histiocytosis, neural tumors, and sarcomas like liposarcoma and chondrosarcoma)
  - Neurofibroma (a neural tumor) shows the presence of S100 and GFAP (Glial Fibrillary Acid Protein). Malignant tumors often lose expression of S-100 antigen.
  - Neuroblastoma expresses NSE, chromogranin and synaptophysin. NSE is more specific whereas chromogranin and synaptophysin are more sensitive tumor markers.
- Angiosarcoma expresses factor VIII, vimentin and CD34 antigen

Key Point

In **neuroblastoma**, **NSE is more specific** whereas *chromogranin and synaptophysin are more sensitive* tumor markers.

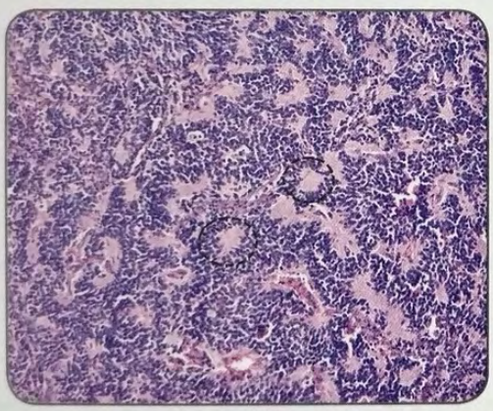


Fig. 5: Neuroblastoma showing Homer-Wright pseudorosettes

Type of tumors associated with intermediate filaments:

Intermediate Filament	Normal Tissue Expression	Tumor
Cytokeratin	All epithelial cells	Carcinoma
Vimentin	Mesenchymal cells	Sarcomas
Desmin	Muscle cells	Leiomyoma Rhabdomyosarcoma
Glial Fibrillary Acidic Protein (GFAP)	Glial cells	Astrocytoma Ependymoma
Neurofilament	Neurons and Neural crest derivatives	Pheochromocytoma Neuroblastoma

CONCEPT OF TUMOR LYSIS SYNDROME

Tumor lysis syndrome is caused by destruction of large number of rapidly proliferating neoplastic cells. It is characterized by

Recent Exam Question

Tumor lysis syndrome is associated with **Burkitt lymphoma**, acute lymphoblastic leukemia **(ALL)**, chronic tumors **(CLL)** and uncommonly solid tumors.
It is associated with **hypocalcemia** and ***NOT*** hypercalcemia.

- **Hyperuricemia** (due to increased turnover of nucleic acids)
- **Hyperkalemia** (due to release of the most abundant intracellular cation potassium)
- **Hyperphosphatemia** (due to release of intracellular phosphate)
- **Hypocalcemia** (due to complexing of calcium with the elevated phosphate)
- **Lactic acidosis**
- **Hyperuricemia** can cause uric acid precipitation in the kidney causing acute renal failure.

Multiple Choice Questions

NEOPLASIA: GENERAL ASPECTS

1. **Which of the following helps in differentiation of follicular carcinoma from follicular adenoma of thyroid gland?** *(AI 2011, AIIMS May 2010)*
   (a) Hurthle cell change
   (b) Lining of tall columnar and cuboidal cells
   (c) Vascular invasion
   (d) Increased mitoses

2. **All are malignant tumors, except:** *(AI 2008)*
   (a) Chloroma
   (b) Fibromatosis
   (c) Askin's tumor
   (d) Liposarcoma

3. **The following is not a feature of malignant transformation by cultured cells:** *(AI 2005)*
   (a) Increased cell density
   (b) Increased requirement for growth factors
   (c) Alterations of cytoskeletal structures
   (d) Loss of anchorage

4. **Which of the following carcinoma most frequently metastasizes to brain?** *(AIIMS Nov 2005)*
   (a) Small cell carcinoma of lung
   (b) Prostate cancer
   (c) Rectal carcinoma
   (d) Endometrial cancer

5. **Chemotherapeutic drugs can cause:** *(AIIMS May 2005)*
   (a) Only necrosis
   (b) Only apoptosis
   (c) Both necrosis and apoptosis
   (d) Anoikis

6. **Reversible loss of polarity with abnormality in size and shape of cells is known as:** *(AIIMS Nov 2001)*
   (a) Metaplasia (b) Dysplasia
   (c) Hyperplasia (d) Anaplasia

7. **Predisposing factors for skin cancer are:** *(PGI Dec 2000)*
   (a) Smoking
   (b) U-V-light
   (c) Chronic ulcer
   (d) Infrared light

8. **Increased risk of cancer is seen in:** *(Delhi PG 2009 RP)*
   (a) Fibroadenoma of breast
   (b) Bronchial asthma
   (c) Chronic ulcerative colitis
   (d) Leiomyoma of the uterus

9. **A strong propensity for vascular invasion is seen in:** *(Karnataka 2008)*
   (a) Prostatic carcinoma
   (b) Hepatocellular carcinoma
   (c) Bronchogenic carcinoma
   (d) Gastric carcinoma

10. **Earliest changes of neoplastic transformation as seen at a microscopic level is called:** *(Karnataka 2004)*
    (a) Hyperplasia
    (b) Metaplasia
    (c) Dysplasia
    (d) Carcinoma in situ

11. **Squamous cell carcinoma spreads by:** *(RJ 2000)*
    (a) Hematogenous route
    (b) Lymphatic route
    (c) Direct invasion
    (d) All

12. **Which one of the following tumors does not cause bony metastasis?** *(AP 2000)*
    (a) Renal cell carcinoma
    (b) Gastric carcinoma
    (c) Thyroid carcinoma
    (d) Breast carcinoma

13. **Hamartoma is:** *(AP 2003)*
    (a) Proliferation of cells in foreign site
    (b) Proliferation of native cells in tissue
    (c) Malignant condition
    (d) Acquired condition

MOST RECENT QUESTIONS

14. **Sure sign of malignancy is:**
    (a) Mitoses
    (b) Polychromasia
    (c) Nuclear pleomorphism
    (d) Metastasis

15. **A lesion 3 cm away from gastroesophageal junction contain columnar epithelium, such a type of lesion is:**
    (a) Metaplasia (b) Hyperplasia
    (c) Dysplasia (d) Anaplasia

16. **Malignancy is typically associated with disordered differentiation and maturation. Which of the following mentioned options best describes anaplasia?**
    (a) Hepatic tumor cells synthesizing bile
    (b) Skin tumor cells producing keratin pearls
    (c) Bronchial epithelial cells producing keratin pearls
    (d) Muscle tumor cells forming giant cells

17. **Which of the following criteria can be used to determine if a pheochromocytoma lesion is benign or malignant?**
   (a) Blood vessel invasion
   (b) Cannot be determined by microscopic examination
   (c) Hemorrhage and necrosis
   (d) Nuclear pleomorphism

18 **Which one is not the pre cancerous condition?**
   (a) Crohn's disease
   (b) Ulcerative colitis
   (c) Leukoplakia
   (d) Xeroderma pigmentosum

19. **Which of the following features differentiates invasive carcinoma from carcinoma in situ?**
   (a) Anaplasia
   (b) Number of mitosis
   (c) Basement membrane invasion
   (d) Pleomorphism

20. **Cell-matrix adhesions are mediated by?**
   (a) Cadherins (b) Integrins
   (c) Selectins (d) Calmodulin

21. **Which of the following is not a labile cell?**
   (a) Bone marrow
   (b) Epidermal cells
   (c) Small intestine mucosa
   (d) Hepatocytes

22. **Sure sign of malignancy is:**
   (a) Mitoses
   (b) Polychromasia
   (c) Nuclear pleomorphism
   (d) Metastasis

23. **Bimodality of incidence occurs in all, except**
   (a) Cancer penis in male
   (b) Hodgkin's diseases
   (c) Breast cancer in females
   (d) Leukemia

24. **All of the following are premalignant except:**
   (a) Ulcerative colitis
   (b) Peutz-Jegher syndrome
   (c) Crohn disease
   (d) Familial adenomatous polyposis

25. **Which of the following is most reliable feature of malignant transformation of pheochromocytoma?**
   (a) Presence of mitotic figures
   (b) Presence of metastasis to other organs
   (c) Vascular/ capsular invasion
   (d) All of the above

26. **Overgrowth of a skin structure at a localised region is:**
   (a) Hamartoma (b) Malignant tumor
   (c) Choristoma (d) Polyp

27. **Peau d'orange in carcinoma breast is due to:**
   (a) Obstruction of sub-dermal lymphatics
   (b) Infiltration of Cooper's ligament
   (c) Hematogenous dissemination
   (d) Nipple involvement

28. **Molecular study is important in the management of which malignancy?**
   (a) Multiple myeloma
   (b) Renal cell carcinoma
   (c) Seminoma
   (d) Basal cell carcinoma

29. **Tumor cells secrete which of the following?**
   (a) Tyrosine kinase (b) Collagenase IV
   (c) Catenins (d) E-cadherins

30. **Substance playing a role in tumor metastasis cascade is?**
   (a) Collagenase IV (b) TNF-alpha
   (c) CD99 (d) NM23

31. **Carcinoma with no or minimal metastasis is?**
   (a) Squamous cell carcinoma
   (b) Basal cell carcinoma
   (c) Melanoma
   (d) Leydig's cell carcinoma

CELL CYCLE AND ITS REGULATION

32. **Ionizing radiation affects which stage of cell cycle**
   (a) G2 S (b) G1 G2
   (c) G2 M (d) G0 G1

33. **The correct sequence of cell cycle is:** *(AI 2003)*
   (a) G0-G1-S-G2-M (b) G0-G1-G2-S-M
   (c) G0-M-G2-S-G1 (d) G0-G1-S-M-G2

34. **During which phase of the cell cycle the cellular content of DNA is doubled:** *(AIIMS Nov 2005)*
   (a) Mitotic phase (b) G1 phase
   (c) G2 phase (d) S phase

35. **The tumor suppressor gene p 53 induces cell cycle arrest at:** *(AIIMS Nov 2005)*
   (a) G_2-M phase (b) S-G_2 phase
   (c) G_1-S phase (d) G_0 phase

36. **Transition from G2 to M phase of the cell cycle is controlled by:** *(AIIMS Nov 2003)*
   (a) Retinoblastoma gene product
   (b) p53 protein
   (c) Cyclin E
   (d) Cyclin B

37. **Fixed time is required for which steps of cell cycle:**
   (a) S *(PGI Dec 2000)*
   (b) M (c) G_1
   (d) G_2 (e) Go

38. **Regarding oncogenesis:** *(PGI June 2002)*
   (a) Topoisomerase II causes breaks in strands
   (b) p53 is the most common oncogene mutation causing malignancy in humans
   (c) At G2-M phase there is loss of inhibitors controlling cell-cycle
   (d) Decrease in telomerase activity causes anti-tumor effects

39. **Regarding oncogenesis:** *(PGI Dec 2002)*
(a) Proto-oncogenes are activated by chromosomal translocation
(b) Malignant transformation involves accumulation of mutations in proto-oncogenes and tumor suppressor gene in stepwise fushion
(c) Point mutation of somatic cells
(d) Increase in telomerase activity causes anti-tumor effects
(e) At G2-M phase there is loss of inhibitors controlling cell cycle

MOST RECENT QUESTIONS

40. **The tumor suppressor gene P53 induces cell arrest at:**
(a) G_2- M phase (b) S- G_2 phase
(c) G_1- S phase (d) G_0- phase

41. **Not a premalignant condition:**
(a) Fragile X syndrome
(b) Down's syndrome
(c) Blount's syndrome
(d) Fanconi's syndrome

42. **Which is associated with G2M transition in cell cycle:**
(a) Cyclin A (b) Cyclin B
(c) Cyclin E (d) Cyclin D

43. **Which of the following is not a cyclin dependent kinase (CDK) inhibitor?**
(a) p21 (b) p27
(c) p53 (d) p57

44. **Cells are most radiosensitive in:**
(a) S - phase (b) M -phase
(c) Gl - phase (d) G0 - phase

45. **E cadherin gene deficiency is seen in:**
(a) Gastric cancer
(b) Intestinal cancer
(c) Thyroid cancer
(d) Pancreatic cancer

46. **Li Fraumeni syndrome is due to mutation of which gene?**
(a) p21 (b) p53
(c) p41 (d) p43

GENETIC MECHANISMS OF CARCINOGENESIS: PROTO-ONCOGENE, TUMOUR SUPPRESSOR GENE, DEFECTIVE DNA REPAIR

47. **All are true about Fanconi anemia, except:** *(Bihar 2006)*
(a) Defect in DNA repair
(b) Bone marrow hyperfunction
(c) Congenital anomaly present
(d) Increased chances of cancer

48. **HER2/neu receptor plays a role in** *(AIIMS Nov. 2010)*
(a) Predicting therapeutic response
(b) Diagnosis of breast cancer
(c) Screening of breast cancer
(d) Recurrence of tumor

49. **The most common secondary malignancy in a patient having retinoblastoma is:** *(AI 2010)*
(a) Osteosarcoma
(b) Renal cell carcinoma
(c) Pineoblastoma
(d) Osteoblastoma

50. **Regarding Fanconi anemia, the wrong statement is:**
(a) Autosomal dominant *(AI 2010)*
(b) Bone marrow show pancytopenia
(c) Usually aplastic anemia
(d) It is due to defective DNA repair

51. **True statements about p53 gene are all except:** *(AI 2008)*
(a) Arrests cell cycle at G_1 phase
(b) Product is 53 kD protein
(c) Located on chromosome 17
(d) Wild/non-mutated form is associated with increased risk of childhood tumors

52. **Growth factor oncogene is:** *(AI 2008)*
(a) Myc (b) Fos
(c) Sis (d) Jun

53. **Rosettes are characteristically seen in:** *(AI 2008)*
(a) Retinoblastoma
(b) Melanoma
(c) Dysgerminoma
(d) Lymphoma

54. **The normal cellular counterparts of oncogenes are important for the following functions, except:** *(AI 2006)*
(a) Promotion of cell cycle progression
(b) Inhibition of apoptosis
(c) Promotion of DNA repair
(d) Promotion of nuclear transcription

55. **An example of a tumor suppressor gene is:** *(AI 2005)*
(a) myc (b) fos
(c) ras (d) Rb

56. **Lynch syndrome is associated with cancers of the:**
(a) Breast, colon, ovary *(AIIMS Nov 2009)*
(b) Breast, endometrium, ovary
(c) Breast, colon, endometrium
(d) Colon, endometrium, ovary

57. **Loss of heterozygosity associated with:**
(a) Acute myeloid leukemia *(AIIMS May 2008)*
(b) ALL
(c) Retinoblastoma
(d) Promyelocytic leukemia

58. **Which is not a tumor suppressor gene?**
(a) WT-1 (b) Rb *(AIIMS May 2008)*
(c) p53 (d) ras

59. **The inheritance pattern of familial Retinoblastoma is:** *(AIIMS Nov 2005)*
(a) Autosomal recessive
(b) Autosomal dominant
(c) X-linked dominant
(d) X-linked recessive

60. **Which of the following is known as the "guardian of the genome"?** *(AIIMS May 2005)*
(a) p53 (b) Mdm2
(c) p14 (d) ATM

61. **The following statements are true about Tumor Suppressor Gene p53, except:** *(AIIMS Nov 2004)*
(a) It regulates certain genes involved in cell cycle regulation
(b) Its increased levels can induce apoptosis
(c) Its activity in the cells decreases following UV irradiation and stimulates cell cycle
(d) Mutations of the p53 gene are most common genetic alteration seen in human cancer

62. **In the mitogen activated protein kinase pathway, the activation of RAS is counteracted by:** *(AIIMS May 2004)*
(a) Protein kinase C
(b) GTPase activating protein
(c) Phosphatidyl inositol
(d) Inositol triphosphate

63. **Which of the following mutations in a tumor suppressor agent causes breast carcinoma?** *(AIIMS May 2002)*
(a) p43 (b) p53
(c) p73 (d) p83

64. **True about proto-oncogenes is:** *(PGI June' 06)*
(a) Important for normal cell growth
(b) May get converted into oncogenes
(c) C-myc over-expression causes lymphoma
(d) Their mutation causes retinoblastoma
(e) Deletion cause Sickle cell disease

65. **True about oncogene is:** *(PGI Dec 2002)*
(a) Present in normal cell
(b) They are of viral origin
(c) They are transduced from virus infected cells
(d) P53 is most common oncogene mutation causing malignancy
(e) Viral oncogenes are identical with humans cellular oncogenes

66. **Cancer cell survival is enhanced by:**
(a) Suppression of p53 protein *(PGI June 2003)*
(b) Over expression of p53 gene
(c) bcl-2
(d) bax
(e) bad

67. **Following are required for normal growth:** *(PGI Dec 2003)*
(a) Proto-oncogenes
(b) Tumor suppressor genes
(c) Oncogenes
(d) DNA repair genes

MOST RECENT QUESTIONS

68. **Xeroderma pigmentosum is caused due to a group of closely related abnormalities in:**
(a) Mismatch repair
(b) Base excision repair
(c) Nucleotide excision repair
(d) SOS repair

69. **Increased expression of which of the following causes oncogenesis**
(a) IGF receptor (b) EGF receptor
(c) GH receptor (d) Aldosterone receptor

70. **Tumor suppressor genes are all, except**
(a) APC (b) p53
(c) Rb (d) C-myc

71. **Angiogenesis is:**
(a) Formation of the new blood vessels
(b) Repair by connective tissues
(c) Formation of the blood clot
(d) All of the above

72. **Medullary carcinoma of thyroid is associated with mutation in:**
(a) RET (b) RAS
(c) NF (d) Rb

73. **APC gene is located on which chromosome:**
(a) Chromosome 5 (b) Chromosome 6
(c) Chromosome 9 (d) Chromosome 11

74. **Endometrial carcinoma is associated with which of the following tumor suppression gene mutation?**
(a) P53 (b) Rb
(c) PTEN (d) APC

75. **Histopathologically, rosettes are not seen in:**
(a) Retinoblastoma (b) Neurocysticercosis
(c) PNET (d) Medulloblastoma

76. **The tumor suppressor gene p 53 induces cell cycle arrest at:**
(a) G2 – M phase (b) S – G2 phase
(c) G1 – S phase (d) G0 phase

77. **Which of the following gene defect is associated with development of medullary carcinoma of thyroid:**
(a) RET gene (b) FAP gene
(c) Rb gene (d) BRCA 1 gene

78. **All of the following are tumor markers, except:**
(a) Beta-2 macroglobulin
(b) HCG
(c) Alpha-fetoprotein
(d) CEA

79. **MYC gene is:**
(a) Protein kinase inhibitor
(b) Growth factor inhibitor
(c) GTPase
(d) Transcription activator

80. **Retinoblastoma is associated with which of the following tumours?**
(a) Osteoclastoma
(b) Hepatocellular cancer
(c) Squamous cell cancer
(d) Osteosarcoma

81. **RET gene mutation is associated with which malignancy?**
(a) Pheochromocytoma
(b) Medullary carcinoma thyroid
(c) Lymphoma
(d) Renal cell carcinoma

82. **An example of a tumour suppressor gene is:**
(a) Myc (b) Fos
(c) Ras (d) RB

83. **Which of the following is DNA repair defect?**
(a) Retinoblastoma
(b) Neurofibromatosis
(c) Xeroderma pigmentosum
(d) MEN-I

84. **An example of a tumor suppressor gene is:**
(a) Myc (b) Fos
(c) Ras (d) Rb

85. **Knudson two hit hypothesis is seen with**
(a) Melanoma (b) Retinoblastoma
(c) Ulcerative colitis (d) Crohn disease

86. **Retinoblastomas arising in the context of germ-line mutations not only may be bilateral, but also may be associated with _____ (so called "trilateral" retinoblastoma)**
(a) Medulloblastoma (b) Pinealoblastoma
(c) Neuroblastoma (d) Hemangioblastoma

87. **HER-2/neu gene causes breast carcinoma due to?**
(a) Overexpression
(b) Suppression
(c) Mutation
(d) Translocation

88. **Gene involved in medullary carcinoma thyroid is:**
(a) Ret proto oncogene
(b) FAP gene
(c) Rb gene
(d) BRCA 1 gene

89. **Which chromosome mutation is associated with medulloblastoma?**
(a) Chromosome 16 (b) Chromosome 17
(c) Chromosome 18 (d) Chromosome 19

90. **VHL syndrome is associated most commonly with which carcinoma?**
(a) Lung carcinoma
(b) Renal cell carcinoma
(c) Endometrial carcinoma
(d) Hepatocellular carcinoma

ETIOLOGICAL AGENTS FOR CANCER: CHEMICAL, RADIATION, MICROBES, MULTISTEP CARCINOGENESIS

91. **Post transplant lymphoma is caused by which of the following?** *(AIIMS May 2012)*
(a) CMV (b) EBV
(c) Herpes simplex (d) HHV-6

92. ***H. pylori* infection is associated with development of which malignancy:** *(DPG 2011)*
(a) MALTomas
(b) Atherosclerosis
(c) Sarcoma
(d) Gastrointestinal stromal tumor (GIST)

93. **Helicobacter pylori infection is associated with all of the following conditions, except:** *(DPG 2011)*
(a) Peptic ulcer disease
(b) Gastric adenocarcinoma
(c) B cell lymphoma
(d) Burkitt's lymphoma

94. **Tumors associated with organisms are all except:**
(a) Hepatocellular cancer *(AIIMS Nov 2009)*
(b) Non-small Cell Carcinoma of Lung
(c) Gastric cancer
(d) Nasopharyngeal cancer

95. **Which of the following is essential for tumor metastasis?** *(AIIMS Nov 2008, DNB 2009)*
(a) Angiogenesis
(b) Tumorogenesis
(c) Apoptosis
(d) Inhibition of tyrosine kinase activity

96. **Which of the following statements about carcinogenesis is *false?*** *(AIIMS May 2006)*
(a) Asbestos exposure increases the incidence of lung cancer
(b) Papilloma viruses produce tumors in animals but not in humans
(c) Exposure to aniline dyes predisposes to cancer of the urinary bladder
(d) Hepatitis B virus has been implicated in hepatocellular carcinoma

97. **Which of the following is an oncogenic RNA virus?**
(a) Hepatitis B virus *(Delhi PG 2009 RP)*
(b) Human papilloma virus
(c) Epstein Barr virus
(d) Hepatitis C virus

98. **LMP-1 gene plays a role in oncogenesis induced by:** *(Karnataka 2008)*
(a) Human T cell leukemia virus type I
(b) Hepatitis B virus
(c) Epstein-Barr virus
(d) Human papilloma virus

MOST RECENT QUESTIONS

99. Skin cancers develop due to sunlight exposure induced by:
(a) UVA rays (b) UVB rays
(c) UVC rays (d) UVD rays

100. Most radiosensitive tumor is:
(a) Renal cell carcinoma
(b) Carcinoma colon
(c) Hepatocellular carcinoma
(d) Testicular seminoma

101. Smoking is a risk factor for all carcinomas, except:
(a) Oral (b) Bronchial
(c) Bladder (d) Thyroid

102. Workers exposed to polyvinyl chloride may develop following liver malignancy:
(a) Cholangiocarcinoma
(b) Fibrolamellar carcinoma
(c) Angiosarcoma
(d) All of the above

103. Which among the following is not a neoplastic virus:
(a) Cytomegalovirus
(b) Hepatitis B virus
(c) Human papilloma virus
(d) All of these

104. One of the following leukemia almost never develops after radiation?
(a) Acute myeloblastic leukemia
(b) Chronic myeloid leukemia
(c) Acute lumphoblastic leukemia
(d) Chronic lymphocytic leukemia

105. The following parasitic infections predispose to malignancies?
(a) Paragonimus westermani
(b) Guinea worm infection
(c) Clonorchiasis
(d) Schistosomiasis

106. Kaposi's sarcoma is seen with:
(a) HCV (b) HPV
(c) HSV (d) HHV

107. UV radiation has which of the following effects on the cells?
(a) Prevents formation of pyrimidine dimers
(b) Stimulates formation of pyrimidine dimers
(c) Prevents formation of purine dimers
(d) All of the above

108. Thorium induced tumor is which of the following?
(a) Renal cell carcinoma
(b) Lymphoma
(c) Angiosarcoma of liver
(d) Astrocytoma

109. Radiation exposure during infancy has been linked to which one of the following carcinoma?
(a) Breast (b) Melanoma
(c) Thyroid (d) Lung

110. The most radiosensitive cells are:
(a) Neutrophils (b) Lymphocytes
(c) Erythrocytes (d) Megakaryocytes

111. The SI unit of radiation absorbed dose is
(a) Rad (b) Becquerel
(c) Gray (d) Sievert

112. Tropical spastic paraparesis is caused by:
(a) Human T-cell Lymphotropic Virus
(b) Hepatitis B virus
(c) Human Immunodeficiency virus
(d) Epstein Barr Virus

113. Which of the following does not predispose to leukemia?
(a) Genetic disorder
(b) Alcohol
(c) Smoking
(d) Chemical exposure

114. HPV oncogene expression is due to:
(a) E1E2 (b) E1E3
(c) E3E5 (d) E6E7

115. Hematological malignancies are commonly linked to which of the following:
(a) Nicotine (b) Lithium
(c) Benzene (d) Alcohol

116. Which of the following has tumor promoting effect?
(a) BRAC (b) myc
(c) RB (d) p16

117. All are true about chromosomal instability syndrome except?
(a) DNA repair defects
(b) AD inheritance
(c) Increased risk of malignancy
(d) May be associated with immunodeficiency

118. BRCA1 gene is associated with:
(a) Lobular carcinoma
(b) Medullary carcinoma
(c) Tubular carcinoma
(d) Papillary carcinoma

119. PTEN gene mutation is seen in:
(a) Ovarian carcinoma
(b) Li-Fraumeni syndrome
(c) Endometrial carcinoma
(d) MEN2A

120. Wilm's tumor gene is located on chromosome?
(a) 13q2.3
(b) 17p21
(c) 17q21
(d) 11p13

PARANEOPLASTIC SYNDROMES, TUMOUR MARKERS, TUMOUR LYSIS SYNDROME

121. A 20 year old female was diagnosed with granulose cell tumor of the ovary. Which of the following bio markers would be most useful for follow-up of patient? *(AIIMS Nov 2011)*
(a) CA 19-9 (b) CA50
(c) Inhibin (d) Neuron – specific enolase

122. Alpha fetoprotein is a marker of: *(AI 2010)*
(a) Hepatoblastoma
(b) Seminoma
(c) Renal cell carcinoma
(d) Choriocarcinoma

123. Hyperglycemia associated with: *(AI 2010)*
(a) Multiple myeloma
(b) Ewing sarcoma
(c) Osteosarcoma
(d) Chondroblastoma

124. Which of the following is Not associated with thymoma? *(AI 2010)*
(a) SIADH
(b) Myasthenia gravis
(c) Polymyositis
(d) Hypogammaglobinemia

125. Which of the following is not true about Neuroblastoma? *(AI 2009)*
(a) Most common extracranial solid tumor in childhood
(b) >50% patients present with metastasis at time of diagnosis
(c) Lung metastases are common
(d) Involve aorta and its branches early

126. Migratory thrombophlebitis is associated with all of the following malignancies, except: *(AI 2008)*
(a) Prostate (b) Lung
(c) GIT (d) Pancreas

127. HMB 45 is a tumor marker for: *(AI 2008, DNB 2008)*
(a) Neuroblastoma
(b) Neurofibroma
(c) Malignant melanoma
(d) Angiosarcoma

128. AFP is a marker of: *(AIIMS Nov 2009)*
(a) Hepatoblastoma
(b) Seminoma
(c) Sertoli-Leydig cell tumor
(d) Choriocarcinoma

129. An undifferentiated malignant tumor on immunohistochemical stain shows cytoplasmic positivity of most of the tumor cells for cytokeratin. The most probable diagnosis of the tumor is: *(AIIMS May 2006)*
(a) Sarcoma (b) Lymphoma
(c) Carcinoma (d) Malignant melanoma

130. For which one of the following tumors Gastrin is a biochemical marker? *(AIIMS May 2005)*
(a) Medullary carcinoma of thyroid
(b) Pancreatic neuroendocrine tumor
(c) Pheochromocytoma
(d) Gastrointestinal stromal tumor

131. All of the following are examples of tumor markers, except: *(AIIMS Nov 2004)*
(a) Alpha-hCG (α-hCG)
(b) Alpha-Feto protein
(c) Thyroglobulin
(d) Beta 2-microglobulin

132. Which of the following tumors have an increased elevation of placental alkaline phosphatase in the serum as well as a positive immunohistochemical staining for placental alkaline phosphatase? *(AIIMS May 2004)*
(a) Seminoma
(b) Hepatoblastoma
(c) Hepatocellular carcinoma
(d) Peripheral neuroectodermal tumor

133. In tumor lysis syndrome, all of the following are seen, except: *(AIIMS May 2002)*
(a) Hypernatremia (b) Hypercalcemia
(c) Hyperkalemia (d) Hyperphosphatemia

134. Uses of tumor marker are: *(PGI Dec 2000)*
(a) Screening of a cancer
(b) Follow up of a cancer patient, esp. for knowing about recurrence
(c) Confirmation of a diagnosed cancer
(d) For monitoring the treatment of a cancer

135. True about Carcinoembryonic antigen (CEA):
(a) Useful for screening of carcinoma colon *(PGI June 01)*
(b) Gives confirmative evidence of Ca. colon
(c) Helpful for follow-up after resection
(d) Levels decrease immediately after resection of tumor
(e) Tumor size correlates with CEA level

136. CA 125 is associated with: *(PGI June 2002)*
(a) Colon ca (b) Breast ca
(c) Ovarian ca (d) Bronchogenic ca
(e) Pancreatic ca

137. Secondaries are common in all, except: *(PGI June 01)*
(a) Skull
(b) Hand and feet bones
(c) Proximal limb bones
(d) Pelvic
(e) Vertebrae

138. Hybridoma refers to *(Delhi PG 2009 RP)*
(a) Collision tumor
(b) A tumor of brown fat
(c) A hamartoma
(d) A technique for raising monoclonal antibodies

139. BCL2 is a marker for: *(Delhi PG-2007)*
(a) Follicular lymphoma
(b) Mycosis fungoides
(c) B-cell lymphoma
(d) Mantle cell lymphoma

140. Alpha-fetoproteins are a marker of: *(Karnataka 2005)*
(a) Secondaries in liver
(b) Cholangiocarcinoma
(c) Hepatoma
(d) None of the above

141. Increased level of alpha fetoprotein is found in
(a) Yolk sac tumor (b) Seminoma *(UP 2001)*
(c) Teratoma (d) Choriocarcinoma

142. Migratory thrombophlebitis is seen in: *(UP 2007)*
(a) Disseminated cancer
(b) Rheumatic heart disease
(c) Libman-Sachs endocarditis
(d) All of the above

143. A 65 years old male diagnosed by biopsy a case of lung carcinoma, with paraneoplastic syndrome and increased calcium. Probable cause is *(UP 2008)*
(a) Parathyroid hormone
(b) Parathyroid hormone related peptide
(c) Calcitonin
(d) Calcitonin related peptide

144. Which is associated with polycythemia: *(RJ 2001)*
(a) Gastric carcinoma
(b) Fibrosarcoma
(c) Cerebellar hemangioblastoma
(d) All

145. Serum AFP is increased in all, except: *(RJ 2003)*
(a) Acute hepatitis
(b) Hepatocellular carcinoma
(c) Hepatoma
(d) Bladder carcinoma

146. Carcinoembryonic antigen is elevated in all, except:
(a) Alcoholic cirrhosis *(RJ 2004)*
(b) Ca colon
(c) Ulcerative colitis
(d) Emphysema

147. Desmoid tumor arises from: *(TN 1991)(AP 2000)*
(a) Wall of the intestine
(b) Anterior abdominal wall
(c) Submucosa
(d) Appendix

148. Alpha-fetoprotein is a tumor marker of: *(AP 2001)*
(a) Carcinoma ovary
(b) Liver malignancies
(c) Endodermal sinus tumor of testis
(d) Both (b) and (c)

149. α-fetoprotein is seen in all except: *(AP 2002)*
(a) Hepatocellular carcinoma *(AI 1997)*
(b) Carcinoma colon *(UP 1996)*
(c) Pancreatic carcinoma
(d) Germ cells of testes

150. The diagnostic tumor marker of liver carcinoma is:
(a) CEA *(AP 2007)*
(b) AFP
(c) CA - 125
(d) All of the above

151. Spontaneous regression of tumor is seen in:
(a) Wilm's tumor *(Kolkata 2002)*
(b) Neuroblastoma
(c) Acute monocytic leukemia
(d) Hepatoblastoma

MOST RECENT QUESTIONS

152. All of the following about tumor markers are properly matched, except:
(a) Prostate cancer - PSA
(b) Colon cancer - CEA
(c) Ovarian cancer – CA 125
(d) Cholangiocarcinoma - AFP

153. Popcorn calcification is seen in:
(a) Chondrosarcoma
(b) Fibrous dysplasia
(c) Osteoblastoma
(d) Wilms' tumor

154. Which one of the following is a frequent cause of serum alpha- fetoprotein level greater than 10 times the normal upper limit?
(a) Seminoma
(b) Hepatocellular carcinoma of liver
(c) Cirrhosis of liver
(d) Oat cell tumor of lung

155. Rise of AFP is noted in all except:
(a) Hepatocellular carcinoma
(b) Cirrhosis
(c) Germ cell tumor
(d) Kidney tumor

156. Catecholamines are increased in:
(a) Neuroblastoma
(b) Retinoblastoma
(c) Medulloblastoma
(d) Nephroblastoma

157. Which of the following is a marker for carcinoma of lung and breast?
(a) CEA (b) AEP
(c) HCG (d) CA-15-3

158. **Secondaries of all the following cause osteolytic lesions except:**
(a) Prostate (b) Kidney
(c) Bronchus (d) Thyroid

159. **Sacrococcygeal teratoma, marker is:**
(a) CEA (b) β- HCG
(c) S100 (d) CA-125

160. **Which of the following mutation is seen in malignant melanoma?**
(a) N-myc (b) CDKN2A
(c) RET (d) Rb

161. **Marker of small cell cancer of lung is:**
(a) Chromogranin (b) Cytokeratin
(c) Desmin (d) Vimentin

162. **Which of the followingis a squamous cell carcinoma marker?**
(a) Vimentin (b) Desmin
(c) Cytokeratin (d) Glial fibrillary acid protein

163. **Marker for ovarian carcinoma in serum is:**
(a) CA-125
(b) Fibronectin
(c) Acid Phosphatase
(d) PSA

164. **Which of the following is tumor marker of seminoma?**
(a) AFP (b) LDH
(c) PLAP (d) HCG

165. **Commonest cancer in which metastasis is seen in brain in**
(a) Breast (b) Lung
(c) Kidney (d) Intestines

166. **Which of the following is incorrect about neuro-blastoma?**
(a) Most common abdominal tumor in infants
(b) X-ray abdomen shows calcification
(c) Can show spontaneous regression
(d) Urine contains 5H.I.A.A

167. **Tumor that follows rule of 10 is:**
(a) Pheochromocytoma
(b) Oncocytoma
(c) Lymphoma
(d) Renal cell carcinoma

168. **Immuno-histopathological markers wrongly matched:**
(a) Desmin-Carcinomas
(b) Vimentin – Sarcomas
(c) Leukocyte specific antigen-Lymphoma
(d) S100-melanoma

169. **Which of the following is a special stain for rhabdomyosarcoma?**
(a) Cytokeratin (b) Synaptophysin
(c) Desmin (d) Myeloperoxidase

170. **The most common cause of malignant adrenal mass is**
(a) Adrenocortical carcinoma
(b) Malignant Phaeochromocytoma
(c) Lymphoma
(d) Metastasis from another solid tissue tumor

171. **About intraoperative histopathological analysis, all are true except:**
(a) Gives an immediate definitive diagnosis of tumor
(b) Used for detecting positive margins after resection
(c) Used to confirm suspected metastasis
(d) Sentinel lymph node biopsy in breast carcinoma is an example

172. **Hypercalcemia is seen in which cancer?**
(a) Renal cell cancer
(b) Carcinoma stomach
(c) Small cell carcinoma lung
(d) Hepatocellular carcinoma

173. **Krukenberg tumor associated mostly with which cancer?**
(a) Stomach (b) Breast
(c) Liver (d) Pancreas

174. **Most common carcinoma is associated with inferior vena caval metastasis?**
(a) Small cell carcinoma lung
(b) Gastric adenocarcinoma
(c) Renal cell carcinoma
(d) Papillary carcinoma thyroid

175. **Carcino Embryonic Antigen is:**
(a) Hormone (b) Glycoprotein
(c) Enzyme (d) Tumor associated protein

176. **Herringbone pattern on histology is seen in which tumor?**
(a) Fibrosarcoma (b) Lipoma
(c) Carcinoma (d) Liposarcoma

Explanations

1. **Ans. (c) Vascular invasion** *(Ref: Robbins 9/e p1094)*

Robbins clearly write.... *'Microscopically, most follicular carcinomas are composed of fairly uniform cells forming small follicles. Follicular carcinomas may be grossly infiltrative or minimally invasive. The latter are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination.* ***This distinction requires extensive histologic sampling of the tumor-capsule-thyroid interface, to exclude capsular and/or vascular invasion.*** *Extensive invasion of adjacent thyroid parenchyma makes the diagnosis of carcinoma obvious in some cases'.*

- Ideal answer for a question for diagnosis of follicular cancer is **capsular invasion**Q (better than even vascular invasion) but in the given options, vascular invasion is the answer of choice.

2. **Ans. (b) Fibromatosis:**
(Ref: Robbins 7th/770, 783-4, Harrison 16th/633, 9/e p1221-1222)

- Fibromatosis are a group of **fibroblastic proliferations**. Though they are **locally aggressive**, they do not metastasize.

Fibromatosis

Superficial Fibromatosis	Deep Fibromatosis
*Palmar fibromatosis **(Dupuytren contracture)** *Plantar fibromatosis *Penile fibromatosis **(Peyronie's disease)**	*Also called **desmoids tumors** *Greater tendency to recur *Grow in a locally aggressive manner *Arise isolated or as component of Gardner syndrome

3. **Ans. (b) Increased requirement of growth factors**
(Ref: Biology of the cell (2003) 357-364)

Both normal cells and cancer cells can be cultured in-vitro. However, they behave quite differently

Normal cell	Cancer cell
Show **replicative senescence** i.e. cells pass through limited number of cell divisions before they decline in vigor and die. It may caused by **inability to synthesize telomerase**	They are immortal i.e. proliferate indefinitely in culture. Cancer cells in culture produce telomerase
Normal cells show the phenomenon of **contact inhibition** i.e. they proliferate until the surface of culture dish is covered by single layer of cells just touching each other	Show no contact inhibition. Even after the surface of dish is covered, the cells continue to divide
Nutrients and growth factors must be supplied to them in their tissue culture medium	**Do not require growth factors**
Normal karyotype is present	Mostly show abnormal karyotype

4. **Ans. (a) Small cell carcinoma of lung**
(Ref: Harrison 17th/2458; Robbins 8th/1339, 7th/1410, 9/e p1315)

Small cell carcinoma of lung most commonly metastasize to the brain. It accounts for about 40% of brain metastases.

Other Tumors Metastasizing to Brain are carcinomas of
• Breast, • Melanoma, • Kidney, • GIT

5. **Ans. (c) Both necrosis and apoptosis**
(Ref: Harrison 17th/519 , 9/e p303, 315)

- Chemotherapeutic drugs can cause both necrosis and apoptosis, but *it is apoptosis which is the basis of action of chemotherapeutic drugs.*

- **Anoikis** *refers to death of epithelial cells after removal from the normal milieu of substrate, particularly from cell to cell contact.*

6. **Ans. (b) Dysplasia** discussed in details in text.
(Ref: Robbins 7th/273-274 , 9/e p271)

7. **Ans. (a) Smoking; (b) U-V-light; (c) Chronic ulcer:**
(Ref: Harrison' 16th/497, Robbins 9/e p1155)

Risk factors

Melanoma	Basal cell and squamous cell carcinoma
• Family history of melanoma • Persistently changing mole • Presence of clinically atypical mole • Immunosuppression • Sun exposure	• Exposure to UV light principally UV-B • Male sex and Older age • Exposure to sun, arsenic, smoking, cyclic aromatic hydrocarbons in tar, soot or shale • HIV, HPV infection, immunosuppression. • Ionizing radiations, thermal burns • Certain scars and chronic ulcerations • Heritable conditions like albinism, Xeroderma pigmentosum, genetic mutations (PATCHED gene) • Premalignant conditions like Actinic keratosis, Bowen's disease, Erythroplasia of Queyrat.

8. **Ans. (c) Chronic ulcerative colitis**

(Ref: Robbins 8th/276 , 9/e p279)

Certain non-neoplastic disorders—*the chronic atrophic gastritis of pernicious anemia, solar keratosis of the skin, chronic ulcerative colitis, and leukoplakia of the oral cavity, vulva, and penis*—have such a well-defined association with cancer that they have been termed *precancerous conditions.*

9. **Ans. (b) Hepatocellular carcinoma**

(Ref: Robbins 7th/925 , 9/e p274)

Renal cell cancer and hepatocellular cancer have high tendency invasion of vascular channels.

10. **Ans. (c) Dysplasia** *(Ref: Robbins 9/e p271-272)*

- **Dysplasia** is the loss of uniformity of individual cells as well as their architectural orientation.
- **Carcinoma *in situ*** (dysplastic changes are marked but lesion remains confined to normal tissue: pre-invasive neoplasm). ***Basement membrane is intact***.
- **Anaplasia** is Complete lack of differentiation of cells both morphologically and functionally (Invasive Ca)

11. **Ans. (b) Lymphatic route** *(Ref: Robbins 9/e p273)*

12. **Ans. (b) Gastric carcinoma** *(Ref: Robbins 9/e p1207)*

13. **Ans. (b) Proliferation of native cells in tissue**

(Ref: Robbins 8th/262; 7th/272 , 9/e p267)

14. **Ans. (d) Metastasis** *(Ref: Robbins 8th/269; 9/e p272)*

15. **Ans. (a) Metaplasia** *(Ref: Robbins 8th/10,265; 9/e p271)*

16. **Ans (d) Muscle tumor cells forming giant cells**

(Ref: Robbins 8th/262-5, 9/e p270)

Neoplastic cells may be similar to normal cells found in the tissue of origin, which defines the malignancy as "well differentiated" or "low grade." Alternatively, the neoplastic cells may lack most of the characteristic features of normal cells found in the tissue of origin, which defines the malignancy as "poorly differentiated" or "high grade." Tumors that contain neoplastic cells in the midst of this spectrum are termed "moderately differentiated" or "medium grade." If the neoplastic cells are described as anaplastic, they demonstrate a complete lack of differentiation.

The appearance of giant multinucleated cells in a muscle tumor would therefore suggest anaplasia.

(Choice A) Cells in hepatic tissue would be expected to synthesize bile. Therefore a hepatic tumor that synthesizes bile is described as being well-differentiated not anaplastic.

(Choice B and C) Cells in the epithelium would be expected to produce keratin pearls. Therefore an epithelial tumor that produces keratin pearls would be described as well-differentiated not anaplastic.

17. **Ans. (b) Cannot be determined by microscopic examination** *(Ref: Robbins 8th/1159-1161, 9/e p1135)*

Pheochromocytomas, and their related counterparts in extra-adrenal sites called paragangliomas, are notorious because the only reliable indicator of metastatic potential is the presence of distant metastases. Very malignant-appearing tumors may not metastasize and benign-appearing tumors may produce metastases. These tumors should all be considered "potentially malignant."

18. **Ans. (a) Crohn's disease** *(Ref: Robbins 9/e p279)*

- Ideal answer to this question is none but in the given situation, the answer of choice is Crohn disease because in the comparison of the two types of inflammatory bowel disease, Crohn disease is less likely to be associated with progression to cancer of the bowel.

19. **Ans. (c) Basement membrane invasion**

(Ref: Robbins 9/e p271)

- **Basement membrane invasion**^{Q} is the most important differentiating feature between **invasive carcinoma from carcinoma in situ.**

20. **Ans (b) Integrins** *(Ref: Robbins 8/e p49, 9/e p24)*

The cell adhesion molecules (CAMs) are classified into four main families:

- Immunoglobulin family CAMs
- *Cadherins*
- *Integrins:* bind to extracellular matrix (ECM) proteins such as fibronectin, laminin, and osteopontin **providing a connection between cells and extracellular matrix** (ECM)
- *Selectins*

21. **Ans. (d) Hepatocytes** *(Ref: Robbins 8/e p81-4, 9/e p101)*

Permanent cells	Quiescent cells	Labile cells
• Cannot divide in postnatal life • Neurons, skeletal muscles	• Low level of replication which increases only on stimulation • Liver cells, kidney cells	• Rapid rate of replication • Skin, GIT, oral cavity

22. **Ans. (d) Metastasis** *(Ref: Robbins 9/e p272)*

Metastasis is the ***most reliable feature*** of a malignant tumor, characterized by the spread of the tumor to other parts because of penetration into blood vessels, lymphatics and the body cavities.

23. **Ans. (a) Cancer penis in male**

(Ref: Various books, internet)

Diseases showing bimodality of age presentation (Mnemonic: ***ABCDEGH)***

1. **A**ortic stenosis/acute leukemia – A.L.L > A.M.L
2. **B**reast cancer (Before advent of mammography
3. **C**rohn's disease
4. **D**ermatomyositis
5. **E**nthesioneurobalstoma
6. Thyroglossal cyst
7. **H**odgkin's lymphoma
8. **V**ulvar carcinoma ***but NOT penile cancer***

24. **Ans. (c) Crohn disease** *(Ref: Robbins 9th/800-1,806,809)*

Robbins pg 806.....***Peutz-Jeghers syndrome*** is associated with a markedly *increased risk of several malignancies.* Lifetime risk is approximately **40%** for these, and regular surveillance is recommended.

Pg 809...Colorectal adenocarcinoma develops in **100%** of *untreated FAP patients*, often before age 30 and nearly always by age 50.

> The risk of colonic adenocarcinoma is increased in patients with long-standing IBD affecting the colon. Please understand that ***increased risk of cancer is seen in colonic variant of Crohn disease and not otherwise.*** Ulcerative colitis is a pre-malignant condition.

25. **Ans. (b) Presence of metastasis to other organs**
(Ref: Robbins 8/e p1159-1161, 9/e p1135)

"There is no histologic feature that reliably predicts clinical behavior. In fact, ***cellular and nuclear pleomorphism, including the presence of giant cells, and mitotic figures are often seen in benign pheochromocytomas,*** while cellular monotony is paradoxically associated with an aggressive behavior. ***Even capsular and vascular invasion may be encountered in benign lesions.*** Therefore, the **definitive diagnosis of malignancy in pheochromocytomas** is based **exclusively on the presence of metastases.**

26. **Ans (a) Hamartoma** *(Ref: Robbins 8/e p262, 9/e p13)*
An overgrowth of a skin structure at a *localized region* is likely to be indigenous as well as benign; this is more likely to be a hamartoma. It is now considered as a neoplasm.

27. **Ans. (a) Obstruction of sub-dermal lymphatics**
(Ref: Robbins 9th/1067)
Breast cancers presenting with breast erythema and skin thickening have a very poor prognosis, as most patients prove to have distant metastases. The edematous skin is tethered to the breast by Cooper ligaments and mimics the surface of an orange peel, an appearance referred to as peau d'orange. These clinical signs are caused by dermal lymphatics filled with metastatic carcinoma that blocks lymphatic drainage.

28. **Ans (a) Multiple myeloma** *(Ref: Robbins 9/e p306)*
Molecular study is important in the management of:

- Multiple myeloma
- Neuroblastoma
- Prostate cancer
- Myelodysplastic disorders

29. **Ans (b) Collagenase IV** *(Ref: Robbins 9/e p308)*
Benign tumors of the breast, colon, and stomach show little type IV collagenase activity, whereas their malignant counterparts over express this enzyme.

30. **Ans (a) Collagenase IV** *(Ref: Robbins 9/e p308)*

31. **Ans (b) Basal cell carcinoma** *(Ref: Robbins 9/e p1158)*

32. **Ans. (c) G2 M**
(Ref: Robbins 8th/286; Harrison 17th/516, 9/e p289)
Direct quote from Robbins.... 'The G2/M checkpoint monitors the completion of the DNA replication and checks whether the cell can safely initiate the mitosis and separate sister chromatids. This checkpoint is particularly important in cells exposed to ionizing radiation. ***Cells damaged by ionizing radiation activate G2/M checkpoint*** and arrest in G2'.

33. **Ans. (a) G0-G1-S-G2-M** *(Ref: Robbins 7th/90, 9/e p25)*

34. **Ans. (d) S phase** *(Ref: Robbins 8th/86, 7th/90, 9/e p25)*

35. **Ans. (c) G_1-S Phase** *(Ref: Robbins 7th/292, 9/e p295)*
- G_1/S check-point is controlled by p53 whereas G_2/M check-point has both p53 dependent as well as independent mechanisms.
- p53 induces the synthesis of p21 which inhibits cyclin D/Cdk4. This results in stoppage of activation of Rb and cell cycle is arrested in G_1/S phase.

36. **Ans. (d) Cyclin B**
(Ref: Robbins 7th/290-291, Robbins 8th/285-286 , 9/e p25-26)
Examples of cyclin/CDK complexes controlling the cell cycle.

Cyclin B/CDK_1	Regulates the transition from G_2 to M phase
Cyclin D/CDK_4 Cyclin D/CDK_6 Cyclin E/CDK_2	Regulates the transition from G_1-S
Cyclin A/CDK_2 and cyclin B/ CDK_1	Active in S phase

37. **Ans. (a) S; (b) M; (d) G_2:** *(Ref: Gray's anatomy 38th/55)*
- The time taken for S, G_2 and M phases are *similar* for most cell types, occupying about 6, 4 and 2 hours respectively.
- The *duration of* G_1 *shows considerable variation. It can be* as short as 2 hours in rapidly dividing cells like embryonic tissues or as long as 12 hours in some adult tissues.
- G_1 phase is most variable because, in this phase cells are not committed to DNA replication. They can either enter resting state or progress to next cell division.

38. **Ans. (a) Topoisomerase II causes break in strands; (c) At G2-M phase there is loss of inhibitors controlling cell-cycle and (d) Decrease in telomerase activity causes anti-tumor effects.**
(Ref: Harrison 16th/453, 454, Robbins 7th/43, 292)

- Topoisomerase I nicks DNA, relieving torsional tension of the replicating helix.
- Topoisomerase II introduces the double strand break to avoid DNA tangle.
- p53 it is a tumor supresser gene.

Contd...

Contd...

- With each cell division, there is some shortening of specialized structures called telomeres (present at ends of chromosomes). In germ cells, telomere shortening is prevented by the enzyme telomerase. This enzyme is absent from most somatic cells, and hence they suffer progressive loss of telomeres. Introduction of telomerase into normal human cells causes considerable extension of their life span, thus supporting that **telomerase loss is causally associated with loss of replication activity.** So, decrease telomerase activity causes anti tumor effect.
- Loss of inhibitors controlling cell cycle occurs at G_1-S phase/G_2-M phase.

39. **Ans. (a) Proto-oncogenes are activated by chromosomal translocation; (b) Malignant transformation involves accumulation of mutations in the proto-oncogenes and tumor suppressor gene in stepwise fashion; (c) Point mutation of somatic cells; (e) At G2-M phase there is loss of inhibitors controlling cell cycle**

(Ref: Robbins' 9/e p284-286)

Activation of proto-oncogene results in cancer causing oncogenes by following mechanisms:

1. Single point mutation e.g. ras oncogene.
2. Gene amplification e.g. n-myc amplification in neuroblastoma.
3. Chromosomal translocation e.g. t (8:14) in Burkitt lymphoma results in c-myc over-expression and hence the tumor.
4. Promoter insertion.
5. Enhancer insertion.

The cell cycle has its own internal controls called checkpoints. There are two main checkpoints:

1. G_1-S transition- The S-phase is the point of no return in cell cycle. G_1-S checkpoint checks for DNA damage and prevents replication of defective cells.
2. At G_2M transition- The G_2M checkpoint monitors the completion of DNA replication and checks whether the cell can safely initiate cell division. Loss of inhibitors at this stage can lead to division of faulty cells and can lead to carcinogenesis.

- Defect in cell-cycle checkpoint components is a major cause of genetic instability in cancer cells.

40. **Ans. (c) G_1- S phase** *(Ref: Robbins 9/e p294-295)*

41. **Ans. (a) Fragile X syndrome** *(Ref: Robbins 9/e p169)*

42. **Ans. (b) Cyclin B** *(Ref: Robbins 8th/286, 7th/290, 9/e p26)*

43. **Ans. (c) p53** *(Ref: (Ref: Robbins Illustrated 7/e p p 292, (Ref: Robbins 8/e p286, 9/e p25-26)*

Cyclins form complex with cyclin dependent kinases and regulate the transition of cell cycle from one stage to the other. These CDK complexes in turn are regulated by CDK inhibitor. The inhibitors control the cell cycle by balancing the activity of CDKs. The signals from these inhibitors determine whether a cell progresses through the cell cycle. Changes in the level of these inhibitors may occur in some tumors, or possibly in aging cells.

- The cyclin dependent kinase inhibitors are

- p21 - p27 - p57 - p15 - p16 - p18 - p19

44. **Ans. (b) M-phase**

- Cells are most radiosensitive in **G_2M interphase**
- Cells are least radiosensitive in **S phase**

45. **Ans. (a) Gastric cancer** *(Ref: Robbins 9/e p291)*

Cadherin is derived from the "calcium-dependent adherence protein." It participates in interactions between cells of the same type. The linkage of cadherins with the cytoskeleton occurs through the catenins. The cell -to-cell interactions mediated by cadherin and catenins play a major role in regulating cell motility, proliferation, and differentiation and account for the inhibition of cell proliferation that occurs when cultured normal cells contact each other ("**contact inhibition**").

- Reduced function of **E-cadherin** is associated with certain types of **breast and gastric cancer.**
- Mutation and altered expression of the ***Wnt/β-catenin*** pathway is implicated in ***gastrointestinal and liver cancer*** development.

46. **Ans. (b) p53** *(Ref: Robbins 8/e p274, 290, 9/e p293-294)*

47. **Ans. (b) Bone marrow hyperfunction** *(Ref: Robbins 8th/663; 7th/647, 9/e p630)*

48. **Ans. (a) Predicting therapeutic response** *(Ref: Robbins 8th/1090, 9/e p1062)*

Friends, direct quote from Robbins....*'HER2/neu overexpression* is associated with *poorer survival* but its *main importance is as a predictor of response to agents that target this transmembrane protein (examples* trastuzumab or lapatinib*).'*

- The overexpression is due to *amplification* of the gene *HER2/neu located on 17q21.*

49. **Ans. (a) Osteosarcoma** *(Ref: Robbins 9/e p293)*

- ***Retinoblastoma is the most common primary intraocular malignancy of children.*** Involvement of both eyes with pineal gland is called as trilateral retinoblastoma.
- The pinealoblastoma in association with retinoblastoma is a *primary tumor.*
- In approximately 40% of cases, retinoblastoma occurs in individuals who inherit a germ-line mutation of one RB allele. This variant of retinoblastoma (familial retinoblastoma) is inherited as an autosomal dominant trait and is associated with osteosarcoma. ***Osteosarcoma*** is therefore the commonest ***secondary maligancy*** associated with retinoblastoma.

50. **Ans. (a) Autosomal dominant** *(Ref: Robbins 8th/302, Harrison 665, 9/e p314-315)*

- Fanconi's anemia is an **autosomal recessive**[Q] disease characterized by progressive **pancytopenia**[Q], increased risk of malignancy **(solid tumors and**

AML[Q]) and congenital developmental anomalies like short stature, café au lait spots, abnormalities affecting thumb, radius and genitourinary tract.

- Fanconi's anemia is associated with **BRCA gene**. The Fanconi anemia proteins and BRCA proteins form a **DNA-damage repair proteins** to correct intrastrand and interstrand DNA cross links induced by chemical cross-linking agents.

51. Ans. (d) Wild/non-mutated form is associated with increased risk of childhood tumors

(Ref: Robbin 7th/302-303, Harrison 17th/499-500, 8th/290-2, 9/e p294)

- p53 gene is a tumor suppressor gene also known as "**guardian of the genome**"[Q] located on **short arm of chromosome 17**[Q] (17p). Its wild/non mutated form is associated with reduced risk of tumors.

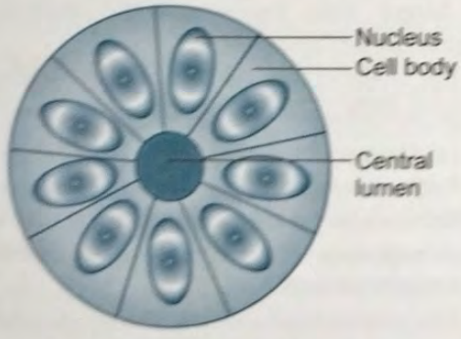
52. Ans. (c) Sis *(Ref: Robbins 7th/182)*

- A number of **nuclear transcription factors** are the products of oncogenes like **myc, fos, jun, myb and rel**. Out of these ***myc is most commonly involved in tumors***[Q].
- **SIS oncogene** is the only example of a growth factor oncogene in the given options. Its over expression is seen in cancers like astrocytoma and osteosarcoma. The other growth factor are described is text.

53. Ans. (a) Retinoblastoma

(Ref: Robbins 7th/1442; Neuropathology for the Neuroradiologist: Rosettes and Pseudorosettes by F.J. Wippold and A. Perry)

Rosettes consist of a halo or spoke-wheel arrangement of cells surrounding a central core or hub.



Rosettes may be considered primary or secondary manifestations of tumor architecture. Primary rosettes form as a characteristic growth pattern of a given tumor type, whereas secondary rosettes result from the influence of external factors on tumor growth.

*Neuropil-rich rosettes are referred to as *pineocytomatous rosettes* in pineocytomas and *neurocytic rosettes* in central neurocytoma. These are similar to the Homer Wright rosette, but they are generally larger and more irregular in contour.

54. Ans. (c) Promotion of DNA repair

(Ref: Robbins 7th/293, 295), http://www.nature.com/scitable/topicpage/proto-oncogenes-to-oncogenes-to-cancer-883 by Heidi Chial, 9/e p284)

The normal cellular counterpart of oncogene is known as proto-oncogene. Proto-oncogenes are important for cellular function related to growth and proliferation. Proteins encoded by these genes may function as growth factor ligands and receptors, signal transducers, transcription factors and cell cycle components.

Chial writes that 'proto-oncogenes encode proteins that function to ***stimulate cell division, inhibit cell differentiation, and halt cell death***. All of these processes are important for normal human development and for the maintenance of tissues and organs. Oncogenes, however, typically exhibit increased production of these proteins, thus leading to increased cell division, decreased cell differentiation, and inhibition of cell death'. So, we can say that '**These genes may also inhibit apoptosis**'.

Promotion of DNA repair is the function of **tumor suppressor genes**. Promotion of DNA repair is protective from oncogenesis and is not the function of proto-oncogenes.

55. Ans. (d) Rb

(Ref: Robbins 7th/300, Harrison 17th/499, 496, 9/e p290)

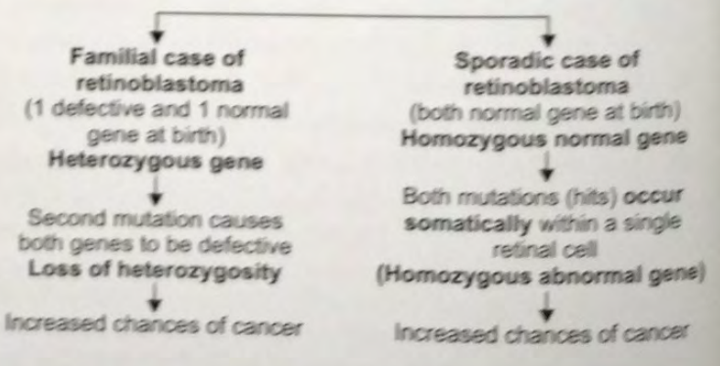
- **Tumor suppressor genes are the genes whose products down regulate the cell cycle, and thus apply brakes to cellular proliferation.**
- Rb gene is a tumor suppressor gene whereas Myc, fos and ras are all examples of proto-oncogenes.

56. Ans. (d) Colon, endometrium, ovary

(Ref: Harrison 17/page 575, Robbins 8th/821-822, 9/e p810)

- Lynch syndrome is an **autosomal dominant**[Q] disorder
- It is also called as ***Hereditary Non-polyposis Colon Cancer (HNPCC) syndrome***[Q]
- It is caused because of **defective DNA repair genes**[Q] *leading to microsatellite instability.*
- There is increased chance of multiple cancers (**colorectal area, endometrium, ovary, stomach, ureter, brain, small intestine, hepatobiliary tract and skin**)

57. Ans. (c) Retinoblastoma *(Ref: Robbins 9/e p292-293)*



58. Ans. (d) ras *(Ref: Robbins 7th/295, 9/e p286)*

59. Ans. (b) Autosomal dominant

(Ref: Robbins 7th/1442, 299-300, 9/e p292-293)

60. **Ans. (a) p53** *(Ref: Robbins 7th/302, 303, 304, 9/e p293)*

61. **Ans. (c) Its activity in the cells decreases following UV irradiation and stimulates cell cycle**
(Ref: Robbins 7th/302, 303, 8th/290-291, 9/e p293-294)
- p53 is a **tumor suppressor gene,** located on chromosome 17. It is also called as "*Guardian of the genome*".
- At the time of DNA injury following irradiation, its **level increases and it acts to cause cell cycle arrest (G_1/S)**
- The cell cycle arrest is to allow time for DNA repair. If repair is unsuccessful, p53 causes apoptosis of the cell by activating bax (apoptosis inducing gene). So, any exposure to UV irradiation would cause increased activity of p53 gene resulting in apoptosis and cell death.

62. **Ans. (b) GTPase activating protein** *(Ref: Robbins 9/e 286)*
Activated ras is present in association with GTP. Enzyme GTPase will degrade GTP to GDP and result in inactivation of ras. Thus, GTPase activating protein will counteract the activation of ras.

63. **Ans. (b) p53** *(Ref: Robbins Illustrated, 9/e 294)*
- Mutation in p53 tumor suppressor gene is strongly associated with breast cancer, as well as many other sarcomas and carcinomas. This condition is called as **Li-Fraumeni syndrome**.

64. **Ans. (a) Important for normal cell growth; (b) May get converted into oncogenesis; (c) C-myc over-expression causes lymphoma** *(Ref: Robbins 9/e 284)*

65. **Ans. (c) They are transduced from virus infected cells**
(Ref: Ananthnarayan 7/580-1, Robbins' 7th/293, 302)
- **Viral oncogenes** (V-onc) commonly known as **'cancer genes'** which encode proteins triggering transformation of normal cells into cancer cells.
- Proto-oncogenes are the **normal cellular genes** that promote normal growth and differentiation.
- Oncogenes isolated from cancer cells are called cellular oncogenes (C-onc).
- Proto-oncogenes are converted to oncogenes and cause cancer by:
  - Transduction into retrovirus (V-oncs) or
  - Changes in situ that affect their expression and function thereby converting them into cellular oncogene (C-oncs).
- The transduction of oncogenes by the virus (e.g. retrovirus) is through recombination with DNA of a (normal) host cell that had been infected by the virus. Thus, they are of host cell origin. The virus act as transducing agent, carrying oncogenes from one cell to another.

Viral oncogenes do not contain introns and that's how they are different from human oncogenes.

66. **Ans. (a) Suppression of p53 protein; (c) bcl-2**
(Ref: Robin's 7th/306, 274, 9/e 302)
- Cell survival would be seen when they are prevented from apoptosis. Genes that favor cell survival and protect from apoptosis are: - bcl-2 , bcl-xL
- Genes that favor programmed cell death are: bax, bad, bcl-xL and p53.

67. **Ans. (a) Proto-oncogenes; (b) Tumor suppressor genes; (d) DNA repair genes**
(Ref: Robbins 7th/290, 298, 9/e 280)

68. **Ans. (c) Nucleotide excision repair**
(Ref: Harrison 17th/d/387 Robbins 7th/d 287, 9/e 314)

69. **Ans. (b) EGF Receptor** *(Ref: Robbins 7th/295, 9/e 285)*

70. **Ans. (d) C-myc** *(Ref: Robbins 7th/295, 300, 9/e 288)*
- C-myc is a proto-oncogene of transcriptional activator category and is associated with Burkitt's lymphoma.

71. **Ans. (a) Formation of the new blood vessels**
(Ref: Robbins 8th/297; 7th/71-72, 9/e 305)

72. **Ans. (a) RET** *(Ref: Robbins 8th/1124-1126, 9/e 284)*

73. **Ans. (a) Chromosome 5** *(Ref: Robbins 9/e 296)*

74. **Ans. (c) PTEN** *(Ref: Robbins 8/e p294, 9/e 298)*

Direct quote from Robbins… "***PTEN*** (***P***hosphatase and ***ten***sin homologue) is a membrane-associated phosphatase encoded by a gene on chromosome 10q23 that is mutated in **Cowden syndrome**, an autosomal dominant disorder marked by frequent benign growths, such as tumors of the skin appendages, and an increased incidence of epithelial cancers, particularly of **the breast, endometrium**, and **thyroid**.

75. **Ans. (b) Neurocysticercosis**
(Robbins 9th/ 1203,1312, 1339)
- Retinoblastoma has the presence of Flexner-Wintersteiner rosette's and fleurettes reflecting photoreceptor differentiation. …. *(Robbins 9th/1339)*
- PNET (Primitive Neuro-Ectodermal Tumour): It is composed of sheets of uniform small, round cells that are slightly larger than lymphocytes. ….
(Robbins 9th/1203)
- Medulloblastoma: The tumor may express neuronal (neurosecretory) granules, form Homer- Wright rosettes…. *(Robbins 9th/1312)*

For details see the answer of a question in chapter of 'Neoplasia'

76. **Ans. (c) G_1 – S phase** *(Ref: Robbins 8/e p290-1, 9/e 294)*
- The cell cycle has its own internal controls, called ***checkpoints***. There are two main checkpoints, one at the **G1/S transition** and another at **G2/M**.
- In the **G1/S checkpoint, cell-cycle arrest is mostly mediated through p53**, which induces the cell-cycle inhibitor p21.
- Arrest of the cell cycle by the **G2/M checkpoint** involves **both p53-dependent (via cyclin A/cdK-2) and independent (via cdc 25)** mechanisms.

As can be deduced from above mentioned information that the p53 is associated with both the types of checkpoints. However, **G2/M checkpoint**can take place even without p53. Hence, option "c" is the preferred answer.

77. **Ans. (a) RET gene** *(Ref: Robbins 9/e 284)*

78. **Ans. (a) Beta-2 macroglobulin** *(Ref: Robbins 8/e p327)*
Beta-2 **microglobulin** and not beta macroglobulin may be used as a tumor marker (as in multiple myeloma).

79. **Ans. (d) Transcription activator** *(Ref: Robbins 8/e p288)*
- A host of oncoproteins, including products of the *MYC, MYB, JUN, FOS,* and *REL* oncogenes, are transcription factors that regulate the expression of growth-promoting genes, such as cyclins.
- Out of all these,***MYC is most commonly involved in human tumors***[Q]
- MYC gene is associated with **"Conflict model"** in carcinogenesis

Tumors associated with different subtypes of MYC

C-*MYC*	Translocation	Burkitt lymphoma
N-*MYC*	Amplification	**N**euroblastoma, small-cell carcinoma of lung
L-*MYC*	Amplification	Small-cell carcinoma of **L**ung

80. **Ans. (d) Osteosarcoma** *(Ref: Robbins 8/e p293)*

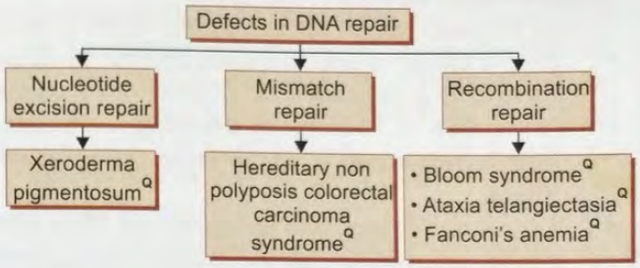
81. **Ans. (b) Medullary carcinoma thyroid** *(Ref: Robbins 8/e p280, 9/e 284)*
The RET protein is a receptor for the glial cell line–derived neurotrophic factor and structurally related proteins that promote cell survival during neural development. RET is normally expressed in neuroendocrine cells, such as parafollicular C cells of the thyroid, adrenal medulla, and parathyroid cell precursors. **Point mutations in the *RET* proto-oncogene** are associated with dominantly inherited **MEN types 2A**[Q] **and 2B**[Q] and **familial medullary thyroid carcinoma**[Q].
RET gene mutation is more commonly associated with **medullary thyroid cancer than pheochromocytoma.**

Clinical significance of RET... *(Ref: Robbins 8/e p)*

*All individuals carrying **germline RET mutations** are advised to undergo **prophylactic thyroidectomy** to prevent the inevitable development of medullary carcinomas.*

82. **Ans. (d) RB...explained earlier** *(Ref: Robbins 9/e p291)*

83. **Ans. (c) Xeroderma pigmentosum** *(Ref: Robbins 8/e p275, 9/e 314)*



84. **Ans. (d) Rb** *(Ref: Robbins 8/e p286, 9/e p291)*

85. **Ans. (b) Retinoblastoma** *(Ref: Robbins 9/e p290)*

86. **Ans. (b) Pinealoblastoma** *(Ref: Robbins 9/e p1339)*

87. **Ans. (a) Overexpression** *(Ref: Robbins 9/e p284)*
HER-2/neu gene is a proto-oncogene whose amplification/ overexpression cause breast carcinoma.

88. **Ans. (a) Ret proto oncogene** *(Ref: Robbins 9/e p1099)*

89. **Ans. (b) Chromosome 17** *(Ref: Robbins 9/e p1312)*

90. **Ans. (b) Renal cell carcinoma** *(Ref: Robbins 9/e p1134)*

91. **Ans. (b) EBV** *(Ref: Robbins 8th/230, Harrison 18th/921, 1124, 9/e 327)*

Infectious Agent	Lymphoid Malignancy
Epstein-Barr virus	• Burkitt's lymphoma • Post–organ transplant lymphoma • Primary CNS diffuse large B cell lymphoma • Hodgkin's disease • Extranodal NK/T cell lymphoma, nasal type
HIV	• Diffuse large B cell lymphoma • Burkitt's lymphoma
Hepatitis C virus	• Lymphoplasmacytic lymphoma
Helicobacter pylori	• Gastric MALT lymphoma
Human herpesvirus 8	• Primary effusion lymphoma • Multicentric Castleman's disease
HTLV-I	• Adult T cell leukemia/lymphoma

92. **Ans. (a) MALToma** *(Ref: Harrison 17th/1858, Robbins 8th/316, 9/e 329)*

93. **Ans. (d) Burkitt's lymphoma** *(Ref: Robbins 7th/814, Robbins 8th/315-6, 9/e 329)*

94. **Ans. (b) Non-small Cell Carcinoma of Lung** *(Ref: Robbins 8th/277, 878, 9/e 325-329)*

CANCERS ASSOCIATED WITH INFECTIOUS AGENTS		
Opisthorchis, cholangitis	***Cholangiosarcoma, colon carcinoma***	***Liver flukes*** (*Opisthorchis viverrini*)
		Bile acids
Chronic cholecystitis	Gallbladder cancer	Bacteria, gallbladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	Helicobacter pylori
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin lymphoma and Hodgkin lymphoma, nasopharyngeal cancer	Epstein-Barr virus
AIDS	Non-Hodgkin lymphoma, squamous cell carcinoma, Kaposi's sarcoma	Human immunodeficiency virus, human herpesvirus type 8
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonorrhea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma	Schistosomiasis

Non small cell lung cancer is not reported to be associated with any infectious organism.

95. **Ans. (a) Angiogenesis** *(Ref: Harrison 17th/. 509, Robbins 9/e 305-306)*

Metastasis is a complex series of steps in which cancer cells leave the original tumor site and migrate to other parts of the body via the bloodstream or the lymphatic system. To do so, malignant cells break away from the primary tumor and degrade **proteins** of the **extracellular matrix** (ECM). One of the **critical events** required for metastasis is the growth of a new network of blood vessels, called tumor **angiogenesis**.

- Without vascularization or angiogenesis, the tumor can **grow only 1-2 mm**[Q]. Vessels are also required for nutrition.
- Vascularisation ***promoted by VEGF and bFGF*** and **inhibited by Angiostatin, Endostatin and Tumstatin**[Q].
- It has been found that **angiogenesis inhibitors** would therefore prevent the growth of metastases.

96. **Ans. (b) Papilloma viruses produce tumors in animals but not in humans** *(Ref: Harrison 17th/487)*

All the options mention about the carcinogens. "Human papilloma virus is the most common etiological factor for cervical cancer"

97. **Ans. (d) Hepatitis C virus** *(Ref: Robbins 8th/315, 9/e 328)*

Hepatitis C virus (HCV) is only oncogenis RNA virus in the options. Others mentioned are oncogenic DNA viruses.

98. **Ans. (c) Epstein-Barr Virus** *(Ref: Robbins 9/e 328)*

LMP-1 gene plays a role in oncogenesis induced by EBV. For details, see text.

99. **Ans. (b) UVB rays** *(Ref: Robbins 7th/323 , 9/e 324)*

100. **Ans. (d) Testicular seminoma** *(Ref: Robbins 8th/989)*

101. **Ans. (d) Thyroid** *(Ref: Robbins 9/e 415)*

102. **Ans. (c) Angiosarcoma** *(Ref: Robbins 9/e 519)*

103. **Ans. (a) Cytomegalovirus** *(Ref: Robbins 9/e 325-326)*

104. **Ans. (d) Chronic lymphocytic leukemia** *(Ref: Robbins 9/e p 431)*

The main sources of ionizing radiation are x-rays and gamma rays (electromagnetic waves of very high frequencies), high-energy neutrons, alpha particles (composed of two protons and two neutrons), and beta particles, which are essentially electrons.

Diagnostics is the most common source of radiation exposure in human beings.

Cancers associated with radiation	Cancers not associated with radiation
• ALL, AML and CML	• CLL
• Cancer of thyroid, breast and lung.	• Hodgkins lymphoma
• Cancer of CNS, bladder, ovary	• Cancer prostate/testis/ cervix

105. **Ans. (c) Clonorchiasis** *(Ref: Robbins 8/e p880, 9/e p 874)*

The following two parasites have definitive etiological association with malignancies:

- *Clonorchis sinensis*: cholangiocarcinoma[Q]
- *Opisthorchis viverrini:* cholangiocarcinoma[Q]
- *Schistosoma haematobium* : squamous cell cancer of urinary bladder[Q]
- *Schistosoma* japonicum: colorectal cancer[Q]

106. **Ans. (d) HHV** *(Ref: Robbins 8/e p313, 9/e p 254)*

107. **Ans. (b) Stimulates formation of pyrimidine dimers** *(Ref: Robbins 8/e p312, 9/e p314)*

Direct quote *from Robbins..* ***"The carcinogenicity of UV-B light is attributed to its formation of pyrimidine dimers in DNA".*** This type of DNA damage is repaired by the nucleotide excision repair pathway. The importance of the nucleotide excision repair pathway of DNA repair is illustrated by the high frequency of cancers in individuals with the hereditary disorder *xeroderma pigmentosum..*

108. **Ans. (c) Angiosarcoma of liver** *(Ref: Robbins 9/e 519)*

Angiosarcoma of the liver is a highly aggressive tumor which is associated with exposure to:

- **Vinyl chloride**[Q],
- **Arsenic**[Q], or
- **Thorotrast**[Q].

Thorotrast is a suspension containing particles of the radioactive compound thorium dioxide. It emits **alpha particles** due to which it has been found to be extremely carcinogenic.

109. **Ans. (c) Thyroid**
(Ref: Robbins 8/e p312, 425 and internet, 9/e p 325)
The most radiosensitive organ sites in children in order of sensitivity are the thyroid gland, breasts, bone marrow (leukemia), brain and skin.

110. **Ans. (b) Lymphocytes** *(Ref: Robbins, 9/e p430)*

- The **most radiosensitive** cell in the ***blood*** is the **lymphocytes**[Q].
- The **least radiosensitive** cell in the ***blood*** is the **platelets**[Q].
- **DNA**[Q] is the most sensitive intracellular organelle to radiation.

111. **Ans. (c) Gray** *(Ref: Robbins 9/e p428)*
Gray (Gy) is a unit that expresses the energy absorbed by the target tissue per unit mass.

112. **Ans. (a) Human T-cell Lymphotropic Virus...was given in this book in chapter 6: Immunity**

113. **Ans. (b) Alcohol** *(Ref: Robbins 9/e p589)*

114. **Ans. (d) E6E7** *(Ref: Robbins 9/e p326)*
The oncogenic potential of HPV can largely be explained by the activities of the two viral genes encoding E6 and E7.

115. **Ans. (c) Benzene** *(Ref: Robbins 9/e p413)*

116. **Ans. (b) myc** *(Ref: Robbins 9/e p284)*

117. **Ans. (b) AD inheritance** *(Ref: Robbins 9/e p304)*

118. **Ans. (b) Medullary carcinoma** *(Ref: Robbins 9/e p1065)*
Among cancers arising in *BRCA1* carriers, 13% are of medullary type, and up to 60% have a subset of medullary features. Please remember, BRCA1 is also associated with mucinous carcinomas.

119. **Ans. (c) Endometrial carcinoma** *(Ref: Robbins 9/e p291)*

120. **Ans. (d) 11p13** *(Ref: Robbins 9/e p298)*

121. **Ans. (c) Inhibin** *(Ref: Robbins 8th/1050, 9/e p1032)*
Granulosa cell tumor

- The most common type of ovarian tumor that is composed of cells that **stain positively with inhibin**[Q].
- Histologically, the cells may form **Call-Exner bodies**[Q]
- The tumor cells may ***secrete estrogens*** and cause ***precocious sexual development in girls*** or increase the risk for ***endometrial hyperplasia and carcinoma in women***.
- *Less commonly* granulosa cell tumors can *secrete androgens* and produce *masculinization*.

Concept: for future exam

- Tumor cells in **Sertoli-Leydig tumors (Androblastomas)** may ***stain positively with inhibin, but Call-Exner bodies are not present***. Sertoli-Leydig tumors also may **secrete androgens and produce virilization in women**.
- The granulosa cell tumors vary in their clinical behavior, but they are considered to be potentially malignant.

122. **Ans. (a) Hepatoblastoma** *(Ref: Robbins 8th/327, 7th/339, 9/e p869-870, Harsh Mohan 6th/637)*

- AFP is glycoprotein synthesized in fetal life by yolk sac, fetal liver and fetal gastrointestinal tract. It is a **marker of hepatocellular cancer and non-seminomatous germ cell tumors of testes**. Elevated plasma AFP is also found less regularly in carcinomas of the colon, lung, and pancreas.

Important points about hepatoblastoma

- Arising from hepatic parenchymal cells
- The **most common tumor of young childhood**
- More commonly seen in ***boys***
- The concentration of AFP is very high
- A *characteristic feature* of hepatoblastomas is the frequent *activation of the Wnt/β-catenin signaling pathway* by stabilizing mutations of β-catenin, contributing to the process of carcinogenesis.

123. **Ans. (c) Osteosarcoma > (a) Multiple myeloma**
(Ref: Journal....Cancer 42:603-610, 1978)
The journal writes that..... "The clinical manifestations, resulting from the production of metabolically active substances by neoplastic tissue, have been labeled paraneoplastic syndromes. Adolescent patients with primary osteosarcoma demonstrate abnormal glucose, insulin and growth hormone responses to oral glucose loading in *78% of the study population*. No statistical association exists between any two of the three factors and, therefore, no primary abnormality can be identified. High somatomedin levels were noted in 72% of the group studied accompanied by simultaneous elevations of growth hormones. Studies of adrenal, gonadal and gonadotropic hormones were essentially normal, thereby ruling these out as associated endocrine abnormalities".

- Hyperglycemia is also associated with chondrosarcoma and fibrosarcoma.
- Some reports associate hyperglycemia with multiple myeloma too but we would prefer osteosarcoma as the answer here because the chances of hyperglycemia is more with osteosarcoma than multiple myeloma.

124. **Ans. (a) SIADH** *(Ref: Robbins 8th/636-637, 9/e p626-627)*
Thymoma is the commenest anterior mediastinal tumor which causes symptoms due to compression on the mediastinal structures. It is associated with the following paraneoplastic syndromes:

- Myasthenia gravis (most common)[Q]
- ***Acquired hypogammaglobulinemia***[Q]
- ***Pure red cell aplasia***[Q]
- Graves disease
- Pernicious anemia
- Dermatomyositis-polymyositis
- Cushing syndrome.

Epstein-Barr virus may be associated with thymomas. Thymoma is the commonest anterior mediastinal tumor.

125. Ans. (d) Involves aorta and its branches early
(Ref: Robbins 8th/475-479, 9/e p476-479)
See text in chapter-18

126. Ans. (a) Prostate *(Ref: Robbin 7th/354, 9/e p332)*

- Migratory thrombophlebitis (**Trousseau sign**Q) is particularly associated with **adenocarcinomas of the pancreas, colon and lung**Q because of associated paraneoplastic syndrome resulting in hypercoagulability.

127. Ans. (c) Malignant melanoma:
(Ref Anderson pathology 144-152, 9/e p1149)

- Malignant melanoma expresses HMB 45, S-100 and vimentin.
- **HMB 45** is present in melanosomes and is **more specific**Q.
- **S-100** is **more sensitive**Q but is non-specific (also present in Langerhans' cell histiocytosis, neural tumors, and sarcomas like liposarcoma and chondrosarcoma)

128. Ans. (a) Hepatoblastoma
(Ref: Robbins 8th/327, 7th/339, 9/e p869-870, Harsh Mohan 6th/637)

129. Ans. (c) Carcinoma *(Ref: Robbins 9/e p334)*
Immunohistochemistry is used for making categorization of undifferentiated tumors. The important examples include: Cytokeratin (carcinoma), Desmin (Leiomyoma and Rhabdomyosarcoma) and vimentin (Sarcomas).

130. Ans. (b) Pancreatic neuroendocrine tumor
(Ref: Harrison 17th/2354, Robbins 9/e 1121)

- Gastrin is secreted by *Gastrinomas,* which are neuroendocrine tumors most commonly found in duodenum.
- Marker of medullary carcinoma of thyroid is calcitonin and GIST is CD117 (c-kit).

131. Ans. (a) Alpha-hCG (α-hCG)
(Ref: Robbins 7th/1045, 1046, 9/e 337-338, C.S.D.T. 11th/1071)
Human chorionic gonadotropin (hCG)
The beta subunit of hCG is typically measured as a tumor marker because it has unique sequence that are not shared with other human glycoprotein hormones. So, it is quite specific.

Alpha h**CG is not used as tumor marker because it is similar to the FSH, LH and TSH.** So there can be cross reactivity between beta subunits of these hormones.

132. Ans. (a) Seminoma
(Ref: Harrison 17th/1925 & Robbins 8th//988-989)

- The normal serum alkaline phosphate consists of **4** ***isoenzymes*** secreted from the following sites:
  (a) Liver (b) Bone
  (c) Intestine (d) Placenta

They are best differentiated by electrophoresis. Another approach is based on the differentiation between the different isoenzymes on the basis of heat susceptibility.

- Alkaline phosphatase from individual tissues differ in susceptibility to inactivation by heat. The finding of an elevated serum alkaline phosphatase level in a patient with a **heat-stable fraction** strongly suggests that the **placenta or a tumor** is the source of the elevated enzyme in serum. *Susceptibility to inactivation by heat* increases, respectively, for the intestinal, liver, and *bone* alkaline phosphatase, bone being by far the *most sensitive* and the **liver** being **most resistant.**
  Mnemonic: **b**one **b**urns but **l**iver **l**asts

- The conditions having ***elevated placental alkaline phosphatase*** include:
  - ***Seminoma***
  - ***Choriocarcinoma***
  - ***Third trimester of pregnancy***

133. Ans. (b) Hypercalcemia *(Ref: Harrison, 17th/1736)*
Tumor lysis syndrome is associated with hyperphosphatemia due to release of intracellular phosphate by the destroyed cancer cells. This is followed by a decrease in serum calcium levels.

134. Ans. (a) Screening of a cancer; (b) Follow up of a cancer patient, esp. for knowing about recurrence; (d) For monitoring the treatment of a cancer
(Ref: Robbins' 7th/338, 9/e p338)

- **Uses of Tumor Markers**
  - Screening of Cancer e.g. in prostate carcinoma (PSA), ovarian carcinoma (CA-125).
  - Follow-up a cancer patient especially for knowing recurrence e.g. AFP in hepatocellular carcinoma, CEA in colon carcinoma.
  - For monitoring of a cancer e.g. AFP + HCG in testicular · malignancy, AFP in hepatocellular carcinoma.
  - Prognosis of a cancer e.g. HCG; AFP in testicular malignancy, CEA in colon Ca.

Tumor markers are not specific, so, **cannot** be used for confirmation of diagnosis. *Confirmation is done by biopsy*

135. Ans. (a) Useful for screening of Carcinoma colon; (c) Helpful for follow-up after resection; (d) Levels decrease immediately after resection of tumor
(Ref: Harrison' l6th/530, 531, Robbin 9/e p338)

- **Carcino embryonic antigen is used in Colon carcinoma as follows;**
  - For screening of carcinoma colon
  - For follow-up after resection
  - Early knowledge about tumor recurrence and metastasis
  - Levels of CEA are elevated in 70% of patients but are poorly correlated with cancer stage.
  - After complete surgical resection, CEA level should be normalized, persistent levels imply a poor prognosis.

Diagnosis of colon carcinoma is confirmed by colonoscopy and biopsy as some benign and other malignant conditions also show high values of CEA:

- Pancreatic, breast and stomach carcinoma
- Alcoholic cirrhosis
- Hepatitis
- IBD

136. **Ans. (c) Ovarian ca**
(Ref: Harrison 16th/439, Robbins 9/e p337)

137. **Ans. (b) Hand and feet bones:** *(Ref: Robbins 9/e 1207)*
- Metastasis may occur any bone but most commonly involve axial skeleton (e.g. vertebra, pelvis, ribs. skull. sternum) > Proximal femur > humerus.
- Metastasis in small bone of hand and feet are uncommon and usually originates in cancer of lung, kidney and colon

> - *Skeletal metastasis are typically multifocal,* however **carcinoma of kidney and thyroid** produce **solitary lesions.**

138. **Ans. (d) A technique for raising monoclonal antibodies**
(Ref: Harsh Mohan 6th/15)

139. **Ans. (a) Follicular lymphoma** *(Ref: Robbin 9/e 594-595)*
- The hallmark of follicular lymphoma is a (14; 18) translocation, which leads to the juxtaposition of the IgH locus on chromosome 14 and BCL 2 locus on chromosome 18.
- This translocation is seen in most but not all follicular lymphomas and leads to over-expression of BCL2 protein.

> - *B-cell lymphoma* is associated with breakpoint involving the BCL 6 locus on chromosome 3.
> - *Mantle cell lymphoma* is associated with a locus on chromosome 11 variously known as BCL1 or PRAD1.

140. **Ans. (c) Hepatoma** *(Ref: Robbins 7th/338, 9/e p337)*
AFP is glycoprotein synthesized in fetal life by yolk sac, fetal liver and fetal GIT. It is a **marker of HCC, hepatoma and non-seminomatous germ cell tumors of testes.**

141. **Ans. (a) Yolk sac tumor** *(Ref: Robbins 9/e p977)*

142. **Ans. (a) Disseminated cancer; (**this is known as **Trosseau sign**[Q]**)** *(Ref: Robbins 8th/322, 7th/335, 9/e p332)*

143. **Ans. (b) Parathyroid hormone related peptide**
(Ref: Robbins 8th/728, 7th/333, 9/e p330)

144. **Ans. (c) Cerebellar hemangioblastoma**
(Ref: Robbins 8th/665, 7th/334, 9/e p331)

145. **Ans. (d) Bladder carcinoma** *(Ref: Robbins 9/e p338)*

146. **Ans. (c) Ulcerative colitis** *(Ref: Robbins 9/e p338)*

147. **Ans. (b) Anterior abdominal wall** *(Ref: Robbins 9/e p1222)*

148. **Ans. (d) Both (b) and (c)** *(Ref: Robbins 9/e p337)*

149. **Ans. (b) Carcinoma colon** *(Ref: Robbins 9/e p337)*

150. **Ans. (b) AFP** *(Ref: Robbins 8th/327, 7th/338, 9/e p873)*

151. **Ans. (b) Neuroblastoma** *(Ref: Robbins 9/e p476)*

152. **Ans. (d) Cholangiocarcinoma - AFP**
(Ref: Robbins 8th/880-881, 7th/926-927, 9/e p337)

153. **Ans. (a) Chondrosarcoma** *(Ref: Robbins 8th/1230)*

154. **Ans. (b) Hepatocellular carcinoma of liver**
(Ref: Robbins 8th/876, 7th/338, 9/e p873)

155. **Ans. (d) Kidney tumor** *(Ref: Robbins 9/e p337)*

156. **Ans. (a) Neuroblastoma** *(Ref: Robbins 9/e p476)*

157. **Ans. (a) CEA.....See text** *(Ref: Robbins 9/e p337)*

158. **Ans. (a) Prostate** *(Ref: Robbins 8/e p1235, 9/e p1207)*
- Carcinomas of the **kidney, lung, and gastrointestinal tract and malignant melanoma** produce **lytic bone destruction.**
- Other metastases elicit a sclerotic response, particularly **prostate adenocarcinoma,** which may do so by secreting WNT proteins that stimulate **osteoblastic bone formation.**
- Most metastases induce a mixed lytic and blastic reaction

159. **Ans. (b) β- HCG**
(Ref: Robbins 8/e p474, 9/e p474-475 The Essentials of Clinical Oncology p490)

> - *Sacrococcygeal teratomas* are the most common teratomas of childhood, accounting for 40% or more of cases). They occur with a frequency of 1 in 20,000 to 40,000 live births, and are four times more common in girls than boys
> - Serum alpha fetoprotein is a useful marker for sacrococcygeal teratoma. Some books mention that even beta HCG is elevated in some patients.

160. **Ans. (b) CDKN2A** *(Ref: Robbins 8/e p1174, 9/e p1147)*
Please do not get confused with the first option friends.
Melanomas are associated with N-Ras and not N-myc.
Coming to the other options,
Direct quote from Robbins.... "The *CDKN2A* gene (is mutated in approximately 40% of pedigrees with **autosomal dominant familial melanoma**".

161. **Ans. (a) Chromogranin** *(Ref: Robbins 9/e p717)*
Direct quote from Robbins.. "The occurrence of **neurosecretory granules,** the ability of some of these tumors to secrete polypeptide hormones, and the presence of neuroendocrine markers such as **chromogranin, synaptophysin** and **CD57** (in 75% of cases) and parathormone-like and other hormonally active products suggest derivation of this tumor from neuroendocrine progenitor cells of the lining bronchial epithelium.

162. **Ans. (c) Cytokeratin**
(Ref: Robbins 8/e p324, 9/e p334) ...see text for details

163. **Ans. (a) CA-125** *(Ref: Robbins 8/e p327, 9/e p337)*

164. **Ans. (c) PLAP** *(Ref: Robbin 8/e p988-9)*
Robbins ... "***Seminoma cells*** are diffusely ***positive*** for ***c-KIT,*** **OCT4** and ***placental alkaline phosphatase*** (PLAP), with sometimes scattered keratin-positive cells"

165. **Ans. (b) Lung** *(Ref: Robbin 9/e p 1315)*

166. **Ans. (d) Urine contains 5H.I.A.A** *(Ref: Robbin 9/e p 478)*

- *Neuroblastoma* is the *most common extracranial solid cancer in childhood* and the most common cancer in infancy.
- *About 90% of neuroblastomas, regardless of location, produce catecholamines*, which are an important diagnostic feature (i.e., elevated blood levels of catecholamines and elevated urine levels of the metabolites vanillylmandelic acid and homovanillic acid.

Increased urinary 5HIAA is a feature of carcinoid tumour and not neuroblastoma.

167. **Ans. (a) Pheochromocytoma** *(Ref: Robbins 9/e p1134)*

Pheochromocytomas have been associated with a *"rule of 10s"*.

- *10% of pheochromocytomas are* extra-adrenal[Q], occurring in sites such as the organs of Zuckerkandl and the carotid body.
- *10% of sporadic adrenal pheochromocytomas are* bilateral[Q].
- *10% of adrenal pheochromocytomas are* biologically malignant[Q], defined by the presence of metastatic disease.
- *10% of adrenal pheochromocytomas are* not associated with hypertension[Q].
- One "traditional" 10% rule that has now been modified pertains to familial cases. Now almost25% of individuals with pheochromocytomas and paragangliomas harbor a germline mutation in the *succinate dehydrogenase* genes.

168. **Ans. (a) Desmin-carcinoma** *...see text for details*

169. **Ans. (c) Desmin** *(Ref: Robbin 8/e p1253)*

- Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood and adolescence. It usually appears before age 20
- Ultrastructurally, rhabdomyoblasts contain sarcomeres, and immunohistochemically they stain with antibodies to the myogenic markers **desmin, MYOD1** and **myogenin.**

Other questions from same topic: for AIIMS/NEET

- Most common location is the *head and neck or genitourinary tract*, where there is little if any skeletal muscle as a normal constituent.
- Rhabdomyoblasts are also known as ***tadpole or strap cells***
- Rhabdomyosarcoma is histologically subclassified into **embryonal**, **alveolar**, and **pleomorphic** variants. The ***embryonal variant is the commonest***.

170. **Ans. (d) Metastasis from another solid tissue tumor** *(Ref: Robbin 9/e p 1133)*

Metastases to the adrenal cortex are significantly more common than primary adrenocortical carcinomas.
Even Harrison says... "The most common cause of adrenal tumors is metastasis from another solid tumor like breast cancer and lung cancer".

Malignant	Prevalence
Adrenocortical carcinoma	2-5
Malignant pheochromocytoma	<1
Adrenal neuroblastoma	<0.1
Lymphoma (incl primary adrenal lymphoma)	<1
Metastases (most frequent: breast, lung)	15

171. **Ans. (a) Gives an immediate definitive diagnosis of tumor** *(Ref: Internet)*

- The frozen section procedure/cryosection is rapid microscopic analysis of a specimen.
- It is used most often in oncological surgery.
- The quality of the slides produced by frozen section is lower than formalin-fixed paraffin-embedded tissue processing.
- While presumptive diagnosis can be rendered in many cases, fixed tissue processing is required for more accurate diagnosis

172. **Ans. (a) Renal cell cancer** *(Ref: Robbins 9/e p331)*

- Tumors most often associated with paraneoplastic hypercalcemia are carcinomas of the kidney, lung, breast and ovary.
- The most common lung neoplasm associated with hypercalcemia is squamous cell carcinoma.

173. **Ans. (a) Stomach** *(Ref: Robbins 9/e p1034)*

174. **Ans. (c) Renal cell carcinoma** *(Ref: Robbins 9/e p515)*

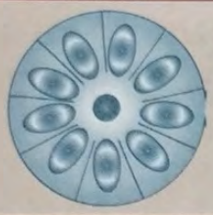
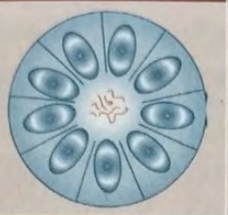
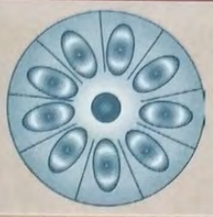
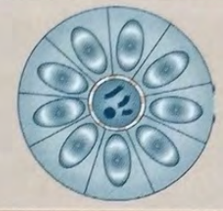
- **Hepatocellular carcinoma and renal cell carcinoma** show a striking tendency to grow within veins, and these can ultimately occlude the IVC.
- **Bronchogenic carcinoma or malignant lymphoma** may cause invasion of the superior vena cava

175. **Ans (b) Glycoprotein** *(Ref: Robbins 9/e p337)*

176. **Ans. (a) Fibrosarcoma** *(Ref: Robbins 9/e p1159)*

ANNEXURE

I. Types of rosette

Types of rosette	Flexner-Wintersteiner rosettes	Homer-Wright rosettes	True Ependymal Rosette	Perivascular Pseudorosette	Neurocytic rosette
Diagram					
Feature	*A halo of cells surrounds a largely empty central hub. Small cytoplasmic extensions from the cells project into the lumen	*A halo of cells surrounds a central hub that contains a meshwork of fibers	*The halo-like cluster of cells in each rosette surrounds an empty central lumen	*A halo of cells surrounds a blood vessel *Called 'pseudo' because the central structure is not actually formed by the tumor itself, but instead represents a native, non-neoplastic element	*Rosette is similar to the Homer Wright rosette,but the central fiber-rich neuropil island is larger and more irregular
Related tumors	Retinoblastoma[Q], Pineoblastomas, Medulloepitheliomas	Supratentorial PNETs, Retinoblastoma[Q], Pineoblastomas	Ependymoblastoma (rare form of PNET)	Medulloblastomas, PNETs, Central neurocytomas, Glioblastomas, Pilomyxoid astrocytomas	Central neurocytoma

II. Epigenetics in cancer

"Epigenetics" refers to factors other than the sequence of DNA that regulate gene expression (and, thereby, cellular phenotype). These factors include histones modifications catalyzed by enzymes associated with chromatin regulatory complexes; DNA methylation, and other less well characterized proteins that regulate the higher order organization of DNA (e.g., looping of enhancer elements onto gene promoters). Epigenetic changes have important roles in many aspects of the malignant phenotype, including the expression of cancer genes, the control of differentiation and self renewal, and even drug sensitivity and drug resistance.

Cancers Showing Epigenetic Changes

Gene(s)	Function	Tumor (Approximate Frequency of Mutation)
DNMT3A	DNA methylation	Acute myeloid leukemia (20%)
MLL1	Histone methylation	Acute leukemia in infants (90%)
MLL2	Histone methylation	Follicular lymphoma (90%)
CREBBP/EP 300	Histone acetylation	Diffuse large B cell lymphoma (40%)
ARD1A	Nucleosome Positioning/chromatin remodeling	Ovarian deer cell carcinoma (60%) endometrial carcinoma (30%-40%)
SNF5	Nucleosome Positioning/chromatin remodeling	Malignant rhaboid tumor (100%)
PERM1	Nucleosome Positioning/chromatin remodeling	Renal carcinoma (30%)

CHAPTER 6

Immunity

Golden Points

- Cell mediated immunity is mediated by T-cells whereas humoral immunity is due to B cells.
- Helper T cells are positive for CD4 whereas cytotoxic T-cells are positive for: CD8.
- T cells undergo both positive and negative selection whereas B cells undergo only negative selection.
- Antibodies production is a function of B cells and not CD4 Helper T cells.
- TH-1 helper t cells produce: IL-2, IFN-gamma, IL-12 whereas TH-2 helper T cells produce: IL-4, IL-5, IL-6, IL-13.
- Production of specific antibodies against a particular antigen is due to the **Clonal selection.**
- *NK cells* are **Not MHC restricted,** not require antibodies.
- Markers of NK cells: CD56 and CD16.
- Primary function of Toll-like receptors: Activation of innate immune system.
- Toll-like receptors activate immune system by: Activation of transcription factors (NF-kb and AP-1).
- **Toll like receptors** recognise bacterial endotoxin of all gram negative bacteria ***except*** leptospira.
- Antigen presenting cells (APC) are **professional APC** (Macrophages, B-cells, Dendritic cells, Langerhans cells) and **non professional APC** (fibroblasts, thymic epithelial cells, endothelial cells.
- Most potent stimulator of Naive T-cells is **Langerhans dendritic cell**.
- **Superantigens** bind to: Directly to lateral portion of T-cell receptor (TCR) b-chain and MHC-II b-chain.
- Major function of MHC (HLA): Present antigen to T-cell for recognition by T-cell receptors.
- MHC-I is present on all nucleated cells and platelets (but not present on RBCs) whereas the HLA-II is present on the antigen presenting cells. Medullary macrophages **do not** express MHC-II.
- **Mixed lymphocyte culture** (mixed leukocyte reaction) is used to identify: **HLA-II** (MHC-II).
- Markers of B-cells (CD-10, CD-19, CD-20, CD-21, CD-23, CD-79a), memory T-cells (CD-45 RO), hematopoietic stem cell (CD-34).
- Epitheloid granuloma is caused by: CD-4 Helper T-cells.
- Allograft is: Graft from genetically unrelated member of same species.
- Transplant rejection involves: Both cellular (cell mediated) and humoral (antibody mediated) rejections. **C4d deposition** in the glomeruli is an indicator of **antibody mediated rejection**.
- Hyperacute rejection is due to: Performed antibodies.
- Mechanism of corneal endothelial graft rejection: Cell mediated (Type-IV) reaction.
- Most important target in graft rejection: Blood vessels (endothelitis, necrotizing vasculitis, fibrinoid necrosis).
- Graft versus host disease (GVHD) occurs when immune-competent donor cells (like bone marrow) is transplanted into immune-compromised host.
- Most commonly affected tissues in GVHD: **Skin (most common) >> liver>> gut.**
- Not a feature of scleroderma: Calcification of long bones.
- Anticentromere antibody is seen with localized scleroderma/ CREST syndrome whereas Anti-DNA topoisomerase type-I (anti-Scl 70) is seen with diffuse scleroderma.
- **Anti-U1RNP antibodies** are seen in: Mixed connective tissue disease (**MCTD**).
- Antibodies in Sjogren syndrome: Anti-Ro (SSA), Anti-La (SSB).
- Biopsy of **minor salivary gland** in *Sjogren's syndrome* shows: ***Lymphocytic infiltration***.
- A common primary immunodeficiency is ***Selective IgA deficiency*** (patients commonly present with *recurrent sinopulmonary infections* and *diarrhea*. In addition, they have an increased risk of autoimmune diseases, particularly ***SLE and rheumatoid arthritis***). They develop *anaphylactic reactions* on blood transfusion with normal IgA containing blood.
- **Adenosine deaminase deficiency** is associated with: Severe combined immunodeficiency (**SCID**).

- Features of common variable immunodeficiency: Hypogammaglobulinemia, normal number of B-cells, inabilitiy of B-cells to become plasma cells.
- Antibodies in Wiskott-Aldrich syndrome:–↓↓ IgM, ↑IgE but normal IgA and IgG.
- **Raji cell assay** is used to quantify the circulating immune complexes.
- Features of amyloid: **Non-branching, fibrillary** congophilic protein with a beta-pleated sheet conformation and is PAS (+)ve. On electron microscopy, it shows Non-branching fibrils with diameter of 7.5–10 nm and indefinite length.
- Most commonly affected organ in amyloidosis: Kidney.
- Most common cause of death in amyloidosis: Cardiac failure.
- Characteristic staining feature of amyloidosis: **Apple green birefringence** under polarized light.

Immunity is the defensive power of the body (protecting the body from various infections). It can be of **two types**: innate immunity and adaptive immunity. **Innate immunity** (also known as natural or native immunity) refers to defense mechanisms that are **present since birth** and have evolved to recognize microbes. It is the **first line of defense**. It is **non-specific** and has **no memory**. ***Adaptive immunity*** (also called acquired or specific immunity) consists of mechanisms that are stimulated by microbes and are capable of recognizing non-microbial substances also. Adaptive immunity develops later (***after exposure to antigens***). It is ***more specific*** as well as powerful as well as has ***memory***.

Key Point

Innate immunity	Adaptive/Acquired immunity
* Present **from birth**	* Acquired in nature
* **First line of defense**	* **Second line of defense**
* **No prior exposure** to antigen	* **Prior exposure** is **present**[Q]
* **Non-specific**	* **Specific**
* **No memory**[Q] is seen	* **Memory**[Q] is seen

The major components of innate immunity are

1. Epithelial barriers like intact skin that blocks entry of environmental microbes
2. Cells like phagocytic cells (mainly neutrophils and macrophages), Natural killer (NK) cells, Dendritic cells
3. Plasma proteins (proteins of the complement system, mannose binding lectin and C-reactive protein)

The innate immunity is due to presence of **pattern recognition receptors (PRR)**. These are peptide molecules on the leukocytes which recognize particular structural pattern on a micro-organism called **p**athogen **a**ssociated **m**olecular **p**atterns (**PAMP**s). A similar group of molecules released by injured cells is called **d**anger **a**ssociated **m**olecular **p**atterns (**DAMP**, uric acid is an example). The PRR can be of the following two types:

Soluble pattern recognition receptors	Surface pattern recognition receptors
• Mannose receptors (for mannose binding lectin) • C-reactive protein	• Scavenger receptors (on macrophages) • Toll like receptors • NOD-like receptors • RIG-like receptors

Key Point

Toll-like receptors causes the activation of **NF-κβ** ("master switch" to the nuclear factor) and AP-1.

Some important Toll like receptors (TLR) and the molecules they recognize are:

- **TLR-2:** peptidoglycan of gram + bacteria; lipopolysaccharide of **leptospira**[Q]
- **TLR-3:** dsRNA viruses
- **TLR-4**[Q]: Chlamydia and lipopolysaccharide **of Gram (–) bacteria**[Q] except leptospira

Signaling by Toll-like receptors causes the activation of nuclear transcription factors (NF-κβ and AP-1). This result in recruitment of inflammatory cytokines, endothelial adhesion molecules (E-selectin) and proteins involved in microbial killing mechanisms (inducible nitric oxide synthase).

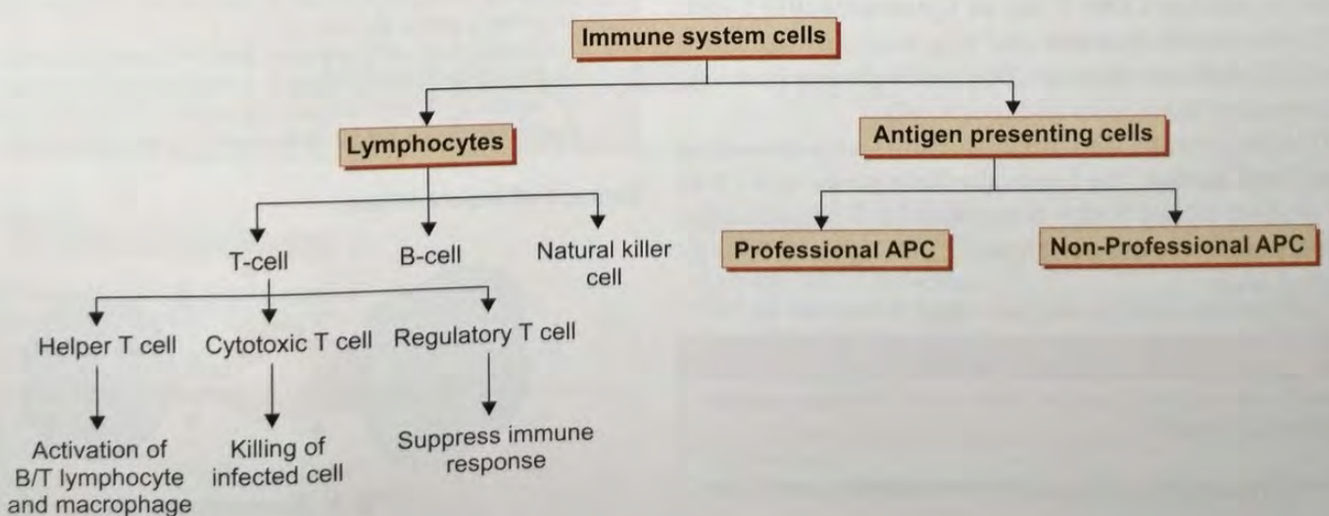
Key Point

All Gram (–) bacteria recognize **TLR-4** *except leptospira* which recognises *TLR-2*

The **adaptive immune system consists** of lymphocytes and their products like antibodies. It has two components: *cellular (or cell mediated) and humoral immunity. The former is protective against intracellular microbes whereas the latter is effective against extracellular microbes.*

IMMUNE CELLS

Apart from the leucocytes, our focus here would be to discuss the other important immune cells (lymphocytes and antigen presenting cells) in detail.



Recent Exam Questions

Both T and B cells undergo **negative selection** but *only the T cells* undergo *positive selection.*

1. T-lymphocytes (Thymus Derived)

They constitute 60-70% of peripheral blood lymphocytes and are located in the *paracortical areas of lymph node and the periarteriolar sheaths of spleen.* These cells have an antigen specific T cell receptor (TCR) [composed of α and β polypeptide chains in 95% cases] to bind with the antigen. The αβ T cells are present in blood and tissues. The other 5% cells have TCR composed of γ/δ chains and are present mostly at the epithelial/mucosal surface. A large number of TCRs can be generated because of rearrangement of genes coding for α and β polypeptide chains. When an antigenic peptide comes in contact with TCR, it activates a particular T cell only and not all the cells. This is called as **clonal selection**.

Recent Exam Questions

CD-3 is known as pan T-cell **marker**. It is also involved in T-cell activation.

Demonstration of TCR gene rearrangement by southern blot is a molecular marker of T cell lineage.

Key Point

The ratio of CD4 and CD8 T-cell is normally **2:1**

The cells have on their surface cluster differentiating (CD) molecules by which they can be readily identified. **The CD molecules present on T cells are CD1, CD2, CD3, CD4, CD5, CD7, CD8 and CD28.** The T cell having CD4 molecule is called **CD4+ T cell or the Helper T cell** and that having CD8 molecule is called as **CD8+ T cell or Cytotoxic/Killer T cell**. CD4+ T cells secrete cytokines and help macrophages and B cells to fight infections whereas CD8+ T cells destroy host cells having microbes like viruses and tumor cells.

CD3 is involved in **signal transduction** and is also called as a **Pan T cell marker**. The T cells also have presence of CD40 ligand on their surface which is required for B cell activation and induction of immunoglobulin 'isotype switching'. (Described later).

Key Point

Helper T cell (or CD4+ T cell) is known as the '**master regulator**' of the immune system.

The activation of T cells requires two signals... see Figure 1

Signal 1: Comes from binding of the TCR to MHC bound antigen. The CD4 or CD8 act as co-receptors and enhance this signal.
Signal 2: Comes from the interaction of CD28 with co-stimulatory molecules B7-1 and B7-2 present on the antigen presenting cells.

The activated T cells gives rise to two groups of cells: effector T cells which manage the antigen at that time only and some differentiate into long lived memory cells (for future exposure to the same antigen).

Location of cell	Molecular marker
All leucocytes	**CD45** (Leukocyte common antigen; **LCA**) and CD45RB
Medullary thymocytes (**'Naive' T- cells**)	CD45 RA and CD45RC
Cortical thymocytes (**Memory T-cells**)	**CD45RO**

Mnemonic

Short Story: T-cell activation is like starting a vehicle. We put in a key and turn on the ignition of the car engine (Signal 1). But the car would move only when we put the gear (signal 2). If we don't put the car in gear, the engine will make the car lose its fuel and the car will stop without moving (anergy).

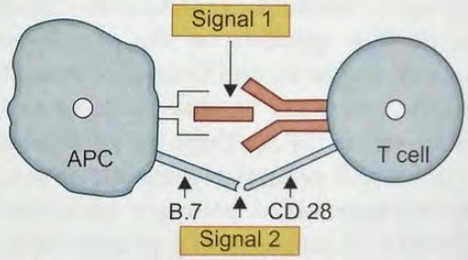


Fig. 1: Interaction between APC and T cell.

Importance of signal 2 in immunity

- Signal 2 ensures that the activation of the T cells is not taking place by chance. It is due to a particular antigen only. So, it acts like a safety signal.
- Secondly, if by any mistake, the APC present a self antigen (normal body tissue), signal 2 is not generated. In the absence of signal 2, T cell undergoes anergy. This is an important mechanism of **peripheral immunological tolerance**.

Concept of Superantigen

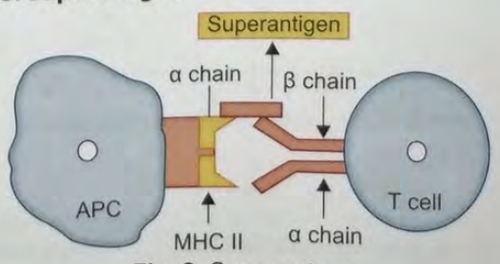
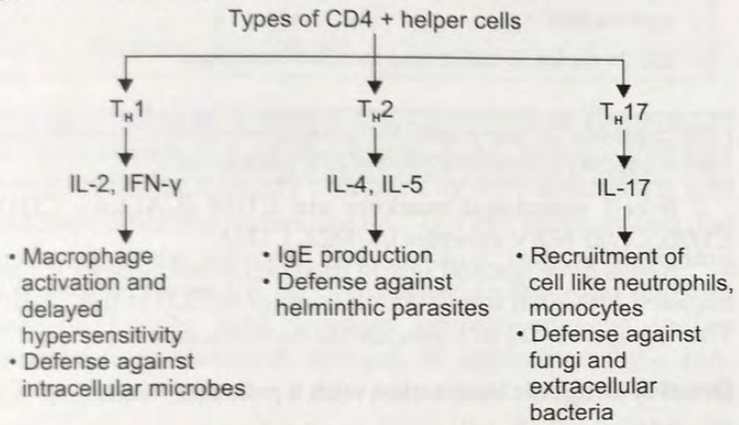


Fig. 2: Superantigen.

Recent Exam Questions

- Antigen which **does not**[Q] require antigenic processing and not specific for a T cell receptor (TCR)
- Attaches itself **outside**[Q] the antigen binding cleft
- Attaches to α **chain of MHC II with** β **chain of T cell receptor**[Q] (TCR)
- Causes T cell activation and **massive release of cytokines** like TNF-α and IL-1
- Examples include **staphylococcal toxic shock syndrome toxin 1**[Q] (TSST-1), **Streptococcal erythrogenic exotoxin**[Q]

Types of CD4+ Helper Cells



Concept

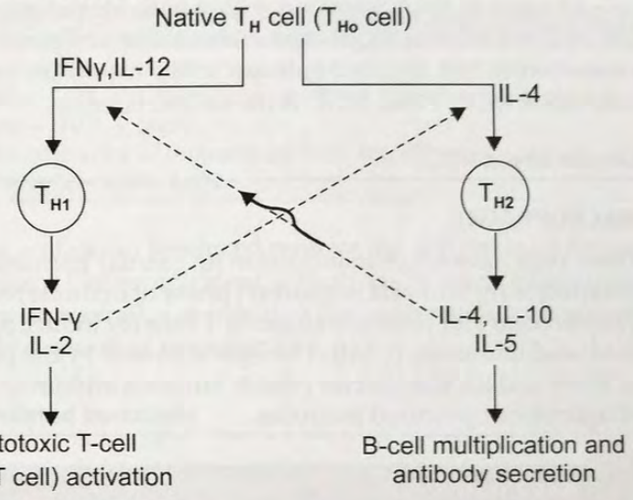
Helper T cell binds only to antigens presented with Class II MHC molecules. So, they are called as **MHC-II restricted**. These recognize *exogenous peptides*.

Cytotoxic T cell (or **CD8+ T cell**) binds only to antigens presented with Class I MHC molecules. So, they are called as **MHC-I restricted**. These recognize endogenous peptides.

- Recently a new group of T cells have been discovered called as **NK-T cells**. These T cells express markers normally present on Natural Killer cells and recognize glycolipid antigens displayed by MHC-like molecule CD1. These are important defense mechanisms against microorganisms like *Listeria monocytogenes* and *M tuberculosis*.

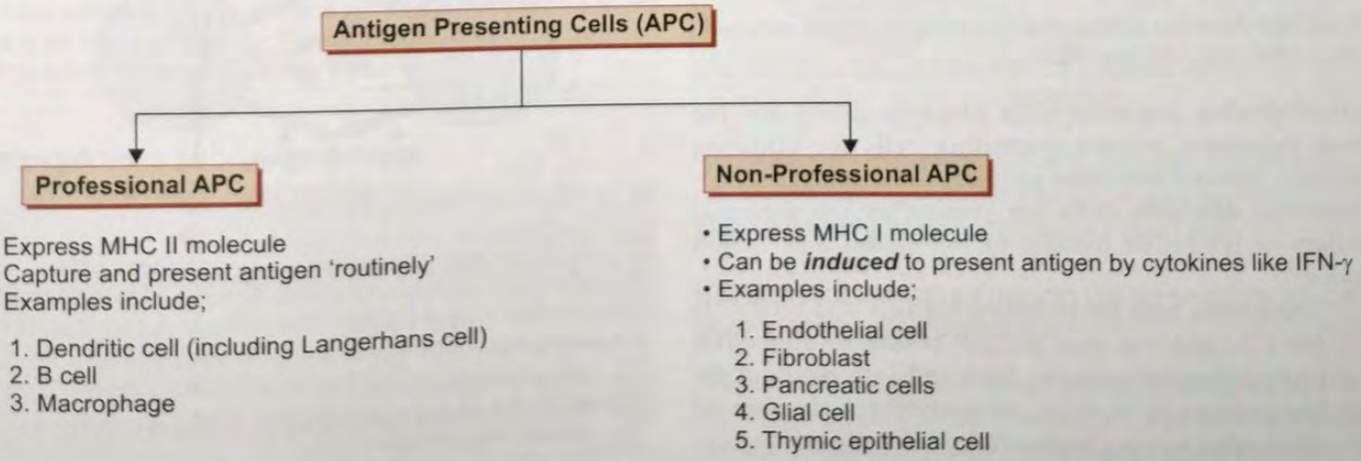
Naive T cell (TH0) can get differentiated into either TH1cell or TH2 cell. The differentiation towards TH1 cell is driven by strong innate response and intracellular organisms (TB, Listeria). TH1 cells release IL-2 and IFN-γ which causes cytotoxic T cell activation and granuloma formation. Constitutively which means most of the times physiologically, TH0 cell differentiates into TH2 cell. TH2 cells release IL-4 and IL-5 which cause B cell activation and multiplication leading to antibody formation.

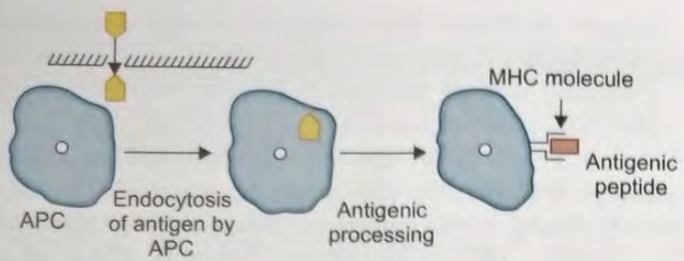
Diagram of different T helper cells



2. Antigen Presenting Cells

When an antigen enters inside the body, it is phagocytosed by the neutrophils following which the antigenic peptides are released in the circulation. However, if antigen presenting cells phagocytose the antigen, they process it inside themselves and present on their surface in association with MHC molecule. This processed antigen is now presented to the T cells.





Mnemonic

- The part of the antigen associated with MHC molecule on the APC is called as *Agretope*.
- The antigenic part in contact with TCR is called **epitope**.

The part of the antigen associated with MHC molecule on the APC is called as **aggretope** whereas the antigenic part in contact with TCR is called **epitope**. MHC molecules can be of two types: MHC I and MHC II (described later).

Details about APCs

MACROPHAGES

These cells have a role in induction (in cellular immunity) and the effector (in humoral immunity) phase of immune response. They process and present antigen to T cells for induction of cell mediated immunity (CMI). They get activated by the presence of *IFN-γ* and are the effector cells in humoral immunity as they phagocytose opsonised microbes.

Key Point

Macrophage associated markers include CD13, CD14, CD15 and CD33. **CD133** induces formation of **glioma**

DENDRITIC CELLS

These are important antigen presenting cells in the body and can be of the following types:

Recent Exam Questions

- **Langerhans cells** are Immature dendritic cells within the epidermis.
- ***Follicular dendritic cells act as reservoir for HIV*** in acquired immunodeficiency syndrome (AIDS).

a. **Interdigitating dendritic cells** *(dendritic cells^{Q})* are the **most important antigen-presenting cells** for initiating primary immune responses against protein antigens.
b. **Follicular dendritic cells** are present in the germinal centers of lymphoid follicles in the spleen and lymph nodes.
   - These cells bear Fc receptors for IgG and receptors for C3b and can trap antigen bound to antibodies or complement proteins. Such cells are required for the process of *'Affinity Maturation'* (**production of antibodies having high affinity for antigens**).

3. B-lymphocytes (Bone Marrow Derived)

They constitute 10-20% of peripheral blood lymphocytes and are located in the *cortical areas of lymph node, white pulp of spleen and mucosa associated lymphoid tissue of pharyngeal tonsils and Peyer's patches of GIT.*

These cells have a B cell receptor (BCR) composed of IgM and IgD on their surface to bind with the antigen. BCR has unique antigen specificity. The rearrangement of immunoglobulin gene can give rise to different types of BCRs. The antigen however binds to the complementary BCR only (clonal selection).

Recent Exam Questions

- **CD19** is involved in signal transduction and is called as a **Pan B cell marker**.
- **CD 21** on the B-cell is also the **EBV receptor.**

The presence of rearranged immunoglobulin genes in a lymphoid cell is used as a molecular marker of B-lineage cells.

B cell associated markers are CD10 (CALLA), CD19, CD20, CD21 (EBV receptor), CD22, CD23.

B cells have Igα and Igβ on their cell membrane which are required for signal transduction (similar to CD3 of the T cells). They also have CD 40 molecule on its surface.

Detail of antigenic interaction with B cells and T cells

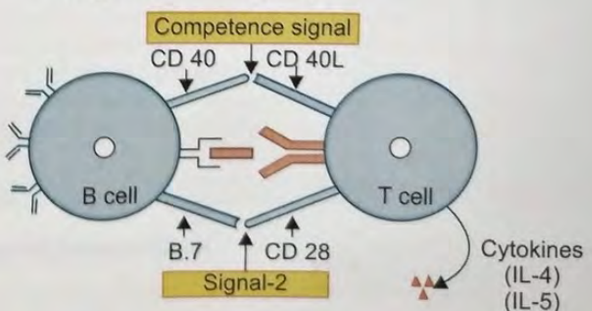
The activation of T cells requires two signals

Recent Exam Questions

- Signal 2 due to *B7 and CD 28* is important for **PERIPHERAL TOLERANCE.**

Signal 1: Comes from binding of the TCR to MHC bound antigen.

Signal 2: Comes from the interaction of CD28 with *co-stimulatory* molecules B7-1 and B7-2 present on the antigen presenting cells.

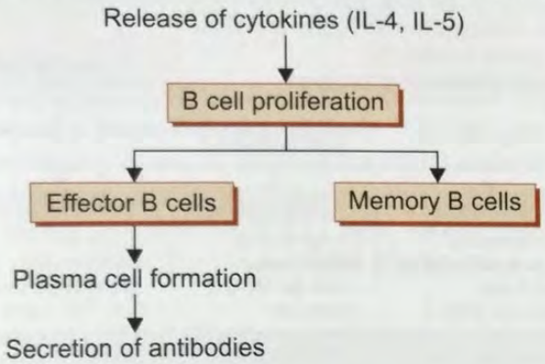


Key Point

Competence signal (CD40-CD40L interaction) is required for the following functions:

1. ***B cell mitogen***
2. Required for ***isotype switching.***
3. ***Affinity maturation***

In addition to these two, there is a **Competence signal** is due to interaction between CD40 molecules on B cells with CD 40 ligand on T helper cells. It results in the release of cytokines like IL-4 and IL-5. These cytokines cause B cell proliferation resulting in formation of plasma cells and memory cells.



The plasma cells secrete immunoglobulins. These can of different classes or isotypes like IgG, IgM, IgD, IgA and IgE. Initially, the first antibody produced by the plasma cell is IgM and later, other antibodies like IgG, IgA etc. are produced due to change in the nature of heavy chains. **Isotype Switching** is due to IFN-γ and IL-4. Polysaccharide and lipid antigens produce mainly IgM whereas protein antigens induce production of different isotypes of antibodies (IgG, IgA, IgE etc.).

Definition

The change in the class of the antibody being produced by the plasma cell is called as **Isotype Switching**

Isotype/Class Switching
IgM ⟶ IgA, IgE, IgG
(Due to change in heavy chain)

Concept

Hyper-IgM immunodeficiency is a paradoxical T-cell disorder in which a defect in CD40 ligand (normally present on Tcells) prevents isotype switching in B lymphocytes. So, these patients have reduced levels of IgG, IgE and IgA but **increased levels of IgM.** It is an **X linked** disorder. Patients have recurrent infections with ***P. jiroveci*** affecting respiratory tract.

IMPORTANT POINTS ABOUT ANTIBODIES

IgG	• Present in **maximum concentration**[Q] the human body • Important for **secondary immune response**[Q] • Can **cross the placenta**[Q]
IgA	• Resent in **physiological secretions**[Q] of the body • Present in **monomer form in serum** and as **dimer**[Q] **form in glandular** secretions • Responsible for activation **alternate pathway**[Q]

Contd...

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IgM	• Important for **primary immune response**[Q] • Having **maximum molecular weight**[Q] • Having **maximum size**[Q] • Present as a **pentamer**[Q] • Also known as '**Millionaire's antibody**'[Q] • Functions as **B cell receptor**[Q] • **IgM**[Q] and IgG (**IgM**[Q] > IgG) are responsible for activation of **classical pathway**[Q]
IgD	• Functions as **B cell receptor**[Q]
IgE	• Increased in **allergic conditions**[Q] • Also known as '**homocytotropic antibody**[Q]' • Also called '**reaginic antibody**'[Q]

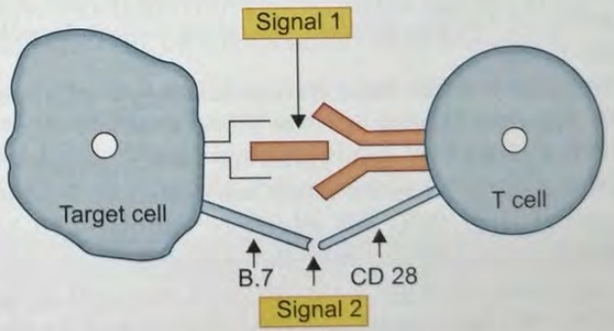
Recent Exam Questions

- One antibody has **two heavy chains** and **two light chains**. Within light and heavy chains, **three hypervariable regions** exist – HV 1, 2 and 3
- The **efficiency of immuno-globulin transfer** across placenta: **Ig G1>** IgG3> IgG4> **IgG2**

The antibodies produced remove the antigen by different mechanisms like complement activation (by membrane attack complex formation), opsonisation (for preferential killing) and antibody dependent cytotoxicity.

Cell Mediated Immunity

It is for more important for intracellular pathogens, virus infected/malignant cells and endogenous antigens. It is mediated by CD8 T cells, macrophages and natural killer cells. Endogenous antigen is expressed with MHC I molecule by the nucleated cells. These cells are also destroyed in the process, so, the preferred name for them is Target cells and not APCs.



Antigen activated CD8T cells undergo proliferation. They release perforin-granzyme molecules and express Fas Ligand both of which initiate apoptosis of Target cells.

NATURAL KILLER CELLS (NK CELLS) OR NULL CELLS OR NON-T, NON-B LYMPHOCYTES

NK cells are also called '**Large granular lymphocytes**' as they are *morphologically larger* than both T and B lymphocytes and *contain azurophilic granules* (which are absent in both T and

B lymphocytes). They constitute 5-10% of peripheral blood lymphocytes. They arise in both bone marrow and thymic microenvironments. NK cells are activated in presence of IL-2 to Lymphocyte activated killer (LAK) cells. These cells express the following molecules:

Recent Exam Questions

Markers for NK-cell

- **CD16^{Q}**: Surface receptors for Fc portion of IgG.
- **CD56^{Q}**: Surface receptors for NCAM – 1.

They are first line defense against cancer and virus infected cells. So, functionally NK cells share features of both monocyte-macrophages and neutrophils. The hyporesponsiveness of NK cells is seen in patients of Chediak-Higashi syndrome.

The NK cells express activating and inhibitory receptors. The functional activity of the NK cells is regulated by a balance between signals from these receptors. Normal cells are not killed because inhibitory signals from normal MHC class I molecules override activating signals. **The ability of NK cells to kill target cells is inversely related to target cell expression of MHC class I molecules.**

Key Point

NK cells are unique as they are capable of direct cell lysis which is:

- Not mediated by an immune response
- ***MHC – unrestricted***
- Does ***not*** involve an antigen antibody interaction

Major Histocompatibility Complex (MHC) or Human Leucocyte Antigen (HLA) Complex

MHC is a cluster of genes located on short arm of **chromosome 6** (*6p^{Q}*) whose main physiologic function is to bind peptide fragments of foreign proteins for presentation to antigen-specific T cells.

It is classified into **three classes namely class I, II and III genes**. The class I genes includes HLA-A, -B, -C, - E, -F and -G. HLA-A,-B and -C gene codes for MHC I molecule and the **HLA-E** molecule is the major **self-recognition target** for the natural killer (NK) cell inhibitory receptors. **HLA-G** is expressed selectively in extravillous trophoblasts, the fetal cell population directly in contact with maternal tissues. It provides inhibitory signals to both NK cells and T cells and maintains **maternofetal tolerance** and the function of *HLA-F* remains largely *unknown*. The class II genes include HLA-D and code for MHC II molecule whereas the class III gene codes for the complement and other proteins.

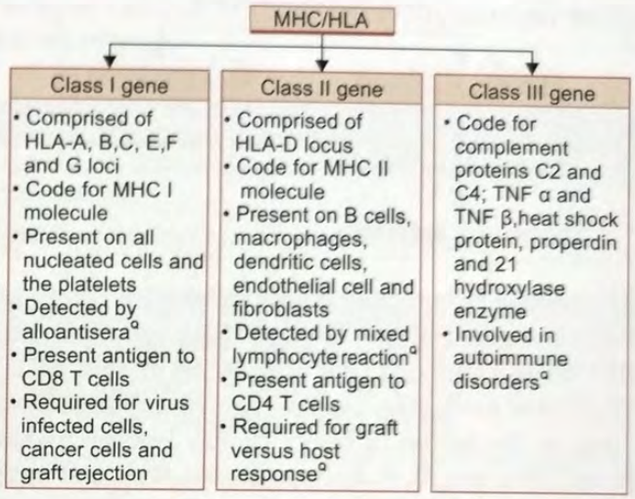
Recent Exam Questions

- **MHC** is a cluster of genes located on **short arm of chromosome** 6 (6p).
- **HLA-G** is required for maternofetal tolerance

Key Point

Class III genes code for:

- Complement components C2 and C4 of classical pathway (Not C3)
- Properdin factor B of alternate pathway
- Tumor necrosis factor: Alpha and Beta
- Heat shock protein 70
- Enzyme tyrosine hydroxylase



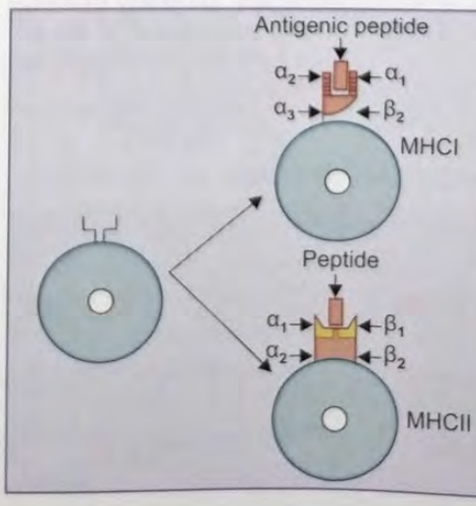
MHC-I MOLECULE

It consists of α *chain (heavy chain) linked to* β_2 *microglobulin (light chain; not encoded within MHC)* and binds to peptides that are derived from proteins *synthesized within the cell* like the viral antigens. The antigen binding cleft is formed by **α1and α2 chain** of the MHC molecule (**distal α domains of MHC^{Q}**). The antigens binding with MHC I molecule are presented to CD8+ T cells. As discussed earlier, cytotoxic T cells/**CD8+ T cells are MHC-I restricted**.

Recent Exam Questions

MHC I molecule is present on all the nucleated cells and platelets It is **not** present on **mature RBCs.**

Structure of antigen binding cleft of MHC molecule on the surface of APC



The antigen binding cleft is made up **α_1 and α_2^{Q}** chains of **MHC I** molecule which is ***structurally the distal domain of these chains.***

The antigen binding cleft is made up **distal α and βchains^{Q}** (α_1 and $\beta_1$chains) of **MHC II** molecule.

Recent Exam Questions

Detection of MHC

- **MHC-I: Alloantisera.**
- *MHC-II: Mixed lymphocyte reaction.*

MHC-II molecule

It consists of α chain linked to β-chain. The antigen binding cleft is formed by α_1 and β_1 chain of the MHC molecule (**distal α and β domains of MHC**Q). The antigens binding with MHC II molecule are presented to CD4+ T cells. As discussed earlier, helper T cells/**CD4+ T cells are MHC-II restricted.**

Mnemonic

Normal CD4: CD8T cell ratio is 2:1. So, MHC 2 with CD4 and MHC 1 with CD8.

Concept

As described earlier, MHCII molecule is required for the development of graft versus host disease. In a condition associated with a congenital deficiency of MHC II molecule as '***Bare Lymphocyte Syndrome***', the affected individuals would never develop Graft versus host disease even on being given mismatched bone marrow transplantation. They also have absence or deficiency of CD4T cells and so, also have hypogammaglobulinemia. These individuals have normal number of CD8T cells.

HLA and Disease Association

HLA- class I

B-27	B-8	B-51	B-47	CW6
Psoriatic arthritis Ankylosing spondylitis Inflammatory bowel disease arthritis Reiter's syndrome (Reactive arthritis)	***Graves' disease*** Myasthenia gravis	Behcet's disease	Congenital adrenal hyperplasia	Psoriasis vulgaris

Key Point

MHC II molecule is present on **macrophages, dendritic cells, B cells** and their expression can be induced on ***endothelial cells*** and ***fibroblasts*** by IFN-γ

HLA- class II	
DR-2	- Japanese SLE - Multiple sclerosis - Narcolepsy - Goodpasture's syndrome

Contd...

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DR-3	• Myasthenia gravis • Graves' disease • Type I DM • Dermatitis herpetiformis • Chronic active hepatitis • Caucasian SLE • Sjogren's syndrome
DR-4	Type 1 DM Pemphigus vulgaris Rheumatoid arthritis
DR-5	Juvenile (pauciarticular) arthritis
DR-8	Type I DM
DQ-1	Pemphigus vulgaris
DQ -	Gluten sensitive enteropathy [celiac sprue]
DQ-7	Bullous pemphigoid
DQ-8	Type 1 DM

Key Point

DR-2 has negative association with type 1 DM i.e. genetic association with protection from DM

DISORDERS OF THE IMMUNE SYSTEM

Hypersensitivity Reactions

These are caused by the activity of the immune system detrimental to the host in response to exposure of the antigens.

Key Point

The clinical features are usually seen during the second time antigen exposure subsequent to sensitization or priming

TYPE I HYPERSENSITIVITY REACTION/ANAPHYLACTIC TYPE/ IMMEDIATE TYPE OF HYPERSENSITIVITY REACTION

It is defined as a rapidly developing immunologic reaction *occurring within minutes* after the combination of an antigen with antibody bound to mast cells in individuals previously sensitized to the antigen. It is commonly referred to as *allergy*.

Key Point

The cell critical in the pathogenesis is the mast cell whereas TH2 also plays an important role in the pathogenesis.

PATHOGENESIS

The first step is the **stage of sensitization** or priming in which there is entry of the antigen inside the body for the first time where it is captured by the antigen presenting cells and presented to the T cell which then differentiates into TH2 cell. The TH2 cell releases mediators like IL-3, IL-4 and IL-5. *IL-4 causes activation of B cell leading to the release of IgE from them whereas IL-5 is responsible for activating the eosinophils.* The

secreted IgE then binds to mast cells in the circulation because of presence of Fc receptors on the mast cells. So, in the initial exposure or sensitization, there is *presence of mast cells* in the circulation having the presence of IgE on their surface.

Key Point

- **Histamine** is responsible for the **early** clinical features because it is **preformed mediator**.
- *PAF* is the major mediator of the *late* phase reaction
- **IgE** is the most important anti-body to cause **type I** hypersensitivity reactions.
- **IL-4** is responsible for the **secretion of IgE** from the B cells.
- **IL-5** is the most potent **eosinophil-activating cytokine** known.

The **subsequent exposure** to the same antigen causes the features in two phases. In the *initial phase* (within minutes of antigen exposure), there is *release of preformed mediators* of the mast cell due to their degranulation causing the *release of histamine, proteases and chemotactic factors*. Histamine causes vasodilation, bronchoconstriction and increased permeability. Late phase (2-24 hours after antigen exposure) is marked by the release of *secondary mediators* from the mast cells that include *prostaglandins, leukotrienes, cytokines and platelet activating factor (PAF)*. PGD2 is abundant in lung mast cells and causes bronchoconstriction as well as increased mucus production. The secondary mediators are responsible for the effects like bronchospasm, increased mucus production and recruitment of the inflammatory cells at the site of inflammation. *PAF* causes bronchospasm, increased permeability and release of histamine and is considered to be *important in the initiation of the late-phase response*. The release of various mediators is responsible for the clinical features seen in type I hypersensitivity reaction.

Concept

Anaphylactic hypersensitivity reaction should **not be** confused with **anaphylactoid reaction.** The important differences are:

- **Anaphylactoid reaction** occurs on **first antigenic exposure**
- It is also **short lived** because its pathogenesis involves only degranulation of the mast cells and not cytokine synthesis.

Examples of type I hypersensitivity includes:

Localized hypersensitivity	Systemic hypersensitivity
• Bronchial asthma • Hay fever/allergic rhinitis • Food allergies • Atopic dermatitis • Urticaria • Angioedema	Anaphylaxis due to: • Antibiotics: Most commonly penicillin (therefore, a test dose should always be given before administration of penicillin to any patient) • Bee stings • Insect bites

TYPE II HYPERSENSITIVITY REACTION/ANTIBODY MEDIATED/CYTOLYTIC HYPERSENSITIVITY REACTION

Type II hypersensitivity is mediated by antibodies directed toward endogenous or exogenous specific antigens present on cell surfaces or extracellular matrix. The effector mechanisms for this reaction include:

Concept

If there is presence of low concentration of antibodies on the cells then they are killed by 'phagocyte and complement independent' process known as antibody dependent cellular cytotoxicity (ADCC). It is mediated by neutrophils, macrophages and NK cells.

I. ***Opsonisation and Complement- and Fc Receptor-Mediated Phagocytosis***
The antibodies are formed against the antigens and these are responsible for complement system activation resulting in the formation of membrane attack complex (MAC) leading to destruction of the antigen. The antibodies may also cause opsonisation (through C3b and C4b) and Fc receptor mediated phagocytosis.

II. ***Complement and Fc Receptor-Mediated Inflammation***
When antibodies deposit in *extracellular tissues*, the injury is because of inflammation and not phagocytosis or lysis of cells. The deposited antibodies activate complement system leading to recruitment of neutrophils and monocytes. These cells also bind to the deposited antibodies via their Fc receptors. The activated leukocytes release enzymes resulting in tissue damage.

III. ***Antibody mediated cellular dysfunction***
In this mechanism, the antibodies directed against *cell-surface receptors* impair or dysregulate function without causing cell injury or inflammation.

Examples of type II hypersensitivity reaction

Opsonization and Complement- and Fc Receptor-Mediated Phagocytosis	• Transfusion reactions • Erythroblastosis fetalis • Autoimmune hemolytic anemia • Autoimmune thrombocytopenic purpura
Complement and Fc Receptor-Mediated Inflammation	• Goodpasture syndrome • Vasculitis due to ANCA • Acute rheumatic fever • Vascular rejection in organ grafts
Antibody mediated cellular dysfunction	• Myasthenia gravis (against acetylcholine receptor) • Graves' disease (against TSH receptor) • Pemphigus vulgaris (against epidermal cadherin) • Pernicious anemia (against intrinsic factor) • Insulin resistant diabetes (against insulin receptor)

Mnemonic

My-	**My**asthenia gravis
Blood-	**Blood** transfusion reactions
Group-	**G**oodpasture syndrome and **G**raves' disease
Is-	**I**nsulin resistant diabetes, **I**TP
R -	**R**heumatic fever
h-	**H**yperacute graft rejection
Positive-	**P**ernicious anemia and **P**emphigus vulgaris

TYPE III HYPERSENSITIVITY REACTION OR IMMUNE COMPLEX DISEASE

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition. The antigen can be either endogenous or exogenous. The immune complexes once formed may be present in the circulation (*circulating immune complexes*) or may get deposited inside the vessels or extravascular sites (*in situ immune complex*). They may either be generalized or localized. Systemic or generalized immune complex disease has the following phases:

Mnemonic

S : **S**erum sickness, **S**chick test and **S**LE
H : **H**enoch-Schönlein Purpura
A : **A**rthus reaction
R : **R**eactive arthritis, **R**aji assay
P : **P**olyarteritis nodosa (PAN) and **P**ost Streptococcal glomerulonephritis (PSGN)

Phase I or Immune Complex Formation

It is characterized by the formation of the antibody ***about 5 days after*** introduction of the antigen. The small or intermediate immune complexes are most pathogenic. The large complexes are rapidly removed by the macrophages.

Phase II or Immune Complex Deposition

In this phase, the immune complexes get deposited in the glomeruli, joints, skin, heart, serosal surfaces and the blood vessels.

Phase III

Immune complex mediated inflammation is ***seen 10 days after antigen administration*** and results in the development of vasculitis, glomerulonephritis and arthritis. The immune complexes cause inflammation by activation of the complement system resulting in the neutrophilic infiltration, vasodilation and edema. They also cause activation of the intrinsic pathway of coagulation system and microthrombi formation contributing to tissue ischemia and necrosis.

The blood vessels show intense neutrophilic infiltration and necrotizing vasculitis having the presence of **fibrinoid necrosis**.

Examples of type III hypersensitivity include:

Localized hypersensitivity	Systemic hypersensitivity
*Arthus reaction	*SLE
*Farmer's lung	*Reactive arthritis
*Polyarteritis nodosa	*Henoch-Schönlein purpura
	*Post streptococcal glomerulonephritis
	*Serum sickness
	*Type II lepra reaction

Concept

The difference between type II and type III hypersensitivity reactions is that in the former, the antigen is tissue specific whereas in type III it is non-specific. In type II reaction, the tissue injury is direct (because antigen is intrinsic component of target cell) whereas in type III, it is mediated by the deposition of antigen antibody complexes in different tissues.

Recent Exam Questions

Hypersensitivity pneumonitis is an example of **type IV >>> type III** hypersensitivity reaction

TYPE IV OR CELL MEDIATED HYPERSENSITIVITY REACTION

The cell-mediated type of hypersensitivity is initiated by antigen-activated (sensitized) T lymphocytes. It includes the *delayed type hypersensitivity reactions* mediated by CD4+ T cells, and *direct cell cytotoxicity* mediated by CD8+ T cells.

Key Point

Antibody-mediated hyper-sensitivity reactions types **I, II and III.**
Type IV hypersensitivity: *cellular immunity*

1. **Pathogenesis of delayed type hypersensitivity reactions** (mediated by CD4+ T cells)
The first step is the entry of the antigen inside the body where it is captured by the APCs and presented to the T cell which then **differentiates into TH1 cell** (*remember that in type I hypersensitivity, the naïve T-cells differentiate into TH2 cells*). The sensitized TH1 cells enter the circulation and remain in the memory pool of the body. When there is re-exposure of the same individual to the antigen for the subsequent time, there is release of cytokines like TNF-α, lymphotoxin, IFN-γ, IL-2 and IL-12.

- TNF-α and lymphotoxins have effects on endothelial cells leading to extravasation of lymphocytes and monocytes.
- IL-2 causes proliferation of antigen specific T-cells.

Key Point

IFN-γ causes activation of macrophages.

The collective release of these mediators recruits a lot of inflammatory cells at the site of inflammation. The activated macrophages give rise to epithelioid cells and these cells surrounded by a collar of lymphocytes all around lead to **formation of a granuloma**. This granuloma formation is seen with tuberculin test, and other intracellular pathogens like mycobacterium, fungi and some parasites. Delayed type hypersensitivity reaction is also important in transplant rejection.

Key Point

IL-12 is produced by macrophages and dendritic cells and is critical in the pathogenesis of delayed hypersensitivity because it induces the TH1 response.

2. **Pathogenesis of T cell mediated cytotoxicity** (mediated by CD8+ T cells)
   Cytotoxic T lymphocytes (CTL) cause destruction of antigen bearing target cells particularly the tumor cells, the virus infected cells and allogeneic tissue during graft rejection. There are two mechanisms involved in this:
   - *Perforin granzyme dependent killing:* The mediators present in the lysosomal granules of the CTLs like perforin cause pore formation and the granzyme activates apoptosis on entering the cells via these pores.
   - *Fas-Fas ligand dependent killing*: Activated CTL express Fas ligand which can bind to Fas expressed on the target cells leading to apoptosis.

Examples of Type IV Hypersensitivity Include:

*Tuberculin reaction	*Lepromin test	*Multiple sclerosis
*Chronic graft rejection	*Contact dermatitis	*Sarcoidosis
*Temporal arteritis	*Primary biliary cirrhosis	*Type I lepra reaction
*Tumor immunity	*Resistance to viral infections	*Crohn's disease
		*Rheumatoid arthritis

TRANSPLANT REJECTION

It is a complex process in which both cellular and humoral immunity plays a role.

T cell Mediated Rejection

The T cell mediated rejection is also called as cellular rejection and it has two pathways:

- *Direct pathway* in which the interstitial dendritic cells of the donor present the antigen to the CD4 and CD8 T cells of the host. The host CD4 Tcells differentiate into TH1 cells and similar to delayed hypersensitivity cause graft injury. CD8 T cells differentiate into cytotoxic T lymphocytes and cause graft tissue damage by perforin-granzyme and Fas-Fas ligand pathways.
- *Indirect pathway* in which the dendritic cells of the recipient present the antigen to CD4 Tcells. There is *no involvement of the CD8 T cells.*

Antibody Mediated Rejection or Humoral Rejection

It is also known as **rejection vasculitis** and takes place by two mechanisms:

Key Point

The **direct pathway** is important for acute graft rejection

- *Hyperacute rejection* takes place when there is preformed anti-donor antibodies present in the circulation of the recipient. It takes place within minutes to hours and is associated with previous blood transfusions, multiparous lady or already rejected transplant. It is an example of **type II hypersensitivity** reaction.
- *Acute rejection* is seen within days to months after transplantation. The mechanisms involved include inflammation, complement dependent cytotoxicity and ADCC.

Key Point

The **indirect pathway** is important for **chronic graft rejection**.

MORPHOLOGY OF TRANSPLANT REJECTION

Hyperacute rejection

It takes place in individuals with preformed antibodies usually **within minutes to hours** of transplantation. The preformed antibodies result in immune complex disease with the presence of neutrophils within arterioles, glomeruli and peritubular capillaries and fibrin-platelet thrombi in vessel wall. There is presence of necrosis of the renal cortex.

Acute rejection

It is seen **days to months** after transplantation. It can be acute humoral rejection or acute cellular rejection.

The ***acute cellular rejection*** is seen within few months after transplantation. There is presence of endothelitis with the presence of CD4 and CD8 T cells in the interstitium along with the mononuclear cells in the glomerular and peritubular capillaries.

The ***acute humoral rejection*** or rejection vasculitis is mediated primarily by anti-donor antibodies and it manifests mainly as damage to the blood vessels in the form of necrotizing vasculitis with endothelial cell necrosis, neutrophilic infiltration, deposition of immunoglobulins, complement, and fibrin, and thrombosis. There is associated necrosis of the renal parenchyma.

Recent Exam Question

C4d deposition is in indicator of **antibody mediated (*humoral*)** graft rejection

Chronic rejection

It occurs **months to years** after transplantation. In this, the vascular changes consist of *dense, obliterative intimal fibrosis in the cortical arteries* resulting in glomerular loss, interstitial fibrosis and tubular atrophy, duplication of basement membranes of the glomeruli (also called as chronic transplant glomerulopathy). The renal interstitium also has mononuclear cell infiltrates containing large numbers of plasma cells and eosinophils.

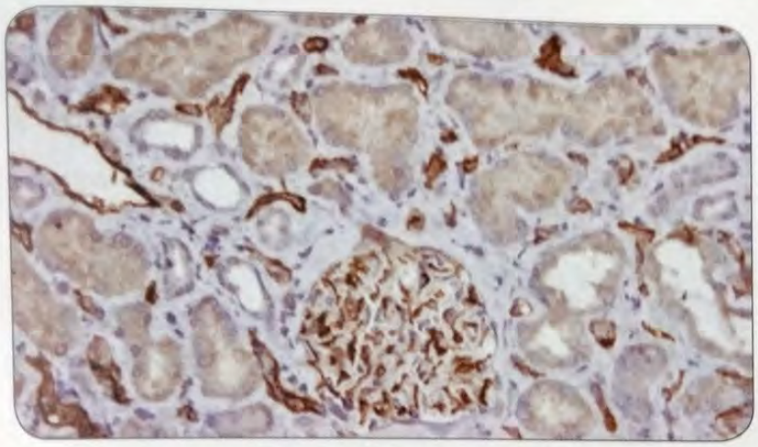


Fig. 3: Acute humoral (antibody mediated) rejection: C4d deposition in peritubular capillaries and a glomerulus.

Key Point

- The **initial target of the anti-bodies** is the **graft vasculature.**
- **Hyperacute rejection** is **type II** hypersensitivity reaction.
- **Acute rejection** is **type II + type IV** reactions **hypersensitivity reaction**.

Concept

Acute rejection can be reversed with immunosuppressive drugs like cyclosporine, muromonab and steroids.

GRAFT VERSUS HOST DISEASE (GVHD)/RUNT DISEASE (in animals)

Graft versus host disease occurs in any situation in which **immunologically competent cells** or their precursors are transplanted into **immunologically crippled patients** and the transferred cells recognize **alloantigens** in the host. It occurs most commonly in the setting of **allogenic bone marrow transplantation.** The recipients of bone marrow transplants are **immunodeficient** because of either their primary disease or prior treatment of the disease with drugs or irradiation. When such recipients receive normal bone marrow cells from allogenic donors, the ***immunocompetent T cells*** present in the donor marrow recognize the ***recipient's HLA antigen*** as foreign ***antigen*** and reacts against them. Both $CD4^+$ and $CD8^+$T cells recognize and attack host tissues.

Key Point

GVH reaction is observed in **skin, intestine** and **liver** leading to skin rash/dermatitis, diarrhea and jaundice.

ACUTE GVHD

- It is characterized by an erythematous maculopapular rash; persistent anorexia or diarrhea, or both; and by liver disease with increased serum levels of bilirubin, alanine and aspartate aminotransferase, and alkaline phosphatase.
- *Diagnosis usually requires skin, liver, or endoscopic intestinal biopsy for confirmation.* In all these organs, endothelial damage and lymphocytic infiltrates are seen.

*Grade I acute GVHD is of little clinical significance, does not affect the likelihood of survival, and does not require treatment. In contrast, grades II to IV GVHD are associated with significant symptoms and a poorer probability of survival, and they require aggressive therapy.

Recent Exam Questions

- No treatment is required for Grade I acute GVHD
- Therapy is required for grades II to IV GVHD

CHRONIC GVHD

Definition

GVHD developing **within the first 3 months** post transplant is termed **acute GVHD**.

Chronic GVHD resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration and cholestasis.

Recent Exam Question

The **risk** of graft versus host can be **decreased** by **Depletion of T cells from graft**

- Because patients with chronic GVHD are susceptible to significant infections, they should receive *prophylactic trimethoprim-sulfamethoxazole.*
- Infection with cytomegalovirus is particularly important.

Definition

GVHD developing or persisting **beyond 3 months** post-transplant is termed **chronic GVHD.**

Tolerance (non-responsiveness to self-antigen)

Central tolerance
1. **Negative selection:** deletion of self reactive B/T cells with the help of AIRE gene
2. **Receptor editing:** self reactive B cells alter the shape of receptor. If they cannot alter, they die by apoptosis

Peripheral tolerance
1. **Regulatory T cells** inhibit lymphocyte activation using CD25 and fox P3 gene
2. **Antigen sequestration** in immune privileged sites (testis/eye/brain)
3. **Anergy:** irrevesible inactivation of B/T cell
   - T cell anergy due to ↓ interaction between CD28 and B7.1/7.2
   - B cell anergy due to ↓ interaction between **CD40** L and **CD40**
   - Self Ag express PD-1 and CTLA-4 which interact with B.7 molecule and reduce activation

Mnemonic

CD25 polymorphism: multiple sclerosis
FOXP3 gene mutation: **IPEX** syndrome
Immune dysregulation
Polyendocrinopathy
Enteropathy
X-linked
Fas gene mutation: autoimmune lymphoproliferative syndrome

Recent Exam Questions

- **PTPN-22** is the most frequently implicated gene in **autoimmunity**.
- In *rheumatic heart disease*, streptococcal proteins cross react with myocardial proteins causing myocarditis (***molecular mimicry***).
- **EBV** and **HIV** can cause autoimmune diseases by **polyclonal B cell activation**

Mechanisms of autoimmunity

- **Loss of tolerance**
- **Genetic mechanisms**
  - PTPN-22 → RA/type 1 DM
  - NOD2 gene → Crohn's disease
  - IL-2/IL-7 receptor → Multiple sclerosis
- **Spread of cryptic epitope**
  - Rheumatic fever
- **Infections**
  - Molecular mimicry (cross reactivity)
  - ↑ Release of self antigen
  - Upregulation of costimulatory molecule

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Recent Exam Questions

Etiological factors of SLE

- Deficiency of early complement proteins (C1, C2 and C4).
- UV light exposure
- Estrogen
- Abnormal B-cell activation and type I interferons

SLE is an autoimmune multi-system disorder of unknown etiology characterised by loss of self tolerance and production of auto-antibodies. It is more commonly seen in the females affecting them around the age of 20-30's. The *deficiency of early complement proteins (C1, C2 and C4) has been postulated to be associated with increased incidence of SLE*. The auto-antibodies in this condition are formed against DNA, histones, non histone proteins bound to RNA and nucleolar antigens. These are collectively called as antinuclear antibodies (ANA).

Recent Exam Questions

SLE

- **Anti-double stranded DNA antibody** and the antibody against Smith **(Sm)** antigen **Highly specific** for SLE.
- Antinuclear antibody (**ANA**) **Highly sensitive** for SLE
- **Anti Ro Antibody – Neonatal lupus**, subacute cutaneous lupus
- **Anti-P antibody** – Associated with **lupus psychosis**
- **Anti-SS-A** and **Anti-SS-B** antibody– Associated with **congenital heart block** and **cutaneous lupus**
- **Anticardiolipin antibodies** may produce a **false positive** VDRL test for syphilis.
- **SLE** is an example of both **type II** (hematological features) and **type III** (visceral lesions) hypersensitivity reactions.

Concept

Clinical significance of antinuclear antibodies

Antiphospholipid antibody syndrome is characterized by antibodies against plasma proteins in complex with phospholipid. In **primary antiphospholipid antibody syndrome** there is hypercoagulable state without evidence of autoimmune disorders. In association with SLE or lupus, the name given is **secondary antiphospholipid antibody syndrome.** There is formation of antibody against **phospholipid beta–2-glycoprotein 1 complex**[Q]. It also binds to cardiolipin antigen and lead to **false positive test for syphilis**[Q]. It also interferes with in vitro clotting time and so, called as lupus anticoagulant. In vivo, these patients have hypercoagulable state resulting in **arterial and venous thrombosis** resulting **spontaneous recurrent miscarriage** and focal or cerebral ischemia.

The **clinical criteria** for the diagnosis of SLE include **any 4 of the following mentioned 11 criteria**:

• Malar rash	• Serositis-Pleuritis or pericarditis
• Discoid rash	• Renal disorder
• Photosensitivity	• Hematological disorder
• Oral ulcer	• Immunological disorder
• Arthritis	• Antinuclear antibody
• Neurological disorder-Seizure or psychosis in the absence of known drug/metabolic abnormality.	

ORGAN INVOLVEMENT

1. **Kidney**: WHO classification of renal involvement or **'lupus nephritis'** is as follows:
   - Class I - Minimal or no change
   - Class II - Mesangial lupus glomerulonephritis
   - Class III - Focal proliferative glomerulonephritis
   - Class IV - Diffuse proliferative glomerulonephritis.
   - Class V - Membranous glomerulonephritis

Recent Exam Questions

SLE

- **Diffuse proliferative or type IV glomerulonephritis** is the **most common** and **most serious** renal lesion.
- The presence of subendothelial deposits gives rise to **'wire loop' lesions** on light microscopy in **SLE**.
- **SLE Nephropathy**[Q] has the findings called as "full house phenomenon"

2. **Heart**: There is development of **pericarditis** (more commonly) as well as Libman-Sacks endocarditis[Q] (less commonly) having vegetations on both the sides of the valvular surface. There is also presence of.
3. **Mouth**: **Oral ulcers** are usually **painless**.
4. **Joints**: **Non-erosive arthritis** involving 2 or more peripheral joints with tenderness and effusion.
5. **Skin**: Erythematous rash present over malar region is also called **'butterfly rash'**. Exposure to sunlight accentuates the erythema.
6. **Lung**: There is presence of **pleuritis** (more commonly) as well as diaphragmatic weakness (shrinking lung syndrome).
7. **Blood**: Presence of autoimmune cytopenia (anemia, neutropenia or thrombocytopenia). The presence of LE cell or hematoxylin body is also seen.

Definition

The **LE cell** is any phagocytic leukocyte (**neutrophil** or **macrophage**) that has engulfed the denatured nucleus of an injured cell.

Tart Cell is usually a **monocyte** which has ingested another cell or nucleus of another cell.

Recent Exam Question

Rat liver is used for detection of ***anti-nuclear antibodies***

SJOGREN SYNDROME

It is an autoimmune disorder characterised by the destruction of lacrimal and salivary glands resulting in the *inability to produce tears and saliva*. It is more commonly seen in females. It can be **primary** when it is called **sicca syndrome** and it may also be secondary to other autoimmune disorders; rheumatoid arthritis being most commonly associated disorder.

Recent Exam Questions

- **Sjogren syndrome:** dry eyes; dry mouth.

  Diagnosis is confirmed with **lip biospy**
- *Sjogren syndrome:* presence of anti-ribonucleoprotein antibodies like **SS-A (Ro)** and **SS-B (La)**.

There is *presence of anti-ribonucleoprotein antibodies like SS-A (Ro) and SS-B (La)*. The presence of former is associated with early disease onset, longer disease duration, and extraglandular manifestations, such as cutaneous vasculitis and nephritis.

Clinical features include dry mouth (*xerostomia*) and dry eyes (*keratoconjunctivitis sicca*), the latter due to lymphocytic infiltration and destruction of the lacrimal gland. *Mickulicz syndrome* include lacrimal and salivary gland enlargement of whatever cause. Patients with Sjogren syndrome have an *increased risk of developing lymphoid malignancies.*

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

It is a disease seen in a group of patients who are identified clinically by the coexistence of features suggestive of SLE, polymyositis, rheumatoid arthritis, and systemic sclerosis. These patients have *high titers of antibodies to RNP particle-containing U1 RNP*. The factors lending distinctiveness to mixed connective tissue disease include the *reduced incidence of renal involvement and a good response to corticosteroids.*

Recent Exam Question

MCTD: Presence of **U1 RNP antibodies.**

SCLERODERMA

- It is an autoimmune disorder characterised by fibroblast stimulation and collagen deposition in the skin and internal rgans. The **skin is most commonly affected**, but the gastrointestinal tract, kidneys, heart, muscles, and lungs also are frequently involved.
- It is more commonly seen in the females and is due to release of growth factors acting on the fibroblasts like fibroblast growth factor *(FGF)*, platelet derived growth factor *(PDGF)* and cytokines like *IL-1*.

The disease has two categories:

- ***Diffuse scleroderma*** is characterized by presence of **anti-DNA topoisomerase**[Q] **antibodies (Scl-70)**. There is widespread skin involvement at onset, with rapid progression and early visceral involvement. The symptoms include dysphagia, malabsorption, arrhythmia (due to cardiac fibrosis), exertional dyspnea and renal insufficiency.

Recent Exam Question

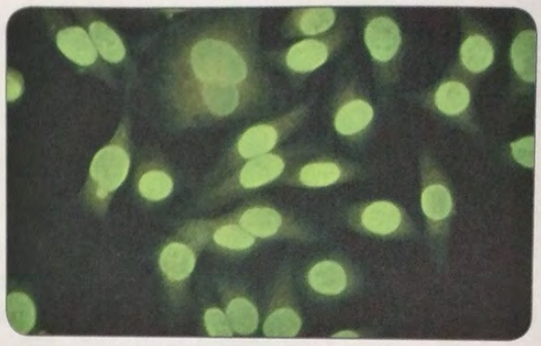
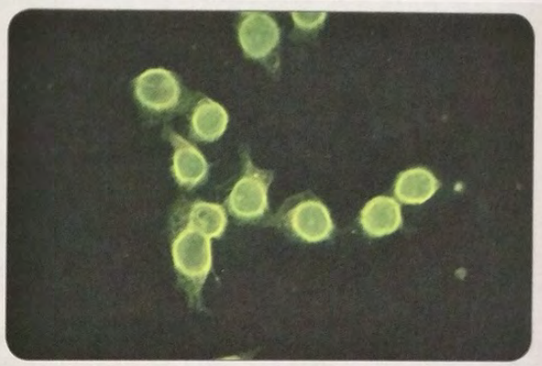
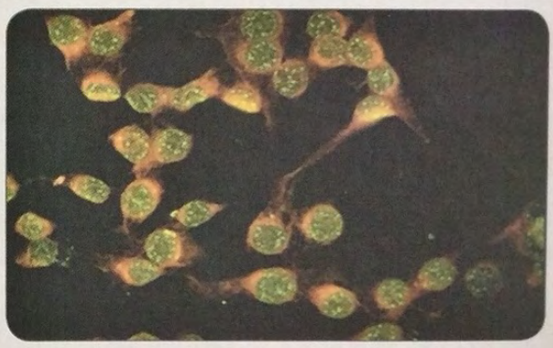
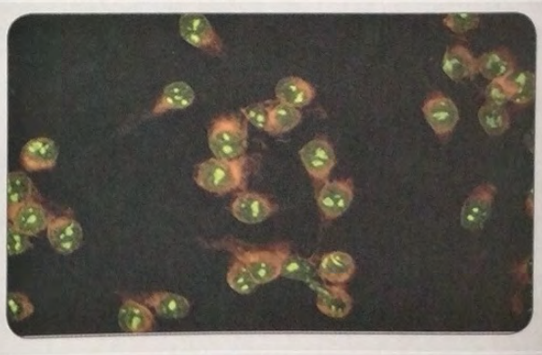
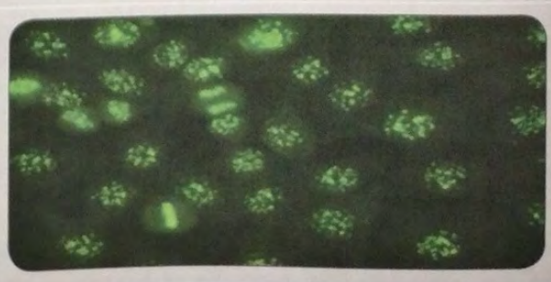
Diffuse scleroderma: anti-DNA topoisomerase[Q] antibodies

Limited scleroderma: anti-centromere[Q] antibodies

- ***Limited scleroderma*** is characterized by the presence of **anti-centromere**[Q] **antibodies**. The skin involvement is often confined to fingers, forearms, and face. Since the visceral involvement occurs late; so, the clinical course is relatively benign. Some patients develop ***CREST syndrome***[Q].

Recent Exam Question

CREST syndrome: **C**alcinosis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly and **T**elangiectasia.

Recent exam topic: Antinuclear antibody staining patterns		
Pattern	**Antigen**	**Image**
Homogeneous or diffuse nuclear staining	Chromatin, histones	
Rim or peripheral staining	Double stranded DNA	
Speckled pattern (MC and least specific pattern)	Antibody against extractable (Non-DNA) nuclear antigens like ribonucleoprotein, Sm antigen, SS-A and SS-B reactive antigens	
Nucleolar pattern (seen in systemic sclerosis)	RNA (Bright fluorescence is seen within the nucleoli)	
Centromeric pattern (seen in CREST syndrome)	Centromeres	

INFLAMMATORY MYOPATHIES

The inflammatory myopathies represent the largest group of acquired and potentially treatable causes of skeletal muscle weakness. They are classified into **three major groups**: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

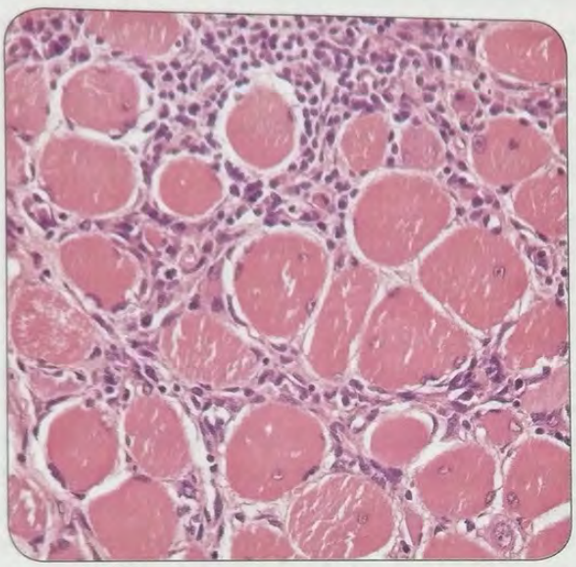


Fig. 4: Polymyositis: lymphocytes surround individual muscle cells

Criteria for Diagnosis of Inflammatory Myopathies

Criterion	Polymyositis	Dermato-myositis	Inclusion body myositis
Myopathic muscle weakness	Yes	Yes	Yes; slow onset, early involvement of distal muscles, frequent falls
Electromyo-graphic findings	Myopathic	Myopathic	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to 50-fold) or normal	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal
Muscle biopsy findings	"Primary" inflammation with the CD8/MHC-I complex and no vacuoles	Perifascicular, perimysial, or perivascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/ MHC-I complex; vacuolated fibers with amyloid deposits; cytochrome oxygenase–negative fibers; signs of chronic myopathy
Rash or calcinosis	Absent	Present	Absent

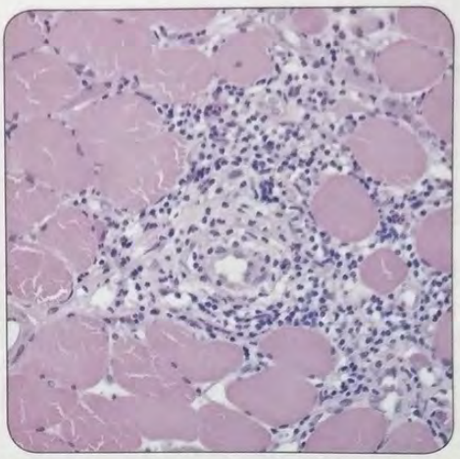


Fig. 5: Dermatomyositis: Perivascular lymphocytic infiltrate

X-LINKED AGAMMAGLOBULINEMIA OF BRUTON

Key Point

- Germinal centers of lymph nodes, Peyer patches, the appendix, and tonsils are under developed or rudimentary
- Bruton's disease usually does not become apparent until about 6 months, when maternal immunoglobulins are depleted.

It is an X-linked immunodeficiency disorder *characterized by the failure of B-cell precursors (pro-B cells and pre-B cells) to mature into B cells* due to *mutation of B-cell tyrosine kinase (Btk)*. Btk is required for the maturation of pre-B cell to mature B cell. The disease is **seen almost entirely in males**. In most cases, recurrent bacterial infections of the respiratory tract, such as acute and chronic pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia, are present. The causative organisms are *Haemophilus influenzae, Streptococcus pneumoniae,* or *Staphylococcus aureus* in most of the patients. It is associated with an increased risk of other autoimmune disorders.

Recent Exam Questions

BRUTON DISEASE

- **X-linked** disease.
- More common in **males**.
- ↓ ***B-cells, Plasma cells and antibodies in serum.***
- Precursor B-cells in **bone marrow** are **normal**.
- **T-cells** reaction is **normal**.

WISKOTT-ALDRICH SYNDROME (WAS)

- X-linked recessive disease[Q].
- Affecting males more commonly.
- Mutations in the WASP gene located on short arm of chromosome X.
- The WASP protein is important in platelets and T cells.
- Cytoskeletal integrity and signal transduction
- Characterized by bruising caused by thrombocytopenia[Q], eczema[Q], recurrent infections[Q], bloody diarrhea (due to thrombocytopenia) and increased risk of autoimmune disorders and malignancies[Q].

Recent Exam Questions

- The **platelets are small**[a] in Wiskott-Aldrich syndrome.
- Triad of WAS = thrombocytopenia+eczema+ recurrent infections.
- In WAS, ↓**IgM**, ↑**IgA** and ↑**IgE**.

Diagnosis is made on the basis of clinical parameters, the blood film and low immunoglobulin levels. **Treatment** it is done with **bone marrow transplantation**. The alternatives include intravenous immunoglobulin infusions or splenectomy.

COMMON VARIABLE IMMUNODEFICIENCY

Most patients with common variable immunodeficiency have normal or near-normal numbers of B cells in the blood and lymphoid tissues which are not able to differentiate into plasma cells. Patients have intrinsic B-cell defects (**defective cytokine receptor called BAFF** which normally promotes B cell differentiation and survival) as well as abnormalities of T cell-mediated regulation of B cells. The clinical manifestations include recurrent sinopulmonary pyogenic infections, recurrent herpesvirus infections and persistent diarrhea caused by *G. lamblia*. It affects **both sexes equally**, and the onset of symptoms is relatively **late (in childhood or adolescence)**. These patients have a high frequency of autoimmune diseases like rheumatoid arthritis and increased risk of lymphoid malignancy (particularly in women).

Key Point

Common variable immuno-deficiency: characterized by ***hypogammaglobulinemia*** affecting all the antibody classes (but sometimes only IgG) even with ***near-normal numbers of B Cells.***

Mnemonic

Mnemonic: (CATCH 22)

C	**C**ardiac abnormalities (especially tetralogy of Fallot)
A	**A**bnormal facies
T	**T**hymic aplasia
C	**C**left palate
H	**H**ypocalcemia (due to hypoplasia or lack of parathyroids)
22	**22**q11 deletion

DIGEORGE SYNDROME OR VELOCARDIOFACIAL SYNDROME

It is a *T-cell deficiency due to* deletion of chromosome 22q11.2. The patients have a **loss of T cell-mediated immunity** (owing to hypoplasia or lack of the thymus), tetany (owing to lack of the parathyroids), and congenital defects of the heart and great vessels. They may also have abnormal facies with defects in the mouth and ears. The absence of cell-mediated immunity results in the development of recurrent fungal and viral infections.

Key Point

DiGeorge syndrome: failure of development of the **third** and **fourth** pharyngeal pouches
Absence of the parathyroid glands and the thymus.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

This retroviral disease is caused by the human immunodeficiency virus (HIV). It is characterized by the triad of immunosuppression associated with opportunistic infections, secondary neoplasms, and neurologic manifestations. The major routes of HIV infection are:

Key Point

AIDS is the commonest **secondary** immunodeficiency disorder

1. *Sexual contact*
   It is the ***most common*** **mode of spread of the infection** throughout the world. It is usually through heterosexual contact. The presence of any other concomitant sexually transmitted disease causing genital ulcerations increases the risk of transmission of HIV also. *Gonorrhea and Chlamydia also act as cofactors for HIV transmission primarily by increasing the seminal fluid content of inflammatory cells carrying HIV.*
2. *Parenteral inoculation*
   Parenteral transmission of HIV is a broad term which includes transmission through:
   a. Intravenous drug abusers (the largest group): transmission occurs through shared needles, syringes etc.
   b. Patients receiving blood or blood components (like hemophiliacs receiving factor VIII or IX concentrates)
   c. Infected patient to the physician through *needle stick injury:*
      The transmission through the parenteral route can be prevented with the screening of the blood and taking precautions like the universal precautions like not recapping the needle after taking blood sample of a patient and use of disinfectants like hypochlorite for blood spillages.

Recent Exam Questions

- **Sexual contact:** Least efficacious yet most common mode of spread of HIV infection.
  The **male to female** transmission is **more common** as compared to transmission from females to males
- The risk of transmission of **HIV is 0.3%** with needle stick injury whereas the risk of hepatitis B is 30%.
- **Vertical transmission** is the commonest cause for AIDS in the pediatric population.

3. Passage of the virus from **infected *mother to newborn*** (mother to child transmission or ***vertical transmission***)
   The transmission from an infected to the child can take place through:

Recent Exam Questions

Blood products which can transmit HIV	Blood products which can NOT transmit HIV
• Whole blood • Packed red blood cells • Platelets • Leukocytes • Plasma .	• Hyperimmune gamma globulin • Hepatitis B immune globulin • Plasma-derived hepatitis B vaccine • Rho immune globulin

a. Transplacental spread.
b. **Infected birth canal during normal vaginal delivery**[Q]: it is the MC route for vertical transmission.
c. Ingestion of breast milk
The transmission through the vertical route can be reduced by the use of elective caesarean section and the use of antiviral drugs like nevirapine and zidovudine. (For details, refer to *Review of Pharmacology* by the same authors).

ETIOLOGY AND PATHOGENESIS

HIV is a retrovirus belonging to the lentivirus family and is of two types HIV-1 and HIV-2. There are two strains of HIV which are:

a. Macrophage-tropic (R5 virus) strain: it infects both monocytes/macrophages and T cells.
b. T-cell tropic (X4 virus) strain: it infects only activated T cell lines.

The HIV-1 virion is spherical and contains an electron-dense, cone-shaped core containing the major capsid protein p24, nucleocapsid protein p7/p9, the viral RNA, and viral enzymes (protease, reverse transcriptase, and integrase) surrounded by a lipid envelope derived from the host cell membrane. p24 is the most readily detected viral antigen and is the target for the antibodies used to diagnose HIV infection in blood screening. The viral envelope has two glycoproteins (gp120 and gp41) required for HIV infection of cells.

Key Point

The commonest cause of AIDS in India is **HIV-1 group M subtype C**

The **two major targets** of HIV infection are the **immune system and the CNS.** The profound immunodeficiency is the hallmark of AIDS. The viral envelope gp120 interacts with CD 4 molecule followed by confirmational change in gp 41. The virus then fuses with the host cell membrane. The commonly affected CD 4 cells in the human body include **helper T cells**[Q] **(worst affected), monocyte-macropahges** and **dendritic cells.**

Defective CCR5 receptors lead to protective effect of providing resistance to the development of AIDS.

The HIV pro-virus causes latent infection or damages host cell by apoptosis or direct killing. This leads to decline in CD4+ cell count and the patient developing clinical symptoms.

Concept

R5 strains use CCR5 as their coreceptor which is expressed on both monocytes and T cells,
X4 strains bind to CXCR4 expressed on T cells and not on monocytes/macrophages.
Almost 90% of HIV infections are **initially transmitted by R5 strains.** However, during the course of infection, X4 viruses replace R5 strains due to mutations in genes that encode gp120.

Natural History of HIV

The acute retroviral syndrome

It is seen for 3-12 weeks and is characterized by high levels of plasma viremia, and *widespread seeding of the lymphoid tissues*. Clinically there is a self-limited acute illness with nonspecific symptoms, including sore throat, myalgias, fever, rash, weight loss, and fatigue, and clinical features, such as rash, cervical adenopathy, diarrhea, and vomiting.

The middle chronic phase

This is characterized by a period of clinical latency. It is usually lasting for an average duration of 10 years. In this phase, there is a continuous battle between the virus and the host immune cells. The immune system is intact, but *there is continuous HIV replication, predominantly in the lymphoid tissues, which may last for several years*. Patients are either asymptomatic or develop persistent generalized lymphadenopathy.

The final phase or the stage of crisis

It is associated with the loss of host immune cells in the battle and the *progression to AIDS*. It is characterized by the patient presenting with a long-lasting fever (>1 month), fatigue, weight loss, and diarrhea.

Recent Exam Questions

- **Acute Stage:** Macrophage affected.
  Chronic Stage: T_{H1} cells affected.
- **HIV:** cytotoxic to CD4 T Cells leading to loss of cell-meditated immunity.
- The weight loss is so severe that AIDS is also known as **"Slim's disease"**.

CLINICAL FEATURES

The typical adult patient with AIDS presents with fever, weight loss, diarrhea, generalized lymphadenopathy, multiple opportunistic infections, neurologic disease and secondary neoplasms.

The opportunistic infections seen are:

Recent Exam Questions

- ***M. tuberculosis** is the most common infection with HIV in ***India.***
- **Candidiasis** is the most common fungal infection in AIDS in ***India.***
  Pneumocystis jiroveci is the most common fungal infection in AIDS in ***World.***
- **Kaposi's sarcoma** is the most common cancer seen in patients having AIDS.

Bacterial infections	Viral infections	Fungal infections	Protozoal infections
• M. tuberculosis • Salmonella • Nocardiosis • Atypical mycobacterial infections	• Cytomegalovirus • Herpes simplex virus • Varicella zoster virus • JC virus causing Progressive multifocal leukoencephalopahty	• Candidiasis • Pneumocystis jiroveci • Cryptococcosis • Histoplasmosis • Coccidiomycosis	• Cryptosporidium • Isosporidium • Toxoplasmosis

Neoplasms in AIDS

1. **Kaposi's sarcoma**[Q]: It is caused due to infection with *Kaposi sarcoma herpesvirus* (KSHV) or *human herpes virus-8* (HHV8). It is characterized by the proliferation of spindle-shaped cells that express markers of **both endothelial (vascular or lymphatic) and smooth muscle cells**[Q]. KSHV infection is related to rare B cell lymphomas in AIDS patients known as body cavity based primary effusion lymphoma and to a multicentric B-cell lymphoproliferative disorder called as **Castleman disease**.

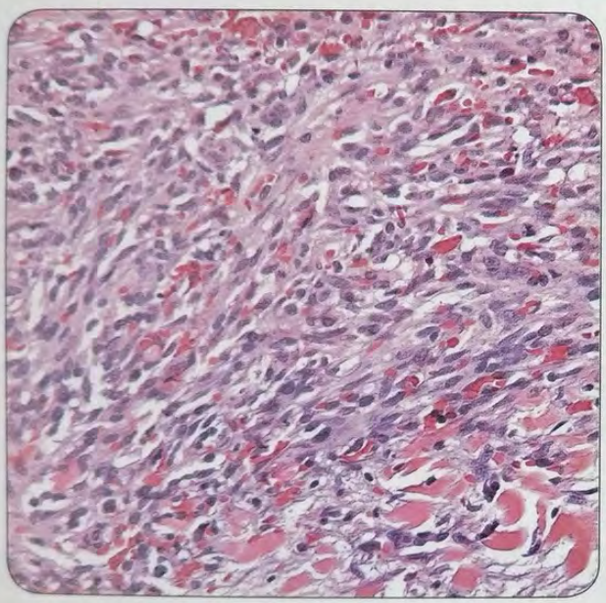


Fig. 6: Kaposi sarcoma with spindle shaped cells

Recent Exam Questions

- **Stomach** is the most common **extranodal site** for development of lymphoma in **non HIV** patients.
- **CNS** is the most common *extranodal site* for development of lymphoma **in HIV infected patients.**

2. **Lymphomas**: AIDS related lymphomas include
   i. Systemic lymphomas having the **CNS as the *most common extranodal site* for development of lymphoma**[Q],
   ii. Primary CNS lymphoma found more commonly in AIDS than in general population
   iii. Body cavity lymphomas present as pleural, peritoneal or pericardial effusions.

These tumors are more frequently seen in patients with CD4+ T cell count <50 per microlitre.

Recent Exam Questions

- **Toxoplasma gondii** is responsible for 50% of all mass lesions in the CNS.
- **AIDS-dementia complex** is the most common **neurological manifestation** of HIV infection.
- **Microglia** is responsible for neurological manifestations in HIV.
- **Inflammatory myopathy** is the commonest **skeletal muscle disorder** in HIV.

3. **Genital cancers** including cancer of the cervix and the anal cancers due to infection with human papilloma virus (HPV).

Neurological Manifestations in AIDS

The neurological manifestations are due to the involvement of the **microglia**[Q]. These include

1.	Opportunistic infections
2.	Neoplasms
3.	Aseptic meningitis
4.	Peripheral neuropathies
5.	**AIDS-dementia complex**[Q]
6.	Vacuolar myelopathy: It is a disorder of the spinal cord found in 20% to 30% of patients with AIDS. The findings resemble those of subacute combined degeneration, though serum levels of vitamin B12 are normal.
7.	Meningoencephalitis: HIV encephalitis is characterized microscopically as a chronic inflammatory reaction with widely distributed infiltrates of microglial nodules around the small blood vessels showing abnormally prominent endothelial cells and perivascular foamy or pigment-laden macrophages. These nodules also contain the macrophage-derived multinucleated giant cell.
8.	**Inflammatory myopathy**[Q]: The histological findings include muscle fiber necrosis and phagocytosis, interstitial infiltration with HIV-positive macrophages. **Characteristically vasculitis is absent**[Q].

Concept

Window period is the term used for **initial 2-4 weeks** when the patient is infectious and the screening test is negative during which the investigation of HIV is made using ***polymerase chain reaction for detection of viral nucleic acids.***

Diagnosis of HIV infection or AIDS

The diagnosis of HIV is established with the following tests:

- ***ELISA***[Q] is used for the detection of antibodies against viral proteins. This is the **most sensitive** and the best screening test for the diagnosis of AIDS.
- ***Western blot***[Q] is the ***most specific*** or the confirmatory test for HIV.
- Direct detection of the viral infection is with p24 antigen capture assay, reverse transcriptase polymerase chain reaction (RT-PCR), DNA-PCR and culture of the virus from the monocytes and CD4+ T cells.

The management of the disease is done by the Highly active antiretroviral therapy (HAART) details of which can be referred from 'Review of Pharmacology' by the same authors.

Some patients with advanced disease in HIV paradoxically deteriorate on initiating the antiviral therapy. This ironical disorder whose basis in not understood is called ***Immune reconstitution inflammatory syndrome***.

Amyloidosis (Beta-Fibrillosis)

It is a group of diseases having in common the deposition of amyloid (a pathologic proteinaceous substance, deposited between cells in various tissues and organs of the body). Amyloid appears as an amorphous, eosinophilic, hyaline, extracellular substance with the light microscope. Its progressive accumulation can cause pressure atrophy of adjacent cells.

Nature of Amyloid

Amyloid is seen to be made up of *nonbranching fibrils of indefinite length and a diameter of approximately 7.5 to 10 nm by the electron microscope*. X-ray crystallography and infrared spectroscopy demonstrate a characteristic cross-β-pleated sheet conformation responsible for the birefringence. Chemically, 95% of the amyloid is made up of fibril proteins.

Key Point

Amyloid

- **EM:** *nonbranching fibrils* of indefinite length
- **X-ray crystallography** and **infrared spectroscopy**: characteristic cross-**β-pleated** sheet conformation

CLASSIFICATION OF AMYLOIDOSIS

Primary Amyloidosis

It is associated with immunocyte dyscrasias like *multiple myeloma* or any other B cell neoplasm.

The tumor cells in multiple myeloma secrete *light chains of the immunoglobulins* of either lamda or kappa type which get deposited in the tissues as amyloid. The chemical nature of the amyloid is **AL**[Q] (A for amyloid and L for light chain).

Secondary Amyloidosis *(also called as **Reactive Systemic Amyloidosis**)*

It is usually seen *secondary* to chronic inflammatory conditions like ***rheumatoid arthritis***[Q] ***(most commonly)***, tuberculosis, bronchiectasis, chronic osteomyelitis, inflammatory bowel disease, ankylosing spondylitis and two cancers namely renal cell cancer and Hodgkin's disease. There is release of IL-1 and IL-6 which act on the liver cells leading to the secretion of SAA protein which gives rise to AA protein being deposited in this condition. The chemical nature of amyloid is **AA**[Q].

Recent Exam Questions

MC cause of 2° amyloidosis

- **World:** Rheumatoid arthritis
- **India:** TB

Hemodialysis Associated Amyloidosis

It is caused by the deposition of the β_2 microglobulin which is a **component of MHC class I molecule** and can not be filtered through the cuprophane dialysis membrane. It gets deposited in the synovium, joints and the tendon sheaths leading to **carpal tunnel syndrome**. The chemical nature of the amyloid is **Aβ_2**[Q].

Recent Exam Questions

Systemic Amyloidosis

- Primary Amyloidosis: B cell neoplasm; AL
- Secondary Amyloidosis: Chronic inflammation: AA
- Chronic renal failure: Aβ_2
- Alzheimer disease: Aβ
- Familial Mediterranean fever: AA; involvement of pyrin.
- Normal TTR: Systemic senile Amyloidosis.
- Abnormal TTR: Familial amyloidotic neuropathies.

Heredofamilial Amyloidosis

i. *Familial Mediterranean fever* is an autosomal recessive condition characterized by development of attacks of fever associated with inflammation of serosal surfaces (pleura, peritoneum and synovial membrane). The amyloid protein deposited is AA protein and the protein associated with this condition is called **pyrin**[Q].

ii. *Familial amyloidotic neuropathies (several types):*
This is a group of ***autosomal dominant*** conditions in which both peripheral and autonomic nerves are involved. There is deposition of **ATTR** (A for amyloid and TTR is for transthyretin, a protein which transports thyroxine and retinol). The transthyretin deposited in this condition is a **mutant form of the normal protein**[Q].

iii. *Systemic senile Amyloidosis*
This is a condition characterized by the deposition of **structurally normal transthyretin**[Q], the chemical nature of amyloid is **ATTR** and it is usually deposited in the heart of aged individuals leading sometimes to the development of restrictive cardiomyopathy.

Recent Exam Questions

Localized Amyloidosis
- Alzheimer disease: Aβ
- Down syndrome: Aβ
- ACal: Medullary thyroid cancer
- AIAPP: Type II DM
- APro: Pituitary endocrinopathy
- ACys: Cerebral amyloid angiopathy
- APrP: Prion disease

LOCALIZED AMYLOIDOSIS

There is presence of nodular deposits most often in lung, larynx, skin, urinary bladder, tongue and around the eyes.

i. *Senile cerebral amyloidosis*
It is seen in **Alzheimer's disease** in which there is deposition of β-amyloid protein. So, chemical nature of amyloid is **Aβ**Q.

ii. *Endocrine*
It is associated with:
- *Medullary carcinoma of thyroid* having the deposition of **ACal**Q derived from calcitonin
- *Islet of Langerhans* in Type II DM having deposits of **AIAPP**Q derived from Islet Amyloid Peptide

iii. *Isolated Atrial Amyloidosis*
In this condition, there is deposition of **AANF** derived from Atrial natriuretic factor.

iv. *Prion disease*
In this condition, there is deposition of misfolded prion proteins **APrP** derived from normal prion protein PrP.

Summary of clinical conditions and the chemical nature of amyloid

S. No.	Amyloid protein	Precursor	Disease
1.	AL	Ig light chain	Multiple myeloma (primary amyloidosis)
2.	AA	SAA	Secondary or reactive amyloidosis
3.	$A\beta_2m$	β_2 microglobulin	Hemodialysis Associated amyloidosis
4.	ATTR	Mutant Transthyretin Normal Transthyretin	Familial amyloidotic neuropathy Systemic senile amyloidosis
5.	Aβ	Aβ precursor protein	Senile cerebral Alzheimer's
6.	ACal	Calcitonin	Medullary carcinoma of thyroid
7.	AIAPP	Islet amyloid polypeptide	Type II diabetes
8.	AANF	ANP	Isolated atrial amyloidosis Misfolded prion protein (APrP) disease
9.	**Aα**	**Fibrinogen**	**Familial renal amyloidosis**
10.	**ACys**	Cystatin	Cerebral amyloid angiopathy

Key Point
- Spleen involvement in amyloidosis
- **Red** pulp: **Lar**daceous spleen
- White pulp: Sago spleen

Morphology in Amyloidosis

Kidney

It is the *most common* and *most serious* form of organ involvement and is usully involved in **secondary amyloidosis**. There is deposition primarily in the **mesangium**Q (initial affected site) followed by glomerular basement membrane and the interstitial peritubular tissue. Arteries and arterioles are also affected (***venules are spared***).

Spleen

There is splenomegaly. If there is involvement of splenic follicles, it is called as **Sago spleen** and if there is involvement of splenic sinuses and red pulp it is called as **Lardaceous spleen**.

Liver

It is **first deposited in the space of Disse** and later result in hepatomegaly. The liver function tests are usually normal.

Heart

It is more commonly associated with ***primary amyloidosis***. It is the most important organ involved in senile systemic amyloidosis. Clinically, there may be development of arrhythmia and it is also the most important cause of restrictive cardiomyopathy. There is deposition in the focal subendocardial region.

Adrenals

The intercellular deposits begin initially in zona glomerulosa.

GIT

The GI tract may be involved through the gingiva to the anus. The deposition of the amyloid in the tongue results in the nodular enlargement of tongue called *macroglossia* or the tumor forming amyloid of the tongue.

Key Point

Macroglossia is the *most specific* feature of **AL** type of amyloidosis. (Ref Wintrobe 12th/2442)

Clinical features are non-specific and the symptoms are seen depending on the organ predominantly affected in the disease. Deposition of the amyloid in **long term hemodialysis** takes place in joints and in the carpal ligament of the wrist, the latter leading to development of 'carpal tunnel syndrome'.

Recent Exam Questions

Harrison 19th/945
- The most easily accesible tissue which is positive in 80% patients is **abdominal fat.**

Diagnosis

The diagnosis is made by the microscopic examination of the *biopsy from renal tissue, rectum, abdominal fat aspiration and gingiva.* The **best site for taking the biopsy**Q is **abdominal fat aspirate**Q followed by rectal biopsy. Grossly, the organs are enlarged and firm with a waxy appearance. The cut surface on painting with iodine imparts a yellow color which on application of sulfuric acid (H_2SO_4) gives a blue violet color.

STAINING FOR AMYLOID

- **Congo red**: It is the most widely used specific stain for amyloid.
- **Iodine staining: It is used for unfixed specimen or histological section. Amyloid stains mahogany brown and if sulfuric acid is added, it turns violet.**
- **Thioflavin 'T' and 'S'** give secondary immunofluorescence with ultraviolet light. ***Thioflavin T*** is more useful for demonstrating ***juxtaglomerular apparatus*** of the kidney.
- **Metachromatic stains** like crystal violet and methyl violet give rose pink appearance.
- Amyloid is **PAS** positive.

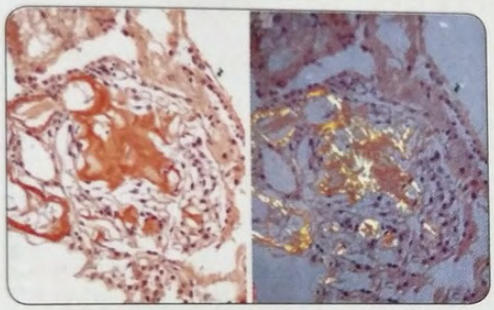


Fig. 7: Amyloid with congo red staining (Left) and Apple green birefringence (Right). **...(All India Image)**

Recent Exam Questions

Congo red
Pink red color under normal *light microscopy*
'***Apple green birefringence***' in the ***polarized*** light.

The condition has usually poor prognosis.

Summary of Appearance of Amyloid for exam questions	
On light microscopy and standard tissue stains (H and E)	Amorphous eosinophilic extracellular substance
Congo red stain on ordinary light	Pink or red color to tissue deposits
Congo red stain on ***polarizing microscopy***	***Apple green birefringence***^{Q}
Fluorescent stains (thioflavin T and S)	Yellow color under UV light
Electron microscopy	***Nonbranching fibrils***^{Q} of ***indefinite length*** and a diameter of approximately 7.5 to 10 nm.
X-ray crystallography and infrared spectroscopy	Characteristic ***cross β pleated***^{Q} sheet conformation

Multiple Choice Questions

IMMUNE CELL: GENERAL ASPECTS

1. **Which of the following features is not shared between 'T cells' and B cells'?** *(AIIMS Nov 2012)*
   (a) Antigen Specific Receptors
   (b) Class I MHC Expression
   (c) Positive selection during development
   (d) All of the above

2. **CD4 is not important for which of the following?**
   (a) Antibody production *(AIIMS May 2011)*
   (b) Cytotoxicity of T cells
   (c) Memory B cells
   (d) Opsonisation

3. **Type 1 MHC presents peptide antigen to T cell , so that peptide binding site is formed by:** *(AI 2010)*
   (a) Alfa and Beta chain
   (b) Distal domain alfa 1 and 2
   (c) Alfa and beta microglobulin
   (d) Proximal domain alfa 1 and 2

4. **Function of CD4 is all except:** *(AI 2009)*
   (a) Memory
   (b) Immunoglobulin production
   (c) Activation of macrophages
   (d) Cytotoxicity

5. **A super-antigen is a bacterial product that** *(AI 2008)*
   (a) Binds to B7 and CD28 co-stimulatory molecules
   (b) Binds to the beta chain of TCR and MHC class II molecules of APC stimulating T cell activation
   (c) Binds to the CD4 + molecule causing T cell activation
   (d) Is presented by macrophages to a larger-than-normal number of T helper CD4 + lymphocytes

6. **Memory T cells can be identified by using the following marker:** *(AI 2003)*
   (a) CD45RA
   (b) CD45RB
   (c) CD45RC
   (d) CD45RO

7. **All of the following statements about NK cells are true except:** *(AI 2003)*
   (a) They are derived from large granular cells
   (b) They comprise about 5% of human peripheral lymphoid cells
   (c) They are MHC restricted cytotoxic cells
   (d) They express IgG Fc receptors

8. **The following feature is common to both cytotoxic T-cells and NK cells:** *(AI 2002)*
   (a) Synthesize antibody
   (b) Require antibodies to be present for action
   (c) Effective against virus infected cells
   (d) Recognize antigen in association with HLA class II markers

9. **MHC restriction to antigen presentation is not done for:** *(AIIMS May 2009)*
   (a) Killing of viruses by cytotoxic cells
   (b) Killing of bacteria by helper cells
   (c) T cell activation in autoimmunity
   (d) Graft rejection

10. **Most potent stimulator of naive T cell is:**
    (a) Mature dendritic cell *(AI 2011, AIIMS Nov 08)*
    (b) Follicular dendritic cell
    (c) Macrophages
    (d) B cell

11. **Natural killer cells attacks which of the following cells:** *(AIIMS Nov 2006)*
    (a) Cells which express MHC1
    (b) Cells which are not able to express MHC1
    (c) MHC cells which express MHC2
    (d) Cells which are not able to express MHC

12. **Toll like receptors, recognize bacterial products and stimulates immune response by:** *(AIIMS Nov 2006)*
    (a) Perforin and granzyme mediated apoptosis
    (b) FADD ligand apoptosis
    (c) Transcription of nuclear factor mediated by N-FκB which recruits cytokines
    (d) Cyclin

13. **The following interleukin is characteristically produced in a TH_1 response:** *(AIIMS Nov 2004)*
    (a) IL-2 (b) IL-4
    (c) IL-5 (d) IL-10

14. **CD-95 has a major role in:** *(AIIMS Nov 2003)*
    (a) Apoptosis
    (b) Cell necrosis
    (c) Interferon activation
    (d) Proteolysis

15. **Which of the following chemical mediators of inflammation is an example of a C-X-C or alpha Chemokine?** *(AIIMS Nov 2003)*
    (a) Lipoxin LXA4
    (b) Interleukin IL-8
    (c) Interleukin IL-6
    (d) Monocyte Chemo-attractant Protein MCP-1

16. The complement is fixed best by which of the following immunoglobulins: *(AIIMS May 2002)*
(a) IgG (b) IgM
(c) IgA (d) IgD

17. Antigen presenting cells are which of the following: *(AIIMS May 2002)*
(a) Astrocytes
(b) Endothelial cells
(c) Epithelial cells
(d) Langerhan's cells

18. Antigen presenting cells are: *(PGI June 2006)*
(a) Langerhan's cell
(b) Macrophage
(c) Cytotoxic T cells
(d) Helper T cells
(e) B-lymphocyte

19. Perforins are produced by: *(PGI Dec 2001)*
(a) Cytotoxic T cells
(b) Suppressor T cells
(c) Memory helper T cells
(d) Plasma cells
(e) NK cells

20. Cell surface molecules involved in peripheral tolerance induction are: *(PGI Dec 2003)*
(a) B_7 and CD_{28} (b) CD_{40} and CD_{40L}
(c) CD_{34} and CD_{51} (d) B_7 and CD_3

21. Marker for B-Lymphocyte: *(PGI Dec 2004)*
(a) CD34 (b) CD33
(c) CD19 (d) CD20
(e) CD22

22. IL-1 causes *(Delhi PG-2008)*
(a) Increased leukocyte adherence
(b) Fibroblast proliferation
(c) Increased collagen synthesis
(d) All of the above

MOST RECENT QUESTIONS

23. Antigen presenting cells present in skin are called
(a) Langerhan's cells
(b) Kupffer's cells
(c) Microglia
(d) Melanocytes

24. Plasma cells
(a) Contain nucleus
(b) Helps in the formation of antibody
(c) Are deficient in cytoplasm
(d) Are derived from T-cells

25. The normal ratio of CD4 to CD8 is
(a) 1: 1 (b) 2: 1
(c) 8: 1 (d) 10: 1

26. CD4 cells is used to identify which of the following
(a) MHC I (b) MHC II
(c) T cells (d) B cells

27. CD3 is marker for:
(a) Monocyte (b) T cell
(c) B cell (d) None

28. Which of the following is not true about innate immunity?
(a) It is present prior to antigenic exposure
(b) It is relatively non-specific
(c) Memory is seen
(d) It is the first line of defense

29. Which one of the listed receptors is the type of receptor on leukocytes that binds to pathogen-associated molecular patterns (PAMPs) and mediates immune response to bacterial lipopolysaccharide?
(a) Cytokine receptor
(b) G-protein-coupled receptor
(c) Mannose receptor
(d) Toll-like receptor

30. Immunity against cancer cells:
(a) Basophils (b) Eosinophils
(c) NK cells (d) Neutrophils

31. NK cells express:
(a) CD 15, CD 55
(b) CD 16, CD 56
(c) CD 16, CD 57
(d) CD 21, CD 66

32. NK cell CD marker is:
(a) 16 (b) 60
(c) 32 (d) 25

33. The following interleukin is characteristically produced in a TH1 response?
(a) IL-2 (b) IL-4
(c) IL-5 (d) IL-10

34. Most potent stimulator of Naïve T-cells:
(a) Mature dendritic cells
(b) Follicular dendritic cells
(c) Macrophages
(d) B-cell

35. Which of the following immune cells have the expression of CD8 on their surface?
(a) T-cells (b) B-cells
(c) Null cells (d) Macrophages

36. Kupffer cells are found in:
(a) Heart (b) Lungs
(c) Liver (d) Spleen

37. Birbeck granules are present in:
(a) Merkel cell
(b) Langerhans cell
(c) Langhans cell
(d) Melanocyte

38. Macroglobulin is derived from:
(a) B cells (b) T cells
(c) Both (d) Natural killer cells

39. **Which of the following is not true regarding IgE antibodies?**
    (a) It mediates release of histamine and other chemical mediators
    (b) It is the primary antibody involved in allergic reactions
    (c) It is involved in anti-parasitic immune responses
    (d) May cross the placenta and fix complement

40. **Which of the following immunoglobulin does not fix complement?**
    (a) IgA (b) IgG
    (c) IgM (d) IgE

41. **B cells are located in which region of lymph nodes:**
    (a) Paracortical region
    (b) Cortical follicles
    (c) Medullar sinuses
    (d) Subcapsular region

42. **Plasma cells produce specific antibodies by**
    (a) Isotope switching
    (b) Class selection
    (c) Isotope selection
    (d) Clonal selection

43. **Surface Immunoglobulin is found in which cell?**
    (a) T-cell
    (b) B-cell
    (c) NK cell
    (d) Plasma cells

MHC

44. **MHC class III genes encode:** *(AI 2003)*
    (a) Complement component C3
    (b) Tumor necrosis factor
    (c) Interleukin 2
    (d) Beta 2 microglobulin

45. **The HLA class III region genes are important elements in:** *(AI 2003)*
    (a) Transplant rejection phenomenon
    (b) Governing susceptibility to autoimmune diseases
    (c) Immune surveillance
    (d) Antigen presentation and elimination

46. **HLA is located on:** *(AIIMS Nov 2009) (DNB 05,09)*
    (a) Long arm of chromosome 6
    (b) Long arm of chromosome 3
    (c) Short arm of chromosome 6
    (d) Short arm of chromosome 3

47. **HLA B27 is positive in:** *(AIIMS Nov 2009)*
    (a) Ankylosing spondylitis
    (b) Rheumatoid arthritis
    (c) SLE
    (d) Behçet syndrome

48. **Mixed lymphocyte culture is used to identify:** *(AIIMS Nov 2002)*
    (a) MHC class I antigen
    (b) MHC class II antigen
    (c) B lymphocytes
    (d) T helper cells

49. **HLA typing is useful in:** *(PGI June 2006)*
    (a) Disputed paternity
    (b) Thanatology
    (c) Organ transplant
    (d) Dactylography

50. **True about MHC-class II:** *(PGI June 2006)*
    (a) Not involved in innate immunity
    (b) Cytotoxic T-cell involved
    (c) Present in nucleated cells
    (d) Present in B-cells

51. **MHC-II positive cells are all except:** *(PGI Dec 2000)*
    (a) B cells (b) T cells
    (c) Macrophages (d) Platelets
    (e) RBCs

52. **True about MHC:** *(PGI June 2003)*
    (a) Transplantation reaction
    (b) Autoimmune disease
    (c) Immunosuppression
    (d) Involved in T-cell function
    (e) Situated at long arm of chromosome 6

MOST RECENT QUESTIONS

53. **Epitope binding floor of the MHC molecule consists of**
    (a) Alpha helices
    (b) Beta pleated structure
    (c) Alpha and beta-1 chain
    (d) Beta-2 microglobulin

54. **HLA B27 is not seen in which of the following?**
    (a) Ankylosing spondylitis
    (b) Reiter's syndrome
    (c) Rheumatoid arthritis
    (d) Psoriatic arthritis

55. **The role played by Major Histocompatibility Complex 1 and 2:**
    (a) Transduce the signal to T cells following antigen recognition
    (b) Mediate immunogenic class switching
    (c) Present antigens for recognition by T cell antigen receptors
    (d) Enhance the secretion of cytokines

56. **MHC class I are present on all except:** *(AIIMS Nov 2016)*
    (a) Platelets
    (b) All nucleated cells
    (c) RBCs
    (d) WBCs

57. **Major histocompatibility complex class I is seen on which of the following cell?**
(a) Macrophages only
(b) All body cells
(c) B cell only
(d) All blood cells except erythrocytes

58. **Antigen presented along with HLA class II stimulate**
(a) CD8 cell
(b) CD4 cell
(c) CD2 cell
(d) CD19 cell

59. **Which of the following is having a 90% association with HLA B27?**
(a) Ankylosing spondylitis
(b) Rheumatoid arthritis
(c) Psoriasis
(d) Reiter syndrome

60. **Which of the following is the function of MHC I and II?**
(a) Signal transduction in T cells
(b) Antibody class switching
(c) Antigen presentation to T cells
(d) Increase the secretion of cytokines

61. **Antigen presenting cells are all except:** *(AIIMS May 2016)*
(a) M-cells (b) Thymocytes
(c) Macrophages (d) Langerhans cells

62. **MHC-2 protein is present in all except:**
(a) Cortical macrophages
(b) Medullary macrophages
(c) Cortical epithelial cells
(d) Medullary epithelial cells

63. **HLA-Cw6 is associated with:**
(a) Myasthenia gravis
(b) Behcets disease
(c) Pemphigus vulgaris
(d) Psoriasis vulgaris

64. **HLA class II is linked with which of the following?**
(a) Graft rejection
(b) Graft versus host disease
(c) Killing of virus infected cells
(d) Susceptibility to autoimmune diseases

65. **HLA association with myasthenia gravis is:**
(a) HLA-B27
(b) HLA-B51
(c) HLA-B47
(d) HLA-B8

66. **HLA associated with pustular psoriasis is:**
(a) HLA CW6
(b) HLA B13
(c) HLA B27
(d) HLA B17

67. **To rule out rheumatoid arthritis, most important among the following is:**
(a) HLA DR8
(b) HLA DR4
(c) HLA DQ1
(d) HLA B27

HYPERSENSITIVITY REACTIONS

68. **What type of hypersensitivity reaction is seen in myasthenia gravis?** *(AI 2012)*
(a) Type 1 hypersensitivity reaction
(b) Type 2 hypersensitivity reaction
(c) Type 3 hypersensitivity reaction
(d) Type 4 hypersensitivity reaction

69. **Hemolytic disease of newborn is an example of:** *(DPG 2011)*
(a) Type 3 hypersensitivity reaction
(b) Type 2 hypersensitivity reaction
(c) Arthus reaction
(d) Type 4 hypersensitivity reaction

70. **Raji cell assays are used to quantitate:** *(DPG 2011)*
(a) Complement levels
(b) Immune complexes
(c) T cells
(d) Interferon levels

71. **Hypersensitivity pneumonitis is classically a/an:** *(AI 2009)*
(a) Allergic reaction
(b) Type II hypersensitivity
(c) Immune complex mediated hypersensitivity
(d) Cell mediated hypersensitivity

72. **The immunoglobulin involved in type I hypersensitivity reaction is:** *(AI 2007)*
(a) IgE
(b) IgM
(c) IgA
(d) IgG

73. **Arthus reaction is what type of hypersensitivity reaction:** *(AI 2007), (UP'03)*
(a) Localized immune complex
(b) Ag-Ab reaction
(c) Complement mediated
(d) Ab mediated

74. **A 40 year old man has chronic cough with fever for several months. The chest radiograph reveals a diffuse reticulonodular pattern. Microscopically on transbronchial biopsy there are focal areas of inflammation containing epithelioid cell granuloma, Langhans giant cells, and lymphocytes. These findings are typical for which of the following type of hypersensitivity immunologic responses:** *(AIIMS May 2003)*
(a) Type I
(b) Type II
(c) Type III
(d) Type IV

75. **Ram Devi presented with generalized edema sweating and flushing tachycardia and fever after bee sting. This is:** *(AIIMS Nov 2001)*
   (a) T cell mediated cytotoxicity
   (b) IgE mediated reaction
   (c) IgG mediated reaction
   (d) IgA mediated hypersensitivity reaction

76. **Example of Type IV Hypersensitivity is/are:**
   (a) Farmer's lung *(PGI June 2006)*
   (b) Contact hypersensitivity
   (c) Immediate hypersensitivity
   (d) Myasthenia gravis

77. **Example of Type II Hypersensitivity is/are:**
   (a) Blood transfusion reaction *(PGI June 2006)*
   (b) Arthus reaction
   (c) Hay Fever
   (d) Post-streptococcal glomerulonephritis

78. **Which of the following diseases is/are mediated through complement activation:** *(PGI Dec 03)*
   (a) Atopic dermatitis
   (b) Graft versus Host disease
   (c) Photoallergy
   (d) Necrotizing vasculitis
   (e) Urticaria

79. **Which of following statements is not true about Mycobacterium tuberculosis infection?** *(Delhi PG 2009 RP)*
   (a) M. tuberculosis leads to development of delayed hypersensitivity
   (b) Lymphocytes are the primary cells infected by M. tuberculosis
   (c) Positive tuberculin test signifies cell mediated hypersensitivity
   (d) Tuberculin test does not differentiate between infection and disease.

MOST RECENT QUESTIONS

80. **A man after consuming sea food develops rashes. It is due to:**
   (a) IgE mediated response
   (b) Complement activation
   (c) Cell mediated response
   (d) None of the above

81. **Granuloma in Sarcoidosis is called**
   (a) Hard sore
   (b) Soft sore
   (c) Hard tubercle
   (d) Caseating granuloma

82. **Myasthenia gravis may be associated with**
   (a) Thymoma
   (b) Systemic lupus erythematosus
   (c) Hyperthyroidism
   (d) All of the above

83. **Which of the following type of hypersensitivity reaction is found in blood transfusion reaction?**
   (a) Anaphylactic type
   (b) Cytotoxic type
   (c) Type III hypersensitivity
   (d) Cell mediated hypersensitivity

84. **Which of the following type of hypersensitivity reactions occurs in Farmer's lung?**
   (a) Type I (b) Type II
   (c) Type III (d) Type IV

85. **Tuberculin test positivity indicates:**
   (a) Good humoral immunity
   (b) Infection with mycobacterium
   (c) Good cell mediated immunity
   (d) None

86. **Cell mediated immunity is:**
   (a) Type I
   (b) Type II
   (c) Type III
   (d) Type IV

87. **Antibody found in patients with myasthenia gravis is directed against**
   (a) Acetylcholine
   (b) Acetylcholine receptors
   (c) Acetylcholine vesicles in nerve terminal
   (d) Actin-myosin complex of the muscle

88. **Myasthenia gravis is most commonly associated with which of the following?**
   (a) Thymoma
   (b) Thymic carcinoma
   (c) Thymic hyperplasia
   (d) Lymphoma

89. **Patient has been given penicillin 48 hours ago, with no history of drug allergy. Now he develops wheeze and hemolysis. Antibody for penicillin is positive. Type of hypersensitivity is which of the following:**
   (a) Type I (b) Type II
   (c) Type III (d) Type IV

90. **IgE receptors are present on:**
   (a) Mast cells
   (b) NK cells
   (c) B cells
   (d) Histiocytes

91. **A 45-year-old patient presents with history of fever, night sweats and weight loss. On X-ray a mass in apical lobe of lung is seen. On histopathology it was found to have caseous necrosis. What is the likely underlying process involved?**
   (a) Enzymatic degeneration
   (b) Hypersensitivity reaction with modified macrophages, lymphocytes and giant cells
   (c) Acute decrease in blood supply
   (d) Decreased supply of growth factors

92. **Serum sickness is:** *(AIIMS May 2016)*
(a) Type 1 Hypersensitivity reaction
(b) Type 2 Hypersensitivity reaction
(c) Type 3 Hypersensitivity reaction
(d) Type 4 Hypersensitivity reaction

93. **Which of the following is true about serum sickness ?**
(a) Type -2 hypersenstivity
(b) Can lead to leukocytoclastic vasculitis
(c) Hypercomplementenemia
(d) Can occue due to homologus antigen

94. **Centre of tubercular granuloma is formed by:**
(a) T-lymphocytes
(b) B-lymphocytes
(c) Langhan's giant cells
(d) Necrotic zone

TRANSPLANT REJECTION, GVHD

95. **Hyperacute rejection is due to** *(AIIMS Nov 2012)*
(a) Preformed antibodies
(b) Cytotoxic T-lymphocyte mediated injury
(c) Circulating macrophage mediated injury
(d) Endothelitis caused by donor antibodies

96. **All are affected in Graft-Versus host reaction:**
(a) Skin (b) GIT *(AIIMS May 2007)*
(c) Liver (d) Lung

97. **Preformed antibodies cause:** *(PGI June 2006)*
(a) Hyperacute rejection
(b) Acute rejection
(c) Chronic rejection
(d) Acute humoral rejection

98. **True about graft versus host disease is:** *(PGI Dec 2005)*
(a) Associated with solid organ transplantation
(b) Graft must contains immunocompetent T cell
(c) It is seen in immunosuppressed persons
(d) Also called as Runt disease in animals

99. **Acute humoral renal transplant rejection is characterized by the following, except:** *(Delhi PG 2009 RP)*
(a) Presence of anti-donor antibodies
(b) Interstitial and tubular mononuclear cell infiltrate
(c) Necrotizing vasculitis
(d) Acute cortical necrosis

100. **Transfer of the graft of different species are called as:**
(a) Isograft *(UP 2002)*
(b) Allograft
(c) Homograft
(d) Xenograft

101. **Acute graft versus host disease reaction occurs in all except:** *(UP 2007)*
(a) Liver (b) Adrenal
(c) Gut (d) Skin

MOST RECENT QUESTIONS

102. **Principal cause of death in renal transplant patient is:**
(a) Uraemia (b) Malignancy
(c) Rejection (d) Infection

103. **Preformed antibodies cause:**
(a) Hyperacute rejection
(b) Acute rejection
(c) Chronic rejection
(d) Acute humoral rejection

104. **Which of these complement factor is a marker of humoral rejection?** *(AIIMS May 2016)*
(a) C3d (b) C5a
(c) C3b (d) C4d

105. **Method of prevention of GVHD in bone marrow transplantation is:**
(a) T-cell removal
(b) Prior immune suppression
(c) Post procedure immune suppression
(d) All of the above

106. **True about adult autologous stem cell transplant are all except:**
(a) Used in the treatment of leukemia
(b) Stem cells are collected directly from the bone marrow
(c) G-CSF is given to expand the number of stem cells
(d) It allows high dose of chemotherapy

107. **Number of criteria for HLA matching are:**
(a) 10 (b) 4
(c) 16 (d) 22

108. **The commonest type of graft rejection is:**
(a) Hyperacute rejection
(b) Acute rejection
(c) Chronic rejection
(d) All are equal in incidence

109. **Organ with least chance of rejection is:**
(a) Blood
(b) Liver
(c) Kidney
(d) Heart

110. **Runt disease is associated with:**
(a) Acute rejection
(b) Hyperacute rejection
(c) Chronic rejection
(d) Graft versus host disease

111. **Prior immune suppression is not helpful in which type of graft rejection:**
(a) Acute rejection
(b) Hyperacute rejection
(c) Chronic rejection
(d) None of the above

112. Which of the following is true about GVHD?
(a) Occurs when host is immunocompetent
(b) Occurs when donor cells are immunocompetent
(c) Most common organ involved is lung
(d) Most common in renal transplant

113. Microcytotoxicity is used for:
(a) Tissue typing
(b) Drug allergy
(c) Infection Susceptibility
(d) Substance toxicity

114. Acute graft rejection occurs within:
(a) 3 hours (b) 3 days
(c) 3 months (d) 3 years

AUTOIMMUNE AND IMMUNODEFICIENCY DISEASES

115. Autoimmunity in EBV infection is the result of: *(AI 2012)*
(a) Molecular mimicry
(b) Polyclonal B cell activation
(c) Expressing sequestrated antigens
(d) Antigenic cross reactivity

116. A 14 yrs old girl on exposure to cold has pallor of extremities followed by pain and cyanosis. In later ages of life she is prone to develop? *(AIIMS May 2011)*
(a) Systemic lupus erythematosus
(b) Scleroderma
(c) Rheumatoid arthritis
(d) Histiocytosis

117. Which is not autoimmune disease? *(AI 2011)*
(a) Systemic Lupus Erythematosus
(b) Grave's Disease
(c) Myasthenia Gravis
(d) Sickle Cell Disease

118. Which among the following is seen in antiphospholipid antibody syndrome? *(AI 2011)*
(a) Beta 2 microglobulin antibody
(b) Anti nuclear antibody
(c) Anti centromere antibody
(d) Anti glycoprotein antibody

119. Necrotizing lymphadenitis is seen in: *(AI 2011)*
(a) Kimura disease
(b) Kikuchi Fujimoto disease
(c) Hodgkin disease
(d) Castelman disease

120. Wire loop lesions are seen in: *(DPG 2011)*
(a) SLE
(b) Diabetic nephropathy
(c) Benign nephrosclerosis
(d) Wegener's granulomatosis

121. Tissue from rat used for detection of antinuclear antibodies? *(AIIMS Nov 2009)*
(a) Kidney (b) Brain
(c) Stomach (d) Liver

122. Which is not found in CNS in a case of AIDS? *(AIIMS May 2009)*
(a) Perivascular giant cell
(b) Vacuolization
(c) Inclusion bodies
(d) Microglial nodule

123. A person present with recurrent swelling on face and lips due to emotional stress. Likely cause is: *(AIIMS May 2009)*
(a) C1 esterase inhibitor deficiency
(b) Allergy
(c) Anaphylaxis
(d) None of the above

124. All of the following statements are true about Wiskott Aldrich syndrome except: *(AIIMS Nov 2008)*
(a) It is an autosomal recessive disorder
(b) There is failure of aggregation of platelets in response to agonists
(c) Thrombocytopenia is seen
(d) Patient presents with eczema

125. Hematoxylin bodies seen in: *(AIIMS May 2008)*
(a) SLE
(b) PAN
(c) Rheumatoid arthritis
(d) Wegener's granulomatosis

126. Wire loop lesions are often characteristic for the following class of lupus nephritis: *(AIIMS May 2004)*
(a) Mesangial proliferative glomerulonephritis (WHO class II)
(b) Focal proliferative glomerulonephritis (WHO class III)
(c) Diffuse proliferative glomerulonephritis (WHO class IV)
(d) Membranous glomerulonephritis (WHO class V)

127. A renal biopsy from a 56 year old woman with progressive renal failure for the past 3 years shows glomerular and vascular deposition of pink amorphous material. It shows apple-green birefringence under polarized light after Congo red staining. These deposits are positive for lambda light chains. The person is most likely to suffer from: *(AIIMS May 2003)*
(a) Rheumatoid arthritis
(b) Tuberculosis
(c) Systemic lupus erythematosus
(d) Multiple myeloma

128. A young lady presented with bilateral nodular lesions on shins. She was also found to have bi-lateral hilar lymphadenopathy on chest X-ray. Mantoux test reveals indurations of 5 mms. Skin biopsy would reveal: *(AIIMS May 2002)*
(a) Non caseating granuloma
(b) Vasculitis
(c) Caseating granuloma
(d) Malignant cells

129. Anti ds-DNA antibodies are commonly seen in: *(PGI June 01)*
(a) SLE
(b) Scleroderma
(c) PAN
(d) Dermatomyositis
(e) Rheumatoid arthritis

130. Low complement levels seen in: *(PGI Dec 2006)*
(a) PSGN
(b) MPGN
(c) Good pasture's syndrome
(d) Wegner's granulomatosis
(e) Infective endocarditis.

131. Which is seen in Chediak-Higashi syndrome?
(a) Leucocytosis *(PGI Dec 2001)*
(b) Neutropenia
(c) Defective microbial killing
(d) Presence of large granules in neutrophil
(e) Immunodeficiency

132. Adenosine deaminase deficiency is seen in:
(a) Severe combined immunodeficiency *(PGI Dec 2003)*
(b) Wiskott Aldrich Syndrome
(c) Agammaglobulinemia as HIV

133. True about alpha-1 antitrypsin deficiency, is/are:
(a) Autosomal dominant *(PGI June 01)*
(b) Pulmonary emphysema
(c) Diastase resistant hepatic cells
(d) Hepatic cells are orcein stain positive
(e) Associated with berry aneurysm

134. All are true regarding Hyper IgE syndrome except: *(Delhi PG 2009)*
(a) Inheritance is as a single locus autosomal dominant trait with variable expression
(b) Coarse facial features
(c) Recurrent staphylococcal abscesses involving skin, lungs
(d) High serum IgE with low IgG, IgA and IgM

135. All are true about Wiskott-Aldrich Syndrome except:
(a) Bloody diarrhea during infancy *(Delhi PG 2009)*
(b) Low IgM and elevated IgA and IgE
(c) Large size platelets
(d) Atopic dermatitis

136. Diagnosis of X linked Agammaglobulinemia should be suspected if: *(Delhi PG 2009)*
(a) Absent tonsils and no palpable lymph nodes on physical examination
(b) Female sex
(c) High isohemagglutinins titers
(d) Low CD3

137. Which of the following cell types is not a target for initiation and maintenance of HIV infection? *(Delhi PG 2009 RP)*
(a) CD4 T cell (b) Macrophage
(c) Dendritic cell (d) Neutrophil

138. All of the following are found in SLE except: *(Delhi PG-2006)*
(a) Oral ulcers
(b) Psychosis
(c) Discoid rash
(d) Leucocytosis

139. Which of the following immunoglobulin is absent in Ataxia telangiectasia: *(Delhi PG-2005)*
(a) IgG (b) IgM
(c) IgA (d) IgD

140. Scl-70 antibody is characteristic of:
(a) Systemic lupus erythematosus *(Karnataka 2007)*
(b) Scleroderma
(c) Dermatomyositis
(d) Sjogren's syndrome

141. LE cell phenomenon is seen in: *(Karnataka 2005)*
(a) Lymphocyte
(b) Neutrophil
(c) Monocyte
(d) Eosinophil

142. Most sensitive test for screening of "Systemic Lupus Erythematosus" (SLE) is: *(Karnataka 2005, RJ 2002)*
(a) LE phenomenon
(b) Rheumatoid factor
(c) Anti-nuclear factor (ANF)
(d) Double stranded DNA test

143. According to WHO, the feature of class II lupus is:
(a) Transient proteinuria *(UP 2000)*
(b) Massive proteinuria
(c) Hematuria
(d) RBC casts

144. ANCA antibody with peripheral rim distribution is indicative of: *(UP 2000)*
(a) Antihistone antibody
(b) Anti smith antibody
(c) Anti double stranded DNA antibody
(d) Anti double stranded RNA antibody

145. Basic pathology in cystic fibrosis is: *(UP 2001)*
(a) Defect in the transport of chloride across epithelia
(b) Defect in the transport of sodium across epithelia
(c) Defect in the transport of potassium across epithelia
(d) Defect in the transport of bicarbonate across epithelia

146. Besbuer Boeck Schaumann disease is also called as: *(UP 2003)*
(a) Sarcoidosis
(b) Crohn's disease
(c) Whipple's disease
(d) Hodgkin's disease

147. Most common viral antigen used for diagnosis of HIV in blood before transfusion is: *(UP 2005)*
(a) p24 (b) p17
(c) p7 (d) p14

148. Most common vascular tumor in AIDS patients is:
(a) Kaposi 's sarcoma *(UP 2000) (UP 2007)*
(b) Angiosarcoma
(c) Lymphangioma
(d) Lymphoma

149. **Which in not an autoimmune disease?** *(RJ 2001)*
(a) Syphilis
(b) SLE
(c) Systemic sclerosis
(d) RA

150. **Bilateral parotid gland enlargement is seen in all except:** *(RJ 2001)*
(a) Sarcoidosis
(b) Sjogren's syndrome
(c) SLE
(d) Viral infections

151. **Sarcoidosis does not involve** *(RJ 2004)*
(a) Brain (b) Heart
(c) Lung (d) Kidney

152. **Characteristic of SLE of kidney is:** *(RJ 2004, Jharkhand 05)*
(a) Focal sclerosis
(b) Focal necrosis
(c) Wire loop lesions
(d) Diffuse glomerulosclerosis

153. **Libman-Sacks endocarditis is seen in:** *(AP 2001)*
(a) Rheumatoid arthritis
(b) SLE
(c) Infective endocarditis
(d) Nonbacterial thrombotic endocarditis

154. **Chediak-Higashi syndrome is due to defect in:** *(Kolkata 2003)*
(a) Opsonisation
(b) Chemotaxis
(c) LAD
(d) Extracellular microbicidal killing

MOST RECENT QUESTIONS

155. **Anti-double stranded DNA is highly specific for:**
(a) Systemic sclerosis
(b) SLE
(c) Polymyositis
(d) Rheumatic sclerosis

156. **Anti-topoisomerase I is marker of:**
(a) Systemic sclerosis
(b) Classic polyarteritis nodosa
(c) Nephrotic syndrome
(d) Rheumatoid arthritis

157. **An 8-year-old boy presents with sarcoidosis. Which of the following is correct?**
(a) Hilar lymphadenopathy with perihilar calcification
(b) Basal infiltrates
(c) Rubbery lymph nodes
(d) Egg-shell-calcification

158. **Most common site for lymphoma in AIDS patients is:**
(a) CNS lesions (b) Spleen
(c) Thymus (d) Abdomen

159. **All are true about histological features of Kaposi's sarcoma except:**
(a) Microscopically lesion similar to granulation tissue
(b) Dilated and irregular blood vessels with interspersed infiltrate of lymphocyte and plasma cells
(c) Atypical blood vessels have solid spindle cell appearance
(d) Nodule is the initial lesion of Kaposi's sarcoma

160. **HIV affects which of the following most commonly?**
(a) Helper cells (b) Suppressor cell
(c) RBCs (d) Platelets

161. **Which of the following lesions/conditions shows most specific anatomic changes in HIV infection?**
(a) Lymph nodes
(b) Opportunistic infections
(c) CNS lesions
(d) Kaposi's sarcoma (blood vessels)

162. **Which of the following autoantibody is least likely associated with SLE?**
(a) Anti ds DNA
(b) Anti Sm
(c) Anti topoisomerase
(d) Anti histone

163. **Which of the following autoantibody is specific for SLE?**
(a) ds DNA
(b) Anti RO
(c) Anticentromere
(d) Anti topoisomerase

164. **Regarding severe combined immunodeficiency disease, which of the following statement is true?**
(a) Adenosine deaminase deficiency
(b) Decreased circulating lymphocytes
(c) NADPH oxidase deficiency
(d) C1 esterase deficiency

165. **Which of the following is a finding in lymphoid tissues in individuals with common variable hypogammaglobulinemia?**
(a) Decreased B cell count
(b) Increased B cell count
(c) Normal B cell count
(d) Absent B cells

166. **Thymic hypoplasia is seen in which of the following?**
(a) Wiskott-Aldrich syndrome
(b) Digeorge syndrome
(c) IgA deficiency
(d) Agammaglobulinemia

167. **Onion peel appearance of splenic capsule is seen in:**
(a) SLE
(b) Scleroderma
(c) Rheumatoid arthritis
(d) Sjogren syndrome

68. **Following is not a feature of AIDS related lymphadenopathy:**
(a) Florid reactive hyperplasia
(b) Follicle lysis
(c) Haematoxylin bodies
(d) Collection of monocytoid B – Cells in sinuses

169. **Most common CNS neoplasm in HIV patient is:**
(a) Meduloblastoma
(b) Astrocytoma
(c) Primary CNS lymphoma
(d) Ependymoma

170. **A false negative tuberculin reaction may be obtained in all of the following situations except:**
(a) Children previously tested with tuberculin test
(b) Post – measles test
(c) Corticosteroid therapy
(d) Miliary tuberculosis

171. **Risk of HIV transmission is not seen with:**
(a) Whole blood
(b) Platelets
(c) Plasma derived Hepatitis B vaccine
(d) Leucocytes

172. **All of the following methods are used for the diagnosis of HIV infection in a 2 months old child, except:**
(a) DNA –PCR (b) Viral culture
(c) HIV ELISA (d) P 24 antigen assay

173. **Mantoux test reading of less than 5 mm indicates:**
(a) Tuberculous infections
(b) Disseminated TB
(c) Susceptibility to TB
(d) Immunity to TB

174. **Epitope spreading refers to:**
(a) A type of mechanism of spread of malignant tumors
(b) One type of mechanism of HIV dissemination
(c) A mechanism for the persistence and evolution of autoimmune disease
(d) One of the mechanisms of apoptosis

175. **Heerfordt's syndrome consists of fever, parotid enlargement, facial palsy and**
(a) Arthralgia
(b) Bilateral hilar adenopathy
(c) Erythema nodosum
(d) Anterior uveitis

176. **HIV affects CD4 cells by which protein?**
(a) Gp 120 (b) Gp 41
(c) CCR5 (d) CXCR4

177. **Treatment for Asymptomatic HIV is done when CD4 count is below**
(a) 200 (b) 350
(c) 400 (d) 500

178. **The poly-arthritic condition that is NOT common in males**
(a) Gout
(b) Psoriatic arthritis
(c) Ankylosing spondylitis
(d) Systemic lupus erythematosus

179. **Hodgkins lymphoma caused for by:**
(a) EBV (b) CMV
(c) HHV6 (d) HHV8

180. **Which of these is an immune-privileged site?**
(a) Area postrema (b) Loop of Henle
(c) Optic nerve (d) Seminiferous tubules

181. **Which of the following is not an autoimmune disorder?**
(a) Ulcerative colitis
(b) Grave's disease
(c) Rheumatoid arthritis
(d) SLE

182. **Autoimmunity is caused by all except:**
(a) Infections
(b) Expression of cryptic antigens
(c) Negative selection of T- cells in the thymus
(d) Inappropriate expression of the MHC proteins

183. **Which of the following is not seen in SLE affected kidneys?**
(a) Focal glomerulonephritis
(b) Diffuse glomerulonephritis
(c) Membranous glomerulonephritis
(d) Lipoid nephrosis

184. **Anti RO (SSA) antibodies are seen in:**
(a) Systemic sclerosis
(b) Subacute cutaneous lupus
(c) Myasthenia gravis
(d) Mixed connective tissue disorder

AMYLOIDOSIS

185. **Secondary amyloidosis is associated with:** *(AI 2012)*
(a) Aβ (b) AL
(c) AA (d) APrP

186. **A 60 year old female is suffering from renal failure and is on hemodialysis since last 8 years. She developed carpal tunnel syndrome. Which of the following finding will be associated?** *(AIIMS Nov 2011)*
(a) AL
(b) AA
(c) ATTR
(d) β_2 microglobulin

187. **The best investigation for the diagnosis of amyloidosis is:** *(AIIMS May 2010)*
(a) Colonoscopy
(b) Rectal biopsy
(c) Upper GI endoscopy
(d) CT scan

188. **Which type of amyloidosis is caused by mutations in transthyretin gene?** *(DPG 2011, AI 2005)*
(a) Familial Mediterranean fever
(b) Familial amyloidosis polyneuropathy
(c) Dialysis associated amyloidosis
(d) Prion protein associated amyloidosis

189. **In Hemodialysis associated amyloidosis, which of the following is seen:** *(AI 2008)*
(a) Transthyretin
(b) β_2 Microglobulin
(c) SAA
(c) α_2 Microglobulin

190. **Bone marrow in AL amyloidosis shows:**
(a) Bone marrow plasmacytosis *(AI 2007)*
(b) Granulomatous reaction
(c) Fibrosis
(d) Giant cell formation

191. **A diabetic patient is undergoing dialysis. Aspiration done around the knee joint would show:**
(a) A beta 2 microglobulin *(AI 2007)*
(b) AA
(c) AL
(d) Lactoferin

192. **What is the best method for confirming amyloidosis?**
(a) Colonoscopy *(AI 2007)*
(b) Sigmoidoscopy
(c) Rectal biopsy
(d) Tongue biopsy

193. **Neointimal hyperplasia causes vascular graft failure as a result of hypertrophy of:** *(AI 2006)*
(a) Endothelial cells
(b) Collagen fibers
(c) Smooth muscle cells
(d) Elastic fibers

194. **Which one of the following stains is specific for Amyloid?** *(AI 2005)*
(a) Periodic Acid Schiff (PAS)
(b) Alizarin red
(c) Congo red
(d) Von-Kossa

195. **In amyloidosis Beta pleated sheet will be seen in:**
(a) X-ray crystallography *(AIIMS Nov 2006)*
(b) Electron microscope
(c) Spiral electron microscope
(d) Congo red stain

196. **A 50-year-old presented with signs and symptoms of restrictive heart disease. A right ventricular endomyocardial biopsy revealed deposition of extracellular eosinophilic hyaline material. On transmission electron microscopy, this material is most likely to reveal the presence of:** *(AIIMS May 2006)*
(a) Nonbranching filaments of indefinite length
(b) Cross banded fibers with 67 m periodicity
(c) Weibel Palade bodies
(d) Concentric whorls of lamellar structures

197. **Amyloid deposits stain positively with all of the following except:** *(AIIMS May 2006)*
(a) Congo-red
(b) Crystal violet
(c) Methanamine silver
(d) Thioflavin T

198. **On electron microscopy amyloid characteristically exhibits:**
(a) Beta-pleated sheat *(AIIMS Nov 2005)*
(b) Hyaline globules
(c) 7.5-10 nm fibrils
(d) 20-25 nm fibrils

199. **Familial amyloidotic polyneuropathy is due to amyloidosis of nerves caused by deposition of:**
(a) Amyloid associated protein *(AIIMS Nov 2002)*
(b) Mutant calcitonin
(c) Mutant transthyretin
(d) Normal transthyretin

200. **Lardaceous spleen is due to deposition of amyloid in:**
(a) Sinusoids of red pulp *(AIIMS Nov 2002)*
(b) White pulp
(c) Pencillary artery
(d) Splenic trabeculae

201. **What are the stains used for Amyloid?** *(PGI Dec 2007)*
(a) Thioflavin
(b) Congo red
(c) Eosin
(d) Auramine
(e) Rhodamine

202. **Gingival biopsy is useful in the diagnosis of:**
(a) Sarcoidosis *(Delhi PG 2010)*
(b) Amyloidosis
(c) Histoplasmosis
(d) Scurvy

203. **Amyloid is:** *(UP 2000)*
(a) Mucopolysaccharide
(b) Lipoprotein
(c) Glycoprotein
(d) Intermediate filament

MOST RECENT QUESTIONS

204. **Serum amyloid associated protein is found in:**
(a) Alzheimer's disease
(b) Chronic inflammatory states
(c) Chronic renal failure
(d) Malignant hypertension

205. **Most common site of biopsy in amyloidosis:**
(a) Liver
(b) Spleen
(c) Kidney
(d) Lung

206. Correctly matched pairs in amyloidosis are:
(a) Multiple myeloma - light chain
(b) Chronic inflammation - AA
(c) Cardiac - ATTR
(d) Neural – Beta-2 microglobulin

207. A diabetic patient is undergoing dialysis. Aspiration done around the knee joint would show:
(a) A-β_2 Microglobulin
(b) AA
(c) AL
(d) Lactoferrin

208. Amyloidosis is most commonly seen in:
(a) Maturity onset DM
(b) Type 1 DM
(c) Type 2 DM
(d) Equally seen with all forms of DM

209. Which of the following is the most serious organ involvement in amyloidosis?
(a) Cardiac tissue
(b) Renal tissue
(c) Splenic tissue
(d) Hepatic tissue

210. Which type of Amyloidosis is caused by mutation of the transthyretin protein?
(a) Familial Mediterranean fever
(b) Familial amyloidotic polyneuropathy
(c) Dialysis associated amyloidosis
(d) Prion protein associated amyloidosis

211. Cause of death in amyloidosis involving kidney:
(a) Cardiac failure
(b) Renal failure
(c) Sepsis
(d) Liver failure

212. Secondary amyloidosis complicates which of the following:
(a) Pneumonia
(b) Chronic glomerulonephritis
(c) Irritable bowel syndrome
(d) Chronic osteomyelitis

213. On Congo- red staining, amyloid is seen as:
(a) Dark brown color
(b) Blue color
(c) Brilliant pink color
(d) Khaki color

214. Lardaceous spleen is due to deposition of amyloid in:
(a) Sinusoids of red pulp
(b) White pulp
(c) Pencillary artery
(d) Splenic trabeculae

215. Which of the following is the chemical nature of Hemodialysis associated with amyloid?
(a) AA
(b) AL
(c) Beta – 2-microglobulin
(d) ATTR

216. Familial amyloidosis is seen in:
(a) Alzheimer's disease
(b) Senile cardiac amyloidosis
(c) Renal amyloidosis
(d) Splenic amyloidosis

217. Excessive accumulation of which hormone protein causes organ dysfunction:
(a) Growth hormone
(b) Prolactin
(c) Calcitonin
(d) Parathormone

218. Serum amyloid associated protein is increased in:
(a) Alzheimer's disease
(b) Ankylosing spondylitis
(c) Chronic renal failure
(d) Malignant hypertension

Explanations

1. **Ans. (c) Positive selection during development**
(Ref: Immunology by SK Gupta 1st/142-150, Robbins 8th/209)

This appeared to be a tough question but let us analyze all the options step wise.

- Both B cells and T cells have antigen specific receptors. T cells have an antigen specific T cell receptor (TCR) composed of α and β polypeptide chains in 95% cases to bind with the antigen. B cells have a B cell receptor (BCR) having unique antigen specificity composed of IgM and IgD on their surface to bind with the antigen.
- Since **MHC I** is expressed on **all the nucleated cells**, so, it is likely to be present on both 'B' as well as 'T' cells.

As discussed in our accompanying DVD on Immunology, the T cells undergo both negative and positive selection. Both these are described below:

- **Positive selection:** T cells in the ***thymic cortex*** are allowed to survive only if their T cell receptor has affinity for the MHC molecule. If the T cells do not have any affinity for the MHC molecule, they are programmed to die. This is important because only if this affinity is present, the T cells can interact with the antigen presenting cells. So, positive selection is required for **self MHC restriction**.
- **Negative selection:** T cells come in the ***thymic medulla*** after being already positively selected in the thymic cortex. In the medulla, if a T cell has affinity for 'self antigens', they are eliminated. This is called as negative selection. It is therefore required for the **self tolerance**.
- Similar to the negative selection of the T cells, the B cells may also recognize *'self antigens'* in the bone marrow. In this situation, the B cell undergoes antigen receptor gene rearrangement so as to express new antigen receptors. These new receptors are designed as to not recognize 'self antigens'. This process is described as '**receptor editing**'. If because of any reason receptor editing does not take place, the B cells undergo apoptosis. This is the **negative selection of B cells** in the **bone marrow**.

Thus, it can be concluded that **both T and B cells undergo negative selection** but ***only the T cells undergo positive selection***.

2. **Ans. None** *(Ref: Robbins 8th/194-5, 9/e 198)*

It is recommended to go through the chapter review for the best understanding of this question. However, I would try to summarize the important points as follows;

Option 'a' and 'd'....CD4 is present on helper T cell and is required for antibody production because it is interacts with B cells for causing activation, conversion into plasma cells and antibody production. The antibody IgG is required for opsonisation (making the bacteria coated for preferential killing).

Option 'b'....Helper T cell subtype 1 is responsible for the secretion of cytokines like IFN-γ and IL-2 which cause naïve T cells to get converted into cytotoxic T cells.

Option 'c'....CD 4 is also important for the following:

- B cell mitogen[Q]
- Required for isotype switching[Q].
- Affinity maturation[Q]
- Presence of memory in immune cells[Q]

So, the answer is none in this question.

3. **Ans. (b) Distal domain alfa 1 and 2**
(Ref: Robbins 8th/190-191, 9/e 195 see tex

The antigen binding cleft is made up α_1 **and** α_2 chains of **MHC I** molecule which is ***structurally the distal domain of these chains....Kuby immunology.***

4. **Ans. (b) Immunoglobulin production**
(Ref: Robbins 8th/186-187, 9/e 190-191)

- On antigenic stimulation, the **naïve helper T cells** get differentiated into either **effector cells or memory cells**. The T helper cells can be of two types (either TH1 or TH2 cells).
- The **TH1** cells can secrete cytokines like **IL-2 and IFN-γ** which cause **activation of macrophages** and cause **activation of CD8+T** cells **into cytotoxic** T cells.
- The **TH2** cell can **secrete IL-4 and IL-5** which cause **B cell proliferation and differentiation** into plasma cells which **secrete antibodies** or immunoglobulins.
- So, we need to understand that the ***helper T cells is only helping in the production of immunoglobulins by plasma cells (they themselves don't produce antibodies).***

5. **Ans. (b) Binds to the beta chain of TCR and MHC class II molecules of APC stimulating T cell activation**
(Ref: Harrison 16th/1920)

6. **Ans. (d) CD45RO** *(Ref: Harrison 17th/2021)*
CD 45 is called as Leukocyte common antigen (LCA)[Q]

Location of cell	Molecular marker
All leucocytes	CD45 and CD45RB
Medullary thymocytes **('Naive' T- cells)**	CD45 RA and CD45RC
Cortical thymocytes **(Memory T-cells)**	CD45RO

7. **Ans. (c) They are MHC restricted cytotoxic cells** *(Ref: Harrison's 17th/2024-2028, 9/e 192)*

***NK cells are unique** as they are capable of MHC – unrestricted[Q] **direct cell lysis** which is not mediated by an immune response[Q]

8. **Ans. (c) Effective against virus infected cells** *(Ref: Harrison 17th/2024 – 2028, 9/e 192)*

9. **Ans. (d) Graft rejection** *(Ref: Robbins 9/e 231-233)*
- CD8+ cytotoxic T lymphocytes (CTLs) recognize cell-bound antigens only in association with class I MHC molecules, so, CD8+ T cells are said to be *class I MHC-restricted.*
- CD4+ T cells can recognize antigens only in the context of self-class II MHC molecules; they are referred to as *class II MHC-restricted.*

So, killing of viruses by cytotoxic cells, killing of bacteria by helper cells and T cell activation in autoimmunity all require MHC molecules for their normal function.

- Talking now about option 'D' i.e. graft rejection;

Rejection is a complex process in which both cell-mediated immunity and circulating antibodies play a role. T cell-mediated graft rejection is called *cellular rejection*, and it is induced by two mechanisms: destruction of graft cells by CD8+ CTLs and delayed hypersensitivity reactions triggered by activated CD4+ helper cells. Both these as discussed above would require MHC molecules.
Antibodies evoked against alloantigens in the graft can also mediate rejection. This process is called *humoral rejection.* It can be of two types

1. Hyperacute rejection occurs when preformed anti-donor antibodies are present in the circulation of the recipient
2. In recipients not previously sensitized to trans-plantation antigens, exposure to the class I and class II HLA antigens of the donor may evoke antibodies which are usually formed against graft vasculature.

So, Humoral graft rejection does not involve T-cells and is **NOT** MHC restricted.

10. **Ans. (a) Mature dendritic cell** *(Ref: Robbins 9/e 191)*

11. **Ans. (b) Cells which are not able to express MHC 1** *(Ref: Robbins 7th/201, 8th/188, 9/e 192)*
- The **NK cells express activating and inhibitory receptors**. The functional activity of the NK cells is regulated by a balance between signals from these receptors. Normal cells are not killed because inhibitory signals from normal MHC class I molecules override activating signals. **The ability of NK cells to kill target cells is inversely related to target cell expression of MHC class I molecules**[Q]. If virus infection or neoplastic transformation disturbs or reduces the expression of class I MHC molecules, inhibitory signals delivered to NK cells are interrupted and lysis occurs.

12. **Ans. (c) Transcription of nuclear factor mediated by NF-κβ which recruits cytokines** *(Ref: Robbins 9/e 187)*
The Toll-like receptors are **membrane proteins** that recognize a variety of ***microbe-derived molecules*** and stimulate innate immune responses against the microbes. These derive there name due to homology to a *Drosophila* protein called 'Toll'. The Toll-like receptors are expressed on many immune cells of the body. *Signaling by Toll-like receptors results in the activation of transcription factors, notably NF-κB and AP-1.*

13. **Ans. (a) IL-2** *(Ref: Robbins 7th/198, 8th/195, 9/e 198)*
T-helper cells can be divided in three distinct types on the basis of **different cytokines they produce.**

- **T-helper – 1 (TH1) secretes:** *IL-2 and interferon γ, these cells are important for type IV hypersensitivity*
- **T-helper– 2 (TH2) secretes:** *IL-4, IL-5, these cells are* important for type I hypersensitivity reaction.
- **TH 17 Cells:** Secrete IL-17, IL-22, these cells provide defense against extracellular bacteria and fungi.

14. **Ans. (a) Apoptosis** *(Ref: Robbins 9/e 56)*

15. **Ans. (b) Interleukin IL – 8** *(Ref: Robbins 9/e 87)*

16. **Ans. (b) IgM** *(Ref: Harrison, 17th/2036)*

17. **Ans. (b) Endothelial cells (c) Epithelial cells and (d) Langerhan's cells** *(Ref: Robbins Illustrated 9/e 195)*
As already discussed in the text also, the antigen presenting cells include macrophages, Dendritic Cells (found in lymphoid organs) and Langerhans' cells (found in epidermis). The question ideally should have been …with 'all except'

18. **Ans. (a) Langerhan's cell; (b) Macrophages; (e) B-lymphocyte** *(Ref: Robbins 7th/197, 9/e 195)*
Antigen presenting cells are: B-cell, Langerhan's cell in skin, Macrophages

19. **Ans. (a) Cytotoxic T cells:** *(Ref: Robbins 9/e p210)*
- Perforins are hole forming proteins synthesized by cytotoxic T-cells. They can perforate the plasma membrane of the target cells that are under attack by CD8+ lymphocytes. Granzymes are delivered into the target cells through these holes formed by perforins. In addition the perforin pores allow water to enter the cells, thus causing osmotic lysis.

20. **Ans. (a) B_7 and CD_{28};**
(Ref: Robbins 7th/225, Harrison 16th/1907, 9/e p213)
Immunological tolerance in peripheral lymphoid organs is called as peripheral tolerance. It requires signal to

(interaction between CD28 and B7). CD28 molecules (co-stimulatory molecule) bind to their ligands-CD80 (B7-l) and/or CD86 (B7-2) and activates T-cell. If the antigen presented by cell do not bear CD28 ligand, a negative signal is delivered and cell become tolerant and anergic.

21. Ans. (c) CD19; (d) CD20; (e) CD22
(Ref: Immunology by Roitt, 6th/29, 30, 19 9/e p191)

CD19, 20 and 22 are main markers of human B cells. Other B cell markers are CD72 to CD78.

CD33 is present in monocyte whereas CD34 is marker of hematopoetic stem cell.

22. Ans. (d) All of the above *(Ref: Robbins 9/e p87)*

23. Ans. (a) Langerhan's cells *(Ref: Robbins 9/e p192)*

24. Ans. (b) Helps in the formation of antibody
(Ref: Robbins 8th/183-184; 7th/82 , 9/e p191)

25. Ans. (b) 2 : 1 *(Ref: Robbins 9/e p190-191)*

26. Ans. (c) T cells *(Ref: Robbins 8th/192, 9/e p191)*

27. Ans. (b) T cell *(Ref: Robbins 7th/670 , 9/e p191)*

28. Ans (c) Memory is seen
(Ref: Robbins 8th/184, 9/e p186-188) ...see text

29. Ans. (d) Toll-like receptor *(Ref: Robbins 9/e p187-188)*

Toll-like receptors (TLRs), stimulate one of the immune responses directed against microbes,
TLRs bind to pathogen-associated molecular patterns (PAMPs), which are small molecular sequences found commonly on pathogens.
Examples of PAMPs include *bacterial lipopolysaccharide (LPS), lipoteichoic acid, and peptidoglycan.*
LPS is probably the prototypical PAMP[Q].
TLRs, in conjunction with CD14, bind to LPS (endotoxin), and activate leukocytes to produce cytokines and reactive leukocytes to produce cytokines and reactive oxygen intermediates (ROIs).

30. Ans. (c) NK cells *(Ref: Robbins 8/e p188, 9/e p192)*

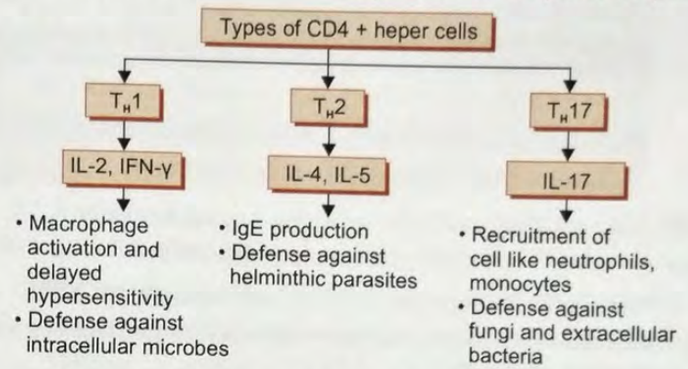
- The NK cells are also known as *large granular lymphocytes* as they have a larger size and contain abundant azurophilic granules.
- NK cells are endowed with the ability to kill a variety of **infected** and **tumor cells, without prior exposure** to or activation by these microbes or tumors.

31. Ans. (b) CD 16, CD 56...explained earlier
(Ref: Robbins 9/e p192)

32. Ans. (a) 16 *(Ref: Robbins 8/e p188, 9/e p192)*

- **Natural Killer cell** is identified with the molecules as **CD16 and CD56**[Q].
- **CD16** is an Fc receptor for IgG, and it confers on NK cells the ability to lyse IgG-coated target cells. This phenomenon is known as ***antibody-dependent cell-mediated cytotoxicity (ADCC)***[Q].

33. Ans. (a) IL-2 *(Ref: Robbins 8/e p195, 9/e p198)*



After coming in contact with antigen presenting cells, CD4+ helper T cells secrete IL-2 and expresses high-affinity receptors for IL-2. **IL-2** is a growth factor that acts on these T lymphocytes and stimulates their proliferation, leading to an **increase in the number of antigen-specific lymphocytes**.

34. Ans. (a) Mature dendritic cells *(Ref: Robbins 9/e p191)*
Direct quote.. *"interdigitating dendritic cells*, or just *dendritic cells* are the most important *antigen-presenting cells (APCs) for initiating primary T-cell responses against protein antigens'*

35. Ans. (a) T-cells *(Ref: Robbins 8/e p186, 9/e p191)*

36. Ans. (c) Liver...refer to text for details
(Ref: Robbins 8/e p834, 7/e p79, 9/e p102)

37. Ans. (b) Langerhans cell *(Ref: Robbins 9/e p622)*

38. Ans. (a) B cells *(Ref: Robbins 9/e p191)*
Macroglobulin is the other name for antibodies. So, the answer becomes obvious. i.e. B cells. The activated B cells are called as plasma cells and are responsible for secretion of antibodies.

39. Ans. (d) May cross the placenta and fix complement

IgG (and ***not IgE***) is the antibody which may cross the placental barrier and fix complement.

40. Ans. (d) IgE... see text table for details

41. Ans. (b) Cortical follicles *(Ref: Robbins 9/e p191)*

42. Ans. (d) Clonal selection *(Ref: Robbins 9/e p190)*

43. Ans. (b) B-cell *(Ref: Robbins 9/e p192)*

44. Ans. (b) Tumor necrosis factor
(Ref: Ananthanarayan 6th/121, Harrison 17th/2047, 9/e p194-195)
*HLA class III contains genes for

- **Complement components C_2 and C_4**[Q] of classical pathway (**Not C_3**[Q])
- **Properdin factor B**[Q] of alternate pathway
- **Tumor necrosis factor**[Q]: Alpha and Beta
- Heat shock protein 70[Q]
- Enzyme **tyrosine hydroxylase**[Q]
- Genes for **MHC** (also known as HLA) are located on **short arm of chromosome 6**[Q].

45. Ans. (b) Governing susceptibility to autoimmune diseases
(Ref: Ananthanarayan 6th/108, Roilt's Essential Immunology – 262, Robbins 9/e p215)
*HLA class III region contains genes for **early complement components C_2 and C_4** of classical pathway.
*Deficiency of these early components of the classical pathway viz C_1, C_2 and C_4 is associated with **autoimmune diseases** like SLE and other collagen vascular diseases.

- These genes are thus, important in regulating susceptibility to autoimmune disease
- **Class III genes do not participate in MHC restriction or graft rejection components.**

46. Ans. (c) Short arm of chromosome 6
(Ref: Robbins 8th/190, 7th/203, 9/e p194)

47. Ans. (a) Ankylosing spondylitis
(Ref: Robbins 8th/193, Harrison 17th/2051, 9/e p215)

48. Ans. (b) MHC class II antigen
(Ref: Harrison 16th/1933, 17th/2047, 9/e p194)

- The MHC **class II region** was originally termed the *D-region*. The allelic gene products were first detected by their ability to stimulate lymphocyte proliferation by ***mixed lymphocyte reaction.*** So, mixed lymphocyte culture is used to identify HLA II. It is present on all antigen presenting cells (B cells, dendritic cells and macrophages) and can be induced on endothelial cells and fibroblasts.

49. Ans. (a) Disputed paternity, (c) Organ transplant
(Ref: Robbins, 9/e p195, 215)

Uses of MHC/HLA typing

Anthropology	Transfusion
Paternity Testing	Forensic science
Transplantation	Disease Correlation

50. Ans. (a) Not involved in innate immunity; (c) Present in nucleated cells; (d) Present in B-cells
(Ref: Robbins 7th/203, 9/eP194-195)

- Class II MHC Proteins are glycoprotein present on the surface of certain cells including **macrophages, B-lymphocytes, dendritic cells of the spleen and Langerhan's cells of the skin.**
- Endothelial cells and fibroblasts can be induced to express Class II MHC by IFN-γ.

51. Ans. (b) T cells, (d) Platelets; (e) RBCs
(Ref: Ananthanarayan' 7th/130, Robbins 7th/203, 9/e p194)

52. Ans. (a) Transplantation reaction; (b) Autoimmune disease; (d) Involved in T-cell function
(Ref: Harrison 16th-1930, 1934; Robbins 7th-204-205)
The principal physiologic function of Major histocompatibility complex (MHC) is to bind peptide fragments of foreign proteins for presentation to appropriate *antigen specific T-cells.* Thus MHC is involved in *transplantation reaction, disease susceptibility (i.e. autoimmune disease, inflammatory disease, infections, etc.), immune response* and *tolerance.*

53. Ans. (a) Alpha helices and (c) Alpha and beta-1 chain
(Ref: Robbins 7th/203-204, 9/e p195)
Friends, the examiner should have specified the type of MHC molecule so that question becomes clear.

> a_1 and a_2 domains form a cleft/groove where the peptides bind to MHC I molecule.
> The antigen binding cleft in MHC II is formed by an interaction of a_1 and b_1 domains of both chains.

54. Ans. (c) Rheumatoid arthritis *(Ref: Robbins 9/e p215)*
HLA B27 is associated with **Seronegative spondyloarthropathies.** Please revise the following important features about these.

Seronegative spondyloarthropathies (Mnemonic: PAIR)	Salient features of these diseases
P: Psoriatic arthritis **A: A**nkylosing spondylitis (AS) **I: I**nflammatory bowel disease arthritis **R: R**eactive arthritis (**R**eiter syndrome)	* **Absence of serum autoantibodies** * Associated with **HLA B27** (MC **AS**) * **Onset before** the age of **40 years** * Presence of **uveitis, spine/large peripheral joint arthritis**

55. Ans. (c) Present antigens for recognition by T cell antigen receptors *(Ref: Robbin 8/e p191)*
The physiologic function of MHC molecules is to display peptide fragments of proteins for recognition by antigen-specific T cells.... *(Ref: Robbin 8/e p190)*
Also now that:

> - **Class I MHC** molecules are required to display antigens to **CD8 T cells**
> - **Class II MHC** molecules are required to display antigens to **CD4 T cells**.

56. Ans. (c) RBCs *(Ref: Robbins 8/e p190, 9/e p194)*

- *Class I MHC molecules* are expressed on **all nucleated cells**[Q] and **platelets**[Q]

57. Ans. (d) All blood cells except erythrocytes
(Ref: Robbins 9/e p194)

58. Ans. (b) CD4 cell *(Ref: Robbins 9/e p195)*

59. Ans. (a) Ankylosing spondylitis *(Ref: Robbins 9th/205)*
Direct quote... "Approximately ***90% of patients are HLA-B27 positive;*** associations have also been found with the IL-23 receptor gene".

Ankylosing spondylitis (also **rheumatoid spondylitis** and **Marie- Strümpell disease)**

It causes destruction of articular cartilage and bony ankylosis, especially of the *sacroiliac and apophyseal joints* (between tuberosities and processes).

It becomes symptomatic in the *2nd and 3rd decades* of life as lower back pain and spinal immobility.

60. Ans. (c) Antigen presentation to T cells

(Ref: Robbins 9th/194)

The **function of MHC molecules** is to ***display peptide fragments of protein antigens for recognition by antigen specific T cells.***

61. Ans. (a) M-cells *(Ref: Atlas of Immunology 3rd/ 206)*

Types of Antigen Presenting Cells

Professional APC	Non-professional APC
Have high expression of MHC II molecule physiologically	Expression of MHC II molecule can be induced by cytokines like IFN-gamma under stress
• Dendritic cells • B cells • Macrophages	• Thymic epithelial cells • Fibroblasts • Glial cells • Endothelial cells • Pancreatic beta cells

M cells are specialized epithelial **cells** of the mucosa-associated lymphoid tissues. They transport antigens from the lumen to **cells** of the immune system, thereby initiating an immune response or tolerance.

62. Ans. (b) Medullary macrophages

The Elements of Immunology/165

- Cortical macrophages, epithelial cells and dendritic cells express high levels of MHCII
- ***Medullary macrophages express only MHCI molecule.***
- Medullary epithelial cells and macrophages express both MHCI and MHC II molecules

63. Ans. (d) Psoriasis vulgaris *(Ref: Robbins 9/e p1165)*

64. Ans. (b) Graft versus host disease

(Ref: Robbins 9/e p195)

65. Ans. (d) HLA-B8 *(Ref: Robbins 9/e p1235)*

66. Ans. (c) HLA B27 *(Ref: Robbins 9/e p1165, internet)*

- Psoriasis is associated with *HLA-Cw*0602* allele.
- **Pustular psoriasis** and **Psoriatic spondylitis** are associated with ***HLA- B27***

67. Ans. (b) HLA DR4 *(Ref: Robbins 9/e p1210, Harrison 19/e p2139, Rheumatology Secrets/35)*

Genes associated with rheumatoid arthritis.

- ***HLA-DRB1 gene***
- ***HLA-DR 4***
- ***PTPN22*** *gene*

68. Ans. (b) Type 2 hypersensitivity reaction

(Ref: Robbins 8th/203, 9/e p206)

Myasthenia gravis is a type 2 hypersensitivity reaction. Other important examples can be remembered from the mnemonic ***"My blood group is R h positive"***. For details see text.

69. Ans. (b) Type 2 hypersensitivity reaction

(Ref: Robbins 7th/211, 9/e p206)

70. Ans. (b) Immune complexes *(Ref: Internet, 9/e p207)*

A Raji cell assay identifies the presence of circulating immune complexes. A positive result suggests the presence of antigen-nonspecific immune complexes in the circulation. The raji cell assay may be helpful in differentiating diseases. Additionally, raji cell tests may assist with the assessment of disease activity. A positive raji cell assay that turns negative may suggest that the disease activity has improved.

71. Ans. (c) Immune complex mediated hypersensitivity

(Ref: Robbins 8th/703, 9/e p207)

Hypersensitivity pneumonitis (***allergic alveolitis***) is ideally an example of **type III and type IV** hypersensitivity. Complement and immunoglobulins demonstrated within vessel walls by immunofluorescence as well as presence of specific antibodies in the serum of affected patients indicate type III (immune complex) hypersensitivity. The presence of non-caseating granulomas in 2/3rd patients suggest the development of a T cell-mediated (type IV) delayed-type hypersensitivity against the implicated antigen(s).

However, the single best answer to be marked would be type III hypersensitivity reaction because immune complex formation plays a relatively more important role in hypersensitivity pneumonitis.

72. Ans. (a) IgE *(Ref: Robbins 9/e p202)*

73. Ans. (a) Localized immune complex

(Ref: Robbins 8th/205, 7th/215, 9/e p207)

The Arthus reaction is a localized area of tissue necrosis resulting from acute immune complex vasculitis, usually elicited in the skin.

Revise the mnemonics "SHARP" from the text.

74. Ans. (d) Type IV *(Ref: Robbins 9/e p210)*

- Presence of epitheloid cell granuloma, langhans giant cells and lymphocytes is characteristic of chronic granulomatous inflammation, which is associated with type IV hypersensitivity action.

75. Ans. (b) IgE mediated reaction *(Ref: Robbins 9/e p202)*

- The symptoms of the patient are due to hypersensitivity type I reaction Type I is mediated by IgE and it flairs up within minutes.
- The symptoms range form rashes to anaphylactic shock with vasodilation hypotension and bronchiolar spasm.

Type I	Type II
• The symptoms range form rashes to anaphylactic shock with vasodilation hypotension and bronchiolar spasm • Mediated by IgE **Examples of Type I** • Eczema* • Hay Fever* • Asthma* • Anaphylactic shock* • Urticaria* • Acute dermatitis* • Theobald Smith Reaction*	• Is characterized by an antigen antibody reaction on the surface of a host cell* • Mediated by IgG or IgM **Examples of Type II** • Blood transfusion reactions* • Transplant rejection* • Autoimmune hemolytic anemia* • Good Pasture's syndrome* • Graves disease* • Myasthenia gravis* • Pemphigus vulgaris • Pernicious anemia* • Rheumatic fever*

Type III	Type IV
• Mediated by antigen/antibody complex* **Examples of type III** • **S**: Serum sickness, Post - streptococcal glomerulonephritis, **SLE**, **S**chick test • **H**: HSP • **A**: **A**rthus reaction, **A**cute viral hepatitis • **R**: Reactive arthritis • **P**: Penicillamine toxicity, • Polyarteritis nodosa (PAN)	• Cell mediated reaction (delayed hypersensitivity)* **Examples of type IV** • Tuberculosis • Sarcoidosis* • Temporal arteritis • Contact dermatitis* • Lepromin test and PPD (Mantoux test)* • Patch test* • Type I DM

76. Ans. (b) Contact hypersensitivity *(Ref: Robbins 9/e p209)*

77. Ans. (a) Blood transfusion reaction *(Ref: Robbins 9/e p206)*

78. Ans. (d) Necrotizing vasculitis *(Ref: Harrison's 16th/327, 328, Robbins 9/e p207)*

- Acute necrotizing vasculitis is the dominant morphological consequences of immune complex injury *[Type-III hypersensitivity reaction]*. The immune complexes incite an activation of complement and produce inflammatory reaction and necrosis.

- Atopic dermatitis and urticaria –Type I.
- Photoallergy- type IV hypersensitivity or delayed hypersensitivity
- Graft versus host disease is mediated by T-cells.

79. Ans. (b) Lymphocytes are the primary cells affected by *M. tuberculosis* *(Ref: Robbins 8th/368, 9/e p371)*

- *Macrophages* are the primary cells infected by *M. tuberculosis*.

80. Ans. (a) IgE mediated response *(Ref: Robbins 9/e p202)*

81. Ans. (a) Hard sore *(Ref: Robbins 7th/738, 9/e p693)*

- Granulomas found in sarcoidosis are non-caseating and so, refered to as *"Hard sore."* They contain.
  - **Asteroid Bodies**
  - **Schaumann bodies and**
  - **Birefringent crystals**

82. Ans. (d) All of the above *(Ref: Robbins 7th/1344, 9/e p1235-1236; Harrison's 16th/2521 table 366-3)*

Myasthenia gravis: revision of key points

Autoimmune mediated neuromuscular disease example of **type II hypersensitivity reaction**

Distinct finding: ↓ ACh receptors (in muscles) and **circulating antibodies to ACh receptors**

Associations
1. Hyperthyroidism
2. **Thymic hyperplasia** – 65%
3. Thymoma – 15%
4. Autoimmune disorders (Hashimoto's thyroiditis, Graves' disease, Rheumatoid arthritis/SLE, positive family history of autoimmune diseases)

83. Ans. (b) Cytotoxic type *(Ref: Robbins 9/e 205)*

84. Ans. (c) Type III *(Ref: Robbins 9/e 207)*

85. Ans. (c) Good cell mediated immunity *(Ref: Robbins 8th/207, 7 th/381, 9/e 210)*

86. Ans. (d) Type IV *(Ref: Robbins 8/e p197, 9/e 24)*

The hypersensitivity reactions have been given the following names:

- **Immediate**or **(type I) hypersensitivity**
- **Antibody-mediated** or **(type II) hypersensitivity**
- **Immune complex-mediated** or **(type III) hypersensitivity**
- **Cell-mediated** or **(type IV) hypersensitivity**

87. Ans. (b) Acetylcholine receptors *(Ref: Robbins 9/e 195)*

88. Ans. (c) Thymic hyperplasia *(Ref: Robbins 9/e 1235-1236)*

Direct quote... "**Thymic hyperplasia** is found in **65%** and ***thymoma in 15%*** of affected patients".

Myasthenia gravis: revision of key points for NEET/ AIIMS!

- Autoimmune mediated neuromuscular disease example of type II hypersensitivity reaction
- When arising before age 40 years it is most commonly seen in women, but it occurs equally in both sexes in older patients.
- Distinct finding: ↓ ACh receptors (in muscles) and circulating antibodies to ACh receptors
- Most sensitive test: single fibre electromyography
- Most specific test: antibodies to ACh receptors^{Q}
- Electrophysiological studies: ↓ in motor response^{Q} on repeated stimulation
- Nerve conduction studies: Normal^{Q}
- Treatment is done with drugs (neostigmine with atropine^{Q}) and thymectomy^{Q}

89. Ans. (b) Type II *(Ref: Robbins 9th/205)*

Administration of penicillin causing no symptoms in 48 hours with no previous history of allergy rules out type I hypersensitivity reaction.

The patient presented with hemolysis which can be because of antibody formation against red cells. The formation of autoantibody is a feature associated with type II hypersensitivity reaction. Thus, it becomes the answer over here.

Clinically, antibody-mediated cell destruction and phagocytosis occur in multiple situations:

- *Transfusion reactions*, in which cells from an incompatible donor react with and are opsonized by preformed antibody in the host
- *Hemolytic disease of the newborn*: antigenic difference between the mother and fetus
- *Autoimmune hemolytic anemia*, agranulocytosis, and thrombocytopenia, in which individuals produce antibodies to their own blood cells, which are then destroyed.
- Certain drug reactions, in which *a drug acts as a "hapten" by attaching to plasma membrane proteins of red cells and antibodies are produced against the drug-protein complex.*

90. Ans. (a) Mast cells *(Ref: Robbins 9th/201)*

Immeiate, or type I, hypersensitivity is a rapid immunologic reaction occurring in a previously sensitized individual that is triggered by the binding of an antigen to IgE antibody on the surface of mast cells.

91. Ans. (b) Hypersensitivity reaction with modified macrophages, lymphocytes and giant cells *(Ref: Robbins 9th/372)*

Presence of a history of fever, night sweats and weight loss with apical lesion having caseous necrosis is a pointer to the presence of tuberculosis in the patient. This is characterized by the stimulation of the macrophages to kill mycobacteria, the TH1 response leading to the formation of granulomas and caseous necrosis. The formation of granuloma is a feature of type IV hypersensitivity reaction.

92. Ans. (c) Type 3 hypersensitivity reaction *(Robbins 9th/ 207)*

Serum sickness is a type of immune complex disease or type 3 hypersensitivity reaction.

93. Ans. (b) Can lead to leukocytoclastic vasculitis *(Ref: Robbins 9/e p207-8)*

- Acute serum sickness is the prototype of a systemic immune complex disease; it was once a frequent sequela to the administration of large amounts of foreign (**heterologous antigen**) serum.
- It is a *type III* hypersensitivity reaction.
- It may lead to hypocomplementemia.
- Serum sickness may lead to leukocytoclastic vasculitis.

94. Ans. (d) Necrotic zone *(Ref: Robbins 9/e p375)*

95. Ans. (a) Preformed antibodies *(Ref: Robbins 9/e 233-234)*

Direct quote from Robbins. 'Hyperacute rejection occurs when preformed antidonor antibodies are present in the circulation of the recipient'. Such antibodies may be present:

- In a recipient who has previously rejected a kidney transplant
- Multiparous women who develop anti-HLA antibodies against paternal antigens shed from the fetus may have preformed antibodies to grafts taken from their husbands or children
- Prior blood transfusions
- In recipients not previously sensitized to transplantation antigens, exposure to the class I and class II HLA antigens of the donor graft may evoke antibodies. *The initial target of these antibodies in rejection seems to be the graft vasculature.* Thus, antibody-dependent *acute humoral rejection* is usually manifested by a vasculitis, sometimes referred to as *rejection vasculitis*

Also know that endothelitis is caused by injury to the vascular endothelial cells *mediated by CD8+ T cells.* This is a component of acute cellular rejection.

96. Ans. (d) Lung *(Ref: Robbin 9/e 236, Harrison's 17th/717)*

- *GVHD affects skin (earliest organ), intestine and liver*
- Lungs are **not** affected in GVHD. For details see text.

97. Ans. (a) Hyperacute rejection *(Ref: Robbins 9/e 233-234)*

Hyperacute rejection takes place when there are preformed antibodies in the circulation of the recipient. It can be due to:

- Patient who has already rejected a transplant
- Multiparous females
- Prior blood transfusions

98. Ans. (a) Associated with solid organ transplantation; (b) Graft must contains immunocompetant T cell; (c) It is seen in immunosuppressed persons; (d) Also called as Runt disease in animals

(Ref: Robbins 7th/222, 9/e 232-233; Harrison 16th/670; Ananthanarayan 7th/180)

Graft versus host reaction (GVH) occurs in any situation in **which immunologically competent cells** or there precursors are transplanted into **immunologically crippled recipient** cells and the transferred cells recognize alloantigens in the host.

GVHD occurs **most commonly in allogenic bone marrow transplantation**Q but may also follow transplantation of **solid organs** rich in lymphoid cells.

99. Ans. (b) Interstitial and tubular mononuclear cell infiltrate *(Ref: Robbins 8th/228-229 , 9/e 232-233)*

100. Ans. (d) Xenograft *(Ref: Harsh Mohan 6th/65)*

- **Isograft:** Is a graft from a different individual genetically identical with recipient e.g. identical twin
- **Autograft:** Is to self
- **Allograft:** Graft from same species but different genotype (from one human to another human)
- **Xenograft:** Graft from different species (from animal to human)

101. Ans. (b) Adrenal *(Ref: Robbins 9/e 236, 8th/230; 7th/125)*

102. Ans. (d) Infection *(Ref Cambell's Urology, 8/e p346,349)*

Principal causes of death in renal transplant patients (in decreasing order): Heart disease, Infection, Stroke

103. Ans. (a) Hyperacute rejection *(Ref: Robbins 9/e 233-234)*

Hyperacute rejection	Acute rejection	Chronic rejection
*Takes place in individuals with **preformed antibodies**Q usually **within minutes to hours** of transplantation	*Seen **days to months** after transplantation. It can be acute humoral rejection or acute cellular rejection	*Occurs **months to years** after transplantation

104. Ans. (d) C4d *(Ref: Robbins 9th/ 234)*

Acute antibody mediated reaction is manifested by lesions consisting of inflammation in the glomeruli and peritubular capillaries associated with *deposition of the complement breakdown product C4d* which is produced by the activation of the complement dependent classical pathway.

105. Ans. (d) All of the above *Ref: cancerresearch.uk.org*

The following are the steps taken to reduce the risk of graft versus host disease:

1. Getting the best donor match: donor is as closely matched to recipient with the technique of tissue typing.
2. Use of immunosuppressive drugs like ciclosporin, tacrolimus etc
3. T cell depletion: Removal of T cells from the donor's bone marrow is called as T cell depletion.
4. Post procedure immune suppression using the drugs like methotrexate and cyclophosphamide.

106. Ans. (b) Stem cells are collected directly from the bone marrow *(Ref: Harrison 19/chapter 139, Robbins 9/e p27-8)*

- *Autologous transplantation* involves the removal and storage of the patient's own stem cells with subsequent reinfusion after the patient ***receives high-dose myeloablative therapy.***
- Unlike allogeneic transplantation, there is **no risk of GVHD or graft rejection** with autologous transplantation.
- Donors are typically ***treated with 4 or 5 days of hematopoietic growth factor***, following which stem cells are collected in 4-hour pheresis sessions.

107. Ans. (a) 10 *(Ref: Immunology & Serology in Laboratory Medicine/464)*

HLA markers like HLA-**A**/ HLA-**B**/ HLA-**C** and HLA-**DRB1** are the **most important markers** to ensure the success of the transplantation. Some centres also use ***HLA-DQ*** as an additional marker which is minimally/less significant than first 4 markers. Since we have 2 alleles for each of them, so, the **total HLA score is 10**.

- For **adult donors, 6 out of 8** HLA markers (HLA-**A**/ HLA-**B**/ HLA-**C** and HLA-**DRB1**) should match.
- For **cord blood units**, the criteria are less stringent and match of **4 out of 6** (HLA-**A**/ HLA-**B** and HLA-**DRB1**) is required.

108. Ans. (b) Acute rejection *(Ref: Fundamentals of Surgical Practice; 258)*

Acute rejection is mediated by T cells and is the **commonest type** of organ **rejection** seen in tissue mismatch after an allotransplant, or when insufficient immunosupression is employed.

109. Ans. (b) Liver *(Ref: Robbins 9/e p236)*

The rejection reaction against liver transplants is not as vigorous as might be expected from the degree of HLA disparity.

110. Ans. (d) Graft versus host disease *(Ref: Robbins 9/e p236, Blood chapter 60)*

Runt disease is a graft versus host disease which occurs when immunologically competent cells or their precursors are transplanted into immunologically crippled recipients, and the transferred cells recognize alloantigens in the host and attack host tissues.

111. Ans. (b) Hyperacute rejection *(Ref: Robbins 9/e p???)*

Hyperacute rejection is caused by **preformed antibodies** against the donor antigens. So, **cross matching prior to transplantation** is helpful in its prevention.

112. Ans. (b) Occurs when donor cells are immunocompetent *(Ref: Robbins 9/e p236)*

GVHD occurs when **immunologically competent cells** or their precursors **are transplanted into immunologically crippled recipients**, and the transferred cells recognize alloantigens in the host and attack host tissues. It is seen ***most commonly in hematopoetic stem cell transplantation.***

113. Ans. (a) Tissue typing *(Ref: Immunology/290)*

- Tissue typing is the technique in which the tissues of a prospective donor and recipient are tested for compatibility before carrying out transplantation.
- The two commonly used techniques are: "mixed leukocyte reaction" and micro-cytotoxicity assay.

114. Ans. (c) 3 months *(Ref: Robbins 9/e p???)*

- **Hyperacute rejection:** Within minutes to hours (due to preformed antibodies)
- **Acute rejection:** Within days to months (due to cell mediated and antibody mechanisms)
- **Chronic rejection:** Within months to years (due to T cell mediated mechanism)

115. Ans. (b) Polyclonal B cell activation *(Ref: Robbins 8th 212, 9/e 216)*

Polyclonal B cell activation is caused by EBVQ and HIVQ resulting in production of autoantibodies for other mechanisms see text

116. Ans. (b) Scleroderma *(Ref: Robbins 8th/225, 518, Harrison 18th/2096, 9/e 228-229)*

The symptoms present in this girl are suggestive of Raynaud's phenomenon (pallor and cyanosis of the digits of hands and feet due to exaggerated vasoconstriction of digital arteries and arterioles). It can either be:

- Primary Raynaud's phenomenon or
- Secondary Raynaud's phenomenon (due to SLE, scleroderma, Buerger's disease, atherosclerosis). Since, Raynaud's phenomenon may the first manifestation of these diseases, the patient with new symptoms need to be evaluated.

Direct quote Robbins 8th/225.... 'though systemic sclerosis shares many features with SLE, rheumatoid arthritis and polymyositis, ***its distinctive features are the striking cutaneous changes,*** notably skin thickening. ***Raynaud phenomenon,*** manifested as episodic vasoconstriction of the arteries and arterioles of the extremities, is ***seen in virtually all patients*** and **precedes other symptoms in 70% of cases.' Dysphagia** is seen in **50%** patients.

Ruling out SLE, the presentation in SLE is....*'Typically, the patient is a young woman with some of the following features: a butterfly rash over the face, fever, pain but no deformity in one or more peripheral joints (feet, ankles, knees, hips, fingers, wrists, elbows, shoulders), pleuritic chest pain, and photosensitivity.'*

117. Ans. (d) Sickle Cell Disease

(Ref: Harrison 17th/2074)

Sickle cell disease is caused by a point mutation in the β_6 chain of hemoglobin. It is **not** an auto immune disease.

118. Ans. (d) Anti glycoprotein antibody

(Ref: Robbins 8th/215, Harrison 17th/2073, 9/e 219)

Antiphospholipid antibody syndrome is characterized by antibodies against **phospholipid beta- 2-glycoprotein 1 complex**Q. For detail, see text under SLE.

119. Ans. (b) Kikuchi Fujimoto disease

(Ref: Harrison 17th/1011)

The other name of Kikuchi Fujimoto disease is histiocytic necrotizing lymphadenitis. This will answer our question.

Kikuchi-Fujimoto disease (KFD)/Histiocytic necrotizing lymphadenitis

- Benign and self-limited disorder in young individuals characterized by regional cervical lymphadenopathy with tenderness, usually accompanied with mild fever and night sweats.
- May be viral in etiology
- Diagnosed on the basis of an excisional biopsy of affected lymph nodes which shows fragmentation, necrosis and karyorrhexis, presenting with posterior cervical lymphadenopathy.
- Patients should be followed-up because of increased chances of development of SLE (systemic lupus erythematosus).

Castleman disease (CD)

- Defined by lymph node hypertrophy with angiofollicular lymphoid hyperplasia.
- Has localised form or multicentric form (several Lymph nodes are affected).
- Clinical features inlcude Peripheral lymphadenopathy, hepatomegaly and/or splenomegaly and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)
- Human herpes virus 8 (HHV-8) is the etiological agent
- Lymph node histological analysis with immunohistochemical staining, shows polyclonal angiofollicular lymphoid hyperplasia, most often of the hyalinovascular type (especially in localised CD) and more rarely of the plasma-cell type (particularly in multicentric CD) or mixed/intermediate type.

120. Ans. (a) SLE

(Ref: Harrison 17th/2077, Robbins 8th/218, 9/e 224)

Subendothelial deposits create a homogeneous thickening of the capillary wall **called wire loop lesion**, which can be seen by means of light microscopy when they are extensive. They usually ***reflect active disease.***

121. Ans. (d) Liver

(Ref: Immunofluorescence Methods for Microscopic Analysis in Methods in Nonradioactive Detection, Lange Publications/247)

Quote from the book.... ***"Serum anti-nuclear antibodies (ANA) bind to the corresponding antigens present in rat liver sections***. The antigen-antibody complexes are detected by means of a fluorescein labeled anti-human immunoglobulin, and visualized with the aid of a fluorescence microscope".

122. Ans. (c) Inclusion bodies *(Ref: Robbins 9/e 250-255)*

123. Ans. (a) C1 esterase inhibitor deficiency

(Ref: Robbins 8th/235, 9/e 238)

124. Ans. (a) It is an autosomal recessive disorder

(Ref: Robbins 9/p242)

125. Ans. (a) SLE *(Ref: Robbins 9/e 218)*

126. Ans. (c) Diffuse proliferative glomerulonephritis (WHO class IV) *(Ref: Harrison 17th/2077, Robbins illustrated 8th/218, 9/e p224)*

127. Ans. (d) Multiple myeloma *(Ref: Robbins 9/e p258-259, 8th/252-254, 7th/261)*

Pink and amorphous material that shows apple green birefringence under polarized light confirms the diagnosis of Amyloidosis. The presence of Lambda light chains is suggestive of multiple myeloma.

128. Ans. (a) Non caseating granulomas

(Ref: Robbins 9/e p693, Harrison, 17th/2135)

- The presence of **bilateral nodules on the shin; bilateral hilar lymphadenopathy** and **negative Mantoux test** in a female patient point to a probable diagnosis of **Sarcoidosis**.
- The skin lesions characteristically show the presence of **non - caseating granulomas**Q in **sarcoidosis**.

129. Ans. (a) SLE: *(Ref: Robbins 9/e p218)*
Antibodies to ds DNA and the so called Smith (Sm) antigens are virtually diagnostic of SLE. Anti ds-DNA is common in SLE (40-60%).
Anti nuclear antibody is present in all the mentioned diseases but anti double stranded DNA is very specific for SLE.

130. Ans. (a) PSGN; (b) MPGN; (e) Infective endocarditis *(Ref: Harrison 16th-/680)*
Causes of hypocomplementemia
- Glomerulonephritis
  - Idiopathic proliferative GN
  - Cresenteric GN
  - MPGN
  - Post-infectious GN
- Lupus nephritis
- Cryoglobulinemia
- Bacterial endocarditis
- Shunt nephritis
- Atheroembolic renal disease
- Sepsis
- Acute pancreatitis
- Advanced liver disease

131. Ans. (b) Neutropenia; (c) Defective microbial killing; (d) Presence of large granules in neutrophils; (e) Immunodeficiency:
(Ref: Harrison' 16th/353, 354, Robbins 9/e p238)
Chediak-Higashi syndrome

- **Autosomal recessive** inheritance
- Due to **defect in lysosomal transport** protein LYST.
- Clinical features include: primary immune deficiency, neutropenia, defective microbial killing, impaired chemotaxis, hypopigmentation of skin, eyes and hair, photophobia and nystagmus
- Microscopic examination shows **giant peroxidase positive inclusions** in the cytoplasm of leukocytes.

132. Ans. (a) Severe combined immunodeficiency.
(Ref: Robbins 7th/244, 9/e p239)

133. Ans. (b) Pulmonary emphysema; (c) Diastase resistant hepatic cells: *(Ref: Robbins 9/e p850-851)*

- α_1-anti-trypsin deficiency is an **autosomal recessive** disease having abnormally low levels of α_1-anti-trypsin
- Deficiency of the enzyme leads to pulmonary **panacinar emphysema**
- Gene located on Chr 14.
- Characterized by **PAS positive** and **diastase resistant** inclusions in hepatocytes.

134. Ans. (d) High serum IgE, with low IgG, IgA and IgM *(Ref: Robbins 9/e p242, Harrison 17th/384, 2061, 2056, 381)*

Hyper IgE syndrome is also known as **Job's syndrome**
Abnormal chemotaxis is a variable feature.
Patients have characteristic facies with **broad nose, kyphoscoliosis, osteoporosis and eczema.**
Recurrent abscesses (known as **cold abscesses**) involving skin, lungs and other organs is a prominent feature
Serum IgE level is significantly elevated whereas IgM, IgG and IgA level are normal.

Note: In Hyper- IgM syndrome, IgM is elevated and IgG, IgA are normal.

135. Ans. (c) Large size platelet
(Ref: Robbins 9e/p242, 8th/235, Harrison 17th/2060, OP Ghai pediatrics 6th/326)

136. Ans. (a) Absent tonsils and no palpable lymph nodes on physical examination *(Ref: Robbins 9/e p240-241)*

137. Ans. (d) Neutrophil *(Ref: Robbins 8th/238, 9/e p248)*

138. Ans. (d) Leucocytosis *(Ref: Robbins 9/e p218)*

139. Ans. (c) IgA *(Ref: Harrison 16th/2423, 9/e p242-243)*

- Patients with ataxia telangiectasia (AT) present in the first decade of life with progressive telangiectatic lesions associated with deficits in cerebellar function and nystagmus. There is a high incidence of recurrent pulmonary infections (**bronchiectasis**[Q]) and neoplasms of the lymphatic and reticuloendothelial system.
- It is caused due to **defect in DNA repair genes**[Q].
- Thymic hypoplasia with **cellular and humoral (IgA**[Q] **and IgG_2) immunodeficiencies**, **premature aging**[Q] and endocrine disorders such as **insulin resistance or type-I DM**[Q].
- The most striking neuropathologic changes include **loss of Purkinje, granule and basket cells** in the cerebellar cortex as well as of neurons in the deep cerebellar nuclei.
- A **poorly developed or absent thymus gland** is the most consistent defect of the lymphoid system.

140. Ans. (b) Scleroderma *(Ref: Robbins 7th/229)*

141. Ans. (b) Neutrophil *(Ref: Robbins 9/e p222)*
LE cell or hematoxylin body is a phagocytic leukocyte (**neutrophil or macrophage**) that has engulfed the denatured nucleus of an injured cell.

Tart Cell is usually a **monocyte** which has ingested another cell or nucleus of another cell.

142. Ans. (c) Anti-nuclear factor *(Ref: Robbins 9/e p218-219)*

143. Ans. (c) Hematuria *(Ref: Robbins 9/e p222)*

144. Ans. (c) Anti double stranded DNA antibody *(Ref: Robbins 9/e p219, 8th/214; 7th/228)*

145. Ans. (a) Defect in the transport of chloride across epithelia *(Ref: Robbins 9/e p466-467)*

146. Ans. (a) Sarcoidosis *(Ref: Harsh Mohan 6th/164-165)*

147. Ans. (a) p24 *(Ref: Robbins 7th/246, 9/e p245)*

148. Ans. (a) Kaposi's sarcoma *(Ref: Robbins 8th/523-524)*

149. Ans. (a) Syphilis *(Ref: Robbins 9/e p217)*

150. Ans. (c) SLE *(Ref: Robbins 9/e p225-227)*

151. Ans. (a) Brain *(Ref: Robbins 9/e p693)*

152. Ans. (c) Wire loop lesions *(Ref: Robbins 9/e p224)*

153. Ans. (b) SLE *(Ref: Robbins 9/e p224)*

154. Ans. (b) Chemotaxis *(Ref: Walter and Israel 7th/150)*

The direct quote from the book is *"Chediak Higashi syndrome is an autosomal recessive condition in which polymorphs exhibit defective random movements,* ***defective chemotaxis*** *and impaired degranulation on phagocytosing particles.*

155. Ans. (b) SLE *(Ref: Robbins 9/e p219)*

156. Ans. (a) Systemic sclerosis *(Ref: Robbins 9/e p228)*

157. Ans. (a) Hilar lymphadenopathy with perihilar calcification *(Ref: Robbins 9/e p693, 8th/703, 7th/738)*

158. Ans. (a) CNS lesions *(Ref: Robbins 9/e p254-255)*

159. Ans. (d) Nodule is the initial lesion of Kaposi's sarcoma *(Ref: Robbins 9/e p254, 8th/529; 7th/549)*

160. Ans. (a) Helper cells *(Ref: Robbins 9/e p246)*

161. Ans. (c) CNS lesions *(Ref: Robbins 9/e p254-255)*

Direct quote from Robbins…. *"The anatomic changes in the tissues* ***(except of lesions in the brain***^{Q}*)* *are neither specific nor diagnostic".*

162. Ans. (c) Anti topoisomerase *(Ref: Robbins 9/e p219)*

Anti topoisomerase is least commonly associated with SLE amongst the given options. The following is a modified table given for a reference from Robbins.

Nature of Antigen	Antibody System	% Positive in SLE
Many nuclear antigens (DNA, RNA, proteins)	Generic ANA (indirect IF)	>95
Native DNA	Anti–double-stranded DNA	40–60
Histones	Antihistone	50–70
Core proteins of small nuclear RNP particles (Smith antigen)	Anti-Sm	20–30
RNP (U1RNP)	Nuclear RNP	30–40
RNP	SS-A(Ro)	30–50
RNP	SS-B(La)	10–15
DNA topoisomerase I	Scl-70	<5
Centromeric proteins	Anticentromere	<5
Histidyl-tRNA synthetase	Jo-1	<5

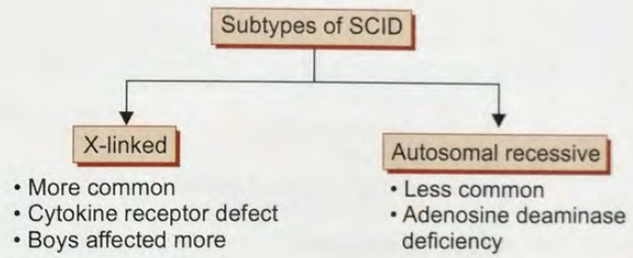
163. Ans. (a) ds DNA

(Ref: Robbins 8/e p214-215, 9/e p218-219) ...see text for detail

164. Ans. (a) Adenosine deaminase deficiency

(Ref: Robbins 8/e p234, 9/e p239)

- Severe combined immunodeficiency (SCID) represents a constellation of genetically distinct syndromes, all having in common *defects in both humoral and cell-mediated immune responses*
- **The most common form**, accounting for 50% to 60% of cases, is **X-linked**, and hence SCID is more common in boys than in girls. The genetic defect in the X-linked form is a ***mutation in the common γ-chain (γc) subunit of cytokine receptors***
- The **remaining cases** of SCID are inherited as **autosomal recessive**. The most common cause of autosomal recessive SCID is a ***deficiency of the enzyme adenosine deaminase*** *(ADA).*



165. Ans. (c) Normal B cell count

(Ref: Robbins 8/e p233, 9/e p241) ...see text for detail

166. Ans. (b) Digeorge syndrome *(Ref: Robbins 9/e p241)*

167. Ans. (a) SLE *(Ref: Robbins 9/e p224)*

In the splenic tissue involvement in SLE, splenomegaly, capsular thickening, and follicular hyperplasia are common features. Central penicilliary arteries may show concentric intimal and smooth muscle cell hyperplasia, producing so-called **onion-skin lesions**^{Q}.

168. Ans. (c) Haematoxylin bodies *(Ref: Robbins 9/e p256)*

- Biopsy specimens from enlarged lymph nodes in the early stages of HIV infection reveal a **marked follicular hyperplasia**.
- **Monocytoid cells** along the blood vessels can be seen in acute lymphadenitis.
- With disease progression, the frenzy of B-cell proliferation subsides and gives way to a pattern of **severe follicular involution**. The follicles are depleted of cells, and the **organized network of follicular dendritic cells is disrupted**. The germinal centers may even become hyalinized.
- During this advanced stage viral burden in the nodes is reduced, in part because of the disruption of the follicular dendritic cells. These **"burnt-out" lymph nodes**^{Q} are atrophic and small.

169. Ans. (c) Primary CNS lymphoma

(Ref: Robbins 9/e p254-255)

- **Primary CNS lymphoma**^{Q} is the most common CNS neoplasm in immunosuppressed individuals, including those with **AIDS** and **immunosuppression after transplantation.**

- It is of **B-cell origin**[Q] and most have infection caused by **EBV**[Q] in the setting of immunosuppression.

> - Histologically, reticulin stains demonstrate that the infiltrating cells are separated from one another by silver-staining material; this pattern, referred to as **"hooping,"** is **characteristic of primary brain lymphoma**.

- In addition to expressing B-cell markers, most of the cells also express **BCL-6**; when tumors arise in the setting of immunosuppression,

170. Ans. (a) Children previously tested with tuberculin test *(Ref: Robbins 9/e p371)*

Children previously tested with tuberculin test may show a *FALSE POSITIVE TUBERULIN TEST.*

False-negative Mantoux test	False-positive Mantoux test
• Sarcoidosis[Q] • Malnutrition[Q] • Hodgkin disease[Q] • Immunosuppression[Q] • Fulminant tuberculosis[Q]	• Infection by atypical mycobacteria[Q] • Previous vaccination with BCG[Q]

171. Ans. (c) Plasma derived Hepatitis B vaccine. ...*see text of AIDS for details*

172. Ans. (c) HIV ELISA

Excellent question testing your basics buddies!

- HIV ELISA is required for detection of antibodies against the virus. The antibodies may be present in the infant because of maternal infection also because IgG antibodies can cross the placental barrier. So,the presence of anti HIV antibodies is not reliable for diagnosis of HIV in a 2 month old child.
- Please don't get foxed by the option viral culture friends. There is indeed a HIV culture method being used which is called as ***'peripheral blood mononuclear cells' (PBMC)*** using the virus microculture in macrophages concept. PBMC are drawn in high concentration from centrifugation of freshly drawn anticoagulated venous blood.
- Viral DNA detection using DNA-PCR andp24 antigen assay are standard techniques used for viral detection.

173. Ans. (b) Disseminated TB *(Ref: Robbins 9/e p371)*

- Mantoux test is simply able to predict the presence or absence of cell mediated immunity against the tubercular antigens. It **CANNOT** differentiate between infection and disease.
- Negative Mantoux test just indicates that the individual has never been exposed to tubercle bacilli earlier; it can't indicate the susceptibility to the disease.

174. Ans. (c) A mechanism for the persistence and evolution of autoimmune disease *(Ref: Robbins 9/e p217)*

Epitope spreading is a phenomenon in which an immune response against one self antigen causes tissue damage, releasing other antigens, and resulting in the activation of lymphocytes by these newly encountered epitopes. This is responsible for the persistence and progression of autoimmune diseases.

175. Ans. (d) Anterior uveitis *(Ref: Harrison 18th/2806)*

> - *Löfgren's syndrome* consists of erythema nodosum, hilar adenopathy on chest X ray and uveitis.
> - Heerfordt's syndrome: fever, parotid enlargement, facial palsy and uveitis.

176. Ans. (a) Gp 120 *(Ref: Robbins 8th/246-7)*

HIV-1 uses CD4 to gain entry into host T-cells and achieves this through its viral envelope protein known as gp120.

177. Ans. (b) 350

Under the revised guidelines the treatment of AIDS patients with respect to opportunistic infections has undergone a change with H.A.A.R.T being initiated at a threshold of CD4 count <350 cells/cu.mm instead of previous 200 cells/cu.mm.

178. Ans. (d) Systemic lupus erythematosus *(Ref: Robbins 9/e p218)*

Similar to many autoimmune diseases, SLE predominantly affects women. A female-to-male ratio of 9:1 is seen during the reproductive age group. By comparison, the female-to-male ratio is only 2:1 for disease developing during childhood or after the age of 65.

179. Ans. (a) EBV *(Ref: Robbins 9th/607)*

180. Ans. (d) Seminiferous tubules *(Ref: Robbins 9th/214)*

The testis, eye, and brain, all of which are called immune-privileged sites because it is difficult to induce immune responses to antigens introduced into these sites. If the antigens of these tissues are released, for example, as a consequence of trauma or infection, the result may be an immune response that leads to prolonged tissue inflammation and injury. This is the postulated mechanism for post-traumatic orchitis and uveitis.

181. And. (a) Ulcerative colitis *(Ref: Robbins 9th/211)*

The given table in Robbins clears all doubts regarding the answer or this question.

Table 6-6 Autoimmune Diseases

Organ-Specific	Systemic
Diseases Mediated by Antibodies	
Autoimmune haemolytic anemia	Systemic lupus erythematosus
Autoimmune thrombocytopenia	
Autoimmune atrophic gastritis of pemicious anemia	
Myasthenia gravis	

Contd...

Contd...

Organ-Specific	Systemic
Graves diseases	
Goodpasture syndrome	
Diseases Mediated by T Cells*	
Type 1 diabetes mellitus	Rheumatoid arthritis
Multiple sclerosis	Systemic sclerosis (scleroderma)† Sjogren syndrome†
Diseases Postulated to be Autoimmune	
Inflammatory bowel diseases {Crohn disease, ulcerative colitis	
Primary Biliary Cirrhosis	**Polyartieritis nodosa†**
Autoimmune (chronic active) hepatitis	Inflammatory myopathies†

*A role for T cells has been demonstrated in these disorders, but antibodies may also be involved in tissue injury.

†An autoimmune basis of these disorders is suspected but the supporting evidence is not strong

182. **Ans. (c) Negative selection of T- cells in the thymus** *(Ref: Robbins 9/e p???)*

Negative selection of T- cells in the thymus is a mechanism of central tolerance. Autoimmune diseases would develop only when there is failure of tolerance. So, the answer.

183. **Ans. (d)) Lipoid nephrosis** *(Ref: Robbins 9/e p222-223)*

184. **Ans. (b)) Subacute cutaneous lupus** *(Ref: Robbins 9/e p219, Harrison 19/ table 319-1)*

Anti RO (SSA) antibodies are not specific for SLE; it ***predisposes to subacute cutaneous lupus***, and to ***neonatal lupus with congenital heart block***. It is associated with ***decreased risk for nephritis***.

185. **Ans. (c) AA** *(Ref: Robbins 8th/252-3, 9/e p257)*

186. **Ans. (d) β_2 microglobulin** *(Ref: Robbins 8th/254, 9/e p258) ...see text*

187. **Ans. (b) Rectal biopsy** *(Ref: Harrison 17th/2145-6; Robbins 8th/255, 9/e p262, Harsh Mohan 6th/88)*

The histological examination of the biopsy material is the commonest and confirmatory method for the diagnosis in a suspected case of amyloidosis. The sites for the biopsy can be the *renal tissue, rectum, abdominal fat aspiration and gingiva*. The **rectum**[Q] is the **best site for taking the biopsy** in the options provided however as per Harrison 19th ed/p 945 the abdominal fat aspirate is positive in 80% of cases.

Note: Congo red staining of **aspirated abdominal fat** is **initial test of choice** in most cases. If it is found to be negative, more invasive biopsy of other affected organ can be taken.

188. **Ans. (b) Familial amyloidosis polyneuropathy** *(Ref: Robbins 8th/252-253, 9/e p259)*

189. **Ans. (b) β_2 microglobulin** *(Ref: Robbins 7th/159-160, 9/e p258) ...see text*

190. **Ans. (a) Bone marrow plasmacytosis** *(Ref: Robbins 7th/pg 260, 8th/252, 9/e p257)*

191. **Ans. (a) A beta 2 microglobulin** *(Ref: Robbins 9/e p258)*

192. **Ans. (c) Rectal biopsy** *(Ref: Harrison 16th/2028, 17th/2145 Robbins 9/e p262)*

193. **Ans. (c) Smooth muscle cells** *(Ref: Robbins 7th/515)*

The proliferation of smooth muscle cells is a critical event in the neointimal hyperplastic response. Several studies have clearly demonstrated that blockade of smooth muscle cell proliferation resulted in preservation of normal vessel phenotype and function, causing the reduction of neointimal hyperplasia and graft failure.

194. **Ans. (c) Congo red** *(Ref: Robbins 9/e p257 Harrison 17th/2145)*

195. **Ans. (a) X-ray crystallography** *(Ref: Robbin 9/e p257)*

- b Pleated structure is seen on X-ray crystallography
- Electro Microscope shows non branching fibrils of indefinite length.

196. **Ans. (a) Nonbranching filaments of indefinite length** *(Ref: Robbins 7th/259, 9/e p257)*

197. **Ans. (c) Methanamine silver** *(Ref: Harsh Mohan 5th/89, 6th/87, Robbins 9/e p262)*

198. **Ans. (c) 7.5-10 nm fibrils** *(Ref: Robbins 6th/259, 8th/249, 9/e p257)*

Remember β-pleated structure of amyloid is seen on X-ray crystallography, whereas it is seen as a non-branching fibril of 7.5-10 nm diameter and infinite length on electron microscopy.

199. **Ans. (c) Mutant transthyretin** *(Ref: Robbin's 9/e p259)*

200. **Ans. (a) Sinusoids of red pulp** *(Ref: Robbins 9/e p261)*

Amyloidosis of spleen

Sago spleen	Lardaceous spleen (Mnemonic: Lal)
Amyloid deposition is largely limited to splenic follicles	Amyloid deposition spares the follicles and involve the walls of the splenic sinuses in **red pulp**

Mnemonic: Red is '**lal**' in hindi, so, similar sounding **lardaceous**.

201. **Ans. (a) Thioflavin; (b) Congo red.** *(Ref: Robbins 7th/254, 9/e p262)*

202. **Ans. (b) Amyloidosis** *(Ref: Harrison 17th/2146; Robbins 7th/264, 9/e p262)*

203. **Ans. (c) Glycoprotein** *(Ref: Robbins 9/e p256)*

204. **Ans. (b) Chronic inflammatory states**
(Ref: Robbins 9/e p257, 8th/251-252; 7th/159)

205. **Ans. (c) Kidney** *(Ref: Robbins 8th/254, 9/e p261)*

206. **Ans. (a) Multiple myeloma-Light chain; (b) Chronic inflammation- AA; (c) Cardiac-ATTR**
(Ref: Harsh Mohan 5th/87, Robbins 9/e p259)

207. **Ans. (a) A-β_2 Microglobulin.....See earlier explanation** *(Ref: Robbins 9/e p258)*

208. **Ans. (c) Type 2 DM** *(Ref: Robbins 8/e p253, 9/e p259)*
Amyloid replacement of islets is a **characteristic finding** in individuals with **long-standing type 2 diabetes**[Q]. It is believed that the islet amyloid protein is directly cytotoxic to islets, analogous to the role played by amyloid plaques implicated in the pathogenesis of Alzheimer disease

209. **Ans. (b) Renal tissue** *(Ref: Robbins 8/e p254, 9/e p261)*
- Amyloidosis of the **kidney** is the **most common** and potentially the **most serious form** of organ involvement

210. **Ans. (b) Familial amyloidotic polyneuropathy**
(Ref: Robbins 8/e p253, 9/e p259)

211. **Ans. (b) Renal failure** *(Ref: Robbins 8/e p254, 9/e p261)*
"Amyloidosis of the kidney is the most common and potentially the most serious form of organ involvement".....direct lines from Robbins.

Renal involvement gives rise to proteinuria that may be severe enough to cause the nephrotic syndrome. Progressive obliteration of glomeruli in advanced cases ultimately leads to renal failure and uremia. Renal failure is a common cause of death.

212. **Ans. (d) Chronic osteomyelitis**
(Ref: Robbins 9/e p257, 8/e p253, 7/e p261)
Direct quote... "tuberculosis, bronchiectasis, and chronic osteomyelitis were the most important underlying conditions, but with the advent of effective antimicrobial chemotherapy the connective tissue disorders such as **rheumatoid arthritis**[Q] **(most common)**, ankylosing spondylitis, and inflammatory bowel disease, particularly Crohn disease and ulcerative colitis".

213. **Ans. (c) Brilliant pink color** *(Ref: Robbins 9/e p257)*
Congo red under *ordinary light* imparts a *pink or red color to amyloid deposits*. Under polarized light, the Congo red–stained amyloid shows a green birefringence.

214. **Ans. (a) Sinusoids of red pulp** *(Ref: Robbins 9/e p261)*

215. **Ans (c) Beta – 2-microglobulin** *(Ref: Robbins 9/e p258)*

216. **Ans (b) Senile cardiac amyloidosis**
(Ref: Robbins 9/e p258)

217. **Ans (c) Calcitonin** *(Ref: Robbins 9/e p259)*
Calcitonin is a protein which gets converted to amyloid and can lead to organ dysfunction.

218. **Ans (b) Ankylosing spondylitis** *(Ref: Robbins 9/e p259)*

ANNEXURE

Non HLA genes associated with autoimmune diseases

Putative Gene Involved	Diseases	Postulated Function of Encoded Protein and Role of Mutation/ Polymorphism in Disease
Genes involved in immune regulation:		
PTPN22	RA, T1 D, IBD	Protein tyrosine phosphatase, may affect signalling in lymphocytes and may after negative selection or activation of self-reactive T cells
IL23R	IBD, PS, AS	Receptor for the $T_1$17-includeing cytokine IL-23; may after differentiation of CD4+ T cells into pathogenic T_1 17 effector cells
CTLA4	T1D, RA	Inhibits T cell responses by terminating activation and promoting activity of regulatory T cells; may interfere with self-tolerance
IL2RA	MS, T1D	a chain of the receptor for IL-2, which is a growth and survival factor for activated and regulatory T cells; may affect development of effector cells and/or regulation of immune responses
Genes involved in immune responses to microbes:		
NOD2	IBD	Cytoplasmic sensor of bacteria expressed in Paneth and other intestinal epithelial cells; may control resistance to gut commensal bacteria
AT616	IBD	Involved in autophagy; possible role in defense against microbes and maintenance of epithelial barrier function
IRF5, IFIH1	SLE	Role in type 1 interferon production; type I IFN is involved the pathogenesis of SLE (See text)

AUTOANTIBODIES IN AUTOIMMUNE DISORDERS

Disease	Specificity of Autoanti Body	Association with specific Disease Features
Systemic lupus erythernatosus (SLE)	Double-stranded DNA	Nephritis; specific for SLE
	U1-RNP	
	Smith (Sm) antigen (Core protein of small RNP particles)	Specific for SLE
	Ro (SS-A)/La (SS-B) nucleoproteins	Congenital heart block; neonatal lupus
	Phospholipid-protein complexes (anti-PL)	Antiphospholipid syndrome (in~10% of SLE patients)
	Multiple nuclear antigen ("generic ANAs")	Found in other autoimmune diseases, not specific.
Systemic sclerosis	DNA topoisomerase 1	Diffuse skin disease, lung disease; specific for systemic sclerosis
	Centromeric proteins (CENPs) A, B, C	Limited skin disease, ischemic digital loss, putomonery hypertension
	RNA polymerase III	Acute onset, sclerodema renal crisis, cancer
Sjögren syndrome	Ro/SS-A La/SS-B	
Autoimmune myositis	Histidyl-tRNA synthetase, Jo1	Interstitial lung disease, Raynaud phenomenon
	Mi-2 nuclear antigen	Dermatomyositis, skin rash
	MDAS (cytoplasmic receptor for viral RNA)	Vascular skin lesions, interstitial lung disease
	TF1y nuclear protein	Dermatomyositis, cancer
Rheumatoid arthritis	**CCP** (cyclic citrullinated peptides); various citrullinated proteins	**Specific for rheumatoid arthritis**
	Rheumatoid factor (not specific)	

For Special Attention... Potential Future AIIMS Question

- ***Anti RNA polymerase III antibody*** is associated with ***Acute onset, scleroderma renal crisis*** and ***cancer.***
- ***Autoimmune myositis*** is associated with antibody against ***Histidyl aminoacyl-tRNA synthetase, Jo1 25, Mi-2 nuclear antigen, MDA5 (cytoplasmic receptor for viral RNA)*** and ***TIF1γ nuclear protein***

IgG4-RELATED DISEASE

- IgG4-related disease (IgG4-RD) is an idiopathic newly recognized constellation of disorders affecting middle aged to old men characterized by tissue infiltrates dominated by **IgG4 antibody-producing plasma cells** and T lymphocytes, storiform fibrosis, obliterative phlebitis, and usually increased serum IgG4.Autoimmune myositis is associated with antibody against Histidyl aminoacyl-tRNA synthetase, Jo1 25, Mi-2 nuclear antigen, MDA5 (cytoplasmic receptor for viral RNA) and TIF1γ nuclear protein.
- It includes disorders like **Mikulicz syndrome** (enlargement and fibrosis of salivary and lacrimal glands), **Riedel thyroiditis**, idiopathic retroperitoneal fibrosis, autoimmune pancreatitis, and inflammatory pseudotumors of the orbit, lungs, and kidneys.

X-linked Lymphoproliferative Disease

It is characterized by an ***inability to eliminate Epstein-Barr virus*** (EBV), eventually leading to **fulminant infectious mononucleosis** and the development of **B-cell tumors.**

In most of the cases it is caused by mutations in the gene for ***SLAM-associated protein (SAP)*** that are associated with the activation of NK cells and T and B lymphocytes. This leads to attenuated NK and T cell activation and result in increased susceptibility to viral infections. SAP is also required for the development of follicular helper T cells, and so, XLP patients are unable to form germinal centers or produce high affinity antibodies.

CHAPTER 7

Anemia and Red Blood Cells

Golden Points

- Erythropoiesis in organs follows the sequence of yolk sac, liver and then bone marrow.
- Ratio of fat cells to hematopoietic cells in bone marrow: 1:1.
- Myeloid to erythroid ratio in bone marrow: 3:1 or 4:1.
- Ratio of fat cells to red cells (erythroid) in bone marrow: 4:1.
- Largest number of bone marrow cells: **Metamyelocytes**.
- Best indicator of anisocytosis: red cell distribution width.
- **Hereditary spherocytosis** is the only important anemia with **increased MCHC.**
- Not a feature of hemolytic anemia Increased heptoglobin (it is decreased). However, reduced haptoglobin level in hemolysis is masked by **bile duct obstruction**.
- **Biconcave shape** of RBC is due to **Spectrin**.
- Most common defect in hereditary spherocytosis is **Ankyrin** (most common) followed by ***Band 3*** (2nd MC). Others include defective spectrin and Band 4.2 (palladin).
- Test for increased osmotic fragility in Hereditary spherocytosis: **Pink test**.
- Most common cause of spherocytes: **Immune haemolytic anemia**.
- Young female with spherocytes, investigation to be done: Coomb's test (to rule out immune hemolytic anemia).
- **Bite cells** and **Heinz body** are seen in **G-6PD deficiency.**
- Sickle cell anemia is due to a Point mutation (and not deletion).
- Sickling is affected by: Concentration of HbS (most important), deoxygenation and pH, duration of deoxygenation in microcirculation.
- Best investigation for hemoglobinopathies is HPLC.
- On Hb electrophoresis: Hb**S** moves **S**lower than HbA towards positive electrode.
- Sickle cell trait provides pretection against: Falciparum malaria.
- Gamma Gandy bodies are seen in Sickle cell anemia, chronc myeloid leukemia and cirrhosis.
- Hb**E** is common in: **E**ast India (Bengal, Assam)
- Mutation in thalassemia: Mainly point mutation (missense mutation) causing aberrant splicing.
- HbA_2 is raised (>3·5%.) in thalassemia trait whereas HbF is highly raised in thalassemia major (Cooley's anemia).
- HbH disease is due to three alpha genes deletion whereas Barts Hb is due to four gene deletions.
- Hair on end (Crew cut appearance) appearance on skull x-ray: Thalassemia, SCA, HS, G6PD deficiency.
- Paroxysmal nocturnal hemoglobinuria is due to **Acquired defect** in red cell **PIG-A gene** leading to defective Glycosylphosphatidylinositol (GPI)- linked proteins. It is best diagnosed by **FLAER flow cytometry.** *(Ref. CMDT 2018)*
- M/C collagen vascular disorder causing Coomb's positive hemolytic anemia is **SLE** whereas the leukemia causing Coomb's positive test is **CLL**.
- Donath-Landsteiner antibody is seen in: Parxysmal cold hemoglobinuria.
- Important infection causing non-immune hemolytic anemia: Malaria.
- Drugs causing warm antibody hemolytic anemia: Methyldopa, qunidine, cephalosporins, penicillin.
- Findings of microangiopathic hemolytic anemia (MAHA): Fragmented RBCs (schistocytes), Burr cells, Helmet cells, Triangle cells. Causes of microangiopathic anemia are TTP, HUS, DIC and malignant hypertension. **Macroangiopathic** anemia is seen with **cardiac prosthetic valve.**
- Important causes of microcytic hypochromic anemia: Iron deficiency, sideroblastic anemia, thalassemia, anemia of chronic disease.
- Blood index which reflects iron deficiency more accurately: MCHC.
- Mentzer index < 13: Thalassemia minor whereas Mentzer index > 13 is seen in iron deficiency anemia.
- M/C anemia in chronic renal failure is Normocytic normochromic anemia.
- Sideroblastic anemia is having production of Ringed sideroblasts and its causes include collagen vascular disorders (SLE), lead (lead poisoning leads to Inhibition of enzymes involved in heme synthesis like ferrochelatase and aminolevulinic acid dehydratase), porphyria, myelofibrosis, iron overload, alcoholism, myelodysplasia.

- Triad of megaloblastic anemia: **Oval macrocytes (earliest finding)**, hypersegmented neutrophils, Howell-Jolly bodies.
- MCHC is **Not increased** in megaloblastic anemia.
- False positive Schilling test: Renal insufficiency.
- Copper deficiency causes: **normocytic hypochromic** anemia
- Aplastic anemia is characterized by pancytopenia and absence of splenomegaly.
- Most common cause of Howell-Jolly bodies: Splenectomy.
- **Cabot ring** is seen in: **Megaloblastic anemia** (most common), lead poisoning (2nd MC), hemolytic anemia, thalassemia, myelodysplastic syndrome and postsplenectomy.
- Types of anemia in lead poisoning: Microcytic hypochromic (with reticulocytosis, basophilic stippling, target cells), sideroblastic anemia, hemolytic anemia.
- Blood group antigens are not found in: CSF.
- Feature of Swachman-Diamond syndrome: Pancreatic insufficiency; bone marrow dysfunc- tion; neutropenia; short stature; skeletal abnormalities.
- Best method for hemoglobin estimation: Cyanmethemoglobin method.
- Stain used for reticulocytes: Supravital stains (methylene blue and Brilliant cresyl blue).
- Conditions protecting against falciparum malaria: G-6PD deficiency, pyruvate kinase deficiency, sickle cell trait, beta thalassemia trait and HbC.

Hematology is the study of the various cells and components of the blood. Hematopoeisis is the process of production of blood cells which primarily takes place in the following organs:

Sites of Hematopoeisis

Till **3rd week** of intrauterine life: Yolk sac.

By **3rd month** of intrauterine life: **Liver** is the main site of blood formation.

At **4th month** of intrauterine life: **Bone marrow** is the main site of hematopoiesis.

Finally **by birth**, the **bone marrow** in whole of the skeleton is hematopoietically active and is the chief source of blood cells and it remains so till puberty.

After puberty, the **red marrow** is present in vertebrae, ribs, sternum, skull, pelvis and proximal epiphyseal regions of humerus and femur.

SALIENT FEATURES OF BONE MARROW

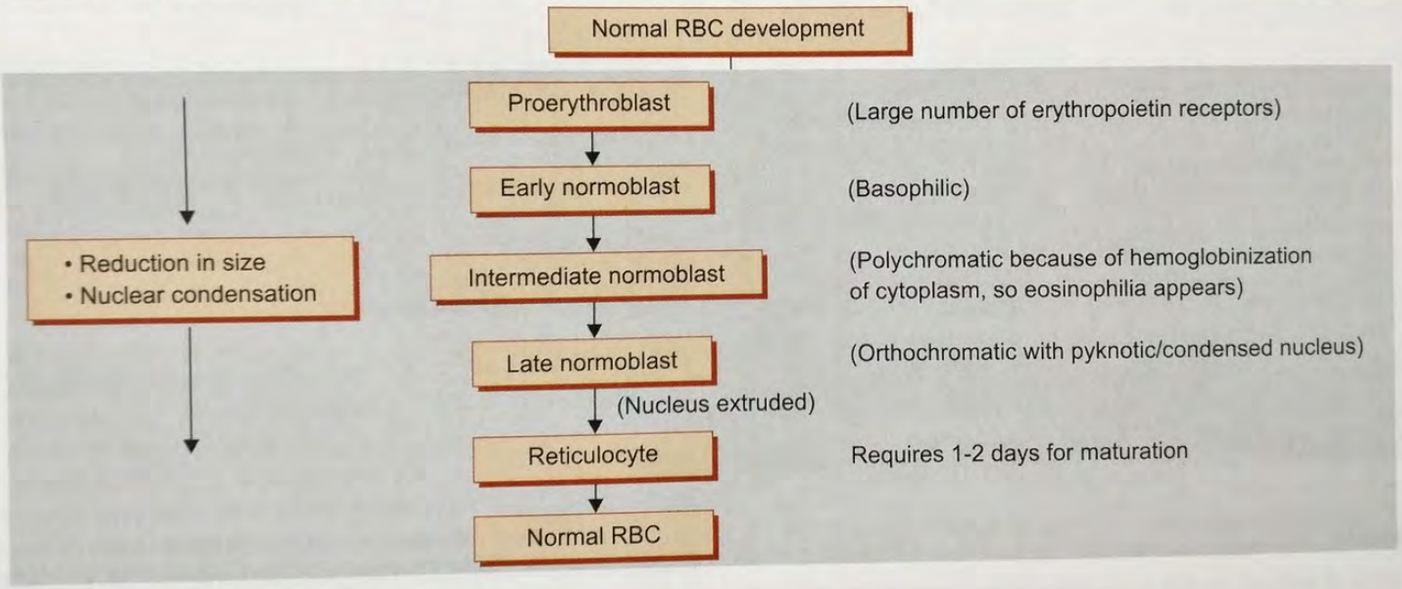
- The ratio of the fat cells and the hematopoeitic cells in an adult is 1:1. The number of the myeloid cells is more than the number of the erythroid cells (normal M:E ratio is 3 to 15:1).
- The investigations for the information about bone marrow are bone marrow aspiration and bone marrow biopsy.

Hematopoietic stem cells are pluripotent stem cells which are *CD34+ cells*. They give rise to the trilineage myeloid cells, lymphoblasts and monoblasts. The trilineage myeloid cell gives rise to the following three cells:

- Normoblast (Gives rise to RBCs)
- Myeloblast (Gives rise to neutrophils, eosinophils and basophils)
- Megakaryocyte (Gives rise to platelets).

Monoblast gives rise to monocytes whereas lymphoblast gives rise to lymphocytes.

Stages of Erythropoiesis



Recent Exam Questions

First detection of hemoglobin

- By ***electron microscope***: ***Proerythroblast***
- By **giemsa** (routine) **stain**: **intermediate normoblast**

General Information About RBCs

The normal red cell is biconcave in shape and has a diameter of 7-8 mm. The cytoskeleton of the RBC is made up of proteins like spectrin, ankyrin, band 2.1, band 3, band 4.1, etc. that provide deformability to the RBCs so that they can cross through tiny blood vessels like capillaries. Importance of these proteins can be appreciated in disorders like hereditary spherocytosis. When the RBCs are of unequal size, this is referred to as *anisocytosis* and when of different shapes, it is called *poikilocytosis*.

Recent Exam Questions

Spectrin is the chief protein responsible for **biconcave shape** of normal red blood cell.

- **Reticulocytes** are nonnucleated spherical cells bigger than normal RBCs and are polychromatic (having a blue color) due to the presence of free ribosomes and RNA.
- **Reticulocyte count:** Percentage of reticulocytes among the red cells present in the peripheral blood is called reticulocyte count. Normal value is around 1.5% in adults and 1.7% in the cord blood cells.

Key Point

The **reticulocyte count** is an *indicator of erythropoetic activity* of the bone marrow.

- **Absolute reticulocyte count (ARC):** Number of reticulocytes present in 1 mm3 of blood.
  ARC = (Reticulocyte %) X Erythrocyte Count/100.
- **Reticulocyte Index (RI):** It adjusts reticulocyte count for hematocrit. It reflects bone marrow activity and is also known as *"Poor man's Bone Marrow Aspirate"*. Normal reticulocyte index is 1-3%.

RI = Reticulocyte Count X (Hb/Age and sex adjusted normal Hb level).

Table 1: Conditions affecting reticulocyte count.

Reticulocytosis (Increased RBC production)	Reticulocytopenia (Decreased RBC production)
***Criteria** Reticulocyte Index > 3% Reticulocyte Count > 1.5%	***Criteria** Reticulocyte Index < 1% Reticulocyte Count < 0.5%
Conditions • Acute blood loss or hemorrhage • Postsplenectomy • Microangiopathic Anemia • Autoimmune Hemolytic Anemia • Hemoglobinopathy (Sickle cell anemia and Thalassemia) • **Post anemia Treatment** like Folate Supplementation, Iron Supplementation and vitamin B_{12} Supplementation.	**Conditions** • Aplastic anemia • Bone marrow infiltration • Bone marrow suppression (Sepsis/Chemotherapy radiotherapy) • Blood transfusion • Liver disease • Disordered RBC maturation (Iron, B_{12}, Folate Deficiency, Hypothyroidism, Sideroblastic Anemia or Anemia of Chronic Disease)

ANEMIAS

Anemia is defined as any reduction below normal limits of the total circulating red cell mass which is characterized by the clinical features of pallor of skin and nails, dizziness, palpitations, lethargy and fatigue.

Some of the important terms used in context of anemias are as follows:

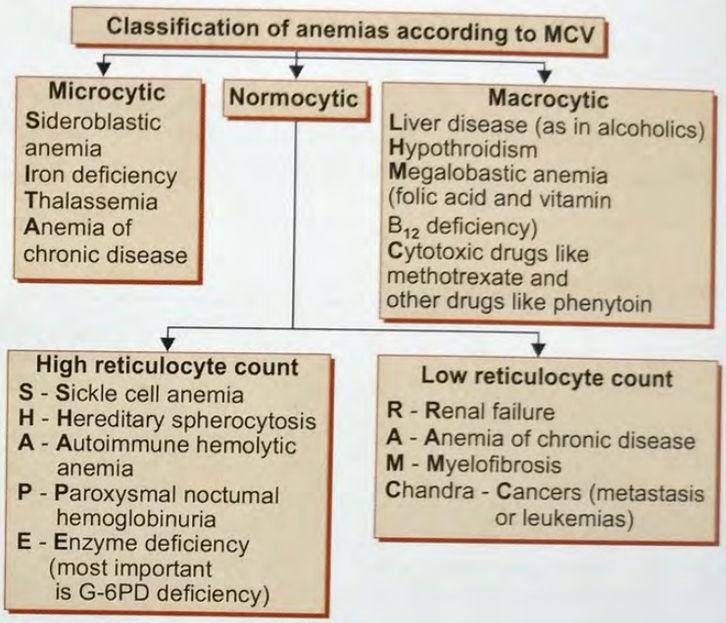
Recent Exam Questions

- MCV **< 80** fl: **Microcytic** RBC.
- MCV **> 100** fl: ***Macrocytic*** RBC.

Key Point

RDW (Red cell distribution width): is an indicator of **anisocytosis** its normal value is 11.5-14.5.

- **MCV (Mean cell volume):** It is the average volume (in femtolitres) of a red blood cell (normal value is 82-96 fl).
- **MCH (Mean corpuscular hemoglobin):** Average mass of hemoglobin (in picograms) per red blood cell is MCH. *Normal value is 27-33 pg.*
- **MCHC (Mean corpuscular hemoglobin concentration):** MCHC is average concentration of hemoglobin in a given volume of packed red blood cells. *Normal value is 33-37g/dl.*
- Normal RBCs have *central pallor of around a third of the diameter* (normochromic). If the color is decreased which means pallor more than one-third, the RBCs are called *hypochromic* and if color is increased (central pallor is lost), the RBCs are called *hyperchromic.*



Anemia can be caused by blood loss, reduced red cell production and excessive red cell destruction.

A. BLOOD LOSS

Blood loss causes decrease in hematocrit resulting in compensatory increased release of erythropoietin from the renal juxtaglomerular cells. Erythropoietin stimulates increased bone marrow activity. However, the *earliest change* in the peripheral blood is *leucocytosis* (caused by increased mobilization from the marginal pools) followed by reticulocytosis and thrombocytosis. Chronic blood loss is usually due to GIT lesions and gynecological disturbances.

Key Point

Earliest change in the peripheral blood after acute blood loss is **leucocytosis** followed by reticulocytosis and thrombocytosis.

B. IMPAIRED RBC PRODUCTION

1. DUE TO DECREASED ERYTHROPOIESIS

This category of anemias may result from the defective DNA synthesis due to vitamin B_{12} or folic acid deficiency (called

megaloblastic anemia) or impaired heme synthesis due to iron deficiency.

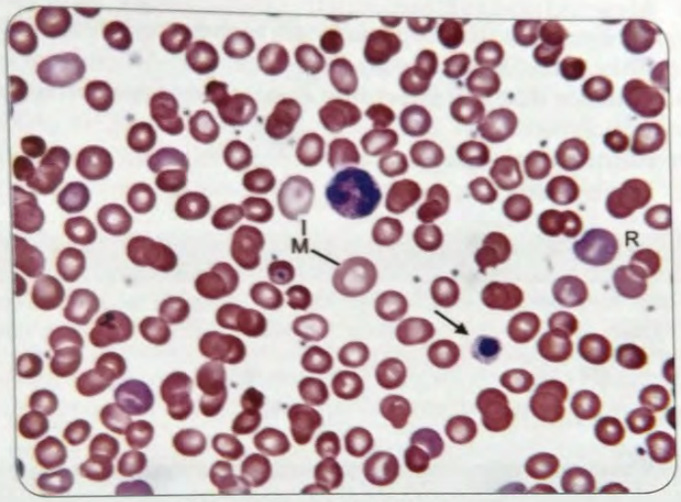


Fig. 1: Megaloblastic Anemia

a. Megaloblastic Anemia

The chief feature in this anemia is impaired DNA synthesis resulting in delayed mitosis while RNA and protein synthesis is not impaired. This leads to *nuclear/cytoplasmic asynchrony* which affects all proliferating cell lines particularly cells of bone marrow and GIT cells. The chief findings are a *hypercellular bone marrow* with megaloblasts in the bone marrow along with presence of abnormal granulocytic precursors (*giant metamyelocyte and band forms*) and *large megakaryocytes* with bizarre multilobated nuclei. The presence of *ineffective erythropoiesis* can result in *pancytopenia* associated with features of hemolytic anemia including jaundice and increased levels of serum bilirubin and LDH enzyme. In the peripheral smear, there is pancytopenia with presence of macrocytes (RBCs having MCV >100 fl) lacking a central pallor. There is characteristically presence of **large and hypersegmented neutrophils** (neutrophils having **> 5 lobes**). The *earliest manifestation* of megaloblastic anemia is *presence of hypersegmented neutrophils*. **Diagnosis is made if even a single neutrophil with ≥ 6 lobes is seen or > 5% neutrophils with 5 lobes are seen.**

Concept

- **Triad** of megaloblastic anemia includes **oval macrocytes, Howell Jolly bodies and hypersegmented neutrophils.**
- MCHC is **not elevated** because hemoglobin increases proportionately to the increased volume of the RBCs.

Key Point

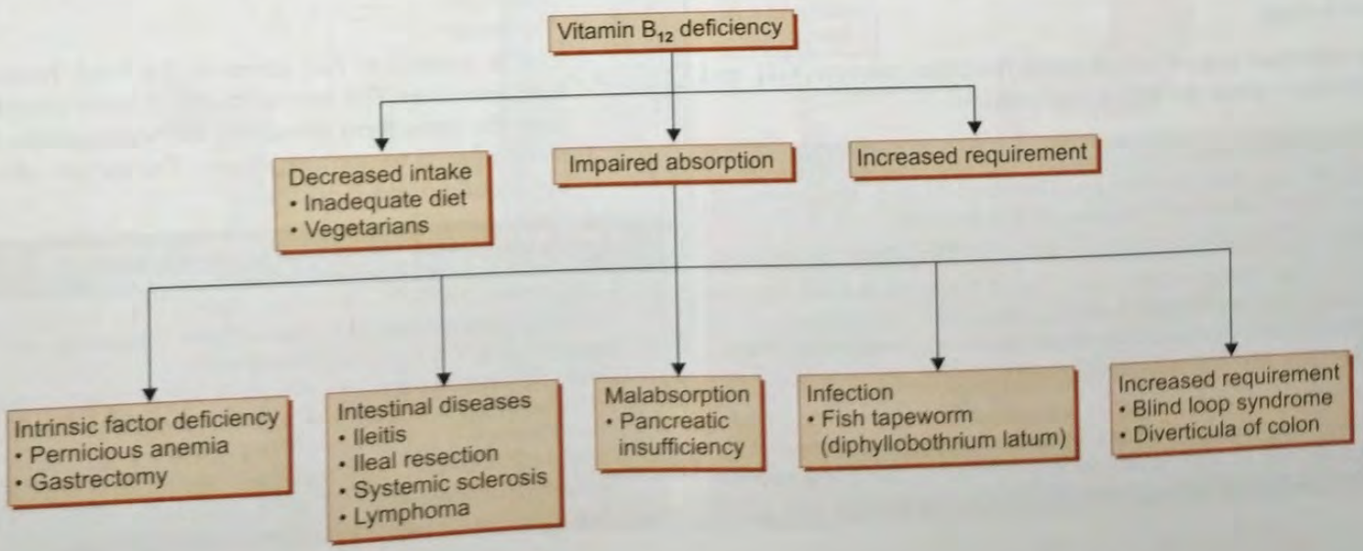
Earliest manifestation of megaloblastic anemia is presence of **macro-ovalocytosis**.

The two main causes of this anemia are vitamin B_{12} and folic acid deficiency.

(*i*) Vitamin B_{12} deficiency

Normal vitamin B_{12} metabolism

The vitamin B_{12} (or cobalamin) is present in the bound form (bound with dietary proteins) in the diet. It is freed by the action of pepsin in stomach and then binds with salivary proteins called *R-binders* (also known as cobalaphilins). In the duodenum, this cobalamin-cobalaphilin complex is broken by the action of pancreatic proteases. Free cobalamin now binds with the intrinsic factor (*Castle's factor*) secreted from the parietal cells of the stomach. Vitamin B_{12}-intrinsic factor complex is *taken by the ileal enterocytes*. Within the intestinal cells, the cobalamin gets bound with a transport protein called transcobalamin II which delivers it to the rapidly proliferating cells of the body (bone marrow and GIT cells). So, the causes of vitamin B_{12} deficiency can be:



Key Point

Vitamin B_{12}-intrinsic factor complex is taken by the **ileal enterocytes**.

Pernicious anemia

It is an autoimmune disorder against parietal cells of the stomach by auto-reactive T cells resulting in chronic atrophic gastritis and parietal cells loss (responsible for decreased intrinsic factor production). The antibodies which are present in the patients are:

Recent Exam Questions

- **Diphyllobothrium latum** is associated with megaloblastic anemia[Q]
- *Ankylostoma duodenale* is associated with *iron deficiency anemia*[Q]

- Type I antibodies[Q] **(most common)**: Block binding of vitamin B_{12} to IF (in 75% patients).
- Type II antibodies: Prevent cobalamin-IF binding with ileal receptors.
- Type III antibodies: formed against the α and β subunits of gastric proton pump (seen in 90% patients but not specific as it also seen in idiopathic chronic gastritis).

It is also associated with other autoimmune disorders like autoimmune thyroiditis and adrenalitis.

Concept

Vitamin B_{12}

- It is required for the conversion of ***homocysteine to methionine***.
- It is also involved in the conversion of **methylmalonyl CoA to succinyl CoA** which is required for the formation of normal neuronal lipids. So, any deficiency of vitamin B_{12} results in neurological features.
- **Pernicious anemia** is associated with increased risk of **gastric cancer** and increased chances of **atherosclerosis** and **thrombosis** (because of elevated homocysteine levels).

Morphology

The principal organs affected are the bone marrow, GIT and CNS which show the following features:

Bone marrow
Megaloblasts, hypersegmented neutrophils and precursors of granulocytes along with megakaryocytes are seen.
GIT
There is presence of shiny and ***"beefy" tongue*** due to atrophic glossitis, almost complete loss of parietal cells and replacement of gastric mucosa by mucus secreting goblet cells ***(intestinalization)***.
CNS
The combined involvement of the axons in the ascending tracts of posterior column and the ***descending pyramidal tract*** is a characteristic feature of vitamin B12 deficiency giving the term as **subacute combined degeneration of the spinal cord**.

Clinical Features

They are as follows:

- Megaloblastic anemia
- Pancytopenia (Leucopenia with hypersegmented neutrophils, thrombocytopenia)
- Jaundice due to ineffective hematopoiesis and peripheral hemolysis
- Neurological features due to posterolateral spinal tract involvement.

Key Point

Schilling test: It is performed to distinguish between different causes of vitamin B_{12} deficiency. It is **NOT USED** for the diagnosis of vitamin B_{12} deficiency.

Laboratory tests

- Serum antibodies against intrinsic factor are present.
- *Achlorhydria even after histamine stimulation.*
- Increased serum levels of methylmalonic acid and homocysteine.
- **Schilling test:** It is performed to distinguish between different causes of vitamin B_{12} deficiency.

Recent Exam Questions

- Gene for **reduced folate transporter** is present on **chromosome 21q**.
- Megaloblastic anemia caused due to folic acid deficiency is **NOT** associated with neuro-logical abnormalities.

(ii) *Folic acid deficiency*

Megaloblastic anemia caused due to folic acid deficiency is clinically indistinguishable from vitamin B_{12} deficiency anemia. However, folic acid deficiency is **NOT** associated with neurological abnormalities.

b. Due to Defective Hemoglobin Synthesis

(i) ***Iron deficiency***

It is the *commonest cause of anemia worldwide.*

Normal iron metabolism

The metabolism of iron can be divided in the following headings:

Absorption

Iron is present in two forms in the food: heme and nonheme iron. The iron is absorbed more completely from the heme form (present in the nonvegetarian food) as compared to nonheme form. The factors affecting absorption of iron include:

Factors increasing absorption	Factors decreasing absorption
• Ferrous form (Fe^{2+}) • Acid (HCl) in the stomach • Ascorbic acid • Amino acid and sugars in the food • Iron deficiency • Physiological conditions (pregnancy and hypoxia)	• Ferric form (Fe^{3+}) • Achlorhydria (absence of HCl secretion) • Alkaline food (pancreatic secretions) • Phytates, tannates and phosphates in diet • Iron overload • Tetracyclines and EDTA • Inflammatory disorders

Iron is *absorbed primarily from the duodenum* in the ferrous form. It is transported inside the enterocytes by an apical transporter called DMT1 (Divalent Metal Transporter 1) and from here, it enters the plasma by two basal membrane transporters **(ferroportin and hephaestin)**. A fraction of ferrous iron gets converted into ferric state by intracellular oxidation. Most of the iron absorbed from the gut is lost because of mucosal lining shedding whereas in increased requirements it is absorbed in a greater percentage.

Concept

A regulatory protein called **hepcidin** regulates the absorption of iron from the gut. In case of iron depletion the level of this negative regulatory protein is decreased thereby increasing the absorption of iron and vice versa. **Mutation** of the gene coding for hepcidin is implicated in the causation of **hemochromatosis.**

Recent Exam Questions

- ***Hepcidin*** is the **master regulator** of ***human iron metabolism.***
- **Iron** is absorbed primarily from the **duodenum** in the **ferrous** form.

Transport and storage of iron

From the enterocytes, the absorbed iron is transferred to a plasma protein called **transferrin** that delivers it to different cells of the body expressing high levels of transferrin receptors on their surface. These cells include *hepatocytes and the developing erythroblasts* in the bone marrow. The serum transferrin saturation is an indicator of serum iron concentration. Normally, transferrin is 33% saturated (one-third saturation) with iron. Since, the serum transferrin concentration is nearly 300-350 µg/dl (also called as total iron binding capacity or TIBC), the normal serum iron levels are in the range of 100-120 µg/dl. The iron which is not immediately required by the cells is stored in the form of **ferritin** which is a protein iron complex present in all the tissues especially liver, spleen and bone marrow. It is the *ferric form of iron which is present in ferritin*. A small amount of ferritin is also present in the plasma which is derived from the storage pools of the body iron; so, **serum ferritin is an indicator of body iron stores**. Intracellular iron is converted into hemosiderin which stains positively with potassium ferrocyanide giving a positive Prussian blue stain.

Key Point

Absorbed iron is transferred to a plasma protein called transferrin.

Recent Exam Questions

Each molecule of **transferrin** can transport **two** molecules of iron to the desired areas.

The normal requirement of iron in the diet is nearly 1 mg/d. The causes of iron deficiency anemia include the following:

Dietary lack	Impaired absorption	Increased requirement	Chronic blood loss
• Infants • Children • Low socio-economic status • Elderly	• Steatorrhea • Sprue • Chronic diarrhea • Gastrectomy	• Growing infants and children • Pregnant females • Premenopausal women	• GIT (peptic ulcer, gastric cancer, hemorrhoids, hookworm disease) • Urinary tract (renal, pelvic or bladder cancers) • Genital tract (uterine cancer, menorrhagia)

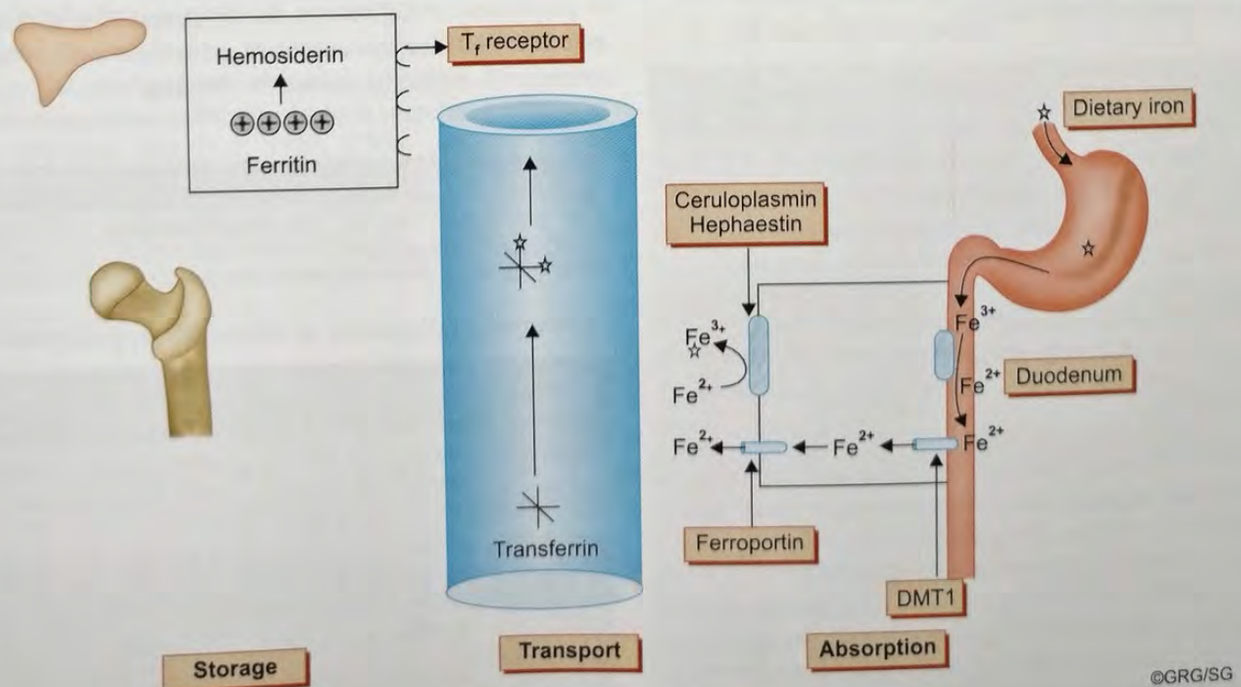


Fig. 2: Normal iron metabolism

Features of Iron Deficiency Anemia

It is characterized by the following stages:

Stage I or stage of negative iron balance

This is a stage characterized by decreased amount of storage iron manifesting as decreased serum ferritin concentration and reduced amount of bone marrow iron staining with Prussian blue stain. *The serum iron and red cell protoporphyrin levels are absolutely normal.* Though TIBC is marginally increased, the *red cell indices and morphology are normal.*

Stage II or stage of iron deficient erythropoiesis

This is a stage of reduced circulating iron in addition to decrease storage form of iron. So, this stage is characterized by deficient iron stores, *reduced serum ferritin, decreased % saturation of serum transferrin and increased TIBC.* The *red cell morphology is normal.*

Stage III or stage of iron deficiency anemia

It is characterized by all features of stage II and in addition *abnormal morphology of the red cells*, i.e. the presence of microcytic and hypochromic cells.

Recent Exam Questions

Most of the body's iron is contained in **hemoglobin** and *not ferritin.*

Clinical features include fatigue, impaired growth and development, pica (eating noedible substances like mud, etc. in children), koilonychia (angular or spoon shaped nails), angular stomatitis (ulceration at the angle of mouth), dysphagia (as in Plummer Vinson syndrome) and palpitations (because of hyperdynamic circulation which can even precipitate congestive heart failure).

Peripheral blood

Microcytic and hypochromic red cells with slight reticulocytosis whereas TLC is normal. Usually, microcytosis is seen before appearance of hypochromia. Poikilocytosis is seen in form of small and elongated red cells called *pencil cells*. It is also characteristic feature of this disease. There is increased red cell distribution width also.

Bone marrow

Hypercellular bone marrow (having increased erythroid progenitors) with depleted bone marrow iron stores. There is presence of ***micronormoblasts***.

Additional findings

- **Serum** *ferritin and serum iron are decreased whereas serum transferrin and TIBC are increased.*
- **Red cell protoporphyrin levels** *are increased* because there is decrease in the availability of heme (due to reduced iron availability) resulting in elevated free erythrocytic protoporphyrin levels. RBC free protoporphyrin is normally 30-50 µg/dl whereas its value reaches > 200 µg/dl in iron deficiency anemia.

Key Point

Serum ferritin is an *indicator* of body **iron stores**.

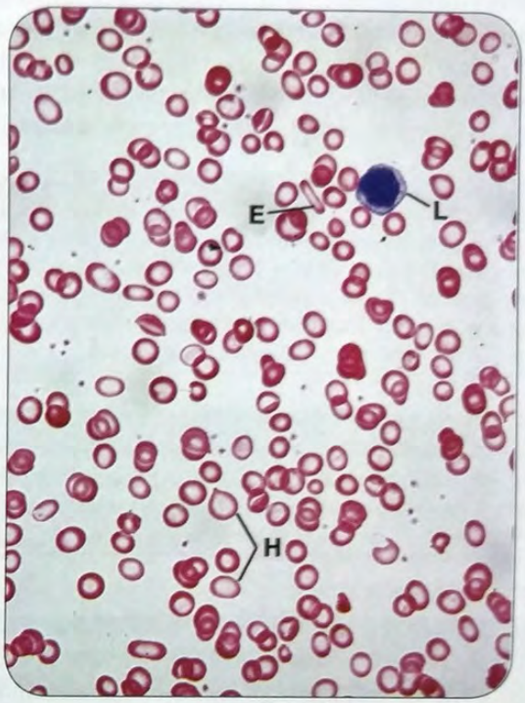


Fig. 3: Iron Def Anemia. (H: Hypochromic cell; E: Elliptocyte)

Key Point

The normal requirement of iron in the diet is nearly **1 mg/d**.

The treatment of anemia is with the help of either oral or parenteral iron therapy the response of which is clinically assessed with improvement in symptoms and increase in the reticulocyte count on **about 8th - 9th day**.

Recent Exam Questions

In the bone marrow, **Micronormoblasts** are present with persistent basophilia.

Differential diagnosis of microcytic hypochromic anemia

Tests	Iron deficiency	Inflammation	Thalassemia	Sideroblastic anemia
Peripheral smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
SI	< 30	< 50	Normal to high	Normal to high
TIBC	> 360	< 300	Normal	Normal
Percent TS	< 10	10-20	30-80	30-80

Contd...

Contd...

Tests	Iron deficiency	Inflammation	Thalassemia	Sideroblastic anemia
Ferritin (mcg/L)	< 15	30-200	50-300	50-300
Hemoglobin pattern	Normal	Normal	Abnormal	Normal

SI, serum iron; TIBC, total iron-binding capacity; TS, transferrin saturation.

(*ii*) **Thalassemia**

It is discussed in detail with other hemolytic diseases. There are many indices to differentiate between iron deficiency anemia (IDA) and beta-thalassemia (BT): Two examples include:

Mnemonic

TIBC levels at
Top = **I**ron deficiency (In iron deficiency anemia, TIBC is raised)
Bottom = **C**hronic disease (In Anemia of Chronic Disease, TIBC is low).

Index	Formula	Value for Iron deficiency anemia	Value for beta-thalassemia
Mentzer index	MCV/RBC count	> 13	< 13
Srivastava index	MCH/RBC	> 3.8	< 3.8

a. **Miscellaneous**

(i) **Anemia of Chronic Disease (AOCD)**

It is characterized by the *decreased utilization of iron* from the storage from of iron, i.e. ferritin. In chronic inflammatory conditions, there is increased secretion of cytokines like IL-1, TNF, IFN-γ, etc. that cause release of the ***protein hepcidin***[Q] because of which release of iron from the storage pool is inhibited. This result in the high serum ferritin levels, reduced TIBC, reduced % transferrin saturation and decreased serum iron levels.

Recent Exam Questions

AOCD causes **normocytic normochromic** anemia **more commonly** but may also lead to microcytic hypochromic anemia (less commonly).

Recent Exam Questions

Anemia of chronic disease is caused by **hepcidin.**

- In the **peripheral blood smear** there is presence of microcytic and hypochromic red cells.
- In the **bone marrow** there is absence of hypercellularity because of inhibition of erythropoetin secretion by renal cells due to the action of cytokines like IL-1, etc.
- Common clinical conditions having AOCD include diseases like rheumatoid arthritis, regional enteritis, osteomyelitis, lung abscess and cancers like Hodgkin's lymphoma, carcinomas of breast and lung.

Concept

Anemia of chronic disease is differentiated from iron deficiency anemia morphologically by the fact that **microcytosis follows hypochromia** *(microcytosis precedes hypochromia in IDA).*

Mnemonic

During a chronic inflammation (microbial or RA)... the microbes want iron, so our body reacts by locking all of its iron within the macrophages and loosing the key
The good news is that the microbe does not get any iron... However, the bad news is that our body doesn't get iron either, which reduces the amount of heme (no iron, no heme), which reduces the amount of hemoglobin. hence, microcytic anemia.

(*ii*) **Anemia due to marrow infiltration**

This type of anemia is caused due to *infiltration of the bone marrow* resulting in *myelophthisic anemia.* It is characterized by presence of immature erythroid and myeloid precursors in the blood (this is called as leukoerythroblastosis). Metastasis from cancers like breast, lung and prostate are the most common cause of marrow infiltration.

Recent Exam Questions

Leukoerythroblastosis and **tear drop RBCs** are seen with **bone marrow infiltration** which is most commonly caused by **metastasis.**

(*iii*) **Sideroblastic anemia**

Sideroblastic anemia is characterized by the *presence of ringed sideroblasts.* These are normoblasts having pin point iron granules (easily demonstrable with the help of Prussian blue dye) in the cytoplasm or perinuclear region. Sideroblastic anemia can be *hereditary* (due to decreased ALA synthase activity) *or acquired* (secondary to leukemias, myelodysplastic syndrome, alcoholism, copper deficiency, pyridoxine deficiency or lead poisoning). The pathogenesis of the diseases involves defective heme synthesis resulting in ineffective erythropoiesis which thereby contributes to iron overload.

Key Point

- **Sideroblastic anemia** is characterized by the presence of **ringed sideroblasts**.
- There is **increase** in serum **iron**, serum **ferritin**, % **transferrin saturation** and free erythrocyte porphyrin whereas ***TIBC is decreased***.

  - Peripheral smear is characterized by presence of *microcytic hypochromic cells* which also demonstrate the presence of anisopoikilocytosis. There is *increase in serum iron, serum ferritin, % transferrin saturation and free erythrocyte porphyrin whereas TIBC is decreased.*

Note: Abnormal sideroblasts are also seen in *thalassemia, megaloblastic anemia and hemolytic anemias.*

2. DUE TO DECREASED STEM CELLS PROLIFERATION

a. **Aplastic anemia**

This is a disorder characterized by marrow failure associated with pancytopenia (anemia, thrombocytopenia and leukopenia). The causes are:

Acquired	Inherited
• Primary stem cell defect • Irradiation • Viral infections [hepatitis (non A, non B , non C, non G), CMV, EBV, varicella zoster virus] • Chemical agents (alkylating agents, antimetabolites, benzene, chloramphenicol, phenylbutazone, arsenicals, insecticides like DDT, parathion)	• Fanconi anemia

Recent Exam Questions

- **Fanconi anemia** is the most important **inherited** cause of **aplastic anemia**.
- **Bone marrow aspiration** in aplastic anemia reveals **"dry tap"**.

It has been postulated that the etiological agents cause alteration in the stem cells thereby activating the T cells of the body against them resulting in destruction of the stem cells contributing to the pancytopenia.

The **bone marrow** biopsy shows it is characteristically hypocellular being replaced by fat cells (in contrast to aleukemic leukemia and myelodysplastic syndrome in which we have pancytopenia associated with hypercellular marrow) whereas *bone marrow aspiration reveals "dry tap".*

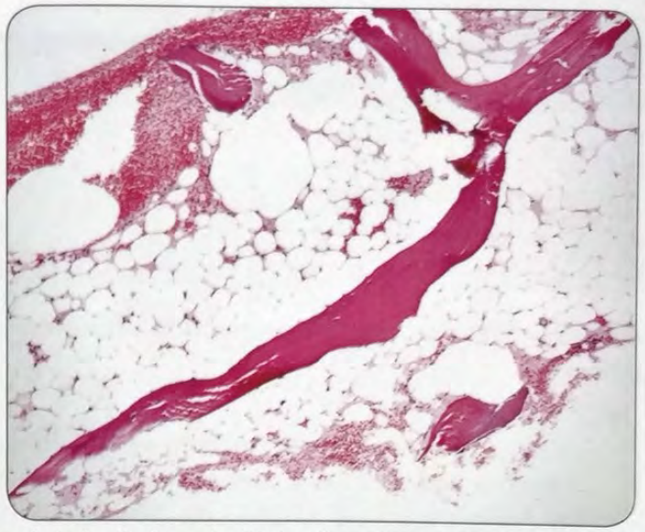


Fig. 4: Aplastic Anemia (Fat cells replace hematopoeitic cells in bone marrow).

Clinical features are caused because of anemia (pallor, weakness and dyspnea), thrombocytopenia (petechiae) and neutropenia (recurrent infections). *Red cells are normocytic and normochromic.*

Concept

Characteristically, ***splenomegaly is absent and reticulocytopenia is the rule*** in aplastic anemia.

It is treated with either bone marrow transplantation (in young patients) or antithymocyte globulin (in old patients).

b. **Anemia of chronic disease (**has been discussed above)

c. **Anemia of renal failure**

It is characterized by inadequate release of erythropoetin resulting in development of anemia. The other contributory factors are:

- Iron deficiency secondary to increased bleeding tendency (seen in uremia)
- Extracorpuscular defect induced hemolysis

Recent Exam Questions

Features of **Shwachman–Diamond syndrome** are exocrine pancreatic insufficiency, bone marrow dysfunction, skeletal abnormalities, **neutropenia** and short stature.

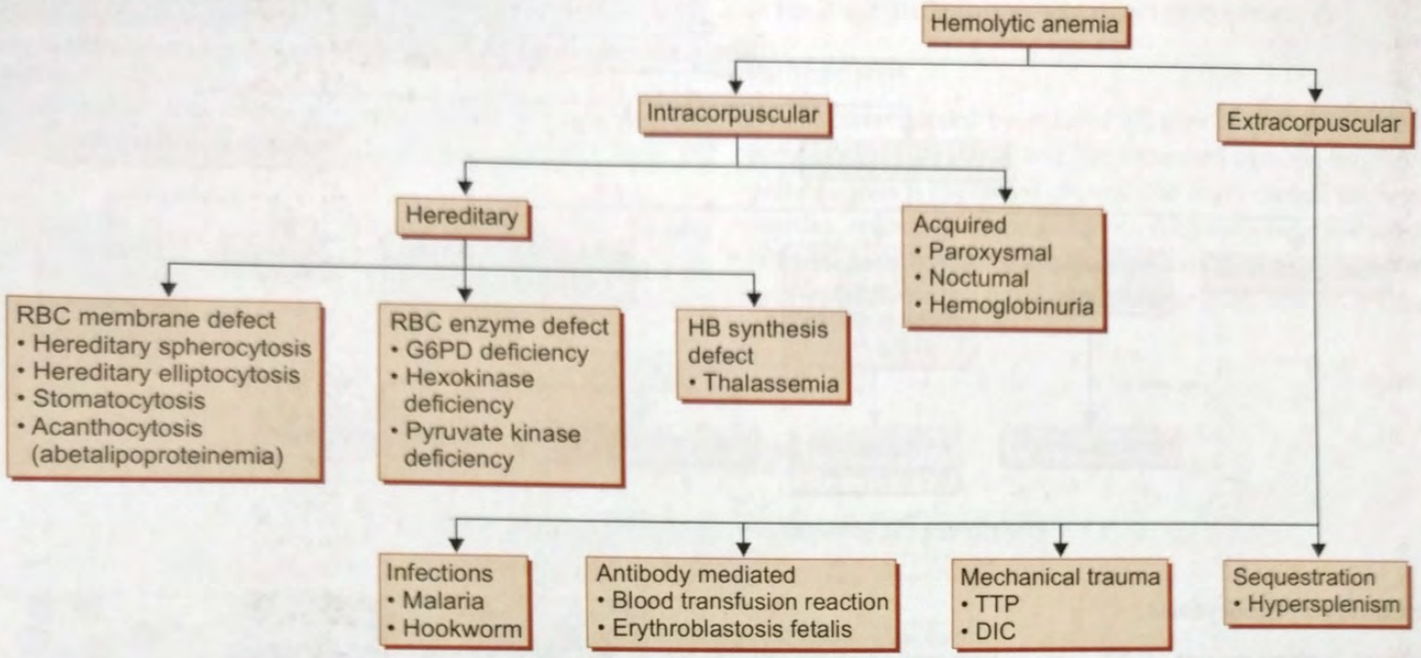
The severity of anemia is proportional to uremia and is usually managed with recombinant erythropoetin.

C. HEMOLYTIC ANEMIA

This type of anemia can be due to intracorpuscular or extracorpuscular defects.

Recent Exam Questions

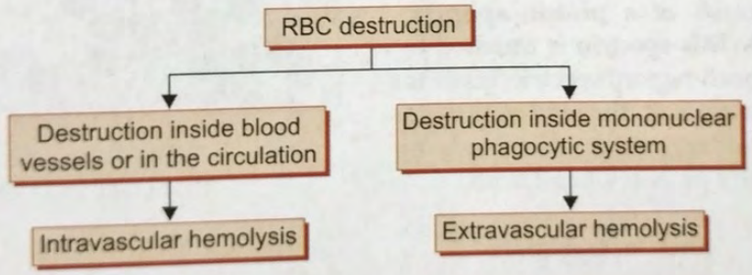
Amount of **hemoglobin** in the blood of a normal adult is **900 grams**.

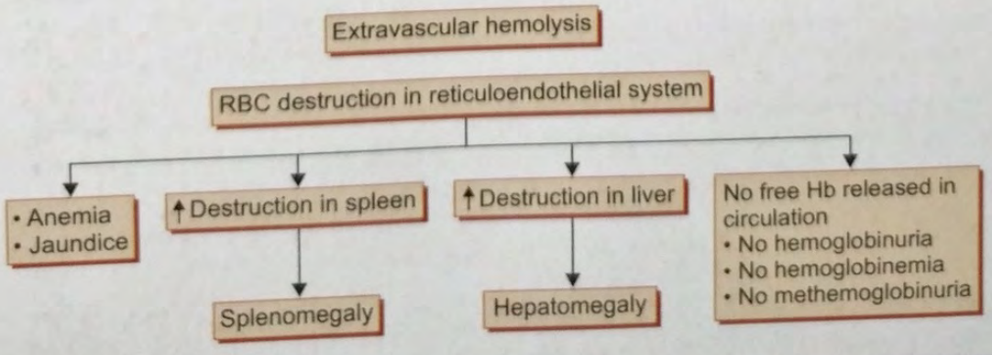


Hemolysis can result due to destruction of RBCs inside the circulation (intravascular) or outside the blood vessels (extravascular).

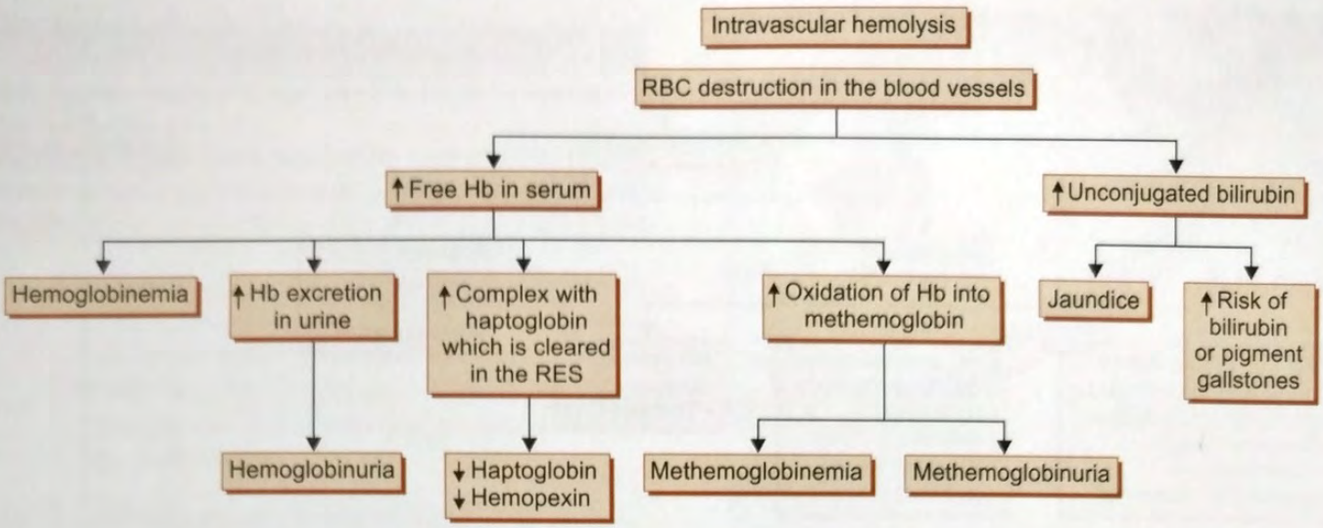
Recent Exam Questions

Haptoglobin followed by hemopexin form the defense against free heme in the plasma.





Note: Serum haptoglobin decreases but not as much as in intravascular hemolysis.



1. Hereditary Spherocytosis

Hereditary spherocytosis (HS), an **autosomal dominant**[Q] disorder, is an important cause of hemolytic anemia.

Recent Exam Questions

- Mostly the mutations in HS are seen in head region most commonly in **ankyrin**[Q].
- α ***spectrin*** mutation usually causes ***hereditary elliptocytosis***.

Normal RBC membrane skeleton

Normally, RBC membrane consists of a protein **spectrin**, which has *two subunits* α *and* β. This spectrin is attached to cell membrane at two sites. At head region, spectrin binds to ion transporter, band 3 of membrane with the help of ankyrin and band 4.2 whereas at the tail region, spectrin binds to glycophorin A of the membrane by protein 4.1 and actin.

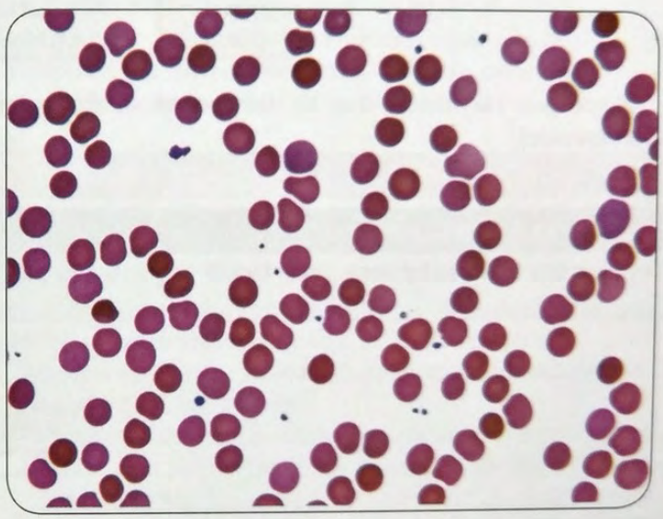
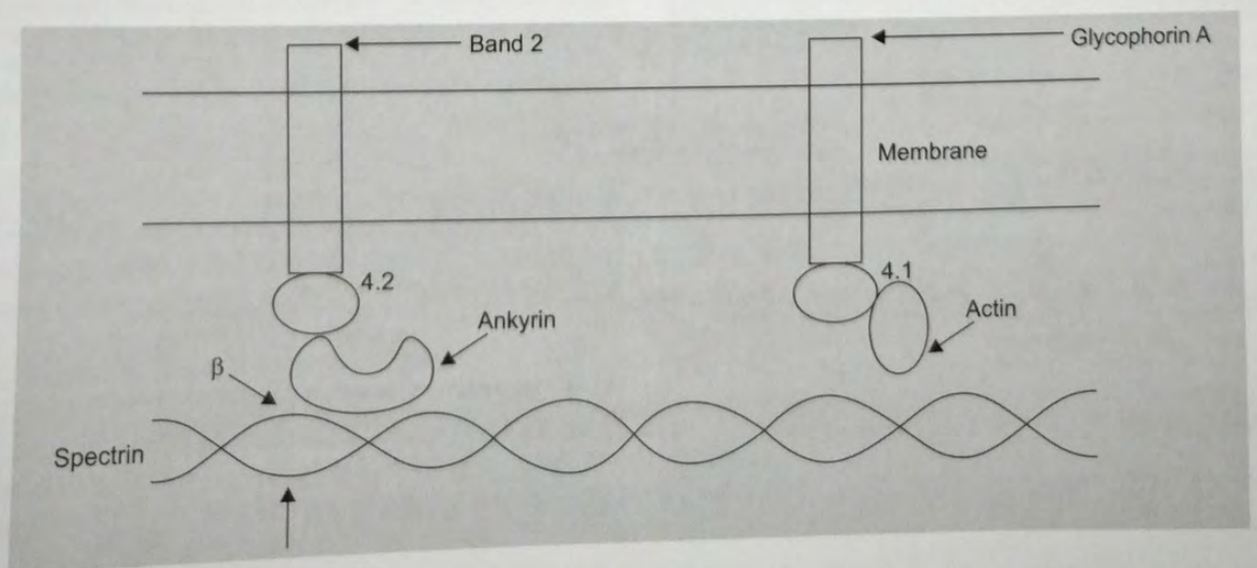


Fig. 5: Hereditary Spherocytosis (Spherical cells lacking central pallor).



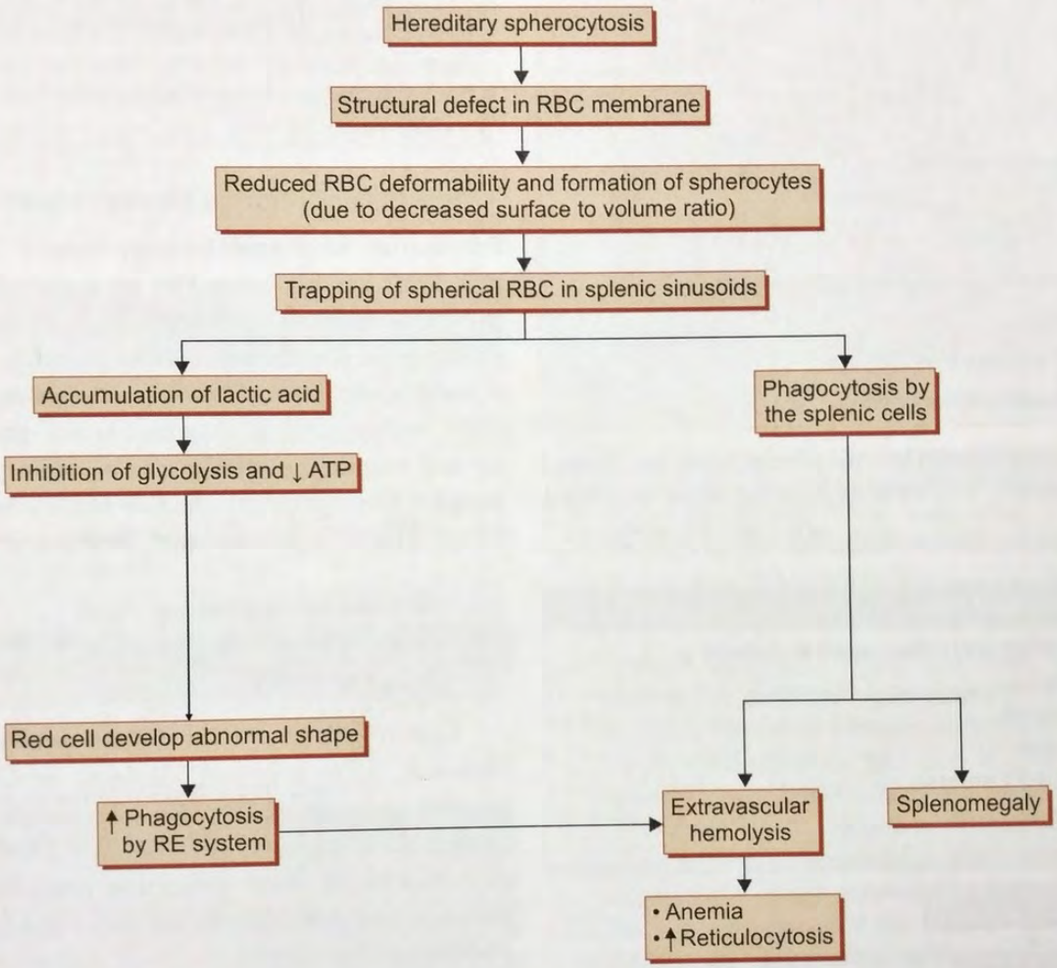
Mnemonic

Most common mutation in **HS** is in **ankyrin** and in *HE* is in a *spectrin*.
To rememeber: S is not for S means spectrin is not in spherocytosis.

Mutations in these proteins can result in HS. Mostly the **mutations** are seen in head region **most commonly in ankyrin**[Q] *[Robbins 8th/e pg 642]* and the next common mutation is in band 3 (Anion channel). Rarely, the mutations can be seen in band 4.2 (Palladin), spectrin and glycophorin A.

Pathogenesis

HS is characterized by *reduced life span of RBC* [10-20 days as compared to 120 days] and has increased osmotic fragility (the pathogenesis is explained above). The main clinical findings are *jaundice, splenomegaly and gallstones*. A characteristic feature of HS is **increase in MCHC**[Q] due to dehydration caused by loss of K^+ and water. It is almost the *only condition where high MCHC is seen*.



Recent Exam Questions

Conditions with spherocytosis
- ***Autoimmune*** hemolytic anemias
- Infections (malaria)
- Burns.
- ABO hemolytic disease ***(NOT with Rh hemolytic disease)***
- G6PD deficiency
- Hereditary spherocytosis

Recent Exam Questions

Autoimmune hemolytic anemias is the **most common** cause of **spherocytosis**.

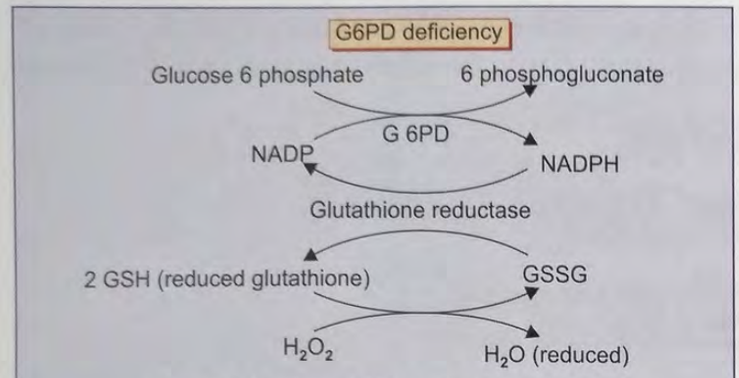
Key Point

- A *characteristic feature* of HS is increase in **MCHC**[Q] due to dehydration caused by loss of K^+ and water.
- *Osmotic fragility* is **increased** in HS.

Pink test[Q] is done to measure the osmotic fragility. **Splenectomy**[Q] is almost always beneficial in HS. After splenectomy anemia is corrected but spherocytes will remain in blood. The vaccination against encapsulated organisms like pneumococccus and H. influenza is also must.

2. Glucose 6-Phosphate Dehydrogenase Deficiency (G-6PD Deficiency)

Abnormalities in the hexose monophosphate shunt or glutathione metabolism resulting from deficient or impaired enzyme function reduce the ability of red cells to protect themselves against oxidative injuries. This results in hemolytic disease. The most important of these is G6PD deficiency. Normal G6PD functioning is required to decrease oxidative damage to RBCs.



Conditions increasing oxidative stress

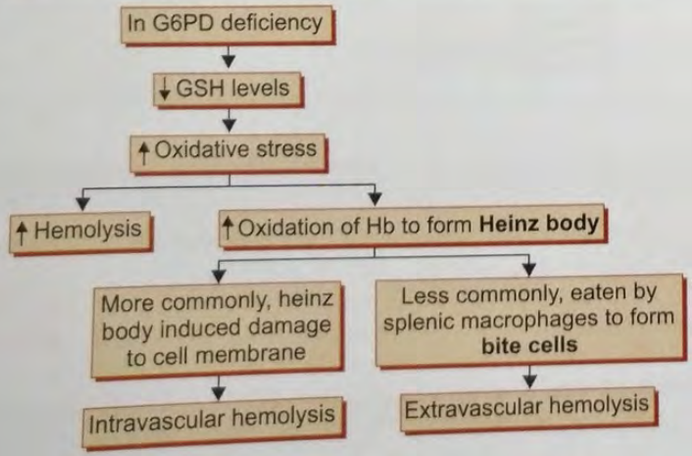
- Food (fava beans)
- Infections (WBC induced free radicals)
- Drugs (antimalarials, sulphonamide).

G6PD deficiency manifests in several distinct clinical patterns. Most common is hemolysis after exposure to oxidant stress.

Recent Exam Questions

Conditions providing protection against malaria

- *G6PD deficiency*
- *α and β thalassemia*
- *Sickle cell disease*
- **Absence of DUFFY antigen**
- Pyruvate kinase deficiency
- HbC



Recent Exam Questions

Heinz body and **bite cells** are seen in G6PD deficiency.

Acute intravascular hemolysis with anemia, hemoglobinemia, and hemoglobinuria usually begins 2 to 3 days following exposure of G6PD-deficient individuals to oxidants. Since only older red cells are at risk for lysis, the episode is *self-limited,* as **hemolysis stops when only the younger red cells remain**. Reticulocytosis is seen in the recovery phase. The **features of chronic hemolytic anemias like splenomegaly and cholelithiasis are absent** because the hemolytic episodes occur intermittently.

Key Point

Features of chronic hemolytic anemias like **splenomegaly** and **cholelithiasis** are **absent** because the hemolytic episodes occur intermittently.

3. Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is the **only hemolytic anemia caused by an acquired intrinsic defect in the cell membrane.** The stem cells of the bone marrow acquire *mutations in Phosphatidyl inositol glycan A (PIGA)* gene, *which is essential for the synthesis of the glycosylphosphatidyl inositol (GPI) anchor.* GPI is responsible for providing an anchor for cell membrane attachment of some proteins. In normal persons, these proteins are also required for inactivating the complement. The examples of these proteins include:

- Decay-accelerating factor or CD55
- Membrane inhibitor of reactive lysis, or **CD59 (most important)**
- C8 binding protein

Out of the above mentioned proteins, *CD 59 is most important.* It is a potent inhibitor of C3 convertase, and thereby prevents spontaneous activation of the alternative complement pathway in vivo. In PNH patients, due to the absence of these protective proteins, red blood cells, platelets and granulocytes become more sensitive to lysis by complement system.

Recent Exam Questions

- PNH is the **only hemolytic anemia** caused by an **acquired intrinsic defect** in the cell membrane.
- The stem cells of the bone marrow acquire mutations in Phosphatidyl inositol glycan A (PIGA) gene.
- The **triad** of **hemolysis, pancytopenia and thrombosis** is *unique to PNH.*
- **Thrombosis** is the ***leading cause of disease related death*** in PNH.

Clinical features include intravascular hemolysis with hemoglobinuria. The complement system is activated by acidotic conditions like exercise (accumulation of lactic acid) or

sleep (due to decreased respiratory rate). Since the respiration decreases at night, so, patient experiences intermittent attacks (**paroxysmal**) of hemolysis at night (**nocturnal**) resulting in passage of red urine (**hemoglobinuria**) in the morning. The dysfunction of the GPI linked proteins on the platelets is responsible for the prothrombotic state.

Diagnosis

- It is best made with **flow cytometry** in which there is presence of **bimodal distribution of the red cells** i.e. cells which are deficient in CD55/CD59 as well normal cells which are CD55+/CD59+.
- Other tests demonstrating increased susceptibility to the complement system which can be used for diagnosis include:
  1. *Ham's acidified serum test:* lysis of erythrocytes on addition of acidified serum.
  2. *Sucrose lysis test:* complement system is increased by the presence of sucrose.

Recent Exam Questions

- PNH is best diagnosed with **flow cytometry** in which there is presence of **bimodal distribution** of the red cells.
- PNH can lead to AML or MDS/aplastic anemia.

4. Immune Hemolytic Anemias

Immune hemolytic anemias are caused because of the formation of anti-RBC antibodies.

Recent Exam Questions

- **Direct Coombs test** detects antibodies on **RBC surface**.
- **Indirect Coombs test** detects anitbodies in **serum**.

Types of Immune Hemolytic Anemia

Warm antibody type	Cold antibody type
Mostly IgG[Q]; rarely IgA	Mostly IgM[Q], rarely IgG
Causes	**Causes**
• Primary (Idiopathic) • **SLE**[Q], rheumatoid arthritis • **B cell** lymphoid neoplasms • Drugs (α-methyldopa, penicillin)	• Primary (Idiopathic) • **M**ycoplasma infection, • Infectious **M**ononucleosis • Lymphoid neoplasms • **Paroxysmal cold hemoglobinuria (IgG)**
Mechanism of hemolysis	**Mechanism of hemolysis**
Extravascular hemolysis (in spleen)	Extravascular hemolysis in cold agglutinin (in liver) Intravascular hemolysis in cold hemolysins
The antibody does not usually fix complement, and is active at 37°C.	Antibodies reacts at 4-6°C, dissociate at 30°C or above

Cold-antibody autoimmune hemolytic anemia (cold AIHA) is subdivided into two clinical categories based on the type of antibodies involved. These two types of cold antibodies are:

a. ***Cold agglutinins***: these are monoclonal IgM antibodies that react at 4 to 6°C. They are called agglutinins because the IgM directed against the I antigen present on the RBCs can agglutinate red cells due to its large size (pentamer). In addition IgM can activate complement resulting in the cells being coated with C3b followed by **extravascular hemolysis**. Examples include *Mycoplasma* pneumonitits and *infectious monoucleosis*. Vascular obstruction by the red cell agglutination can produce Raynaud's pheonomenon, which is characterized by ischemia in the fingers when expose to the cold.

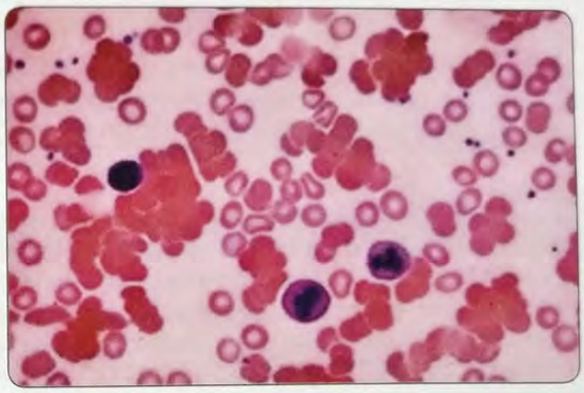


Fig. 6: Cold agglutinin disease

Recent Exam Questions

- **Cold agglutinins:** Are associated with **Mycoplasma** pneumonitits and **infectious mononucleosis**.
- Paroxysmal cold hemolglobinuria (PCH) has the presence of **Donath-Landsteiner antibody**.

b. ***Cold hemolysins***: these are seen in patients with ***paroxysmal cold hemolglobinuria*** (PCH). They are unique because they are *biphasic antierythrocyte autoantibodies*. These antibodies are IgG that is directed against the P blood group antigen. They are called biphasic because they attach to red cells and bind complement at 4°C but the complement activation takes place when the temperature is increased. This is followed by **intravascular hemolysis.** The antibody is called the **Donath-Landsteiner antibody** (previously associated with syphilis, but also with mycoplasma pneumonia measles, mumps, and ill defined viral and "flu" syndromes[Q].

5. Microangiopathic hemolytic anemia (MAHA)

MAHA is a microangiopathic subgroup of hemolytic anemia (anemia, loss of red blood cells through destruction) caused by factors in the small blood vessels. The endothelial layer of small vessels is damaged with resulting fibrin deposition and platelet aggregation. As red blood cells travel through these damaged vessels, they are fragmented resulting in intravascular hemolysis. It is identified by the finding of anemia and **schistocytes, "burr cells," "helmet cells," and "triangle cells"on microscopy (should be > 3/5000 cells) and these should have 1-3 sharp spicules.** It is associated with conditions like **DIC[Q] (most commonly)**, malignant hypertension, SLE, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and disseminated cancer.

Recent Exam Questions

- **DIC** is the **most common** cause of **MAHA**.
- **Prosthetic cardiac valves**, aortic aneurysm and cavernous hemangioma are associated with **Macroangiopathic** hemolytic anemia.

6. Hemoglobinopathies

Key Point

- HbA is $\alpha_2\beta_2$ (95-96%)
- HbA_2 is $\alpha_2\delta_2$ (3-3.5%)
- HbF is $\alpha_2\gamma_2$ (present in the fetal life). As gestational age increases, the γ chains are replaced by the β chains, resulting in formation of adult hemoglobin, HbA.

A. Sickle cell anemia

This is characterized by the presence of an abnormal type of hemoglobin called HbS. It results from a point mutation that causes the glutamic acid to be replaced by valine at the β6 position of the globin chain. If the individual is homozygous, it is represented as HbSS (1 gene each from both the parents) whereas the heterozygous is HbAS (1 gene from one parent is for HbS and the other gene is for HbA). Heterozygotes are *protected against falciparum malaria.*

Recent Exam Questions

In Sickle cell anemia, **point mutation** at **β6** position causes replacement of glutamic acid by valine.

Mnemonic

Glutamic acid can **G**o and **V**aline is **W**elcome

Pathogenesis

When deoxygenated, HbS molecules becomes insoluble, undergoes aggregation and *polymerization* producing a sickle cell or holly leaf shape of the RBCs. Initially, this process is reversible (on getting oxygenated, the cells attain there normal shape) but repeated attacks of aggregation can cause irreversible sickling of the RBCs which also causes oxidative damage to the red cells.

Key Point

Sickling of hemoglobin affects its **solubility** and **NOT** its *function/stability/affinity.*

Reversible sickled cells exhibit increased adhesiveness within the microcirculation of organs with sluggish blood flow thereby causing episodes of hypoxia and infarction called as *vasoocclusive crisis or pain crisis.* Hemoglobin released from the lysed red cells causes inactivation of NO thereby increasing the severity of ischemia.

Irreversible sickled cells get sequestrated in the spleen thereby contributing to *extravascular hemolysis.*

Recent Exam Questions

- **Sequestration crisis** is the **most dangerous** crisis in sickle cell anemia because it can cause heart failure.
- **Vaso occlusive crisis** are the **most common** type of crisis in sickle cell disease.

Factors Affecting Sickling of the Hemoglobin

Amount of HbS *(most important factor)* and its interaction with other hemoglobins
The presence of relatively low concentration of HbS (25-40%) and the presence of HbA in heterozygotes prevents efficient HbS sickling thereby contributing to decreased severity of the disease in them. In comparison, the homozygotes have full blown disease. Other hemoglobins like *fetal hemoglobin (HbF) and HbC* (having a substitution of lysine for glutamic acid at β6 position) *have inhibitory effect* on the disease.
Hemoglobin concentration of the red cell
Hb concentration of the cell, i.e. MCHC affects polymerization to a great extent.
Decrease in pH
Acidosis increases chances of sickling.
Duration of time red cells are exposed to decreased oxygen tension
Organs having slow or sluggish circulation (bone and spleen) have an increased chance of sickling.

Key Point

- Sickle cell anemia initially shows splenomegaly and later **autosplenectomy** because of hypoxia and infarction.
- In most other causes of anemia, ESR is high **except** in sickle cell disease. ***ESR is less is sickle cell disease.***

Clinical features

- Severe anemia results in *jaundice and pigment gallstone formation* and is associated with *reticulocytosis.* Vaso-occlusive crisis clinically manifests as painful episodes in affected organs of the body. In the bone, it presents as dactylitis or inflammation of the bones of hands and feet, so called *Hand foot syndrome,* increased chances of *Salmonella* osteomyelitis, avascular necrosis of femoral head, *fish mouth appearance of vertebra* (due to occlusion of vertebral arteries) and prominent cheek bones and *crew cut appearance of skull* (both because of extramedullary hematopoiesis).
- Other organs of the body may also be affected, e.g. lungs (*acute chest syndrome* characterized by cough, fever and chest pain), brain (seizures or stroke), skin (leg ulcers), penis (stagnation in corpora cavernosa leads to priapism) or spleen. In the initial stages, there is splenomegaly due to congestion and trapping of red cells in the vascular sinusoids (**Gamma gandy bodies;** consisting of *foci of fibrosis having iron or calcium salts* deposited in connective tissue are seen).

- Prolonged hypoxia and infarction can lead to **autosplenectomy** which increases susceptibility to infection with capsulated organisms like *Hemophilus influenzae, Pneumococcus, etc.*
- Parvovirus infection can precipitate an attack of aplastic crisis also. Chronic anemia can cause hyperdynamic circulation resulting in cardiomegaly.

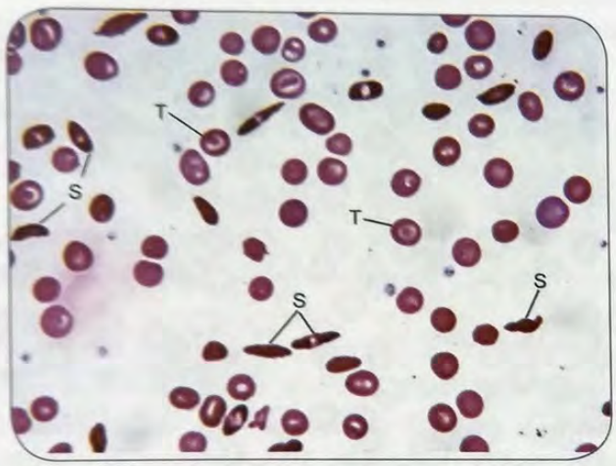


Fig. 7: Sickle Cell Anemia (S: Sickled cells; T: Target cells).

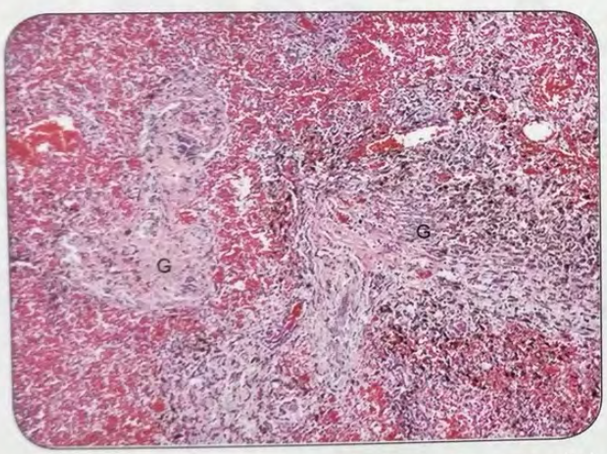


Fig. 8: Spleen in sickle Cell Anemia (G: Gamma gandy body).

Recent Exam Questions

Keywords of sickle cell disease

- Fish mouth vertebra.
- Salmonella osteomyelitis.
- Crew cut appearance of skull.
- Gamma gandy bodies.
- ↓ ESR.
- Autosplenectomy.
- **HPLC:** Best technique for diagnosis.

Peripheral smear shows anisopoikilocytosis, presence of sickle cells, **target cells**, polychromatophilia and ovalocytes. **Howell Jolly bodies** (composed of chromatin aggregates in red cells) are *seen particularly after autosplenectomy.*

Diagnosis is done with the help of the following:

- **Sickling test**: Sickling is induced by a reducing agent like ***2% metabisulfite or dithionite*** to blood. However, this test cannot differentiate between sickle cell disease and sickle cell trait.
- **Hb electrophoresis:** It is carried out on a cellulose acetate membrane (pH 8.6). HbS is slower moving as compared to normal HbA, so, heterozygotes show 2 bands of hemoglobin.
- **HbF estimation** (by alkali denaturation method) shows HbF to be 10-30% in homozygotes.
- **HPLC** is the **best investigation** for the diagnosis of sickle cell disease.
- **Prenatal genetic testing** can be done using the enzyme **MstII endonuclease**. **Chorionic villus sampling** at **10-12 weeks of gestation** is used to estimate fetal DNA abnormality.

Recent Exam Questions

On Hb electrophoresis

- Hb**S** moves **S**lowly towards Anode.
- Hb**A** moves *faster* towards **A**node.

B. Thalassemia

It is a group of autosomal recessive inherited disorders characterized by decreased synthesis of either α or β globin chain of HbA. It is the most common *type of hemoglobinopathy in the world.* β and α thalassemia is caused by deficient synthesis of β and α chains respectively.

Key Point

Management of sickle cell anemia is done by ensuring that the patient should be properly hydrated and with the help of drugs like **hydroxyurea** (it increases HbF and NO and acts as an anti-inflammatory agent), 5'**azacytidine**, etc.

The a globin chain is coded by a gene on chromosome 16 and the gene for β globin chain is located on chromosome 11. The clinical features therefore result from deficiency of one chain and the relative excess of the other chain.

Pathogenesis of β thalassemia

i. **β thalassemia syndromes**

This type of thalassemia is caused by point mutations. These are of two types:

1. β^0 *thalassemia* – Characterized by total absence of β chains in the homozygous state.
2. β^+ *thalassemia* – Characterized by reduced synthesis of β chains in the homozygous state.

Recent Exam Questions

BEWARE!

- β thalassemia: Gene **mutation**.
- α thalassemia: Gene ***deletion***.

Mutations can be caused due to the following mechanisms:

a. *Promoter region mutation*: Causes reduced transcription of the β chains leading to β^+ thalassemia.
b. *Chain terminator mutations*: Either creation of a stop codon in exon or frameshift mutation inducing a downstream stop codon leads to premature chain termination resulting in β° thalassemia.

Key Point

Splicing mutations: Are the *most common* cause of β **thalassemia**.

c. *Splicing mutation*: They are the most common *cause* of thalassemia resulting in unspliced mRNA being degraded in the nucleus leading to the development of either β^+ thalassemia or β° thalassemia.

Recent Exam Questions

Normal ratios in bone marrow

- Myeloid: Erythroid is 3:1.
- Fat cell: Erythroid is 1:4.
- Fat cell: Hematopoietic cell is 1:1.

Recent Exam Questions

- **Reversal** of Myeloid Erythroid **(M:E) ratio** is seen in **thalassemia major**.
- **Thalassemia major** (also called **Cooley anemia**): is a severe **transfusion dependent** anemia in this condition **HbF** is **markedly increased**.

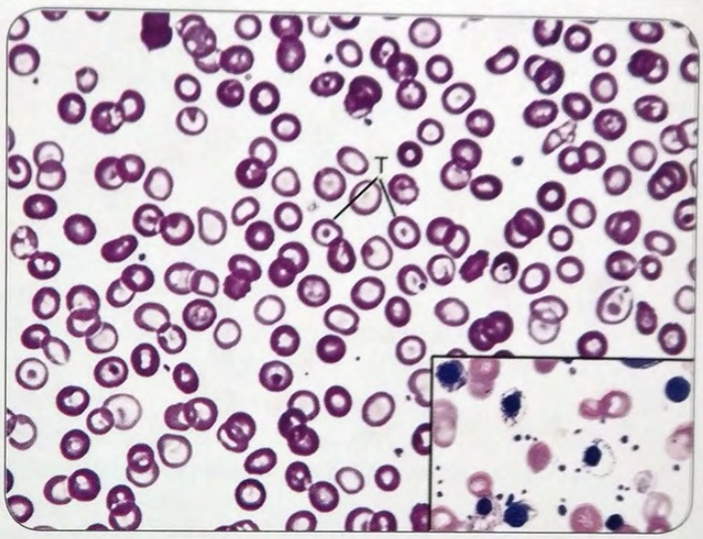
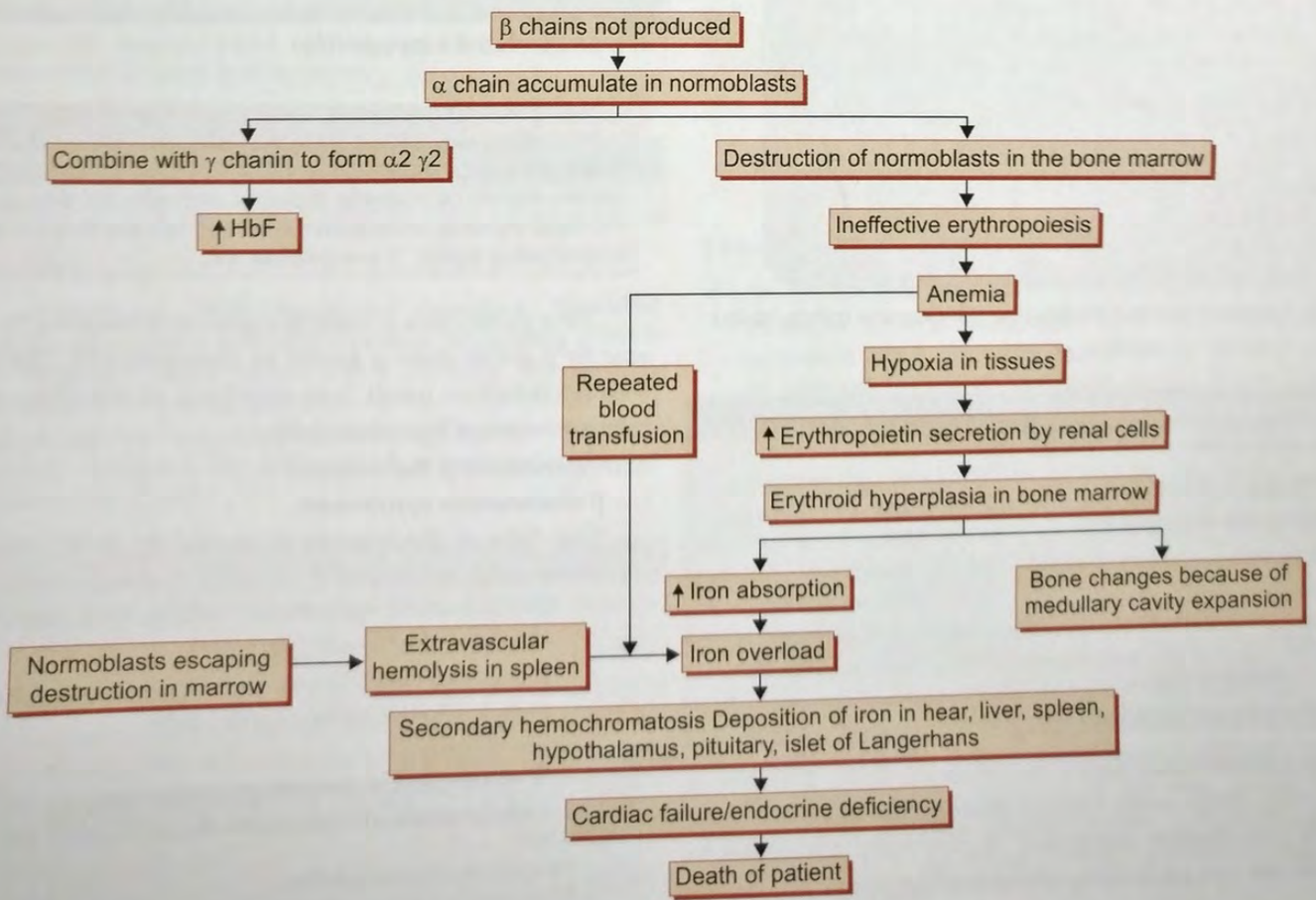


Fig. 9: Thalassemia smear heaving hypochromic cells, target cells (T). Inset shows nucleated RBC.



Clinical features

Clinically β, thalassemia is of three types: thalassemia major, thalassemia intermedia and thalassemia minor.

a. **Thalassemia major** (also called **Cooley anemia**): It is seen in individuals *homozygous for the β thalassemia genes* (β^+/β^+or β°/β°); these individuals have a severe *transfusion dependent anemia* which manifests at usually 6 to 9 months after birth. There is presence of prominent frontal and cheek bones, hepatosplenomegaly (due to extramedullary hemopoiesis), jaundice, increased risk of pigment stones and endocrinological manifestations as delayed puberty (due to GH deficiency), bone fractures (hypoparathyroidism) and/or diabetes mellitus (iron in islet of Langerhans).

Peripheral smear shows moderate to *severe anemia, anisocytosis, microcytic hypochromic red cells, target cells, nucleated red cells, basophilic stippling, Howell Jolly bodies*, etc. There is reticulocytosis and **left shift in the leukocytes**. Since β chains are not produced but γ chains are synthesized normally, **HbF is markedly increased and is the major constituent of red cells (90%).** MCH, MCV and MCHC are reduced.

Bone marrow is hypercellular with erythroid hyperplasia causing **reversal of normal M:E ratio** (it becomes 1:3 in thalassemia). Pink inclusions are seen in the normoblasts (caused by α chain accumulation). Widening of the diploe gives rise to *crew cut appearance* on skull X-ray.

Key Point

Thalassemia minor (also called **Thalassemia trait**): HbA_2 is characteristically elevated.

b. **Thalassemia minor or trait:** It is seen in individuals heterozygous with one β thalassemia gene and one normal gene (β^+/β or β^0/β). It is more common clinically than the major variant and offers resistance against falciparum malaria. These patients are usually asymptomatic with only mild anemia.

Peripheral smear shows *microcytic, hypochromic cells with basophilic stippling and presence of target cells.* MCH, MCV and MCHC are reduced. The levels of **HbA_2 are characteristically elevated** (It is normally 3-3.5% but in thalassemia trait, the level is *3.6-8%*; this is a *diagnostic feature* of this disease). HbF is mildly increased (5%).

Key Point

Naked Eye Single Tube Red cell Osmotic Fragility (NESTROF) is a **Screening test** and ***NOT a diagnostic*** test used for this condition.

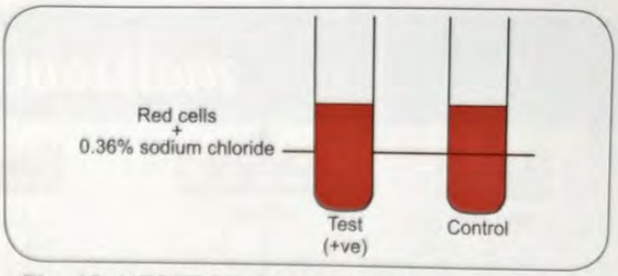


Fig. 10: NESTROF test to screen thalassemia trait.

NESTROF Test

A Screening test used for this condition is **N**aked **E**ye **S**ingle **T**ube **R**ed cell **O**smotic **F**ragility **(NESTROF)** test. In this test 2 blood samples (1of a normal person serving as control and 1 of patient) are added to 2 tubes with 0.35% saline. After 30 min a white paper with a black line is placed behind both the tubes. The RBCs in control sample undergo hemolysis so the black line is visible whereas cells in thalassemia trait are resistant so black line is not clearly visible.

c. **Thalassemia intermedia:** The patients show anemia but do not require transfusions. The features of the disease are intermediate between the two other types of thalassemia discussed above.

Recent Exam Questions

- **HbF** is shown by acid elution method (**Kleihauer's** cytochemical method[Q]).
- **Qualitative** estimation of HbF is done by **Apt test**[Q].
- **Quantitive** estimation of HbF is done by **Kleihauer test**[Q]..

Important Investigations

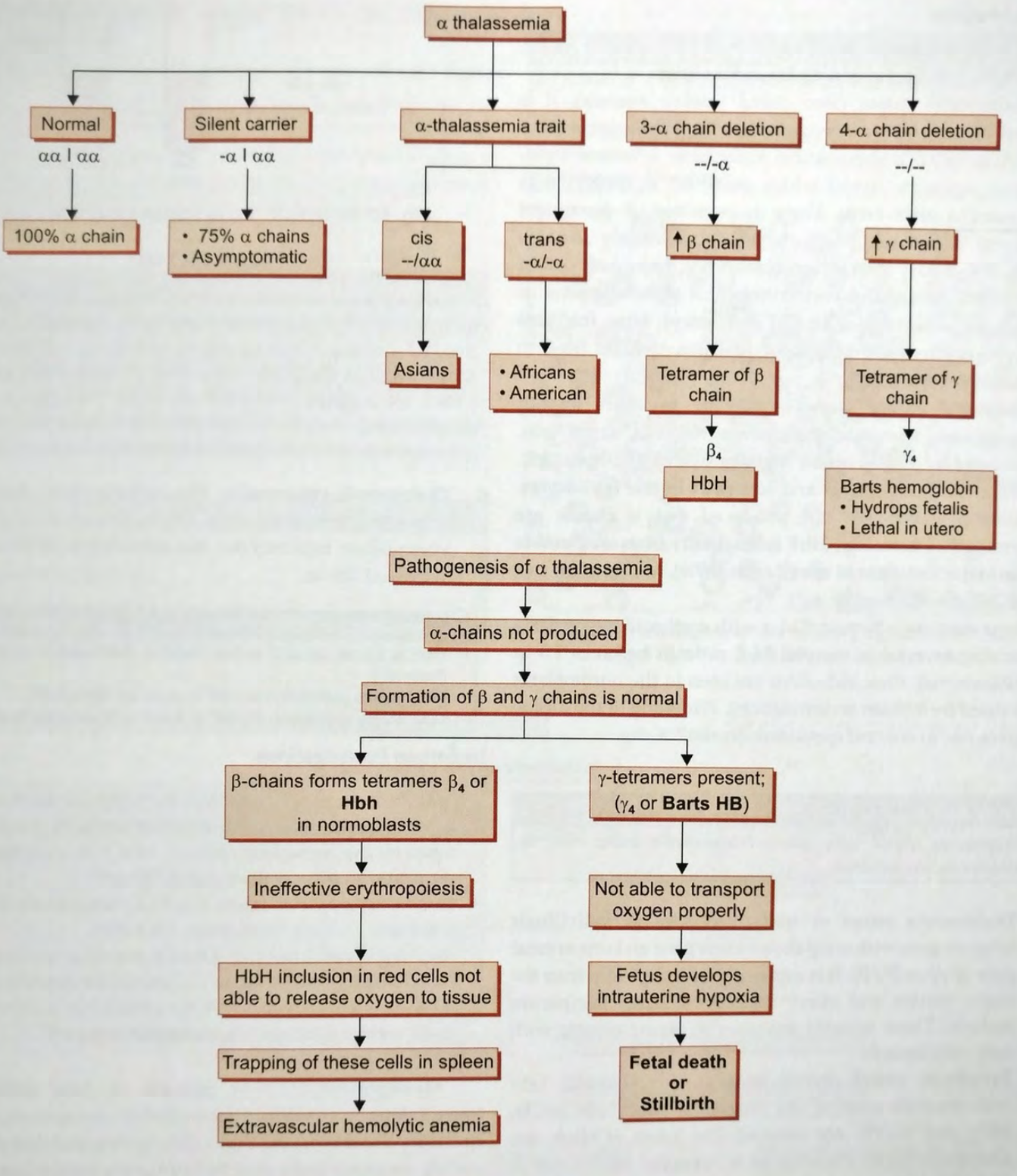
- Apart from the above mentioned investigations, the thalassemia patients must undergo **Hb electrophoresis** to determine the nature of the hemoglobin present. HbA_2[Q] is characteristically elevated in a patient of **thalassemia minor**[Q].
- Globin chain synthesis can be studied by calculating a: **β ratio**. It is normally 1:1 but in thalassemia, it is **5-30:1**.
- **Alkali denaturation method**[Q] is done to determine the concentration of HbF which is relatively resistant to denaturation by strong alkali like NaOH/KOH as compared to HbA. In the RBCs, HbF is shown by acid elution method **(Kleihauer's cytochemical method**[Q]**)**.

Management of these patients is done with **blood transfusions** (to maintain hemoglobin concentration), **iron chelators** like desferrioxamine, deferiprone and defrasirox (to chelate excessive iron) and **bone marrow transplantation** (if HLA matched donor is available).

Preventive measures include marriage counseling and chorionic villus sampling at 9-10 weeks followed by PCR analysis. All antenatal females with Hb <11 gm% should undergo NESTROF test.

ii. **α thalassemia syndromes**

This type of thalassemia is **caused by gene deletion**[Q]. These are of four types as depicted in the flowchart.



Concept

Since free β and γ chains are more soluble than free α chains and form fairly stable homotetramers, hemolysis and ineffective erythropoiesis are **less severe** than in β-thalassemias.

In the **silent carrier** state, the patients are clinically asymptomatic. The clinical picture in **α-thalassemia trait** is similar to that discussed in β-thalassemia minor which means there is presence of microcytosis, minimal or no anemia, and no abnormal physical signs. **HbH**^{Q} is a major cause of anemia, as precipitates of oxidized HbH form in older red cells, which are then removed by splenic macrophages. This produces a moderately severe anemia resembling β-thalassemia intermedia. **Hydrops fetalis** is the *most dangerous form of a-thalassemia* and severe tissue anoxia leads to intrauterine fetal death. The fetus shows severe pallor, generalized edema, and massive hepatosplenomegaly.

Multiple Choice Questions

RBC: GENERAL ASPECTS

1. **Which of the following is associated with an intrinsic defect in the RBC membrane?** *(AIIMS May 2012)*
   (a) Autoimmune hemolytic anemia
   (b) Hereditary spherocytosis
   (c) Microangiopathic haemolytic anemia
   (d) Thermal injury causing anemia

2. **Which of the following is not a stem cell of the bone marrow?** *(AI 2012)*
   (a) Lymphoblast (b) Myeloblast
   (c) Myoblast (d) Normoblast

3. **Which of the following surface glycoproteins is most often expressed in human hematopoietic stem cell?**
   (a) CD 22 (b) CD 40 *(AIIMS May 2008)*
   (c) CD 15 (d) CD 34

4. **Reticulocytosis is seen in all except:**
   (a) P.N.H. *(AIIMS May 2007)*
   (b) Hemolysis
   (c) Nutritional anemia
   (d) Dyserythropoietic syndrome

5. **Which of these are seen on Romanowsky stain?**
   (a) Reticulocytes *(PGI Dec 2004)*
   (b) Basophilic stippling
   (c) Heinz bodies
   (d) Howell-Jolly bodies
   (e) Cabot ring

6. **Which of the following surface glycoproteins is most often expressed in human hematopoietic stem cell?**
   (a) CD22 (b) CD40 *(Delhi PG 2010)*
   (c) CD15 (d) CD34

7. **Inappropriate erythropoietin level is found in all except:** *(UP 2001)*
   (a) Renal cell carcinoma
   (b) Lung disease
   (c) High altitude
   (d) Benign liver tumor

8. **The size of the red blood cells is measured by:**
   (a) MCV (b) MCHC *(UP 2007)*
   (c) ESR (d) MCH

MOST RECENT QUESTIONS

9. **Anemia which is associated with pancytopenia is:**
   (a) Hemolytic (c) Megaloblastic
   (b) Iron deficiency (d) All

10. **Hematuria with dysmorphic RBCs are seen in:**
    (a) Acute glomerulonephritis
    (b) Renal TB
    (c) Renal calculi
    (d) Chronic renal failure

11. **MCHC is increased in:**
    (a) Iron deficiency anemia
    (b) Spherocytosis
    (c) Thalassemia
    (d) All

12. **In polycythemia vera, all are raised except:**
    (a) Hematocrit
    (b) Platelet count
    (c) RBCs
    (d) Erythropoietin

13. **The type of anemia seen in chronic renal failure is:**
    (a) Microcytic (b) Normocytic
    (c) Macrocytic (d) All of the above

14. **Burr cell is seen in:**
    (a) Uremia
    (b) Hepatocellular carcinoma
    (c) Gastric carcinoma
    (d) Ovarian carcinoma

15. **Acanthocytes are seen in:**
    (a) Abetalipoproteinemia
    (b) Hartnup disease
    (c) Whipple disease
    (d) None

16. **Reticulocytes are stained with:**
    (a) Methyl violet
    (b) Brilliant Cresyl blue
    (c) Sudan black
    (d) Indigo carmine

17. **Storage form of iron:**
    (a) Ferritin (b) Transferrin
    (c) Hepcidin (d) Ferroportin

18. **Hb is a good buffer because of:**
    (a) Histidine residues
    (b) Protein nature
    (c) Acidic nature
    (d) Iron molecule

19. **Normal platelet count is found in:**
    (a) Wiskott Aldrich syndrome
    (b) Henoch Schonlein purpura
    (c) Immune thrombocytopenia
    (d) Dengue fever

20. In an adult man, there is about how much grams of hemoglobin in the circulating blood?
(a) 350 (b) 500
(c) 900 (d) 1000

21. The longest living WBC is which one of the following
(a) Lymphocyte (b) Eosinophil
(c) Neutrophil (d) Monocyte

22. Freezing point of normal human plasma is:
(a) 4°C (b) 0°C
(c) –0.54°C (d) –1.54°C

23. The normal albumin: globulin (A/G) ratio blood is
(a) 5:1 (b) 2:1
(c) 1:2 (d) 1:1

24. Thrombosthenin is:
(a) Coagulation protein
(b) Contractile protein
(c) Thrombus inhibiting protein
(d) Protein for platelet production

25. The best method for estimation of hemoglobin concentration in blood is:
(a) Acid hematin method
(b) Alkali hematin method
(c) Cyanmethemoglobin method
(d) Any of the above

26. The number of Fe^{2+} atoms in one Hb molecule:
(a) 1 (b) 2
(c) 4 (d) 8

27. Linzenmeyer is used to measure:
(a) Bleeding time
(b) Clotting time
(c) Prothrombin time
(d) ESR

28. Serum contains all the clotting factors except:
(a) Plasma thromboplastin
(b) Labile factor
(c) Hageman factor
(d) Christmas factor

29. Progenitor hematopoetic stem cells originate in which of the following?
(a) Bone marrow (b) Thymus
(c) Lymph node (d) Spleen

30. Haematocrit is the ratio of:
(a) WBC to whole blood
(b) Platelets to whole blood
(c) RBCs to whole blood
(d) Total blood cells to plasma

31 The anaemia associated with leukaemia is:
(a) Iron deficiency
(b) Megaloblastic type
(c) Myelophthisic type
(d) None of the above

32. Which of the following is a distinguishing feature of reticulocyte?
(a) Constitute 10% of the red cells
(b) No nucleus
(c) Smaller in the size than RBCs
(d) Mature in lymph nodes

33. Life span of RBCs in infant is:
(a) 100–120 days (b) 60–80 days
(c) 80–100 days (d) 40–60 days

34. Increase in MCHC is associated with?
(a) Iron deficiency anemia
(b) Megaloblastic anemia
(c) Anemia of chronic disease
(d) Hereditary spherocytosis

35. MCHC criteria to diagnose iron deficiency anemia:
(a) <32 (b) <34
(c) <28 (d) <30

MEGALOBLASTIC ANEMIA, APLASTIC ANEMIA

36. Which of these does not indicate megaloblastic anemia? *(AIIMS Nov 2012)*
(a) Increased reticulocyte count
(b) Raised Bilirubin
(c) Mild splenomegaly
(d) Nucleated RBC

37. A patient with Hb-6 gm%, TLC 1200, platelet-60,000, MCV 12fl, what is the diagnosis? *(AIIMS May 2008)*
(a) Aplastic anemia
(b) Megaloblastic anemia
(c) PNH
(d) Myelofibrosis

38. Macrocytosis in complete blood count can be diagnosed by: *(PGI Dec 2006)*
(a) ↑ MCV
(b) ↑ MCHC
(c) ↑ Hematocrit
(d) ↑ Red cell distribution width

39. Which is the true statement regarding megaloblastic anemia? *(PGI Dec 01)*
(a) Megaloblastic precursors are present in bone marrow
(b) Mean corpuscular volume is increased
(c) Serum LDH is increased
(d) Thrombocytosis occurs
(e) Target cells are found

40. Macrocytic anemia may be seen in all of these except: *(PGI June 2002)*
(a) Liver disease
(b) Copper deficiency
(c) Thiamine deficiency
(d) Vitamin B_{12} deficiency
(e) Orotic aciduria

41. Causes of vitamin B_{12} deficiency megaloblastic anemia are: *(PGI June 2005)*
(a) Fish tap worm infestation
(b) Dilantin therapy

(c) Gastrectomy
(d) Ileal resection
(e) Methotrexate

42. Aplastic anemia can progress to all except: *(Delhi PG 2010)*
(a) AML
(b) Myelodysplastic anemia
(c) Pure red cell aplasia
(d) Paroxysmal nocturnal hemoglobinuria

43. Serum vitamin B_{12} level is increased in all except: *(UP 2000)*
(a) Hepatitis
(b) Cirrhosis of liver
(c) Hepatocellular carcinoma
(d) Cholestatic jaundice

MOST RECENT QUESTIONS

44. Normocytic normochromic anemia is seen in all except:
(a) Aplastic anemia
(b) Chronic renal disease
(c) Pure red cell aplasia
(d) Thalassemia

45. A 76 years old male presented with anemia with splenomegaly. PBS shows tear drop shaped cells and bone marrow examination was normal. The diagnosis is:
(a) Myelofibrosis
(b) Iron deficiency anemia
(c) Folic acid deficiency
(d) CML

46. Abnormality in Schilling test can be seen in all of the following except:
(a) B_{12} deficiency (b) Folic acid deficiency
(c) Ileal disease (d) Bacterial overgrowth

47. Cause of macrocytic anemia is:
(a) Sideroblastic anemia
(b) Iron deficiency
(c) Thalassemia
(d) Hypothyroidism

48. Pure red cell aplasia is associated with:
(a) Thymoma
(b) Renal cell carcinoma
(c) Hepatocellular carcinoma
(d) Prostate carcinoma

49. Vitamin B_{12} malabsorption is caused by:
(a) Ankylostoma duodenale
(b) Diphyllobothrium latum
(c) Giardiasis
(d) Taenia solium

50. Maturation failure in poor absorption of the vitamin B_{12} is associated with:
(a) Microcytic hypochromic anemia
(b) Sickle cell anemia
(c) Anemia occurs after 3-4 months of poor absorption
(d) Causes polycythemia

51. FIGLU test is done for:
(a) Cyanocobalamin deficiency
(b) Folic acid deficiency
(c) Thiamine deficiency
(d) Riboflavin deficiency

52. Hypersegmented neutrophils are present in which of the following anemia?
(a) Hemolytic (b) Iron deficiency
(c) Megaloblastic (d) Aplastic

53. Hypersegmented neutrophils are seen in:
(a) Thalassemia
(b) Iron deficiency
(c) Megaloblastic anemia
(d) All

54. Howell-Jolly bodies are seen in:
(a) Alcoholics
(b) Cirrhosis
(c) Nephrotic syndrome
(d) Postsplenectomy

55. Macrocytic anemia is caused by:
(a) Hookworm infestation
(b) Iron deficiency
(c) Diphyllobothrium latum infestation
(d) All of the above

56. An adult who develops pure red cell aplasia should be explicitly evaluated for which of the following?
(a) Gastric adenocarcinoma
(b) Pancreatic adenocarcinoma
(c) Papillary thyroid cancer
(d) Thymoma

57. All of the following can cause reticulocytosis except:
(a) Aplastic anemia
(b) Thalassemia
(c) Sickle cell anemia
(d) Chronic blood loss

58. Which of following viruses causes hemolysis of red blood cells?
(a) Rubella
(b) Human parvo virus B19
(c) Measles
(d) Dengue virus

59. Which of the does not indicate megaloblastic anemia?
(a) Raised bilirubin
(b) Mild splenomegaly
(c) Increased reticulocyte count
(d) Nucleated red cells

60. Hb A2 is raised in which of the following conditions?
(a) Beta thalassemia trait
(b) Sickle cell anemia
(c) Hereditory spherocytosis
(d) G6 PD deficiency

61. **Reticulocytosis is not seen in which of the following conditions?**
(a) Thalassemia
(b) Hereditary spherocytosis
(c) Chronic renal failure
(d) Sickle cell anemia

62. **Schilling test is used for identification of which of the following?**
(a) Fat absorption
(b) Vit K absorption
(c) Vitamin B12 absorption
(d) Vitamin D absorption

MICROCYTIC ANEMIA: IDA, AOCD, SIDEROBLASTIC ANEMIA

63. **A 60-year-old male patient with history of rheumatoid arthritis presents with the following: Hb:4.5g/dL. platelet count is 2 lakh/mm³. TLC: 6000/mL, serum ferritin is 200µg/dL, serum iron 30mg/dL and TIBC 280ng/L. Which of the following is the most likely diagnosis?**
(a) Anaemia of chronic disease *(AIIMS Nov 2011)*
(b) Thalassemia minor
(c) Iron deficiency anemia
(d) Autoimmune haemolytic anemia

64. **A 20-year-old female presents with the following laboratory values: hemoglobin 9gm%, MCV is 55%, RBC is 4.5 million/mm³. There is no history of blood transfusion. What is the most likely diagnosis out of the following?** *(AIIMS Nov 2011)*
(a) Thalassemia major
(b) Thalassemia minor
(c) Iron deficiency anemia
(d) Anemia of chronic disease

65. **A 13-yr-girl with fatigue and weakness was found to be having reduced hemoglobin. Her MCV 70fl, MCH 22pg and RDW was 28. What is her most likely diagnosis?**
(a) Iron deficiency anemia *(AI 2010)*
(b) Thalassemia minor
(c) Sideroblastic anemia
(d) Thalassemia major

66. **Ringed sideroblasts are seen in:** *(AI 2008)*
(a) Iron deficiency anemia
(b) Myelodysplastic syndrome
(c) Thalassemia
(d) Anemia of chronic disease

67. **A 30 years old female, RBC count 4.5 million, MCV 55fl, TLC 8000/mm³. There is no history of blood transfusion. What is the likely diagnosis?**
(a) Iron deficiency anemia *(AIIMS May 2008)*
(b) Thalassemia major
(c) Thalassemia minor
(d) Megaloblastic anemia

68. **The pathogenesis of hypochromic anemia in lead poisoning is due to:** *(AIIMS Nov 2002)*
(a) Inhibition of enzymes involved in heme biosynthesis
(b) Binding of lead to transferrin, inhibiting the transport of iron
(c) Binding of lead to cell membrane of erythroid precursors.
(d) Binding of lead to ferritin inhibiting their breakdown into hemosiderin

69. **A patient presents with increased serum ferritin, decreased TIBC, increased serum iron, % saturation increased. Most probable diagnosis is:**
(a) Anemia of chronic disease *(AIIMS Nov 2006)*
(b) Sideroblastic anemia
(c) Iron deficiency anemia
(d) Thalassemia minor

70. **Anemia in CRF is due to:** *(PGI Dec 2006)*
(a) ↓ erythropoietin
(b) ↓RBC survival
(c) ↓ folate
(d) Bone marrow hypoplasia
(e) Iron deficiency

71. **Iron deficiency anemia is seen in:** *(PGI Dec 2006)*
(a) Chronic renal failure
(b) Billroth II operation
(c) Hookworm infection
(d) Celiac sprue
(e) Carcinoma cecum

72. **Bone marrow iron is increased in:** *(PGI Dec 2003)*
(a) Thalassemi(a)
(b) Iron deficiency anemi(a)
(c) Anemia in chronic disease.
(d) PNH
(e) Megaloblastic anemi(a)

73. **Microcytosis is seen in:** *(PGI June 2004)*
(a) Thalassemia (b) Hb Lepore
(c) Hb Barts (d) Gastrectomy
(e) Systemic sclerosis

74. **True about iron deficiency anemia is:** *(PGI June 2005)*
(a) Microcytic hypochromic anemia
(b) Decreased TIBC
(c) Increased ferritin
(d) Bone marrow iron decreased earlier than serum iron

75. **In Anemia of chronic disease, what is seen?**
(a) TIBC ↑ (b) S. Iron ↑ *(Delhi PG-2008)*
(c) BM iron ↓ (d) S. ferritin ↑

76. **A 30 years old female asymptomatic not requiring blood transfusion has Hb-13 gm%, HbF-95%, HbA_2 1.5%. Which of the following is the most likely diagnosis?**
(a) Beta-Heterozygous thalassemia *(Delhi PG-2008)*
(b) Beta-Homozygous thalassemia
(c) Intermediate thalassemia
(d) Persistently raised HbF

77. **The condition which does not cause microcytic hypochromic anemia is:** *(Karnataka 2008)*
(a) Iron deficiency
(b) Hookworm infestation
(c) Absence of intrinsic factor
(d) Prolonged bleeding episodes

78. **Hypochromic microcytic blood picture is seen in all of the following conditions except:** *(Karnataka 2007)*
(a) Iron deficiency anemia
(b) Lead poisoning
(c) Rheumatoid arthritis
(d) Sideroblastic anemia

MOST RECENT QUESTIONS

79. **Lead poisoning is associated with:**
(a) Microcytic hypochromic anemia
(b) Macrocytic anemia
(c) Decreased levels of zinc protoporphyrin
(d) Howell-Jolly bodies

80. **Microspherocytes in peripheral blood smear are seen in:**
(a) Congenital spherocytosis
(b) Autoimmune acquired hemolytic anemia
(c) Thalassemia
(d) All of the above

81. **"Macropolycytes" in peripheral smear is a feature of:**
(a) Hereditary spherocytosis
(b) Iron deficiency anemia
(c) Sickle cell anemia
(d) Megaloblastic anemia

82. **Anemia of chronic disease is characterized by of all except:**
(a) ↓ Serum iron level
(b) ↓ TIBC
(c) ↓ Serum ferritin level
(d) Increased macrophages iron in marrow

83. **Most common cause of anemia is:**
(a) Iron deficiency
(b) Folic acid deficiency
(c) Sideroblastic anemia
(d) Pernicious anemia

84. **A patient of anemia due to chronic inflammation, the positive finding is:**
(a) Serum iron is increased
(b) S. ferritin is decreased
(c) TIBC is decreased
(d) Presence of normal iron in blasts

85. **Which of the following glycoproteins is transported in plasma in iron metabolism?**
(a) Spectrin (b) Transferrin
(c) Ferritin (d) Hemosiderin

86. **All are laboratory finding in iron deficiency anemia except:**
(a) Decreased serum iron
(b) Increased total iron binding capacity
(c) Decreased serum ferritin
(d) Increased mean corpuscular volume

87. **Best parameter for assessment of body iron stores is:**
(a) Serum iron
(b) Serum TIBC
(c) Serum ferritin
(d) Serum transferin

88. **Hemochromatosis affects all of the following organs except:**
(a) Liver
(b) Pancreas
(c) Heart
(d) Salivary gland

89. **Skin pigmentation in hemochromatosis occurs due to:**
(a) Melanin (b) Ferritin
(c) Hemosiderin (d) All

90. **Storage form of iron in body is:**
(a) Ferritin (b) Transferrin
(c) Ceruloplasmin (d) Ferriportin

91. **Microcytic hypochromic anemia is seen in:**
(a) Hereditary spherocytosis
(b) Thalassemia major
(c) Iron deficiency anemia
(d) Pernicious anemia

92. **Earliest feature of correction of iron deficiency anemia is:**
(a) Reticulocytosis
(b) Increase in serum ferritin
(c) Increase in RBC count
(d) Increase in serum iron level immediately

93. **Lead causes following except:**
(a) Uroporphyrinuria
(b) Sideroblastic anemia
(c) Basophilic stippling
(d) Macrocytic anemia

94. **Low iron and low TIBC is seen in:**
(a) Anaemia of chronic disease
(b) Sideroblasticanaemia
(c) Iron deficiency anaemia
(d) Aplastic anemia

95. **Anemia in humans can be caused by which of the following worm?**
(a) Roundworm (b) Hookworm
(c) Strongyloides (d) Tapeworm

96. **Sideroblastic anemia is seen in chronic poisoning with:**
(a) Lead (b) Arsenic
(c) Copper (d) Mercury

97. **Echinocytes are types of:**
(a) RBCs (b) Lymphocytes
(c) Monocytes (d) Platelets

98. **Response of iron therapy in a patient with iron deficiency anemia is denoted by:**
(a) Restoration of enzymes
(b) Reticulocytosis
(c) Increase in iron binding capacity
(d) Increase in hemoglobin

99. **Sideroblastic anemia is caused by all except:**
(a) Collagen vascular disease
(b) Erythropoetic porphyria
(c) Lead poisoning
(d) Cutaneous porphyria

100. **Rate of iron uptake is regulated by which one of the following:**
(a) Mucosal cell iron stores
(b) Route of administration
(c) Preparation administered
(d) Age of the patient

101. **All of the following if present provide protection against malaria except:**
(a) Duffy blood group
(b) Sickle cell anemia
(c) Thalassemia
(d) G6PD deficiency

102. **Most important but nonspecific regulator of iron metabolism is:**
(a) Hepcidin (b) DMT1
(c) Ferroportin (d) Ferritin

HEMOLYTIC ANEMIA: PNH, HS, G6PD, IMMUNE HEMOLYTIC ANEMIA

103. **A 23-year-old female presented with jaundice and pallor for 2 months. Her peripheral blood smear shows the presence of spherocytes. The most relevant investigation to arrive at a diagnosis is which of the following?** *(AIIMS May 2012)*
(a) Tests for PNH
(b) Osmotic fragility test
(c) Coombs test
(d) Reticulocyte count

104. **An abnormal Ham test is most likely associated with which of the following?** *(AIIMS Nov 2011)*
(a) Spectrin
(b) Defect in complement activating proteins
(c) Defective GPI anchor
(d) Mannose-binding residue effect

105. **A 5-year-old male child presents with episodic anemia and jaundice since birth. He is least likely to have which of the following?** *(AIIMS Nov 2011)*
(a) Hereditary spherocytosis
(b) Sickle cell disease
(c) G6PD deficiency
(d) Paroxysmal nocturnal hemoglobinuria

106. **Thrombotic event is seen in all of following except:** *(AIIMS May 2011)*
(a) Paroxysmal nocturnal hemogloninuria
(b) Disseminated intravascular coagulation
(c) Idiopathic thrombocytopenic purpura
(d) Heparin induced thrombocytopenia

107. **PNH associated with somatic mutation affecting:**
(a) Decay accelerating factor (DAF) *(AI 2010)*
(b) Membrane inhibitor of reactive lysis (MIRL)
(c) Glycosylphosphatidylinositol (GPI)
(d) C8 binding protein

108. **Cold hemagglutinin is associated with:** *(AI 2008)*
(a) Anti IgM
(b) Anti IgG
(c) Anti IgA
(d) Donath-Landsteiner antibody

109. **The following protein defects can cause hereditary spherocytosis except:** *(AI 2007)*
(a) Ankyrin
(b) Palladin
(c) Glycophorin C
(d) Anion transport protein

110. **Autoimmune hemolytic anemia is seen in:** *(AI 2001)*
(a) ALL
(b) AML
(c) CLL
(d) CML

111. **Microangiopathic hemolytic anemia is seen in all of the following diseases except:** *(AIIMS Nov 2008)*
(a) Antiphospholipid antibody syndrome
(b) Thrombotic thrombocytopenic purpura
(c) Microscopic polyangiitis
(d) Metallic cardiac valves

112. **An Rh -ve woman became pregnant with Rh +ve fetus. Within few days after birth, the infant developed jaundice, ascites, hepatomegaly and edema. The likely substance(s) deposited in skin and sclera in jaundice is/are given below. Which is the best possible answer?** *(AIIMS Nov 2003)*
(a) Biliverdin
(b) Conjugated and unconjugated bilirubin
(c) Unconjugated bilirubin
(d) Conjugated bilirubin

113. **Features seen in hemolytic anemia are all except:**
(a) Teardrop and Burr cells
(b) ↓ Haptoglobin
(c) Reticulocytosis
(d) Hemoglobinuria

114. Intravascular hemolysis occurs in: *(PGI Dec 2000)*
(a) Hereditary spherocytosis
(b) Acute G6PD deficiency
(c) Sickle cell disease
(d) Thalassemia
(e) PNH

115. Microangiopathic hemolytic anemia is seen in: *(PGI June 01)*
(a) HUS
(b) ITP
(c) Malignant hypertension
(d) Prosthetic valves
(e) TTP

116. Spherocytosis in blood smear is seen in: *(PGI June 2004)*
(a) Hemoglobin C
(b) Mechanical trauma
(c) Hereditary spherocytosis
(d) Hereditary elliptosis

117. Cause of fragmented RBC in peripheral blood: *(PGI June 2005)*
(a) Microangiopathic hemolytic anemia
(b) DIC
(c) Hemophilia-A
(d) Malignant hypertension
(e) HELLP syndrome

118. Intravascular hemolysis is seen in: *(PGI June 2005)*
(a) Glucose-6 phosphate dehydrogenase deficiency
(b) Thalassemia
(c) Sickle cell anemia
(d) Hemophilia

119. The peripheral smear of hereditary spherocytosis will show spherocytes: *(PGI Dec 2006)*
(a) Usually of same size
(b) Reticulocytosis seen
(c) Smaller size
(d) Anemia is negligible
(e) Always associated with ↑ MCHC

120. Microangiopathic hemolytic anemia seen in: *(PGI Dec 2003)*
(a) Thrombotic thrombocytopenic purpura
(b) Hemolytic uremic syndrome
(c) Henoch-Schonlein purpura
(d) DIC
(e) IgA nephropathy

MOST RECENT QUESTIONS

121. Donath-Landsteiner antibodies are seen in:
(a) Warm agglutination
(b) Cold agglutination
(c) Paroxysmal nocturnal hemoglobinuria
(d) ITP

122. In hereditary spherocytosis an inherited abnormality is seen in which of the following red blood cell component:
(a) α-globin chain
(b) β-globin chain
(c) Phosphatidyl inositol glycan A
(d) Spectrin

123. Hereditary spherocytosis is due to:
(a) Acquired membrane defect
(b) Ankyrin deficiency
(c) Defective hemoglobin synthesis
(d) Mechanical trauma to red cells

124. Not seen in paroxysmal nocturnal hemoglobinuria is:
(a) LDH levels are raised
(b) Increased hemosiderin in urine
(c) Decreased leukocyte alkaline phosphatase
(d) Increased platelets

125. 'Warm' autoantibodies are seen in:
(a) SLE
(b) Mycoplasma
(c) Syphilis
(d) Varicella

126. Hot agglutinin is found in all except: *(Bihar 2006)*
(a) Mycoplasma infection
(b) SLE
(c) Methyl dopa
(d) Rheumatoid arthritis

127. PNH due to defect in:
(a) CD 59 (b) CD 15
(c) CD 100 (d) CD 20

128. D.I.C is seen in:
(a) Acute promyelocytic leukemia
(b) Acute myelomonocytic leukemia
(c) CML
(d) Autoimmune haemolytic anemia

129. Intravascular hemolysis occurs in:
(a) Hereditary spherocytosis
(b) Autoimmune haemolytic anemia
(c) Paroxysmal nocturnal hemoglobinuria
(d) Thalassemia

130. G6PD help in maintaining the integrity of RBC by:
(a) Controlling reduction stress on RBC
(b) Controlling oxidative stress on RBC
(c) Maintaining flexibility of cell membrane
(d) Component of electron transport chain

131. Cold agglutinin is:
(a) IgG
(b) IgM
(c) IgA
(d) IgD

132. Helmet cells are characteristic of anemia of:
(a) Hemolytic uremic syndrome
(b) Polysplenia
(c) Spherocytosis
(d) Acanthocytosis

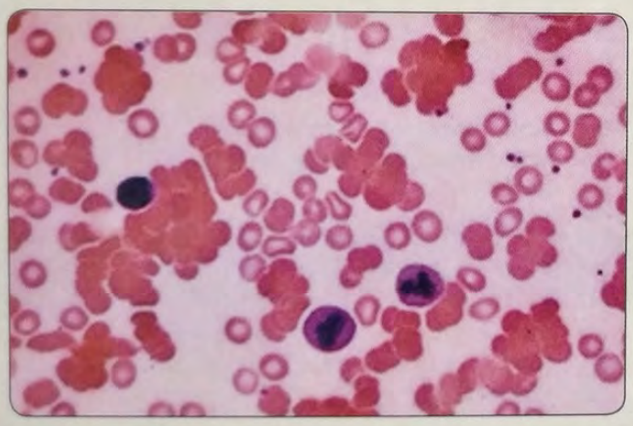
133. Schistocyte is/are found in:
(a) TTP
(b) March hemoglobinuria
(c) Severe iron deficiency
(d) All of the above

134. In DIC, following are seen except:
(a) Fibrinogen decreased
(b) Thrombocytopenia
(c) Normal APTT
(d) PT elevation

135. All are the features of hemolytic anemia except:
(a) Hemoglobinuria
(b) Jaundice
(c) Increased haptoglobin
(d) Hemosiderinuria

136. Bite cells are seen in:
(a) G6PD deficiency
(b) Sickle cell anemia
(c) Hereditary spherocytosis
(d) Trauma

137. A 56-year-old female presents in the month of December with chronic fatigue and cyanosis of nose with blue lips. A peripheral blood smear showed the following image. What is the most likely cause of the findings seen?



(a) Clumps of RBCs due to IgM mediated cold autoimmune haemolytic anemia
(b) Clumps of RBCs due to IgG mediated warm autoimmune haemolytic anemia
(c) RBC lysis due to hemoglobinopathy
(d) Clumps of RBCs due to IgG mediated cold autoimmune haemolytic anemia

138. All of these are seen in hemolytic anaemia *except*: *(AIIMS Nov 2016)*
(a) Yellowing of eyes and sclera
(b) Increased LDH
(c) Decrease in haptoglobin
(d) Low reticulocyte count

139. Direct Coombs test is positive in all of the following *except*:
(a) Drug induced AIHA
(b) Aplastic anemia
(c) Hemolytic anemia due to transfusion
(d) Hemolytic disease of newborn

140. A 26-year-old female presents with pallor with a hemoglobin of 9.5 mg/dL, PCV 30 mm Hg and RBC count of 2 million per cubic millimeters. What is the likely diagnosis? *(AIIMS Nov 2016)*
(a) Sideroblastic anemia
(b) Iron deficiency anemia
(c) Thalassemia
(d) Folic acid deficiency

141. Peripheral smear with small pale red cells, anisocytosis and poikilocytosis is suggestive of:
(a) Aplastic anemia
(b) Iron deficiency anemia
(c) Hereditary spherocytosis
(d) Megaloblastic anemia

142. Hemolytic uremic syndrome is associated with which of the following:
(a) Most commonly caused by verocytogenic E.coli
(b) Causes mild to severe coombs positive hemolytic anemia
(c) Recurrences are rare
(d) Transient thrombocytopenia

143. Intrinsic causes of hemolytic anemia are all except:
(a) G6PD deficiency
(b) Hereditary spherocytosis
(c) Hypersplenism
(d) Pyruvate kinase deficiency

144. Which of the following is the nature of the warm antibody in autoimmune hemolytic anemia?
(a) IgE (b) IgG
(c)IgM (d)IgD

HEMOGLOBINOPATHIES: SICKLE CELL ANEMIA, THALASSEMIA

145. Person having heterozygous sickle cell trait are protected from infection of: *(AIIMS Nov 2012)*
(a) P. falciparum
(b) P. vivax
(c) Pneumococcous
(d) Salmonella

146. A 6-years-old child belonging to Punjabi family with past history of blood transfusions presented with hemoglobin 3.5 g/dl, MCV - 30 fl, MCHC - 20. Peripheral smear findings of microcytic hypochromic anemia with target cell and reduced osmotic fragility. What is the he probable diagnosis of patient? *(AIIMS Nov 2012)*
(a) Alpha thalassemia
(b) Beta thalassemia
(c) Sickle cell anemia
(d) G6PD deficiency

147. **NESTROF test is a screening test for which of the following conditions?** *(AIIMS Nov 2011)*
(a) β- thalassemia
(b) Hereditary spherocytosis
(c) Autoimmune haemolytic anaemia
(d) Megaloblastic anaemia

148. **Which of the following is the cause of alpha thalassemia?** *(AIIMS May 2011)*
(a) Deletion of alpha genes
(b) Deletion of beta genes
(c) Excess of alpha genes
(d) Single amino acid substitution in alpha chain

149. **HbH is formed due to which of the following?**
(a) Deletion of 4 alpha chains *(AI 2011)*
(b) Deletion of 3 alpha chains
(c) Deletion of 2 alpha chains
(d) Deletion of 1 alpha chain

150. **Mutation causing sickle cell anemia is protective for which of the following?** *(AI 2010)*
(a) Malaria
(b) Filaria
(c) Leishmania
(d) None of the above

151. **What is affected in HbS (Hemoglobin S)?** *(AI 2009)*
(a) Stability (b) Function
(c) Affinity (d) Solubility

152. **A couple, with a family history of beta thalassemia major in a distant relative, has come for counseling. The husband has HbA2 of 4.8% and the wife has HbA2 of 2.3%. The risk of having a child with beta thalassemia major is:** *(AI 2003)*
(a) 50% (b) 25%
(c) 5% (d) 0%

153. **The primary defect which leads to sickle cell anemia is:** *(AI 2003)*
(a) An abnormality in porphyrin part of hemoglobin
(b) Replacement of glutamate by valine in b-chain of HbA
(c) A nonsense mutation in the b-chain of HbA
(d) Substitution of valine by glutamate in the a-chain of HbA

154. **Which one of the following statements about hemoglobin S (HbS) is not true?** *(AIIMS Nov 2004)*
(a) Hemoglobin HbS differs from hemoglobin HbA by the substitution of Val for Glu in position 6 of the beta chain
(b) One altered peptide of HbS migrates faster towards the cathode (–) than the corresponding peptide of HbA
(c) Binding of HbS to the deoxygenated HbA can extend the polymer and cause sickling of the red blood cells
(d) Lowering the concentration of deoxygenated HbS can prevent sickling

155. **Sickle cell trait patient do not have manifestations of sickle cell disease, because:** *(AIIMS Nov 2001)*
(a) 50% HbS is required for occurrence of sickling
(b) HbA prevents sickling
(c) 50% sickles
(d) HbA prevents polymerization of HbS

156. **True about Sickle cell anemia are all except:**
(a) Commonly seen in blacks *(PGI June 2004)*
(b) RBC size is altered
(c) Valine is substituted for glutamic acid in beta chain of globin.
(d) Deletion of gene
(e) Target cell are present

157. **True about beta-thalassemia trait is:** *(PGI June 2004)*
(a) Increased HbF (b) Increased HbA2
(c) Microcytosis (d) Severe anemia
(e) Target cell

MOST RECENT QUESTIONS

158. **Sickle cell anemia is the clinical manifestation of homozygous genes for an abnormal haemoglobin molecule. The event responsible for the mutation in the β chain is:**
(a) Insertion (b) Deletion
(c) Non-disjunction (d) Point mutation

159. **Hemoglobin H disease is caused by deletion of:**
(a) A single α globin gene
(b) Two α globin genes
(c) Three α globin genes
(d) All four α globin genes

160. **All of the following aggravate sickling phenomenon in sickle cell disease except:**
(a) Higher concentration of HbS
(b) Higher concentration of HbF
(c) Lower concentration of HbC
(d) A fall in blood pH

161. **Sickle cell anemia is due to:**
(a) Presence of a structurally abnormal Hb
(b) Red cell enzyme deficiency
(c) Unknown multiple mechanisms
(d) Disturbance of proliferation and differentiation of stem cells

162. **In sickle cell disease, the defect is in:**
(a) α-chain (b) β-chain
(c) γ-chain (d) Hb formation

163. **Which of the following manifestations is common to sickle cell anemia and thalassemia major?**
(a) Autosplenectomy
(b) Bone marrow expansion in the calvarium
(c) Ineffective erythropoiesis
(d) Predisposition to *Hemophilus influenzae* infections

164. One of the common variants of sickle cell anemia frequently marked by lesser degree of haemolytic anemia and greater propensity for the development of retinopathy and aseptic necrosis of bones is:
(a) Sickle cell trait
(b) Haemoglobin SC disease
(c) Sickle thalassaemia
(d) Sickle –Hb E disease

165. In α-thalassemia, which of the following is a finding?
(a) No β-chain
(b) Excess α-chain
(c) No α-chain
(d) Relative excess of β, γ, and δ chains

166. Ideally children with thalassemia should be transfused with:
(a) Packed RBC
(b) Platelet rich plasma
(c) Saline washed packed RBC
(d) Whole blood

167. All are seen in Thalasemia major except:
(a) Transfusion dependency
(b) Splenoheptatomegaly
(c) Ineffective erythropoiesis
(d) Macrocytic anaemia

168. Bone infarcts are seen in:
(a) Iron deficiency anemia
(b) Thalassemia
(c) Sickle cell anemia
(d) Hereditary spherocytosis

169. In sickle cell anemia defect is in which chain:
(a) Alpha chain (b) Beta chain
(c) Both the chains (d) None of these

170. A 18-year-old Afro American boy presenting with a non healing ulcer of the foot, with recurrent pneumonia and chronic hemolytic anemia. The peripheral blood erythrocytes showed some peculiar appearance. Most likely cause is:
(a) Trinucleotide repeat
(b) Genomic imprinting
(c) Single amino acid base substitution
(d) Antibody to red cell membrane

171. Molecular pathogenesis of α thalassemia involves:
(a) Mutation in transcription sequence
(b) Gene deletion
(c) Codon termination mutation
(d) mRNA splicing defect

172. The primary defect which lead to stickle cell anemia is?
(a) An abnormality in porphyrin part of haemoglobin
(b) Substitution of valine by glutamate in the β-chain of HbA
(c) Replacement of glutamate by valine in β-chain of HbA
(d) A nonsense mutation in the β-chain of HbA

173. Sickle cell red blood cells have:
(a) Altered stability
(b) Altered functions
(c) Decreased oxygen carrying capacity
(d) Protective action against adult malaria

174. In a case of Plasmodium falciparum malaria, the peripheral blood smear does not demonstrate trophozoites and schizonts. The reason for this is: *(AIIMS Nov 2016)*
(a) Apoptosis of red cells because of hemozoin pigments
(b) Lysis of red cells with malarial parasite
(c) Infested cells are trapped in the spleen
(d) Infested red blood cells stick to the capillaries

175. Which of the following is true about sickle cells?
(a) Sickling occurs both in heterozygous and homozygous
(b) Fetal hemoglobin facilitates sickling
(c) Sickling is reversible with oxygenation
(d) Sickling is associated with reduced MCHC

176. Which of the following is true about sickle anemia?
(a) Leucopenia (b) Decreased ESR
(c) Microcardia (d) Ringed sideroblast

Explanations

1. **Ans. (b) Hereditary spherocytosis** *(Ref: Robbins 9/e p632)*
Regarding Hereditary spherocytosis;
Direct quote from Robbins....*'this inherited disorder is caused by* intrinsic defects in the red cell membrane *that render red cells spheroid, less deformable, and vulnerab le to splenic sequestration and destruction'*
Other disorders with intrinsic defect in red cell membrane are hereditary elliptocytosis and abetalipoproteinemia.

2. **Ans. (c) Myoblast** *(Ref: Robbins 8th/85, 9/e p580)*
Bone marrow cells include

- **Hematopoietic stem cells** include **lymphoblast, myeloblast** and **normoblast**.
- **Marrow stromal cell**/multipotent stem cells (MSC) including **myoblast, osteoblasts, chondrocytes, adipocytes** and **endothelial cell precursors**. Myoblast is an example of MSC giving rise to muscle cells or myocytes.

3. **Ans. (d) CD 34** *(Ref: Robbins 7th/670, 9th/590)*

CD34 is expressed on pluripotent hematopoietic stem cells and progenitor cells of many lineages

4. **Ans. (c) Nutritional anemia**
(Ref: Harrison 18th/454, 17th/359-361 and Ghai 6th/306) ...see Table 7.1

Reticulocytes are nonnucleated spherical cells bigger than normal RBCs and are polychromatic (having a blue color) due to the presence of free ribosomes and RNA.

5. **Ans. (b) Basophilic stippling; (d) Howell-Jolly bodies; (e) Cabot ring** *(Ref: PJ Mehta 16th/372, T. Singh 1st/34)*
   - **Romanowsky dyes** are used for staining blood films. They are made up of combination of acid and basic dyes. The nucleus and neutrophilic granules are basophilic and stains blue. Hemoglobin is acidophilic and stains red.
   - Various modifications available are **Leishman's stain, Wright's stain, Giemsa and Jenner's stain.**
   - Basophilic stippling, Howell-Jolly body and Cabot rings are seen by Romanowsky stain.

   - **Basophilic stippling:** These are small blue or black granules in red cells seen in megaloblastic anemia, heavy metal poisonings, etc.
   - **Howell-Jolly Body:** These are remnants of the nucleus seen as small, round dark blue particles near the periphery of the cells; found in postsplenectomy, asplenia and severe hemolytic anemia.

Contd...

Contd...

   - **Cabot ring:** These are pale staining nuclear remnants in the form of rings or figure of eight seen in hemolytic anemia, megaloblastic anemia, leukemia and after splenectomy. These are arginine rich and acidophilic.
   - Heinz bodies are denatured hemoglobin which does not stained with Romanowsky stain. It is demonstrated by supravital stains such as crystal violets. Reticulocytes also require Supravital staining.

6. **Ans. (d) CD 34** *(Ref: Robbins 7th/670, 9/e p590)*
7. **Ans. (d) Benign liver tumor** *(Ref: Robbins 9/e p331)*
8. **Ans. (a) MCV** *(Ref: Robbins 9/e p630)*
9. **Ans. (c) Megaloblastic** *(Ref: Robbins 9/e p645)*
10. **Ans. (a) Acute glomerulonephritis** *(Ref: Robbins 9/e p898)*
11. **Ans. (b) Spherocytosis** *(Ref: Robbins 9/e p633)*
12. **Ans. (d) Erythropoietin** *(Ref: Robbins 9/e p656)*
13. **Ans. (d) All of the above**
(Ref: Robbins 8th/665; 7th/960, Harrison 18 Table 280 (5))
14. **Ans. (a) Uremia** *(Ref: Tejinder Singh 1st/38)*
15. **Ans. (a) Abetalipoproteinemia**
(Ref: Tejinder Singh 1st/38)
16. **Ans. (b) Brilliant Cresyl blue** *(Ref: Robbins, 9/e 635)*
    - **Reticulocytes** are stained in **living state** *in vitro* so staining with dyes like brilliant cresyl blue and **new methylene blue (Best stain)** is referred to as ***supravital staining***.
17. **Ans. (a) Ferritin** *(Ref: Robbins, 9/e 650)*
18. **Ans. (a) Histidine residues**
Harper mentions ...'Hemoglobin also functions in CO_2 and proton transport from tissues to lungs. Release of O_2 from oxy Hb at the tissues is accompanied by uptake of protons due to lowering of the pKa of ***histidine residues***.'
19. **Ans. (b) Henoch Schonlein purpura**
(Ref: Robbins, 9/e p526-527 8/e p666; 7/e p986-987)
All other options have decreased platelet count except Henoch Schonlein purpura. Though it has the name purpura, but the ***platelet count in this condition is normal***. The skin manifestations in HSP are due to **small vessel vasculitis**.
20. **Ans. (c) 900... About 900 g^{Q} of hemoglobin is present in the circulating blood of an adult man.**
21. **Ans. (a) Lymphocyte** *(Read below)*

    - **Lymphocyte** is the **longest living**^{Q} white blood cell.
    - **Neutrophil** is the most **numerous**^{Q} white blood cell.

22. **Ans. (c) –0.54° C** *(See below)*

- The **freezing point** of normal **human plasma** averages **-0.54 °C**Q, which corresponds to an osmolal concentration in plasma of **290 mOsm/L**Q.
- The term **tonicity** is used to describe the osmolality of a solution relative to plasma
- A **0.9% saline solution** and **5% glucose solution is isotonic** when initially infused intravenously.

Also know how to calculate osmolality: medicine link!

Osmolality (mOsm/L) = 2[Na+] (mEq/L) + 0.055 [Glucose] (mg/dL) + 0.36[BUN] (mg/dL)

23. **Ans. (b) 2:1** *(Read below)*
    - Normal **albumin-globulin ratio** is **1.8 : 1 to 2 : 1**Q.
    - Synthesis of **albumin exclusively occurs in liver** but many ***globulins (immunoglobulins) are synthesized by B-lymphocyte.***

Conditions with altered albumin globulin ratio

High Albumin Globulin Ratio	Low Albumin Globulin Ratio
• Hypothyroidism • Hypogammaglobulinemia • Leukemia • Glucocorticoid excess	• Overproduction of globulins in conditions like **multiple myeloma, chronic infections** and in some autoimmune diseases. • Under production of albumin in conditions like **liver cirrhosis, malnutrition and nephrotic syndrome**.

24. **Ans. (b) Contractile protein**

(Ref: Harsh Mohan 5th/ 177, The Circulating Platelet/ 215-8)

- Thrombosthenin is a contractile protein in platelets that is active in the formation of blood clots.

25. **Ans. (c) Cyanmethemoglobin method** *(Read below)*

Hemoglobin estimation		
Visual Colorimetric method	Sahli's (acid hematin method) Alkali hematin method	Most popular method
Photocolorimetric method	Cyanmethemoglobin method	**Most accurate** and currently used

26. **Ans. (c) 4**

Hemoglobin is a globular molecule made up of four subunits. Each subunit contains a **heme** moiety conjugated to a polypeptide. Heme is an iron-containing porphyrin derivative. So, **hemoglobin = 4 globins + 4 heme groups** Since each heme molecule contains an iron, so total iron atoms present in hemoglobin are 4 in number.

- **70%** of the iron in the body is in **hemoglobin**, 3% in myoglobin, and the rest in ferritin, which is present not only in enterocytes, but also in many other cells.

27. **Ans. (d) ESR** *(Ref: A Textbook of Hematology p133)*

28. **Ans. (b) Labile factor**

If whole blood is allowed to clot and the clot is removed, the remaining fluid is called **serum.** Serum has essentially the same composition as plasma, except that:

- **Fibrinogen (factor I)** and clotting factors **II**, **V**, and **VIII** have been **removed** and.
- Has **higher serotonin content** because of the breakdown of platelets during clotting.

Also know that **factor 5** is called as **labile factor**Q.

29. **Ans. (a) Bone marrow** *(Ref: Robbins 8/e p590, 9/e p580)*

By birth, marrow throughout the skeleton is hematopoietically active and hepatic hematopoiesis dwindles to a trickle, persisting only in widely scattered foci that become inactive soon after birth.

30. **Ans. (c) RBCs to whole blood** *(Ref: Robbins, 9/e 631)*

Haematocrit (also known as packed cell volume) is the volume percentage (%) of red blood cells in blood.

31. **Ans. (c) Myelophthisic type** *(Ref: Robbins 9/e p655)*

- *Myelophthisic anemia* describes a form of marrow failure in which space-occupying lesions replace normal marrow elements. **The commonest cause is metastatic cancer**, most often carcinomas arising in the breast, lung, and prostate.

32. **Ans. (b) No nucleus** *(Ref: Wintrobe 11th/200)*

33. **Ans. (b) 60-80 days** *(Ref: Oski's Hematology /28)*

- Premature infant: 35-50 days
- Term infant: 60-70 days
- Adult: 100-120 days

34. **Ans. (d) Hereditary spherocytosis** *(Ref: Robbins 9th/633)*

35. **Ans. (b) <34**

(Ref: Park's PSM textbook/Nutrition and health)

At all ages **the normal MCHC should be 34**; values below that indicate that red cells are hypochromic, which occurs in iron deficiency anaemia.

36. **Ans. (a) Increased reticulocyte count**

(Ref: Robbins 9/e 645, 8th/655, Wintrobe's 12th/1151-3)

Direct quote from Robbins … *'The reticulocyte count is low'.*

Please be clear of the concept friends that the ***reticulocyte count is increased*** when the megaloblastic anemia is being treated with ***vitamin B12 and folate supplementation*** i.e. after the initiation of the treatment in these patients.

- Nucleated red cell progenitors occasionally appear in the circulating blood when anemia is severe.

- The derangement in DNA synthesis causes most precursors to undergo apoptosis in the marrow (ineffective hematopoiesis) and leads to pancytopenia. The anemia is further exacerbated by a mild degree of red cell hemolysis. This leads to raised bilirubin.
- Wintrobe mentions ... 'Mild reversible splenomegaly is present in megaloblastic anemia'.

37. Ans. (d) Myelofibrosis *(Ref: Harrison 17th/661, 674, 646)*

The findings in the given question are:
Anemia (Hb = 6g)
Reduced leukocyte count (TLC= 1200)
Reduced platelet count (60000)
Reduced MCV (12fL)

- Normal value of MCV is 80-100 fL. It is the measure of size of RBC. Reduced MCV means microcytic and increased MCV means macrocytic RBCs. Normal TLC is 4000-11000, normal platelet count is 1,50,000 to 4,50,000 and normal Hb is above 12 g/dL.
- Now, considering the options one by one:

- **Aplastic anemia** has reduced RBC, WBC as well as platelet counts. Anemia is normocytic normochromic, thus it can be easily ruled out.
- **Paroxysomal nocturnal hemoglobinuria (PNH)** typically presents with anemia which is usually normomacrocytic. If MCV is high, it is due to reticulocytosis. Neutropenia and thrombocytopenia may or may not be present. Therefore, this option also cannot be the answer.
- **Megaloblastic anemia** presents with raised MCV. There may be leukopenia as well as thrombocytopenia. Severity of these changes parallels the degree of anemia.
- **Myelofibrosis** usually presents with anemia, leukopenia and thrombocytopenia. Mostly anemia is normocytic but in 30% cases microcytic anemia can be present.

Based on the above discussion, the most probable answer is 'Myelofibrosis'.

However, the value of MCV given is 12 fL which is practically not possible. Normal value of MCV is 80-100 fL. MCV < 50 fL is considered to be extremely low. Therefore, one possibility is that it may be 112 fL and due to typographical error in the question, written as 12 fL. If this is the case, then the answer will become megaloblastic anemia.

As we cannot say for sure that it is a printing mistake, so we will go for 'Myelofibrosis'.

38. Ans. (a) ↑MCV.

(Ref: T. Singh 1st/35, Harrison 17th/357, Robbins 9/e 629-630)

MCV > 100fL indicates *macrocytosis.*

39. Ans. (a) Megaloblastic precursors are present in bone marrow; (b) Mean corpuscular volume is increased; (c) Serum LDH is increased

(Ref: Robbins 9/e 645, Harrison' 17th/645-646)

- Megaloblastic anemia is a maturation disorder of red cells
- **Cells are macrocytic and hyperchromic. Anisocytosis and** hypersegmented neutrophils are also seen.
- Bone marrow shows hypercellularity, erythrocyte precursors at different stages of development is found. Increased megaloblast causes ineffective erythropoiesis.
- In severe anemia as many as 90% of RBC precursors may be destroyed before their release into the circulation (Normal 10-15%). Thereby **increased unconjugated bilirubin and lactic acid dehydrogenase**.
- *Target cells* result due to increased ratio of RBC surface area to volume, seen in *hemoglobin disorders, thalassemia, liver disease.* **Reticulocytes, platelet count and leukocyte count decreased**.

40. Ans. (b) Copper deficiency *(Ref: Harrison 17th/449)*

Copper deficiency is manifested by hypochromic normocytic anemia, osteopenia, depigmentation, mental retardation and psychomotor abnormalities.

Thiamine, pyridoxine and B_{12} deficiency leads to megaloblastic anemia.

Classification of megaloblastic anemia

	Drugs	Diseases	Unknown etiology
Cobalamin deficiency Folic acid deficiency	Purine and Pyrimidine antagonists Others-procarbazine, zidovudine hydroxyurea, acyclovir	Hereditary orotic aciduria Lesch-Nyhan syndrome	Refractory megaloblastic anemia. Di-Gueglielmo syndrome Congenital dyserythropoietic anemia

- Causes of anemia in Liver diseases are gastrointestinal bleeding, folate deficiency and hypersplenism.

41. Ans. (a) Fish tapeworm infestation; (c) Gastrectomy; (d) Ileal resection *(Ref: Robbins 7th/640, 9/e 645)*

The other two cause megaloblastic anemia by interfering with folic acid metabolism.

42. Ans. (c) Pure red cell aplasia

(Ref: T. Singh 1st/140; Robbins 7th/648, 636, 9/e 642)

PNH is the only hemolytic anemia caused by an acquired intrinsic defect in the cell membrane. PNH arises in the setting of aplastic anemia and these patients are at increased risk of developing acute myelogenous leukemia.

Aplastic anemia may progress to PNH and MDS.

43. Ans. (d) Cholestatic jaundice *(Ref: Robbins 9/e 645)*

44. Ans. (d) Thalassemia *(Ref: Robbins 9/e 639)*

45. Ans. (a) Myelofibrosis *(Ref: Robbins 9/e 620-621)*

46. **Ans. (b) Folic acid deficiency** *(Ref: Robbins 9/e 648)*

47. **Ans. (d) Hypothyroidism**
(Ref: Tejinder Singh 1st/66, Robbins 9/e 645)

48. **Ans. (a) Thymoma** *(Ref: Robbins 9/e 627)*

49. **Ans. (b) Diphyllobothrium latum** *(Ref: Robbins 9/e 648)*

50. **Ans. (c) Anemia occurs after 3-4 months of poor absorption**
(Ref: Robbins 9/e 648, 8th/657; 7th/682)

51. **Ans. (b) Folic acid deficiency**
(Ref: Harsh Mohan 6th/308, Robbins 9/e 647)

52. **Ans. (c) Megaloblastic** *(Ref: Robbins 9/e 645)*

53. **Ans. (c) Megaloblastic anemia** *(Ref: Robbins 9/e 645)*

54. **Ans. (d) Postsplenectomy**
(Ref: Robbins 9/e 627, 633, 8th/646, 7th/627, Harrison 17th/375)

55. **Ans. (c) Diphyllobothrium latum infestation**
(Ref: Robbins 9/e 648, 8th/655)

56. **Ans. (d) Thymoma** *(Ref: Robbins 9/e 627, 8th/664)*
In the rare pure red cell aplasia, the erythroid marrow elements are absent or nearly absent, while granulopoiesis and thrombopoiesis remain unaltered. This condition occurs in both primary and secondary forms, both of which are thought to be related to autoimmune destruction of erythroid precursors. There is a specific association between thymic tumors (thymoma) and autoimmune hematologic diseases, specifically including pure red cell aplasia.

57. **Ans. (a) Aplastic anemia** *(Ref: Robbin 9/e p653)*
Aplastic anemia refers to a syndrome of chronic primary hematopoietic failure and attendant *pancytopenia* (anemia, neutropenia, and thrombocytopenia).

58. **Ans. (b) Human parvo virus B19** *(Ref: Robbin 9/e p460)*
Parvovirus B19 causes erythema infectiosum or "fifth disease of childhood" in immunocompetent older children. Parvovirus B19 has a particular ***tropism for erythroid*** cells, and diagnostic viral inclusions can be seen in early erythroid progenitors in infected infants.

Parvovirus infection in pregnant women is associated with hydrops fetalis due to severe fetal anemia, sometimes leading to miscarriage or stillbirth.

59. **Ans. (c) Increased reticulocyte count** *(Ref: Robbin 8/e p655, Wintrobe's 12/e p1151-3)*
Repeat from AIIMS Nov 12 see earlier explanation of answer 32

60. **Ans. (a) Beta thalassemia trait** *(Ref: Robbins 9/e 641)*
Hemoglobin electrophoresis usually reveals an **increase in HbA_2 ($\alpha_2\delta_2$) to 4% to 8%** of the total hemoglobin (normal, 2.5% ± 0.3%), which is a reflection of an elevated ratio of δ-chain to β-chain synthesis. *HbF levels are generally normal or occasionally slightly increased.*

61. **Ans. (c) Chronic renal failure..... read below**
The same question was asked in different sets with different choices. Choices a,b,d are examples of hemolytic anemias and hence the answer by exclusion is chronic renal failure. CRF has low erythropoietin levels due to less production and has normocytic normochromic anaemia.

62. **Ans. (c) Vitamin B12 absorption** *(Ref: Robbins 9/e 648)*
The **Schilling test** is performed to determine the cause for **cobalamin malabsorption**. Since cobalamin absorption requires multiple steps, including gastric, pancreatic, and ileal processes, the Schilling test also can be used to assess the integrity of those other organs.

Differential Results of Schilling Test in Several Diseases with Cobalamin (Cbl) Malabsorption

	^{58}Co-Cbl	With Intrinsic Factor	With Pancreatic Enzymes	After 5 Days of Antibiotics
Pernicious anemia	Reduced	**Normal**	Reduced	Reduced
Chronic pancreatitis	Reduced	Reduced	**Normal**	Reduced
Bacterial overgrowth	Reduced	Reduced	Reduced	**Normal**
Ileal disease	***Reduced***	***Reduced***	***Reduced***	***Reduced***

63. **Ans. (a) Anaemia of chronic disease**
(Ref: Robbins 9/e 652-653, Wintrobe 12th/1221-2)
Looking at the data one by one friends, we infer that:
- We have an old patient with chronic inflammatory condition. In addition,

Parameter with value in question	Normal range	Inference in our patient
Hemoglobin 4.5gm/dl	13-17g/dl	Decreased
Platelet count 2 lakh/ml	1.5-4.5lakh/ml	Normal
TLC 6000/mm^3	4000-11000/mm^3	Normal
Serum ferritin 200 µg/L	15-300 µg/L	Normal
Serum iron 30 mg/L	50-150 µg/L	Reduced
TIBC 280 ng/L	300-400 mg/L	Reduced

Final conclusion, *decreased serum iron, increased storage iron i.e. serum ferritin, decreased serum transferring and decreased total iron binding capacity suggest the diagnosis of anaemia of chronic disease.*

64. **Ans. (b) Thalassemia minor**
(Ref: Hematology by Renu Saxena 1st/174)
Thalassemia major patient presents with *severe anemia* and cannot survive without blood transfusion, so this option can be easily ruled out. For other options, **Mentzer index** is useful for differentiating between thalassemia minor and iron deficiency anemia.

Mentzer index is calculated as MCV/RBC count. Its value is >13 in iron deficiency anemia and <13 in thalassemia minor. For our given question, the value on calculation comes out to be 55/4.5 = 12.22.

As the value is < 13, so it is a case of thalassemia minor.

65. **Ans. (a) Iron deficiency anemia**

(Ref: Robbins 8th/651, 9/e 652, T.Singh 1st/34)

- Decreased hemoglobin with the clinical features of fatigue and weakness is diagnostic of anemia
- MCV is 70 fl, so, microcytosis is present (normal MCV is 82-96fl)
- MCH is 22pg, so, decreased MCH is suggestive of hypochromic anemia (normal MCH is 27-33pg)
- Red cell distribution width (RDW) is the coefficient of variation of size of RBCs. Normal value is 11.5-14.5. It is an indicator of anisocytosis which may present in IDA as well as hemolytic anemias.
- In early iron deficiency anemia, RDW increases along with low MCV while in beta thalassemia trait, RDW is normal with low MCV, thus distinguishing from each other.

Increased reticulocytosis is a feature of treatment with iron therapy in a patient of iron deficiency anemia.

66. **Ans. (b) Myelodysplastic syndrome**

(Ref: Robbins 9/e 615, Wintrobe's 10th/1022-25)

Sideroblastic anemia can be ***hereditary*** (due to decreased ALA synthase activity) *or* ***acquired*** (secondary to leukemias, myelodysplastic syndrome, alcoholism, copper deficiency, pyridoxine deficiency or lead poisoning).

67. **Ans. (c) Thalassemia minor** *(Ref: Robbins 9/e 641)*

- Thalassemia major patient presents with ***severe anemia*** and **cannot survive** without blood transfusion, so this option can be easily ruled out.
- This cannot be a case of megaloblastic anemia because in megaloblastic anemia, **M.C.V. is increased** (> 100 fL)
- So, we are left with two options, i.e. Iron deficiency anemia and thalassemia minor. Both of these presents with **microcytic hypochromic anemia.**

The key point in the differential diagnosis of these two conditions is the RBC count.

- In thalassemia minor, the **RBC count is near normal and** only the hemoglobin is reduced. *In this condition the R.B.C. count is not reduced as much as the hemoglobin and hematocrit in fact it is usually normal.* This due to the fact that the marrow can keep on producing the cell at normal rate but it cannot fill them with hemoglobin. Hence, the hemoglobin is low and the empty cells occupy less space thus lowering the hematocrit relative to the erythrocyte count.
- On the other hand, in Iron deficiency anemia, the **RBC *production is also impaired.***

There are many indices to differentiate between iron deficiency anemia (IDA) and beta-thalassemia (BT) Applying mentzer index as discussed in a previous question, the value is < 13, so it is a case of thalassemia minor:

68. **Ans. (a) Inhibition of enzymes involved in heme biosynthesis** *(Ref: Robbins 9/e 411, Tejinder Singh 1st/147)*

- **Lead inhibits** the enzymes **δ aminolevulinic acid dehydrase**, red cell **pyrimidine 5′ nucleotidase** and **ferrochelatase** which are involved in the synthesis of heme.
- Deficiency of heme causes microcytic hypochromic anemia because heme is an integral part of hemoglobin and hemoglobin deficiency causes microcytic hypochromic anemia.

69. **Ans. (b) Sideroblastic anemia**

(Ref: Harrison 17th/631-32 (t) 98-4)

The hematological findings suggest the diagnosis of **sideroblastic anemia.**

70. **Ans. (a) ↓ Erythropoietin; (b) ↓ RBC survival; (c) ↓ folate; (d) Bone marrow hypoplasia; (e) Iron deficiency**

(Ref: Harrison 17th/633-634, 18th/e (t) 280 (5))

71. **Ans. All**

(Ref: Robbins 9th/651, Harrison' 19th/Table 335-3)

72. **Ans. (a) Thalassemi(a); (c) Anemia in chronic disease; (e) Megaloblastic anemi(a)**

(Ref: Harsh Mohan 6th/302, 307)

- Increased bone marrow iron is seen in:
  - Sideroblastic anemia
  - Anemia of chronic disease
  - Megaloblastic anemia
  - Pernicious anemia
  - Thalassemia.

73. **Ans. (a) Thalassemia; (b) Hb Lepore; (c) Hb Barts.**

(Ref: Harsh Mohan 6th/323-324)

Causes of microcytosis (MCV < 80fl)

- Iron deficiency anemia
- Thalassemia
- Sideroblastic anemia
- Anemia of chronic disease

In *Hb Barts,* all the four α chain genes are deleted resulting in formation of Barts Hb.

In Hb Lepore, there is nonhomologus *fusion* of β and δ genes and forms an abnormal hemoglobin with total *absence* of normal β *chain.* It is one of the form of β *thalassemia minor.*

74. **Ans. (a) Microcytic hypochromic anemia; (d) Bone marrow iron decreased earlier than serum iron**

(Ref: Robbins 7th/645, de Gruchy's 5th/42)

75. **Ans. (d) S. ferritin ↑**

(Ref: Harrison 17th/632-4, Robbins 9/e 625-653, 8th/662)

76. **Ans. (d) Persistently raised HbF**

(Ref: Wintrobes 11th/1326; Nelson 17th/1630)

It is a case of persistently raised HbF.

Characteristics

- There is persistence of fetal Hb in adult life so that almost whole of the Hb of patient is HbF.
- Patient remains asymptomatic even without blood transfusion.
- No anemia or splenomegaly seen.

	Beta-globin genes	HbA	HbA2	HbF
Normal	Homozygous β	97-99%	1-3%	< 1%
Thalassemia major	Homozygous β^0	0%	4-10%	90-96%
	Homozygous β^+(mild)	0-30%	0-10%	60-100%
Thalassemia intermedia	Homozygous β^+ (mild)	0-30%	0-10%	60-100%
Thalassemia minor	Homozygous β^0	80-95%	4-8%	1-5%
	Homozygous β^+	80-95%	4-89%	1-5%

- From the values given in question it can be thalassemia major or thalassemia intermedia.
- In thalassemia major patient presents with severe hemolytic anemia at the age of 6 months and cannot survive without blood transfusions.
- In thalassemia intermedia patient can survive without transfusion but they are not asymptomatic.

77. **Ans. (c) Absence of intrinsic factor** *(Ref: Robbins 9/e 645)*
Absence of IF causes *Pernicious anemia* which is an example of *megaloblastic anemia.*

78. **Ans. (c) Rheumatoid arthritis** *(Ref: Robbins 7th/639-640)*

> **Note:** In anemia of chronic disease (of Rheumatoid Arthritis, TB, UTI, etc), the red cells are mainly normocytic; normochromic red cells. In some cases, red cells may be hypochromic. So, we would go with **RA** as the best answer in this question.

79. **Ans. (a) Microcytic hypochromic anemia**
(Ref: Hematology by Tejinder Singh/83)
Explained in text.

80. **Ans. (a) Congenital spherocytosis** *(Ref: Robbins 7th/625)*
Hereditary spherocytosis – Small RBCs are seen without central pallor (normal RBCs have central 1/3rd pallor). It is also seen conditions where spherocytes are present in peripheral blood like:

• **Hereditary spherocytosis**	• **Burns**
• **Autoimmune hemolytic anemia**	• **G6PD deficiency**
• **Cirrhosis**	• **ABO incompatibility**
• **Clostridial sepsis**	

81. **Ans. (d) Megaloblastic anemia**
(Ref: Robbins 9/e 645, 7th/639/643/626/629)
- Megaloblastic anemia: Two principal types
- **Pathology:** Defective DNA synthesis and diminished erythropoiesis
- **Morphology** - Anisocytosis (various size + shape), Macrocytosis (MCV > 100 fl), MCHC is normal and, Macropolymorphonuclear (hyper segmented) neutrophils

82. **Ans. (c) ↓ Serum ferritin level** *(Ref: Robbins 9/e 652-653)*

83. **Ans. (a) Iron deficiency** *(Ref: Robbins 9/e 652-653)*

84. **Ans. (c) TIBC is decreased**
(Ref: Robbins 9/e 652-653, 8th/662; Harrison 17th/632)

85. **Ans. (b) Transferrin** *(Ref: Robbins 9/e 650)*

86. **Ans. (d) Increased mean corpuscular volume**
(Ref: Robbins 9/e 652, 8th/660-661, 7th/645)

87. **Ans. (c) Serum ferritin**
(Ref: Robbins 9/e 652)

88. **Ans. (d) Salivary gland** *(Ref: Robbins 9/e 848-849)*

89. **Ans. (a) Melanin** *(Ref: Robbins 9/e 849)*

90. **Ans. (a) Ferritin** *(Ref: Robbins 9/e 650)*

91. **Ans. (c) Iron deficiency anemia** *(Ref: Robbins 9/e 652)*

92. **Ans. (a) Reticulocytosis...explained earlier**
(Ref: Robbins 9/e 652, 8/e p641, 7/e p624)

93. **Ans. (d) Macrocytic anemia** *(Ref: Robbins 9/e 411)*

- **Lead inhibits** the activity of enzymes involved in heme synthesis; δ-aminolevulinic acid dehydratase[Q] **and ferrochelatase**[Q] (BIOCHEMISTRY NEET QUESTION INFO)
- Ferrochelatase catalyzes the incorporation of iron into protoporphyrin, and its inhibition causes a **rise in protoporphyrin** levels as well as appearance of scattered **ringed sideroblasts**[Q]. The elevated levels of protoporphyrin may appear in the urine of an individual.
- There is a distinctive **punctate basophilic stippling**[Q] **of the red cells** and the presence of *microcytic, hypochromic anemia*[Q].
- Also know that in lead poisoning is associated with reduction in uric acid excretion which can lead to gout (**"saturnine gout"**[Q])

94. **Ans. (a) Anaemia of chronic disease....** see text for details

95. **Ans. (b) Hookworm** *(Ref: Robbins 9/e 651)*
Hookworm infestation can cause chronic blood loss and therefore may cause iron deficiency anemia.

96. **Ans. (a) Lead** *(Ref: Robbins 9/e 411)*
Lead is associated with sideroblastic anemia.....details are discussed in a separate question.

97. **Ans. (a) RBCs** *(Ref: Harrison 17/e p77)*

98. **Ans. (b) Reticulocytosis** *(Ref: Robbins 9/e 652)*
In uncomplicated cases, oral iron supplementation produces an increase in reticulocytosis in about 5-7 days that is followed by a steady increase in blood counts and normalization of red cell indices.

99. **Ans. (d) Cutaneous porphyria**
(Ref: Hematology: Diagnosis and Treatment p467)

Sideroblastic anemia is associated with the following

Hereditary: X linked, autosomal recessive, autosomal dominant
Acquired: previous chemotherapy, irradiation, myelodysplasia, myelproliferative disorders
Drugs: alcohol isoanizid, choramphenicol, pyridoxine deficiency, lead poisoning
Rare causes: copper deficiency, zinc overload, hypothermia, **erythropoetic porphyria**
Hereditary syndromic: Pearson syndrome, thiamine responsive megaloblastic anemia,

100. **Ans. (a) Mucosal cell iron stores** *(Ref: Robbins 9/e 650)*
Rate of iron uptake is dependent on the levels of a protein called hepcidin. This protein functions to regulate (inhibit) iron transport across the gut mucosa, thereby preventing excess iron absorption and maintaining normal iron levels within the body. Hepcidin also inhibits transport of iron out of macrophages (where iron is stored).

- **Mutation** of the gene coding for hepcidin is implicated in the causation of **hemochromatosis.**

101. **Ans. (a) Duffy blood group** *(Ref: Robbins 9/e 391)*
Conditions providing protection against malaria with the reasons

- **Sickle cell disease**: *P falciparum* can not multiply properly in the presence of HbS
- **α and β thalassemia:**
- **Absence** of **duffy blood group**: duffy antigen is required for parasite to enter the RBCs
- **G6 PD deficiency**: G6PD is required for respiration of plasmodium

102. **Ans. (b) DMT1** *(Ref: Robbins 9th/650)*
Iron absorption is regulated by hepcidin, a small circulating peptide that is synthesized and released from the liver in response to increases in intrahepatic iron levels. Hepcidin inhibits iron transfer from the enterocyte to plasma by binding to ferroportin and causing it to be endocytosed and degraded.
Fe2+ iron is then transported across the apical membrane by divalent metal transporter 1 (DMT1). However, as DMT-1 also transports other divalent metal ions like Cu, Zn, Cd, it is non specific. This is the answer of choice here.

103. **Ans. (c) Coombs test** *(Ref: Robbins 9/e 643, 8th/653)*
The presence of spherocytes can be seen in the following conditions:

- ***Hereditary spherocytosis***
- ***Autoimmune hemlolytic anemia***
- ***G6PD deficiency***
- ***Infections***
- ***Burns***
- ***Hemolytic disease of new born***

- PNH is not a cause for the presence of spherocytes; so, no test for this condition is required.
- Osmotic fragility is increased with spherocytes. So, it does not add anything to our existing information about the disease causing spherocyte formation.
- Reticulocyte count is expected to be elevated in the setting of haemolytic anemia (suggested by jaundice and pallor).

Coombs test going to be positive in autoimmune hemolytic anemia whereas negative in hereditary spherocytosis. Thus, a differentiation between these conditions can be done.

104. **Ans. (c) Defective GPI anchor**
(Ref: Robbins 9/e 642, 8th/65, Harrison 17th/660)
Ham's acidified serum test is used for the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH). In this condition, defective GPI anchor prevents the attachment of CD55, CD59 and C8 binding protein.

105. **Ans. (d) Paroxysmal nocturnal hemoglobinuria**
(Ref Wintrobe's 12th/1007, 1044-5, Nathan and Oski's Hematology of infancy and childhood 7th/45, Guha's NEONATOLOGY Principles and Practice vol 2, 3rd/910)

- G6PD and Hereditary spherocytosis can cause anemia and jaundice since birth and are causes of haemolytic anemias. So, they are easily ruled out.
- Friends I got some worthy information after spending few days and multiple book searching which should bring a smile on your face.
- These are the lines from **Oski's Hematology** "β chain mutations generally produce no clinical symptomatology in the newborn period. This does not mean that chain variants are never a problem in the neonate. ***Sickle cell hemoglobinopathies are the most commmonly encountered β chain variants in the newborn period***. Several cases of ***homozygous sickle cell disease have been seen in neoanates***. In infants in whom sickle cell anemia has been diagnosed in first days of life because of some specific symptoms specifcally jaundice, fever, pallor, respiratory distress and abdominal distension".
- ***'Hyperbilirubinemia appears to be more common in newborns with sickle cell anemia.'***.. **Nathan and Oski 7th/45**

- ***'β chain defects do not manifest in newborn. An important exception*** *is* ***sickle cell disease*** *which can manifest in newborn as up to 30% of hemoglobin at birth may be adult hemoglobin.* Sickling and hemolytic jaundice may result and is best treated with exchange transfusion.'... **Guha 3rd/910,** Jaypee

Therefore the answer of exclusion is option 'd' .. paroxysmal nocturnal hemogloninuria. Its mean age of presentation is in the 30's. Even after extensive search, I could not get hold of any material which supports presence of symptomatic PNH in infancy.

106. Ans. (c) Idiopathic thrombocytopenic purpura

(Ref: Robbins 9/e 658-659, 8th/668, Harrison 17th/367)

Primary or idiopathic ITP has two clinical subtypes: acute and chronic. Both of them are autoimmune disorders in which platelet destruction results from the formation of antiplatelet autoantibodies. The opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system.

Option 'a': *The* ***triad of hemolysis, pancytopenia*** *and* **thrombosis** *is* ***unique*** *to this condition. Thrombosis is the leading cause of death in individuals with PNH....*Robbins 8th/653

Option 'b': *DIC is an acute, subacute, or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases. It is characterized by activation of the coagulation sequence that leads to the formation of* **microthrombi throughout the microcirculation** *of the body..* Robbins 8th/673

Option 'd': Heparin Induced Thrombocytopenia can be two types; type I thrombocytopenia which occurs rapidly after onset of therapy, is moderately severe, clinically insignificant and may resolve despite continuation of heparin therapy. Type II thrombocytopenia is more severe and occurs 5 to 14 days after initiation of therapy. It can, **paradoxically**, lead to life-threatening **venous and arterial thrombosis.**

Why do we have paradoxical thrombosis in HIT type II?

It is caused by an immune reaction against a complex of heparin and platelet factor 4 (a normal component of platelet granules). The attachment of ***antibody to platelet factor 4 produces immune complexes that activate platelets, promoting thrombosis even in the setting of marked thrombocytopenia.***

Additional important features of Heparin Induced Thrombocytopenia

- Platelet count < 100,000/μL or decreased by > 50%.
- Starts 5-10 days after starting heparin.
- More common with unfractionated heparin (than LMW heparin), Surgical patients (than medical patients) and females (than males)
- Venous thrombosis is more common than arterial.

107. Ans. (c) Glycosylphosphatidylinositol (GPI)

(Ref: Robbins 9/e 642, 8th/65, Harrison 17th/660)

108. Ans. (d) Donath-Landsteiner antibody

(Ref: Robbins 9/e 644, 7th/407-408; Harrison 16th/611-614)

Cold hemagglutinin is associated with more commonly **IgM** or rarely **IgG** antibodies. These are not to be confused with anti-IgM or anti-IgG antibodies given as other options in the question. An important example of cold hemagglutinin disease is paroxysmal cold hemoglobinuria. For details, see text

109. Ans. (c) Glycophorin C

(Ref: Harrison 17th/653-655, Robbins 9/e 632, 8th/642-644, 7th/625)

- Normally, RBC membrane consists of a protein **spectrin**, ion transporter called band 3 of membrane with the help of ankyrin and band 4.2.
- Mutations in glycophorin A has **not** been reported.

110. Ans. (c) CLL *(Ref: Harrison 17th/693, Robbins 9/e 643)*

Leukemias especially of the CLL type are associated with warm autoimmune hemolytic anemia.

111. Ans. (d) Metallic cardiac valves

(Ref: Rubin's pathology 5th/878, Nathan and Oski hematology 7th/643, Goljan pathology edn 2013/ 314)

Microangiopathic hemolytic anemia is associated with fragmentation of the red cells in the microcirculation. It is associated with antiphospholopid antibody syndrome... NMS Medicine 5th/348

Pathologically, macroangiopathic hemolytic anemia is associated with prosthetic cardiac valves..

Macroangiopathic hemolytic anemia may be caused by:

- Direct red cell trauma from abnormal valvular surface: prosthetic valve grafts, tight aortic stenosis and synthetic vascular grafts.
- Large vessel disorders that may cause shearing of red cells: cavernous hemangioma (Kasabach Merrit syndrome),
- Other causes include coarctation of aorta, ruptured sinus of valsalva, ruptured chordae tendinae and aortic aneurysm.

Causes of Microangiopathic hemolytic anemia

1. Vasculitis like microscopic polyangiitis
2. Malignant hypertension
3. Eclampsia
4. Renal graft rejection
5. Scleroderma
6. Thrombotic thrombocytopenic purpura (TTP) and Hemolytic uremic Syndrome (HUS)
7. DIC
8. March hemoglobinuria

112. Ans. (b) Conjugated and unconjugated bilirubin

(Ref: Robbins illustrated, 9/e 853, 8th/840-841, 7th/886-887)

- It is a case of *erythroblastosis fetalis*. (**type II Hypersensitivity reaction**)
- In erythroblastosis fetalis there is excessive breakdown of RBC's leading to increased production of bilirubin in the blood. This **increased** bilirubin is predominantly **unconjugated** but the level of **conjugated bilirubin** will also increase because of compensatory increase in bilirubin conjugation process by the liver. So, both unconjugated bilirubin and bilirubin glucuronides may accumulate systemically and deposit in tissues, giving rise to the yellow discoloration of jaundice. This is particularly seen in yellowing of the **sclera** (because of presence of **elastin fibers**).

113. Ans. (a) Teardrop and Burr cells *(Ref: Robbins 9/e 620)*

- Teardrop cells also known as dacryocytes are seen in ***myelofibrosis***. Rest of the features are seen in hemolytic anemia.

114. Ans. (b) Acute G6PD deficiency; (e) PNH

(Ref: Robbins' 7th/624, 625, 9/e 631-632)

Intravascular hemolysis occurs due to disruption of red cell membrane in circulation. The RBCs are damaged mechanically, by *complement fixation, malaria, toxins and drugs*. **It is seen in:** Acute G6PD deficiency and PNH

- In Sickle cell disease and hereditary spherocytosis, RBC destruction occurs in spleen (extravascular hemolysis)
- Thalassemia is a hemoglobinopathy.

115. Ans. (a) HUS; (c) Malignant hypertension; (e) TTP

(Ref: Robbins' 7th/638, 9/e 630)

Prosthetic valves cause Macroangiopathic hemolytic anemia.

116. Ans. (a) Hemoglobin C; (c) Hereditary spherocytosis

(Ref: de Gruchy's 5th/184, Robbins 9/e 632)

117. Ans. (a) Microangiopathic hemolytic anemia; (b) DIC; (d) Malignant hypertension; (e) HELLP syndrome

(Ref: de Gruchy's 5th/209 , Wintrobes 11th/1236, Robbins 9/e 630)

Schistocytosis or fragmented RBCs are found in

Thalassemia	Severe burn	DIC
Hereditary elliptocytosis	Microangiopathic hemolytic anemia	Malignant hypertension
Megaloblastic anemia	Iron deficiency anemia	HUS
HELLP syndrome		

118. Ans. (a) Glucose-6 phosphate dehydrogenase deficiency

(Ref: Robbins 7th/624, 628, 9/e 631)

119. Ans. (b) Reticulocytosis seen; (c) Smaller size; (e) Always associated with ↑ MCHC *(Ref: Robbins 9/e 633)*

Hereditary spherocytosis is an usually autosomal dominant condition in which the ratio of surface area to volume decreases and hence the RBC becomes rounded. Spherocytes are **small** densely staining RBC without central pallor. Mean cell Hb concentration **(MCHC) is always increased** in this disease because the size is decreased. Reticulocytosis would be seen because HS is an important cause of hemolytic anemia.

RBCs are macrocytic; hyperchromic and show anisocytosis. Hypersegmented neutrophils are also seen.

120. Ans. (a) Thrombotic Thrombocytopenic purpura; (b) Hemolytic uremic syndrome; (d) DIC

(Ref: Robbins 7th/638, 9/e 630)

- In Henoch-Schonlein purpura, there is hematuria and palpable purpura.

DIC is the commonest cause of Microangiopathic hemolytic anemia.

121. Ans. (b) Cold agglutination

(Ref: Harrison 17th/660, Robbins 7th/657, Robbins 9/e 644)

Paroxysomal cold hemoglobinuria is characterized by the presence of Donath-Landsteiner antibody. It has anti-P specificity and bind to red cells only at low temperature (Optimally at 4°C)

122. Ans. (d) Spectrin *(Ref: Robbins 9/e 632, 8th/642)*

Ideal answer is ankyrin (most commonly) but in the given options, spectrin is the best option.

123. Ans. (b) Ankyrin deficiency *(Ref: Robbins 9/e 632)*

124. Ans. (d) Increased platelets *(Ref: Robbins 9/e 642)*

125. Ans. (a) SLE *(Ref: Robbins 9/e 642-644)*

126. Ans. (a) Mycoplasma infection *(Ref: Robbins 9/e 643-644)*

127. Ans. (a) CD 59 *(Ref: Robbins 9/e 642) ...see text*

128. Ans. (a) Acute promyelocytic leukemia

(Ref: Robbins 9/e 664, 8/e p673-4, Harrison 18/e p)

The most common causes are **bacterial sepsis**, malignant disorders such as solid tumors or **acute promyelocytic leukemia**[Q], and obstetric causes (pregnant women with **abruptio placentae**, or with **amniotic fluid embolism**).

129. Ans. (c) Paroxysmal nocturnal hemoglobinuria

(Ref: Robbins 9/e 642, 8/e p652)

130. Ans. (b) Controlling oxidative stress on RBC

(Ref: Robbins 9/e 634)

G6PD helps in neutralizing the effect of oxidative stress on the RBC. Oxidative stress is induced by drugs like primaquine and hence in patients of G6PD there is accelerated hemolysis (intravascular during the hemolytic episode) resulting in hemoglobinuria and passage of shockingly black urine by the patient.

131. Ans. (b) IgM *(Ref: Robbins 9/e 644, 8/e p653)*

Cold agglutinins are monoclonal IgM antibodies that react at **4 to 6°C**. They are called agglutinins because the IgM directed against the 'I' antigen present on the RBCs can agglutinate red cells due to its large size (pentamer).

132. Ans. (a) Hemolytic uremic syndrome

(Ref: Robbins 9/e 660, 8/e p952)

Schistocytes are typically irregularly shaped, jagged, and have two pointed ends. *A true schistocyte does* ***not*** *have central pallor.*

Helmet cells are also known as **schistocytes/triangle cells/burr cells** are a feature of microangiopathic diseasesincluding disseminated intravascular coagulation (**DIC**), thrombotic microangiopathies (**TTP**), **mechanical artificial heart valves** and hemolytic uremic syndrome (**HUS**).

133. Ans. (d) All of the above *(Ref: Robbins 8/e p952)*

Yes friends, only additional important thing that you need to be aware of is that schistocytes can also be seen in severe iron deficiency anemia.

Echinocytes/Burr cells **Acanthocytes/Spur cells** **Stomatocytes** **Schistocytes** **Leptocytes** **Codocytes** **Dacrocytes** **Drepanocytes** **Elliptocytes** **Keratocytes** **Knizocytes**	• Regular spine-like projections on cell surface; • irregular thorn-like projections; • Slit-like (mouth like) area of pallor • Fragmented RBCs; triangular, comma-shaped or helmet shaped • Thin flat cells • Mexican hat cells • Tear drop cells or Target cells (red cells with central dark area; • Sickle cells • Pencil cells or cigar cells • Helmet cells	• **Megaloblastic anemia/ hemolytic anemia /burns** • in **liver disease, abetalipoproteinemia** • in liver disease, anemia of chronic disease)

134. Ans. (c) Normal APTT
(Ref: Robbins 8/e p673-4, 9/e 665, Harrison 18/e p)

DIC is an acute, subacute, or chronic thrombohemorrhagic disorder characterized by the excessive activation of coagulation, which leads to the formation of thrombi in the microvasculature of the body.

Harrison 18/e pmentions... "Common findings include the **prolongation of PT and/or aPTT**; **platelet counts** ≤100,000/μL^3, or a rapid decline in platelet numbers; the presence of **schistocytes** (fragmented red cells) in the blood smear; and **elevated levels of FDP**.

- The D-dimer test is more specific for detection of fibrin—but not fibrinogen—degradation products and indicates that the cross-linked fibrin has been digested by plasmin. Because ***fibrinogen has a prolonged half-life, plasma levels diminish acutely only in severe cases of DIC.***

The **most sensitive test** for DIC is the **FDP level**[Q]. DIC is *an unlikely diagnosis in the presence of normal levels of FDP.*

135. Ans. (c) Increased haptoglobin *(Ref: Robbins 9/e 631)*

136. Ans. (a) G6PD deficiency *(Ref: Robbins 9/e 634, 8/e p645)*

137. Ans. (a) Clumps of RBCs due to IgM mediated cold autoimmune haemolytic anemia *(Ref: Robbins 9th/643-4)*
The image shows agglutinated red cells. Since the history mentions that cyanosis is seen affecting fingers and tips of nose in the month of December, it suggests that the red cells agglutinated with cold antibody associated autoimmune haemolytic anemia.

138. Ans. (d) Low reticulocyte count *(Ref: Robbins 9th/631)*
Haemolytic anaemia is characterised by the *increased reticulocyte count, splenomegaly* (especially extravascular hemolysis) and *increased concentration of bilirubin and urobilinogen.*

139. Ans. (b) Aplastic anemia *(Ref: Robbins 9th/653)*
Direct coombs test is positive in conditions associated with presence of antibodies on the surface of the cells. It is therefore Negative in a patient of aplastic anemia. Some of the important conditions with positive Coombs test include:

- Autoimmune haemolytic anaemia
- Haemolytic disease of new born or Rh incompatibility
- Haemolytic anaemia due to mismatched blood transfusion

140. Ans. (d) Folic acid deficiency
Looking at the parameters being mentioned in the question, we analyse and understand the type of anemia the patient is having:

$$MCV = \frac{\text{haematocrit} \times 10}{\text{RBC count in million}}$$

$$\frac{30 \times 10}{2} = 150$$

Hence, the patient is having macrocytic anemia. The answer is folic acid deficiency anemia. All other option lead to microcytic anemia.

141. Ans. (b) Iron deficiency anemia *(Ref: Robbins 9th/650)*

142. Ans. (b) Causes mild to severe coombs positive hemolytic anemia *(Ref: Robbins 9/e 643, 660)*
Coombs test is done for immune hemolytic anemia whereas HUS is non immune hemolytic anemia.

143. Ans. (c) Hypersplenism *(Ref: Robbins 9/e 631)*
Hypersplenism is an extracorpuscular cause of hemolytic anemia. All other options are intracorpuscular/ intrinsic causes of hemolytic anemia.

144. Ans. (b) IgG *(Ref: Robbins 9/e 643)*

145. Ans. (a) P. Falciparum *(Ref: Robbins 9/e 391)*

- People who are heterozygous for the **sickle cell trait (HbS)** become infected with *P. falciparum*, but they are less likely to die from infection. The HbS trait causes the parasites to grow poorly or die because *of the low oxygen concentrations.*
- **HbC**, another common hemoglobin mutation, also protects against severe malaria *by reducing parasite proliferation.*
- People can also be resistant to malaria due to the absence of proteins to which the parasites bind. **P. vivax enters red cells by binding to the Duffy blood group antigen**. Many individuals (usually Africans), are not susceptible to infection by *P. vivax* because they do not have the Duffy antigen.

146. Ans. (b) Beta thalassemia
(Ref: Robbind 9/e 640-641, 8th/648-652, Textbook of Hematology 1st/89)
Friends, let's get the answer of this question in a methodical manner. The clues in the question:

- Reduced values of MCV and MCHC: microcytic hypochromic anemia (G6PD deficiency is ruled out)
- Age of presentation and ethnicity: 6 year old and Punjabi ethnicity
- History of repeated blood transfusion: in favour of thalassemia
- Osmotic fragility is reduced: in favour of thalassemia again though it may be seen in sickle cell also

If we compare the above mentioned points, we can deduce that the stem talks about a patient suffering from thalassemia. Now comparing the incidence of alpha and beta thalassemia, it is clear that beta thalassemia is far more common than alpha thalassemia. Hence, it is a better option than alpha thalassemia.

Also, the hemoglobin is the question is more suggestive of **severe anemia** with **positive history of multiple blood transfusions** both being important pointers towards **thalassemia major.**

Please note that apart from Punjabis, other ethnic groups having high prevalence of thalassemia are Sindhis, Gujaratis, Parsis, Begalis and Lohanas.

147. Ans. (a) β- thalassemia
(Ref Recent Advances in Hematology -3, 1st/173)

148. Ans. (a) Deletion of alpha genes
(Ref: Robbins 8th/651, T. Singh 2nd/95)

149. Ans. (b) Deletion of 3 alpha chains
(Ref: Robbins 8th/652, 9/e 642)

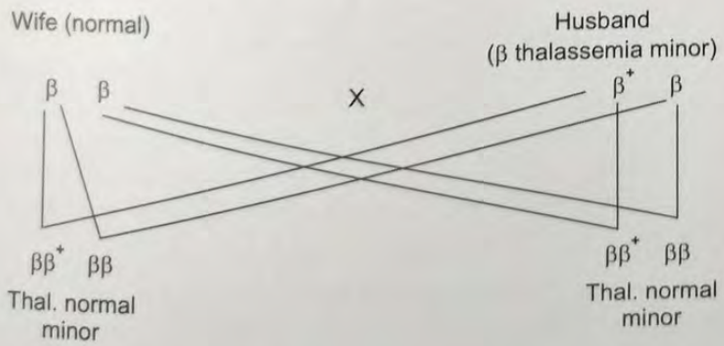
150. Ans. (a) Malaria
(Ref: Robbins 9/e 638, 8th/645, T. singh 1st/270)

151. Ans. (d) Solubility *(Ref: Robbins 9/e 635-636)*

152. Ans. (d) 0% *(Ref: Robbins 7e/632-33, Harrison – 17th/641)*

Normal percentage of HbA2 ranges from 1.5 to 3%.

- In thalassemia trait (β thalassemia minor), HbA2 level may be elevated (3.5-7.5%).
- Thus, wife in this question has normal genotype (bb) whereas husband has thalassemia – trait (β+β).
- β-Thalassemia is an **autosomal recessive** disease



- None of the offsprings thus will have thalassemia major (β⁺ β⁺), thus, the risk of having a child with thalassemia major is therefore 0%.
- 50% of the offspring (β⁺β) will be carriers like father.

153. Ans. (b) Replacement of glutamate by valine in b-chain of HbA *(Ref: Robbins 9/e 635, Harrison 17th/637)*

154. Ans. (c) Binding of HbS to the deoxygenated HbA can extend the polymer and cause sickling of the red blood cells
(Ref: Harper 25th/71, Robbins 7th/628, 630, 8th/645-646, 9/e 636)

- **Sickle cell anemia** is caused by a point mutation is which there is *replacement of glutamine by valine* at *position 6* of the *beta chain* generating a **sticky patch on** the surface of HbS.
- The sticky patch on the surface of adjacent HbS molecules cause their polymerization resulting in formation of long fibrous precipitates.

HbA molecule can complementarily bind with the sticky patch by HbS but cannot promote the formation of long fibers because it does not have a patch itself. So, the option c is false in the given question.

Other hemoglobins which also weakly interact with HbS and prevent its polymerization include *HbF* and *HbC.*

155. Ans. (a) 50% HbS is required for occurrence of sickling
(Ref: Robbins 7th/628-629, 9/e 635-636)

- Sickle cell disease is a hemoglobinopathy in which HbS due to point mutation. If an individual is homozygous for sickle mutation almost all the Hb in erythrocyte is HbS, if he is heterozygote only 40% is HbS the remainder being normal.

In addition, Nelson also mentions that **'persons with sickle cell trait have totally benign clinical course because the low level of HbS present in them (35-40% of total) is insufficient to produce sickling manifestation'**. So, option 'a' is a better answer than option 'b'...

156. Ans. (d) Deletion of gene *(Ref: Robbin 9/e 635)*

157. Ans. (a) Increased HbF; (b) Increased HbA2; (c) Microcytosis; (e) Target cell
(Ref: Harrison 17th/641, Robbins 7th/634-635, 9/e 641)

158. Ans. (d) Point mutation
(Ref: Harrison 17th/637 Robbins 7th/628, 9/e 635)

159. Ans. (c) Three α globin genes *(Ref: Robbins 9/e 642)*

160. Ans. (b) Higher concentration of HbF
(Ref: Robbins 7th/629, 9/e 642)

161. Ans. (a) Presence of a structurally abnormal Hb
(Ref: Robbins 8th/645; 7th/628)

162. Ans. (b) β-chain *(Ref: Robbins 8th/645; 7 th/628, 9/e 635)*

163. Ans. (b) Bone marrow expansion in the calvarium
(Ref: Robbins 8th/646-651, 9/e 636-638)

164. Ans. (c) Sickle thalassaemia
(Ref: Robbin 9/e and Harrison chapter 104, disorders of hemoglobin synthesis)

Condition	Clinical Abnormalities	Hemogblobin Level g/l (g/dL)	MCV. fL	Hemoglobin Electrophoresis
Sickle cell trait	None: rare painless hematunia	Normal	Normal	Hb S/A: 40/60
Sickle cell anemia	Vasooclusive crises; aseptic necrosis of bone	70-100 (7-10)	80-100	Hb S/A: 100/0 Hb F:2-25%
S/ B0 thalassemia	Vasoocclusive crises: aseptic necrosis of bone	70-100 (7-10)	60-80	Hb S/A: 100/0 Hb F;1-10%
S/B+ thalassemia	Rare crises and aseptic necrosis	100-140 (10-14)	70-80	Hb S/A: 60/40
Hemoglobin SC	Rare crises and aseptic necrosis; painless hematuria	100-140 (10-14)	80-100	Hb S/A:50/0

165. Ans. (d) Relative excess of β, γ, and δ chains

(Ref: Robbins 8/e p651, 9/e 635-636)

- *The α-thalassemias are caused by inherited deletions that result in reduced or absent synthesis of α-globin chains and relative excess of other chains.*

The options which created confusion were options "c" and "d".

Total absence of *α-chains* is a feature of most severe form of α-thalassemia resulting in **hydrops fetalis**.

Every patient having α-*thalassemia* would **not** be having total absence of α- *chains but all patients would be having relative excess of β, γ, and δ chains as per their age of presentation*. Hence, we prefer option "d" as the answer for this question.

166. Ans. (c) Saline washed packed RBC *Ref: Choudhary p80*

Saline washed RBCs are specially indicated in conditions requiring repeated transfusion when the chances of urticarial reactions due to plasma is high. These have negligible plasma proteins and just 10% leucocytes. It is also preferred in the management of babies suffering from **thalassemia** and **paroxysmal nocturnal hemoglobinuria**.

167. Ans. (d) Macrocytic anaemia *(Ref: Robbin 9/e)*

Thalassemia major presents before 1 yr of age with severe anemia which necessitates packed RBC transfusions every 2-3 months. The child is said to be transfusion dependent as survival is decided by RBC being transfused.

The ineffective erythropoiesis in bone marrow results in shift of hematopoiesis to liver and the bone marrow. Hence the liver and spleen enlarge in size. But the net result is defective microcytes being produced. The type of anaemia is microcytic hypochromic anaemia.

Mnemonic to remember causes of macrocytic anemia:

ABCDEF

- **A**lcohol + liver disease
- **B**12 deficiency
- **C**ompensatory reticulocytosis (blood loss and hemolysis)
- **D**rug (cytotoxic and AZT)/**D**ysplasia (marrow problems)
- **E**ndocrine (hypothyroidism)
- **F**olate deficieny/ **F**etus (pregnancy)

168. Ans. (c) Sickle cell anemia *(Ref: Robbins 9/e 635)*

Sickled cells can cause microvascular occlusion affecting bones, brain, kidney, liver, retina and pulmonary vessels.

169. Ans. (b) Beta chain....too obvious friends

(Ref: Robbins 9/e 635, 8/e p645, 7/e p628)

170. Ans. (c) Single amino acid base substitution

(Ref: Robbin 8/e p645-6)

Afro American male presenting with the mentioned features is suggestive of sickle cell anemia is due to vaso-occlusion caused by sickled cells. Sickle cell anemia can cause chronic hemolytic anemia, recurrent pneumonia and non haling painful ulcer.

"Sickle cell anemia is caused by a point mutation in the sixth codon of β-globin that leads to the replacement of a glutamate residue with a valine residue"... (Ref: Robbind 8/e p645)

171. Ans. (b) Gene deletion *(Ref: Robbin 9/e p641)*

172. Ans. (c) Replacement of glutamate by valine in β-chain of HbA *(Ref: Robbins 8/e p645, 9/e 635)9*

173. Ans. (d) Protective action against adult malaria

(Ref: Robbins 9/e 638, 8/e p645-648, 7/e p629)

174. Ans. (d) Infested red blood cells stick to the capillaries

(Ref: Robbins 9th/391)

Plasmodium falciparum is associated with infected red cells expressing PfEMP (*Plasmodium falciparum* erythrocyte membrane protein) leading to their attachment to the endothelial cells. This leads to sequestration of infected red cells in the capillaries. That's the reason for the non-appearance of trophozoites and schizonts in the peripheral blood smear.

175. Ans. (c) Sickling is reversible with oxygenation

(Ref: Robbins 9/e 635)

176. Ans. (b) Decreased ESR *(Ref: Robbins 9th/636)*

Sickle cell is associated with increased ESR (only important exception amongst anemias since all other anemias are associated with reduced ESR).

ANNEXURE

You must know: Different type of red blood cells are:

- Echinocytes/Burr cells : Regular spine-like projections on cell surface; in Megaloblastic anemia/burns/hemolytic anemia
- Acanthocytes/Spur cells : irregular thorn-like projections; in liver disease, abetalipoproteinemia
- Stomatocytes : Slit-like (mouth like) area of pallor
- Schistocytes : Fragmented RBCs; triangular, comma-shaped or helmet shaped
- Leptocytes : Thin flat cells
- Codocytes : Mexican hat cells
- Dacrocytes : Tear drop cells or Target cells (red cells with central dark area; in liver disease, anemia of chronic disease)
- Drepanocytes : Sickle cells
- Elliptocytes : Pencil cells or cigar cells
- Keratocytes : Helmet cells
- Knizocytes : Cells with more than one concavities

CHAPTER 8

White Blood Cells

Golden Points

- Alkaline phosphatase is specific for Neutrophils and is called as NAP.
- **High LAP score**: Infection, pregnancy, myeloproliferative disorder ***except CML***, drugs (oral contraceptive pills, growth factors, lithium, Corticosteroids etc)
- **Low LAP score**: *CML, PNH and myelodysplastic syndrome.*
- Dohle bodies are rough ER remnants in neutrophils which are seen in infections and Chediak-Higashi syndrome.
- **Downey cells** are seen in **infectious mononucleosis.**
- **P**henytoin causes ***Pseudolymphoma*** as it causes **P**aracortical hyperplasia.
- Leukamoid reaction is differentiated from leukemia by LAP score (increased in leukamoid reaction).
- Important causes of leukamoid reaction: Infections, hemorrhage, drugs (glucocorticoids), malignancies, Down syndrome.
- Important markers of myeloid lineage: CD 13, CD 33, CD 11b, Cd 15, CD4, Cd 117, cMPO.
- Important marker of B-cells: CD 19, CD 20, CD 22, CD 79a, cCD 22, cCD 79a.
- Most of **acute lymphoblastic leukemia** is arising from immature **precursor B-cells**.
- T cell ALL presents as a mediastinal mass whereas ALL-L_3 has morphology identical to Burkitt's lymphoma cells.
- Lymphoblasts stain positive for PAS (Periodic acid schiff) and tdT whereas myeloblasts stain for myeloperoxidase, Sudan Black-B and Non-specific esterase.
- Gingival hypertrophy, hepatomegaly, splenomegaly, and infiltration of skin (leukemia cutis) is seen with M_4/M_5 AML whereas **chloroma** formation is seen with **M2 AML**.
- **Biphenotypic acute leukemia** is acute leukemia with a ***single blast cells population showing markers of two different lineage.***
- **Bilinear acute leukemia** is acute *leukemia with two different blast cells population*
- **Sezary syndrome** and **Mycosis fungoides** are seen with **Cutaneous T-cell leukemias**.
- Myelodysplastic syndrome shows presence of ringed sideroblasts, Pseudo-Pelger-Huet cells and pawn ball megakaryocytes. It is associated with monosomy 7 (in children) and deletion 5 (adults).
- Peripheral smear with neutrophilia, basophilia, eosinophilia and increased platelets is seen with CML. It is also having the presence of Philadelphia chromosome.
- Features of Juvenile CML (CMML): Raised HbF; Ph chromosome negative; monocytosis ($>1\times10^9$L) and thrombocytopenia; it is associated with NF-1.
- Most common myeloproliferative disorder is **Polycythemia vera**.
- Characteristic bone marrow **aspiration** finding in myelofibrosis is **Dry tap** and so, diagnosis is made with **bone marrow biopsy**.
- Hodgkin lymphoma is a lymphoma characterized by involvement of painless lymphadenopathy and Pel Ebstein fever. It has characteristically presence of Reed-sternberg cells (RS cells).
- RS like cells are seen in infectious mononucleosis, immunoblastic lymphoma, carcinoma ans sarcoma.
- Classification of HD proposed by international lymphoma study group: REAL.
- Non Hodgkin lymphoma is more common lymphoma and has several subtypes.
- Low grade NHL: Small lymphocytic, follicular small cleaved cells, follicutar mixed.
- Intermediate grade NHL: Follicular large cells, Diffuse small cleaved/mixed/large cells.
- Diffuse large B cell lymphoma is the commonest NHL in the world.
- Most common extranodal site for NHL is Stomach whereas M/C extranodal site for NHL in HIV infected patients is CNS.
- **Post transplant lymphoma** arises from **B-cells** (as T cells are destroyed by therapeutic drugs).
- Multiple myeloma is a plasma cell cancer secreting excessive immunoglobulin light or heavy chains. It has NORMAL alkaline phosphatase.
- Most important prognostic factor of multiple myeloma is serum **β2-microglobulin**
- **Histiocytosis-X** (Langerhans cell histiocytosis) includes *Letterer-siwe disease, Hand-Schuller- Christian disease* and *Eosinophilic granuloma.* The characteristic of Langerhans cell histiocytosis is ***Birbeck granules*** (have **Tennis racket appearance**).
- Multiple permeating (osteolytic) lesions in a child: Histiocytosis-X.
- Generalized **necrotizing lymphadenopathy** is a feature of **Kikuchi disease** whereas ***eosinophilic abscess*** in lymph nodes is seen with ***Kimura's disease***.

HEMATOGENOUS NEOPLASMS

Leukemia is a term used to describe the widespread **involvement of the bone marrow accompanied with large number of cancer cells in the peripheral blood** whereas *lymphoma* is a term used for *proliferation of lymphoid cells arising as discrete tissue masses.*

Key Point

- According to **WHO** classification, *blasts should be* **>20%** in bone marrow for diagnosis of acute leukemia.
- So **bone marrow biopsy** is the **investigation of choice** for diagnosing leukemia.

WHO Classification of the Lymphoid Neoplasms

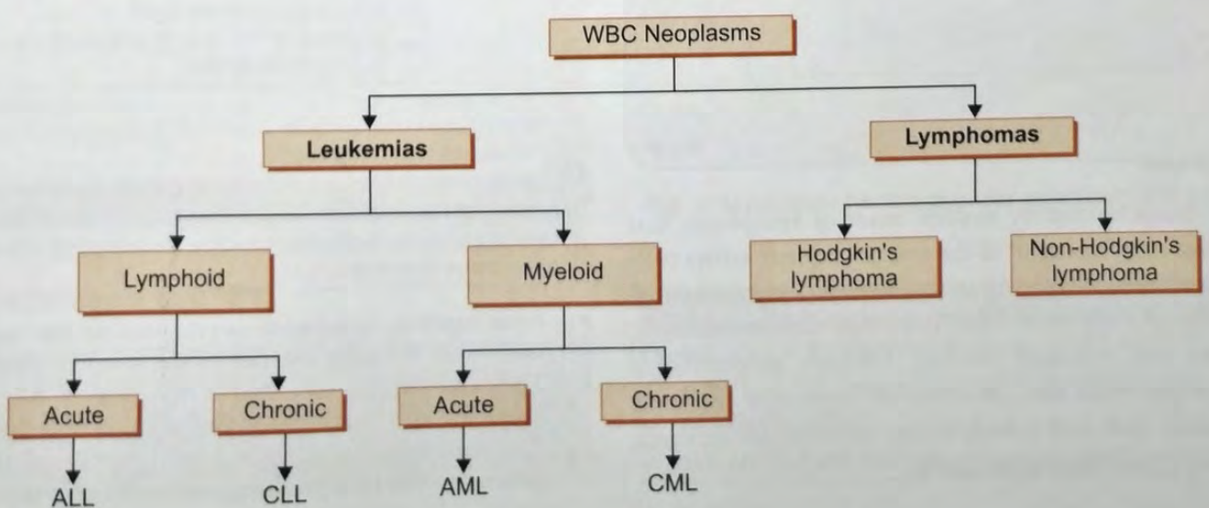
I. Precursor B-Cell Neoplasms	II. Peripheral B-Cell Neoplasms	III. Precursor T-Cell Neoplasms	IV. Peripheral T-Cell Neoplasms
* Precursor-B lymphoblastic leukemia or lymphoma	Chronic lymphocytic leukemia/small lymphocytic lymphoma	*Precursor-T lymphoblastic leukemia or lymphoma	Angioimmunoblastic T-cell lymphoma
	B-cell prolymphocytic leukemia		Large granular lymphocytic leukemia
	Lymphoplasmacytic lymphoma		T-cell prolymphocytic leukemia
	Splenic and nodal marginal zone lymphomas		Peripheral T-cell lymphoma, unspecified
	Extranodal marginal zone lymphoma		Anaplastic large cell lymphoma
	Mantle cell lymphoma		Mycosis fungoides/Sezary syndrome
	Follicular lymphoma		Enteropathy-associated T-cell lymphoma
	Marginal zone lymphoma		Panniculitis-like T-cell lymphoma
	Hairy cell leukemia		Hepatosplenic γδ T-cell lymphoma
	Plasmacytoma/plasma cell myeloma		Adult T-cell leukemia/lymphoma
	Diffuse large B-cell lymphoma		NK/T-cell lymphoma, nasal type
	Burkitt lymphoma		NK-cell leukemia

V. HODGKIN LYMPHOMA

Classic subtypes	Nonclassical
• Nodular sclerosis	• Lymphocyte predominant
• Mixed cellularity	
• Lymphocyte-rich	
• Lymphocyte depletion	

- **The FAB** (French-American-British Classification) diagnostic criteria for acute leukemia is the **presence of >30% blasts** in the bone marrow (normally, they are <5%) and increased number of cells in the blood.
- **Acute leukemias** have a **high rate of proliferation without differentiation** and their clinical course is **rapid**.
- ***Chronic leukemias*** have a ***low rate*** of proliferation of tumor cells with ***good differentiation*** and their clinical course is ***slow***.

For broad understanding, WBC neoplasms can be classified as:



LEUKEMIAS

1. Acute Lymphoblastic Leukemia (ALL)

It is the ***commonest leukemia seen in childhood***[Q] having slight predilection for males. The etiological agents include exposure to ionizing radiations as X rays, chemical like benzene, genetic disorders like Down syndrome, ataxia telangiectasia and acquire disorders like paroxysmal nocturnal hemoglobinuria and aplastic anemia.

Key Point

Lymphoblast[Q] staining positively with PAS and (TdT).

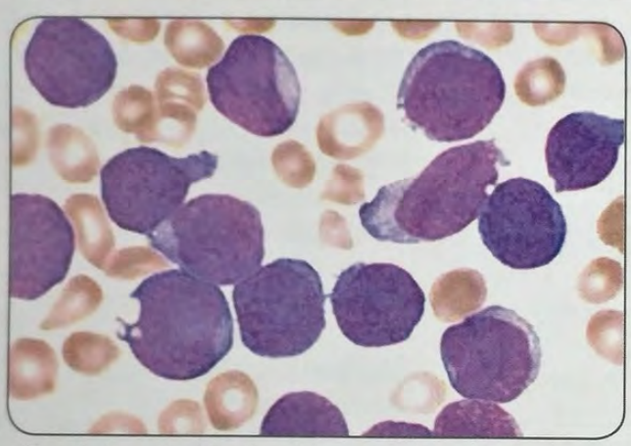


Fig. 1: *Lymphoblast* having *agranular cytoplasm* and minimal nucleoli.

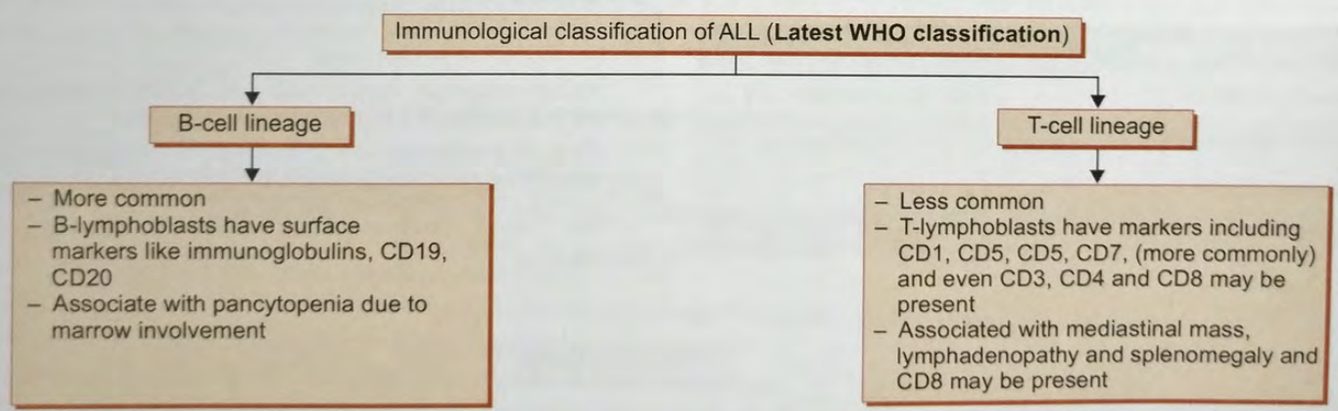
The *predominant cell seen in this leukemia is lymphoblast*[Q] characterized by coarse nuclear chromatin, 1-2 nucleoli, high N:C (nuclear:cytoplasmic) ratio and *staining positively with PAS (block positivity) and terminal deoxynucleotidyltransferase (TdT).*

FAB (French-American-British) classification of ALL (Older classification)

L1 ALL	L2 ALL	L3 ALL
Commonest[Q] type of ALL having the ***best prognosis***.	Next common type having worse prognosis.	Rarest type of ALL with the worst[Q] prognosis.
Small homogenous blast, scanty cytoplasm, indistinct nucleoli	Large, heterogenous blast, indented nuclei, one or more nucleoli, moderately abundant cytoplasm, minimal cytoplasmic vacoulation	Large homogenous blast, abundant basophilic cytoplasm with prominent cytoplasmic vacoulation staining positive with Oil Red 'O'.

Key Point

- **L1 ALL** is the **Commonest**[Q] type of ALL having the **best prognosis**.
- **L3 ALL** is the **rarest** type of ALL having the **worst prognosis**.



Clinical features

- ALL is characterized by ***sudden onset*** of symptoms that arise due to replacement of the normal bone marrow cells with blast cells, thereby causing features/symptoms due to decreased number of RBC, WBC and platelets *(anemia, infections and increased bleeding tendency* respectively). The leukemic cells also infiltrate the organs of the body like spleen, liver and lymph nodes causing *splenomegaly, hepatomegaly and lymphadenopathy.*

Key Point

Aleukemic leukemia is diagnosed by the presence of **>20% blasts** in the **bone marrow**.

- Bone marrow expansion is responsible for bone *pain and tenderness* (usually sternal tenderness) in these patients. *Testicular involvement and CNS features* like headache, vomiting and nerve palsies are also seen in these patients. This leukemia can either be a precursor B-cell or T-cell type (these are the two predominant types of lymphocytes). In

the pre-T-cell type, there is presence of mediastinal mass due to thymus involvement which can compress either the vessels or airways in the region.

Recent Exam Question

Testicular and mediastinal involvement is seen with **T type ALL** and is associated with **bad prognosis**.

Investigations

Blood findings

They include *markedly elevated WBC count*. Uncommonly, some patients may show *pancytopenia with few or no blast cells in peripheral blood* which is called as **aleukemic leukemia**. *However*, diagnosis is made in this condition by the presence of *>20% blasts in the bone marrow*. Blast cells with Periodic Acid Schiff (PAS) positivity are seen. There is presence of anemia, neutropenia and thrombocytopenia.

Bone marrow

It is hypercellular with *blast cells >20%* of the marrow cells.

Biochemical investigations

It includes *elevated serum uric acid and phosphate* levels accompanied by *hypocalcemia* (because of hyperphoshatemia). *Serum LDH is also increased* as a result of increased turnover of the cancer cells.

Recent Exam Question

- **Commonest cytogenetic abnormality** in **ALL** is **Hyperdiploidy**.
- Apart from CML, Philadelphia chromosome is also seen in ALL and is associated with worse prognosis.

Prognostic factors in ALL

Good Prognosis	Bad Prognosis
• Age 2-10 years • Female sex • L1 cell • Peripheral blast count <1,00,000 • Pre B-cell phenotype • Absence of mediastinal mass • **Hyperdiploidy** (>50 chromosomes) or t(12;21) • Trisomy 4,7 and 10	• **Age <1 year** or > 10 years • Male sex • L2 or L3 cell • Peripheral blast count >1,00,000 • Pre T-cell phenotype • **Mediastinal mass/CNS/ testicular involvement** • Pseudodiploidy or t (9;22) (Philadelphia chromosome) or t (8;14) or t (4;11)

Genetic associations of ALL

- **T cell ALL** is associated with *gain of function* mutation in **NOTCH 1 gene** (normally required for T cell development)
- **B cell ALL** is associated with *loss of function* mutation in **PAX5, E2A** and **EBF** or balanced t (12; 21) affecting TEL and AML1 genes (normally required for B cell development).

Key Point

Treatment of choice for ALL is **allogenic bone marrow transplantation** and cancer drug regime used for induction is **VAPD** (vincristine + asparaginase + prednisolone + daunoribicin) with **intrathecal methotrexate**.

2. Acute Myelogenous Leukemia (AML)

It is the leukemia affecting adults seen most commonly between the ages of 15-39 years. The etiological agents include exposure to ionizing radiations such as X-rays, chemicals like benzene, secondary to myelodysplastic syndrome, drugs like anti-cancer drugs and genetic disorders like Down's syndrome and Fanconi's anemia.

Key Point

Myeloblast stains positively with **Sudan black B**, myeloperoxidase **(MPO)** and Non Specific Esterase **(NSE)**.

The *predominant cell* seen in this leukemia is *myeloblast* characterized by fine nuclear chromatin, 3-5 nucleoli, high N: C (nuclear: cytoplasmic) ratio, presence of *Auer rods* (these are abnormal azurophilic granules) and *staining positively with Sudan black B, myeloperoxidase (MPO) and Non Specific Esterase (NSE)*.

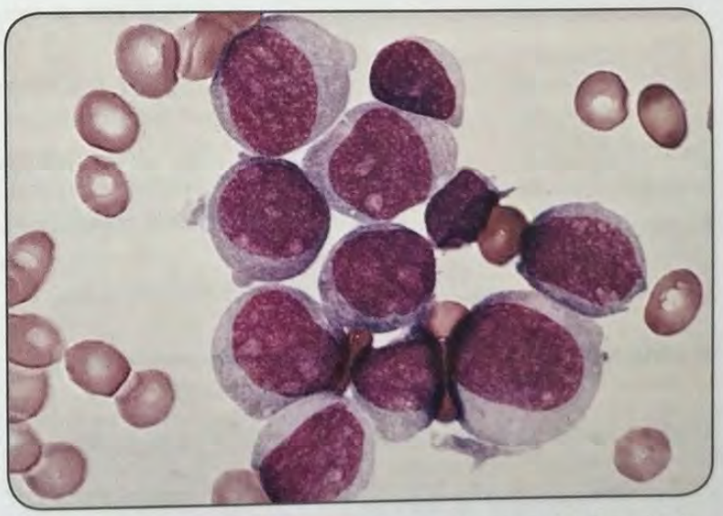


Fig. 2: Myeloblast having granular cytoplasm and 4-5 nucleoli.

Recent Exam Question

- **M2:** AML is the **Commonest**[Q] type of AML.
- **M3:** AML is associated with disseminated intravascular coagulation (***DIC***).
- **M7:** AML is the **Commonest**[Q] type of **AML in Down syndrome**.

FAB (French-American-British) classification of AML

Class	Salient Features
M0: Minimally differentiated AML	Myeloid lineage blasts
M1: AM L without maturation	Myeloblasts without maturation (> 3% blasts MPO or SBB positive)
M2: AML with maturation	**t (8;21)**[Q] is present, ***maximum incidence of chloroma***[Q], Auer rods are seen
M3: Acute (Hypergranular) promyelocytic leukemia	**t (15;17)**[Q] seen, Associated with **DIC**[Q], Auer rods are seen
M4: Acute myelomonocytic leukemia ***(Naegli type)***	***Inversion 16***[Q] present, Presence of both myeloblasts and monoblasts (blasts > 20%; neutrophil and its precursors > 20%; monocyte and precursors > 20%)
M5: Acute monocytic leukemia ***(Schilling type)***	t (9;11) seen, Highest incidence of ***tissue infiltration***[Q], organomegaly, and lymphadenopathy
M6: Acute erythroleukemia ***(Di Gugliemo disease)***	Abnormal erythroid precursors are seen
M7: Acute megakaryocytic leukemia	Least common type of AML, associated with **myelofibrosis** and **Down syndrome**

Recent Exam Questions

- AML **M3/M4/M5** is positive for **non specific esterase**.

Key Point

Cells with multiple Auer rods are called **"faggot cells"** and are seen in M3- AML.

Additional Salient Points

Concept

Generally AML following myelodysplastic syndrome (MDS) is associated with monosomy involving chromosomes 5 and 7 and lack chromosomal translocation **except** AML following treatment with topoisomerase II inhibitors (which is associated with translocation on chromosome 11 involving MLL gene).

Clinical features

They are similar to ALL i.e. fatigue due to anemia, bleeding and infections in oral cavity, lungs etc. Patients may develop bleeding diathesis due to DIC which results from release of thromboplastic substances in the granules (most common with M3 AML). Infiltration of these cells into the organs is relatively less common as compared to ALL resulting in only mild hepatosplenomegaly and lymphadenopathy.

Recent Exam Questions

Granulocytic sarcoma

- Also called **myeloblastoma/chloroma**.
- MC associated with **M2 AML**.
- **Markers:** CD43, CD45, CD117 and MPO.
- MC clinical feature: **proptosis**

However, *gum hypertrophy and infiltration in the skin (called as leukemia cutis) is common with* ***particularly M5 AML***. Less frequently, patients may present with localized masses in absence of marrow or peripheral blood involvement called **myeloblastoma, granulocytic sarcoma or chloroma** (so named as they turn green in presence of dilute acid due to the presence of MPO). **Lysozyme, CD43, CD45, CD117** and *MPO* are positive markers of granulocytic sarcoma. These manifest as **proptosis**[Q] (due to orbital involvement) **most commonly** or may present as bone or periosteal masses.

Investigations

Blood findings

It includes markedly elevated WBC count. Findings are similar to that in ALL except that the blast cells show positivity with **MPO, NSE or Sudan black**. There is presence of anemia, neutropenia and thrombocytopenia.

Bone marrow

It is hypercellular with blast cells **>20%** of the marrow cells.

Biochemical investigations

These show elevated serum uric acid and phosphate levels accompanied by hypocalcemia (because of hyperphosphatemia). Serum **Muramidase** levels is also **increased** in **M4** and **M5** AML. The fibrin degradation products (FDPs) are elevated in M3 AML due to DIC.

Prognostic factors in AML

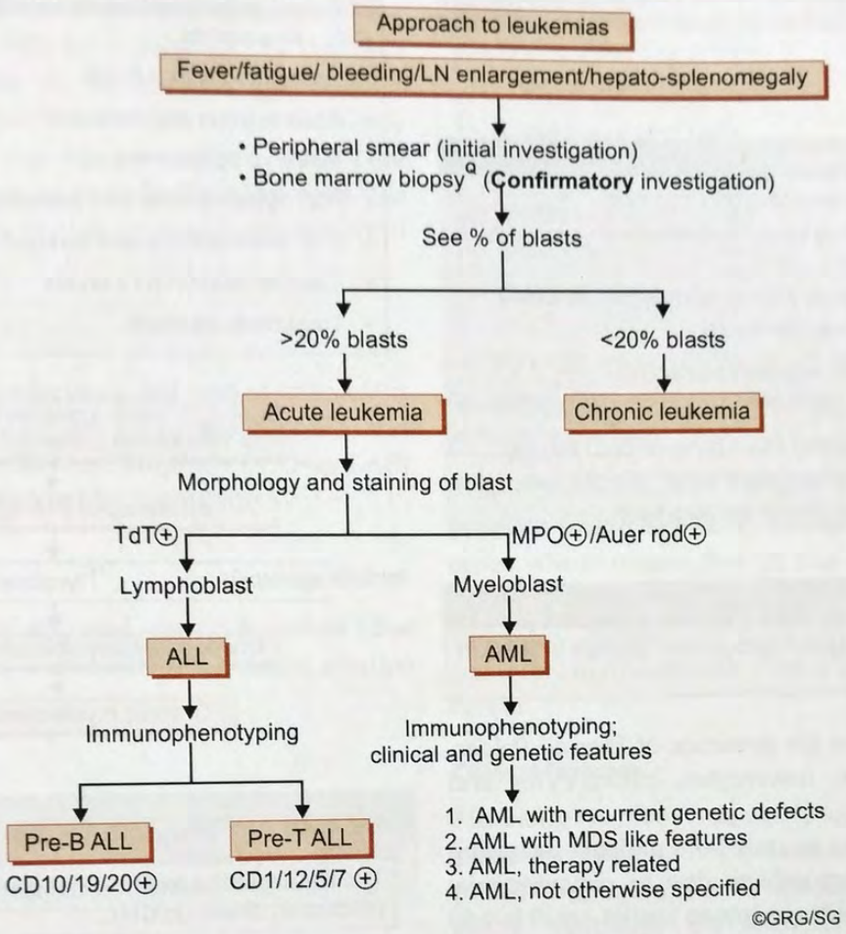
Good prognosis	Bad prognosis
• Age <40 years	• Age <2 years or >55 years
• M2,M3,M4 forms of AML	• M0,M6,M7 forms of AML
• Blast cell with **Auer rods**	• Complex karyotypes
• TLC < 25 X 10^9/L	• TLC > 100 X10^9/L
• **t(15;17), t (8;21), inv 16**	• Deletions 5q, **7q**
• Rapid response to therapy	• Delayed response to therapy
• Leukemia without preceding MDS	• **AML with preceding MDS or anticancer drug exposure**

Key Point

Management of AML

- Therapy in **M3 AML** specifically can be done with all trans retinoic acid[Q] **(ATRA)** or **arsenic oxide**[Q].
- For other types of AML, the drugs used are **cytarabine with daunorubicin**.
- However, **treatment of choice** of AML is **allogenic bone marrow transplantation.**

Flowchart 1: Diagnostic approach to leukemias.



LEUKEMOID REACTION

It is defined as the presence of elevated leucocyte count (>50,000 cells/ml) in the peripheral blood resembling leukemia in an individual who actually does not have leukemia.

Concept

Leukemoid reaction is differentiated from leukemia by:
- Immature cells/**blasts <5%.**
- ↑ leukocyte alkaline phosphatase **(LAP) score**.
- **Dohle bodies +** in neutrophils.
- **Toxic granulations** + in WBC.
- **Less** hepatosplenomegaly, lymphadenopathy and hemorrhage.

Myeloid leukemoid reaction	Lymphoid leukemoid reaction
Seen in conditions like: • Infections (sepsis, TB, endocarditis) • Severe hemorrhage and hemolysis • Malignancies (Hodgkin's, multiple myeloma, metastasis, myelofibrosis) • Miscellaneous (burns, eclampsia, mercury poisoning).	Seen in conditions like: • Infections (usually viral like measles, chicken pox, CMV, infectious mononucleosis or bacterial like TB, pertussis) • Rare with malignancies.

MYELODYSPLASTIC SYNDROMES (MDS)

Myelodysplastic syndromes refer to a *clonal stem cell disorder* resulting in *ineffective hematopoiesis and increased risk of* development into acute myelogenous leukemia (*AML*). The bone marrow is replaced with multipotent stem cells which can differentiate but in an unorganized and ineffective manner only.

It has been linked to the exposure to radiation, benzene, alkylating agents and some chromosomal abnormalities. MDS can be classified into:

1. **Primary MDS** – Develops slowly usually after 50 years of age.
2. **Secondary or Therapy related MDS (t-MDS)** – Usually 2 to 8 years after toxic drug or radiation exposure. The secondary MDS ***gets transformed to AML*** most frequently and so ***has a poorer prognosis***.

Recent Exam Question

Deletions in the long arm of chromosome 5 are the most frequent cytogenetic changes in **MDS in adults**[Q].

The *bone marrow is usually hypercellular* in this condition but the myelodysplastic precursor cells undergo apoptosis at a

fast rate resulting in *ineffective hematopoiesis*. MDS is frequently associated with chromosomal abnormalities including monosomy 5 and 7, deletion of 5q and 7q, trisomy 8 and deletion of 20 q.

Bone marrow findings

Cells affected	Features seen
Erythroid cells	**Ringed sideroblasts**[Q] (Iron laden mitochondria in erythroblasts) with increased iron stores Megaloblasts, nuclear budding, intranuclear bridging, irregular nuclei
Megakaryocytes	**Pawn ball megakaryocytes**[Q] (Megakaryocytes with multiple separate nuclei)
Neutrophils	**Dohle bodies**[Q] (toxic granulations) are seen, **Pseudo-Pelger-Huet cells**[Q] (Neutrophils with two nuclear lobes) are also seen

Key Point

Monosomy 7 is the most frequent cytogenetic change in **MDS in children**[Q].

Peripheral blood shows the presence of Pseudo-Pelger-Huet cells, giant platelets, macrocytes, poikilocytes and monocytosis.

Clinical features are seen in only 50% patients including weakness, infection and hemorrhage due to pancytopenia. Usually patients are of an old age (mean age of onset is >60 years). The prognosis is poor.

Recent Exam Question

Juvenile myelomonocytic leukemia[Q] is a childhood myelodysplastic syndrome. It is the commonest leukemia seen in children suffering from **neurofibromatosis-1**[Q].

3. Chronic Myelogenous Leukemia (CML)

It is a type of myeloproliferative disorder characterized by the increased number of immature leukocytes, basophilia and splenomegaly seen in adults between the ages of 25-60 years. An increased risk of CML is seen in people exposed to ionizing radiation (survivors of nuclear bombs). There is presence of ABL gene (a proto-oncogene) on chromosome 9 and BCR (break point cluster) gene on chromosome 22. A reciprocal translocation between these two chromosomes causes formation of BCR-ABL fusion gene on chromosome 22 (called **Philadelphia chromosome**[Q] or Ph). This fused gene causes synthesis of a 210 kDa fusion protein.

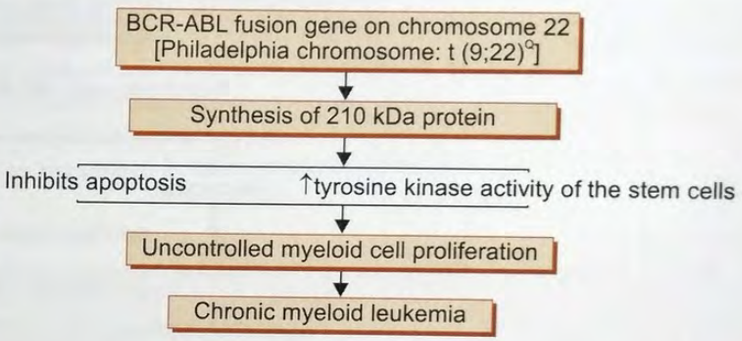
Key Point

CML is resulting in formation of **Philadelphia chromosome**[Q].

Recent Exam Questions

CML: Key points

- Associated with **(t 9;22)**.
- **Philadelphia** chromosome[Q].
- **Massive splenomegaly**[Q].
- BM: **hypercellular** with **pseudo-Gaucher cells**[Q].
- P/S: ***eosinophilia and basophilia***.
- ↑ serum vitamin **B12 levels**.
- Treatment: **Imatinib**.



Key Point

The **Neutrophil Alkaline Phosphate** (NAP or LAP) is **decreased** (in chronic phase) in **CML**.

Clinical features

CML has a gradual onset with fatigue, anorexia and weight loss as the initial complaints. Characteristically, there is presence of **splenomegaly**[Q] caused by infiltration of leukemic cells as well as extramedullary hematopoiesis. *Hepatomegaly* is also seen but lymphadenopathy is uncommon in these patients. Leukocytic infiltration and hypercellularity can cause *sternal tenderness* whereas leukostasis can cause priapism, venous thrombosis and visual disturbances.

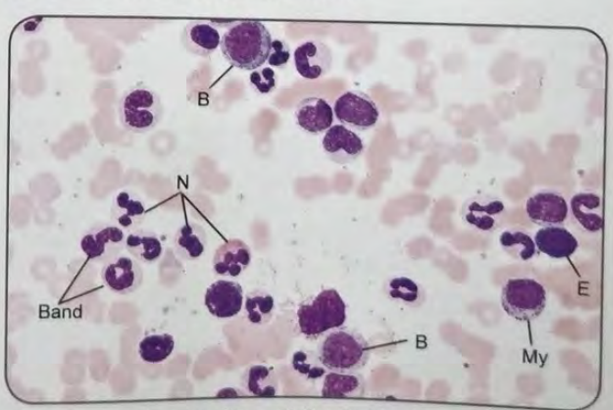


Fig. 3: CML showing. B: Basophils; E: Eosinophil; N: Neutrophil; My: Myeloblast; Band: Band cells.

Bone marrow

It is 100% cellular in these patients (in normal individuals, the marrow is 50% cellular and 50% fat is present). *The erythroid precursors are decreased* (due to replacement by myeloid precursors) whereas *abnormal megakaryocytes are commonly seen*. The presence of scattered histiocytes with blue granules (sea-blue histiocytes or **pseudo-Gaucher cells**Q) is characteristically seen. There is also increased deposition of reticulin fibres.

PERIPHERAL SMEAR

It shows the presence of *thrombocytosis and marked leukocytosis* with presence of immature white cells, eosinophilia and basophilia. The ***Neutrophil Alkaline Phosphate (NAP or LAP)* is decreased (in chronic phase)** in these patients.

BIOCHEMICALLY

There are increased levels of uric acid, serum B_{12} levels (due to increased transcobalamin) serum LDH and serum alkaline phosphatase.

Recent Exam Question

LAP score is reduced in CML but it often increases when CML transforms to a blast crisis or accelerated phase.

PHASES OF CML

1. **Chronic phase**
   - Lasting for about 3-6 years having **<10% blasts** in the blood or bone marrow.
2. **Accelerated phase**
   - Aggressive phase lasting for few months showing increased anemia and thrombocytopenia.
   - Number of *blasts are >10% but <20%.*
   - Cytogenetic abnormalities like trisomy 8, isochromosome 17q, duplication of Ph chromosome may develop.
3. **Blast phase**
   - Resembles AML
   - Characterized by the presence of *>20% blasts* in the blood/bone marrow.
   - Two third of the blasts are of myeloid lineage whereas the remaining 1/3rd are of lymphoid lineage (expressing CD10 & CD19; TdT).

Key Point

Drug of choice as well as **treatment of choice** for CML is a *tyrosine kinase inhibitor* **Imatinib mesylate**.

Recent Exam Question

Juvenile CML: Key points

- CML variant seen in **children**.
- Presence of **skin rash**.
- **Philadelphia** chromosome is **absent**.
- **Increased** levels of **HbF**
- **Poor** prognosis.
- **Normal LAP** score.

4. Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

It is a proliferation of mature lymphocytes seen in the **old patients (mean age is 60 years)** having a chronic course of onset which means that in this cancer, replacement of the bone marrow hematopoietic cells occurs after a period of few years. So, anemia, thrombocytopenia and granulocytopenia occur late in this disease. TNF-α and TGF-β have a role in this cancer.

Clinical features

The cancer is more commonly seen in males and is asymptomatic in a large number of cases. **Fatigue**Q is the commonest presenting complaint associated with lymphadenopathy (initially, cervical followed by a generalized lymphadenopathy). There is also presence of pallor, mild hepatosplenomegaly, skin rash and petechiae. However, ***sternal tenderness is absent*** (it is seen in acute leukemia). These cells are not able to produce normal immunoglobulins resulting in the increased susceptibility to infections. As already discussed above, the presence of anemia, thrombocytopenia and granulocytopenia signify the late stage of the disease.

Recent Exam Question

- Mean age of patients having **CLL** is **60 years**.
- **Deletion of 13q**Q is the commonest defect in CLL.
- **CLL** is the only blood cancer **NOT** associated with **radiation exposure**.
- **CLL** is also associated with ***Autoimmune Hemolytic anemia*** So, **Coombs test is positive** in this condition.

Investigations

The **diagnostic criteria** for CLL are:

- Peripheral blood lymphocyte count >5000 cells/mm3with <55% cells being atypical.
- Bone marrow aspirate showing >30 % lymphocytes.

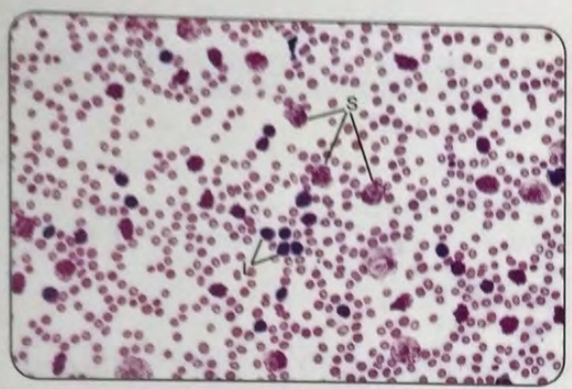


Fig. 4: CLL showing smudge cells (S) and numerous lymphocytes (L)

Blood investigation

It reveals **low Hb, elevated TLC with lymphocytosis** being the hallmark of the disease. Peripheral smear shows increased number of lymphocytes with scanty cytoplasm. These cells are fragile, so they get disrupted while making a smear and are called as **'smudge' cells or 'basket' cells or 'parachute' cells.**

Bone marrow

It is hypercellular with *>30% of the nucleated cells being lymphocytes* as the diagnostic feature of the leukemia. The aggregation of small lymphocytes and larger cells called 'prolymphocytes' is called **proliferation center** which is a characteristic finding of CLL.

Immunophenotyping

The cancer cells are positive for **CD19, CD20, CD23 and CD5.** There is also low level expression of **surface immunoglobulin** heavy and light chains.

Additional point

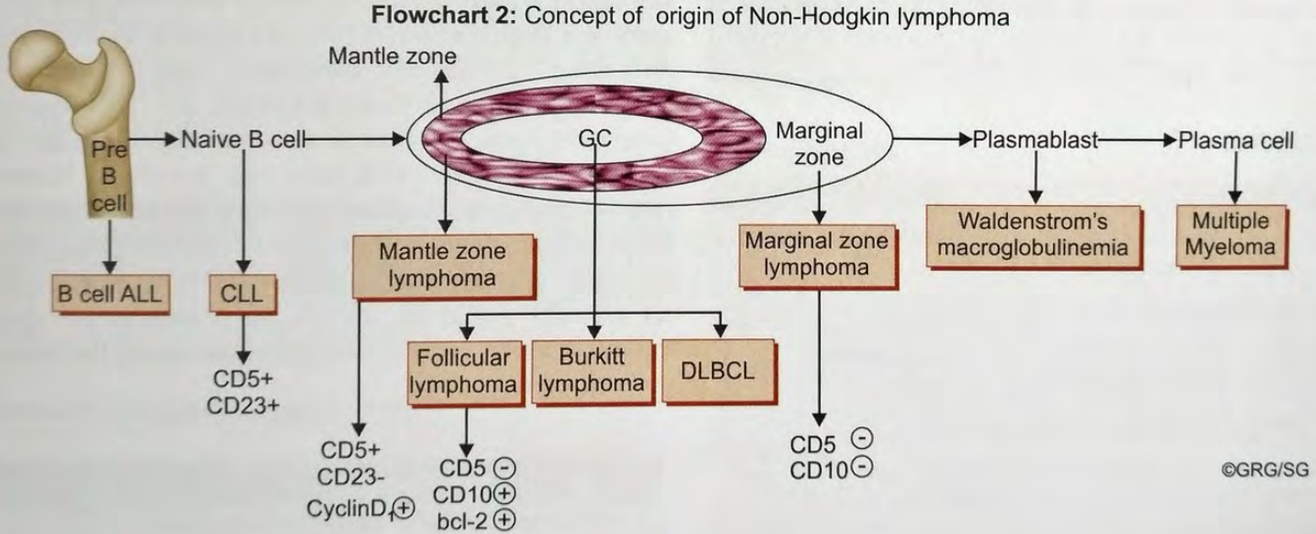
- The distinguishing feature of **CLL** and SLL is that in the former **blood involvement is predominant** presenting feature whereas in **SLL** the patients usually have **lymph node findings.**

Recent Exam Questions

CLL

- Inv. of choice: ***flow cytometry.***
- **Absolute lymphocyte count >5000 cells/mm³.**
- P/S: ***smudge/parachute cells.***
- Cl/F: fatigue, ↑ infections.
- LN Bx: ***diffuse effacement*** of architecture due to ***proliferation centre.***
- Transformation to DLBCL: ***Richter syndrome.***

Flowchart 2: Concept of origin of Non-Hodgkin lymphoma



NON-HODGKIN LYMPHOMA (NHL)

Many subtypes of NHL are there. However, diffuse large B cell lymphoma ***(DLBCL) is the commonest NHL.***

Recent Exam Questions

DLBCL

- Commonest NHL
- Most commonly seen with **BCL6** gene mutation

1. Diffuse large B cell lymphoma

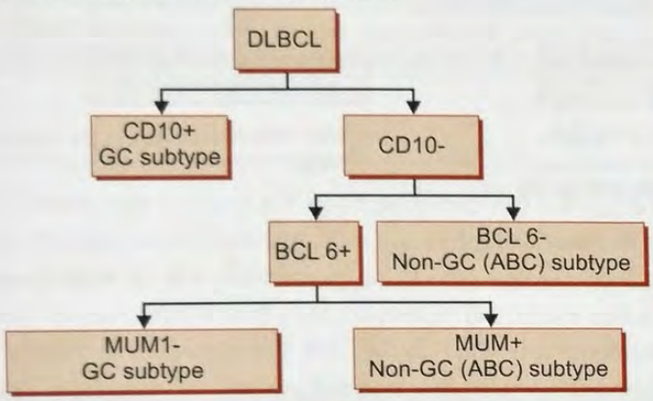
Diffuse large B cell lymphoma arises from a Germinal-center or postgerminal center B cell. It is associated with diverse chromosomal rearrangements, most often of **BCL6** (30%), *BCL2* (10%), or *MYC* (5%). It affects patients of all ages, but is most common in older adults (***mean age is 60 years***). It often appears as a rapidly growing mass and affects Waldeyer ring commonly. 30% of the tumors are extranodal affecting liver and spleen.

Morphologically: there is presence of a relatively **large cell size** (usually four to five times the diameter of a small lymphocyte) and a **diffuse pattern of growth** in the tumor.

Immunophenotype. These mature B-cell tumors express CD19 and CD20 and show variable expression of germinal center B-cell markers such as CD10 and BCL6. Most have surface Ig.

It is an aggressive tumor is subdivided using immunophenotyping in the following subtypes

- **Germinal centre DLBCL** has **better prognosis** whereas
- *ABC- DLBCL* has *worse prognosis.*



2. Follicular Lymphoma

It is the commonest NHL in the US **(otherwise the commonest NHL is Diffuse large B cell lymphoma)** derived from the **B-lymphocytes** usually presenting in the middle age. It shows the presence of translocation **t(14;18)**^{Q}. Normally chromosome 14 has immunoglobulin heavy chain gene whereas the chromosome 18 has bcl-2 gene. The translocation results in the increased expression of **bcl-2**^{Q}. The bcl-2 being the inhibitor of apoptosis causes promotion of the follicular lymphoma cells resulting in the cancer.

Key Point

Follicular lymphoma has the presence of translocation **t(14;18)** leading to **bcl-2** over expression.

Clinical features

The cancer presents usually as painless generalized lymphadenopathy with less commonly the involvement of CNS, GIT or testes. The median survival is for 7-9 years. In almost 50% of patients, this cancer gets transformed to diffuse large B-cell lymphoma.

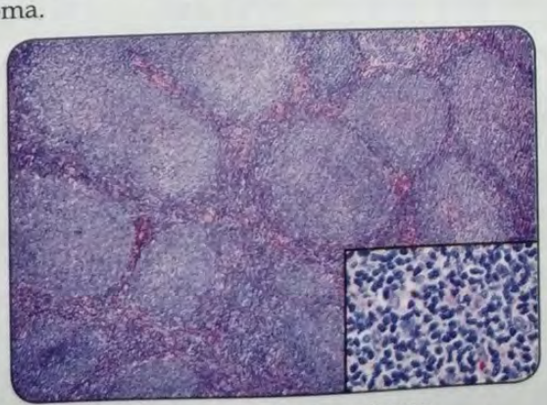


Fig. 5: Follicular Lymphoma

Investigations

Immunophenotyping
The cells expressing *bcl-2 protein, surface Ig, CD19, CD20 and CD10* (CALLA). CD5 is negative in these cells *(differentiating feature from mantle cell lymphoma and CLL).*
Lymph node biopsy
There is presence of *centrocytes* (small cell with cleaved nucleus and scant cytoplasm) and *centroblasts* (large cell with open nuclear chromatin and multiple nucleoli).
Peripheral blood
Presence of lymphocytosis.
Bone marrow
It shows the presence of characteristic *para-trabecular lymphoid aggregates.*

Key Point

The cells in **follicular lymphoma** express **bcl-2** protein, **surface Ig**, CD19, CD20 and CD10 (CALLA). **CD5 is negative** in these cells.

3. Mantle Cell Lymphoma

It is a neoplasm in which the tumor cells resemble the normal mantle zone B-cells which surround germinal centers. These have the translocation t(11; 14)^{Q} leading to in the increased expression of cyclin D1^{Q} and subsequently neoplasia.

Clinical features

The cancer usually presents as painless generalized lymphadenopathy, splenomegaly or involvement of the GIT. Uncommonly, multifocal mucosal involvement of the small bowel and colon produces **lymphomatoid polyposis.**

Recent Exam Question

Mantle Cell Lymphoma

- Presence of **t(11;14)**^{Q}.
- ↑ **cyclin D1 (bcl-1)** expression.
- CI/F: painless generalized lymphadenopathy.
- Cells are **CD23 negative**.
- In CLL/SLL cells are CD23 ⊕.

Investigations

Immunophenotyping reveals the cells expressing *cyclin D1, surface Ig and CD 5.* **CD23 is negative** in these cells. **Lymph node biopsy** reveals typically the presence of small cleaved cells with diffuse effacement of lymph nodes.

- *Centroblasts are absent*Q (differentiating feature from mantle cell lymphoma and CLL).
- **CD23 is negative**Q in these cells (differentiating feature from CLL)

4. Burkitt's Lymphoma/Small Non Cleaved Lymphoma

It is a cancer of the germinal center B cell origin characterized by the presence of hallmark translocation **t(8;14)**Q. The other translocations which may be present include t (2;8) or t (8;22). It has the following 3 categories:

Burkitt's lymphoma subtypes

African (endemic) form
- All are associated with EBV infection
- Seen in children and young adults
- Predilection for involvement of **mandible;** maxilla and abdominal organs like kidney, ovaries and adrenal glands

Sporadic (Non-endemic) form
- EBV infection in 15-20% cases
- Affects children and young adults
- Involvement of ileocecum and **peritoneum**

Aggressive form in HIV infected individuals
- EBV infection in 25% cases

Recent Exam Questions

Burkitt's Lymphoma
- **Burkitt's** lymphoma has the presence of translocation **t(8;14)**Q.
- **Burkitt's** lymphoma has the presence of **starry sky** pattern in the *lymph node biopsy*.
- It is the **commonest cause of tumor lysis syndrome**.

Concept

Unlike the other tumors arising from the germinal centre, there is **failure of expression** of the anti-apoptotic gene **bcl-2** in Burkitt's lymphoma.

Investigations

Immunophenotyping reveals the cells expressing ***bcl-6***Q *protein, surface Ig, CD19, CD20 and CD10* (CALLA).

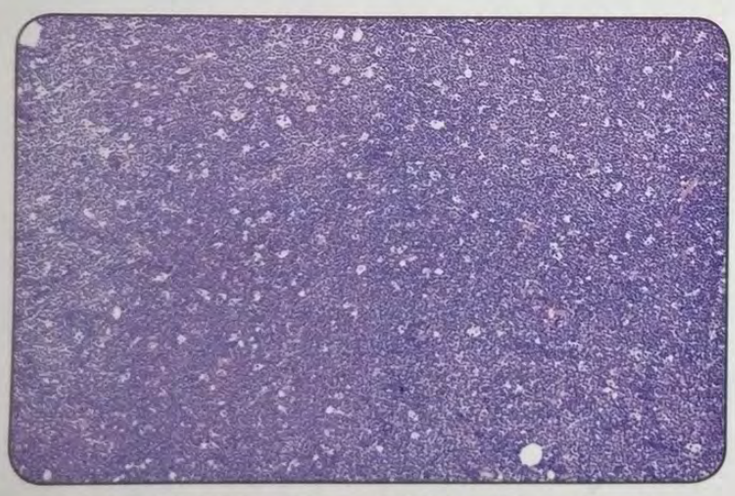


Fig. 6: Burkitt Lymphoma (Starry sky appearance)

Lymph node biopsy reveals typically the *presence of a high mitotic index* of lymphoid cells associated with apoptotic cell death. The presence of tissue macrophages with clear cytoplasm distributed with tumor cells creates the typical **starry sky**Q pattern.

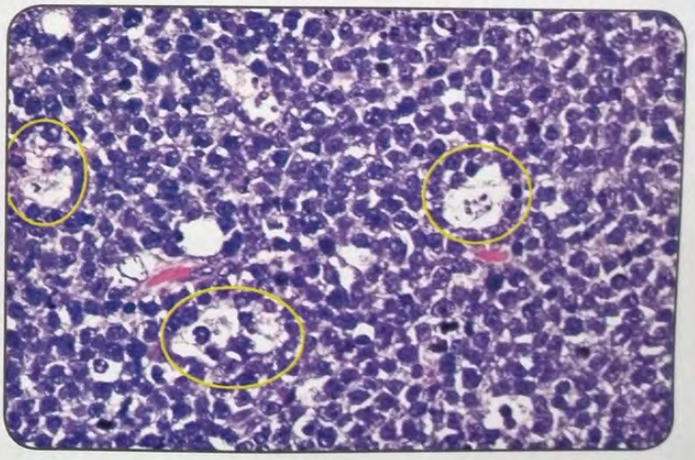


Fig. 7: Burkitt Lymphoma
(Circled area shows dead cells taken by macrophages).

5. Marginal Zone Lymphoma (MALToma)

It is a group of **B-cell** tumors arising within the lymph nodes, spleen or extranodal tissues in which the tumor cells resemble the normal marginal zone B cells. They are associated with mucosa associated lymphoid tissue, so, are called maltoma. Their salient features include:

- Begin as polyclonal activation associated with autoimmune disorders, chronic inflammatory conditions or having infectious etiology.
- Remain localized for a long duration of time.
- May regress if causative agent is removed.
- Splenic marginal zone lymphomas are TRAP +ve (like hairy cell leukemia)

The extranodal lymphomas can occur in stomach (H. pylori), orbit (Chlamydia), skin (Borrelia), lung, salivary gland, intestine, etc. Tumors may respond to antibiotic therapy. If they have cytogenetic abnormality **t (11;18)**^{Q} as in extranodal marginal zone lymphoma, they are refractory to antibiotic therapy.

Recent Exam Question

- **Marginal zone** lymphoma has the presence of translocation **t(11;18)**^{Q}. It is associated with ***H. pylori*** infection.

6. Hairy Cell Leukemia

It is a misnomer because it is not a leukemia but a *B cell NHL* of the old age predominantly affecting males (M:F ratio is 4:1) characterized by the presence of hairy cells in the peripheral blood, splenomegaly and pancytopenia. The exact cause of this cancer is unknown but the role of TNF- α is postulated which is responsible for proliferation of hairy cells and are responsible for the suppression of the proliferation of the normal bone marrow cells resulting in pancytopenia. The chromosomal abnormalities associated with this leukemia like trisomy 5 etc have been detected.

Investigations

Blood

There is presence of *pancytopenia* with the presence of atypical lymphoid cells despite the presence of neutropenia. Characteristic cells are hairy cells which are leukemic cells having hair-like projections due to fine cytoplasmic processes seen best *under phase contrast microscope*. Electron microscope shows the presence of ribosomal lamellar complexes in the cytoplasm.
Peripheral blood shows hairy cells with nuclei of different shapes.

Bone marrow aspirate

There is presence of **dry tap**^{Q} due to presence of reticulin fibrils along with the leukemic cells.

Bone marrow biopsy

It reveals infiltration by the cancer cells called as **honeycomb appearance**^{Q} and leukemic cells have nucleus surrounded by cytoplasmic halo called as **fried egg appearance**^{Q} which is diagnostic of hairy cell leukemia.

Recent Exam Questions

Hairy cell leukemia

- Cytochemistry: **TRAP** ⊕ (Tartarate resistant acid phosphate) cells.
- Cells have **Annexin A1, CD11c, CD25** and **CD103** positivity.

Clinical features are ***massive splenomegaly*** and less commonly there is presence of hepatomegaly (note that *lymphadenopathy is distinctly rare* in this disorder). Marrow failure contributes to pancytopenia resulting in increased chances of infection, fatigue and easy bruisability in these patients.

Recent Exam Questions

Hairy cell leukemia

- Cause by activating mutations in **BRAF**.
- Affects **males** > females.
- Involves **red pulp** in spleen.
- **Splenomegaly** is very common but lymphadenopathy is distinctly rare.
- ***Phase contrast microscopy: Hairy cell.***
- BM ***aspirate: dry tap.***
- BM ***biopsy:*** cancer cell have ***fried egg appearance***.
- **Drug of choice** for Hairy cell leukemia is **cladribine**.

Mnemonic

Be aware!

- **Annexin A1:** hairy cell leukemia.
- ***Annexin V: apoptosis.***

Concept

- TRAP is also **positive** in some cases of **splenic marginal zone lymphoma**.
- Hairy cell leukemia appears benign even though it is malignant because it is having less mitotic rate resulting in reduced N:C ratio (normally malignant cells have increased N:C ratio) and there is ample space between tumor cells (normally malignant cells are overcrowded).

Key Point

All **NHLs** involve **white pulp** of the spleen *except* Hairy cell leukemia and hepatosplenic lymphoma which involve red pulp of the spleen. In hairy cell leukemia, the white pulp is atrophic.

Recent Exam Question

- Post-transplant lymphoproliferative disorder is a **B-cell** malignancy caused by **EBV** *after solid organ transplantation.*

HODGKIN'S LYMPHOMA (HL)

It is a group of lymphoid neoplasms arising in a single node and spreads from the nodes to spleen, then liver and finally bone marrow. Clinical importance of this predictable route of spread is highlighted by the importance of staging which determines prognosis as well guides the choice of therapy of HL.

Key Point

The malignant cell in **Hodgkin's lymphoma** is a **Reed Sternberg** (RS) cell which is having an "**owl-eye**" appearance

It is differentiated from non- Hodgkin's lymphoma by the following features:

Hodgkin's lymphoma	Non-Hodgkin's lymphoma
• More often localized to a **single axial group** of nodes (cervical, mediastinal, para-aortic)	• More frequent involvement of multiple peripheral nodes
• Orderly spread by **contiguity**	• Non contiguous spread
• Mesenteric nodes and Waldeyer ring rarely involved	• **Waldeyer ring** and **mesenteric nodes** commonly involved
• Extra nodal involvement uncommon	• Extranodal involvement **common**

Recent Exam Questions

Reed Sternberg cell
- Most **sensitive** marker: **CD 30.**
- Most *specific* marker: *PAX 5.*

There is presence of neoplastic giant cell called **Reed-Sternberg cell** *(derived from the germinal center B cell)* which induces the accumulation of reactive lymphocytes, macrophages and granulocytes.

Recent Exam Question

Lymphocyte predominant Hodgkin's lymphoma is also called as **Non classical Hodgkin's lyphoma.**

The cause for the development of HL is inappropriate ***activation of NF-κB*** usually induced by the latent membrane protein-1 of Ebstein Barr virus (EBV) in majority of the cases.

The malignant cell is Reed Sternberg (RS) cell which is having an **"owl-eye" appearance** due to the presence of symmetric (mirror image) bilobed nucleus with prominent nucleoli surrounded by clear space. The **RS cells are positive for CD15 and CD30 for most subtypes except in lymphocyte predominant HL** in which the neoplastic cells *stain for CD20 and BCL-6* and are negative for CD15 and CD30.

Key Point

Condition with RS cell like Owl-eye appearance
- *Hodgkin lymphoma.*
- *Infectious mononucleosis.*
- *Solid tissue cancers.*
- NHL **(Immunoblastic lymphoma).**

Concept

- Since many conditions can have RS-cells so, these cells must be present in an appropriate background of non-neoplastic inflammatory cells (lymphocytes, plasma cells, eosinophils for the diagnosis of Hodgkin lymphoma..

WHO classification of Hodgkin lymphoma

Nodular sclerosis	Mixed cellularity	Lymphocyte rich	Lymphocyte depleted	Lymphocyte predominant (non classical HL)
– MC type of HL	– MC type of HL **in India**		– Associated with HIV	
– Incidence equal in M and F	– M > F	– M > F	– M > F	– M > F
– RS cell variant in **lacunar cell** (clear space surrounding cell)	– Has eosinophils and plasma cells – **Maximum number** of RS cell	– Mononuclear and RS cell – **Lowest number of** of RS cell	– 3 unique RS cell (pleomorphic, mummified, necrobiotic type) – Maximum area of necrosis	– LH cells (**popcorn cells**) in background – Other cells scanty or absence of B cells
– Cells are CD15 + CD30+	– Cells are CD15 + CD30+	– Cells are CD15 + CD30 + and CD20–	– Cells are CD15 + CD30+	– RS cell are **CD20 + CD15 –, CD30 – BCL6, EMA +**[Q]
– No association with EBV	– Associated with EBV	– Associated with EBV	– **Most commonly** associated **with EBV**	– Not associated with EBV
– **Excellent prognosis**	– Prognosis very good	– Good to excellent prognosis	– Poor prognosis	– **Excellent prognosis**
– Adolescent and young adult	– **Biphasic incidence**[Q] (young adults as well as > 55 years)	– Old age group	– Old age group	– Young males

*EMA is epithelial membrane antigen

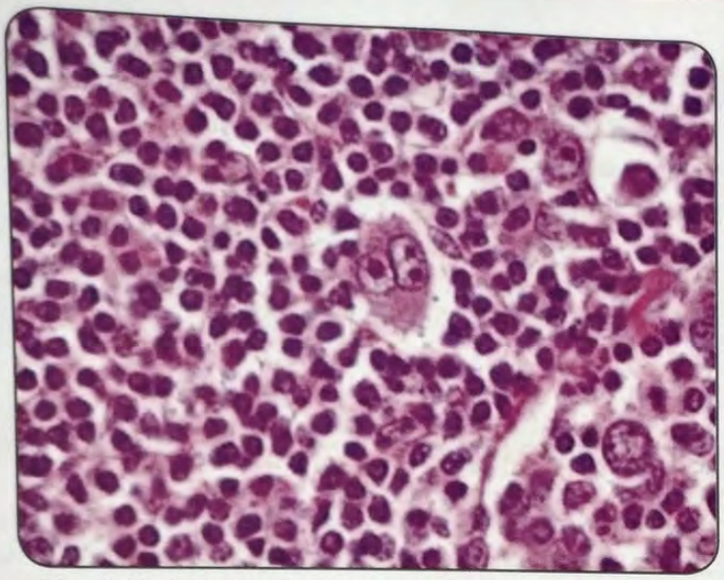


Fig. 8: Hodgkin lymphoma: Reed Stermberg cells having owl eye appearance.

Clinical Features

Presence of painless enlargement of lymph nodes is the common presenting symptom and is associated with fever (**Pel Ebstein fever**) and night sweats in disseminated disease. A strange paraneoplastic syndrome in HL is *pain in the affected lymph nodes on consumption of alcohol*. The prognosis is directly related to the number of RS cells present.

Key Point

Treatment of Hodgkin's lymphoma is done with **ABVD** (**A**driamycine, **B**leomycin, **V**inblastine and **D**acarbazine.

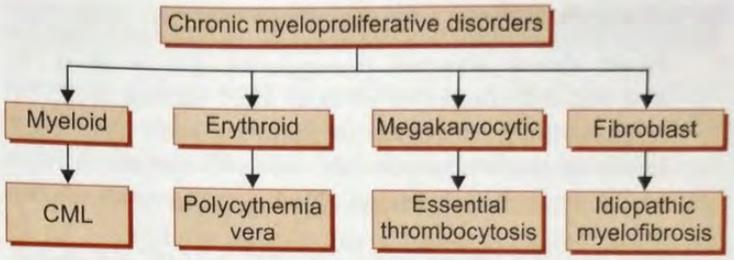
CHRONIC MYELOPROLIFERATIVE DISORDERS

The common pathogenic feature of the myeloproliferative disorders is the presence of mutated, constitutively activated tyrosine kinases which lead to growth factor independent proliferation and survival of marrow progenitor cells. These arise from the *clonal proliferation of multipotent stem cells* which proliferate along the three cell lines (erythroid, megakaryocytic and granulocytic) except in CML in which with the pluripotent cell gives rise to myeloid cells.

Myeloproliferative disorders

- Chronic myelogenous leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- Systemic Mastocytosis
- Stem cell leukemia

Depending on the predominant cell in the myeloproliferative disorder, the following more frequently asked disorders are:



Recent Exam Question

All myeloproliferative disorders have ↑ LAP scores ***except CML***

1. Chronic Myelogenous Leukemia (CML)

It has been discussed earlier with other leukemias.

2. Polycythemia Vera (PV)

This is a myeloproliferative disorder characterized by the increased number of erythroid, granulocytic and megakaryocytic cells. Polycythemia vera progenitor cells have markedly decreased requirements for erythropoietin and other hematopoietic growth factors.

Recent Exam Questions

↓ LAP scores

- Chronic phase of CML.
- PNH (paroxysmal nocturnal hemoglobinuria)

Recent Exam Questions

- PV: ↓↓ serum erythropoietin.
- Absolute polycythemia: ↑ serum erythropoietin

Clinical features

1. Increase in hematocrit and red cell mass contributing to *sluggish blood flow* and even *increased chances of thrombosis*. These manifest in the form of dusky cyanosis, visual disturbances, headache, dizziness, venous thrombosis (causes Budd-Chiari syndrome due to hepatic vein thrombosis), bowel infarction and stroke.
2. Increased basophils release histamine causing *intense itching and increased incidence of peptic ulcer*
3. *Hyperuricemia* is seen due to increased cell turnover.
4. The patients also have *splenomegaly* due to extramedullary hematopoiesis.

Key Point

Polycythemia Vera is strongly associated with activating point mutation in the **tyrosine kinase JAK2**.

Investigations

- Blood shows **elevated hemoglobin** (Hb > 18 g %) **and red cell count** (>6 million/mm^3; normal is 3.5-5.0 million/mm^3), **increased hematocrit** with **decreased levels of erythropoietin**. The last differentiate it from secondary polycythemia in which serum erythropoietin is elevated.
- Peripheral blood shows **increased basophils and abnormal platelets**.
- Bone marrow is hypercellular having increased number of erythroid, granulocytic and megakaryocytic cells. In later stage, there is presence of myelofibrosis.

Key Point

Transformation to AML is **uncommon** in polycythemia vera.

Recent info in exams

Proposed Revised WHO Criteria for Diagnosis of Polycythemia Vera*	
Major criteria	1. Hemoglobin **> 18.5 g/dL** in men or > 16.5 g/dL in women or evidence of increased red cell volume 2. Presence of **JAK2 mutation**
Minor criteria	1. Hypercellular bone marrow biopsy with **panmyelosis** with prominent erythroid, granulocytic, and megakaryocytic hyperplasia 2. **Low serum erythropoietin** level 3. Endogenous erythroid colony formation **in vitro**

Key Point

Management of polycythemia vera is done with **venesection** or **alpha interferon**.

Polycythemia vera is the most common of the chronic myeloproliferative disorders. Its diagnosis requires presence of both the major criteria and one minor criterion or the presence of the first major criterion plus 2 minor criteria.

3. Essential Thrombocytosis

It is associated with **activating mutation in JAK2** (more commonly) or MPL, a receptor tyrosine kinase normally activated by thrombopoietin. This is the stem cell disorder having increased proliferation of the megakaryocytes in bone marrow and *high platelet count* in the blood (> 4.5 lakh/mm^3; normal level is 1.5-4.5 lakh/mm^3). It is usually a *diagnosis of exclusion.*

It is strongly associated with activating point mutation in the tyrosine kinase JAK2 or MPL, the latter is receptor tyrosine kinase activated by thrombopoietin.

Recent Exam Questions

Essential Thrombocytosis

- **JAK2** activating mutation.
- Platelet count **>4.5 lakh**/mm^3.
- **Erythromelalgia** is a characteristic symptom.
- Management is done with **aspirin or hydroxyurea** or **anagrelide**.

Clinical Features arise because of:

1. *Non-functioning platelets: bleeding* (mucosal, skin, post trauma).
2. Dysfunctional platelets: thrombosis (arterial thrombosis more common than venous)resulting in headache, dizziness or ischemia of the digits.

Definition

Erythromelalgia is a characteristic symptom caused by throbbing pain and burning of hands and feet due to occlusion of small arterioles by platelet aggregates.

Investigations

- **Bone marrow** *is hypercellular* with increase in number of giant megakaryocytes along with dysmegakaryopoeisis. Erythroid and myeloid cell show only mild hyperplasia, if at all.
- **Blood** shows elevated platelet count in the blood *(diagnostic criteria is > 6 lakh/mm^3)*, normal Hb levels and *elevated LAP scores.*

4. Idiopathic or Primary Myelofibrosis

It is characterized by the presence of marrow fibrosis associated with extramedullary hemopoeisis in the spleen in old patients (usually more than 60 years of age). It is associated with **activating mutation in JAK2** (more commonly) or MPL. There is presence of *neoplastic megakaryocytes* which are *responsible for the release of fibrogenic factors like PDGF* (platelet derived growth factor) and *TGF-β*. These factors cause progression of marrow fibrosis. This results in:

Recent Exam Questions

Idiopathic Myelofibrosis

- **JAK2** activating mutation.
- BM aspiration: **dry tap**.
- Inv of choice: **BM biopsy**.
- Peripheral smear: *tear drop RBC* **(dacryocytes)** and **leukoerythroblastosis...** (see Figure 9).

- Replacement of normal hematopoietic stem cells by fibrous tissue.

- Movement of hematopoietic stem cells to spleen and liver (responsible for hepatosplenomegaly).

Both the above contribute to development of decreased cell count resulting in the symptoms of fatigue, weight loss or bleeding episodes along with hepatosplenomegaly. Hyperuricemia is seen due to increased cell turnover.

Bone marrow aspiration reveals **dry tap** due to fibrosis of the bone marrow.

Concept

The fibrosis of the bone marrow can occur as a primary hematological process (called **primary myelofibrosis or myeloid metaplasia).**

So,* bone marrow biopsy is the investigation of choice for the diagnosis *which shows the presence of* hypocellularity *with increased deposition of reticulin inside the marrow, abnormal megakaryocytes and the characteristic finding of dilated marrow sinusoids.

Peripheral blood findings include presence of nucleated red cells and immature white cells (called as **leukoerythroblastosis**).

There is also presence of abnormal red cells called *dacryocytes* (or *tear drop RBC*) formed due to damage to red cell membrane caused by fibrous tissue in the marrow. Blood shows mild leukocytosis, decreased Hb and hematocrit levels and *elevated LAP scores.*

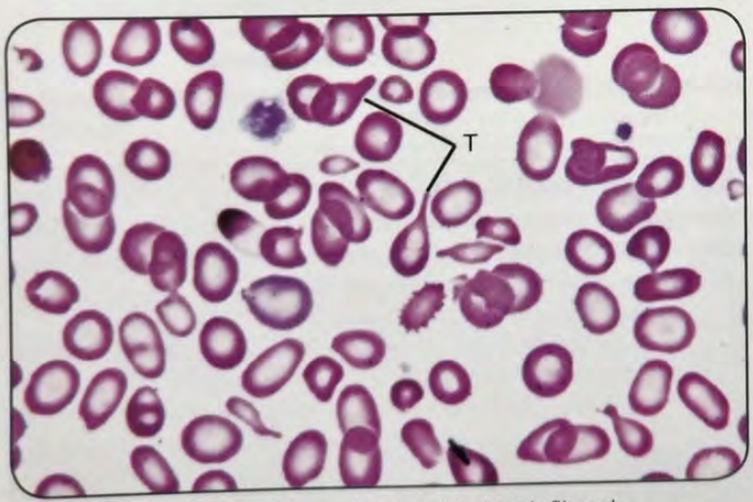


Fig. 9: Tear Shaped Cell (T) in Myelofibrosis.

Definition

Myelophthisis ia a term used for *secondary myelofibrosis* due to tumors (breast/lung/prostate cancers or neuroblastoma) or granulomatous processes (infections like TB/fungi/HIV) or radiation therapy.

PLASMA CELL DYSCRASIAS

These are characterized by proliferation of B-cell clone which synthesizes and secretes a single homogenous immunoglobulin or its fragments. The entity includes the following conditions:

- **Multiple myeloma** (Plasma cell myeloma) - presents as multiple masses in the skeletal system. Smoldering myeloma is an asymptomatic subtype with high plasma M component.
- **Waldenstrom's macroglobulinemia** - Caused by blood hyperviscosity due to high level of *IgM*. It is seen in adults with *lymphoplasmacytic lymphoma.*
- **Heavy chain disease** - Characterized by synthesis and secretion of free heavy chain fragments and is seen in association with CLL/SLL, Mediterranean lymphoma, lymphoplasmacytic lymphoma.
- **Primary or immunocyte associated amyloidosis** - Results from a monoclonal proliferation of plasma cell secreting free light chains (most commonly α isotype).
- **Monoclonal Gammopathy of Undetermined Significance (MGUS)** - It is the *most common* symptomatic monoclonal gammopathy.Usually asymptomatic disease seen in elderly patients. Rarely, it may progress to symptomatic monoclonal gammopathy (most often multiple myeloma).

Recent Exam Question

- **Normal relative viscosity** of serum as compared to water is **1.8**.

1. Multiple Myeloma

It is a plasma cell cancer having skeletal involvement at multiple sites. The most common karyotypic abnormalities in this condition are ***deletions of 13q and translocation involving Ig heavy chain locus on 14q.***

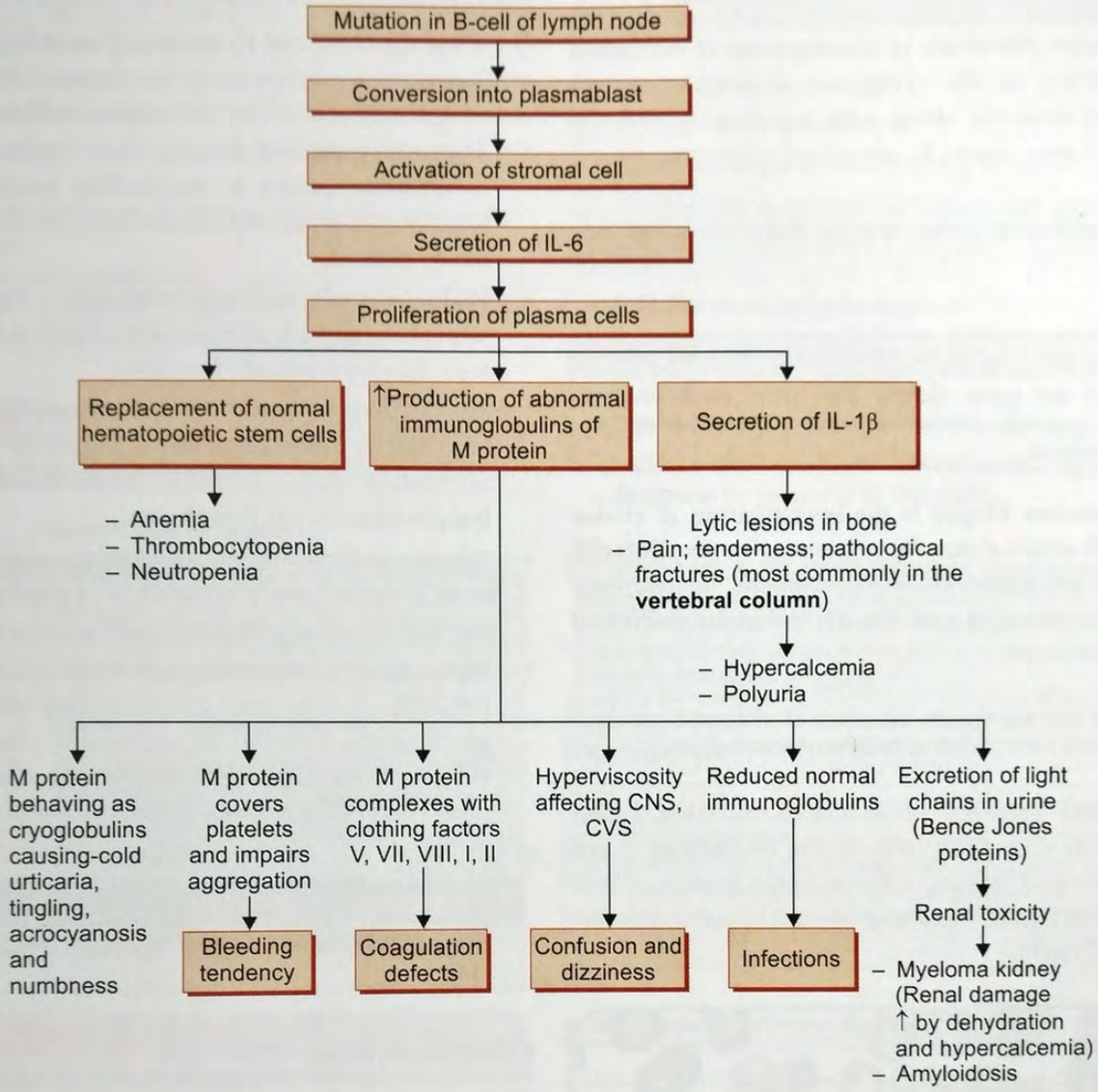
Recent Exam Questions

Condition with hyperviscosity
- Multiple myeloma.
- Waldenstrom's macroglobulinemia.
- Cryoglobulinemia.
- Myeloproliferative disorders.

Recent Exam Questions

- **Multiple Myeloma** is a **monoclonal** plasma cell disorder[Q].
- **IL-6** is the **most important cytokine** for the proliferation of the plasma cells.
- **Infections** are the *commonest cause* of death.

Pathogenesis and clinical features in multiple myeloma



Key Point

X-ray shows the presence of **punched out lytic lesions** in flat bones like skull, ribs, pelvis and vertebra.

Recent Exam Question

Multiple myeloma

- MC site for pathological fracture: **vertebral column**.
- Serum β_2 **microglobulin** is the most important **prognostic marker**.
- Definitive diagnosis is by **Bone marrow examination**[Q].
- Treatment is done with **melphalan, bortezomib and lenalidomide**[Q].

Symptomatic plasma cell myeloma

Clonal bone marrow plasma cell percentage ≥**10%** or biopsy-proven plasmacytoma and ≥1 of the following ***myeloma-defining events***:

a. **Evidence of End-organ damage (CRAB)**
   - **H**yper**C**alcaemia: serum calcium > 11 mg/dL
   - **R**enal insufficiency: Creatinine clearance < 40 ml/minute or senum creatinine > 2 mg/dL
   - **A**naemia: (Hb< 10g/dl or >2g/dl lower than normal)
   - **B**one lesions: ≥1 osteolytic lesion on skeletal radiography, CT, or PET/CT

b. **>1 of the following biomarkers of malignancy:**
   - Clonal bone marrow plasma cell percentage > 60%
   - An involved-to-uninvolved serum free light chain ratio >100
   - >1 focal lesion on MRI

Diagnosis

In 2017 WHO diagnostic criteria for diagnosis of plasma cell myeloma are

The diagnosis can be made on the basis of blood, bone marrow and urine findings as described the following flowchart:

Investigations in multiple myeloma

Blood finding

1. Normocytic, normochronic anemia
2. Normal TLC and platelet count
3. ↑Globulin levels cause ↑ESR and Rouleaux formation
4. ↑Serum uric acid, creatinine and ↑blood urea
5. ↑Serum β2 microglobulin
   - Prognostic marker of MM
   - High levels correlate with poor prognosis

Bone marrow findings

1. Hypercellular bone marrow
2. Increased number of plasma cells usually >30%
3. Presence of plasma cells or its modified forms
   - Flame cells (have fiery red cytoplasm)
   - Mott cell (have blue grape like cytoplasmic droplets)
   - Cell having immunoglobulin inclusions in the cytoplasm **(Russell body)** or nucleus **(Dutcher body)**
4. Normal myelopoiesis and megakaryopoiesis with reduced erythropiesis

Electrophoresis

1. Urine (>6g/dL of protein)
   - Presence of light chains in urine
2. Serum (>3g/dL protein)
   - Presence of M band or monoclonal band of immunoglobulins (most commonly of IgG)

2. Monoclonal Gammopathy of Undetermined Significance (MGUS)

It is characterized by the *presence of M spike without associated disease of the B cells*. MGUS is the *commonest cause of monoclonal gammopathy*. Around 1% of the patients with MGUS progress to develop multiple myeloma per year. It is usually a diagnosis of exclusion. Patients of MGUS have *less than 3 g/dL* of monoclonal protein in the serum and no Bence Jones proteinuria.

Key Point

MGUS is the commonest cause of monoclonal gammopathy.

3. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma

It is a B cell neoplasm presenting in 6th or 7th decade of life having features similar to CLL/SLL and multiple myeloma.

Recent Exam Questions

Waldenstrom Macroglobulinemia

- **Deletion in 6q:** MC defect.
- 'M' spike caused due to **IgM**.
- **Organ** (spleen/lymph node/ bone) **infiltration** present.
- **No** lytic lesions.
- **No** hypercalcemia.
- ***Less renal failure and amyloidosis***.

Clinical features

These include non specific symptoms like fatigue, weakness, weight loss, hepatosplenomegaly and cervical lymphadenopathy. The immunoglobulin increases viscosity of the blood resulting in hyperviscosity syndrome affecting CNS and retina characterized by the headache, dizziness, visual disturbances etc. Abnormal globulins may interfere with platelet function resulting in bleeding and cryoglobulins may lead to acrocyanosis and cold urticaria.

Investigations

- **Bone marrow** reveals the presence of *plasmacytoid lymphocytes' infiltration*. PAS + inclusions containing immunoglobulins are seen in the cytoplasm (called *Russell bodies*) or in the nucleus (called *Dutcher bodies*) of the plasmacytoid cells.
- **Blood** investigations show *anemia with atypical plasmacytoid lymphocytes*. ESR is elevated and rouleaux formation is seen. Immunoelectrophoresis reveals the presence of 'M' spike composed of IgM.
- **Immunophenotyping** reveals the lymphocytic cells expressing *B-cell markers like CD20*. These cells are negative for CD5 and CD10. The plasma cell secretes a monoclonal immunoglobulin.

Langerhans Cell Histiocytosis (LCH)

The term histiocytosis is a broad term for a variety of proliferative disorders of dendritic cells (DCs) or macrophages. Langerhans cell is a special type of dendritic cell in the skin functioning as antigen presenting cell. Langerhans cell histiocytosis (LCH) has the following entities:

1. Letterer-Siwe syndrome (multifocal multisystem LCH)
2. Pulmonary Langerhans' cell histiocytosis: seen in adult smokers and may regress on cessation of smoking.
3. Eosinophilic granuloma.

Recent Exam Questions

LCH

- MC cause: activating BRAF mutation.
- The presence of **Birbeck's granules** in the cytoplasm is characteristic.
- **Hand-Schuller-Christian triad** is composed of ***calvarial bone defects, diabetes insipidus and exophthalmos***.

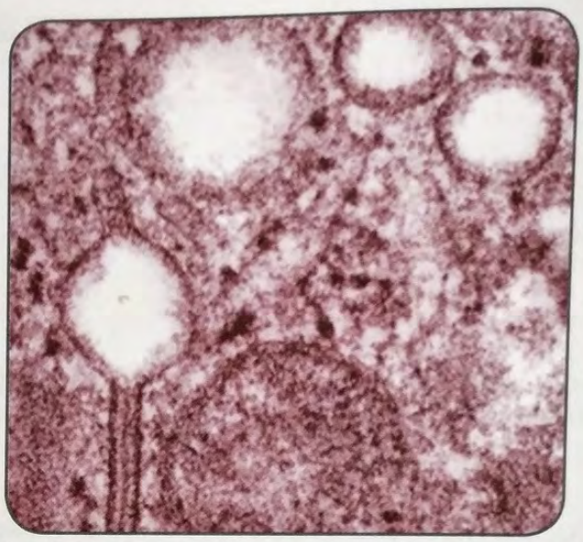


Fig. 10: Tennis-racket appearance of Langerhans cell.

Recent Exam Questions

Langerhans cell

- Tennis-racket appearance
- Markers: HLA-DR, S-100, and CD1a

- These three conditions are now considered different expressions of the same basic disorder. The tumor cells in each are derived from dendritic cells and express **HLA-DR, S-100, and CD1a**. They have abundant, often vacuolated cytoplasm and vesicular nuclei containing linear grooves or folds.
- *The presence of* ***Birbeck's granules*** *in the cytoplasm is characteristic. These granules,* under the electron microscope, have a pentalaminar, rod like, tubular appearance and a dilated terminal end (**tennis-racket appearance**) which contains the protein *langerin*.

Multiple Choice Questions

LEUKEMIA: ALL, AML, CLL, CML

1. **Flow cytometry is done in:** *(AIIMS Nov 2012)*
   (a) Polycythemia (b) Thrombocytosis
   (c) Neutrophilia (d) Lymphocytosis

2. **Myelofibrosis leading to a dry tap on bone marrow aspiration is seen with which of the following conditions?** *(AIIMS Nov 2012)*
   (a) Burkitt's lymphoma
   (b) Acute erythroblastic leukemia
   (c) Acute megakaryocytic leukemia
   (d) Acute undifferentiated leukemia

3. **Marker of myeloid cancers:** *(AIIMS Nov 2012)*
   (a) S100
   (b) HMB45
   (c) Common leukocyte antigen
   (d) Cyto-keratin

4. **Adult patient presents with generalized lymphadenopathy and blood film shows 70% immature looking lymphocytes. What should be the next best investigation?** *(AIIMS Nov 2012)*
   (a) Genotyping/karyotyping
   (b) Immunophenotyping
   (c) Bone marrow
   (d) Peripheral smear study

5. **Which of the following statements in context of leukemias is true?** *(AIIMS May 2012)*
   (a) Chronic myeloid leukemia occurs in less than 50 years of age
   (b) Hairy cell leukemic in less than 50 years has a good prognosis
   (c) Acute lymphoid leukemic in less than 1 year has a poor prognosis
   (d) Chronic lymphocytic leukemia occurs in less than 50 years of age

6. **In an ablated animal, myeloid series cells are injected. Which of following is seen after incubation period?** *(AIIMS May 2012)*
   (a) Fibroblast
   (b) T lymphocytes
   (c) RBC
   (d) Hematopoetic stem cell

7. **A young boy came with dyspnea and was found to have a mediastinal mass. Which of the following is known to produce mediastinal lymphadenopathy?** *(AI 2012)*
   (a) Diffuse large B cell Lymphoma
   (b) B cell rich T cell lymphoma
   (c) Mediastinal rich B cell lymphoma
   (d) T cell Lymphoblastic ALL

8. **Which of the following is the least likely to be a pre-leukaemic condition?** *(AIIMS Nov 2011)*
   (a) Paroxysmal nocturnal haemoglobinuria
   (b) Aplastic anaemia
   (c) Paroxysmal cold haemoglobinuria
   (d) Myelodysplastic syndrome

9. **A 6-year-old child presents with pallor that required two blood transfusions previously. He has now developed fever and petechial haemorrhages. His hemoglobin is is 9 g/dL, platelet count is 20,000/mm^3 and TLC is 60,000/mm^3. Flow cytometry reveals the cells to be CD10+ve, MPO+ ve, CD 19 + ve, CD 33 – ve, CD 117 + ve, and CD3 – ve. Which of the following is the most likely diagnosis?** *(AIIMS Nov 2011)*
   (a) ALL
   (b) AML
   (c) Mixed phenotypic leukaemia
   (d) Undifferentiated leukaemia

10. **In a patient with acute leukemia, immunophenotype pattern is CD 19+ve, CD 10+ve, CD33+ve, CD 13+ve. He may probably have:** *(AIIMS May 2004)*
    (a) Biphenotypic leukemia
    (b) ALL
    (c) AML-M
    (d) AML-M_0^2

11. **All the following are poor prognostic indicators in AML except:** *(AIIMS Nov. 2010)*
    (a) Inv 16
    (b) Complex karyotype
    (c) AML M7
    (d) Deletion 7q

12. **Most specific marker for myeloid series is:**
    (a) CD 34 (b) CD 45 *(AIIMS May 2010)*
    (c) CD 99 (d) CD 117

13. **t (2,8) is associated with:** *(AI 2010)*
    (a) T cell ALL (b) B cell ALL
    (c) CML (d) CLL

14. **ALL L3 morphology is a malignancy arising from which cell lineage?** *(AI 2007)*
    (a) Mature B-cell
    (b) Precursor B-cell
    (c) Immature T-cell
    (d) Mixed B cell and T-cell

15. **Non-specific esterase is positive in all the categories of AML except:** *(AI 2007)*
    (a) M3 (b) M4
    (c) M5 (d) M6

16. **Which of the following statements pertaining to leukemia is correct?** *(AI 2005)*
(a) Blasts of acute myeloid leukemia are typically Sudan black negative
(b) Blasts of acute lymphoblastic leukemia are typically myeloperoxidase positive
(c) Low leucocyte alkaline phosphatase score is characteristically seen in blastic phase of chronic myeloid leukemia
(d) Tartarate resistant acid phosphatase positivity is typically seen in hairy cell leukemia

17. **Which is the most common cytogenetic abnormality in adult myelodysplastic syndrome (MDS)?** *(AI 2004)*
(a) Trisomy 8
(b) 20q–
(c) 5 q–
(d) Monosomy 7

18. **Which of the following is a pan-T lymphocyte marker?** *(AI 2003)*
(a) CD2 (b) CD3
(c) CD19 (d) CD25

19. **B cell marker are all except:** *(AIIMS Nov 09)*
(a) CD 19 (b) CD 20
(c) CD 10 (d) CD135

20. **Which of the following is having poor prognosis in ALL:**
(a) TLC 4000-10000 *(AIIMS Nov 09)*
(b) Age < 2 yrs
(c) Presence of testicular involvement at presentation
(d) Presence of blasts in peripheral smear

21. **All of the following are good prognostic factors for acute lymphoblastic leukemia except:** *(AIIMS Nov 2008)*
(a) Age of onset between 2-8 years
(b) Initial WBC count less than 50000
(c) Hyperdiploidy
(d) t(9:22), t(8:14), t(4:11)

22. **AML with gum infiltration, hepato- splenomegaly is most likely to be:** *(AIIMS May 2008)*
(a) ALL (b) M3
(c) M2 (d) M4

23. **Marker for granulocytic sarcoma:** *(AIIMS May 2008)*
(a) CD33 (b) CD38
(c) CD117 (d) CD137

24. **All are B-cell marker except:** *(AIIMS May 2007)*
(a) CD-15 (b) CD-19
(c) CD-21 (d) CD-24

25. **Acid phosphatase is specific to which of the following cells:** *(AIIMS Nov 2006)*
(a) Monocyte
(b) T-lymphocyte
(c) B-lymphocyte
(d) Myelocytes

26. **A peripheral smear with increased neutrophils, basophils, eosinophils, and platelets is highly suggestive of:** *(AIIMS May 2006)*
(a) Acute myeloid leukemia
(b) Acute lymphoblastic leukemia
(c) Chronic myelogenous leukemia
(d) Myelodysplastic syndrome

27. **A 17-year-old boy presented with TLC of 138 × 10^9/L with 80% blasts on the peripheral smear. Chest X-ray demonstrated a large mediastinal mass. Immunophenotyping of this patient's blasts would most likely demonstrate:** *(AIIMS May 2006)*
(a) No surface antigens (null phenotype)
(b) An immature T-cell phenotype (Tdt/CD34/CD7 positive)
(c) Myeloid markers, such as CD13, CD33 and CD15
(d) B cell markers, such as CD19, CD20 and CD22

28. **A 15-year-old boy presented with one day history of bleeding gums, subconjunctival bleed and purpuric rash. Investigations revealed the following results: Hb-6.4 gm/dL; TLC-26,500/mm^3 Platelet 35,000 mm^3; prothrombin time-20 sec with a control of 13 sec; partial thromboplastin time-50 sec; and Fibrinogen 10mg/dL. Peripheral smear was suggestive of acute myeloblastic leukemia. Which of the following is the most likely?**
(a) Myeloblastic leukemia without maturation
(b) Myeloblastic leukemia with maturation
(c) Promyelocytic leukemia *(AIIMS May 2006)*
(d) Myelomonocytic leukemia

29. **Poor prognostic factor for ALL is:** *(AI 2011)*
(a) Hyperdiploidy
(b) t(9;22) t(4;11)
(c) Age at presentation is 2-8 yrs
(d) Total Leucocyte count <50000

30. **Which of the following is not compatible with a diagnosis of chronic myelomonocytic leukemia?** *(AIIMS Nov 2003)*
(a) Peripheral blood monocytosis more than 1×10^9/L
(b) Absence of Philadelphia chromosome
(c) More than 20% blasts in blood or bone marrow
(d) Absent or minimal dysplasia in myeloid lineages

31. **A 60-year-old man presented with fatigue, weight loss and heaviness in left hypochondrium for 6 months. The hemogram showed Hb, 10gm/dL, TLC 5 lakhs/mm^3, platelet count 4 lakhs/mm^3, DLC, neutrophil 55%, lymphocytes 4%, monocytes 2%, basophils 6%, metamyelocytes 10%, myelocytes 18%, promyelocytes 2% and blasts 3%. The most likely cytogenetic abnormality in this case is:** *(AIIMS May 2003)*
(a) t (1:21)
(b) t (9:22)
(c) t (15, 17)
(d) Trisomy 21

32. A 42-year old man was referred with a 2 week history of fever weakness and bleeding gum. Peripheral smear showed pancytopenia. The bone marrow examination revealed 26% blasts frequency exhibiting Auer rods and mature myeloid cells. An occasional neutrophil with pseudo Pelger-Huet anomaly was also detected. Which of the following cytochemical stains is most likely to be positive? *(AIIMS Nov 2002)*
(a) Acid phosphatase
(b) Non-specific esterase
(c) Myeloperoxidase
(d) Toluidine blue

33. AML with worst prognosis: *(AIIMS May 2007)*
(a) 8/21 translocation
(b) Inversion 16
(c) Normal cytogenetics
(d) Monosomy 7

34. Pancytopenia with cellular marrow is seen in all except: *(AIIMS Nov 2006)*
(a) Megaloblastic anemia
(b) Myelodysplasia
(c) Paroxysmal nocturnal hemoglobinuria
(d) G6PD deficiency

35. Highest LAP score is seen in: *(PGI Dec 2001)*
(a) CML (b) Polycythemia vera
(c) PNH (d) Pregnancy
(e) Lymphoma

36. Causes of eosinophilia are: *(PGI June 2004)*
(a) Hodgkin's disease
(b) Filariasis
(c) MI
(d) HIV infection

37. Sideroblasts are seen in: *(PGI Dec 2005)*
(a) Thalassemia (b) Myelofibrosis
(c) Alcoholism (d) Iron overload

38. Absolute monocytosis is seen in: *(PGI Dec 2006)*
(a) Infectious mononucleosis
(b) Kala-azar
(c) TB
(d) Brucellosis

39. Aplastic anemia can progress to: *(PGI Dec 01)*
(a) AML
(b) Myelodysplastic syndrome
(c) CLL
(d) PNH
(e) Iron deficiency anemia

40. True about aplastic anemia: *(PGI June 2005)*
(a) Splenomegaly
(b) Nucleated RBC in peripheral blood.
(c) Reticulocytopenia
(d) Thrombocytopenia
(e) Neutropenia

41. Leucocytosis is seen in all except: *(Delhi 2010)*
(a) Brucellosis (b) Acute MI
(c) Typhoid (d) Diphtheria

MOST RECENT QUESTIONS

42. The blast cells of acute lymphocytic leukemia in childhood contain:
(a) Surface antigen
(b) CALLA Ag
(c) Antibodies to WBC
(d) Thrombocytosis

43. "Smudge cells" in the peripheral smear are characteristic of:
(a) Chronic myelogenous leukemia
(b) Chronic lymphocytic leukemia
(c) Acute myelogenous leukemia
(d) Acute lymphoblastic leukemia

44. Chromosomal translocation characteristic in acute promyelocytic leukemia is:
(a) t (15: 17) (b) t (22: 9)
(c) t (21: 17) (d) t (8: 21)

45. TRUE abut acute myelogenous leukemia
(a) Philadelphia chromosome is seen
(b) Auer bodies are seen
(c) Common in childhood
(d) Peroxidase negative granules

46. In CML, serum vitamin B12 level is
(a) Slightly decreased
(b) Normal
(c) Markedly decreased
(d) Increased

47. BCR-ABL hybrid gene is present in
(a) Burkitt's lymphoma
(b) Retinoblastoma
(c) Breast carcinoma
(d) CML

48. The difference between leukemia and leukemoid reaction is done by:
(a) Total leukocyte count
(b) Leucocyte alkaline phosphatase
(c) Erythrocyte sedimentation rate
(d) Immature cells

49. Neutropenia is caused by all except:
(a) Typhoid fever
(b) Viral infection
(c) Brucellosis
(d) Glucocorticoids

50. Basophilic leucocytosis occurs in:
(a) AML (b) ALL
(c) CML (d) CLL

51. All are causes of splenomegaly except:
(a) Malaria
(b) Kala azar
(c) Hemolytic anemia
(d) Aplastic anemia

52. In myelodysplastic syndrome, the following statement is incorrect:
(a) Platelet counts are normal or elevated
(b) Leucocyte counts are normal or elevated
(c) Hypocellular bone marrow
(d) Refractory anemia

53. Leukoerythroblastic picture is seen in all except:
(a) Myelofibrosis
(b) Secondary malignancy of bone marrow
(c) Thalassemia
(d) Gaucher disease

54. A round cell having, fine nuclear chromatin, prominent nucleoli and fine azurophillic granule, cell is:
(a) Myeloblast (b) Lymphoblast
(c) Monoblast (d) None

55. Autoimmune hemolytic anemia is seen in:
(a) ALL (b) AML
(c) CLL (d) CML

56. The presence of the Philadelphia chromosome is associated with a worse prognosis in patients with which of the following diseases?
(a) Acute lymphoblastic leukemia
(b) Acute myelogenous leukemia
(c) Chronic lymphocytic leukemia
(d) Chronic myelogenous leukemia

57. Examination of a peripheral blood smear demonstrates leukemia composed of small mature lymphocytes without blast forms. Which of the following is the most likely age of this patient?
(a) 1 year (b) 20 years
(c) 45 years (d) 65 years

58. Which of the following is associated with good prognosis in ALL?
(a) T cell line
(b) Philadelphia chromosome
(c) Hyperdiploidy
(d) Hypodiploidy

59. B cell ALL is due to which of the following?
(a) T cells
(b) Immature B cells
(c) Immature T cells
(d) Both T and B cells

60. CD-10 is seen in:
(a) ALL (b) CLL
(c) GCL (d) CML

61. Dohle bodies in neutrophils are comprising of:
(a) Mitochondria
(b) Golgi apparatus
(c) Lysosomes
(d) Dilated endoplasmic reticulum

62. What is the chromosomal translocation in AML M3:
(a) t (18, 21) (b) t (15, 17)
(c) t (8, 21) (d) t (9, 11)

63. Reed Sternberg cells are found in:
(a) Hodkin's disease (b) Sickle cell anaemia
(c) Thalassemia (d) CML

64. Specific stain for myeloblasts is:
(a) Sudan black
(b) PAS
(c) Myeloperoxidase (MPO)
(d) LAP

65. Dohle bodies are seen in which of the following?
(a) Multiple myeloma
(b) May-Heggline anomaly
(c) Waldenstorm Macroglobulinemia
(d) Lymphoma

66. Auer rods are seen in:
(a) Lymphoblast (b) Myeloblast
(c) Erythroblast (d) Megakaryoblast

67. The peripheral blood eosinophil count in Eosinophilia myalgia syndrome is usually:
(a) Between 500 to 2000 cells microilter
(b) 2000 to 5000 cells/microliter
(c) Less than 500 cells/microliter
(d) More than 5000 cells/microliter

68. Most common ALL subtype?
(a) Pre B cell (b) Pre T cell
(c) T cell (d) B cell

69. Which of these is the most important prognostic factor in ALL?
(a) Hyperploidy
(b) Total leucocyte count greater than 50,000
(c) Age
(d) Response to steroids

70. ALL-L3 resembles:
(a) Mantle cell lymphoma
(b) MDS
(c) Burkitt's lymphoma
(d) AML

71. AML – bad prognostic factor is:
(a) Preceding MDS (b) Inv 16
(c) Auer rods (d) Type M4

72. Which variety of AML is associated with good prognosis?
(a) M0 (b) M3
(c) M6 (d) M7

NON HODGKIN LYMPHOMA

73. Progressive transformation of germinal centres (PTGC) is a precursor lesion of: *(DPG 2011)*
(a) Hodgkin's Lymphoma, nodular sclerosis
(b) Hodgkin's Lymphoma, mixed cellularity
(c) Anaplastic large cell Lymphoma
(d) Peripheral T cell Lymphoma

74. **Eosinophilic Abscess in lymph node is characteristically seen in:** *(DPG 2011)*
(a) Kimura's disease
(b) Hodgkin's Lymphoma
(c) Tuberculosis
(d) Sarcoidosis

75. **A 50 years old male presents with massive splenomegaly. His differential diagnosis will include all, except:** *(DPG 2011)*
(a) Chronic myeloid leukemia
(b) Polycythemia rubra vera
(c) Hairy cell leukemia
(d) Aplastic anemia

76. **Burkitt's lymphoma is associated with:** *(AI 2010)*
(a) t (8:14) (b) t (9:22)
(c) t (11; 14) (d) t (8:21)

77. **All of the following immunohistochemical markers are positive in the neoplastic cells of granulocytic sarcoma, except:** *(AI 2006)*
(a) CD 45 RO (b) CD 43
(c) Myeloperoxidase (d) Lysozyme

78. **Mantle cell lymphomas are positive for all of the following, except:** *(AI 2006)*
(a) CD 23 (b) CD 20
(c) CD 5 (d) CD 43

79. **The classification proposed by the International Lymphoma Study Group for non-Hodgkin lymphoma is:** *(AI 2005)*
(a) Kiel classification
(b) REAL classification
(c) WHO classification
(d) Rappaport classification

80. **A 48-year-old woman was admitted with a history of weakness for two months. On examination, cervical lymph nodes were found enlarged and spleen was palpable 2 cm below the costal margin. Her hemoglobin was 10.5 g/dl, platelet count 2.7×10^9/L and total leukocyte count 40×10^9/L, which included 80% mature lymphoid cells with coarse clumped chromatin. Bone marrow revealed a nodular lymphoid infiltrate. The peripheral blood lymphoid cells were positive for CD 19, CD 20 and CD 23 and were negative for CD 79B and FMC-7.**

The histopathological examination of the lymph node in this patient will most likely exhibit effacement of lymph node architecture by: *(AI 2005)*
(a) A pseudofollicular pattern with proliferation centers
(b) A monomorphic lymphoid proliferation with a nodular pattern
(c) A predominantly follicular pattern
(d) A diffuse proliferation of medium to large lymphoid cells with high mitotic rate

81. **A four-year-old boy was admitted with a history of abdominal pain and fever for two months, maculopapular rash for ten days, and dry cough, dyspnea and wheezing for three days. On examination, liver and spleen were enlarged 4 cm and 3 cm respectively below the costal margins. His hemoglobin was 10.0 g/dl, platelet count 37×10^9/L and total leukocyte count 70×10^9/L, which included 80% eosinophils. Bone marrow examination revealed a cellular marrow comprising 45% blasts and 34% eosinophils and eosinophilic precursors. The blasts stained negative for myeloperoxidase and nonspecific esterase and were positive for CD 19, CD 10, CD 22 and CD 20. Which one of the following statements is not true about this disease?** *(AI 2005)*
(a) Eosinophils are not part of the neoplastic clone
(b) t (5:14) rearrangement may be detected in blasts
(c) Peripheral blood eosinophilia may normalize with chemotherapy
(d) Inv (16) is often detected in the blasts and the eosinophil

82. **All of the following statements about hairy cell leukemia are true except:** *(AI 2004)*
(a) Splenomegaly is conspicuous
(b) Results from an expansion of neoplastic T-lymphocytes
(c) Cells are positive for Tartarate Resistant Acid phosphatase
(d) The cells express CD25 consistently

83. **True about Burkitt's lymphoma:** *(AIIMS Nov 09)*
(a) CD 34 and surface Ig both +ve
(b) CD 34 negative but surface Ig+
(c) CD 34 positive but surface Ig -
(d) CD 34 and surface Ig both (–) ve

84. **Which of the following is false?** *(AIIMS Nov 09)*
(a) Bcl-6 is associated with Burkitts lymphoma
(b) Bcl-2 is associated with follicular lymphoma
(c) CD-10 is associated with mantle cell lymphoma
(d) CD 34 is associated with Diffuse large B Cell Lymphoma

85. **Post transplant lymphoma occurs due to proliferation of which of the following cells:** *(AIIMS Nov 2006)*
(a) T-cell (b) B-cell
(c) NK cell (d) Monocyte

86. **Which of the following statements on lymphoma is not true?** *(AIIMS May 2006)*
(a) A single classification system for Hodgkin's disease (HD) is almost universally accepted
(b) HD more often tends to remain localized to a single group of lymph nodes and spreads by contiguity
(c) Several types of non Hodgkin's lymphoma (NHL) may have a leukemic phase
(d) In general follicular (nodular) NHL has worse prognosis compared to diffuse NHL

MOST RECENT QUESTIONS

87. **Mantle cell lymphomas are positive for all of the following except:**
(a) CD23 (b) CD20
(c) CD5 (d) Cyclin D1

88. **Over-expression of BCL-2 proteins occurs in:**
(a) Burkitt's lymphoma
(b) Follicular lymphoma
(c) Diffuse large B-cell lymphoma
(d) Small lymphocytic lymphoma

89. **'Starry sky' appearance is seen in:**
(a) Burkitt's lymphoma
(b) Mantle cell lymphoma
(c) Extra nodal marginal zone B-cell lymphoma of MALT type
(d) Chronic myeloid leukemia

90. **All are B cell lymphomas except:**
(a) Burkitt's lymphoma
(b) Mycosis fungoides
(c) Mantle cell lymphoma
(d) Follicular cell lymphoma

91. **True statement regarding non Hodgkin's lymphoma of follicular type is:**
(a) Increased incidence in adolescents
(b) Predominantly in males
(c) Prognosis is better than in diffuse type
(d) Affects T cells only

92. **MALToma is:**
(a) B-cell lymphoma
(b) APUDoma
(c) NK cell tumor
(d) T cell lymphoma

93. **Which of the following is the most common site for extranodal lymphoma?**
(a) Esophagus (b) Stomach
(c) Intestine (d) Skin

94. **Cell of origin of hairy cell leukemia is:**
(a) T cell (b) B cell
(c) NK cell (d) Dendritic cell

95. **Which one of the following Non-Hodgkin Lymphomas is aggressive?**
(a) Follicular Lymphoma
(b) Burkitt Lymphoma
(c) Small lymphocytic lymphoma
(d) Lymphoplasmacytic lymphoma

96. **The low grade non- Hodgkin's lymphoma is:**
(a) Follicular small cleaved lymphoma
(b) Follicular large cell lymphoma
(c) Diffuse large cell lymphoma
(d) Lymphoblastic lymphoma

97. **Which of the following is the most common non Hodgkin lymphoma?**
(a) Follicular lymphoma
(b) Anaplastic large cell lymphoma
(c) Diffuse large B cell lymphoma
(d) Marginal zone lymphoma

98. **Most common Non-Hodgkin's lymphoma of orbit:**
(a) B cell (b) T cell
(c) NK cell (d) Plasma cell

99. **Marginal lymphoma is type of:**
(a) B cell lymphoma
(b) T cell lymphoma
(c) NK cell lymphoma
(d) Hodgkin lymphoma

100. **Which of the following is the marker of mantle cell cancer?**
(a) CD5 +, CD25 –
(b) CD 5 +, CD 10 +
(c) CD 5 +, CD 23 +
(d) CD 5 +, CD 23 –

101. **Mycosis fungoides is:**
(a) Fungal infections of skin
(b) Leukemia
(c) Exfoliative erythroderma
(d) Cutaneous lymphoma

102. **Histological presence of "Hallmark Cells" with horse shoe-like or embryoid like nuclei and voluminous cytoplasm are seen in:**
(a) Anaplastic large cell lymphoma (ALK positive)
(b) Familial Medullary Carcinoma
(c) Familial Neuroblastoma
(d) Lymphocyte predominance type Hodgkin's lymphoma

103. **Prevalence of burkitt lymphoma is highest in?**
(a) Australia
(b) Africa
(c) Asia
(d) America

104. **Cells seen in cutaneous T cell lymphoma are called as**
(a) Councilman body
(b) Barr body
(c) Sezary cells
(d) Dohle body

105. **Not a B cell lymphoma**
(a) Mycosis fungoides
(b) CLL
(c) Hairy cell leukemia
(d) Mantle cell lymphoma

106. **Sezary cells show which type of nucleus?**
(a) Pleomorphic (b) Round
(c) Eosinophilic (d) Cerebriform

HODGKIN LYMPHOMA

107. **Classical markers for Hodgkin's disease are:** *(AI 2008)*
(a) CD 15 and CD 30
(b) CD 15 and CD 22
(c) CD 15 and CD 20
(d) CD 20 and CD 30

108. All of the following are the good prognostic features for Hodgkin's disease except: *(AI 2004)*
(a) Hemoglobin > 10 gm/dl
(b) WBC count < 15000/mm^3
(c) Absolute lymphocyte count < 600/µl
(d) Age < 45 years

109. The lymphocytic and histiocytic variant of Reed-Sternberg cell is seen in: *(AIIMS Nov 2005)*
(a) Follicular center lymphoma
(b) Lymphocyte depleted Hodgkin's disease
(c) Nodular sclerosis Hodgkin's disease
(d) Lymphocyte predominant Hodgkin's disease

MOST RECENT QUESTIONS

110. Which cell is not seen in Hodgkins lymphoma:
(a) Reed Sternberg cell
(b) Lacunar cell
(c) L and H cell
(d) Langerhan's cell
(e) Hodgkin cell

111. The sub-type of Hodgkin's lymphoma characteri zed by L and H cells is:
(a) Nodular sclerosis
(b) Mixed cellularity
(c) Lymphocyte depletion
(d) Lymphocyte predominant

112. An elderly patient presented with hypercellular bone marrow, peripheral blood smear shows pancytopenia, and 15% myeloblast cells. Most likely diagnosis is:
(a) Myelodysplastic syndrome
(b) Blast crisis in CML
(c) AML
(d) Polycythemia vera

113. The subtype of Hodgkin's disease, which is histo-genetically distinct from all the other subtypes, is:
(a) Lymphocyte predominant
(b) Nodular sclerosis
(c) Mixed cellularity
(d) Lymphocyte depleted

114. 'Popcorn cells' are seen in which type of Hodgkin's disease?
(a) Lymphocyte dominant
(b) Lymphocyte depleted
(c) Nodular sclerosis
(d) Mixed type

115. In a 45-year-old female presenting with painless supraclavicular lymphadenopathy, biopsy was taken. It revealed the presence of binucleated acidophlic owl eye appearance with clear vacuolated space. The cell was CD15 and CD30 positive. Which is the most likely diagnosis?
(a) Lymphocyte predominant Hodgkin lymphoma
(b) Nodular sclerosis Hodgkin lymphoma
(c) Mixed cellularity Hodgkin lymphoma
(d) Lymphocyte depleted Hodgkin lymphoma

116. Which Hodgkin's disease is associated with best prognosis:
(a) Lymphocyte depletion
(b) Mixed cellularity
(c) Lymphocytic predominance
(d) Nodular sclerosis

117. Lacunar cells are seen in which type of Hodgkin's lymphoma:
(a) Lymphocyte predominance
(b) Lyphocyte depletion
(c) Nodular sclerosis
(d) Mixed cellularity

MYELOPROLIFERATIVE DISORDERS

118. Splenomegaly is associated with all except: *(AI 2012)*
(a) CML
(b) Polycythemia vera
(c) Essential thrombocythemia
(d) Primary myelofibrosis

119. Essential criteria for polycythemia vera according to WHO is: *(AI 2010)*
(a) Low EPO
(b) JAK 2 mutation
(c) Bone marrow showing panmyelosis
(d) MPL point mutation

MOST RECENT QUESTIONS

120. Which of the following is not a chronic myeloproliferative disorder?
(a) Polycythemia vera
(b) Myeloid metaplasia
(c) CML
(d) Essential thrombocytopenia

121. Leucocyte alkaline phosphatase (LAP) is raised in all conditions except:
(a) Myelofibrosis
(b) Essential thrombocythemia
(c) Chronic myeloid leukemia
(d) Polycythemia

122. Leukoerythroblastic reaction is seen in the following except:
(a) Secondaries in bone
(b) Multiple myeloma
(c) Hemolytic anemia
(d) Lymphoma

123. Increase in alkaline phosphatase is seen in:
(a) Chronic myeloid leukemia; CML
(b) Leukemoid reaction
(c) Eosinophilia
(d) Malaria

124. Polycythemia is absolute venous haematocrit of more than:
(a) 45%
(b) 55%
(c) 65%
(d) 70%

125. CD marker of histiocytosis is:
(a) CD 1a
(b) CD 1b
(c) CD 1c
(d) CD 1d

126. Shape of Birbeck granules is which of the following?
(a) Hockey stick
(b) Bat
(c) Ball
(d) Tennis racket

127. One of the following is not a myelo-proliferative disorder?
(a) Essential thrombocytosis
(b) Myelofibrosis with myeloid metaplasia
(c) Acute myeloblastic leukemia
(d) Chronic myeloid leukemia

128. Isolated deletion of which chromosome is associated with myelodysplastic syndrome?
(a) 2q (b) 5q
(c) 8q (d) 11q

PLASMA CELL DYSCRASIAS

129. Which of the following is the least common presentation of multiple myeloma? *(AI 2012)*
(a) Anemia (b) Hyperviscosity
(c) Bone pains (d) Infection

130. Which of the following metabolic abnormality is seen in multiple myeloma? *(DPG 2011)*
(a) Hypernatremia (b) Hypokalemia
(c) Hypercalcemia (d) Hyperphosphatemia

131. Lymphoplasmacytoid lymphoma is associated with:
(a) IgG (b) IgA *(AI 2010)*
(c) IgD (d) IgM

132. Which of the following statement is not true? *(AI 2005)*
(a) Patients with IgD myeloma may present with no evident M-spike on serum electrophoresis.
(b) A diagnosis of plasma cell leukemia can be made if circulating peripheral blood plasma blasts comprise 14% of peripheral blood white cells in a patient with white blood cell count of 1×10^9/L and platelet count of 88×10^9/L
(c) In smoldering myeloma plasma cells constitute 10-30% of total bone marrow cellularity
(d) In a patient with multiple myeloma, a monoclonal light chain may be detected in both serum and urine

133. Which of the following is not a minor diagnostic criterion for multiple myeloma? *(AIIMS Nov 08, 10)*
(a) Lytic bone lesions
(b) Plasmacytosis greater than 20%
(c) Plasmacytoma on biopsy
(d) Monoclonal globulin spike on serum electrophoresis of < 2.5 g/dl for IgG, < 1.5 g/dl for IgA)

134. A-3-year old female child presented with skin papules. Which of the following is a marker of Langerhan's cell histiocytosis? *(AIIMS Nov 2007)*
(a) CD 1a (b) CD 3
(c) CD 68 (d) CD 57

135. A 70-year-old male has a pathologic fracture of femur. The lesion appears a lytic on X-rays film with a circumscribed punched out appearance. The curetting from fracture site is most likely to show which of the following? *(AIIMS May 2006)*
(a) Diminished and thinned trabecular bone
(b) Sheets of atypical plasma cells
(c) Metastatic prostatic adenocarcinoma
(d) Malignant cells forming osteoid bone

136. Hyperviscosity is seen in: *(PGI Dec 2003)*
(a) Cryoglobulinemia
(b) Multiple myeloma
(c) MGUS
(d) Lymphoma
(e) Macroglobulinemia

137. Hyperviscosity syndrome is seen in:
(a) NHL *(PGI Dec 2004)*
(b) Waldenstrom's macroglobulinemia
(c) Multiple myeloma
(d) Hodgkin's lymphoma
(e) Acute promyelocytic leukemia

138. True about Langerhan's cell histiocytosis is:
(a) CD 68+ *(PGI Dec 2005)*
(b) CD 1+
(c) Birbeck's granules are pathognomic
(d) Proliferation of antigen presenting cells
(e) Resembles dendritic cells

MOST RECENT QUESTIONS

139. Finding of multiple myeloma in kidney are all except:
(a) Tubular casts
(b) Amyloidosis
(c) Wire loop lesions
(d) Renal tubular necrosis

140. Proliferation and survival of myeloma cells are dependent on which of the following cytokines?
(a) IL-1 (b) IL-6
(c) IL-2 (d) IL-5

141. Plasma cell dyscrasias include all of the following except:
(a) Waldenstorm's macroglobulinemia
(b) Heavy chain disease
(c) Monoclonal gammopathy of uncertain significance
(d) Systemic lupus erythematosus

142. Histiocytosis is NOT associated with:
(a) Spontaneous fractures
(b) Cutaneous eruptions
(c) Bone marrow suppression
(d) No lymphadenopathy

143. M-spike in multiple myeloma is due to?
(a) IgM
(b) IgA
(c) IgG
(d) None of these

144. Birbeck's granule is found in:
(a) Langerhans cell
(b) Langhans giant cell
(c) Lepra cell
(d) Clue cell

145. Which of the following is not a characteristic feature of multiple myeloma?
(a) Increased Ig levels in serum
(b) Positive ANA
(c) Plasmacytosis
(d) M spike on electrophoresis

146. Which histiocytosis involves the bones:
(a) Malignant
(b) Langherhans
(c) Sinus histiocytosis
(d) Option not recalled

147. Beta-2 microglobulin is a tumor marker for:
(a) Multiple myeloma
(b) Lung cancer
(c) Colonic neoplasm
(d) Choriocarcinoma

148. Russell bodies are found in which of the following conditions?
(a) Multiple Myeloma
(b) Gonadal tumor
(c) Parkinsonism
(d) Intracranial neoplasms

149. In Langerhans cell histiocytosis, the characteristic abnormality seen on microscopy is:
(a) Birbecks granules
(b) Foamy macrophages
(c) Giant cells
(d) Plasma Cells

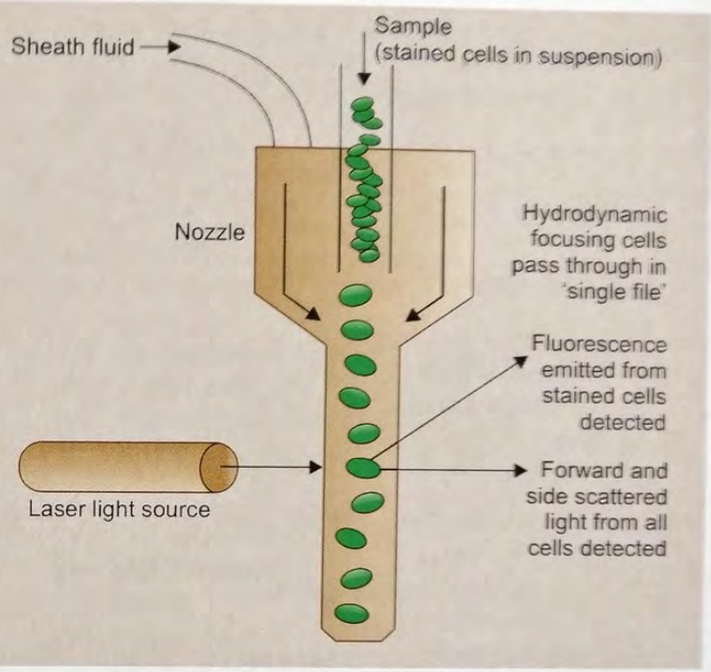
150. For the diagnosis of hypereosinophilia syndrome, after exclusion of all parasitic infections and in the presence of end organ damage, the absolute eosinophil count needed for the diagnosis is: *(AIIMS Nov 2016)*
(a) 500 (b) 1000
(c) 1500 (d) 2000

Explanations

1. **Ans. (d) Lymphocytosis** *(Ref: Robbins 8th/324)*

Flow cytometry can rapidly and quantitatively measure several individual cell characteristics, such as membrane antigens and the DNA content of tumor cells.
Flow cytometry has also proved useful in the identification and classification of tumors arising from **T and B lymphocytes** and from mononuclear-phagocytic cells.

In flow cytometry, it is observed that large objects will refract more light than small objects leading to high forward scatter signals and vice versa. So, **forward scatter in flow cytometry denotes cell size..... AIIMS May 15 question**



2. **Ans. (c) Acute megakaryocytic leukemia.**
(Ref: Robbins 8th/622, 9/e p612, Wintrobe's 12th/1857-8)
Direct quote from Robbins... *'In some AMLs, blasts show **megakaryocytic differentiation**, which is **often accompanied by marrow fibrosis** caused by the release of fibrogenic cytokines'*

Acute megakaryocytic leukemia is the most common variant of AML associated with **Down syndrome.** The release of PDGF (platelet derived growth factor) is responsible for marrow fibrosis.

3. **Ans. (c) Common leukocyte antigen**
(Ref: Robbins 8th/600, 9/e p590)
- CD45 is present on all the leukocytes; it is also known as leukocyte common antigen (LCA).

4. **Ans. (b) Immunophenotyping** *(Ref: Robbins 9/e p593)*
Adult patient presenting with generalized lymphadenopathy and blood film shows 70% immature looking lymphocytes is highly suggestive of chronic lymphocytic leukemia. Immnophenotyping can be one of the best ways to differentiate between CLL and other B cell neoplasms.

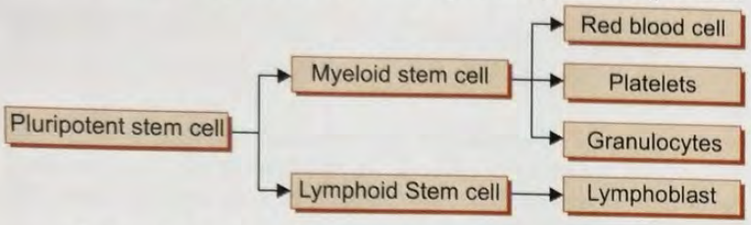
Important points about CLL
- Most of the patients are often asymptomatic at diagnosis. When symptoms appear, they are nonspecific and include easy fatigability, weight loss, and anorexia. Hepatosplenomegaly and generalized lymphadenopathy are present in 50% to 60% of symptomatic patients.
- The immunophenotype of CLL is distinct. The tumor cells express the pan-B cell markers CD19 and CD20, as well as CD23 and CD5, the latter a marker that is found on a small subset of normal B cells. Low-level expression of surface Ig (usually IgM or IgM and IgD) is also typical.

5. **Ans. (c) Acute lymphoid leukemic in less than 1 year has a poor prognosis**
(Ref: Robbins 9/e p592, Wintrobe 12th)
Prognostic factors in ALL have been discussed in text
Explaining other options,
- Chronic myeloid leukemia occurs beyond 50 years of age...Robbins 8th/
- Hairy cell leukemic is present in median age of 55 years and has M:F ratio of 5:1. HCL tends to follow an indolent course. For unclear reasons, the tumor cells are exceptionally sensitive to particular chemotherapeutic regimens, which produce long-lasting remissions. The overall prognosis is excellent. So, the condition is not having additional increase in improvement with age less than 50 years.

- The median age of diagnosis of Chronic lymphocytic leukemia is 60 years and there is a 2:1 male predominance....Robbins 8th/603

6. Ans. (c) RBC *(Ref: Robbins 8th/592-593, 9/e p580)*

The following flowchart is self explanatory for this question:



So, on the injection of a myeloid stem cell, it can give rise to a cell of its lineage which can be either of the RBCs, monocytes, neutrophils, eosinophils, basophils and platelets. The answer is therefore, red blood cells.

7. Ans. (d) T cell Lymphoblastic ALL

(Ref: Robbins 8th/601-3, 9/e p592)

8. Ans. (c) Paroxysmal cold haemoglobinuria

(Ref: Robbins 8th/625, 653,664, 9/e p544, Wintrobes 12th/965)

Analyzing all the options one by one;

Option 'a'...direct quote.. 'about 5% to 10% of patients eventually develop acute myeloid leukemia or a myelodysplastic syndrome, possibly because hematopoietic stem cell have suffered some type of genetic damage'. (Robbins 8th/653)

Even PNH is associated with aplastic anemia as both the disorders have an autoimmune basis.

Option 'b'...direct quote.., aplastic anemia results from a fundamental stem cell defect supported by the presence of karyotypic aberrations in many cases; the occasional transformation of aplasias into myeloid neoplasms, typically myelodysplasia or acute myeloid leukemia; and the association with abnormally short telomeres. (Robbins 8th/664)

Option 'd'...direct quote.. The term "myelodysplastic syndrome" (MDS) refers to a group of clonal stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis and a high risk of transformation to AML. (Robbins 8th/625).

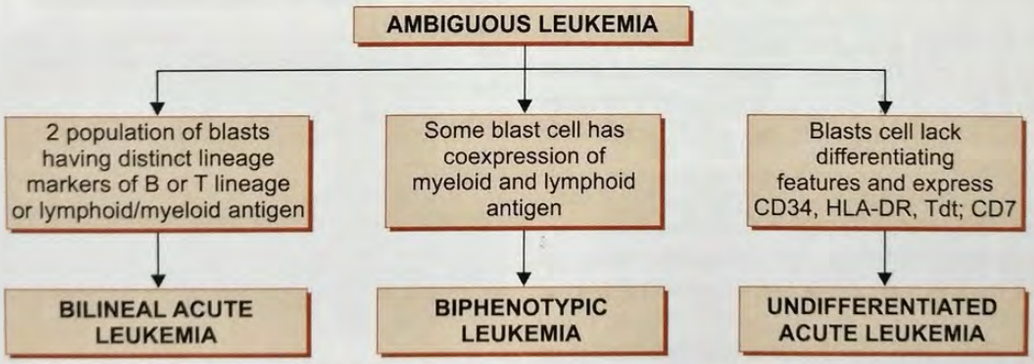
So the answer of exclusion is PCH (paroxysmal cold hemoglobinuria). It is an autoimmune haemolytic anemia due to IgG autoantibodies which bind to P blood group antigen and cause intravascular hemolysis and hemoglobinuria. Most cases are seen in children and have recovery within a month.....Wintrobes.

9. Ans. (c) Mixed phenotypic leukaemia

(Ref: Wintrobes 12th/1814-8, Dacie and Lewis hematology 10th/344-6)

Markers on different cells

- B lymphoid markers: CD10, CD19 and CD79
- T lineage markers: CD2, CD3 and CD7
- Myeloid markers; CD13, CD33, CD117 and myeloperoxidase (MPO).
- Non lineage specific markers which are expressed in hematopoietic progenitor cells: CD34, HLA-DR and TdT



Comparing this with the information provided in the stem of our question, it is easy to decipher that the cells mentioned are CD10+ve, MPO +ve, CD19+ve, CD33-ve, CD117 +ve and CD3-ve which is showing both **lymphoid (CD10, CD19;***B lymphoid lineage*) and **myeloid** (CD117 and MPO+-) markers in the same cell. So, the answer is **Mixed phenotypic leukemia**

10. Ans. (a) Biphenotypic leukemia

(Ref: Robbins illustrated 8th/600)

- *Refering to the flowchart in the previous explanation, we understand that CD 10 +ve and CD 19+ve are the markers for B-cell lineage, whereas CD 33 and CD 13 are associated with monocyte and macrophages.* So, the patient is having **acute leukemia** with **immunophenotype** pattern with coexpression of **more than one cell lineage.** The answer is therefore Biphenotypic leukemia.

11. Ans. (a) Inv 16

(Ref: Wintrobe 12th/1859, Robbins 8th/624, 9/th 614, T. Singh 2nd/168) ...see text

12. Ans. (d) CD 117 *(Ref: Wintrobes 11th/4145)*

As per Wintrobe's the markers for myeloid series are CD13, CD33, CD 11b, CD15, CD117 and cMPO.

c MPO is the most lineage specific marker amongst these.

Regarding other options, • CD 34 - Myeloid and lymphoid blasts, stem cells, • CD 45 - Leukocyte common antigen (nonerythroid hematopoietic cells), • CD 99 - Ewing's sarcoma/primitive neuroectodermal cells.

13. **Ans. (b) B cell ALL**
(Ref: Robbins 8th/608, 9/th/597, Harrison 17th/696)
t (2;8) is causing translocation between immunoglobulin κ chain on chromosome 2 and the myc gene present on chromosome 8 and is seen in **Burkitt's lymphoma/leukemia**. The translocation results in the increased expression of **c-MYC** resulting in development of neoplasia.

14. **Ans. (a) Mature B-cell** *(Ref: Robbins 7th/677, 9th/590)*
- *Acute Lymphoblastic Leukemias (ALL) of the L3 (FAB) subtype are tumors of Mature B-cells (e.g. Burkitt's lymphoma)*

15. **Ans. (d) M6**
(Ref: Robbins 7th/759, Hematology Basic Principles and Practice, Hoffman, Benz et al.4th/1080)

> Nonspecific esterase (NSE) is characteristic of M4 (Acute myelomonocytic) and M5 (Acute monocytic) leukemia only. *NSE positivity is not a characteristic feature of other subclasses of AML.*

- However, NSE positivity may also be seen in 15-20% of cases of M3 and in some cases of M7.
- ***NSE positivity is not a feature of M0, M1, M2 and M6 classes of AML.***

16. **Ans. (d) Tartarate resistant acid phosphatase positivity is typically seen in hairy cell leukemia**
(Ref: Wintrobe's 11th/2468, 2470, 2471, Robbin 9/e p603-604)
- **Tartarate resistant acid phosphatase (TRAP)** is an important tool in differential diagnosis of **hairy cell leukemia** (HCL). The test is positive in 95% of cases of HCL and usually negative or weakly positive in other disorders.
- TRAP is also **positive** in some cases of **splenic marginal zone lymphoma**.
- LAP (leukocyte alkaline phosphatase) score is decreased in CML and PNH (paroxysmal nocturnal hemoglobinuria). However, LAP score often increases when CML transforms to a blast crisis or accelerated phase.

17. **Ans. (c) $5q^-$**
(Ref: Wintrobe's 12th/1959-64, Ann Hematol. 2008 July; 87(7): 515–526)
The article in the Annals of hematology ***'Cytogenetic features in myelodysplastic syndromes'*** by Detlef Haase gives the different causes as percentage of myelopdysplastic syndromes. This is a typical example of question where the changed data may lead to the question being repeated in the future exam friends.
'Myelodysplastic syndromes' are a group of clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective hematopoiesis in one or more of the major myeloid stem lines.

Direct quote from the Haase's paper.....*'Deletions within the* ***long arm of chromosome 5*** *are the* ***most frequent cytogenetic changes in MDS***[Q] *accounting for* ***roughly 30%*** *of abnormal cases.'*
The cytogenetic abnormalities in adult myelodysplastic syndrome are:

5q	30%
Monosomy 7	20%

> Complex chromosome abnormalities are defined by the simultaneous occurrence of at least three independent abnormalities within one cell clone. They are also seen in almost 30% cases.

Direct quote from **Williams Hematology** 8th/edn ***"The most common abnormalities are 5q–, -7/7q–, +8, –18/18q–, and 20q–. Monosomy 7 is the second most frequent cytogenetic abnormality in the marrow cells of patients with myelodysplasia."***
So, we would prefer to go with (c) deletion of 5q as the preferred answer.

18. **Ans. (b) CD3**
(Ref: Harrison 17th/2020, 2032, Robbins 9/e 190)
When a cluster of monoclonal antibodies were found to react with particular antigen it was defined as a separate marker and given a CD (cluster of differentiation) number.
- **CD3 is used as a pan T-cell marker** (present on all stages of T-cells [Pro–T, Pre-T, Immature and mature T-cells]
- **CD19 is a Pan B-cell marker.**

CD-1	Thymocytes and Langerhans' associated
CD - 1, 2, 3, 4, 5, 7, 8	T-cell markers
CD - 10, 19, 20, 21, 22, 23	B-cell markers
CD - 10	CALLA antigen
CD - 13, 14, 15, 33	Monocyte macrophage associated
CD - 16, 56	NK- associated
CD - 41	Platelet marker
CD - 21	EBV receptors

19. **Ans. (d) CD135**
(Ref: Robbins 9/e 590, 8th/600, 7th/670, www.wikipedia.com)
- B cell associated markers are CD10 (CALLA), CD19, CD20, CD21 (EBV receptor), CD22 and CD23.

Concept of CD135

> - CD135 is a proto-oncogene. It is also the receptor for the cytokine Flt3 ligand (Flt3L) and has the presence of tyrosine kinase activity. Its mutation can lead to acute myelogenous leukemia (AML) and is associated with a poor prognosis.

20. **Ans. (c) Presence of testicular involvement at presentation** *(Ref: Robbins 9/e 592, 8th/603)*

Prognostic factors in ALL

GOOD PROGNOSIS	BAD PROGNOSIS
• Age 1-10 years	• Age <1 year or > 10 years
• Female sex	• Male sex
• L1 cell	• L2 or L3 cell
• Peripheral blast count <1,00,000	• Peripheral blast count >1,00,000
• Pre B cell phenotype	• Pre T cell phenotype
• Absence of mediastinal mass	• Mediastinal mass
• Hyperdiploidy (>50 chromosomes) or t(12;21)	• Pseudodiploidy or t (9;22) or presence of Philadelphia chromosome, t (8;14), t (4;11)
• Trisomy of chromosomes 4,7,10	

Friends, please remember age is less than 2 years is given as bad prognosis in Robbins whereas in NELSON it is mentioned that the age for bad prognosis is less than 1 year. Nelson also mentions the testicular involvement to be a bad prognostic factor. Since in the given question, both (less than 2 years as well as testicular involvement) are mentioned we would go for testicular involvement as the better answer here.

21. Ans. (d) t(9:22), t(8:14), t(4:11) explained earlier.
(Ref: Robbins 9/e 592, 8th/603)

22. Ans. (d) M4
(Ref: Robbin 7th/693, Harrison 17th/680, Wintrobe's 12th/1857)

Signs and symptoms related to infiltration of tissues are usually less striking in AML than in ALL. Mild lymphadenopathy and organomegaly can occur. In tumors with monocytic differentiation M4 and M5 **(more commonly)**, infiltration of the skin (leukemia cutis) and the gingiva leading to gum hypertrophy can be observed, likely reflecting the normal tendency of non-neoplastic monocytes to extravasate into tissues.

- **M5 AML is the commonest AML** associated **with extramedullary disease**[Q] (skin lesions/gum infiltration/ CNS disease/testicular involvement).
- After M3 AML, **M5 AML**[Q] **is the commonest AML** associated with the development of **DIC**.

23. Ans. (c) CD117
(Ref: Devita 6th/503, Robbins 7th/826, 9/e 614)

Explained in an earlier question

24. Ans. (a) CD-15
(Ref: Robbins 7th/670, 9/e 590, Harrison 17th/1908, 689, Wintrobe's 12th/2507)

Direct lines from Wintrobes hematology…..'CD-15 is expressed on neutrophils, eosinophils and monocytes but not on platelets, lymphocytes and erythrocytes'.

About option (d), CD 24 is expressed on B cells but it decreased with B cell activation and differentiation and is lost at the plasma cell stage. It is also present ion granulocytes and thymocytes but not on mature T cells. Data shows its increased levels are associated with colon/ breast and pancreatic cancer.

25. Ans. (a) Monocytes *(Ref: Wintrobe's 12th/15)*

- *Acid phosphatase is found in all hematopoietic cells, but the highest levels are found in macrophages and osteoclasts.* A dot like pattern is seen in many T lymphoblasts.
- Tartarate resistant acid phosphatase (TRAP) is seen in osteoclasts and Hairy cell leukemia. Positive TRAP staining may be seen in activated T lymphocytes, macrophages, Gaucher cells, mast cells and some marginal zone lymphomas. Conditions associated with increased TRAP staining are:
  - **Hairy cell leukemia**
  - **Gaucher's diease**
  - **HIV-induced encephalopathy**
  - **Osteoclastoma**
  - **Osteoporosis**
  - **Metabolic bone diseases**

26. Ans. (c) Chronic myelogenous leukemia
(Ref: Harrison 17th/683-684; Robbins 7th/697, 698, 9/e 617-618)

The peripheral blood picture of this patient is quite characteristic of **chronic myeloid leukemia.**

Chronic myeloid leukemia is a stem cell disease that is characterized by leukocytosis with granulocytic immaturities, basophilia, splenomegaly and distinct chromosomal abnormality Philadelphia chromosome.

27. Ans. (b) An immature T cell phenotype [Tdt/CD34/ CD7 positive] *(Ref: Robbins 7th/670-673, 9/e 590-593)*

- *Increased leukocyte count in the range of 138 × 10^9/L and on peripheral blood examination 80% of them constituting blast cells indicate acute leukemia.*
- *The age group (adolescent) and the mediastinal mass suggests that this leukemia is likely to be a T-cell leukemia.*
- ***"T-cell ALL tends to present in adolescent males as lymphomas often with thymic involvement"***

So, the diagnosis is **T-cell ALL.**

Immunophenotypic classification of acute lymphoblastic leukemia	
Pre-T-cell ALL	TdT, CD2, CD3, CD4, CD5, CD7, CD8, CD34
Early pre-B	TdT, DR, CD10, CD19, CD24
Pre-B-cell	TdT, DR, CD10, CD19, CD20, CD24, Surface Ig
B-cell	DR, CD19, CD20, CD24, Surface Ig

28. Ans. (c) Promyelocytic leukemia
(Ref: Robbins 7th/693, 656-658)

The child presented with acute onset of bleeding, along with the following laboratory findings:

- *Thrombocytopenia* (35000/mm^3 as compared to normal value of 1, 50,000/mm^3)
- *Increased prothrombin time* (20s as compared to control of 13s)
- *Increased partial thromboplastin time* (50s vs. normal 26-32s)
- *Decreased fibrinogen* (10 mg/dL vs. normal of 233-496 mg/dl)

These hematological abnormalities indicate ***disseminated intravascular coagulation.***

Most common form of AML associated with DIC is M_3-AML (Acute promyelocytic leukemia).

29. **Ans. (b) t(9;22) t(4;11)** *(Ref: Robbins 9/e p592-593)*

Prognostic factors in ALL

GOOD PROGNOSIS	BAD PROGNOSIS
• Age 2-10 years • Female sex • L1 cell • Peripheral blast count <1,00,000 • Pre B cell phenotype • Absence of mediastinal mass • Hyperdiploidy (>50 chromosomes) or t(12;21) • Trisomy of chromosomes 4,7,10	• Age <1 year or > 10 years • Male sex • L2 or L3 cell • Peripheral blast count >1,00,000 • Pre T cell phenotype • Mediastinal mass • Pseudodiploidy or t (9;22) or presence of Philadelphia chromosome, t (8;14), t (4;11)

30. **Ans. (c) More than 20% of blasts in blood or bone marrow.** *(Ref: Wintrobe's 12th/1999-2000)*

WHO criteria for chronic myelomonocytic leukemia (CMML)

1. **Absolute monocytosis > 1 × 10^9/L** in the peripheral blood
2. **Blasts + monocytes < 20%** in blood and bone marrow
3. **Absence of philadelphia chromosome** or **BCR/ABL fusion gene**
4. **Dysplasia in one or more of myeloid lineages**
   - If bone marrow blasts + monocytes > 20%, it is diagnosed as acute myeloid leukemia
   - **Unlike** classic CML, chronic myelomonocytic leukemia has **absence** of basophilia and eosinophilia and more monocytes. Also CML does not have granulocyte dysplasia (**present in CMML**).

31. **Ans. (b) t (9;22)**
(Ref: Robbins 9/e 614, 8th/627-628, T. Singh 1st/186-190, Harrison 17th/683 - 84)

- An old man having fatigue and weight loss (*due to anemia and cancer*) and heaviness in left hypochondrium (*most likely due to splenomegaly*). He also has elevated TLC (most likely due to leukemia). But the no. of blast cells is 3%, so it cannot be acute leukemia. Old man with leukemia and splenomegaly is suggestive of CML which is associated with t (9; 22).

Other options

- **t (15, 17)** is associated with **acute myeloid leukemia**. For the diagnosis of acute leukemia, the number of blasts in the blood should be >20%.

32. **Ans. (c) Myeloperoxidase**
(Ref: Robbin's illustrated 7th/692-693, 9/e p613)

Patient here gives a short history (acute onset) of development of pancytopenia (fever; weakness and gum bleeding suggest leucopenia; anemia and thrombocytopenia respectively).

The presence of 26% blasts in the bone narrow suggests the development of acute leukemia and the presence of Auer rods means that the diagnosis is most likely AML. Pseudo Pelger Huet cells are neutrophils having greater than 2 nuclear lobes and are usually seen in myelodysplastic syndrome. In 10% patients, MDS can give rise to AML. So, the AML in question may have developed from MDS.
The chief cell in AML is myeloblast for which the staining is positive for myeloperoxidase.

Note: Acid phosphatase is useful for lymphoblasts which are seen in ALL

33. **Ans. (d) Monosomy 7**
(Ref: T. singh 1st/175, Robbins 9/e p612) ...see text

34. **Ans. (d) G6PD deficiency** *(Ref: Harrison 17th/663)*

35. **Ans. (b) Polycythemia vera**
(Ref: Wintrobe's Clinical Haematology 12th/15)

High levels of LAP score are found in:

- Infection
- Inflammatory disorder
- Growth factor therapy
- Pregnancy
- OCP
- Stress
- Myeloproliferative disorders (***except CML***)
- Drugs (e.g. Lithium, Corticosteroid, Estrogen)

*Abnormally high values of LAP is seen in myeloproliferative disorder e.g. polycythemia vera and myelofibrosis
*Decreased LAP score is seen in CML (chronic phase) and PNH (paroxysmal nocturnal hemoglobinuria).

36. **Ans. (a) Hodgkin's disease; (b) Filariasis; (d) HIV**
(Ref: Harrison 17th/383)

Conditions producing allergic reactions and resulting eosinophilia are:
Drugs: Iodides, Aspirin, Sulfonamides, Nitrofurantoin, Penicillins, Cephalosporins.
Disease conditions: Hay fever, Asthma, Eczema, Serum sickness, Allergic vasculitis, Pemphigus, All types of parasitic infections.
Collagen vascular diseases: RA, Eosinophilic fasciitis, Allergic angiitis, Polyarteritis nodosa.
Malignancy: Hodgkin's disease, Mycosis fungoides, CML, Carcinoma of stomach, ovary, lung, Pancreas and uterus.
Other diseases: Job's syndrome, Sarcoidosis, Skin disease.
Viral infection like HIV and human T-cell lymphotropic virus (HTLV-l).

In MI polymorphonuclear leukocytosis seen.

37. **Ans. (b) Myelofibrosis; (c) Alcoholism; (d) Iron Overload;** *(Ref. de Gruchy's 5th/56)*

Sideroblasts are erythroblasts with Prussian blue positive iron granules in their cytoplasm. They can be found in circulation in the following diseases:

*Drugs and chemicals:	*Hematological disorders:	*Inflammatory disorders:
Antitubercular drugs (INH, cycloserine)	Myelofibrosis	Rheumatoid arthritis
Lead	Polycythemia vera	SLE
Ethanol	Myeloma	Carcinoma
	Acute leukemia	Myxedema
	Hodgkin's disease	Malabsorption
	Hemolytic anemia	Iron overload.

38. Ans. (b) Kala-azar; (c) TB; (d) Brucellosis
(Ref: Harrison 17th/342, Harsh Mohan 6th/350)

CAUSES OF MONOCYTOSIS:

- Bacterial infections: TB, sub acute bacterial endocarditis, syphilis, brucellosis.
- Viral infections
- Protozoa and Rickettsial infections: Malaria, typhus, trypanosomiasis, kala-azar, RMSF.
- Hematopoietic disorder: Monocytic leukemia, lymphoma, myeloproliferative disorder, multiple myeloma, lipid storage disorder.
- Malignancies: Ca ovary, stomach and breast.
- Granulomatous diseases e.g. sarcoidosis, IBD.
- Collagen vascular diseases.

39. Ans. (a) AML; (b) Myelodysplastic syndrome; (d) Paroxysmal nocturnal hemoglobinuria
(Ref: DeGruchy's 5th/127, Harrison 17th/663)

- Aplastic anemia is a pancytopenia with bone marrow hypocellularity. It can progress to –
  - Paroxysmal Nocturnal hemoglobinuria
  - Myelodysplastic anemia
  - Rarely acute leukemia

Pure red cell aplasia is a selective disease of absence of erythrocyte progenitor cells. In contrast to aplastic anemia and MDS, the unaffected lineage (WBC and platelets) appear quantitatively and qualitatively normal.

- Myelofibrosis is a clonal disorder of a multipotent hematopoietic progenitor cell of unknown origin and is characterized by
  - Marrow fibrosis
  - Myeloid metaplasia with extramedullary erythropoiesis
  - Splenomegaly

40. Ans. (c) Reticulocytopenia; (d) Thrombocytopenia; (e) Neutropenia *(Ref: Robbins 7th/647, 9/e p653)*

Aplastic anemia is a disorder of marrow failure which stems from suppression or disappearance of multipotent myeloid stem cells. It is characterized by: Anemia, Neutropenia , Thrombocytopenia, and Reticulocytopenia. **Splenomegaly is characteristically absent**; if present, the diagnosis of aplastic anemia is almost ruled out. Bone marrow shows hypocellular marrow largely devoid of hematopoietic cells, often only fat cells, fibrous stroma, and scattered or clustered foci of lymphocytes and plasma cells.
Nucleated RBCs in peripheral smear (**leukoerythroblastic picture**) are found in cases of marrow fibrosis.

41. Ans. (c) Typhoid *(Ref: Harsh Mohan 6th/348)*

42. Ans. (b) CALLA Ag *(Ref: Robbins 7th/330)*

- CALLA (common acute lymphoblastic leukemia antigen) is CD 10
- CALLA positive acute leukemias have best prognosis.
- CD45 is known as common leukocyte antigen.

43. Ans. (b) Chronic lymphocytic leukemia
(Ref: Robbins 7th/673, 9/e 593)

In CLL, the peripheral blood contains increased numbers of small, round lymphocytes with scant cytoplasm. These cells are fragile and are frequently disrupted in the process of making smears, producing so-called **smudge cells.**

44. Ans. (a) t (15: 17) *(Ref: Robbins 9/e 612, 8th/624; 7th/692)*

45. Ans. (b) Auer bodies are seen *(Ref: Robbins 9/e 613)*

46. Ans. (d) Increased
(Ref: Robbins 7th/697-698, Wintrobes 12th/205, Williams CMDT 2010/458)

Wintrobe's hematology mentiones..... 'granulocytes contain and release B12 binding proteins. **Markedly elevated transcobalmin I level are seen in chronic myelocytic leukemia and myeloid metaplasia** whereas **low levels are seen in chronic leucopenia and aplastic anemia**'.
Williams hematology 8th/adds that 'the increase is proportional to the total leukocyte count in untreated patients and falls with treatment'.

Conditions having elevated levels of cobalamin

Hematological conditions	Non-hematological conditions
• Chronic myelogenous leukemia	• Acute hepatitis
• Promyelocytic leukemia	• Cirrhosis
• Polycythemia vera	• Hepatocellular carcinoma
• Hypereosinophilic syndrome	• Metastatic liver disease

47. Ans. (d) CML *(Ref: Robbins 8th/627; 7th/697-698)*

48. Ans. (b) Leucocyte alkaline phosphatase
(Ref: Robbins 8th/595, 9/e 584)

49. Ans. (d) Glucocorticoids *(Ref: Harsh Mohan 6th/348)*

50. Ans. (c) CML *(Ref: Robbins 8th/627; 7th/438, 9/e 584)*

51. Ans. (d) Aplastic anemia *(Ref: Robbins 9/e p654)*

52. Ans. (c) Hypocellular bone marrow
(Ref: Robbins 9/e 615, 8th/625; 7th/695)

53. **Ans. (c) Thalassemia** *(Ref: Robbins 9/e p582, 620, 653)*

54. **Ans. (c) Myeloblast** *(Ref: Robbins 8th/602, 9/e p613)*

55. **Ans. (c) CLL** *(Ref: Robbins 8th/605, 9/e p594)*

56. **Ans. (a) Acute lymphoblastic leukemia** *(Ref: Robbins 8th/603, 9/e p593)*
The presence of the Philadelphia chromosome, a translocation from the long arm of chromosome 22 to chromosome 9 [t(9;22)], is associated with a more favorable prognosis in patients with chronic myelogenous leukemia but it associated with an unfavorable outcome in Acute lymphoblastic leukemia (ALL).

57. **Ans. (d) 65 years** *(Ref: Robbins 8th/604, 9/e p593)*
Different leukemias tend to affect populations of different ages. The disease described is chronic lymphocytic leukemia (CLL), which is a disease of older adults.

> The 1 year-old (choice A) would be most likely to have acute lymphocytic leukemia (ALL).
> The 20 year-old (choice B) would be most likely to have acute myelocytic leukemia (AML).
> The 45 year-old (choice C) would be likely to have either AML or chronic myelogenous leukemia (CML).

58. **Ans. (c) Hyperdiploidy** *(Ref: Robbins 8/e p602-3, 9/e p592-593) ...see text*

59. **Ans. (b) Immature B cells** *(Ref: Robbins 8/e p600)*
As per the table given in Robbins, B cell ALL is due to **immature B cells**.

60. **Ans. (a) ALL** *(Ref: Robbins 8/e p602, 7/e p670)*
CD 10 is called as **common acute lymphoblastic leukemia antigen** or **CALLA**. It is seen in acute lymphoid leukemia (ALL).

61. **Ans. (d) Dilated endoplasmic reticulum ... explained earlier**

62. **Ans. (b) t (15,17)** *(Ref: Robbins 9/e p612, 8/e p624)*
Commonly asked information in NEET EXAM!

• **t(9;22) (Philadelphia chromosome):** CML (bcr-abl hybrid)
• t(8;14) Burkitt's lymphoma (c-myc activation)
• **t(II ; I4):** Mantle cell lymphoma (cyclin D1 activation)
• t(I4; 18): Follicular lymphomas (bcl-2 activation)
• **t(I5;17):** M3 type of AML (responsive to all-trans retinoic acid)

63. **Ans. (a) Hodkin's disease** *(Ref: Robbins 8/e p618-9) ...see text*

64. **Ans. (c) Myeloperoxidase**
(Ref: Robbins 8/e p602 Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues p79)
This is what we have knowledge of:
- Lymphoblast: PAS positive
- Myeloblast: Sudan black, myeloperoxidase and non-specific esterase

Please know that:

> WHO manual pg 69 writes that.. "MPO is specific for myeloid differentiation. Sudan Black B reactivity is similar to MPO in myeloblasts and monoblasts. The ***specificity of Sudan Black is less than MPO***."

65. **Ans. (b) May-Heggline anomaly**
(Ref: A Color Atlas and Instruction Manual of Peripheral Blood Cell Morphology pg 221)
Döhle bodies are basophilic leukocyte inclusions located in the peripheral cytoplasm of neutrophils. They are said to be remnants of the *rough endoplasmic reticulum*.
Conditions associated with Dohle bodies
- Burns
- Infections
- Physical trauma
- Neoplastic diseases
- Wissler's disease
- May-Hegglin anomaly (seen in neutrophil, monocyte, lymphocyte)
- Chédiak-Steinbrinck-Higashi's syndrome

66. **Ans (b) Myeloblast** *(Ref: Robbins 9th/612-3)*

67. **Ans (d) More than 5000 cells/microliter** *(Ref: Washington Manual 2013, table 11-4)*

68. **Ans: (a) Pre B cell** *(Ref: Robbins 9th/590)*
Most common subtype of A.L.L is L1 according to older classification and Pre B cell variety by the latest WHO classification. The recent WHO International panel on ALL recommends that the FAB classification be abandoned, since the morphological classification has no clinical or prognostic relevance. It instead advocates the use of the immunophenotypic classification.

69. **Ans. (d) Response to steroids** *(Ref: Robbins 9th/590-3)*
Response to steroids is the most consistent marker in the patients of ALL. For other factors, see text.

70. **Ans. (c) Burkitt's lymphoma** *(Ref: Robbins 9th/590)*
As per the old classification, L3 ALL had cells resembling Burkitt's lymphoma like cells morphologically as well in nature.

71. **Ans. (a) Preceding MDS** *(Ref: Robbins 9th/612)*

72. **Ans (b) M3** *(Ref: Robbins 9th/612)*

73. **Ans. (a) Hodgkin's Lymphoma, nodular sclerosis** *(Ref: Loachim's lymph node pathology/186)*
Direct quote. 'Progressive transformation of germinal centers (PTGC) is a benign reaction pattern in lymph nodes. It is most often associated with reactive *follicular hyperplasia*. It is also associated with nodu-

lar sclerosis and lymphocyte predominant Hodgkin's lymphoma'.

74. Ans. (a) Kimura's disease

(Ref: Loachim's lymph node pathology/190)

Kimura Disease is a chronic inflammatory disorder prevalent in Asians. It involves subcutaneous tissues and lymph nodes predominantly in the head and neck region and is characterized by angiolymphoid proliferation and eosinophilia.

Histopathology

- Lymphoid infiltrates with formation of follicles and germinal centers accompanied by plasma cells, mast cells and particularly large amount of eosinophils are present in subcutis.
- Lymph nodes are enlarged and show markedly hyperplastic follicles with reactive germinal centers and a well-defined peripheral mantle.
- Diffuse eosinophilia, eosinophilic abcesses and infiltration of germinal centres, sometimes resulting in folliculolysis, are part of the process.
- Polykaryocytes of the **Warthin Finkeldey type**, characterized by the overlapping, grape-like arrangement of nuclei, are common, often within the germinal centers.

75. Ans. (d) Aplastic anemia

(Ref: Harrison 17th/374, Robbins 9/e p653)

Massive splenomegaly is labeled when spleen extends greater than 8 cm below left costal margin and/or weighs more than 1000 g.

Diseases Associated with Massive Splenomegaly	
Chronic myelogenous leukemia	Gaucher's disease
Lymphomas	Chronic lymphocytic leukemia
Hairy cell leukemia	Sarcoidosis
Myelofibrosis with myeloid metaplasia	Autoimmune hemolytic anemia
Polycythemia vera	Diffuse splenic hemangiomatosis

76. Ans. (a) t (8:14) *(Ref: Robbins 8th/608, 9/e p597)*

77. Ans. (a) CD 45 RO

(Ref: Flow Cytometry and Immunohistochemistry for Hematologic Neoplasms, Lippincott Williams and Wilkins, Tsieh Sun 1st/133; Neoplastic Hematology Daniel Knowles 2nd/1342

Direct quote from Tsieh Sun ....."*myeloid sarcoma usually expresses CD45 but rare cases may demonstrate T cell markers, such as CD45RO, CD3 and CD7*". So, the answer of choice is CD45RO.

Salient features of Lab diagnosis of Granulocytic sarcoma

1. Screening panel for **CD45, CD19** and **CD20**.
2. **Standard flowcytometry** panel includes **CD13, 14, 15 , 33 and myeloperoxidase**
3. Immunohistochemistry panel may include chloroacetate esterase (Leder stain), lysozyme, CD15, CD43 and CD 68
4. **Lysozyme**^{Q} and **CD43**^{Q} are the **most sensitive markers**
5. Two new markers **CD99**^{Q} and **CD117**^{Q} can be added in equivocal cases.
6. Common cytogenetic abnormalities include **t(8;21), inv (16)** and **t(9;11)**^{Q}

Additionally, the percentage of these molecules can be derived from the data given in *Neoplastic Hematology....*

Immunohistochemistry Molecule	%
CD 45	90%
CD 43	50%
Lysozyme	75%
Leder stain (chloroacetate esterase)	>75%

No mention of staining with CD45RO is there, so, we prefer CD45 RO as the answer of choice.

78. Ans. (a) CD 23

(Ref: Robbins 7th/683; http://www.emedicine.com/med/topic1358.htm, Robbins 9/e p603) ...see text

Mantle cells lymphomas are usually CD23 negative. They are positive for CD5, CD20 and CD43.

79. Ans. (b) REAL Classification

(Ref: Robbins 7th/688; AJC cancer staging handbook)

In 1994, a group of hematopathologists, oncologists and molecular biologists came together (International Lymphoma Study Group) and introduced a new classification, called the 'Revised European- American Classification of Lymphoid Neoplasms (REAL).

WHO has reviewed and updated the REAL classification in 1999 resulting in inclusion of additional rare entities.

Non-Hodgkin's lymphoma (NHL) has been classification by many groups. Major classification systems are:

- Rappaport classification (Developed in 1966)
- Working formation classification
- REAL classification (Developed in 1994)
- WHO classification (modified REAL classification, 1999)

1. **Rappaport classification:** It is based on microscopic appearance of tumor cells.
   - Size: Lymphocytic or histiocytic
   - Growth pattern: Diffuse or nodular
2. **Working classification:** According to this system, NHL is divided according to prognostic criteria into:

Low grade	Intermediate grade	High grade
• Small lymphocytic NHL • Follicular small cleaved NHL • Follicular mixed small cleaved and large-cell NHL	• Follicular large cell NHL • Diffuse small cleaved NHL • Diffuse small cleaved NHL • Diffuse mixed small cleaved and large-cell NHL • Diffuse large-cell NHL	• Small non-cleaved NHL (Burkitt's) • Immunoblastic lymphoma • Lymphoblastic lymphoma

3. **Revised European-American classification of lymphoma (REAL) It includes:**
   - Precursor B-cell neoplasm
   - Peripheral B-cell neoplasm
   - Precursor T-cell neoplasm
   - Peripheral T-cell neoplasm
   - Hodgkin's lymphoma
4. **WHO classification:** It takes into account morphologic, clinical, immunological and genetic information. *For its details, see text.*

80. **Ans. (d) A diffuse proliferation of medium to large lymphoid cells with high mitotic rate**
(Ref: Robbins: 7th/673-674, 9th/p 593-594, several journals through internet)
- This is a case of **chronic lymphocytic leukemia (CLL)** as indicated by the characteristic clinical picture and immunophenotypic characteristics. (Typically, **CLL cells express CD5, CD19, CD23 and show absence of CD79B, CD22 and FMC7**)
- Histopathological examination in a case of typical CLL shows **diffuse effacement of lymphocyte architecture** by small to medium sized lymphocytes with clumped chromatin, indistinct or absent nucleoli and scanty cytoplasm.
- The round lymphocytes may give way focally to paler areas consisting of larger round cells (prolymphocytes). These paler areas are often referred to as **proliferation centers** and when present are **pathognomic for CLL/SLL**. They contain relatively large number of mitotically active cells.
- Follicular lymphoma is positive for CD10, CD79b and FMC7 but negative for CD25 and CD43.
- CLL and prolymphocytic leukemia are CD23 positive.

> Mantle cell lymphoma is also CD5 positive but here the cells are CD23 negative and CD 79b and FMC7 positive.

81. **Ans. (d) Inv (16) is often detected in the blasts and the eosinophils**
(Ref: Annals of Hematology: 2000 May: 79(5): 272-4)
This is a case of ALL with hypereosinophllic syndrome. Inv (16) is associated with AML and not ALL, and therefore represents the incorrect statement amongst the option. **About other options, the relevant points:**

> Eosinophils are not a part of this neoplasm differentiating it from eosinophilic leukemia.
> t(5;14) may be observed in about half of such patients. The symptoms may resolve after dug therapy.

For details, see the journal with the relevant article.

82. **Ans. (b) Results from an expansion of neoplastic T-lymphocytes**
(Ref: Harrison's 17th/697; Robbins 7th/683, 9/e p588)
Hairy cell leukemia is a type of *B-cell leukemia.* For details, see text.

83. **Ans. (b) CD 34 negative but surface Ig+**
(Ref: Robbins 9/e p597-598, 8th/608, 7th/677-678, Harrison 17th/, 696)
- **Burkitt's lymphoma** is a cancer characterized by the presence of hallmark translocation **t (8;14)**Q.
- The translocation results in the **increased expression of c-MYC**Q resulting in development of neoplasia.
- **Immunophenotyping** reveals the tumor cells expressing ***bcl-6 protein, surface Ig, CD19, CD20*** *and* ***CD10*** **(CALLA**Q.

84. **Ans. (d) CD 34 is associated with Diffuse large B Cell Lymphoma**
(Ref: Robbins 9/e p603 8th/605-608, 612-613, 7th/675-678, Wintrobe's 12th/2223)

	Burkitt's lymphoma	Follicular lymphoma	Mantle cell lymphoma
Hallmark translocation	t (8;14)	t (14;18)	t (11; 14)
Over expression of gene	bcl-6	bcl-2	bcl-1
Immunophenotyping	sIgM+, **CD5–**, CD10+, CD19+, CD20+, **CD23–**, CD45+	sIg, **CD5–**, CD10+, CD19+, bright CD20+, **CD23+/–**, CD38+, CD45+	sIgM+, sIgD+, **CD5+**, CD10–, CD19+, CD20+, **CD23–**, Cyclin D1+, FMC-7+

Though *Williams hematology* mentiones (Table 92.1) and even we normally read that the **Mantle cell lymphoma** is CD10- but **WHO manual** writes that '**mantle cell lymphoma may show expression of CD10 molecule rarely'.** This is also supported by Wintrobe's 12th/ pg 2223 where the table clearly mentions that Mantle cell lymphoma may be **CD10+/-**. So, option C may be assumed to be true (after all AIIMS questions can be nerve wrecking friends. This question has been altered to suit the easy goals in other MCQ books).
The answer of exclusion is therefore 'D' as CD 34 is the marker for hematopoetic stem cell. Diffuse large B cell lymphoma has the phenotype of ***sIgM+, sIgD+/–, CD5–/+, CD10–/+, CD19+, CD20+, CD45+, PAX5+.*** **The tumor cells** can be **BCL-6 positive** in 40% cases when associated with **t (3;14)** or **bcl-2 positive** in 20% with **t(14;18).**

85. **Ans. (b) B-cell**
(Ref: Harrison 17th/845, 847, Robbins 9/e p1313)
- 'Post-transplant Lymphoproliferative Disorders' (**PTLDs**) are lymphomas developing after solid organ transplantation e.g. kidney, liver, heart or lung transplants.
- PTLDs are almost always related to infection by the Epstein-Barr virus (EBV) which causes a cancerous

transformation of B-cells. In normal individuals immune cells can tackle the EBV infection, but in organ transplants, the high doses of drugs used suppress the immune system and the the chances of developing lymphomas increase.

> Difference between Post transplant lymphomas and non Hodgkin's lymphomas. PTLDS have the following:
> - **Extranodal involvement** (brain, lungs and the intestines)
> - Poorer prognosis

86. Ans. (d) In general follicular (nodular) NHL has worse prognosis compared to diffuse NHL

(Ref: Robbins 7th/674- 6, 667-8)

- Hodgkin's lymphoma is clinically and histologically distinct from the non-Hodgkin's lymphoma. **While non-Hodgkin lymphomas frequently occur at extranodal sites and spreads in an unpredictable fashion, Hodgkin's lymphoma arises in a single node or chain of nodes and spreads first to anatomically contiguous nodes.** Several ways of classifying Hodgkin's lymphoma exist **Rappaport, REAL classification and now WHO (modified REAL classification).**

> The prognosis of non Hodgkin's lymphoma varies markedly with various histological types of non Hodgkin's lymphoma, "In general, **lymphomas with a follicular histological pattern** are of **lower grade** (*longer survival*) than those of diffuse pattern".

87. Ans. (b) CD 23

(Ref: Harrison 17th/695, Robbins 7th/683, 9/e p602-603)

Mantle cell lymphomas are positive for CD43, CD20, BCl-1 Protein (Cyclin D1) and CD5.

88. Ans. (b) Follicular lymphoma *(Ref: Robbins 9/e p594)*

89. Ans. (a) Burkitt's lymphoma *(Ref: Robbins 9/e p597)*

90. Ans. (b) Mycosis fungoides

(Ref: Robbins 9/e p605, 8th/1184-1185; 7th/685)

91. Ans. (c) Prognosis is better than in diffuse type

(Ref: Robbins 9/e p594-595, 8th/619)

92. Ans. (a) B-cell lymphoma

(Ref: Robbins 9/e p603, 8th/613, 7th/826)

93. Ans. (b) Stomach *(Ref: Robbin 9th/ 773)*

Although extranodal lymphomas can arise in virtually any tissue, they do so most commonly in the GI tract, particularly the stomach.

94. Ans. (b) B cell *(Ref: Robbin 9/e p603)*

95. Ans. (b) Burkitt Lymphoma *(Ref: Robbin 9/e p597)*

"Burkitt lymphoma is believed to be the fastest growing human tumor"...direct line

96. Ans. (a) Follicular small cleaved lymphoma

(Ref: Robbins 8/e p605, 7/e p675)

This was based on the working classification of NHL:

Low grade	Intermediate grade	High grade
• Small lymphocytic NHL • Follicular small cleaved NHL • Follicular mixed small cleaved and large-cell NHL	• Follicular large cell NHL • Diffuse small cleaved NHL • Diffuse small cleaved NHL • Diffuse mixed small cleaved and large-cell NHL • Diffuse large-cell NHL	• Small non-cleaved NHL (Burkitt's) • Immunoblastic lymphoma • Lymphoblastic lymphoma

97. Ans. (c) Diffuse large B cell lymphoma

(Ref: Robbin 8/e p606)

"Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL"... (Ref: Robbind 8/e p606)

98. Ans. (a) B cell

(Ref: Robbin 8/e p1348, Eyelid, Conjunctival, and Orbital Tumors 2/e p746)

Direct quote... ***"Non Hodgkin Lymphoma of the B cell lineage is the most common type in the orbit"***..... Eyelid, Conjunctival, and Orbital Tumors

Also know: for a future question

> - *The most frequently encountered primary neoplasms of the orbit are vascular in origin like the* capillary hemangioma, the lymphangioma and the encapsulated cavernous hemangioma.
> - *MC intraocular tumour in children: Retinoblastoma*
> - *MC intraocular tumour in adults: choroidal malignant melanoma*

99. Ans. (a) B cell lymphoma

(Ref: Robbins 9/e p603, 8/e p613)

Marginal zone lymphoma is a **B cell**[Q] **tumour** has the presence of translocation **t(11;18)** [Q]. It is associated with ***H. pylori***[Q] infection. They have the following exceptional characteristics:

- Often arise within tissues involved by *chronic inflammatory disorders of autoimmune or infectious etiology*
- Remain *localized for prolonged periods, spreading systemically only late in their course*
- *May regress if the inciting agent (e.g., Helicobacter pylori) is eradicated*

100. Ans. (d) CD 5 +, CD 23 –

(Ref: Robbins 9/e p602-603, 8/e p612-3) ...see text

101. Ans. (d) Cutaneous lymphoma

(Ref: Robbins 9/e p605, 8/e p1184-1185, 7/e p1685)

> - *Mycosis fungoides* is a **T cell lymphoma** affecting **skin** which can evolve into generalized lymphoma.
> - *Histological hallmark*: **Sezary Lutzner cells**[Q] which are helper T cells forming band like aggregates in superficial dermis and have **cerebriform contour**[Q].
> - May invade epidermis as single cells and small clusters called as **Pautrier microabscesses**[Q].

102. Ans. (a) Anaplastic large cell lymphoma (ALK positive)
(Ref: Robbin 8/e p605)

- Anaplastic Large-Cell Lymphoma (ALK Positive) is an uncommon entity which is defined by the presence of rearrangements in the ALK gene on chromosome 2p23.
- This tumor is typically composed of large anaplastic cells, some containing horseshoe-shaped nuclei and voluminous cytoplasm (so-called *hallmark cells*).

103. Ans. (b) Africa.....*Indian exam asking global question*

104. Ans (c) Sezary cells *(Ref: Robbins 9/e 606)*

105. Ans (a) Mycosis fungoides *(Ref: Robbins 9th/ 1159)*
Mycosis fungoides is a lymphoma of **skin-homing CD4+ T helper cells** that presents in the skin.

106. Ans (d) Cerebriform *(Ref: Robbins 9/e 606)*

107. Ans. (a) CD 15 and CD 30
(Ref: Robbins 9/e p608, 7th/422-423)
In classical HL, CD15 and CD30 are the surface markers. In non classical HL, CD20 and BCL/6 are the markers.

108. Ans. (c) Absolute lymphocyte count < 600/µl
(Ref: Hodgkin's lymphoma: A Comprehensive Update on Diagnostics and Clinics By Andreas Engert/2010/104)
Seven adverse prognostic factors described for advanced Hodgkin's disease are

1. Male gender
2. Age > 45 years
3. Stage IV disease
4. Hemoglobin < 10.5 g/dl
5. Leukocytosis with WBC > 15,000/µl
6. A serum albumin level <4 g/dl
7. Lymphocytopenia with either Absolute lymphocyte count < 600/µl or lymphocyte being < 8% of WBCs

109. Ans. (d) Lymphocyte predominant Hodgkin's disease
(Ref: Robbins 7th/686, 9/e p609) ...see text

110. Ans. (d) Langerhans' cell.
(Ref: Robbins 9/e p 608-609, 7th/686, 688)
Langerhans' cells *are epidermal dendritic cells that take up and* process antigenic signals and communicate the information to lymphoid cells.

111. Ans. (d) Lymphocyte predominant
(Ref: Robbins 7th/688, 9/e p609)

112. Ans. (a) Myelodysplastic syndrome
(Ref: Robbins 9/e p614-615, 8th/625-626; 7th/695-696)

113. Ans. (a) Lymphocyte predominant
(Ref: Robbins 9/e p609, 7th/668, 686, 689) ...see text

114. Ans. (a) Lymphocyte dominant
(Ref: Robbins 9/e p609, 8th/619; 7th/689)

115. Ans. (b) Nodular sclerosis Hodgkin lymphoma
(Ref: Robbin 8/e p618-9)
Presence of binucleated acidophlic owl eye appearance with CD15 and CD 30 is suggestive of Reed Sternberg cell.

- **Lymphocyte depletion HL** occurs predominantly in the **elderly** and in **HIV+** individuals
- In **lymphocyte predominant HL**, the Reed Sternberg cells are ***positive for CD20 and BCL6***, and are usually ***negative for CD15 and CD30***.
- **Mixed-cellularity** HL is more common in *males*, in *elderly* with ***presence of constitutional symptoms.*** Involved lymph nodes are diffusely effaced by a heterogeneous cellular infiltrate, which includes T cells, eosinophils, plasma cells, and benign macrophages admixed with Reed-Sternberg cells

116. Ans. (c) Lymphocytic predominance
(Ref: Robbins 9/e p608-609, 8/e p618-9) ...see text

117. Ans (c) Nodular sclerosis...See earlier explanation
(Ref: Robbins 9/e p608)

118. Ans. (c) Essential thrombocythemia
(Ref: Robbins 8th/629, 9/e p620 Harrison 17th/374)
This. is a modified version of DPG2011 question. Please see the table for causes of Massive Splenomegaly given earlier.
In CML ... 'first symptom of CML is a dragging sensation in the abdomen caused by splenomegaly' Robbins 8th/627-8
Polycythemia vera Robbins 8th/629, 9/e p619.. spent phase of polycythemia has extensive extramedullary hematopoeisis principally in the spleen which enlarges greatly ''
Primary myelofibrosis page 631, 9/e p621... 'it comes to attention because of progressive anemia and splenomegaly'

119. Ans. (b) JAK 2 mutation
(Ref: Robbins 9/e p618, 8th/626-8, Wintrobe's hematology 12th/1991-2; Journal Blood 110:1092, 2007)
Polycythemia vera is the most common of the chronic myeloproliferative disorders. As discussed is text: JAK 2 mutation is a major criteria. However this mutation is not diagnostic of PV as it is also seen in essential thrombocytosis, chronic idiopathic myelofibrosis (CIMF) and atypical myeloproliferative disorders.

Other options, options "a" and "c" are minor criteria whereas Option 'd', remember friends that

- **MPL point mutation** is seen in 5-10% patients with **essential thrombocytosis** and **primary myelofibrosis**.

120. Ans. (d) Essential thrombocytopenia
(Ref: Robbins 7th/696, 9/e p616)
Essential thrombocytosis (and not Essential thrombocytopenia) is a myeloproliferative disorder.

121. Ans. (c) Chronic myeloid leukemia

(Ref: Robbins 8/e p628 , 9/e p618)

Leukocyte alkaline phosphatase (LAP) is found within the white blood cells. Revise the following condition s asked in the exam:

High LAP score	Low LAP score
• Leukemoid reaction	• Chronic myelogenous leukemia (CML)
• Polycythemia vera (PV)	• Paroxysmal nocturnal hemoglobinuria (PNH)
• Essential thrombocytosis (ET)	• Acute myelogenous leukaemia (AML).
• Primary myelofibrosis (PM)	• Sideroblastic anemia

122. Ans. (c) Hemolytic anemia

(Ref: Robbins 8/e p595, Blood 2/e p255, T. Singh 1/e p198)

Leukoerythroblastosis is a term used for "an anemia characterized by the presence in the peripheral blood of immature red cells and a few immature white cells of the myeloid series" that is erythroblasts and leukoblasts. The following are the causes of leukoerythroblastosis:

Causes of leukoerythroblastosis

Marrow invasion	**Tumors** (lymphoma, Hodgkin disease, leukemia, multiple myeloma, bony metastasis) **Infections** (sepsis, TB, osteomyelitis) **Miscellaneous** (osteopetrosis, histiocytosis, storage disease, vasculitis including rheumatoid arthritis)
Myeloproliferative disorders	Polycythemia vera Myelofibrosis CML Erythroleukemia Thrombocythemia Down syndrome
Hematological disease	Erythroblastosis fetalis Pernicious anemia Thalassemia major Severe hemolytic anemia
Hypoxia	Congestive heart failure Cyanotic congenital heart disease Respiratory disease

Please remember friends that severe hemolytic anemias may be associated with a similar picture but routinely, leukoerythroblastosis is not observed with hemolytic anemia.

123. Ans. (b) Leukemoid reaction.

(Ref: Robbins 8/e p595, 9/e p584, Hematology 3/e p402)

LAP is found in the membranes of secondary granules of neutrophils. Its activity is measured in **mature neutrophils and band cells only**Q.

Eosinophils do notQ *show* ***alkaline phosphatase activity*** and must not be mistaken with mature neutrophils with a score of zero. **Malaria** is characterized by **monocytosis**.

124. Ans. (c) 65%

(Ref: Textbook of Clinical Pediatrics 2/e p356)

Direct lines.... "Polycythemia is defined as venous hematocrit **exceeding 65%**".

Just be cautious not to confuse polycythemia with the polycythemia vera.

125. Ans. (a) CD 1a *(Ref: Robbins 9/e p622, 8/e p631)*

- In Langerhans cell histiocytosis, *the presence of Birbeck granules in the cytoplasm is characteristic.*
- In this condition, **Birbeck granules**Q are pentalaminar tubules, often with a dilated terminal end producing a **tennis racket–like appearance**Q, which contain the protein langerin.
- In addition, the tumor cells also typically express **HLA-DR, S-100, and CD1a**Q.

126. Ans. (d) Tennis racket *(Ref: Robbins 8/e p631, 9/e p622)*

127. Ans. (c) Acute myeloblastic leukemia

(Ref: Robbins 9th/ 616)

Myeloproliferative disorders are charcterised by an increased production of one or more types of blood cells. The common pathogenic feature is the presence of mutated, constitutively activated tyrosine kinases or other acquired mutations resulting in growth factor independence. The examples include:

- Chronic myelogenous leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia
- Systemic Mastocytosis
- Stem cell leukemia

128. Ans. (b) 5q *(Ref: Robbins 9/e p615)*

129. Ans. (b) Hyperviscosity

(Ref: Robbins 8th/610-1, 9/e p600, Harrison 18th/938-940, Wintrobes hematology 12th/2374-8)

According to Harrison,

- **Bone pain** is seen in 70% patients
- **Infections** is the next common (>75% have serious infection at some time in their course)
- **Normocytic normochromic anemia** is seen in 80% patients

130. Ans. (c) Hypercalcemia

(Ref: Harrison 17th/702, 9/e p600)

131. Ans. (d) IgM *(Ref: Robbins 8th/65, 9/e p601)*

Lymphoplasmacytoid lymphoma (or **Waldenstrom's macroglobulinemia)** is a B cell neoplasm presenting in 6th or 7th decade of life having features similar to CLL/SLL and multiple myeloma (MM). Like MM, there is presence of a 'M' or monoclonal spike (caused due to IgM whereas in MM, it is caused by IgG).

Also Remember

- Deletion involving chromosome 6q is the commonest abnormality in Waldenstrom's macroglobulinemia.

132. Ans. (b) A diagnosis of plasma cell leukemia.....

(Ref: Wintrobe's haematology 11th/2620, 2593)

Plasma cell leukemia by definition is characterized by more than 20% plasma cells in the peripheral blood.

The patient in question has 14% plasma blasts in the peripheral blood and thus does not fit into category of plasma cell leukemia.

133. Ans. (c) Plasmacytoma on biopsy

(Ref: T. Singh 1st/210-211, Robbins 9/e p600-601)

The commonly used diagnostic criteria of multiple myeloma are:

MULTIPLE MYELOMA

Major criteria	
1.	Plasmacytoma on tissue biopsy
2.	Bone marrow plasmacytosis with > 30% plasma cells
3.	Monoclonal globulin spike on serum electrophoresis (> 3.5g/dL for IgG, > 2 g/dL for IgA) or on urine (> 1g/24 h of Bence-Jones protein)
Minor criteria	
1.	Bone marrow plasmacytosis 10 to 30% plasma cells
2.	Monoclonal globulin spike less than the level defined above
3.	Lytic bone lesions
4.	Reduced normal immunoglobulin (<50% of normal); IgM <0.05 g/dL, IgA < 0.1g/dL, IgG < 0.6 g/dL

The diagnosis of multiple myeloma requires a minimum of two major criteria or one major criteria + one minor criteria, or three minor criteria.

134. Ans. (a) CD 1a *(Ref: Robbins 9/e p622, 7th/701, 702)*

135. Ans. (b) Sheets of atypical plasma cells

(Ref: Robbins 9/e p599, 7th/679)

- Old patient along with *lytic circumscribed punched out* X-ray appearance suggests **multiple myeloma**
- **Multiple myeloma** most often presents as multifocal destructive bone tumors composed of **plasma cells** throughout the skeletal system.

136. Ans. (a) Cryoglobulinemia; (b) Multiple myeloma; (d) Lymphoma; (e) Macroglobulinemia

(Ref: William's Haemotology 6/1268)

Hyperviscosity is seen in

- Multiple myeloma
- Waldenstrom's macroglobulinemia
- Cryoglobulinemia
- Myeloproliferative disorders

MGUS (Monoclonal Gammopathy of uncertain significance): Here M Protein can be identified in the Serum of 1% of healthy individual >50 years. age and 3% in older than 70 years of it is the most common form of monoclonal gammopathy. In MGUS less than 3g/dL of monoclonal protein is present in serum and there is no Bence Jones proteinuria.

Hyperviscosity is defined on the basis of the relative viscosity of serum as compared with water. *Normal relative viscosity of serum is 1.8*

137. Ans. (b) Waldenstrom's macroglobulinemia; (c) Multiple myeloma. *(Ref: William's Hematology 6th-1268)*

138. Ans. (b) CD 1+ ; (c) Birbeck's granules are pathognomonic; (d) Proliferation of antigen presenting cells; (e) Resembles Dendritic cells; *(Ref: Robbins 9/e p622)*

139. Ans. (c) Wire loop lesions

(Ref: Harrison 17th/573, Robbins 7th/232 9/e p223)

Wire loop lesions are characteristic of **SLE** and are ***not seen in multiple myeloma.***

140. Ans. (b) IL-6 *(Ref: Robbins 7th/679, 9/e p599)*

141. Ans. (d) Systemic lupus erythematosus

(Ref: Robbins 7th/678-679)

Plasma cell dyscrasias are characterized by proliferation of B-cell clone which synthesizes and secretes a single homogenous immunoglobulin or its fragments. This entity includes **Multiple myeloma, Waldenstrom's macroglobulinemia, Heavy chain diseases, Primary or immunocyte associated amyloidosis and Monoclonal Gammopathy of Undetermined Significance (MGUS).**

142. Ans. (d) No lymphadenopathy *(Ref: Robbins 9/e p622)*

143. Ans. (c) IgG *(Ref: Robbins 9/e p600)*

144. Ans. (a) Langerhans cell *(Ref: Robbins 9/e p622)*

145. Ans. (b) Positive ANA *(Robbins 9th/598-601)*

Increased serum levels if immunoglobulins, plasmacytosis and M spike on electrophoresis are all seen in multiple myeloma. For details, see text of chapter 8.

146. Ans. (b) Langherhans *(Ref: Robbins 9/e p622, 8/e p631-2)*

LCH has the following presentations:

- ***Multifocal multisystem Langerhans cell histiocytosis (Letterer-Siwe disease)***
  - Occursmost frequently **before 2 years** of age
  - Dominant clinical feature is the development of **cutaneous lesions** resembling a seborrheic eruption over the front and back of the trunk and on the scalp.
  - Presence of concurrent hepatosplenomegaly, lymphadenopathy, pulmonary lesions, and (eventually) destructive osteolytic bone lesions.

- ***Unifocal and multifocal unisystem Langerhans cell histiocytosis (eosinophilic granuloma)***
  - Characterized by proliferations of Langerhans cells admixed with variable numbers of eosinophils, lymphocytes, plasma cells, and neutrophils.
  - Typically arises within the ***medullary cavities of bones***, most commonly the calvarium, ribs, and femur. Less commonly, unisystem lesions of identical histology arise in the skin, lungs, or stomach.
  - Unifocal lesions most commonly affect the skeletal system in older children or adults. Unifocal disease is indolent and may heal spontaneously or be cured by local excision or irradiation.
  - Multifocal unisystem disease usually affects young children, who present with multiple erosive bony masses that sometimes expand into adjacent soft tissue.

Hand-Schuller-Christian triad: calvarial bone defects + diabetes insipidus + exophthalmos

Pulmonary Langerhans cell histiocytosis
- Seen in *adult smokers*
- *Regress spontaneously upon cessation of smoking.*

147. Ans. (a) Multiple myeloma
(Ref: Harsh Mohan 6th/383, Robbins 9th/)

Increased levels of microglobulin are seen in the urine and serum of patients with multiple myeloma.
Harrison 18th/941.... *Serum β 2 -microglobulin is the single most powerful predictor of survival and can substitute for staging.*

148. Ans. (a) Multiple Myeloma *(Ref: Robbins 9/e p599)*

In multiple myeloma, cytologic variants stem from the dysregulated synthesis and secretion of immunoglobulins, which often leads to intracellular accumulation of intact or partially degraded protein. Such variants include:

- **Flame cells:** with fiery red cytoplasm,
- **Mott cells:** with multiple grapelike cytoplasmic droplets

The globular inclusions are referred to as **Russell bodies** (if cytoplasmic) or **Dutcher bodies** (if nuclear).

149. Ans. (a) Birbecks granules *(Ref: Robbins 9th/622)*

Langerhans cell histiocytosis is characterized by the presence of "Birbeck granules" in the cytoplasm

150. Ans. (c) 1500 *(Ref: Harrison 18th/135-e-7)*

Idiopathic hypereosinophilia syndrome is characterized by eosinophilia (>1500 cells/mm^3) persisting for at least 6 months for which no underlying cause is found.

ANNEXURE

Distinguishing Features In Various Types of Plasma Cell Disorders:

1. Plasma cell leukemia

- More than 20% plasma cells in the peripheral blood
- Absolute plasma cell count of more than 2 X 10^9/L

2. IgD Myeloma

- Presence of Monoclonal IgD in the serum usually indicates IgD myeloma
- No evident M– spike on serum protein electrophoresis
- Higher incidence of renal insufficiency, amyloidosis and proteinuria than IgG/IgA myeloma.
- Higher incidence of extramedullary involvement and inferior survival rates.

3. Monoclonal gammopathy of undetermined significance (MGUS)

- Serum monoclonal protein <3g/dl
- Clonal bone marrow plasma cells < 10%
- Absence of end organ damage such as hypercalcemia, renal failure, anemia and bone lesions (**CRAB**)
- No lytic bone lesions
- No evidence of other B-cell proliferative lesion

4. Smoldering multiple myeloma (Asymptomatic multiple myeloma)

Both criteria must be met

- Serum monoclonal protein (≥ 3 g/dl) and/or 10-60% clonal bone marrow plasma cells or both
- Absence of myeloma defining events or amyloidosis

5. Multiple myeloma

Diagnostic criteria for plasma cell myeloma

Clonal bone marrow plasma cell percentage ≥**10%** or biopsy-proven plasmacytoma and ≥1 of the following ***myeloma-defining events***:

a. Evidence of End-organ damage (CRAB)
- **H**yper**C**alcaemia: serum calcium > 11 mg/dL
- **R**enal insufficiency: Creatinine clearance < 40 ml/minute or senum creatinine > 2 mg/dL
- **A**naemia: (Hb < 10g/dl or >2g/dl lower than normal)
- **B**one lesions: ≥1 osteolytic lesion on skeletal radiography, CT, or PET/CT

b. >1 of the following biomarkers of malignancy:
- Clonal bone marrow plasma cell percentage > 60%
- An involved-to-uninvolved serum free light chain ratio >100
- >1 focal lesion on MRI

Characteristic Immunophenotypes of Major Subtypes of Lymphoma

Lymphoma	Immunophenotype
Follicular	$CD20^+$, $CD3^-$, $CD10^+$, $CD5^-$
Small lymphocytic	$CD20^+$, $CD3^-$, $CD10^-$, $CD5^+$, $CD23^+$
Marginal zone/MALT	$CD20^+$, $CD3^-$, $CD10^-$, $CD5^-$, $CD23^-$
Mantle cell	$CD20^+$, $CD3^-$, $CD10^-$, $CD5^+$, $CD23^-$, $CD43^+$, $PRADI^+$
Diffuse large B-cell	$CD20^+$, $CD3^-$, $CD5^-$, $CD45^+$
Burkitt	$CD20^+$, $CD3^-$, $CD10^+$, $CD5^-$; Tdt^-
Lymphoblastic	$CD20^-$, $CD3^+$, Tdt^+
Anaplastic large cell	$CD20^-$, $CD3^+$, $CD30^+$, $CD15^-$, EMA^+, ALK^+
Peripheral T-cell	$CD20^-$, $CD3^+$
Hodgkin	$CD30^+$, $CD15^+$

CHAPTER 9

Platelets and Blood Transfusion

Golden Points

- Bleeding time is the test for platelet defect.
- **Hess test** is done for **capillary fragility**.
- Prothrombin time is used to assess extrinsic pathway whereas aPTT is used to assess intrinsic pathway. These should be measured **within two hours** once blood is drawn.
- Bernard-soulier syndrome is due to congenital defect in platelet **adhesion** due to deficiency/dysfunction of **Gp Ib-IX**. In this disease, platelet aggregation is normal with collagen/ADP but abnormal with ristocetin.
- Glanzmann thrombasthenia is due to congenital defect in **platelet aggregation** due to deficiency/ dysfunction of **Gp IIb-IIIa.** It presents as bleeding from umbilical stump in newborn. In this disease, the platelet aggregation is normal with ristocetin but abnormal with collagen/ADP/ thrombin.
- **Small sized platelets** in peripheral smear are characteristic of **Wiskot-Aldrich syndrome**.
- **Aplastic anemia** causes **amegakaryocytic t**hrombocytopenia.
- Immune thrombocytopenia is caused by autoantibodies (**IgG**) against platelet glycoproteins IIb-IIIa or Ib-IX.
- Triad of **hemolytic uremic syndrome** (HUS): *Microangiopathic hemolytic anemia, renal failure and thrombocytopenia.*
- Pentad of **thrombotic thrombocytopenic purpura (TTP)**: Triad of HUS plus fever and neurological symptoms.
- Blood banking using certain additives for the blood to be transfused later. Shelf life of blood with **CPD-A** is **5 weeks** (35 days).
- **Platelets** are stored at room temperature **around 20–24°C**. So, they have maximal chances of transmission of infections.
- Cryoprecipitate is used in deficiency of factors I (Hypofibrinogenemia), VIII (Hemophilia A), von Willebrand factor (vW disease).
- Disease transmitted *by all components* of blood is **malaria.**

PLATELETS

Platelets are enucleated cells in the circulation released from the megakaryocyte, likely under the influence of flow in the capillary sinuses. The normal blood platelet count is 1.5- 4.5 lakhs/mm^3. The production of the platelets is regulated by the hormone thrombopoietin produced in the liver.

The platelet synthesis is also specifically increased by interleukin 6. The average life span of the platelets is 7–10 days.

Key Point

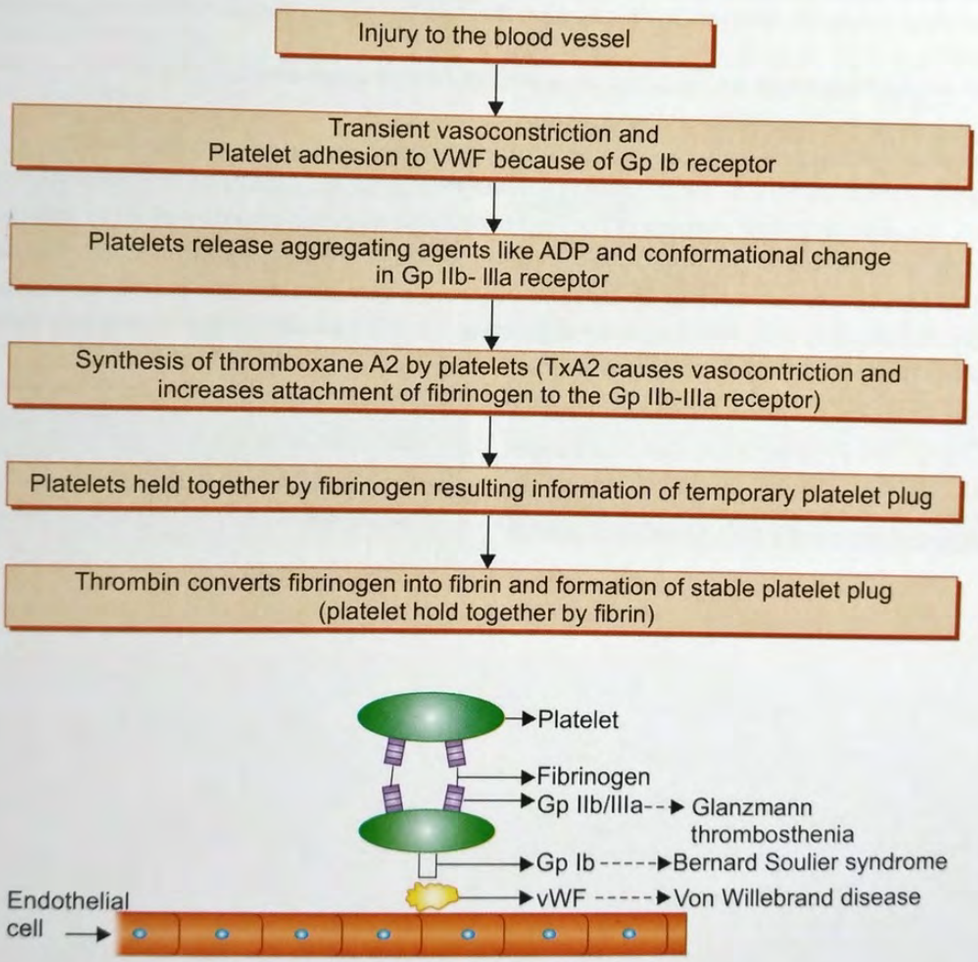
- A defect in the **glycoprotein Ib** factor results in defective platelet adhesion known as **Bernard-Soulier syndrome**
- A deficiency of **Gp IIb-IIIa** lead to **Glanzmann thrombasthenia**, a disorder having defective platelet aggregation.

Recent Exam Questions

- **B***ig platelets* are seen in **B***ernard Soulier syndrome.*
- Small platelets are seen in Wiskott Aldrich syndrome.

Mnemonic

Glanzmann is a defect in platelet aggregation (both have 'g' in them).
Bernard Soulier syndrome is a defect in platelet adhesion (both have'd' in them).



Bleeding time represents the time taken for a standardized skin puncture to stop bleeding and it gives an in vivo assessment of platelet response to limited vascular injury. The value varies from 2 to 9 minutes. It is abnormal when there is a defect in platelet numbers or function. Currently, quantitative measures of platelet function are being introduced by using an electronic particle counter.

Key Point

- **Thrombocytopenia** is defined as a platelet count of **1 lakh cells/µL or less** though **spontaneous bleeding** is seen usually when the count falls **below 20000 cells/µL**.
- Normal bleeding time is 2-9 minutes.

Thrombocytopenia is characterized by spontaneous bleeding a prolonged bleeding time and a normal PT and PTT.

Platelet disorders can be of the following two types:

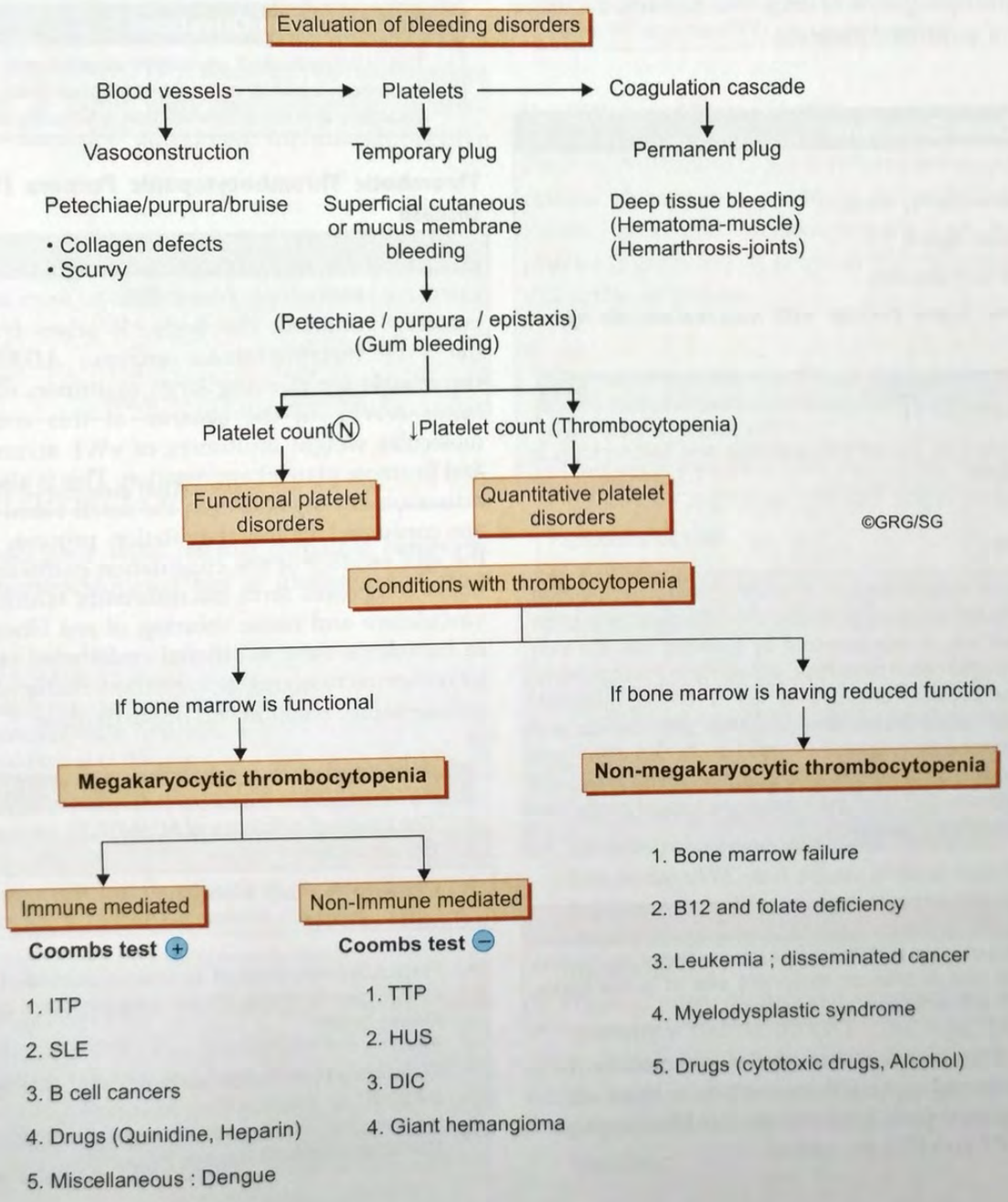
1. **Functional platelet disorders:** The platelet **count is normal** but there is a ***qualitatitve defect*** in the platelets
2. **Quantitative platelet disorders:** The platelet count is reduced but there is no qualitative defect in the platelets

Classification of functional platelet disorders	
Disorders of adhesion	
Inherited	**Acquired**
Bernard-Soulier syndrome	Uremia
von Willebrand disease	Acquired vWD

Contd...

Contd...

Classification of functional platelet disorders	
Disorders of aggregation	
Inherited	**Acquired**
Glanzmann thrombasthenia	FDP inhibition
Afibrinogenemia	Dysproteinemias
	Drugs-Ticlopidine, GpIIb/IIIa inhibitors
Disorders of granule release	
Inherited	**Acquired**
Oculocutaneous albinism	Cardiopulmonary bypass
Chediak-Higashi syndrome	Myeloproliferative disease
Isolated dense granule deficiency	Drugs- NSAIDs
Gray platelet syndrome (combined α and β granule deficiency)	



Immune Thrombocytopenic Purpura (ITP)

ITP can be either primary (idiopathic) or secondary (SLE, AIDS, viral infections and drug induced). The primary ITP can be dependent on the duration of the disease, acute (less than 6 months) or chronic (> 6 months). The platelet destruction in both of them results from the formation of antiplatelet autoantibodies (type II hypersensitivity reaction).

Pathogenesis

Chronic ITP is caused by the formation of autoantibodies mostly of the **IgG** class against platelet membrane glycoproteins, most often ***IIb-IIIa*** or ***Ib-IX***. The opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system. The spleen is the major site of removal of sensitized platelets.

Recent Exam Questions

Chronic ITP

- **Type II** hypersensitivity reaction.
- Female-to-male ratio is 3:1.
- Mucosal and skin bleeding.
- Bone marrow: ***hyper cellular with megakaryocytic hyperplasia.***
- P/S: megathrombocytes.
- ***↑ BT, normal PT/aPTT.***
- Treatment: steroids, i.v. immunoglobulins and splenectomy in refractory cases.

Clinical features

Chronic ITP occurs most commonly in **adult women** younger than age 40 years. The female-to-male ratio is 3:1. This disorder is often insidious in onset and is characterized by bleeding into the skin (*pinpoint hemorrhages* called petechiae, especially in the dependent areas where the capillary pressure is higher or ecchymoses), mucosal surfaces (nose bleed, post brushing gum bleeds and hematuria), menorrhagia (menstrual bleeding in females) and intracranial bleeds. *Splenomegaly and lymphadenopathy are uncommon in primary ITP, and their presence should make one consider other possible diagnoses.*

Concept

Splenectomy is beneficial in ITP because it is the site of destruction of the platelets and is also an important site of autoantibody synthesis which are reduced after its removal.

Findings: The blood smear shows abnormally large platelets (**megathrombocytes**), Bone marrow is hypercellular and shows megakaryocytic hyperplasia. The bleeding time is prolonged, but PT and PTT are normal.

Acute Immune Thrombocytopenic Purpura

It is similar to chronic ITP (caused by anti platelet antibodies) but is differentiated from the same by the following:

- Seen in **children**
- **Less** duration (2-6 weeks)
- Occurs with **equal frequency** in both sexes
- **Abrupt onset** of thrombocytopenia
- Preceded by a **viral illness** and is
- **Self-limiting** (resolving spontaneously within 6 months). Steroids may be required in few cases only.

The diagnosis of Idiopathic Thrombocytopenic Purpura should be made only after exclusion of other known causes of thrombocytopenia.

Recent Exam Questions

- The combination of hemolytic anemia with fragmented RBCs, thrombocytopenia, normal coagulation tests, fever, neurological disorders and renal dysfunction is virtually pathognomic of TTP.

Thrombotic Thrombocytopenic Purpura (TTP)/Moschcowitz Disease

It is a rare disorder of the blood-coagulation system, causing extensive microscopic blood clots to form in the small blood vessels throughout the body. It arises from deficiency of the vWF metalloprotease enzyme ***ADAMTS13*** which is responsible for cleaving large multimers of von Willebrand factor (vWF). In the absence of this enzyme, very high molecular weight multimers of vWF accumulate in plasma and promote platelet aggregation. This is also associated with activation of coagulation in the small blood vessels. Platelets are consumed in the coagulation process, and bind fibrin, the end product of the coagulation pathway. These platelet-fibrin complexes form microthrombi which circulate in the vasculature and cause shearing of red blood cells, resulting in hemolysis. Any additional endothelial cell injury further increases microaggregate formation. Reduced blood flow and cellular injury result in end organ damage.

Recent Exam Questions

- The inherited deficiency of ADAMTS13, known as the Upshaw-Schulman syndrome.

Classically, the following five features ("**pentad**") are indicative of TTP:

- Fluctuating neurological symptoms, such as bizarre behavior, altered mental status, stroke or headaches
- Kidney failure
- Fever
- Thrombocytopenia (low platelet count), leading to bruising or purpura
- Microangiopathic hemolytic anemia (anemia, jaundice and a characteristic blood film see Figure 11)

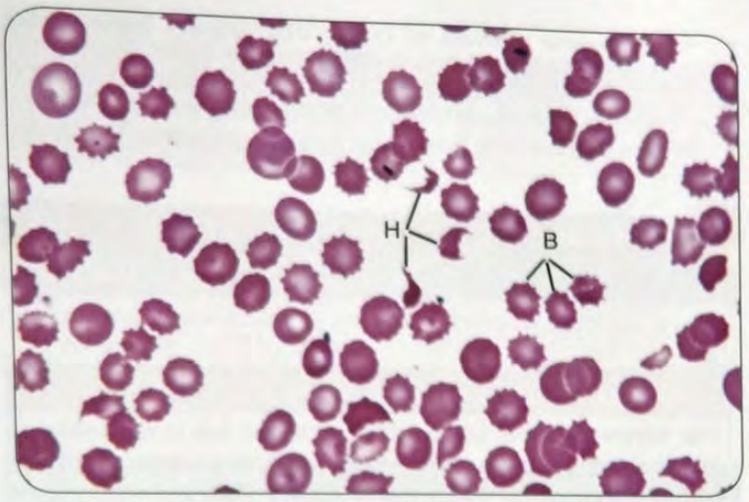


Fig. 1: Microangiopathic hemolytic anemia showing (H: Helmet Cells; B: Burr Cells)

If coagulation tests indicate a major consumption of procoagulants, the diagnosis of TTP is doubtful. The management of these patients is done with plasmapheresis (plasma exchange) and sometimes additional immunosuppressive therapy.

Mnemonic

	TTP	HUS
ADAMT 13	↓	Normal
CNS involvement	+	Not affected
Renal involvement	+	+++
Age	Adult	Children

Hemolytic Uremic Syndrome (HUS)

HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished from TTP by:

- Normal ADAMTS13 levels
- Absence of neurological symptoms
- Dominance of acute renal failure
- Childhood onset of disease

Concept

In HUS, microthrombi mainly contain fibrin *whereas in TTP these are composed of platelet aggregates, fibrin and VWF.*

It can be of the following types:

1. **Epidemic or typical HUS:** It is associated with infectious gastroenteritis caused by *E. coli* strain O157: H7. This bacterium releases a Shiga-like toxin damaging endothelial cells followed by platelet activation and aggregation. The patients presents with bloody diarrhea followed by HUS after few days.
2. **Non-epidemic or atypical HUS:** It is associated with mutations in the gene encoding complement regulatory proteins like ***factor H, factor I or membrane cofactor protein CD46***. These proteins normally prevent excessive activation of alternate pathway of the complement system. So, their deficiency is associated leads to uncontrolled complement activation after minor endothelial injury, resulting in thrombosis. The patients have a relapsing remitting course.

HUS can also be seen due to other factors (e.g., certain drugs, radiation therapy) that damage endothelial cells.

Key Point

Activation of the coagulation cascade is not of primary importance in HUS and TTP and so, the laboratory tests of coagulation (such as the PT and the PTT) are usually **normal**.

Von Willebrand Disease (vWD)

The von-Willebrand factor (vWF) is a heterogenous multimeric plasma glycoprotein produced by endothelial cells (*Weibel Palade bodies*) and megakaryocytes (can be shown inside platelet α-granules). It helps in platelet adhesion and factor VIII carrier in plasma.

Recent Exam Questions

Synthesis of factor VIII

- Sinusoidal endothelial cells and Kupffer cells in the liver.
- Glomerular and tubular epithelial cells in the kidney.

Functions of vWF

- Facilitates platelet adhesion.
- Plasma carrier for the factor VIII

The disease can have the following variants:

1. Type 1 and type 3 von Willebrand disease are associated with a *reduced quantity of circulating vWF*. Type 1 (commonest variant) is an autosomal dominant disorder and is mild clinically. Type 3 (an autosomal recessive disorder) is associated with extremely low levels of functional vWF, and severe clinical manifestations. Type 1 disease is associated with missense mutations whereas Type 3 disease is associated with deletions or frameshift mutations
2. Type 2 von Willebrand disease is characterized by qualitative defects in vWF. The type 2A variant is the most common subtype of type 2 vWD. It is inherited as an autosomal dominant disorder and is associated with missense mutations. It is associated with mild to moderate bleeding.

Key Point

Ristocetin is an antibiotic which increase the interaction between VWF and GpIb receptor on platelets.

Clinical features in von Willebrand disease are due to

Platelet Adhesion defects

Deficiency of vWF results in defect in the adhesion of platelets to collagen preventing the formation of haemostatic plug. It leads to mucus and cutaneous bleeding in the form of epistaxis, menorrhagia and GI bleeding.

Coagulation defect

There is reduced half life of factor VIII leading to its deficiency resulting in hemorrhages and intramuscular hematoma.

LABORATORY FINDINGS

1. A ***prolonged bleeding time*** in the presence of a ***normal platelet count***.
2. The defective platelet adhesion also results in a ***positive tourniquet test*** (***Hess test***).
3. In deficiency of vWF, ristocetin induced platelet aggregation does not take place. So, ***ristocetin induced aggregation is defective*** and is diagnostic of this disease. However, platelet aggregation with ADP, collagen and thrombin is normal.
4. Though the synthesis of factor VIII remains normal but half life of VIII in plasma decreases due to reduced vWF (carrier) levels. This leads to secondary VIIIC deficiency in plasma. So, intrinsic pathway of coagulation is affected and thus, ***aPTT is increased*** in these patients.

Recent Exams Question

Von Willebrand Disease

- MC inherited disorder of bleeding in humans.
- MC variant: **type 1 vWD.**
- **Normal** platelet count.
- ↑ **BT,** ↑ **aPTT,** and ***normal PT.***
- **Positive Hess**/ tourniquet test.
- **Abnormal** *ristocetin test.*
- Management: **desmopressin** and **cryoprecipitate**.

Hemophilia A (Factor VIII Deficiency)

Hemophilia A is the most common *hereditary disease associated with serious bleeding*. This X linked disorder is caused by a reduction in the amount or activity of factor VIII which is a cofactor for factor IX in the activation of factor X in the coagulation cascade. The disease can have the following variants:

1. Mild disease – levels of factor VIII activity between 6% and 50% of normal
2. Moderate disease - levels between 2% and 5% of normal
3. Severe disease- the levels less than 1% of normal activity.

Key Point

Petechiae are characteristically **absent** in **hemophilia**.

Concept

The severe variant of hemophilia A is caused due to an inversion of the intron 22 sequence involving the X chromosome that completely abolishes the synthesis of factor VIII.

Clinical features: it includes easy bruising and massive hemorrhage after trauma or operative procedures. The disease is evident early in life when there is bleeding after circumcision or when the child begins to walk or crawl. The hemorrhages occur frequently in the joints (*hemarthroses*) and recurrent bleeding may lead to progressive deformities. Acute hemarthroses is painful and to avoid pain, the patient may adopt a fixed position leading to muscle contractures. It mainly affect knees, elbows, ankles, shoulders, and hips ***Petechiae are characteristically absent***. Muscle hematoma can also be seen leading to a compartment syndrome. Fascial hemorrhages can result in the formation of blood filled cysts with calcification and proliferation of fibroblasts giving the appearance of a tumor **(pseudotumor syndrome).** Self limiting episodes of hematuria in the absence of genitourinary pathology are frequent in the patients.

LABORATORY FINDINGS

1. Patients with hemophilia A typically have a ***normal bleeding time, platelet count***, and ***PT***
2. There is a ***prolongation of aPTT*** due to an abnormality of the intrinsic coagulation pathway.
3. Factor VIII-specific assays are required for diagnosis.

Key Point

Hemophilia A patients are managed with **desmopressin, cryoprecipitate** and **recombinant factor VIII**. disease.

Hemophilia B (Christmas disease, Factor IX Deficiency)

The factor IX deficiency produces a disorder similar to hemophilia A. It is inherited as an X-linked recessive trait and the PTT is prolonged and the PT is normal, as is the bleeding time. The diagnosis is done only by assay of the factor IX levels.

Key Point

Fresh frozen plasma or recombi-nant **factor IX** is useful for the management of **Chrismas disease**.

Recent Exam Questions

- Aquired factor inhibitors are most commonly produced against **factor VIII.**

Recent Exam Topic

FACTOR INHIBITORS

A relatively rare cause of prolonged aPTT is presence of antibodies against coagulation plasma proteins called inhibitors. It can be seen due to the following reasons:

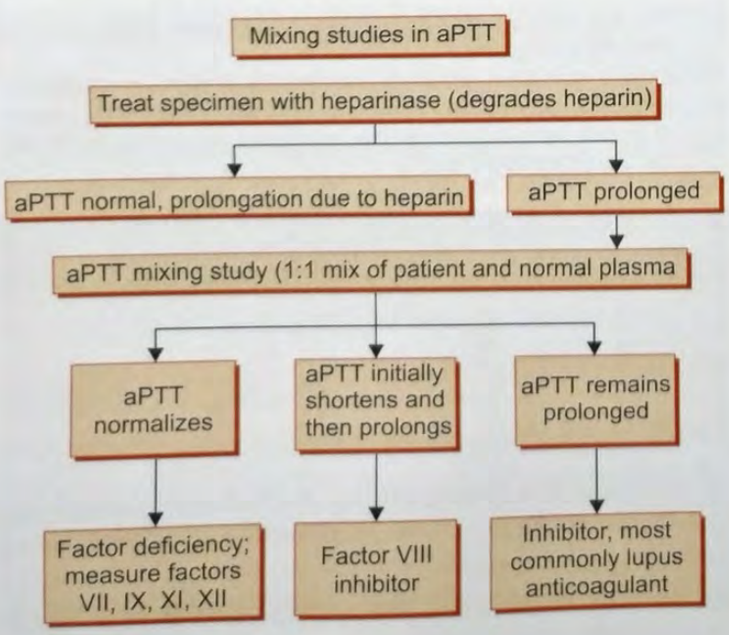
- ***Hemophilia A and B*** patients receiving clotting factors *to control their bleeding episodes*
- ***Pregnancy***
- Autoimmune diseases
- Malignancies (lymphoma, prostate cancer)
- Dermatologic conditions

Clinical manifestations include bleeding episodes in soft tissues, skin, GIT and genitourinary tract.

The diagnosis is made with a **prolonged aPTT** with normal PT and TT which is **not corrected** with **mixing the test plasma with normal pooled plasma** for 2hrs at 37°C.

Treatment is done with **high dose i.v. immunoglobulins** and **anti CD20 monoclonal antibody**.

To differentiate between different causes of isolated prolongation of aPTT, the following flowchart is useful.



HIGH YIELDS TOPICS FOR EXAMS

1. Blood Grouping

The red blood cells have many antigens expressed on their surface which is the basis of multiple subtypes of blood groups (ABO, Rh, Kell, Duffy, P antigen). In transfusion medicine, the most important blood groupings that are practiced are the ABO and the Rh grouping.

ABO is most important for the following reasons:

- When the ABO antigen is not expressed on the red cell, individuals always have ABO antibodies in their plasma
- The ABO antibodies formed are frequently mixtures of immunoglobulins (IgM >>>IgG) antibodies, both having thermal reactivity at 37°C and both capable of activating complement.

Genetics of ABO Antigens

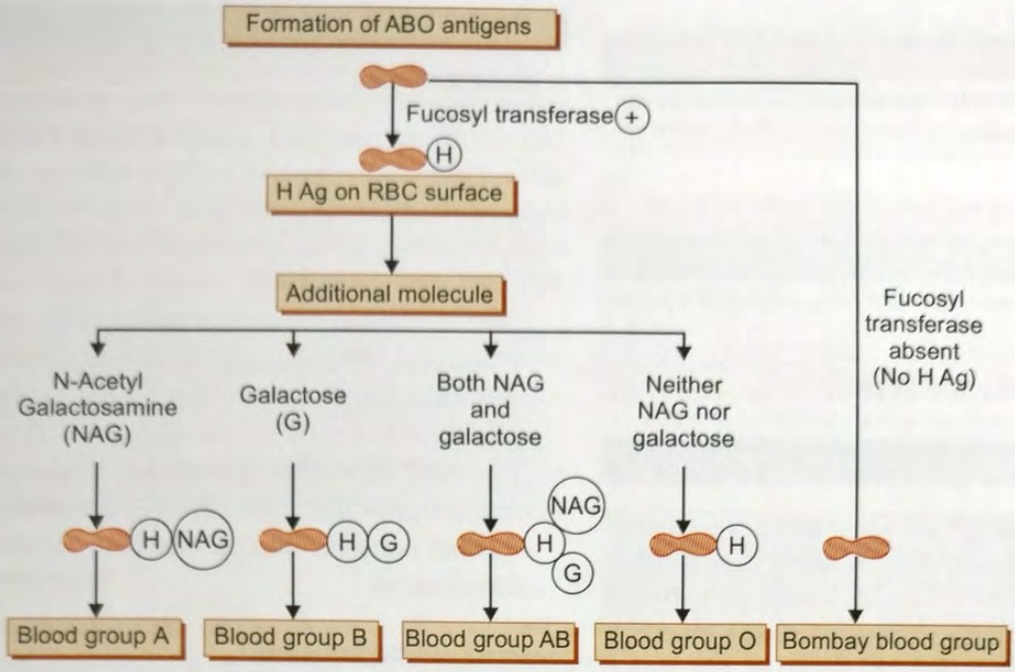
- The genes determining the A and B phenotypes are found on **chromosome 9p** and are expressed in a **Mendelian codominant manner**.
- **H gene** is present on **chromosome 19** and is inherited in an **autosomal recessive** manner.
- The Rh antigen genes are present on **chromosome 1**. These antigens are **proteins**. The antigens which may represent the Rhesus antigen are C, **D** (**most important**) and E. The D antigen is a potent alloantigen which is present in 85% individuals.

Formation of ABO Antigens

ABO antigens are **glycoproteins**. On the red blood cell surface, H substance is formed by the addition of fucose to the glycolipid or glycoprotein backbone. The subsequent addition of *N*-acetyl galactosamine (NAG) creates the A antigen, whereas the addition of galactose (Gal) produces the B antigen. People lacking both transferases are phenotypically type 'O' whereas those who inherit both transferases are type 'AB'.

Bombay Blood Group

Discovered by **Dr YM Bhende**, it is a very rare blood group. If an **individual lacks the H gene** coding for the fucosyl transferase, he cannot form H substance. These individuals are homozygous for the silent h allele (hh) and have **Bombay phenotype (Oh).** These people have **anti H, anti A and anti B antibodies in their serum**. They are detected by reverse blood grouping (explained below). *The only blood which is safe for transfusion in these individuals is Bombay blood group.*



Detection of blood grouping is done by forward and reverse grouping

- Forward grouping is done with anti A or anti B antisera. This detects the presence of antigens on the RBCs of the individual.
- Reverse grouping is done with serum taken from the person and known cells of A/B/O subtype.

Forward grouping			Reverse grouping		
Blood group	Anti A	Anti B	A cell	B cell	O cell
O	-	-	+	+	-
A	+	-	-	+	-
B	-	+	+	-	-
AB	+	+	-	-	-
Bombay blood	-	-	+	+	+

Secretors and Nonsecretors

Some people secrete the A, B and H antigens in the body fluids (such as plasma, gastric juice, saliva, sweat, tears, semen, milk, etc. with **an exception** being the **cerebrospinal fluid**). This ability is dependent on presence of a dominant secretor gene (Se). About 80% of individuals are secretors. *Both secretors and non-secretors express ABO antigens on red cells.*

Blood group antigens and disease association

1. Gastric cancer with blood group A
2. *Peptic ulcer is more often in group O individuals.*
3. von Willebrand factor *(vWF) antigen level varies among individuals with different ABO blood groups. Individuals with blood group O have the lowest vWF antigen level, followed by group A, then group B, and, last, group AB.*
4. *P. vivax infection* is increased by *presence of Duffy antigen.*

2. Blood Transfusion

A. Donor selection

- The donor should be **between 18–65 years** of age.
- Weight should **>45 kg**
- Blood pressure should be controlled
- No skin disease at the phlebotomy site
- Time interval between 2 blood donations: **3 months**
- Whole blood donation to be deferred for **3 days** after platelet/ plasmaphersis
- Donor should have **eaten** something in the **last 3 hours**

B. Routine transfusion

- The first choice is the donor blood of the same ABO group as that of the recipient.
- If blood of the same ABO group may occasionally be not available and if blood transfusion is likely to be potentially lifesaving, blood of an alternate but compatible group may be transfused as per the table mentioned below.

Recipient blood group	Donor blood group	
	First choice	Alternative
A	A	O
B	B	O
AB	AB	A, B, O (in this order)
O	O	Nil

- To reduce the risk of haemolysis in a case of non-identical but compatible ABO transfusion, ***packed red cells instead of whole blood*** should be transfused (i.e. most of the plasma which contains anti-A and/or anti-B should be removed).

C. Emergency transfusion

- For patients in **hemorrhagic shock**, it is necessary to transfuse blood immediately. The risk of transfusing **group O "uncrossmatched" red cells** is extremely low and is certainly much lower than the risk of the patient's death if blood transfusion is delayed.

↓

- For **AB group recipients**, if red cells of group **AB** are not available, **group A donor blood is preferred** over other alternatives since anti-B in group A is weaker than anti-A in group B.

↓

- In the Rh system, **individuals with Rh-negative blood group should be transfused only with Rh-negative blood,** especially Rh-negative females of childbearing age and young girls (to prevent Rh immunisation and future haemolytic disease of newborn).

↓

- **In an emergency, Rh-positive blood may be transfused to older females and males of unknown blood group** (if Rh-negative blood is not available). Persons with Rh-positive group should be transfused with Rh-positive blood preferably.

↓

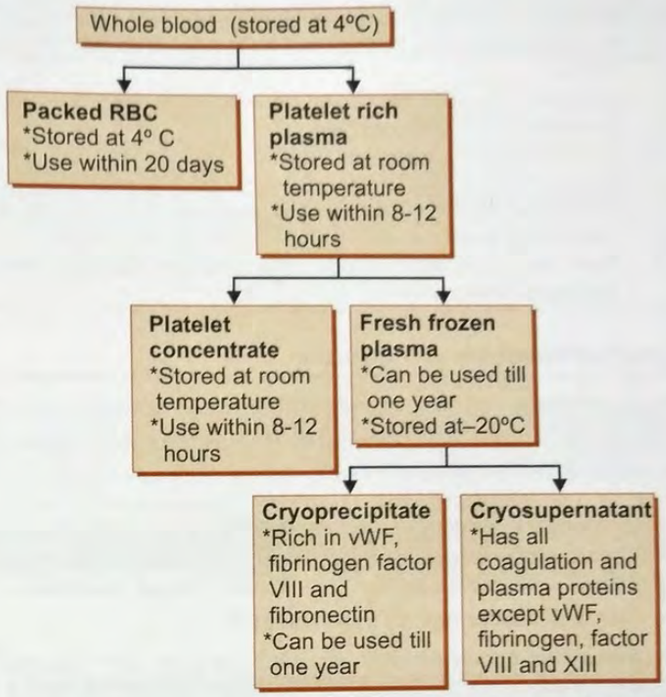
- If the patient's blood group cannot be determined, then he should be transfused with ***O group red cells which are Rh-negative*** with colloids/crystalloids.

Salient Features about Blood Transfusion

- Blood should be transfused through a sterile, disposable administration set incorporating a standard filter (**170 µm pore size**[Q]**).** This filter retains small clots or cellular aggregates but permits passage of single cells and microaggregates.
- The usual needle size is **18-or 19-gauge**[Q]**.**
- The solution in the blood bag usually contains citrate phosphate dextrose adenine (CPDA)-1 (**49**[Q] **ml** for *350 ml of blood* and *63 ml for 450 ml of blood*). Function of each of the constituents is mentioned below:

i. **Citrate**: *Anticoagulation* by binding of calcium in plasma
ii. **Phosphate**: Acts as **a buffer**[Q] to minimize the effects of decreasing pH in blood
iii. **Dextrose**: Maintenance of *red cell membrane and metabolism*
iv. **Adenine**: Generation of ATP (***energy source***).

Components of Blood



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1. Time frame for transfusion of different components of blood

Blood component	Initiation of transfusion	Completion of transfusion
Whole blood	Within **30 minutes**[Q]	Within **4 hours**[Q]
Cryoprecipitate / FFP	*As early as possible*	Within **20 minutes**[Q]

2. Shelf life and storage of different blood components

Blood component	Storage temperature	Shelf life	Indications
Whole blood	2-6°C	**42 days**	• Acute blood loss • Exchange transfusion
Packed red cells	2-6°C	42 days	• Severe anemia • Exchange transfusion
Platelets	**20-24°C**	5 days *(platelet agitator)*	• Thrombocytopenia
Cryoprecipitate	-24°C	1 year	• Hemophilia A • vW disease • Factor 13 deficiency • Fibrinogen deficiency
Fresh frozen plasma	-24°C	1 year	• DIC • Hemophilia B • Liver disease

Recent Exam Questions

- **Saline washed red blood cells** have a shelf life of **only 24 hours**.
- All blood components should be ABO compatible with the **exception of cryoprecipitate.**
- 1 unit of blood transfusion increases Hb level by 1g/dl and hematocrit by 3%
- The *most common cause* ***of a haemolytic transfusion reaction*** is **clerical error**[Q]
- Red cell substitutes include: Haemoglobin solutions and **Perfluorocarbons**[Q].

Complications of Blood Transfusion

Blood products are often responsible for saving lives of individuals but may be associated with the development of the complications. These include:

Recent Exam Questions

- **FNHTR** is the **most common** complication of **blood transfusion**.
- **TRALI** is most commonly seen with **FFP**.
- **Infectious complications** are most common with **platelet preparations**.
- The ***most common cause of a haemolytic transfusion reaction*** is **clerical error**[Q]
- Red cell substitutes include: Haemoglobin solutions and **Perfluorocarbons**[Q].

- *Febrile Non Hemolytic Transfusion Reaction (FNHTR):* this is the ***most common complication*** leading to fever and chills, **within 6 hours of a transfusion** of red cells or platelets. It is caused by the release of inflammatory chemicals from the donor leukocytes. It is treated symptomatically with **antipyretics**.
- *Allergic Reactions:* Severe, potentially fatal allergic reactions may occur when ***blood products containing certain antigens are given to previously sensitized*** recipients. These occur more commonly in patients with IgA deficiency. *Urticarial allergic reactions* may occur more commonly due to an allergen in the donated blood product. The condition is managed with antihistaminic drugs.
- *Hemolytic Reactions:* Acute hemolytic reactions are usually caused by **preformed IgM** antibodies **against donor red cells** that fix complement. They occur due to improper labeling in the blood bank **(ABO incompatibility)**. Clinical features include fever with chills, flank pain, intravascular hemolysis, and hemoglobinuria. It is diagnosed with a **positive direct Coombs test**. It may be fatal in rare cases.
- *Delayed hemolytic reactions:* they are caused by **antibodies that recognize red cell antigens that the recipient was sensitized to previously,** for example, through a prior blood transfusion. These are typically caused by *IgG antibodies to foreign protein antigens* and are associated with a positive direct Coombs test.
- *Transfusion-Related Acute Lung Injury* **(TRALI)**

Recent Exam Questions

Salient features of TRALI

- TRALI develops **within 6 hours** of transfusion.
- It is a cause of **non cardiogenic** pulmonary edema
- **Fresh frozen plasma** is the commonest blood product to cause it.
- Mostly seen after *sepsis* and *cardiac surgeries*
- Clinically, it is ***characterised by acute onset of respiratory distress, associated with oxygen desaturation (hypoxemia) and bilateral lung infiltrates.***

- Reason for TRALI is presence of antibodies in the donor's plasma against recipient's **HLA II antigens located on the neutrophils** which leads to neutrophilic aggregation in the pulmonary vasculature and endothelial damage there. This leads to the clinical symptoms in the patient.
- *Infectious Complications:* They are **more common with platelet** preparations. These can be prevented by Donor screening.

Recent Exam Questions

Massive blood transfusion

- **Adults:** it is defined as replacement of ***>1 blood volume in 24 hours*** or **>50%** of blood volume in **3 hours** (adult blood volume is approximately 70 mL/kg).
- **Children:** transfusion of ***>50% total blood volume in 3 hour*** or transfusion >100% total blood volume in 24 hours.
- MC cause of bleeding: **dilutional thromobocytopenia**.
- MC abnormality of acid base imbalance: **metabolic alkalosis**.

Anticoagulants

Agents	Trisodium EDTA	3.2% Trisodium Citrate	Heparin	Potassium Oxalate
Mechanism of action	Remove calcium	Remove calcium	Activation of antithrombin III	Binds calcium
Preferred Uses	• **Blood cell counts and morphology**[Q]	• **Platelet studies**[Q] • **Coagulation studies**[Q] • **ESR**[Q]	• **Osmotic fragility test**[Q] • **WBC Functional or immunophenotyping**[Q] • **Red cell testing**[Q] • **Arterial blood gas analysis**	• **Anticoagulant (not preferred because labile factors are unstable in oxalate)**
Advantages	Complete anticoagulation with **minimal morphologic and physical effects on the cell**	Preserves the labile coagulation factors	Does **not** affect shape and size	Cheap Easily available
Disadvantages			• Not suitable for blood counts because it cannot inhibit platelet and leucocyte clumping • ***Bluish discoloration*** to blood smear slide on applying Wright Giemsa stain.	• **Distorts cell morphology** • Shrinks red cell size, so, **not used for hematocrit estimation**

- **Anticoagulated blood** may be **stored at 4°C**[Q] for **24 hour period** without significantly altering cell counts or cellular morphology but hematologic analysis should be done as soon as possible.
- **Any anticoagulant**[Q] can be used for collecting blood for **Flow cytometry**[Q].

Recent Exam Question

- Blood: Anticoagulant (trisodium citrate) ratio is **9:1**.
- **Lithium heparin** is used for estimation of **serum electrolytes**

Multiple Choice Questions

PLATLETS AND BLEEDING DISORDERS

1. **A newborn baby presented with profuse bleeding from the umbilical stump after birth. Rest of the examination and PT, APTT are within normal limits. Most likely diagnosis is which of the following?**
   (a) Factor X deficiency
   (b) Glanzmann's thrombasthenia
   (c) von Willebrand disease
   (d) Bernard Soulier disease

2. **A 25 years old asymptomatic pregnant female underwent a pre-op coagulation test. Her bleeding time is 3minutes, PT is 15/14sec, a PTT is 45/35 sec, platelet count is 2.5 lac/mm^3 and factor VIII levels were 60IU/dL. What is her most likely diagnosis?** *(AIIMS Nov 2011)*
   (a) Factor IX deficiency
   (b) Lupus anticoagulant
   (c) Factor VIII inhibitors
   (d) VWD – Type III

3. **True about prothrombin time to:** *(AIIMS Nov 2011)*
   (a) Immediate refrigeration to preserve factor viability
   (b) Platelet-rich plasma is essential
   (c) Done within 2 hours
   (d) Activated with kaolin

4. **A 22 year old female having a family history of autoimmune disease presents with the complaints of recurrent joint pains after pregnancy. She has now developed petechial hemorrhages. She is most likely to have which of the following disorders?** *(AIIMS Nov 2011)*
   (a) Megakaryocytic thrombocytopenia
   (b) Amegakaryocytic thrombocytopenia
   (c) Platelet function defects/Functional platelet defect
   (d) Acquired Factor VIII inhibitors

5. **Patient with bleeding due to platelet function defects has which of the following features?** *(AI 2011)*
   (a) Normal platelet count and normal bleeding time
   (b) Normal platelet count and increased bleeding time
   (c) Decreased platelet count and increased bleeding time
   (d) Normal platelet count and decreased bleeding time

6. **A 9-year-old boy presents with elevation in both PT and aPTT. What is the diagnosis?** *(AIIMS Nov. 2010)*
   (a) Defect in extrinsic pathway
   (b) Defect in intrinsic pathway
   (c) Platelet function defect
   (d) Defect in common pathway

7. **All are true about thrombotic thrombocytopenic purpura except?** *(AIIMS Nov 2008)*
   (a) Microangiopathic hemolytic anemia
   (b) Thrombocytopenia
   (c) Normal complement level
   (d) Grossly abnormal coagulation tests

8. **D.I.C. is seen in:** *(AIIMS May 2007)*
   (a) Acute promyelocytic leukemia
   (b) Acute myelomonocytic leukemia
   (c) CMC
   (d) Autoimmune hemolytic anemia

9. **All of the following can cause megakaryocytic thrombocytopenia, except:** *(AIIMS Nov 2004)*
   (a) Idiopathic thrombocytopenia purpura
   (b) Systemic lupus erythematosus
   (c) Aplastic anemia
   (d) Disseminated intravascular coagulation (DIC)

10. **A patient with cirrhosis of liver has the following coagulation parameters, Platelet count 2,00,000, Prothrombin time 25s/12s, Activated partial throm-boplastin time 60s/35s, thrombin time 15s/15s. In this patient:**
    (a) D-dimer will be normal *(AIIMS May 2004)*
    (b) Fibrinogen will be < 100 mg
    (c) ATIII will be high
    (d) Protein C will be elevated

11. **The presence of small sized platelets on the peripheral smear is characteristic of:** *(AIIMS Nov 2003)*
    (a) Idiopathic thrombocytopenia purpura (ITP)
    (b) Bernard Soulier syndrome
    (c) Disseminated intravascular coagulation
    (d) Wiskott Aldrich syndrome

12. **Platelet aggregation *in vivo* is mediated by:**
    (a) Serotonin *(PGI Dec 2003)*
    (b) Ig mediators.
    (c) Interaction among the leukocytes
    (d) Interaction among the platelets
    (e) Macromolecules.

13. **Conditions associated with incoagulable state:**
    (a) Abruption placentae *(PGI Dec 2004)*
    (b) Acute promyelocytic leukemia
    (c) Severe falciparum malaria
    (d) Snake envenomation
    (e) Heparin overdose

14. **In DIC, which is/are seen:** *(PGI June 2005)*
    (a) Normal aPTT
    (b) Increased PT
    (c) Increased factor VIII
    (d) Decreased fibrinogen
    (e) Decreased platelets

15. Causes for DIC are: *(PGI Dec 2005)*
(a) Anaerobic sepsis (b) Malignancy
(c) Lymphoma (d) Leukemia
(e) Massive blood transfusion

16. Platelet function defect is seen in: *(PGI June 03)*
(a) Glanzmann syndrome.
(b) Bernard Soulier syndrome
(c) Wiskott Aldrich syndrome
(d) Von-Willebrand disease
(e) Weber Christian disease

17. VWF factor deficiency causes: *(Delhi PG 2008)*
(a) ↓ Platelet aggregation
(b) ↓ Factor VIII in plasma
(c) Defective platelet adhesion
(d) All of the above

18. Thrombospondin is: *(Delhi PG 2008)*
(a) Coagulation protein
(b) Coagulation promoting protein
(c) Contractile protein
(d) Angiogenesis inhibitory protein

19. Which is must for prothrombins time (PT)?
(a) Thromboplastin *(Delhi PG 2007)*
(b) Prothrombin
(c) Fibrin
(d) Fibrinogen

20. Thrombocytosis is seen in: *(Delhi PG 2005)*
(a) Myelofibrosis
(b) SLE
(c) Azidothymidine therapy
(d) Myelodysplastic syndrome

21. All of the following are true about Willebrand factor except: *(Delhi PG-2005)*
(a) Synthesized by hepatocytes
(b) Its deficiency can cause factor 8 defect also
(c) Its deficiency may cause problem with platelet adhesion
(d) It serves as carrier for the factor eight

22. All of the following clotting factors are completely synthesized from liver except: *(UP 2002)*
(a) II
(b) V
(c) VII
(d) VIII

MOST RECENT QUESTIONS

23. Cryoprecipitate contain all except:
(a) Fibrinogen
(b) Factor VIII
(c) von Willebrand factor
(d) Antithrombin

24. Bleeding time is abnormal in:
(a) Hemophilia
(b) Christmas disease
(c) von Willebrand disease
(d) Vitamin K-deficiency

25. The chromosomal translocation involving bcl-2 in B-cell lymphoma is:
(a) t (8: 14) (b) t (8: 12)
(c) t (14: 18) (d) t (14: 22)

26. Agranulocytosis means:
(a) Decrease in neutrophil count
(b) Decrease in platelet count
(c) Increase in RBC count
(d) Decrease in RBC count

27. Thrombocytopenia syndrome is caused by decrease in platelet counts below: *(Bihar 2004)*
(a) 50,000/cmm (b) 1,00,000/cmm
(c) 1.2 lac/cmm (d) 20, 000/cmm

28. Glycoprotein IIb-IIa complex is deficient in
(a) Bernard Soulier syndrome
(b) Glanzmann disease
(c) Von willebrand disease
(d) Gray platelet syndrome

29. All the following statements are correct about treatment in chronic immune thrombocytopenic purpura except:
(a) Most of the patients respond to immunosuppressive doses of glucocorticoids
(b) Relapse is rare
(c) Splenectomy is the treatment of choice for relapse
(d) Minority have refractory forms of ITP and difficult to treat

30. Splenectomy is useful in which of the following?
(a) Chronic ITP
(b) Sickle cell anemia
(c) Tuberculosis
(d) Good pasture syndrome

31. Glanzmann disease is characterised by which of the following?
(a) Congenital defect of RBCs
(b) Defect of neutrophils
(c) Congenital defect of platelets
(d) Clotting factor deficiency

32. All of the following are true about DIC except:
(a) Platelet aggregation
(b) Fibrin deposition in microcirculation
(c) Decreased fibrin degradation products
(d) Release of tissue factor

33. All are true regarding thrombotic thrombocytopenic purpura except:
(a) Normal ADAMTS levels
(b) Microangiopathic hemolytic anemia
(c) Thrombocytopenia
(d) Thrombosis

34. **Pancreatic insufficiency and cyclic neutropenia is a part of which syndrome:**
(a) Young syndrome
(b) Colts syndrome
(c) Shwachman syndrome
(d) Roots syndrome

35. **Best blood product to be given in a patient of multiple clotting factor deficiency with active bleeding:**
(a) Fresh frozen plasma
(b) Whole blood
(c) Packed RBCs
(d) Cryoprecipitate

36. **Which of the following is false about Transfusion-Related Acute Lung Injury?**
(a) Develops within 24 hours
(b) Mostly seen after sepsis and cardiac surgeries
(c) It's a cause of non cardiogenic pulmonary edema
(d) Plasma is more likely to cause it than whole blood

37. **Cyclin D1/Ig H gene is associated with?**
(a) Diffuse large B-cell lymphoma
(b) Hairy cell leukemia
(c) Follicular lymphoma
(d) Mantle cell lymphoma

38. **Ristocetin test in von Willebrand disease shows?**
(a) Increased agglutination
(b) Decreased agglutination
(c) Normal agglutination
(d) No agglutination

39. **Glanzmann's thrombasthenia is characterized by defective**
(a) Gp IB/IIIA
(b) Gp IB/IX
(c) Gp IIB/IIIA
(d) Gp IIB/IX

40. **Shelf life of platelets is?**
(a) 24 hours
(b) 5 days
(c) 9 days
(d) 3 days

41. **Mega platelets are seen in which of the following disease?**
(a) Glanzmann thrombasthenia
(b) Von Willebrand disease
(c) Wiskot-Aldrich Syndrome (WAS)
(d) Bernard-Soulier syndrome

42. **Hemolytic uremic syndrome is associated with which of the following:**
(a) Most commonly caused by verocytogenic E.coli
(b) Causes mild to severe coombs positive hemolytic anemia
(c) Recurrences are rare
(d) Transient thrombocytopenia

BLOOD GROUPING, BLOOD TRANSFUSION, ANTI COAGULANTS

43. **Which of the following regarding Bombay blood group is false?** *(AIIMS May 2012)*
(a) Lack of H, A and B antigen on RBCs
(b) Lack of H, A and B substance in saliva
(c) Lack of antigens of several blood group systems
(d) H, A and B antibody will always be present in serum

44. **Which of the following is the genotype of a person with blood group A?** *(AI 2012)*
(a) BO (b) AO
(c) AB (d) OO

45. **Secondary hemochromatosis is associated with all except:** *(AI 2012)*
(a) Thalassemia
(b) Sideroblastic anemia
(c) Multiple drug transfusions
(d) Paroxysmal nocturnal hemoglobinuria

46. **The anticoagulant of choice for anticoagulation testing:**
(a) Heparin *(AIIMS Nov 2011)*
(b) EDTA
(c) Sodium oxalate
(d) 3.2% trisodium citrate

47. **You are working in a PHC and have to send a sample for blood glucose estimation. Which of the following anticoagulant will you use for sending your sample?**
(a) EDTA *(AIIMS Nov 2011)*
(b) Heparin
(c) Potassium oxalate + sodium fluoride
(d) Tri Sodium citrate

48. **A newborn with ABO incompatibility, the characteristic feature on peripheral smear is the presence of:**
(a) Microspherocytes *(AIIMS Nov. 2010)*
(b) Fragmented RBC
(c) Polychromasia
(d) Elliptocytosis

49. **Most common blood transfusion reaction is:**
(a) Febrile non-hemolytic transfusion reaction
(b) Hemolysis *(AI 2008)*
(c) Transmission of infections
(d) Electrolyte imbalance

50. **Rh antigen is a/an:** *(AI 2008)*
(a) Antibody (b) Mucopolysaccharide
(c) Protein (d) Fatty acid

51. **A 40 years old male had undergone splenectomy 20 years ago. Peripheral blood smear examination would show the presence of:** *(AI 2003)*
(a) Dohle bodies
(b) Hypersegmented neutrophils
(c) Spherocytes
(d) Howell-Jolly bodies

52. Which of the following complications is likely to result after several units of blood have been transferred? *(AI 2001)*
(a) Metabolic alkalosis
(b) Metabolic acidosis
(c) Respiratory alkalosis
(d) Respiratory acidosis

53. ABO incompatibility not seen with: *(AIIMS Nov 2009)*
(a) Fresh frozen plasma
(b) Platelet rich plasma
(c) Single donor platelets
(d) Cryoprecipitate

54. A 55 years old male accident victim in casualty urgently needs blood. The blood bank is unable to determine his ABO group, as his red cell group and plasma group do not match. Emergency transfusion of the patient should be with: *(AIIMS Nov 2002)*
(a) RBC corresponding to his red cell group and colloids/crystalloid
(b) Whole blood corresponding to his plasma group
(c) O positive RBC and colloids/crystalloid
(d) AB negative whole blood

55. Although more than 400 blood groups have been identified, the ABO blood system re-mains the most important in clinical medicine because: *(AIIMS Nov 2002)*
(a) It was the first blood group system to be discovered
(b) It has four different blood group A, B, AB, O (H)
(c) ABO (H) antigens are present in most body tissues and fluids
(d) ABO (H) antibodies are invariably present in plasma when persons RBC lack the corresponding antigen

56. Which of the following is seen in peripheral smear of a patient who has underwent splenectomy: *(PGI Dec 2001)*
(a) Howell-Jolly bodies
(b) Eosinophilia
(c) Macrocytosis
(d) Thrombocytopenia
(e) Neutrophilia

57. Blood component products are all except: *(PGI Dec 2005)*
(a) Whole blood
(b) Platelets
(c) Fresh frozen plasma
(d) Packed red blood cells
(e) Leukocyte reduced RBC

MOST RECENT QUESTIONS

58. The anticoagulant of choice for performing coagulation studies is:
(a) EDTA
(b) Heparin
(c) Trisodium citrate
(d) Double oxalate

59. Howell Jolly bodies are seen in:
(a) Liver disease
(b) Postsplenectomy
(c) Hemolysis
(d) DIC

60. Spur cell anemia is caused by:
(a) Chronic liver disease
(b) Acute blood loss
(c) Chronic blood loss
(d) None

61. Hypersplenism is characterized by all except:
(a) Leukemoid reaction
(b) Thrombocytopenia
(c) Splenomegaly
(d) Responds to splenectomy

62. The antigen lacking in Rh negative person is:
(a) C
(b) D
(c) d
(d) E

63. Platelets growth factor are synthesized by:
(a) Glial cells
(b) Endothelium
(c) Fibroblasts
(d) All of the above

64. Hemophilia B is due to deficiency of:
(a) Factor VIII (b) Factor VII
(c) Factor IX (d) Factor X

65. All are true about polycythemia vera except:
(a) Increased LAP score
(b) Increased erythropoietin level
(c) Splenomegaly
(d) May cause Budd-Chiari syndrome

66. Elevated ESR is seen in following conditions except:
(a) Polymyositis rheumatica
(b) Multiple myeloma
(c) Temporal arteritis
(d) Polycythemia rubra

67. The major hemoglobin present in an adult is:
(a) HbA_2 (b) HbA_1
(c) HbA_{1c} (d) HbA_{1b}

68. Patient with hemophilia A have bleeding disorder because of:
(a) Lack of platelet aggregation
(b) Lack of reaction accelerator during activation of factor X in coagulation cascade
(c) Neutralization of antithrombin III
(d) Release of Thromboxane A2

69. Stored plasma is deficient in:
(a) Factors 7 and 8 (b) Factors 5 and 7
(c) Factors 5 and 8 (d) Factors 5, 7 and 8

70. All cause pseudohyperkalemia, except:
(a) Thrombocytopenia
(b) Leucocytosis
(c) Clenching of fists
(d) Hemolysis

71. True about hemophilia is:
(a) If the male is affected, it will transmit to male
(b) Normal PT
(c) Low PT
(d) Low aPTT

72. True about von Willebrand factor are all except:
(a) Component of factor VIII
(b) Synthesized by spleen
(c) Facilitate the adhesion of platelets
(d) Leads to increased APTT

73. Bence Jones protein in urine are due to the presence of:
(a) Light chain of monoclonal immunoglobulins
(b) Heavy chain of monoclonal immunoglobulins
(c) Light chain of polyclonal immunoglobulins
(d) Heavy chain of polyclonal immunoglobulins

74. "Starry Sky" pattern is seen in all of these except:
(a) Burkitt's lymphoma
(b) Large B cell lymphoma
(c) Small cleaved cell lymphoma
(d) Lymphoblast lymphoma

75. Hemophilia is associated with:
(a) X chromosome (b) Y Chromosome
(c) Chromosome 3 (d) Chromosome 16

76. Blood group antigens are:
(a) Carried by sex chromosomes
(b) Attached to plasma proteins
(c) Attached to hemoglobin molecule
(d) Sometimes found in saliva

77. A 7-year-old girl presents with bleeding in joints. She has prolonged aPTT, normal PT and platelet counts. What could be the deficiency?
(a) Factor IX (b) Factor VIII
(c) Factor VII (d) von Willebrand Factor

78. Carbohydrate present in blood group substance is:
(a) Fucose (b) Deoxyribose
(c) Ribulose (d) Ribose

79. Hemophilia A is characterized by:
(a) Prolonged PTT
(b) Prolonged PT
(c) Low platelet count
(d) Abnormal BT

80. RBCs are stored at what temperature: *(AIIMS May 2016)*
(a) 2–6 °C (b) –2 to–4 °C
(c) 37 °C (d) 20–25°C

81. RBC should be transfused with a needle having which of the following size? *(AIIMS May 2016)*
(a) With a 16–18 G needle
(b) With a 18–20 G needle
(c) With a 20–22 G needle
(d) With a 22–24 G needle

82. Blood group antigens chemically are made up of ?
(a) Carbohydrate (b) Glycoprotein
(c) Phospholipids (d) Polysaccharide

83. Routine Rh typing includes testing?
(a) A antigen (b) B antigen
(c) C antigen (d) D antigen

84. Which of the following is true about h/h blood group?
(a) Lacks H-antigen
(b) Lacks A-antigen
(c) Lacks H-antigen
(d) All of the above

85. Which of the following is the chromosomal location of Rh antigen?
(a) 1 (b) 9
(c) 19 (d) 13

86. Anticoagulant used in coagulation study is?
(a) Calcium citrate
(b) EDTA
(c) Sodium bromide
(d) Trisodium citrate

87. Anticoagulant used for chelating calcium-
(a) EDTA (b) Oxalate
(c) Sodium citrate (d) All of the above

Explanations

1. Ans. (b) Glanzmann's thrombasthenia > (d) Bernard Soulier disease

(Ref: Robbins 8th/, Wintrobe's 12th/1365-1370)

Presence of normal PT and aPTT rules out the presence of any clotting factor deficiency. So, options like factor X deficiency and von Willebrand disease are ruled out. Clinically, both Glanzmann thrombasthenia and Bernard Soulier syndrome are indistinguishable. However, most of the haematologists agreed on placing Glanzmann thrombasthenia in preference to Bernard Soulier syndrome as the answer. We got an article supporting the increased prevalence of Glanzmann in comparison to Bernard Soulier in Western India as well.

Name of disease	Bernard Soulier disease	Glanzmann's thrombasthenia
Cause of disease	Defect in the platelet GpIb-IX complex	Defect in platelet Gp IIb/IIIa
Lab findings	↑BT, mild thrombocytopenia, deficient or low levels of platelet GpIb-IX complex by flowcytometry	↑BT, deficient clot retraction time, deficient platelet aggregation with ADP, collagen, thrombin, adrenaline
	Ristocetin aggregation test is defective	Ristocetin aggregation test and coagulation tests are normal
Platelet morphology	Giant platelets under normal smear	Platelets are normal under microscope

2. Ans. (c) Factor VIII inhibitors

(Ref: Robbins 8th/672-3, Wintrobe 12th/1447-1453, Harrison 18th/982)

This is a case of 25 year old asymptomatic female whose parametric inference is as follows:

- BT is 3 min (normal)
- PT is 15 sec/14 sec (normal)
- aPTT is 45 sec/35 sec (raised)
- Platelet count is 2.5lac/mm^3 (normal)
- Factor VIII levels were 60IU/dL (normal i.e. between 50-150IU/dL).

Analyzing all the options one by one

Option 'a'... Factor IX deficiency would have resulted in increased aPTT. However females are less likely to suffer from hemophilia B because it is an X-linked disease. Additionally, the lady is pregnant. This favours an autoimmune etiology.

Option 'b'..... **Lupus anticoagulant** (Wintrobe 12th/1452, Harrison 18th/982) clearly says that these patients have **thrombocytopenia** (here platelet count is normal), **prolonged PTT** and **hypoprothrombinemia** due to antibodies against prothrombin (normal in this case)

Option 'c'....Factor VIII inhibitors (Wintrobe 12th/1441-1444, Harrison 18th/982); Tejender Singh hematology page no 308)

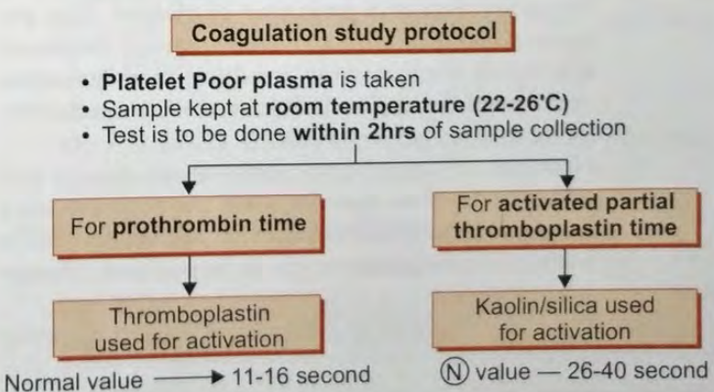
- Acquired coagulant inhibitor is immune-mediated condition characterized by autoantibody against a specific clotting factor and factor VIII is most common target.
- In 50% of patients no underlying disease is indentified at the time of diagnosis. In remaining the causes are autoimmune disease, malignancies, dermatologic diseases, pregnancy and post partum.
- Diagnosed by **isolated prolongation of PTT with normal PT** (coagulation profile is similar to haemophilia A). Platelet count and bleeding time is normal (matches with the data given in our question).

Option 'd'.... VWD – type III (Robbins 8th/672-3): **Bleeding time** will be **prolonged** (in this patient BT is normal) with abnormal platelet count. So, option'd' is excluded.

So the likely diagnosis for the patient in the stem of the question is presence of acquired coagulation inhibitors against Factor VIII.

3. Ans. (c) Done within 2 hours

(Ref: Dacie and Lewis practical hematology 10th/392, 398)



Be aware!

Platelet poor plasma ***is for coagulation studies*** whereas ***platelet rich plasma is used for platelet disorder studies.***

4. **Ans. (d) Acquired Factor VIII inhibitors**
(Ref: Wintrobes 12th/1442-4, 1274)
The clinical presentation in a young female of recurrent joint pains with petechial hemorrhage is suggestive of an autoimmune disease. Options 'a', 'b' and 'c' are rare because these would present with some additional symptoms apart from the ones mentioned in the question. They would also be present since birth.
Talking about option 'd',
A female patient is unlike to have hemophilia as it is an X linked disorder. However, she can have autoantibodies against factor VIII. This could be due to other conditions like pregnancy or coexisting autoimmune disease.

5. **Ans. (b) Normal platelet count and increased BT**
(Ref: Harrison 17th/723, Robbins 8th/670, Robbins 9/e 656)
The stem of the question clearly mention the fact that there is platelet function defect. **It means that the platelet count is normal with a problem in the functioning of platelets. see text for details.**

6. **Ans. (d) Defect in common pathway**
(Ref: Robbins 9th/119)

- Defect in the **extrinsic pathway** causes elevation of **PT**
- Defect in the **intrinsic pathway** causes elevation of **aPTT**.
- Defect in **common pathway** cause elevation of **both PT and aPTT**.
- **Platelet function defect** causes elevation of **BT**.

7. **Ans. (d) Grossly abnormal coagulation tests**
(Ref: Harrison 17th/722, Robbins 9/e p659-660)
If coagulation tests indicate a major consumption of procoagulants, the diagnosis of TTP is doubtful.

8. **Ans. (a) Acute promyelocytic leukemia**
(Ref: Harrison 17th/679, Robbins 9/e p612)

9. **Ans. (c) Aplastic anemia**
(Ref: Harrison 17th/719,720, 667-668 & 16th/674, 622)
- Megakaryocyte is a precursor of platelet. Any peripheral destruction of platelets causes increased activity of bone marrow resulting in **megakaryocytic thrombocytopenia** because of compensatory increase in megakaryocytes.
- However, if thrombocytopenia occurs due to any defect in the bone marrow itself, the compensatory increase in megakaryocytes will not occur. This is known as **amegakaryocytic or hypoplastic thrombocytopenia.**

Aplastic anemia is also an example of amegakaryocytic thrombocytopenia.

10. **Ans. (a) D-dimer will be normal**
(Ref: Wintrobe's Hematology 11th/1672)
- Coagulation defects in severe liver disease include elevated thrombin time, prothrombin time and activated partial thromboplastin time.
- All factors procoagulant as well as anti clotting factors (antithrombin III, protein C and protein S) being synthesized in the liver are reduced in liver dysfunction.
- Fibrin degradation products are increased in patients with severe liver disease and DIC because endogenous plasminogen activators are removed by the normal liver. In severe liver disease, they circulate for long time and cause activation of the fibrinolytic system.

D-dimer is usually normal in liver disease patients. It is increased with DIC.

Wintrobe's mentions page 1396-7 that *..Normal fibrinogen level is 150-350 mg/dl and the levels between 50-100mg/dl are required for normal hemostasis.* However, I could not find any level specifically in cirrhosis patients friends.

11. **Ans. (d) Wiskott Aldrich syndrome**
(Ref: Robbins 7th/244, 8th/235, 9/e p242)
Wiskott Aldrich syndrome is characterized by the **triad** of:
- Severe eczema
- Thrombocytopenia
- Recurrent infections

The platelets are small and are reduced in number in Wiskott Aldrich syndrome.

About other options, in ITP, Bernard Soulier syndrome and Myelofibrosis, there is increase in size of platelets.

12. **Ans. (a) Serotonin; (b) Ig mediators; (d) Interaction among the platelets; (e) Macromolecules;**
(Ref: William's Haematology 61th/1366, Harrison 17th/363-364, Robbins 9/e p117-118)
Agonists of platelet aggregation:

Adhesins	vWF	Plasmin	Serotonin
Thrombospondin	Fibrinogen	Immunocomplex	Vasopressin
TxA_2	ADP	Epinephrine	

P-selectin mediates the interaction between WBC and platelets.

13. **Ans. (a) Abruptio placentae; (b) Acute promyelocytic leukemia; (c) Severe falciparum malaria; (d) 'Snake envenomation; (e) Heparin overdose.**
(Ref: Robbins 7th/657, 9/e 663-664, KDT 5th- 562)

14. **Ans. (b) Increased PT; (d) Decreased fibrinogen; (e) Decreased platelets** *(Ref: Robbins 9/e 664-665)*
Laboratory findings in DIC:

*Low platelet count.
*Microangiopathic hemolytic anemia
*Elevated PT, PTTK, TT
*Plasma fibrinogen level **decreased**
*Fibrin degradation products (FDP) are **raised**.
*Factor V and factor VIII decreased.

15. **Ans. (a) Anaerobic sepsis; (b) Malignancy; (c) Leukemia.** *(Ref: Robbins 7th/657, 9/e 663-664)*

16. **Ans. (a) Glanzmann's syndrome; (b) Bernard-Soulier syndrome; (c) Wiskott Aldrich syndrome; (d) von Willebrand disease**
(Ref: Harrison 17th/723, Robbins 9th/660)
For details, See text
Leucocytosis is seen in all of the given options i.e. brucellosis, acute MI, and diphtheria but in typhoid, there is leucopenia.

17. **Ans. (d) All of the above**
(Ref: Harrison 17th/723-724; Robbins 8th/118, 9/e p662)

18. **Ans. (d) Angiogenesis inhibitory protein**
(Ref: Robbins 9/e p306, 8th/96, 7th/105)
- **Thrombospondin**, is a family of large multi-functional proteins, some of which, similar to **SPARC** (secreted protein acidic and rich in cysteine), inhibit angiogenesis.
- The production of thrombospondin-I has been shown to be inversely related to the ability of a cell line to produce a tumor and vessels *in vivo*; loss of thrombospondin-I production allowed non-tumorigenic cells to become tumorigenic.
- Thrombospondin-I is regulated by wild-type p53.

19. **Ans. (a) Thromboplastin** *(Ref: Robbins, 7th/649, 9/e 656)*

20. **Ans. (a) Myelofibrosis** *(Ref: Harrison 17th/723)*

Causes of Thrombocytosis

- Iron deficiency anemia
- Hyposplenism
- Postsplenectomy
- Malignancy
- Collagen vascular disorder
- Idiopathic myelofibrosis
- Essential thrombocytosis
- CML
- Myelodysplasia
- Post surgery
- Infection
- Polycythemia vera
- Hemolysis
- Hemorrhage
- Idiopathic sideroblastic anemia
- Rebound (cessation of ethanol intake, correction of B_{12} and folate deficiency).

21. **Ans. (a) Synthesized by hepatocytes**
(Ref: Robbins 8th/670-671, 9/e 661)
In the given options, (a) seems to be the best answer though even the liver cells can produce a small amount of von-Willebrand factor. For clarification of other options, *see text*

22. **Ans. (d) VIII** *(Ref: Robbins 8th/835, 9/e 661)*

23. **Ans. (d) Antithrombin** *(Ref: Harsh Mohan 6th/340)*

24. **Ans. (c) von Willebrand disease** *(Ref: Robbins 9/e 662)*

25. **Ans. (c) t (14: 18)** *(Ref: Robbins 9/e 591)*

26. **Ans. (a) Decrease in neutrophil count**
(Ref: Robbins 8th/592-593, 9/e p582)

27. **Ans. (b) 1,00,000/cmm** *(Ref: Robbins 9/e p657)*

28. **Ans (b) Glanzmann disease** *(Ref: Robbins 9th/118)*
Inherited deficiency of GpIIb-IIIa results in a bleeding disorder called Glanzmann thrombasthenia.

29. **Ans (b) Relapse is rare** *(Robbins 9th/658)*
Direct quote.... "Almost all patients respond to glucocorticoids (which inhibit phagocyte function), but many eventually relapse."
- In individuals with severe thrombocytopenia, splenectomy normalizes the platelet counts.
- Immunomodulatory agents such as intravenous immunoglobulin or anti-CD20 antibody (rituximab) are often effective in patients who relapse after splenectomy or for whom splenectomy is contraindicated.
- Peptides that mimic the effects of thrombopoietin (so-called TPO-mimetics) are also useful for improving the platelet counts of the patients.

30. **Ans: (a) Chronic ITP**...see earlier explanation

31. **Ans. (c) Congenital defect of platelets**
(Ref: Robbins 8/e p670, 9/e p660)

- **Glanzmann *thrombasthenia*** is a defect in **platelet aggregation** (both have 'g' in them).
- *Bernard Soulier syndrome* is a defect in platelet ***adhesion*** (both have'd' in them).

Glanzmann thrombasthenia, which is also transmitted as an *autosomal recessive* trait. Thrombasthenic platelets fail to aggregate in response to adenosine diphosphate (ADP), collagen, epinephrine, or thrombin because of **dysfunction of glycoprotein IIb-IIIa,** an integrin that participates in "bridge formation" between platelets by binding fibrinogen

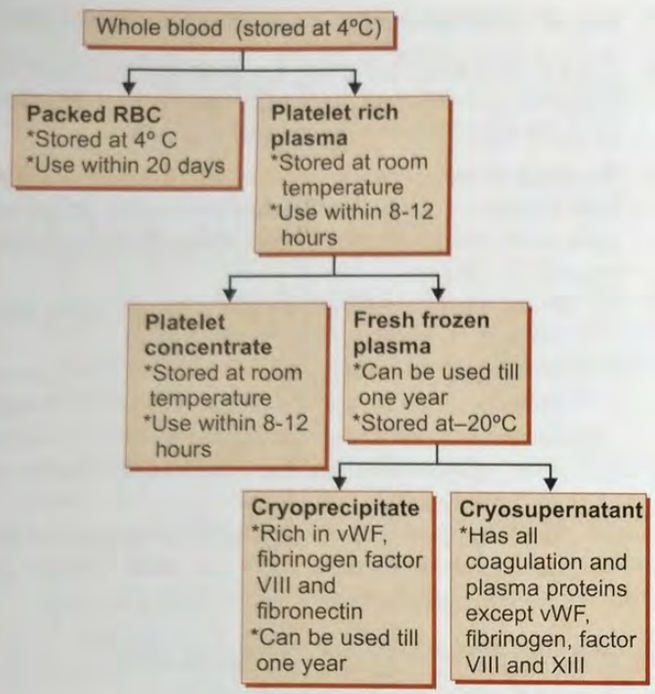
32. **Ans. (c) Decreased fibrin degradation products...discussed earlier** *(Ref: Robbins 9/e 662-663)*
- **DIC** is associated with **increased** *fibrin degradation products.*

33. **Ans. (a) Normal ADAMTS levels**
(Ref: Robbins 9/e 659-660, 8/e p669-670, 7/e p652-653)
...see text for details

34. **Ans (c) Shwachman syndrome**.....
(Ref: Harrison 18th/Ch 107)

Shwachman-Diamond syndrome is associated with pancreatic insufficiency, marrow failure and malabsorption.

35. **Ans. (a) Fresh frozen plasma** *(Ref: Robbins 9th/664)*
The following flowchart helps us to understand that fresh frozen plasma is the best blood product to be given in a patient of multiple clotting factor deficiency with active bleeding.



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36. **Ans. (a) Develops within 24 hours**
(Ref: Critical Care Study Guide 2nd/1102)

Salient features of TRALI

- TRALI develops **within 6 hours** of transfusion.
- It is a cause of **non cardiogenic** pulmonary edema
- **Fresh frozen plasma** is the commonest blood product to cause it.
- Mostly seen after *sepsis* and *cardiac surgeries*
- Clinically, it is ***characterised by acute onset of respiratory distress, associated with oxygen desaturation (hypoxemia) and bilateral lung infiltrates.***

37. **Ans (d) Mantle cell lymphoma** *(Ref: Robbins 9/e p602)*

38. **Ans (b) decreased agglutination** *(Ref: Robbins 9/e p662)*

39. **Ans (c) Gp IIB/IIIA** *(Ref: Robbins 9/e p118)*

40. **Ans (b) 5 days** *(Essentials of Hematology 2/e p492)*
Maximum shelf life of platelets is 5 days.

41. **Ans (d) Bernard soulier syndrome**
(Ref: Wintrobe 12/e p1277, CMDT2018/563)

42. **Ans (b) Causes mild to severe coombs positive hemolytic anemia** *(Ref: Robbins 9/e p643-660*
Coombs test is done for immune hemolytic anemia whereas HUS is non immune hemolytic anemia.

43. **Ans. (c) Lack of antigens of several blood group systems**
(Ref: Wintrobe's hematology 12th/635-6; Harrison 18th/951)
- Red cells of **group O** individuals lack A and B antigens but carry **H substance**
- The enzyme in **group A** individuals is **N-acetylgalactosaminosyl transferase**
- The enzyme in **group B** individuals is **D-galactosyltransferase**
- People with Bombay phenotype (rarest blood group in the world) express no A, B or H antigens on the red blood cells. These are homozygous for the silent h allele (being represented hh). So, these antigens are not present in the saliva also. As the antigens are not expressed, so, the H, A and B antibody will always be present in serum.
- ABO antigens are present not only on the red blood cells abut *also on the other blood cells, in most body fluids* (**except CSF**), cell membrane of tissues such as intestine, urothelium and vascular endothelium.
- Clinical significance of knowing about Bombay blood group is that in case of requirement of blood transfusion, these people would be compatible only with Bombay blood from another individual.

44. **Ans. (b) AO ...Too obvious to explain friends.**

45. **Ans. (d) Paroxysmal nocturnal hemoglobinuria**
(Ref: Robbins 8th/861 (table 18-6, 9/e 847)

I. Hereditary Hemochromatosis
• Mutation in the gene coding for HFE, transferring receptor 2 or hepcidin • Mutation in the gene coding for hemojuvilin:juvenile hemochromatosis
II. Secondary Hemochromatosis
A.Parenteral iron overload: Transfusions, Long-term hemodialysis, Aplastic anemia, Sickle cell disease, Leukemias, Myelodysplastic syndromes Iron-dextran injections
B.Ineffective erythropoiesis with increased erythroid activity β-Thalassemia, Sideroblastic anemia and Pyruvate kinase deficiency
C.Increased oral intake of iron: African iron overload (Bantu siderosis)
D. Congenital atransferrinemia
E. Chronic liver disease: Chronic alcoholic liver disease and Porphyria cutanea tarda.

46. **Ans. (d) 3.2% trisodium citrate**
(Ref: Wintrobe 12th/1, Dacie and Lewis practical hematology 10th/7, 391) ...See text

47. **Ans. (c) Potassium oxalate + sodium fluoride**
(Ref: Henry's Clinical Diagnosis and Management by Laboratory Methods 21st/188, Clinical Chemistry Theory, Analysis and Correlation (Mosby) 4th/23-4, 71, Harper 27th/152)
Direct quote from Harper.... *'enolase enzyme in the glycolysis is inhibited by fluoride, and when blood samples are taken for measurement of glucose, it is collected in tubes containing fluoride to inhibit glycolysis.'*

48. **Ans. (a) Microspherocytes**
(Ref: Wintrobe's 12th/982-3, T. Singh Hematology 2nd/32-3, Handbook of pediatric transfusion medicine by Hillyer 1st/198)

- Wintrobe's mentions ***'spherocytes predominate in the peripheral blood smear of infants with ABO hemolytic disease of newborn.'*** Peripheral blood smear shows numerous spherocytes, occasional nucleated red cells, anisocytosis and polychromasia.
- The blood film in ABO hemolytic disease of the newborn (ABO HDN) is marked by the presence of microspherocytes (a feature not usually seen in Rh hemolytic disease of the newborn). The spherocytosis is attributed to loss of membrane surface area when the spleen removes antigen-antibody complexes from the affected cell.

Other options

Option B... Fragmented RBC or schistocytes are feature of microangiopathic hemolytic anemia, DIC and cardiac hemolytic anemia.

Option C...polychromasia is the term used for red cells staining bluish red with Roamnowsky stains. These cells are larger than normal and show fine reticulin network in supravital staining. They are commonly observed in response to therapy in deficiency anemias and hemolytic anemia. So, is not specific for ABO incompatibility.

Option D... Elliptocytosis is a feature of hereditary elliptocytosis and macrocytic anemias.

49. Ans. (a) Febrile non-hemolytic transfusion reaction

(Ref: Harrison 16th/665-666, Robbin 9/e 665)

The **most frequent reaction** associated with the transfusion of cellular blood components is a **febrile non-hemolytic transfusion reaction**.

FNHTR is characterized by chills and rigor and > 1°C rise in temperature.

50. Ans. (c) Protein

(Ref: Wintrobe's hematology, 11th/797; Harrison 17th/708)

- Unlike other red cell antigens, **Rh antigens do not contain any sugar**. The Rh proteins are multipass membrane proteins that traverse the RBC membrane 12 times. The Rh proteins form a complex with other membrane glycoproteins.

Please remember friends that the Rh antigen should not be confused with Rh factor which is an antibody (Ig) against the Fc portion of IgG seen in patients of rheumatoid arthritis..

51. Ans. (d) Howell-Jolly bodies

(Ref: Harrison's 17th/374-375, 9/e 623, 636)

Howell-Jolly bodies are spherical or ovoid eccentrically located granules in stroma of erythrocytes in stained preparations. These represent nuclear remnants and these occur most frequently after:

1. Splenectomy 2. Megaloblastic anemia 3. Severe hemolytic anemia

Acute manifestations of splenectomy include *leukocytosis* (up to 25000/µl) and *thrombocytosis* (up to 1 × 106/µl) but these return back to baseline levels within 2-3 weeks.

Chronic Manifestations of splenectomy include:

- Anisocytosis and poikilocytosis
- Howell-Jolly bodies (nuclear remnants)
- Heinz bodies (denatured hemoglobin)
- Basophilic stippling
- Occasional nucleated erythrocyte in peripheral blood

When such erythrocyte abnormalities are seen without splenectomy, splenic infiltration by tumor should be suspected.

Other options

- **Dohle bodies** are discrete round or oval bodies. These represent rough ER and glycogen granules and are found in neutrophils. These may be seen in patients with infections, burns, trauma, pregnancy or cancer.
- **Hypersegmented neutrophills** are seen in **megaloblastic anemia.**
- **Spherocyte** *may be seen in hypersplenism and not after splenectomy.*

52. Ans. (a) Metabolic alkalosis

(Ref: Harrison 17th/293, 9/e 666)

Massive Transfusion is defined as the need to transfuse from one to two times the patient's normal blood volume. In a normal adult, this is equivalent to **10-20 units**. Most common abnormality is metabolic alkalosis. It results from conversion of citrate (present in stored blood) and lactate (accumulated due to hypoperfusion) to bicarbonate

53. Ans. (d) Cryoprecipitate

(Ref: Harrison 17th/708-710, Wintrobes 11th/846-8)

Wintrobe's clearly mentions that 'ABO incompatible plasma carries high risk of transfusion reactions, therefore, plasma transfusions should always be ABO incompatible'. So, option 'a' and 'b' are ruled out.

The platelets bear the intrinsic ABO antigens. So, platelet rich plasma and single donor platelets also should be preferably ABO compatible. So, **answer of exclusion is cryoprecipitate.** It is not carrying ABO antigens but should preferably be ABO compatible to avoid even the minimal risk of hemolytic reaction.

Apheresis technology is used for the collection of multiple units of platelets from a single donor. These single-donor apheresis platelets (SDAP) contain the equivalent of at least six units of random donor (RD) platelets and have fewer contaminating leukocytes than pooled RD platelets. Still **the risk of severe hemolytic reactions is much more with single donor incompatible platelets than pooled plasma because the dose of incompatible plasma is also increased.**

FFP is an acellular component and does not transmit intracellular infections, e.g. CMV

54. Ans. (c) O positive RBC and colloids/crystalloid

(Ref: Wintrobes Clinical Hematology vol.I, 10th/833, CMDT 2010/477)

Selection of blood for emergency transfusion

- **If patient's blood group is known,** unmatched blood group of the same group may be used.
- **If the patient's blood cannot be determined,** Group O red blood cells should be chosen. The use of such unmatched blood should be Rh (–ve) when used in woman of child-bearing age in whom we do not want sensitization to Rh antigen. As Rh negative blood is often in limited supply, Rh positive blood is used in the emergency transfusion of older females and males of unknown blood group. In such cases sensitization may occur but the risk of an immediate hemolytic reaction is low. O blood group is the universal donor and therefore, should be given to this patient.

55. Ans. (d) ABO (H) antibodies are invariably present in plasma when persons RBC lacks the corresponding antigen *(Ref: Harrison 17th/708, CMDT 2010/477)*

- In clinical transfusion practice the ABO blood groups are the most important and can never be ignored in red cell transfusion, because individuals, who genetically lack any antigen, have antibodies against the red cell types that they have not inherited. These antibodies can destroy red cells rapidly in circulation.
- The same is not the case with other blood groups where antibodies are formed only after exposure to the sensitive antigen (**Preformed antibodies are absent**).

56. Ans. (a) Howell-Jolly bodies; (c) Macrocytosis
(Ref: Harrison' 17th/374-375, 9/e 623-636)

Chronic manifestations of splenectomy (Postsplenectomy hematological features) are:

- Red cells: Marked variation in size and shape (**anisocytosis, poikilocytosis**)
- **Macrocytosis**
- Presence of **Howell-Jolly bodies** (nuclear remnants)
- **Heinz bodies** (denatured hemoglobin)
- **Basophilic stippling**
- Occasional nucleated red cells in the peripheral blood
- **Target cells**
- **Pappenheimer bodies** (contain sideroblastic granules)
- Irregular contracted red cells.
  - WBC count usually normal but there may be mild lymphocytosis and monocytosis.
  - Thrombocytosis persists in about 30% of cases.

57. Ans. (a) Whole blood *(Ref: Harrison 17th/709)*

Whole blood is processed into its components intended for transfusion. The blood component products are:

Packed RBC	FFP
Platelets	Cryoprecipitate
Plasma derivatives, e.g. albumin, antithrombin, coagulation factors	Leukocyte reduced RBC

58. Ans. (c) Trisodium citrate
(Ref: Wintrobe's Clinical Hematology 11th/4)

59. Ans. (b) Postsplenectomy (c) Hemolysis
(Ref: Tejinder singh's 1st/38-39, internet)

Friends, in hemolytic anemia Howell Jolly body is seen only if anemia is very severe. So, the preferred answer is **post splenectomy**[Q]

Howell-Jolly bodies are nuclear remnants seen in red cells, intermediate or late normoblasts. They are seen in:

- Normally in neonates (spleen is immature)
- Megaloblastic anemia is due to dyserythropoiesis
- Post splenectomy due to absence of pitting function of the spleen
- Acute severe hemolytic anemias
- Hyposplenia (radiation exposure, splenic trauma, autosplenectomy due to sickle cells disease)
- Myelodysplastic syndrome

60. Ans. (a) Chronic liver disease
(Ref: Harrison 17th/359, T. Singh 1st/86)

61. Ans. (a) Leukemoid reaction *(Ref: Robbins 9/e 719)*

62. Ans. (b) D *(Ref: Robbins 8th/460, 7th/485)*

63. Ans. (b) Endothelium *(Ref: Robbins 8/e p434, 9/e p19-20)*

Platelet-derived growth factor (PDGF) is present in the following:

- The alpha granules of the **platelets**
- **Macrophages**
- **Endothelial cells**
- **Keratinocytes and**
- **Smooth muscle cells.**

64. Ans. (c) Factor IX *(Ref: Robbins 8/e p672, 9/e 662-663)*

Disorder	Deficiency
• Hemophilia A	• Factor **8**
• Hemophilia B	• Factor **9 (Christmas factor)**
Hemophilia C	• Factor **11**
• Parahemophilia	• Factor **5 (labile factor)**

65. Ans. (b) Increased erythropoietin level
(Ref: Robbins 9/e 656, 8/e p628, 7/e p699)

Polycythemia vera progenitor cells have markedly decreased requirements for erythropoietin and other hematopoietic growth factors. Accordingly, ***serum erythropoietin levels in polycythemia vera are very low,*** whereas almost all other forms of absolute polycythemia are caused by elevated erythropoietin levels.

66. Ans. (d) Polycythemia rubra *(Ref: Robbins 9/e 619)*

Lab manifestations in polycythemia rubra (CMDT)

- Elevated hemoglobin level and hematocrit: due to increased number of red blood cells
- Platelet count or white blood cell count may also be increased.
- Erythrocyte sedimentation rate (ESR) is **decreased** due to an increase in zeta potential.
- Low erythropoietin (EPO) levels.

67. Ans. (b) HbA_1 *(Read below)*

68. Ans. (b) Lack of reaction accelerator during activation of factor X in coagulation cascade. *(Ref: Robbins 9/e 662)*

- Hemophilia A is caused by the deficiency of clotting factor 8.
- The chief role of the extrinsic pathway in hemostasis is to initiate a limited burst of thrombin activation upon tissue injury. This initial procoagulant stimulus is reinforced and amplified by a critical feedback loop in which thrombin activates factors XI and IX of the intrinsic pathway. ***In the absence of factor VIII, this feedback loop is inactive and insufficient thrombin (and fibrin) is generated*** to create a stable clot.

69. Ans. (c) Factors 5 and 8 *(Ref: Internet)*

FFP contains an average of 1 IU/mL of each coagulation factor, including the labile factors V and VIII. In the question it was asked regarding stored plasma.

By day 5 of storage the amount of factor VIII (8) is reduced by up to 40% and factors V (5) and VII (7) may be reduced by up to 20.

70. Ans. (d) Hemolysis *(Ref: Hematology manual)*

Conditions with pseudohyperkalemia

- Cessive muscle activity during venipuncture (fist clenching),
- Thrombocytosis, leukocytosis, and/or erythrocytosis
- Acute anxiety
- Cooling of blood after venipuncture
- Gene defects leading to hereditary pseudohyperkalemia

Hemolysis causes real hyperkalemia.

71. Ans. (b) Normal PT *(Ref: Robbins 9/e 662)*

As discussed earlier, hemophilia A is an X linked disorder, so, if a male is affected, he cannot transmit it to his son (option 'a' is false). In this sdiorder, there is an **increase in the activated partial thrombolastin time** and **normal values of prothrombin time**.

72. Ans. (b) Synthesized by spleen *(Ref: Robbins 9/e 661)*

vWF is produced by endothelial cells, megakaryocytes and liver.

73. Ans. (a) Light chain of monoclonal immunoglobulins *(Ref: Robbins 9/e p600)*

Bence Jones proteins are made up of light chains of the immunoglobulin and are monoclonal in nature.

74. Ans. (c) Small cleaved cell lymphoma
(Ref : Pattern Approach to Lymph Node Diagnosis by Anthony S-Y Leong)

Friends, I know people would require reference for this question for believing the answer! JJ The tumor cells, which are large with minimal cytoplasm, are closely apposed to each other, forming a dark blue background (the "sky"). These cells have a ***very high turnover rate***, so the macrophages that happen to be hanging around get stuffed with cellular debris (they are at this point called "tingible body macrophages"), and upon fixation, the cytoplasm falls away, leaving round white spaces filled with debris (the "stars"). This pattern can be seen on both bone marrow or lymph node sections. It is seen with:

- Burkitt's lymphoma (earlier called as ***small non cleaved lymphoma***)
- Mantle cell lymphoma
- Large B cell lymphoma (including plasmablastic lymphoma)
- T lymphoblastic lymphoma

75. Ans. (a) X chromosome *(Ref: Robbins 8/e p672, 9/e 662)*

Hemophilia A is caused by mutations in factor VIII, which is an essential cofactor for factor IX in the coagulation cascade. It is inherited as an **X-linked recessive trait**Q and thus affects **mainly males** and *homozygous females*.

Read the following lines carefully for a future NEET question!

- *Hemophilia A is the most common hereditary disease associated* ***with life-threatening bleeding***.
- **Von Willebrand disease** *is the* **most common inherited bleeding disorder** *of humans.*

76. Ans. (d) Sometimes found in saliva *(Read below)*

- The A and B antigens are inherited as mendelian allelomorphs, A and B being dominants and they are located on **chromosome 9**.
- They are located on the **membranes of human red cells**
- Antigens very similar to A and B are common in intestinal bacteria and possibly in foods to which newborn individuals are exposed. Therefore, infants rapidly develop antibodies against the antigens not present in their own cells. Thus, type A individuals develop anti-B antibodies, type B individuals develop anti-A antibodies, type O individuals develop both, and type AB individuals develop neither
- **Secretors** are individuals who secrete ABH antigens in body fluids like **saliva** and **plasma**.

77. Ans. (d) von Willebrand Factor *(Ref: Robbins 9/e 661-662)*

The clues given in the stem of the question are:

- Female patient
- Bleeding tendency
- Prolonged aPTT
- Normal PT
- Normal platelet count
  - As platelet count is normal, thrombocytopenia as a cause of bleeding can be easily ruled out.
  - PT is prolonged in defects of extrinsic pathway of coagulation whereas aPTT increases in defective intrinsic pathway. Therefore, deficiency of factor VII can be ruled out, because it is involved in extrinsic pathway and its deficiency will prolong PT.

- Factor VIII and IX are involved in intrinsic coagulation pathway and vWF stabilizes factor VIII. Therefore, deficiency of any of these will prolong aPTT with PT remaining normal. However, both Hemophilia A (factor VIII deficiency) and Hemophilia B (Christmas disease; factor IX deficiency) are X-linked recessive diseases and commonly affect males. Females are affected only in homozygous state, which is rare.
- So, the answer is **vWF deficiency** which is mostly inherited as **autosomal dominant disorder**.

78. **Ans (a) Fucose** *(Ref: Harrison 18th/ 951)*

The first blood group antigen system was ABO and is the most important in transfusion medicine. The major blood groups of this system are A, B, AB, and O. H substance is the immediate precursor on which the A and B antigens are added. This H substance is formed by the addition of fucose to the glycolipid or glycoprotein backbone. The subsequent addition of N-acetylgalactosamine creates the A antigen, while the addition of galactose produces the B antigen.

79. **Ans. (a) Prolonged PTT** *(Ref: Robbins 9/e 662)*

- **aPTT** is prolonged by **deficiency** of factors **XII, XI, IX, III, X, V, prothrombin and fibrinogen**[Q] and drugs like **heparin**[Q]
- **Hemophilia A** is characterized by the deficiency of **factor 8** and decreased activity of intrinsic pathway. This is associated with prolongation of **partial thromboplastin time**[Q].

80. **Ans. (d) 20–25°C**

(Ref: Essentials of Hematology 2nd/500)

Red cells are stored at a temperature of 22–26°C.

81. **Ans. (b) With a 18–20 G needle**

(Ref: Essentials of Hematology 2nd/500)

The Concept of using a big sized needle is to reduce the risk of hemolysis and speed up the blood flow rate. As per the norms, the needle to be *used in the adults for blood transfusion is* **18-19 guage**.

The transfusion has to be started *within 4hrs* of issue from the blood bank.

82. **Ans. (b) Glycoprotein** *(Ref: Harrison 19th/ 138 e1)*

83. **Ans. (d) D antigen**

(Ref: Robbins 9th/ 462, Harrison 19th/ 138e-1)

84. **Ans. (d) All of the above**

(Ref: Harrison 19th/420)

h/h blood group is the other name of Bombay blood group. It is characterized by absence of H, A and B antigen expression on the surface of red cells.

85. **Ans. (a) 1** *(Ref: Harrison 19th/ 138e-1)*

The three Rh genes, E/e, D, and C/c, are arranged in tandem on chromosome 1.

86. **Ans. (d) Trisodium citrate**

(Ref: Wintrobe 12th/ chapter 1)

Trisodium citrate is the preferred anticoagulant for platelet and coagulation studies.

87. **Ans. (d) All of the above**

(Ref: Wintrobe 12th/ chapter 1)

ANNEXURE

SUMMARY OF LABORATORY FINDINGS IN HEMOSTATIC DISORDERS

Diseases	Platelet count	Bleeding time	PT	APTT	FDP
Hemophilia A	N	N	N	↑	Absent
Hemophilia B	N	N	N	↑	Absent
vWD	N	↑	N	↑	Absent
Liver failure	↓	↑	↑	↑	Absent
DIC	↓	↑	↑	↑	**Present**
Vascular purpura	N	N	N	N	Absent
Aspirin	N	↑	N	N	Absent
Warfarin	N	N	↑ (Even in low dose)	↑ (In high dose)	Absent

CHAPTER 10

Cardiovascular System

Golden Points

- Concentric hypertrophy is seen in conditions with pressure overload like hypertension and aortic stenosis.
- Eccentric hypertrophy is seen in conditions with volume overload like aortic regurgitation.
- Heart failure cells are ***hemosiderin laden*** alveolar macrophages seen in the **lungs**.
- Commonest cause of right heart failure is Left heart failure.
- **Critical narrowing** of coronary vessels to cause angina **>75%.**
- Most common coronary artery involved in atherosclerosis and MI: Left anterior descending (LAD) artery and so, most common type of MI is anterior (antero-lateral) wall MI. of left ventricle, anterior 2/3rd of ventricular septum.
- Inferior (posterior) wall MI is caused by occlusion of Posterior inter-ventricular artery.
- **Earliest light microscopy** change in MI: **Waviness of fibres**.
- **Rheumatic fever** is due to **molecular mimicry** (*Cross reactivity* of streptococcal antigen to endogenous human antigen). Its characteristic pathological finding is **Aschoff bodies**.
- Infective endocarditis vegetations: Large, bulky, friable, non-sterile, on upper surface of cusps, less commonly on mural endocardium.
- Libman Sack enodocarditis vegetation: Small/medium, flat, verrucous, sterile, affects both surfaces of valve.
- Vegetations of NBTE: Small, friable, sterile, along the line of closure of valves.
- Rheumatic fever vegetation: Small, firm, sterile, along the line of closure of valves.
- True about hypertrophic obstructive cardiomyopathy: Myocardial hypertrophy without ventricular dilatation, Asymmetrical septal hypertrophy, outflow obstruction and dilatation of atria.
- **Carcinoid heart disease** is characterized by fibrous endocardial thickening of **right ventricle and tricuspid valve**.
- **Tigered effect** in myocardium is due to **fat deposition**.
- ***Cardiac polyp*** is a **post-mortem fibrinous clot** in heart.
- Mitral valve prolapse microscopically shows **Myxomatous degeneration**.
- Weibel-Palade bodies of endothelial cells have von WIllebrand factor and P selectin.
- Neointimal hyperplasia in vascular graft is due to hypertrophy of **smooth muscles**.
- Medial calcification is seen in :Monckebergs sclerosis.
- Important features of atheromatous plaque: thick or thin fibrous cap, macrophages, smooth muscle cells (undergo apoptosis in later stages), from cells cell debris.
- Common sites of atherosclerosis (in decreasing order): Abdominal aorta > coronary arteries > popliteal artery > internal carotid artery.
- Vessels spared in atherosclerosis include vessels of upper extremities, mesenteric and renal vessels (except at their ostia).
- Tree bark calcification is seen in : Syphilitic aneurysm.
- Most common cause of aortic dissection : Hypertension.
- Vascular changes in benign hypertension : Hyaline arteriosclerosis.
- Vascular changes in malignant hypertension : Hyperplastic arteriosclerosis, onion skin appearance and fibrinoid necrosis (necrotizing arteriolitis).
- Hyperplastic arteriosclerosis affects : Kidney (necrotizing glomerulonephritis), small intestine, gall bladder peripancreatic fat, periadrenal fat.
- cANCA is produced Proteinase-3 and is seen in Wegner's granulomatosis.
- pANCA is produced against Myeloperoxidase (MPO) and is seen in Microscopic polyangitis, Churg-strauss syndrome, idiopathic crescentic glomerulonephritis, Good-pasture syndrome, renal-limited vasculitis.
- Conditions with **granulomatous vasculitis**: Giant cell arteritis, Takayasu's disease, Wegner's granulomatosis and Churg Strauss syndrome.
- Characteristic tetrad of Henoch Schonlein purpura: Palpable purpura, arthritis/arthralgia, glomerulonephritis and abdominal pain.
- There is **no structural abnormality** or change in vessel wall in **Raynaud's disease**.
- Most common benign vascular tumor : Hemangioma.
- Vascular tumor with spontaneous regression is a Strawberry angioma (a type of capillary hemanioma).
- Kaposi sarcoma is caused HHV 8 infection and arises from vessels.
- Most common cause of SVC syndrome: Extrinsic compression by malignant tumors.

HEART

The human heart is a muscular pump responsible for maintaining the circulation of the blood and perfusion of different organs of the body. The *thickness of the left ventricle is almost three times that of the right ventricle.* The cardiac output is about 5 liters per minute. The heart is supplied by the right and the left coronary artery (through left anterior descending artery; LAD and the left circumflex artery; LCX).

Key Point

LAD supplies 3 "A"

- **A**pex of the heart.
- **A**nterior 2/3rd of the interventricular septum
- **A**nterior wall of the left ventricle

Out of the three layers of the heart (pericardium, myocardium and endocardium), the least collateral perfusion is present in the endocardium and so, it is most prone to ischemic injury The coronary artery supplying the posterior 1/3rd of the ventricular septum (by giving rise to the posterior descending branch) is called *dominant*. Therefore, most people have **right dominant circulation**. Since, cardiac myocytes cannot undergo division, so, they only undergo hypertrophy which can be of the following types:

- **Concentric hypertrophy/pressure overload hypertrophy:** It is due to deposition of the sarcomeres in parallel to the long axis of the cells. It is associated with ***hypertension and aortic stenosis***.
- **Volume overload hypertrophy:** In this, dilatation with increased ventricular diameter is present. It is seen with valvular regurgitation ***(mitral or aortic regurgitation), thyrotoxicosis and severe anemia***.

HEART FAILURE

It is a clinical condition characterized by the inability of the heart to pump blood in proportion with the requirements of the metabolic tissues of the body or being able to do so at increased filling pressures. It may be divided into **systolic or diastolic failure.** We can also classify heart failure as:

Recent Exam Questions

RECALL!

- **Normal ejection fraction** is **65%.**
- **Stroke volume** (about **70 ml**).
- M Imp **source of energy** for the cardiac myocytes is the **fatty acids**.

LEFT VENTRICULAR FAILURE/LEFT SIDED HEART FAILURE (LVF)

It is most commonly caused by *ischemic heart disease, hypertension, aortic or mitral valvular disease and myocardial disease* (non-ischemic). The features include hypertrophy and fibrosis in the myocardium associated with secondary involvement of the atria which shows enlargement. Atrial involvement results in the development of the atrial fibrillation which is responsible for thrombus formation or embolic stroke. The other organs affected include:

Recent Exam Questions

- **SA node** is the **"pacemaker"** of the heart
- **AV node** is the **"gatekeeper"** of the heart

Key Point

Lungs are the **most commonly** affected organ in **LVF**.
Siderophages or **heart failure cells** are *hemosiderin containing macrophages.*

Lungs

- It is the most commonly affected organ. The increased pressure in the pulmonary vein causes *pulmonary edema* (heavy wet lungs). The edema fluid accumulates in the alveolar space.
- There is leakage of hemosiderin and other iron containing particles which are phagocytosed by macrophages. The iron gets converted to hemosiderin leading to the formation of **siderophages or heart failure cells** (*hemosiderin containing macrophages*).
- The alveolar fluid impairs gaseous exchange giving rise to breathlessness or ***dyspnea (earliest feature of LVF)***, orthopnea (dyspnea on lying down) and paroxysmal nocturnal dyspnea (dyspnea at night).
- There is presence of **Kerley B lines** on chest X-ray due to transudate in the interlobular septa.

Kidneys

In the early stages, decreased renal perfusion causes activation of the renin-angiotensin-aldosterone system whereas in the later stages, continued reduced renal perfusion may precipitate prerenal azotemia.

Brain

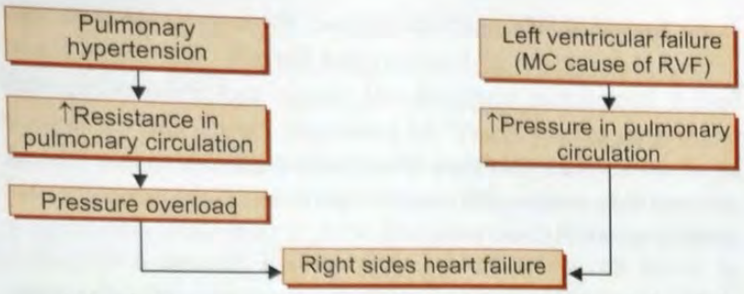
It may suffer from hypoxic ischemic encephalopathy.

RIGHT-SIDED HEART FAILURE

Left ventricular failure is the most common cause of the right sided heart failure whereas pure right sided failure is seen in chronic severe pulmonary hypertension and is called as **cor pulmonale**.

Recent Exam Questions

- **Left ventricular failure** is the **most common** cause of the **right sided heart failure**.
- **Cardiac cirrhosis** is characterised by **nutmeg liver**.



The features seen as a result of the inability of the right heart to pump blood in different organs include:

Liver

There is presence of congestive hepatomegaly. In addition, if associated LVF is present, the centrilobular necrosis is also seen which is replaced by fibrotic tissue in longstanding cases and is known as cardiac sclerosis or cardiac cirrhosis.

Spleen

Congestive splenomegaly is seen.

Kidney

These show the congestion resulting in severe azotemia. The congestion is more prominent in RVF than in LVF.

- Pleural effusion, pericardial effusion and ascites are also seen.
- The hallmark of the right sided heart failure is peripheral edema of the dependent parts of the body particularly pedal and pretibial edema.
- **Anasarca** is the ***generalized massive edema*** seen in heart failure.

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE (RHD)

Rheumatic fever is an acute *immunologically mediated* multisystem inflammatory disease that occurs few weeks after an attack of *group A β- hemolytic streptococcal pharyngitis*. It is not an infective disease. The most commonly affected age group is children between the ages of **5-15 years**Q. **Only 3%**Q of patients with group A streptococcal pharyngitis develop acute rheumatic fever.

Key Point

Most commonly affected age group in **rheumatic fever** is **5-15 years.**

The disease is a **type II hypersensitivity** reaction in which *antibodies against 'M' protein* of some streptococcal strains (1, 3, 5, 6, and 18) cross-react with the glycoprotein antigens in the heart, joints and other tissues **(molecular mimicry)**.

Key Point

Migratory polyarthritis is the commonest **major manifestation** of *Jones criteria* seen clinically.

WHO criteria for diagnosis of RF and RHD [Based on revised (1992) Jones criteria]

1.	**Major manifestations:**
	J **O** — **Joint involvement (Polyarthritis)**
	N - **N**odules (Subcutaneous)
	E - **E**rythema marginatum
	S - **S**ydenham's chorea
	Criteria - **C**arditis
2.	**Minor manifestations:**
	Clinical: Fever polyarthralgia
	Laboratory: Increased ESR or C-RP
	ECG: Prolonged PR interval
3.	**Supporting evidence of a preceding streptococcal infection within last 45 days:**
	Elevated or rising ASO or other Ab titers
	Positive throat culture
	Rapid antigen test for group A streptococcus.

Note:

1. Two major or one major and two minor manifestations plus any of the evidence of preceding group A streptococcal infection is required for diagnosis of primary episode of rheumatic fever.
2. 1992 revised Jones criteria do not include elevated TLC (total leukocyte count) as a laboratory minor manifestation [instead, it includes elevated C-reactive protein] and do not include recent scarlet fever as supporting evidence of recent streptococcal infection.

Key Point

Pancarditis is a characteristic manifestation of the cardiac involvement in **rheumatic fever**.

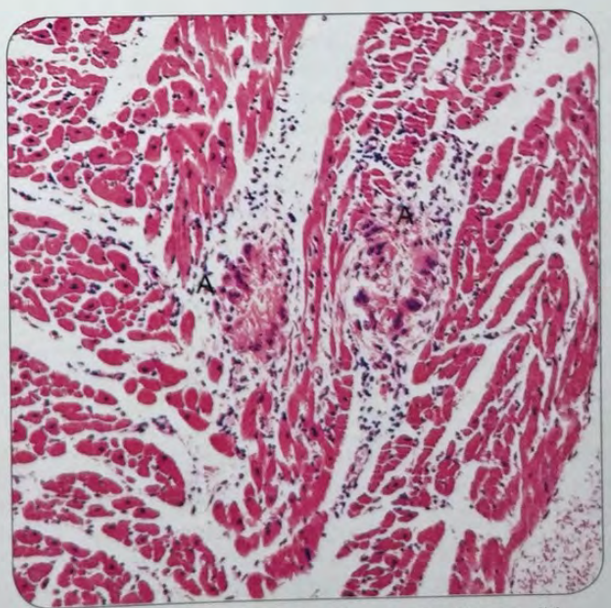


Fig. 1: Aschoff Body (A) in Rheumatic Myocarditis.
...(All India Image)

SALIENT FEATURES OF THE MAJOR CRITERIA

Carditis

All the layers of the heart namely pericardium, myocardium and endocardium are involved, so this is called **pancarditis**. The pericarditis is associated with fibrinous/serofibrinous exudate and is called as **'bread and butter' pericarditis**. Valvular involvement is common in rheumatic heart disease. The *most common valve to be affected is the mitral valve and least commonly affected is pulmonary valve*. **In acute rheumatic heart disease, the most common valvular lesion is mitral regurgitation and in chronic rheumatic heart disease, it is mitral stenosis.**

Migratory polyarthritis

There is involvement of the large joints of the body. It is more commonly seen in the adults as compared to children. The arthritis involves one joint after the other (migratory) and subsides spontaneously without any residual deformability in the joints **(non-erosive arthritis)**. Clinically, this is the *most commonly seen manifestation* and the joint pain shows **dramatic response to salicylates** like aspirin.

Subcutaneous nodules

These are painless subcutaneous lesions found on the **extensor surface** of the elbows, shin and the occiput.

Erythema marginatum

There is presence of red macular rash more easily appreciated in fair skinned individuals sparing the face and without residual scarring.

Sydenham's chorea

It is a ***late*** *manifestation* of the disease characterized by presence of involuntary, purposeless movements associated with emotional lability of the patient.

Key Point

The plump macrophages called **Anitschkow cells** are *pathognomonic* for rheumatic fever.

Recent Exam Question

Most commonly affected valve is **mitral valve** and the ***least commonly*** affected is ***pulmonary valve***.

Microscopically, the characteristic feature of rheumatic heart disease is **Aschoff's body (Fig. 1)**. The latter consist of foci of swollen eosinophilic collagen surrounded by T-lymphocytes, few plasma cells and plump macrophages called **Anitschkow cells (pathognomonic for RF).** These distinctive cells have abundant cytoplasm and central round-to-ovoid nuclei in which the chromatin is disposed in a central, slender, wavy ribbon (hence, they are also called as **"caterpillar cells").**

The myocardium has Aschoff's bodies in the perivascular location. The involvement of the endocardium results in **fibrinoid necrosis** within the cusps or along the tendinous cords which also have small vegetations called *verrucae* present along the lines of closure. The presence of mitral regurgitation also induces irregular thickening in the *left atrial wall* called as **MacCallum plaques**.

Chronic RHD is characterized by organization of the acute inflammation and subsequent fibrosis. The valves show leaflet thickening, commissural fusion and shortening, and thickening and fusion of the tendinous cords. There is mitral stenosis called as **'fish-mouth' or 'button-hole' stenosis**. Mitral stenosis may also lead to atrial fibrillation and thromboembolic phenomenon in these patients.

Recent Exam Questions

Acute RHD

- **A**schoff's body
- **A**nitschkow cells

Recent Exam Questions

Chronic RHD

- MacCallum plaques
- Fish-mouth' or 'button-hole' stenosis

INFECTIVE ENDOCARDITIS (IE)

It is colonization or invasion of heart valves and mural endocardium by microbiologic agent leading to formation of bulky, friable vegetations composed of thrombotic debris and organisms with destruction of underlying cardiac tissues. It can be

- Acute
- Subacute

Recent Exam Questions

Organism in infective endocarditis

- ***Staphylococcus aureus***
  - Intravenous drug abusers
  - Native cardiac valve
- ***Staphylococcus epididermis***
  - Artificial cardiac valve
- ***Streptococcus viridians***
  - Previously damaged valve
- ***Streptococcus mutans***
  - Recent tooth extraction
- **HACEK** group of bacteria (**H**emophillus, **A**ctinobacillus, **C**ardiobacterium, **E**ikenella and **K**ingella) and enterococci can also cause infective endocarditis in some patients.

Acute endocarditis	Subacute endocarditis
• Necrotizing, ulcerative, invasive valvular infection on a **previously normal** valve. • **Highly** virulent organisms • Death of the patient within days to weeks • MC caused by ***Staph. aureus***	• Insidious infection following a protracted course on a **previously damaged** valve • Low virulence organisms • Recover after antibiotic therapy • MC caused by ***α-hemolytic (viridans) Streptococcus***

MORPHOLOGY

The friable, bulky destructive vegetations containing fibrin, bacteria and inflammatory cells are found on the valve cusps. These can also extend on to chordae. ***The aortic valve and the mitral valve are most commonly infected*** whereas *the right side of heart is affected in intravenous drug abusers*. When the vegetations erode into myocardium, they can form an abscess called *Ring abscess*. The systemic embolisation can result in *septic infarcts*.

CLINICAL FEATURES

Fever is the *most consistent sign of IE*. The other features include weight loss, flu-like syndrome, cardiac murmur, systemic emboli, **Roth spots** (due to retinal emboli), **Osler nodes** (painful, subcutaneous nodules on the fingers and toes) and **Janeway lesions** (red painless lesions on the palms and soles).

- The disease is diagnosed by **Dukes criteria**.

Recent Exam Questions

Infective endocarditis

- The **aortic valve** is the most commonly affected valve in **prosthetic valve endocarditis**.
- **Right sided cardiac valves** (tricuspid and pulmonary) are affected in **i.v. drug abusers**.
- **Blood culture** is the *investigation of choice* in **infective endocarditis**.

COMPLICATIONS

Cardiac complications

- Valvular insufficiency or stenosis
- Myocardial ring abscess
- Suppurative pericarditis
- Valvular dehiscence

Embolic complications

- With left sided lesion – Brain, spleen, kidney
- With right sided lesion – Lung infarct, lung abscess

Renal complications

- Embolic infarct
- **Focal (more common)** or *diffuse glomerulonephritis (less common)*

MARANTIC ENDOCARDITIS/NON BACTERIAL THROMBOTIC NON BACTERIAL THROMBOTIC ENDOCARDITIS (NBTE)

- It is seen in patients suffering from debilitating diseases like malignancy (carcinoma pancreas and acute promyelocytic leukemia) and hypercoagulable states (DIC)
- **Vegetations on heart valves are sterile** (do not contain microorganisms). These are usually **present along the line of closure**, single or multiple.

LIBMAN-SACKS ENDOCARDITIS (SLE)

- Seen in patients of SLE
- Vegetations are small or medium sized, **sterile, granular and pink** on either or both sides of valve leaflets.
- Mitral and tricuspid valves are involved and show *fibrinoid necrosis*.

Table 1: Summary of salient features of vegetations in different endocarditis

Rheumatic Fever	Non Bacterial Thrombotic (Marantic Endocarditis)	Libman-Sacks Endocarditis	Infective Endocarditis
• Small, warty • Firm • Friable	• Small, warty • Friable	• Medium sized (small) • Flat, Verrucous • Irregular	• Large • Bulky • Irregular
• Along **lines of closure**	• Along lines of closure	• On **surface of cusps** • (both surfaces may be involved but the undersurface is more likely affected, less commonly mural endocardium is involved • In pockets of valves	• Vegetations on the valve cusps • Less often on mural endocardium
• Sterile (no organism)	• Sterile	• Sterile	• **Non-sterile** (bacteria)
• Embolisation is uncommon	• Embolisation is common	• Embolisation is uncommon	• Embolisation is **very common** (max chances)
• In **rheumatic heart disease**	• In cancers (like **M3-AML, pancreatic cancer), deep vein thrombosis, Trosseau syndrome**	• In **SLE**	• In infective endocarditis

Valvular lesions	MC cause
Aortic stenosis	Congenitally bicuspid aortic valves
Aortic regurgitation	Hypertension
Mitral stenosis	RHD
Mitral regurgitation	***Mitral valve prolapse***

BARLOW SYNDROME (MITRAL VALVE PROLAPSE; MVP)

- Valvular abnormality seen **predominantly in females** where one or both mitral leaflets are "floppy" and *prolapse*, or balloon back into the left atrium during systole. This gives rise to the mid systolic click.
- Most of the patients are usually **asymptomatic**Q
- The condition is discovered only *on routine examination*Q by the presence of a ***midsystolic click***Q as an incidental finding on physical examination.
- Some patients may present with ***chest pain mimicking angina, dyspnea, and fatigue*** or, ***psychiatric manifestations, such as depression, anxiety reactions, and personality disorders***
- The risk of complications like *Infective endocarditis, Mitral insufficiency, Stroke or other systemic infarct and Arrhythmias* is higher in men, older patients, and those with either arrhythmias or some mitral regurgitation, as evidenced by holosystolic murmurs and left-sided chamber enlargement.

Recent Exam Questions

MVP

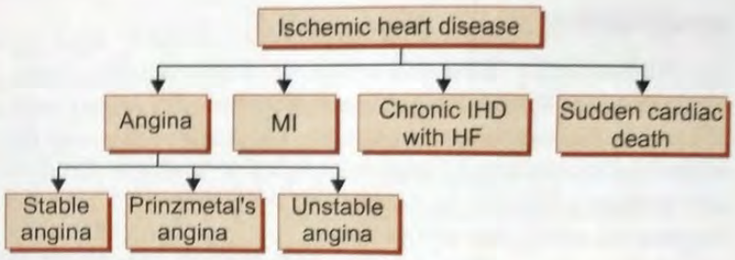
- ***Annular dilation*** is a characteristic association(this finding is rare in other causes of mitral insufficiency).
- *Microscopic characteristic* feature of MVP: ***myxomatous degeneration of valve leaflets.***
- **MVP** is *diagnosed* by **echocardiography**Q.

Key Point

- **Suden cardiac death** is most commonly due to **ventricular fibrillation**. It occurs **within 1 hour** of onset of symptoms.
- In the ECG, **subendocardial ischemia** manifests as **ST segment depression**.

ISCHEMIC HEART DISEASE

Ischemia of the heart is a result of imbalance between the perfusion and demand of the heart for oxygenated blood. Atherosclerotic narrowing resulting in coronary arterial obstruction is the cause of ischemic heart disease in almost 90% of the patients.



Stable Angina

Stable angina occurs when the myocardial oxygen demand is more than the supply. It takes place when the **coronary artery is occluded >75%.** Stable angina is characterized by pain on exertion which is relieved on taking rest or taking vasodilators like nitrates. There is neither any plaque disruption nor any plaque associated thrombus.

Prinzmetal or Variant or Vasospastic Angina

It is an episodic angina due to **coronary artery spasm** resulting in pain at rest. It is characterized by ST segment elevation on the ECG (due to transmural ischemia).

Key Point

In the ECG, **transmural ischemia** manifests as **ST segment elevation**.

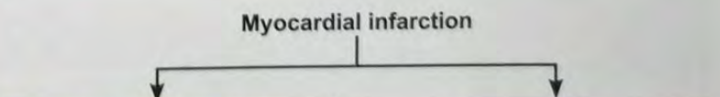
Unstable or Crescendo Angina

It is induced by atherosclerotic plaque disruption with superimposed partial thrombosis or vasospasm or both of them. The pain occurs with increasing frequency and for a longer duration and is characteristically precipitated by progressively less exertion.

Concept

The main difference between angina and the MI is elevation of cardiac enzymes in the latter which is not seen usually with angina. In one third of the patients, angina may be associated with elevation of cardiac enzymes.

Myocardial Infarction (MI)



Subendocardial MI	Transmural MI
• Ischemic necrosis limited to 1/3rd of ventricular wall • Caused by incomplete coronary artery occlusion.	• Ischemic necrosis involves **full thickness** of ventricular wall • Caused by severe coronary atherosclerosis, with acute plaque rupture and superimposed occlusive thrombus.

Pathogenesis of MI

Changes in atheromatous plaque (hemorrhage/ulceration/rupture)
↓
Exposure of underlying collagen and platelet aggregation
↓
Platelets release mediators which cause vasospasm
↓
Activation of extrinsic clotting pathway and increased thrombus formation
↓
Complete occulsion of coronary vessel by thrombus

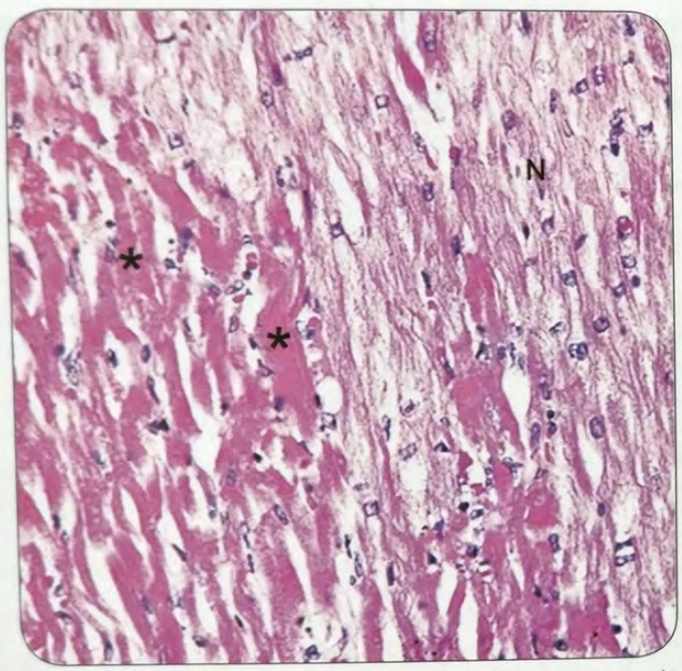


Fig. 2: Coagulative necrosis with eosinophilic cytoplasm*.

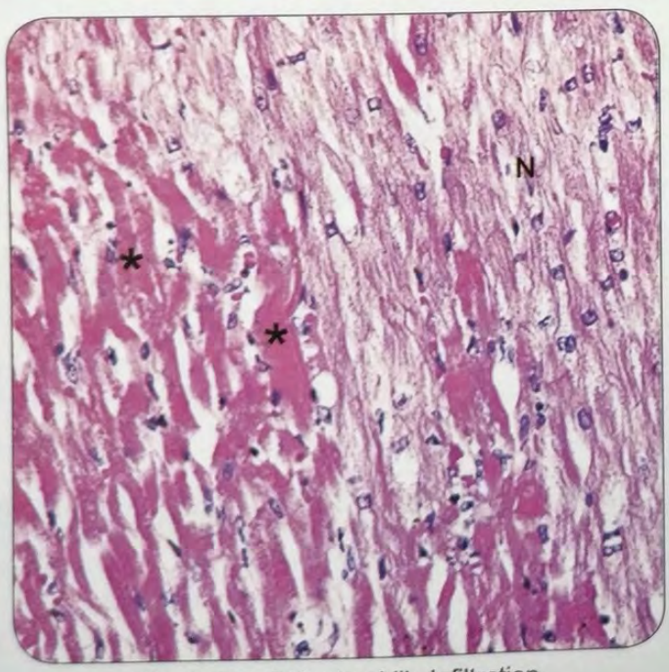


Fig. 3: Day 2 Neutrophilic Infiltration.

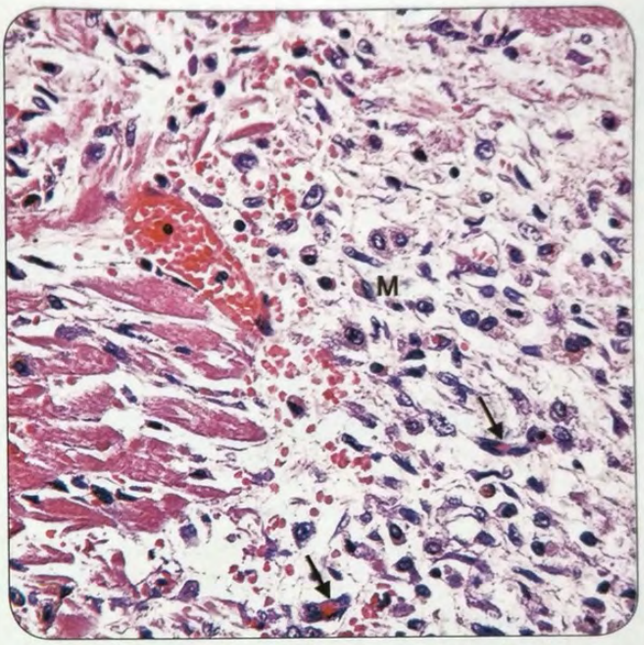


Fig. 4: Macrophage (M) and Granulation Tissue.

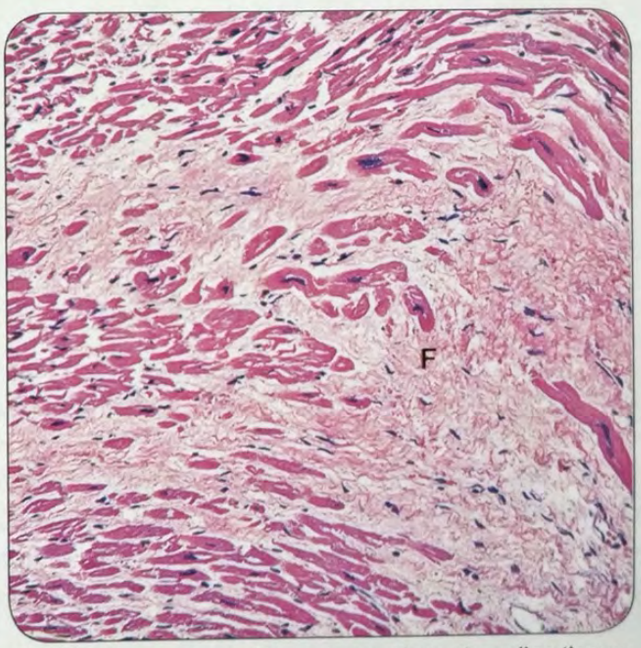


Fig. 5: Fibrous tissue (F) replaces Normal cardiac tissue.

Myocardial Response

Feature	Time
Cessation of aerobic respiration or onset of ATP depletion	Seconds
Loss of contractility	<2 min
ATP reduced to 50% of normal	10 min
ATP reduced to 10% of normal	40 min
Irreversible cell injury	20-40 min
Microvascular injury	>1 hr

Table 2: Evolution of Morphological Changes in MI

Time	Gross	Light Microscopy
Reversible injury		
0-30 min.	None	None
Irreversible injury		
30 min to 4 hr.	None	**Waviness of fibers at border** ***(earliest change)***
4-12 hr.	Occasional dark mottling	Beginning of coagulative necrosis, edema and hemorrhage
12-24 hr.	Dark mottling	Ongoing coagulative necrosis, marginal contraction band necrosis, beginning of neutrophilic infiltration
1-3 days	Mottling with yellow tan infarct center.	Coagulation necrosis, interstitial neutrophilic infiltrate
3-7 days	Hyperemic borders, central yellow tan softening	Beginning of disintegration with dying neutrophils, early phagocytosis by macrophages
7-10 days	Maximum yellow tan and soft depressed red-tan margin	Early formation of fibrovascular granulation tissue at margins
10-14 days	Red gray depressed infarct borders	Well established granulation tissue and collagen deposition
2-8 weeks	Gray-white scar progressive from border towards infarct core	Collagen deposition, ↓ Cellularity
> 2 months	Scarring complete	Dense collagenous scar

Diagnosis of MI

MI should be suspected in any patient developing severe chest pain, rapid weak pulse, sweating, dyspnea and edema. Infact, ***rapid pulse is the first sign*** and ***dyspnea is the first symptom of acute MI***. The ECG shows the ***ST segment elevation*** in ***acute MI*** whereas **'Q' wave** indicates **old MI.**

Laboratory investigations show nonspecific markers like increased ESR, leukcocytosis and elevated C-reactive protein. The specific markers include:

Enzyme	Initiation of rise	Peak	Return to baseline
CK-MB	2-4 hours	24 hours	48-72 hours
Troponin T and I (TnT, TnI)	2-4 hours	48 hours	7-10 days
AST/SGOT	In 12 hours	48 hours	4-5 days
LDH	24 hours	3-6 days	2 weeks

Key Point

The **neutrophils** are present between **48-72 hours** but **after 72 hours, the macrophages predominate** and cause early phagocytosis.

Recent Exam Question

Triphenyl tetrazolium chloride **(TTC)** reacts with intracellular *LDH* in the **living cardiac fibers** to give **brick-red color**. In contrast, infarcted tissue shows the unstained pale zone.

IMPORTANT POINTS ABOUT THE CARDIAC ENZYMES

Troponin T and Troponin I

These are the proteins that mediate calcium mediated contraction of the cardiac and the skeletal muscles. They are very specific for MI. Troponin I is more important than troponin T (remember, I for Important). If the patient has another MI (due to reinfarction within 1 week), these enzymes cannot be used for diagnosis of reinfarction because their levels remain elevated for a long time from the first attack. In that condition, we prefer an enzyme elevated for a short duration. This is the ***enzyme of choice for diagnosing reinfarction***.

Creatine kinase (CK)

It is an alternative to troponin measurement. It has got 3 isoforms:
- CK-MM—Present in the skeletal muscle and heart
- CK-MB—Present in the myocardium and a small amount in skeletal muscle
- CK-BB—Present in the brain, lung and other tissues.

Elevation of the CK-MB isoforms is seen in MI. Any absence of elevation of CK-MB in the first-two days excludes the diagnosis of MI.

Myoglobin

It is a small monomer with a rapid rise and fall in serum (has a narrow window). It is the earliest enzyme to increase after MI.

LDH

Normally, serum LDH2 is greater than LDH1 but in MI, LDH1 is more than LDH2. This is called **"flipping of LDH ratio".**

Key Point

- ***MI is the leading cause*** of death in *diabetes mellitus*. Diabetics and elderly patients have **'silent MI'**.
- Risk of MI is 2 times in diabetics in comparison to non-diabetics.
- Risk of gangrene is 100 times in diabetics in in comparison to non-diabetics

Mnemonic

Sequence of elevated enzymes after MI (Time to CALL emergency)

Time to	Troponin
C	**C**K-MB
A	**A**ST
L	LDH1

Recent Exam Questions

- **Myoglobin: earliest** enzyme to increase after MI.
- **Troponin:** Most **sensitive** as well as **specific** for MI.
- **Troponin** is now enzyme of choice for diagnosing **reinfarction**.
- Normally, serum LDH2 is greater than LDH1 but in MI, LDH1 is more than LDH2. This is called **"flipping of LDH ratio"**.

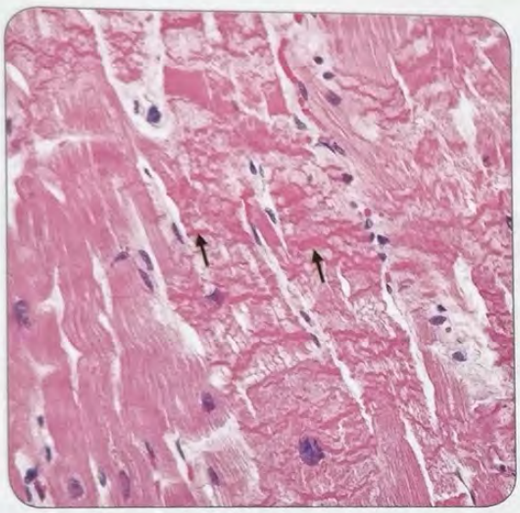


Fig. 6: Reperfusion Injury with Contraction Band Necrosis.

Recent Exam Questions

Reperfusion injury

- Results in hypercontraction of the sarcomeres due to calcium overload. This leads to **contraction band necrosis (see figure 6)**.

COMPLICATIONS OF MI

- **Contractile dysfunction** resulting in cardiogenic shock.
- **Arrhythmia:** *Ventricular fibrillation* is the most common arrhythmia *within one hour* whereas *supraventricular tachycardia* is the most common arrhythmia *after one hour* of MI.
- **Cardiac rupture syndrome:** *Rupture of ventricular free wall* is the most common cardiac rupture syndrome. It results in cardiac tamponade. The *anterolateral wall at the midventricular level* is the most common site for postinfarction free wall rupture. It is most frequent ***3 to 7 days after*** MI. The rupture of ventricular septum leads to formation of left to right shunt. The rupture of papillary muscles can cause mitral regurgitation.
- **Pericarditis:** It is the epicardial manifestation of the underlying myocardial injury and is also known as Dressler syndrome or post MI syndrome. It is an autoimmune reaction, which takes place around 2-3 weeks after a transmural MI. though it has been reported to occur even after 48 hrs. It is associated with pleural effusion, pleuritic chest pain and pericardial effusion.
- Right ventricular infarction.
- **Ventricular aneurysm:** This may contribute to thromboembolism also
- **Papillary muscle dysfunction:** This leads to post infarct mitral regurgitation.

Key Point

Dressler syndrome (post MI **autoimmune** *pericarditis*) is treated with the help of **NSAIDs** with/without the use of **steroids**.

Concept

Rupture of the left ventricle, a complication of acute myocardial infarction, usually occurs when ***the necrotic area has the least tensile strength, about 4 to 7 days after an infarction***, when repair is just beginning.

CARDIAC TUMORS

Myxoma

Myxomas are the most common primary tumor of the heart in adults. Though they may arise in any cavity of the heart but nearly *90% are located in the atria,* with a left-to-right ratio of approximately 4:1 *(atrial myxomas)*. The major clinical manifestations are due to valvular *"ball-valve" obstruction,* embolization, or a syndrome of constitutional symptoms, such as fever and malaise the latter most commonly due to the effect of interleukin-6.

The tumors are almost always single. The region of the **fossa ovalis in the atrial septum is the favored site of origin.** Histologically, myxomas are composed of stellate or globular myxoma ("lepidic") cells, endothelial cells, smooth muscle cells, and undifferentiated cells embedded within an abundant acid mucopolysaccharide ground substance and covered on the surface by endothelium.

Recent Exam Questions

- MC ***cardiac tumor: secondaries or metastasis***.
- MC **primary** cardiac tumor in the **adults: myxoma**.
- MC **cardiac tumor** in the **children: rhabdomyoma**.

Recent Exam Questions

Myxoma

- **MC site: left atrium**
- **Origin: fossa ovalis** in atrial septum
- **Histo: lepidic cells** in mucopolysaccharide ground substance
- **90% are sporadic;** 10% familial
- **Carney syndrome:** *AD* transmission; PRKAR1 gene mutation familial myxoma + spotty pigmentation + endocrine overactivity

Rhabdomyoma

Rhabdomyomas are the most frequent primary benign tumor of the heart in infants and children. They are actually hamartomas or malformations rather than true neoplasms. Cardiac rhabdomyoma is associated with **tuberous sclerosis**

due to defect in the TSCI or TSC2 tumor suppressor gene. The TSC proteins stimulate the cell growth and are involved in myocyte overgrowth.

Recent Exam Questions

Rhabdomyoma

- Seen in *infants and children.*
- MC **site: ventricles.**
- Asscociated with **tuberous sclerosis.**
- Histo: **spider cells.**

Vessel	Property
Arteriole	***Resistance vessels***
Capillaries	maximum cross-sectional surface area
Venules	Most important vessel in inflammation
Vein	***Maximum blood volume***

Rhabdomyomas are generally small, gray-white myocardial masses protruding into the ventricular chambers. Histologically they are composed of large, rounded, or polygonal cells containing numerous glycogen-laden vacuoles separated by strands of cytoplasm running from the plasma membrane to the more or less centrally located nucleus, the so-called **spider cells.**

BLOOD VESSELS

The blood vessels are responsible for the transport of blood in the circulation from the heart to the various organs and back to the heart.

The histological layers which are seen in a blood vessel (particularly arteries) are:

1. Tunica intima (Innermost layer)
2. Internal elastic lamina
3. Tunica media (Middle layer)
4. External elastic lamina
5. Tunica adventitia (Outermost layer)

The outer half of the tunica media and the whole of tunica adventitia are supplied by *vasa vasorum* whereas the other inner layers of the blood vessel get their nourishment by diffusion.

Any injury/denudation of endothelial cells stimulate thrombosis and smooth muscle cell proliferation. **'Sclerosis"** means loss of elasticity of vessels commonly associated with thickening. It may be of the following types:

Concept

Endothelial cells contain Weibel Palade Bodies having von Willebrand factor and are identified by antibodies to CD31, CD34 and vWF.

1. **Arteriolosclerosis -** It affects small arteries and arterioles, it can be of the following types:

Hyaline arteriolosclerosis

- Pink, hyaline thickening of arteriolar walls.
- Seen in elderly, more commonly in benign hypertension, *diabetes mellitus (DM) and benign nephrosclerosis.*

Hyperplastic arteriolosclerosis

- 'Onion skinning' or concentric thickening of the arteriolar wall seen in malignant hypertension.
- Fibrinoid necrosis/necrotizing arteriolitis (inflammatory cells in vessel wall particularly in kidney)

Recent Exam Questions

- **Windkessel effect** is the **elastic recoil property** of the blood vessels.
- **Coronary circulation** is an example of **autoregulatory circulation.**

2. **Monckeberg's medial calcific stenosis**
   - Seen is muscular arteries of people > 50 years of age.
   - Associated with *dystrophic calcification*Q and is asymptomatic.
3. **Atherosclerosis**

It is characterized by deposition of atheroma/fibrofatty plaque consisting of raised focal lesion. Plaque is present within the **intima,** has a core of lipid (cholesterol and cholesterol esters) and a covering of fibrous cap.

The histopathology shows:

Atherosclerosis: risk factors	
A -	**A**ge (↑ with age)
T -	**T**ype 'A' personality
H -	**H**yperhomocysteinemia
E -	**E**xtra lipids (Hyperlipidemia); **E**xtra BP (hypertension); **E**xtra sugar (DM)
R -	**R**educed physical activity
O -	**O**besity
S -	**S**ex (males >> females)
C -	**C**MV; Chlamydia infection; **C**igarette smoking
L -	**L**ipoprotein 'A'; Lp(a)

1. Fibrous cap - Consists of smooth muscle cells, macrophages and foam cells.
2. 'Shoulder' - Cellular area around cap having macrophages, smooth muscle cells and T lymphocytes.
3. Necrotic core - Debris of dead cells, foam cells and cholesterol clefts.

Pathogenesis

It is best explained by the **'Response to Injury Hypothesis'**[Q]

According to this hypothesis, chronic endothelial injury results in increased permeability, leukocyte adhesion and thrombotic potential. This is associated with accumulation of lipoproteins (*mainly LDL*)[Q] followed by oxidation of lipoproteins in the vessel wall. The blood monocytes initially adhere to the endothelium followed by their transformation into macrophages and foam cells inside the intima along with adhesion of platelets. The activated platelets release factors causing migration of smooth muscle cells from the media to intima and their proliferation along with release of proteoglycans and collagen. This results in enhanced accumulation of lipids. In advanced atheroma, the smooth muscle cells may undergo apoptosis and so, smooth muscle cell paucity may be observed.

Foam cells are formed because oxidized LDL is ingested by the scavenger receptors present on the macrophages and smooth muscle cells both intracellularly as well as extracellularly.

Concept

Lipoprotein a is an altered form of LDL that has structural similarity to plasminogen. So, it **competes with plasminogen** in clots decreasing the latter's ability to form plasmin and clear clots.

Key Point

Foam cells are lipid laden *Smooth muscles cells/Tissue macrophages or Blood monocytes.*

Natural History of Atherosclerosis

American Heart Association classification of human atherosclerosis:

Type	Gross	Microscopy
Clinically silent		
Type I	Fatty dot (initial lesion)	Isolated macrophage; foam cell
Type II	Fatty streak	Intracellular lipid accumulation
Type III	Intermediate lesion	Type II change + small extracellular lipid pool
Clinically silent or overt		
Type IV	Atheroma lesion	Type II + core of extracellular lipids
Type V	Fibroatheroma	Lipid core and fibrotic layer
Type VI	Complicated lesion	Surface defect, Hemorrhage and thrombus

Recent Exam Question

Leriche syndrome is **aortoiliac occlusive disease** due to atherosclerotic occlusion affecting the bifurcation of the abdominal aorta as it transitions into the common iliac arteries. It is characterised by: **buttock claudication** plus **sexual impotence** along with **reduced femoral pulses**.

FATTY STREAK

- *It is the earliest lesion of atherosclerosis and is composed of lipid filled foam cells. It begins as* yellow flat spots less than 1 mm which gradually progress to atheroma formation.

Key Point

Fatty streak is the **earliest lesion of atherosclerosis**.

Significance of involved blood vessels in atherosclerosis

Abdominal Aorta	- Most common site of atherosclerotic aneurysm in body
Coronary Arteries	- Left Anterior Descending is MC coronary artery involved[Q]
Poplitial Artery	- MC peripheral vessel showing aneurysm formation[Q]
Descending Thoracic Aorta	
Internal carotid artery	
Circle of Willis	

Mnemonic

Involvement of blood vessels affected in atherosclerosis in descending order: **ACP** of **D**elhi **T**raffic **I**s **C**ute:

Abdominal Aorta
Coronary Arteries
Poplitial Artery
Descending Thoracic Aorta
Internal carotid artery
Circle of Willis

ANEURYSM

A localized abnormal dilation of a blood vessel or the wall of the heart is called aneurysm. It is of two types:

1. **True aneurysm:** Involves intact attenuated arterial wall or thinned ventricular wall of the heart. The common causes include *Atherosclerosis, syphilis and post MI ventricular aneurysms.*
2. **False/Pseudo- aneurysm:** It is characterised by a breach in the vascular wall leading to extravascular hematoma communicating with intravascular space. The two most common causes of pseudoaneurysm are *post MI rupture* and *leakage at the site of vascular anastomosis.*

Mnemonic

Complications of Atherosclerosis are **ACUTE**
Aneurysm (weakness of T media)
Calcification,
Ulceration,
Thrombosis, (feared complication)
Embolism,

Causes of True Aneurysm in Aorta

1. Atherosclerosis	*It is the most common cause of true aneurysm in aorta *The most commonly affected vessel is the abdominal aorta (below the origin of renal artery and above bifurcation into common iliac artery).
2. Syphilis	*The thoracic aorta is involved in tertiary stage of syphilis *Endarteritis of vasa vasorum results in patchy ischemia of tunica media. This is responsible for the often seen **"tree barking" appearance of the thoracic aorta**. *Aortic valve insufficiency can also occur which may result in cardiac hypertrophy. The increase in the size of heart is called as **cor bovinum**/ cow heart.
3. Other causes	Trauma; infection (mycotic aneurysm; mostly due to Salmonella gastroenteritis) and systemic disease (vasculitis)

Key Point

Atherosclerosis causes **abdominal aortic aneurysm**.

Recent Exam Questions

Aneurysm

- MC **peripheral vessel** affected: **popliteal artery**.
- MC ***visceral vessel*** affected: ***splenic artery***.
- MC **central vessel** affected: **abdominal aorta**.
- ***Overall MC vessel*** affected: ***abdominal aorta***.

Inherited Causes of Aneurysm

- **Marfan's syndrome:** defective synthesis of the protein **fibrillin**.
- **Ehlers-Danlos syndrome:** defect in collagen type III
- **Loeys Dietz syndrome:** defect in elastin and collagen types I and III due to mutation in TGF-β receptor.

- **Marfan's syndrome:** defective synthesis of the protein **fibrillin**.
- **Ehlers-Danlos syndrome:** defect in collagen type III
- **Loeys Dietz syndrome:** defect in elastin and collagen types I and III due to mutation in TGF-β receptor.

Key Point

Hypertension is the commonest cause of **ascending aortic aneurysm**.

AORTIC DISSECTION

- It occurs when blood splays apart the laminar planes of the media with the formation of blood-filled channel within the aortic wall.
- It is mostly seen in men due to hypertension (age group of 40-60 years) or Marfan's syndrome (young patients)
- Medial degeneration is a characteristic pre-existing lesion in most of the patients.

Recent Exam Questions

Aortic dissection

- MC **cause: hypertension.**
- Characteristic lesion: **Medial degeneration.**
- **Double barrel aorta.**
- MC cause of death: **rupture**.

Dissection is classified into two types:

1. **Type A** - Involves ascending aorta with/without descending aorta. It is **more common** and is **more dangerous**.
2. **Type B** - Does not involve ascending aorta but **lesion begins distal to *subclavian artery***.

VASCULITIS

The inflammation of the vessel wall is called vasculitis. It may be classified on the basis of pathogenesis or on the basis of size of the involved vessel.

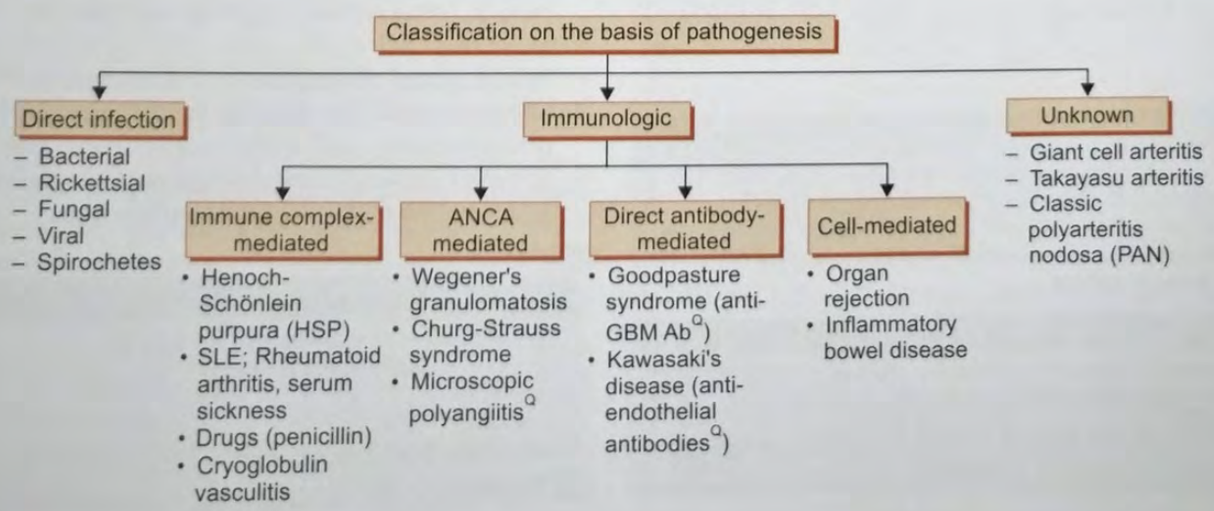


Table 3: Classification based on vessel size.

Large vessel vasculitis	Medium vessel vasculitis	Small vessel vasculitis	
		Immune complex mediated	Paucity of Immune complex
• Giant cell (temporal) arteritis • Takayasu arteritis	• Classic PAN • Kawasaki's disease • Buerger's disease	• SLE • Henoch-schonlein purpura • Cryoglobulin vasculitis • Goodpature syndrome	• Wegener's granulo-matosis • Microscopic polyangitis • Churg-strauss syndrome

Concept

Antiendothelial antibodies are found in SLE and Kawasaki's disease.

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCAs)

ANCAs are autoantibodies against enzymes inside the neutrophils c-ANCA is formed against a neutrophil azurophilic granule constituent proteinase 3 (PR3) whereas p-ANCA is formed against a lysosomal granul constituent myeloperoxidase (MPO). These can be of the following types:

ANCA	
PR3 ANCA	**MPO ANCA**
• *Earlier called* as C-ANCA	• Earlier called as P-ANCA
• Antigen is proteinase 3	• Antigen is myeloperoxidase
• Cytoplasmic staining	• Perinuclear staining
• Seen in conditions like – **Wegener's granulomatosis**	• Seen in conditions like – **Microscopic polyangiitis** – **Churg-Strauss polyangiitis** – Goodpastures syndrome – Creascentic glomeruelonephritis – **Ulcerative colitis** – Primary sclerosing cholangitis – Drugs (hydralazine, propythiouracil)

Recent Exam Questions

NEET Update!

- **C ANCA** is now called as **PR3 ANCA**.
- *P ANCA* is now called as *MPO ANCA*.

LARGE VESSEL VASCULITIS

1. **Giant cell (Temporal) arteritis/Cranial arteritis**

- It is the most common type of vasculitis in adults[Q] (usually >50[Q] years)
- This vasculitis is characterized by granulomatous arteritis of the aorta and its major branches particularly the extracranial branches of the carotid artery. Since the superficial temporal artery[Q] is the most commonly involved vessel, the giant cell arteritis is called as temporal arteritis.
- Clinical features include constitutional symptoms like fever, fatigue, weight loss, **jaw pain**[Q] facial pain, **localized headache**[Q] (most intense along the anatomical course of the superficial temporal artery) and sudden onset of blindness (due to involvement of ophthalmic artery).
- ***Biopsy of temporal artery[Q] is the investigation of choice.***
- Microscopically, there is presence of granulomatous inflammation with multinucleated giant cells and fragmentation of internal elastic lamina.

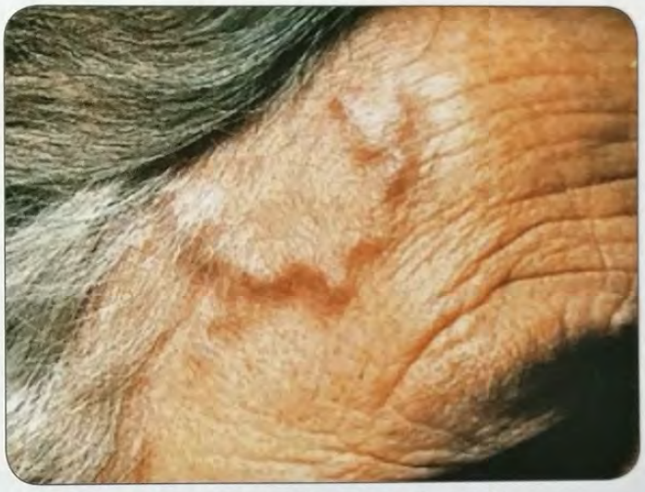


Fig. 7: Giant cell (temporal) arteritis

Recent Exam Questions

- **Temporal arteritis** is the *most common* type of vasculitis in **adults**.
- MC symptom: **localized headache.**
- M specific symptom: **jaw pain.**
- **Inv. of choice: temporal artery biopsy.**
- **Corticosteroids** are the **drug of choice** for treatment of temporal arteritis.

2. **Takayasu arteritis/ Aortoarteritis/Aortic Arch syndrome**
   - It is seen in adult females < 50 years of age.
   - This condition is characterized by granulomatous vasculitis followed by thickening of the aortic arch and decreased lumen of the vessels arising from the aortic arch. The pulmonary, renal and coronary arteries may also be involved.
   - Clinical features include weak pulses in the upper limbs (so, the disease is also called as **pulseless disease**[Q]), ocular disturbances, hypertension and neurological defects.

Key Point

The **subclavian** artery is most commonly involved vessel in Takayasu arteritis.

MEDIUM VESSEL VASCULITIS

1. Classic Polyarteritis Nodosa (PAN)

- It is a systemic vasculitis of medium sized muscular arteries (**no involvement of arterioles/capillaries/venules**Q).
- The most frequently involved vessels are those of the kidney and other viscera vessels. The vessels of the **pulmonary circulation**Q **are typically NOT involved.**
- Characteristic feature of this disease is sharp segmental lesions showing transmural inflammation of vessel wall accompanied by fibrinoid necrosis and existence of **all stages of inflammation in the same vessel.**
- 30% patients have association with *Hepatitis B antigen*Q in their serum.
- **No glomerulonephritis**Q is seen.
- It is the commonest cause of **mononeuritis multiplex**Q.

Key Point

Glomerulonephritis and vessels of pulmonary circulation are typically not involved in PAN.

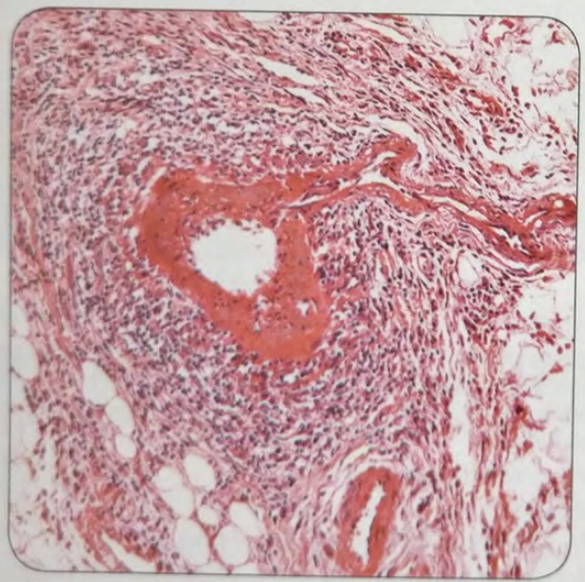


Fig. 8: Transmural Inflammation with fibrinoid necrosis in Polyarteritis Nodosa.

2. Kawasaki's disease (Mucocutaneous Lymph Node Syndrome)

- It is the vasculitis affecting children **< 5 years**Q of age. It is characterized by fever, conjunctivitis and oral erythema, skin rash often with desquamation, erythema of palms and soles and cervical lymphadenopathy.
- For the diagnosis of Kawasaki disease, there must be presence of **fever**Q (most important constitutional symtpom) for greater than 5 days plus any 4 of the following:

Mnemonic

- **C** - **C**onjunctivitis (**non-exudative**Q; non purulent conjunctivitis)
- **R** - **R**ash (polymorphous non-vesicular)
- **E** - **E**dema (or erythema of hands or feet)
- **A** - **A**denopathy (**cervical**Q, **often unilateral**Q and **non suppurative**Q)
- **M** - **M**ucosal involvement (erythema or fissures or crusting at times referred as **strawberry tongue**Q)

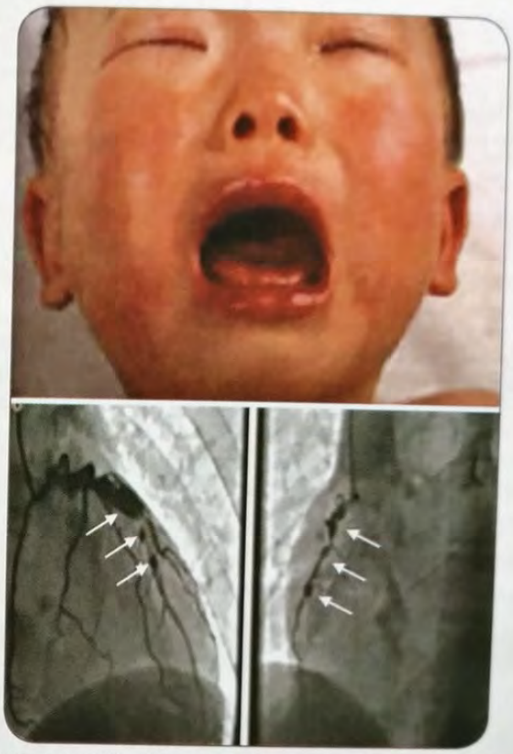


Fig. 9: Kawasaki's disease with coronary artery narrowing

Recent Exam Questions

Kawasaki's disease

- Older name: **infantile polyarteritis.**
- **Anti-endothelial cell antibodies** present.
- ↑ platelets **(thrombocytosis).**
- MC cause of **MI in children.**
- Treatment: **intravenous γ globulin with aspirin.**

- It may present with myocardial infarction^{Q} in children. It is having the presence of *anti-endothelial cell antibodies*Q. There is typically intimal proliferation and mononuclear infiltration of vessel wall. The patients also have elevated platelet count in this condition.

SMALL VESSEL VASCULITIS

1. Microscopic Polyarteritis/Microscopic Polyangiitis/ Leukocytoclastic Vasculitis

- Necrotizing vasculitis affecting arterioles/capillaries/ venules in which **all lesions are of the same age.**

- **Granulomatous inflammation** is **absent**[Q]
- *Necrotizing glomerulonephritis* and capillaritis are common.
- Fibrinoid necrosis associated with infiltration of neutrophils which become fragmented (*leukocytoclasia*).

Key Point

p-ANCA is present in Microscopic Polyangiitis but is **NOT** seen with **PAN**.

2. **Henoch-Schönlein purpura (HSP)/Anaphylactoid purpura**[Q]
   - It is the **commonest vasculitis in childen**[Q].
   - This is a vasculitis with **IgA**[Q] deposits affecting small vessels like arterioles, capillaries and venules of the skin, gut and glomeruli and commonly associated with arthralgia.
   - Clinical features include **palpable purpura (due to vasculitis** and not reduced platelet count)[Q], **colicky abdominal pain**[Q], arthralgia in multiple joints and glomerulonephritis.
   - It is caused due to immune complex deposition but **complement levels are usually normal**[Q].

Recent Exam Questions

Henoch-Schönlein purpura

- Also called **Anaphylactoid purpura.**
- *MC vasculitis* in **childen**.
- Deposition of **IgA**.
- Skin **rash/palpable purpura** is due to **vasculitis**.
- **Normal** *platelet count.*
- **Normal** *complement levels.*

3. **Hypersensitivity vasculitis/Cutaneous vasculitis**
   - Defined as inflammation of the blood vessels of the dermis.
   - Also called as **hypersensitivity vasculitis/cutaneous leukocytoclastic angiitis**.
   - Microscopic features include presence of vasculitis of small vessels characterized by a *leukocytoclasis*[Q] (refers to the nuclear debris remaining from the neutrophils that have infiltrated in and around the vessels during the acute stages).
   - Hallmark clinical feature is **skin involvement** typically appearing as **palpable purpura**[Q] appearing on most commonly lower limbs
   - Diagnosis is best made with **biopsy** showing vasculitis.
   - Removal of offending agent (if any) and steroids help most of the patients.

Recent Exam Question

Latest Information (9th Edn.)Wegener's granulomatosis is now called as **granulomatosis** with polyangitis.

4. **Churg-Strauss syndrome (Allergic granulomatosis and angiitis)**
   - Characteristically have necrotizing vasculitis accompanied by granulomas with eosinophilic necrosis.
   - p-ANCA present in 50% of patients.
   - Strong association with allergic rhinitis, bronchial asthma and eosinophilia.
   - Principal cause of death includes coronary arteritis and myocarditis.
5. **Wegener's granulomatosis (Granulomatosis with polyangitis)**

Necrotizing vasculitis which is characterized by **triad of**

1. Acute necrotizing *granulomas of either upper* (more commonly) *or lower respiratory tract or both.*
2. *Focal necrotizing or granulomatous vasculitis* most commonly affecting lungs and upper airways.
3. *Renal involvement* in the form of focal necrotizing, often crescentic glomerulonephritis.

- Clinical features include fever, weight loss, otitis media, nasal septal perforation[Q], strawberry gums[Q], cough, hemoptyis, **palpable purpura**[Q], joint pain and ocular features (uveitis, conjunctivitis)
- Investigations show serum **c-ANCA**[Q] positivity, **cavitatory lesions**[Q] in the chest X ray and red cell casts (indicative of glomerulonephritis) in the urine.

Concept

Limited Wegener's granulo-matosis is characterized by **only respiratory tract** involvement without any renal involvement.

RAYNAUD'S PHENOMENON

Raynaud's disease or Primary Raynaud's phenomenon is seen in young females. It is characterized by intense vasospasm of *small vessels* in the digits of hands and feet induced by cold and emotional stimuli (so, ***pulses are NOT affected***).

- Characteristic sequence of color change is

White	→	Blue	→	Red
(Local syncope)		(Local asphyxia)		(Local recovery)

- Structural changes are absent *except* in later course when thickening of intima is seen.

Secondary Raynaud's phenomenon is associated with conditions like **systemic sclerosis**[Q] (commonest cause), SLE, atherosclerosis and Buerger's disease. It usually affects people of age >30 years. The index and middle fingers are more sensitive to attacks.

Key Point

Systemic sclerosis is the **commonest cause** of **secondary Raynaud's** phenomenon.

Buerger's disease (Thromboangiitis obliterans)

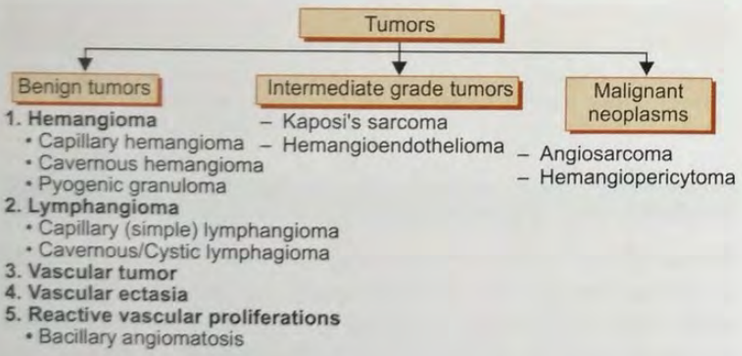
- It is usually seen among **heavy cigarette smokers**.
- Onset is **before age 35**
- It is associated with **hypersensitivity to intradermal injections of tobacco** extracts.
- Microscopic examination demonstrates **segmental thrombosing vasculitis often extends into contiguous veins and nerves** (*a feature rarely seen in other types of vasculitis*), encasing them in fibrous tissue.
- Thrombus contains *microabscess with granulomatous inflammation.*[Q]
- This patient has distal lower extremity vascular insufficiency which may present as Calf, foot or hand intermittent claudication, superficial nodular phlebitis and cold sensitivity (Raynaud's phenomenon). Severe distal pain even at rest can result and may be due to neural involvement. Later complications include ulcerations and gangrene of the toes feet or fingers.
- **Treatment** includes **smoking cessation**, drugs (peripheral vasodilators) and may even require surgery.

Recent Exam Questions

Buerger's disease

- Segmental thrombosing **vasculitis** often extends into **contiguous veins** and **nerves** is a **characteristic feature** of Buerger's disease.
- **Lymphatics** are **NOT affected** in this condition.

VASCULAR TUMORS



Benign Tumors

Hemangioma

1. **Capillary hemangioma**

- It is the most common type of vascular tumor which occurs in skin, mucus membrane and viscera.
- "Strawberry" type of capillary hemangioma (also called as juvenile hemangioma) is very common, ***growing rapidly in the first few months***[Q] and **regresses by age 7**[Q] in newborns. The child is **normal**[Q] **at birth** in almost 90% of cases.
- Histologically, they are lobulated unencapsulated aggregates of closely packed, thin walled capillaries which are blood filled and lined by a flattened endothelium.

Key Point

Strawberry gums are seen in **Wegener's granulomatosis**.

Key Point

Strawberry tongue is seen in **Kawasaki disease**.

Key Point

Strawberry hemangioma is a type of **capillary hemagioma**.

2. **Cavernous hemangioma**
   - It is less common than capillary hemangioma with same age and anatomic distribution. It more frequently involves deep structures as it shows no tendency to regress. So, it usually requires surgery.
   - Morphologically, Cavernous hemangiomas are made up of large, cavernous vascular spaces in which intravascular thrombosis and dystrophic calcification is common.
   - They may be life-threatening as in von Hippel Lindau disease where they occur in cerebellum, brainstem and the eye.

Recent Exam Questions

Cavernous lymphangioma

- It occurs in **Turner's syndrome** at the neck region.
- Also seen in patients of von Hippel Lindau disease.

3. **Pyogenic granuloma**
   It is a polypoid form of capillary hemangioma seen attached by a stalk to skin or oral mucosa. It is associated with edema and inflammatory cells.

Granuloma gravidarum is present in the gingiva of pregnant women and it regresses after delivery.

LYMPHANGIOMA

1. **Cavernous lymphangioma** (also called as **cystic hygroma**)

- This is present in the neck region of the children.
- Made up of dilated, cystic lymphatic spaces lined by endothelial cells.
- Lesions are non-encapsulated, so, removal is difficult.

2. **Capillary lymphangioma**
   It is a lesion composed of small lymphatic channels occurring subcutaneously in the head and neck region and in the axilla.

Concept

Capillary lymphangioma is distinguished from the capillary channels only by the absence of blood cells.

GLOMUS TUMOR (GLOMANGIOMA)

- Benign tumor arising from the smooth muscle cells of the glomus body which is an arteriovenous anastomosis involved in thermoregulation.
- Most commonly present in the distal portion of the digits (under fingernails).

- Histologically, there is presence of branching vascular channels and stroma containing nests/aggregates of glomus cells arranged around vessels.

INTERMEDIATE/BORDERLINE TUMORS

Kaposi's Sarcoma (KS)

It is caused by **KS Herpes virus** or **Human herpes virus 8** (HHV8) and has the following 4 forms:

Type of Kaposi sarcoma	Association with HIV	Chief affected organs
Classic/Chronic/ European KS	Absent	Skin plaques and nodules
African/Endemic KS	Absent	No skin lesions; lymphadenopathy present
Transplant associated/ Immunosuppression-associated KS	Absent	Lymph nodes, mucosa and visceral organs
Epidemic/AIDS associated KS	**Present**[Q]	Lymph nodes and viscera involved

Recent Exam Questions

Kaposi Sarcoma

- Caused by **HHV8**.
- **MC cancer** in **HIV**.
- **MC site: skin of lower limbs**.
- MC **extracutaneous** site: **lymph nodes**.

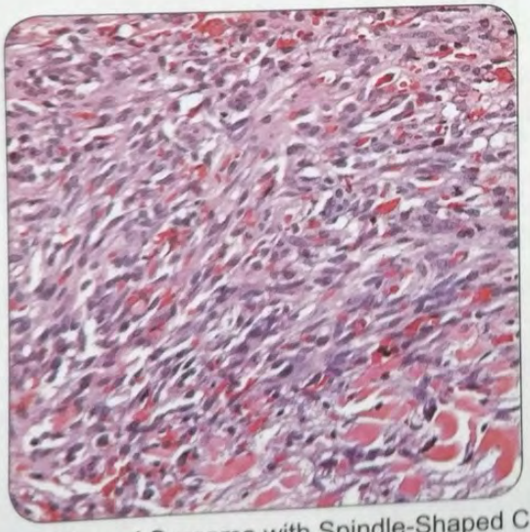


Fig. 10: Kaposi Sarcoma with Spindle-Shaped Cells.

The morphology is characterized by three stages:

1. Patch stage
2. Plaque stage
3. Nodular stage – Often accompanied by involvement of lymph nodes and of viscera particularly in African and AIDS-associated disease.

MALIGNANT TUMORS

Angiosarcoma

- Malignant endothelial cell neoplasm most commonly seen in skin, soft tissue, breast and liver.
- May also arise from dilated lymphatic vessels (lymphangiosarcoma).
- Endothelial cell origin is demonstrated by staining for CD31, CD34 or vWF.

Key Point

Hepatic angiosarcoma is associated with carcinogens including **arsenic**, **thorotrast** (a radioactive contrast) and **polyvinyl chloride** (PVC; a plastic).

Hemangiopericytoma

- Tumor derived from pericytes which are the cells present along the capillaries and venules.
- These tumors most commonly arise from pelvic retroperitoneum or the lower limbs (particularly thighs).
- Capillaries are arranged in *'fish-hook pattern'* and *silver stain* is used for diagnosing this condition.

Quick review of superior vena cava and inferior vena cava syndromes

Syndromes	Associated Cancers	Clinical Features
Superior Vena Cava (SVC) syndrome	• Bronchogenic cancer[Q] • Mediastinal lymphoma[Q]	• Dilation of the veins of the head, neck and arms • Cyanosis • Respiratory distress
Inferior Vena Cava (IVC) syndrome	• Renal cell carcinoma[Q] • Hepatocellular carcinoma[Q]	• Lower limb edema • Dilation of the superficial collateral veins of the lower abdomen • Massive proteinuria (if renal vein is involved)

Multiple Choice Questions

HEART FAILURE, RHEUMATIC HEART DISEASE, ENDOCARDITIS

1. **A young female patient came for routine examination. On examination a mid systolic click was found. There is no history of rheumatic heart disease. The histopathological examination is most likely to show which of the following?** *(AIIMS May 2012)*
   (a) Myxomatous degeneration and prolapse of the mitral valve
   (b) Fibrinous deposition on the tip of papillary muscle
   (c) Rupture of chordae tendinae
   (d) Aschoff nodule on the mitral valve

2. **Least chances of infective endocarditis is associated with** *(AI India 2012)*
   (a) Mild MS (b) Mild MR
   (c) Small ASD (d) Small VSD

3. **A 45 yrs old male had severe chest pain and was admitted to the hospital with a diagnosis of acute myocardial infarction. Four days later he died and autopsy showed transmural coagulative necrosis. Which of the following microscopic features will be seen on further examination?** *(AIIMS May 2011)*
   (a) Fibroblasts and collagen
   (b) Granulation tissue
   (c) Neutrophilic infiltration surrounding coagulative necrosis
   (d) Granulomatous inflammation

4. **Which one of the following is not included as major criteria in Jones criteria?** *(AIIMS Nov. 2010)*
   (a) Pancarditis
   (b) Arthritis
   (c) Subcutaneous nodules
   (d) Elevated ESR

5. **The mechanism of the development of Acute Rheumatic Fever is which of the following?** *(AIIMS May 2010)*
   (a) Cross reactivity with exogenous antigen
   (b) Innocent bystander effect
   (c) Due to toxin secretion by streptococci
   (d) Release of pyrogenic cytokines

6. **Cardiac involvement in carcinoid syndrome is characterized by:** *(AI 2010)*
   (a) Calcification tricuspid valve
   (b) Intimal fibrosis of right ventricle, tricuspid and pulmonary valve.
   (c) Involvement of the major blood vessels is commonly seen
   (d) Equal involvement of both the sides of the heart

7. **Most friable vegetation is seen in:** *(AI 2010)*
   (a) Infective endocarditis
   (b) Libman Sacks endocarditis
   (c) Rheumatic heart disease
   (d) Rheumatoid heart disease

8. **Aschoff's nodules are seen in:** *(AI 2005)*
   (a) Subacute bacterial endocarditis
   (b) Libman-Sacks endocarditis
   (c) Rheumatic carditis
   (d) Non-bacterial thrombotic endocarditis

9. **A 10-year-old boy, Pappu, died of acute rheumatic fever. All the following can be expected at autopsy except:** *(AI 2002)*
   (a) Aschoff's nodules
   (b) Rupture of Chordae tendinae
   (c) McCallum patch
   (d) Fibrinous pericarditis

10. **NOT true about ASO titer:** *(AIIMS Nov 2009)*
    (a) May be positive in normal people
    (b) Major Jones' criteria
    (c) May be negative in post streptococcal glomerulonephritis
    (d) May not be elevated even in presence of Carditis

11. **In mitral valve prolapse syndrome, histopathology of mitral valve shows:** *(AIIMS Nov 2007)*
    (a) Hyaline degeneration
    (b) Elastic degeneration
    (c) Myxomatous degeneration
    (d) Fibrinoid necrosis

12. **Which of the following is not a complication of infective endocarditis?** *(AIIMS Nov 2003)*
    (a) Myocardial ring abscess
    (b) Suppurative pericarditis
    (c) Myocardial infarction
    (d) Focal and diffuse glomerulonephritis

13. **Aschoff bodies in Rheumatic heart disease show all of the following features, except:** *(AIIMS Nov 2002)*
    (a) Anitschkow cells (b) Epithelioid cells
    (c) Giant cells (d) Fibrinoid necrosis

14. **Rheumatic heart disease can be diagnosed on the basis of:** *(PGI Dec 2001)*
    (a) Aschoff bodies
    (b) Vegetation along the line of closure of valves
    (c) Endocardial involvement only
    (d) Follows skin and throat infection

15. **Pathognomic feature of acute rheumatic fever is:** *(Delhi 2009 RP)*
(a) Pericarditis
(b) Myocarditis
(c) Mitral stenosis
(d) Aschoff's nodules

16. **Vegetations on under surface of cusps are found in:** *(Delhi PG-2008, P 2006)*
(a) Infective endocarditis
(b) Libman-Sacks endocarditis
(c) SABE
(d) Rheumatic fever

17. **Aschoff's nodules are seen in:** *(Delhi PG-2007)*
(a) Acute rheumatic fever
(b) Bacterial endocarditis
(c) Pneumoconiosis
(d) Asbestosis

18. **Anitschkow cells are pathognomonic for:** *(Delhi PG-2006)*
(a) Acute rheumatic fever
(b) Yellow fever
(c) Malarial spleen
(d) ITP

19. **All are the causes of myocarditis except:** *(Karnataka 2005)*
(a) Trichinosis
(b) Mycobacterium tuberculosis
(c) Corynebacterium diphtheriae
(d) Systemic lupus erythematosus

20. **Disarrangement of myofibrils is found in:** *(UP 2001)*
(a) Dilated cardiomyopathy
(b) Constrictive cardiomyopathy
(c) Fibroelastic cardiomyopathy
(d) Hypertrophic cardiomyopathy

MOST RECENT QUESTIONS

21. **Most common cause of mitral stenosis is:**
(a) Rheumatic heart disease
(b) Infective-endocarditis
(c) Diabetes mellitus
(d) Congenital

22. **Calcification of aortic valve is seen in:**
(a) Hurler's syndrome
(b) Marfan's syndrome
(c) Syphilis
(d) None

23. **Most common cause of left sided cardiac failure is:**
(a) Myocardial infarction
(b) Systemic hypertension
(c) Rheumatic heart disease
(d) Infective endocarditis

24. **Libman-Sacks endocarditis is found in:**
(a) Rheumatoid arthritis
(b) SLE
(c) Syphilis
(d) Lymphoma

25. **Chronic constrictive pericarditis is most commonly caused by:**
(a) Staphylococcus (b) TB
(c) Viral (d) Autoimmune

26. **Aschoff's bodies are seen in:**
(a) Acute rheumatic fever
(b) SLE
(c) SABE
(d) TB

27. **Diagnostic feature of rheumatic fever is:**
(a) Antischkow cells
(b) Aschoff's nodule
(c) MacCallum's patch
(d) Epithelioid cells

28. **Rheumatoid factor is:**
(a) lgM directed against lgG
(b) lgE directed against lgM
(c) lgG directed against lgM
(d) None

29. **Major criteria for rheumatic fever, consists of all except:**
(a) Pancarditis
(b) Arthritis
(c) Subcutaneous nodule
(d) Erythema nodosum

30. **Which type of endocarditis has vegetation on both sides of the valves ?**
(a) Infective endocarditis
(b) Libman-Sacks endocarditis
(c) Rheumatic fever
(d) Non bacterial thrombotic enodcarditis

31. **Which of the following is the feature of vegetations in Libmann Sacks endocarditis?**
(a) Large and fragile
(b) Small warty along the line of closure of valve
(c) Small or medium sized on either or both sides of valve
(d) Small bland vegetations

32. **Heart failure cells are seen in which of the following organs?**
(a) Kidney (b) Heart
(c) Lungs (d) Brain

33. **Mc Callum's patch is diagnostic of:**
(a) Infective endocarditis
(b) Rheumatic endocarditis
(c) Myocardial infarction
(d) Tetralogy of Fallot (ToF)

34. **Tigered effect in myocardium is due to:**
(a) Malignant change
(b) Fat deposition
(c) Seen in rheumatic fever
(d) Associated with myocarditis

35. **Mitral valve vegetations do not embolise usually to:**
(a) Brain (b) Liver
(c) Spleen (d) Lung

36. **ASLO titers are used in the diagnosis of:**
(a) Acute rheumatoid arthritis
(b) Acute rheumatic fever
(c) Ankylosing spondylitis
(d) Osteoarthritis

37. **Most common heart valve involved in IV drug user is**
(a) Mitral valve
(b) Aortic valve
(c) Pulmonary valve
(d) Tricuspid valve

38. **Angina, dyspnea and syncope is seen in:**
(a) Pulmonary stenosis
(b) Atrial septal defect
(c) Ventricular septal defect
(d) Aortic stenosis

39. **Which of the following cardiac valves is not commonly involved in rheumatic fever?**
(a) Mitral (b) Aortic
(c) Pulmonary (d) Tricuspid

40. **In a patient with mitral valve vegetations, the vegetations are present along lines of closure along with fusion of commisures. Which of the following is the most likely diagnosis?** *(AIIMS May 2016)*
(a) Infective endocarditis
(b) Marantic endocarditis
(c) Rheumatic endocarditis
(d) Libman sacks endocarditis

41. **Level of which of the following is not elevated in heart disease?**
(a) LDH (b) 5′-nucleotidase
(c) SGOT (d) ALP

42. **Which of the following is not a feature of rheumatic heart disease?**
(a) Chorea (b) Arthritis
(c) Janeways lesion (d) Carditis

43. **Which protein is defective in dilated cardiomyopathy?**
(a) Myosin (b) Tropomyosin
(c) Dystropin (d) Troponin

ISCHEMIC HEART DISEASE

44. **A 70-year-old male Rohan with advanced visceral cancer dies of extensive myocardial infarction. Autopsy also reveals sterile non-destructive vegetations along the mitral leaflet edges. The pathogenesis of this patient's vegetations is most similar to that of:**
(a) Hypercalcemia of malignancy
(b) Distant metastases
(c) Trousseau syndrome
(d) Raynaud's phenomenon

45. **A 56-year-old male presented with sudden substernal pain, impending doom and died 4 days after. On autopsy, there was a large transmural anterior wall infarction. It would be associated with:**
(a) Presence of collagen and fibroblasts *(AI 2009)*
(b) Presence of neutrophils
(c) Granulomatous inflammation
(d) Granulation tissue

46. **All of the following statements regarding subendocardial infarction are true, except:**
(a) These are multifocal in nature *(AI 2006)*
(b) These often result from hypotension or shock
(c) Epicarditis is not seen
(d) These may result in aneurysm

47. **A 60-year-old male presented with acute chest pain of 4 hours duration. Electrocardiographic examination revealed new Q wave with ST segment depression. He succumbed to his illness within 24 hours of admission. The heart revealed presence of a transmural hemorrhagic area over the septum and anterior wall of the left ventricle. Light microscopic examination is most likely to reveal:** *(AI 2004)*
(a) Edema in between normal myofibers
(b) Necrotic myofibers with presence of neutrophils
(c) Coagulative necrosis of the myocytes with presence of granulation tissue
(d) Infiltration by histiocytes with hemosiderin laden macrophages

48. **Which of the following increases the susceptibility to coronary artery disease?** *(AI 2003)*
(a) Type V hyperlipoproteinemia
(b) von Willebrand's disease
(c) Nephrotic syndrome
(d) Systemic lupus erythematosus

49. **A myocardial infarct showing early granulation tissue has most likely occurred:** *(AI 2002)*
(a) Less than 1 hour (b) Within 24 hours
(c) Within 1 week (d) Within 1 month

50. **Troponin-T is a marker of:** *(AIIMS May 2004)*
(a) Renal disease
(b) Muscular dystrophy
(c) Cirrhosis of liver
(d) Myocardial infarction

51. **Autopsy finding after 12 hrs in a case of death due to M.I. is** *(Delhi 2010)*
(a) Caseous pecrosis
(b) Coagulative necrosis
(c) Fat necrosis
(d) Liquefactive necrosis

52. **In MI with hypothyroidism, what is the marker of choice?** *(Delhi PG-2008)*
(a) LDH (b) CPK-MB
(c) Aldolase (d) Troponin-I

53. **What is the investigation for second MI after 1 week of previous MI?** *(Delhi PG-2008)*
(a) Troponin I (b) Myoglobin
(c) CPK-MB (d) LDH

54. **Earliest light microscopic change in myocardial infarction is:** *(UP 04, Bihar 03)*
(a) Waviness of the fibers
(b) Neutrophilic infiltration
(c) Phagocytic infiltration
(d) Coagulative necrosis

MOST RECENT QUESTIONS

55. **Most common artery involved in myocardial infarction is:**
(a) Right coronary artery
(b) Left coronary artery
(c) Left anterior descending coronary artery
(d) Left circumflex coronary artery

56. **In myocardial infarction scarring completes by:**
(a) 1 day (b) 1 week
(c) 1 month (d) 3 months

57. **Dressler's syndrome is:**
(a) Viral (b) Bacterial
(c) Fungal (d) Autoimmune

58. **Heart muscle contains the isoenzymes:**
(a) MM (b) MB
(c) MM and MB (d) BB

59. **Enzyme elevated in first 2 hours of MI is:**
(a) CPK MB (b) LDH
(c) SGPT (d) Acid phosphatase

60. **Post MI day 10 which enzyme is raised:**
(a) CPK (b) Troponin
(c) LDH (d) Myoglobin

61. **7 day old MI the most sensitive biochemical marker:**
(a) Troponin T (b) CPK MB
(c) LDH (d) Myoglobin

62. **In myocardial reperfusion injury, the maximum effect is caused due to which of the following?**
(a) Neutrophil (b) Monocytes
(c) Eosinophils (d) Free radicals

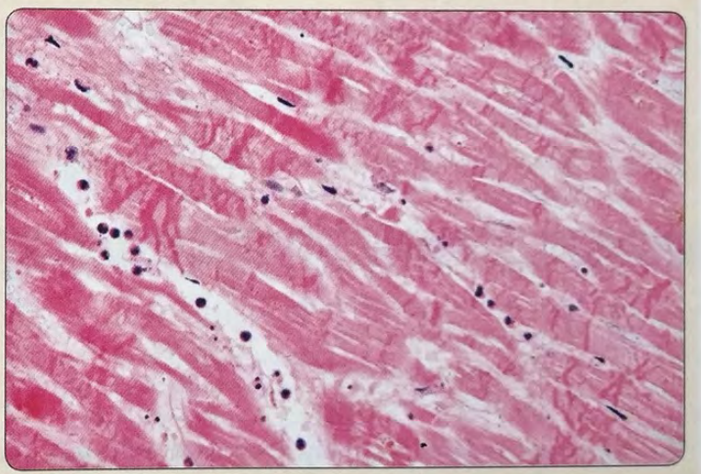
63. **The cells seen after 72 hours in the infarcted area in MI are:**
(a) Neutrophils (b) Lymphocytes
(c) Macrophages (d) Monocytes

64. **Myocarditis is most commonly caused by**
(a) Influenza
(b) Measles virus
(c) Coxsackie virus
(d) Epstein barr virus

65. **In myocardial infarctions, microscopes picture of coagulation necrosis with neutrophilic infiltration is seen after:**
(a) 4-12 hr (b) 12-24 hr
(c) 1-3 days (d) 3-7 days

66. **During autopsy of a patient died due to suspected myocardial infarction, the heart was stained with triphenyl tetrazolium tetra-chloride dye. What wil be the color of the viable myocardium?** *(AIIMS Nov 2016)*
(a) Blue (b) White
(c) Yellow (d) Brick red

67. **The following is the Hematoxylin and Eosin stained section from the heart of a patient after Myocardial Infarction. What can you say about the age of the infarction?** *(AIIMS May 2016)*



(a) 1–2 days (b) 3 weeks
(c) 6 hours (d) 1 week

CARDIAC TUMOUR

68. **Which malignancy metastasizes to heart?** *(AP 2007)*
(a) Bronchial carcinoma
(b) Prostate carcinoma
(c) Breast carcinoma
(d) Wilms' tumor

MOST RECENT QUESTIONS

69. **Most common tumour of heart is:**
(a) Myxoma
(b) Rhabdomyosarcoma
(c) Fibroma
(d) Leiomyosarcoma

70. **Atrial myxoma commonly arises from:**
(a) Left ventricle (b) Left atrium
(c) Right ventricle (d) Right atrium

71. **Most common benign heart tumor is:**
(a) Rhabdomyoma
(b) Hemangioma
(c) Lipoma
(d) Myxoma

HTN, ATHEROSCLEROSIS, ANEURYSM

72. **In 2 patients with atherosclerosis, one is diabetic and the other is non diabetic. In relation to the non diabetic, the diabetic patient has 100 times risk of which of the following?** *(AIIMS May 2012)*
(a) MI
(b) Stroke
(c) Lower limb ischemia
(d) Vertebrobasilar insufficiency

73. **ALL of the following statements regarding atherosclerosis are true except:** *(AIIMS Nov 2012)*
(a) Omega-3 fatty acid (abundant in fish oil) decrease LDL
(b) Atherosclerosis is less important in age more than 45 years age
(c) Cigarette smoking is independent risk factor for M.I
(d) C reactive protein is independent risk factor for M.I

74. **Which of the following is the commonest histological finding in benign hypertension?** *(AIIMS May 2011)*
(a) Proliferative end arteritits
(b) Necrotizing arteriolitis
(c) Hyaline arteriosclerosis
(d) Cystic medial necrosis

75. **The presence of stroke, peripheral vascular disease and atherosclerosis is associated with which hormone?**
(a) Insulin deficiency *(AI 2010)*
(b) Hyperestrogenemia
(c) Hypothyroidism
(d) Progesterone

76. **Most common cause of abdominal aortic aneurysm is:**
(a) Atherosclerosis (b) Syphilis *(AI 2010)*
(c) Trauma (d) Congenital

77. **Hallmark feature of benign HTN is:** *(AI 2009)*
(a) Hyaline arteriosclerosis
(b) Cystic medial necrosis
(c) Fibrinoid necrosis
(d) Hyperplastic arteriosclerosis

78. **All are seen in malignant hypertension, except:**
(a) Fibrinoid necrosis *(AI 2008)*
(b) Hyaline arteriosclerosis
(c) Necrotizing glomerulonephritis
(d) Hyperplastic arteriosclerosis

79. **Recurrent ischemic events following thrombolysis has been pathophysiologically linked to which of the following factors:** *(AI 2003)*
(a) Antibodies to thrombolytic agents
(b) Fibrinopeptide A
(c) Lipoprotein A
(d) Triglycerides

80. **70-year-old man has abdominal pain with mass in abdomen. Angiography reveals aneurysm of aorta. Most likely cause is:** *(AIIMS Nov 2001)*
(a) Trauma
(b) Atherosclerosis
(c) Syphilis
(d) Congenital

81. **In malignant hypertension hyperplastic arteriosclerosis is seen in all except:** *(AIIMS May 2001)*
(a) Heart
(b) Kidney
(c) Pericardial fat
(d) Peripancreatic fat

82. **CAD predisposing factors:** *(PGI Dec 2002)*
(a) Homocysteinemia
(b) Increased lipoprotein B
(c) Increased fibrinogen
(d) Increased HDL
(e) Increased plasminogen activator inhibitors

83. **Features of essential hypertension:** *(PGI Dec 2002)*
(a) Concentric hypertrophy of LV
(b) Increased heart size
(c) Increased size of the heart muscles
(d) Myohypertrophy
(e) Myohyperplasia

84. **In atherosclerosis, increased LDL in monocyte macrophage is due to:** *(Delhi 2010)*
(a) LDL receptors on macrophage
(b) LDL receptors on endothelium
(c) Lipids in LDL get auto-oxidized
(d) All of the above

85. **Which of the following is the least common site of atherosclerotic lesions?** *(Delhi 2009 RP)*
(a) Aortic bifurcation
(b) Pulmonary arterial trunk
(c) Common carotid artery
(d) Middle cerebral artery

86. **Vascular pathology of benign hypertension includes:**
(a) Segmental fibrinoid necrosis *(Delhi 2009 RP)*
(b) Hyaline arteriosclerosis
(c) Periarteritis
(d) Loss of internal elastic lamina

MOST RECENT QUESTIONS

87. **Accelerated phase of hypertension is characterized microscopically by:**
(a) Fibrinoid necrosis of arteriolar wall
(b) Hyaline arteriosclerosis
(c) Elastosis of the intima
(d) Marked calcification of the media

88. **Most common site of atherosclerotic aneurysm is:**
(a) Coronary artery (b) Renal artery
(c) Arch of aorta (d) Abdominal aorta

89. **Monckeberg's calcific sclerosis affects the medium sized muscular arteries by involving the structure of:**
(a) Intima (b) Media
(c) Adventitia (d) All of the above

90. **Malignant hypertension causes which of the following changes in the kidney?**
(a) No change in kidney
(b) Flea bitten kidney
(c) Irregular granular contracted kidney
(d) Large white kidney

91. **Most common site of artery of atherosclerosis:**
(a) Right coronary artery
(b) Left anterior descending coronary artery
(c) Left circumflex artery
(d) Diagonal branch of LAD

92. **Most common cause of dissecting hematoma is because of:**
(a) Hypertension (b) Marfan syndrome
(c) Iatrogenic (d) Kawasaki

93. **Cystic medical necrosis is seen in:**
(a) Marfan syndrome
(b) Friedrichs ataxia
(c) Down syndrome
(d) Kawasaki disease

94. **Visceral aneurysm is most commonly seen in:**
(a) Splenic (b) Renal
(c) Hepatic (d) Coronary

95. **Medial calcification is seen in:**
(a) Atherosclerosis
(b) Arteriolosclerosis
(c) Monckeberg's sclerosis
(d) Dissecting aneurysm

96. **Atheromatous changes of blood vessels affects early in ?**
(a) Kidney (b) Heart
(c) Liver (d) Spleen

97. **Most common cause of aortic aneurysm is:**
(a) Syphilis (b) Marfan's syndrome
(c) Atherosclerosis (d) Congenital

98. **Ascending aorta involvement is the commonest site of which aneurysm:**
(a) Syphilitic (b) Atherosclerotic
(c) Berry aneurysm (d) Traumatic

99. **Atherosclerosis is seen with which bacteria:**
(a) Staph aureus
(b) Streptococcus pneumonia
(c) Chlamydia pneumoniae
(d) Chlamydia trachomatis

100. **Commonest histological finding in benign hypertension is:**
(a) Proliferating endarteritis
(b) Necrotising arteriolitis
(c) Hyaline arteriosclerosis
(d) Cystic medial necrosis

101. **Onion skin thickening of arteriolar wall is seen in:**
(a) Atherosclerosis
(b) Median calcific sclerosis
(c) Hyaline arteriosclerosis
(d) Hyperplastic arteriosclerosis

102. **HDL receptors:**
(a) SR-B1 (b) HDLR
(c) LDLR (d) SR-B2

103. **Obliterative endarteritis is vasa vasorum is seen in:**
(a) hypertension (b) TB
(c) SLE (d) Syphilis

VASCULITIS, RAYNAUD DISEASE

104. **Which of the following is a feature of temporal arteritis?** *(AIIMS Nov 2012)*
(a) Giant cell arteritis
(b) Granulomatous vasculitis
(c) Necrotizing vasculitis
(d) Leucocytoclastic vasculitis

105. **Small vessels vasculitis seen in** *(AI India 2012)*
(a) Giant cell arteritis
(b) Takayasu arteritis
(c) PAN
(d) Microscopic polyangiitis

106. **A 5-year-old child presents with perivascular IgA deposition and neutrophilic collection. There is erythematous rash on the lower limbs and non-blanching purpura. The likely diagnosis in the child is:** *(AIIMS Nov 2011)*
(a) Henoch-Schonlein Purpura
(b) Wegner's granulomatosis
(c) Giant cell Vasculitis
(d) Kawasaki's disease

107. **Pathogenesis of all of the following is granulomatous, except:** *(AI 2010)*
(a) Wegener's granulomatosis
(b) Buerger's disease
(c) Takayasu's arteritis
(d) Microscopic polyangiitis

108. ANCA is associated with: *(AIIMS Nov 2009)*
(a) Henoch-Schonlein Purpura
(b) Goodpasture syndrome
(c) Rheumatoid arthritis
(d) Wegener's granulomatosis

109. Which of the following is not a common cause of Vasculitis in adults? *(AIIMS Nov 2009)*
(a) Giant Cell Arteritis
(b) Polyarteritis nodosa
(c) Kawasaki's disease
(d) Henoch-Schonlein Purpura

110. Hypersensitivity vasculitis most commonly involves:
(a) Arterioles *(AIIMS May 09, Nov 08, DNB 2008)*
(b) Post-capillary venules
(c) Capillaries
(d) Medium sized arteries

111. A patient presents with respiratory symptoms, i.e. cough, hemoptysis and glomerulonephritis. His c-ANCA levels in serum were found to be raised. The most likely diagnosis is: *(AIIMS Nov 2002)*
(a) Goodpasture's syndrome
(b) Classic polyarteritis nodosa
(c) Wegener's granulomatosis
(d) Kawasaki's syndrome

112. Vasculitis is seen in: *(PGI Dec 2002)*
(a) Buerger's disease
(b) HSP
(c) Gout
(d) Reiter's disease
(e) Behcet's syndrome

113. Wegener's granulomatosis involve: *(PGI Dec 2003)*
(a) Lung (b) Liver
(c) Kidney (d) Upper respiratory tract
(e) Heart

114. Wegener's granulomatosis: *(PGI Dec 2006)*
(a) Involves lungs
(b) Involves nose
(c) Involves kidney
(d) Treated with cytotoxic agent and/or steroids

115. All are true about ANCA associated crescentic glomerulonephritis, except: *(Delhi 2009 RP)*
(a) Seen in Wegener's granulomatosis
(b) Seen in microscopic polyangitis
(c) Seen in Henoch-Schönlein purpura
(d) Is pauci immune in nature

116. All of the following are small vessel vasculitis except:
(a) Kawasaki's disease *(Delhi PG-2006)*
(b) Churg-Strauss syndrome
(c) Wegener granulomatosis
(d) None of the above

117. Polyarteritis nodosa can occur in association with which of the following: *(Delhi PG-2005)*
(a) Hypertension (b) Trauma
(c) Drugs (d) Bronchial asthma

MOST RECENT QUESTIONS

118. The term infantile polyarteritis nodosa was formerly used for:
(a) Goodpasture's disease
(b) Henoch-Schönlein purpura
(c) Kawasaki disease
(d) Takayasu's arteritis

119. Most common organs involved in Wegener's granulomatosis are:
(a) Skin and nose
(b) Lung and kidney
(c) Heart and kidney
(d) Kidney and nervous system

120. Polyarteritis nodosa does not involve:
(a) Pulmonary artery
(b) Bronchial artery
(c) Renal artery
(d) Cerebral artery

121. C-ANCA antibodies are characteristic of:
(a) Sjögren's syndrome
(b) Giant cell arteritis
(c) Wegener's granulomatosis
(d) Kawasaki's disease

122. ANCA is seen in all except:
(a) Wegener's granulomatosis
(b) Henoch-Schönlein purpura
(c) Microscopic polyangiitis
(d) Churg-Strauss disease
(e) Tuberculosis

123. Which is associated with vasculitis of medium size vessels:
(a) Temporal arteritis
(b) Wegener's granulomatosis
(c) Polyarteritis nodosa
(d) Henoch-Schönlein purpura

124. All is true about Giant cell arteritis except:
(a) Involves large to small sized arteries
(b) Granulomatous inflammation
(c) Most commonly involved artery is abdominal aorta
(d) Segmental nature of the involvement

125. In PAN, the lesions are seen in all except:
(a) Lung (b) Pancreas
(c) Liver (d) Heart

126. **Which of the following is not a characteristic of Wegener's granulomatosis?**
(a) Granuloma is vessel wall
(b) Focal necrotising glomerulonephritis
(c) Positive for cANCA
(d) Involves large vessels

127. **Raynaud's phenomenon what change is seen in vessels initial stage:**
(a) No change
(b) Thrombosis
(c) Fibrinoid necrosis
(d) Hyaline sclerosis

128. **Frequency of renal involvement in Henoch Schonlein Purpura (HSP) is ?**
(a) 20-40% (b) >80%
(c) 40-60% (d) 10%

129. **Which of the following is abdominal angiitis?**
(a) Giant cell arteritis
(b) Takayasu arteritis
(c) Kawasaki disease
(d) Polyarteritis nodosa

130. **Glomus cells are found in which of the following conditions?**
(a) Carotid body tumour
(b) Thyroid carcinoma
(c) Liver carcinoma
(d) Glomus tumor

131. **Sturge weber syndrome is associated with:**
(a) Port wine stain
(b) Cavernous hemangioma
(c) Lymphangioma
(d) Hemangiosarcoma

132. **All of the following are true about pyogenic granuloma except**
(a) Bacterial infection
(b) Bleeding
(c) Benign tumour
(d) Capillary hemangioma

133. **Glomus tumor is seen in:**
(a) Retroperitoneum
(b) Soft tissue
(c) Distal portion of digits
(d) Proximal portion of digits

134. **Anti-neutrophil cytoplasmic antibodies (ANCA) is seen in:**
(a) Wegener's granulomatosis
(b) Diabetes mellitus
(c) Rheumatoid arthritis
(d) Churg-Strauss syndrome

135. **A 6-year old girl presents with fever for the past 5 days, generalized erythematous rash, strawberry tongue and cervical lymphadenopathy. The most likely diagnosis is:**
(a) Kimura disease
(b) Kawasaki disease
(c) Scarlet fever
(d) Rosie-Dorfman syndrome

136. **Neutrophilic infiltration with fibrinoid necrosis in walls of vessels is seen in:**
(a) Giant cell arteritis
(b) Takayasu arteritis
(c) Churg-Strauss syndrome
(d) Polyarteritis nodosa

137. **Most dreadful complication of Kawasaki's disease is:**
(a) Rash
(b) Lymph node
(c) Cardiac involvement
(d) Thrombocytosis

138. **Bilateral pulselessness in hand which of the following conditions?**
(a) Giant cell arteritis
(b) Takayasu arteritis
(c) Kawasaki disease
(d) Polyartertis nodosa

139. **False regarding cavernous hemangioma is:**
(a) More infiltrative than capillary hemangioma
(b) Undergo spontaneous regression
(c) Intravascular thrombosis and dystrophic calcification seen commonly
(d) Associated with VHL disease

140. **Kawasaki disease not true:**
(a) Erythema
(b) Posterior cervical lymphadenopathy
(c) Thrombocytopenia
(d) Conjuctivitis

Explanations

1. **Ans. (a) Myxomatous degeneration and prolapse of the mitral valve** *(Ref: Robbins 9/e p556, 8th/563-565)*

The important clues given in the question;

- Female patient
- Presenting for Routine examination (means she was asymptomatic)
- Presence of mid systolic click on physical examination
- Absence of history of rheumatic heart disease

All these are significant pointers towards a diagnosis of mitral valve prolapse or Barlow syndrome. The other name of the same condition is *Myxomatous degeneration of the mitral valve. So, the answer is option 'a'*

Direct lines from Robbins '***Most patients*** with mitral valve prolapse are ***asymptomatic,*** and the condition is ***discovered only on routine examination by the presence of a midsystolic click as an incidental finding on physical examination***'

Concept

- **Commissural fusion** that *typifies rheumatic heart disease* is **absent** in mitral valve prolapse.

2. **Ans. (c) Small ASD**

(Ref: Ghai 7th/390,403, Adult congenital heart disease: a practical guide page/36-37)

Direct quote Ghai... '*Infective endocarditis is **very rare** in patients of ostium secundum atrial septal defect, **unless floppy mitral valve is present***'.

Risk of infective endocarditis in various lesions

High Risk	Moderate Risk	Low Risk
• Prosthetic heart value • Tetralogy of Fallot • PDA • Aortic regurgitation • Aortic stenosis • Coarctation of Aorta • VSD • Mitral regurgitation	• MVP + M.R. • Tricuspid stenosis • Tricuspid regurgitation • Pulmonary stenosis • Mitral stenosis	• ASD • MVP without MR

3. **Ans. (c) Neutrophilic infiltration surrounding coagulative necrosis** *(Ref: Robbins 8th/550; 7th/579)*

4. **Ans. (d) Elevated ESR** *(Ref: Robbins 9/e 559, 8th/566)*

5. **Ans. (a) Cross reactivity with exogenous antigen** *(Ref: Robbins 8th/566, 9/e 558)*

Acute rheumatic fever results from immune response to group A streptococci (Strep. pyogenes) which cross-reacts with host tissues. The antibodies directed against the M proteins of streptococci cross react with the self antigens in the heart. In addition, CD4+ T cells specific for streptococcal peptides also react with self proteins in the heart and produce macrophage activating cytokines. So, the damage to the heart tissue is a combination of antibody and T-cell mediated reactions.

6. **Ans. (b) Intimal fibrosis of right ventricle, tricuspid and pulmonary valve.** *(Ref: Robbins 8th/569, 9/e 562)*

- Cardiac lesions are present in 50% of the patients with the *carcinoid syndrome.*
- These are **largely right-sided** due to inactivation of both serotonin and bradykinin in the blood during passage through the lungs by the monoamine oxidase present in the pulmonary vascular endothelium.

7. **Ans. (a) Infective endocarditis** *(Ref: Robbins 9/e 560)*

The *hallmark of infective endocarditis* is the presence of *friable, bulky* and *potentially destructive vegetations* containing fibrin, inflammatory cells and bacteria or other organisms on the heart valves. Do refer to the table comparing different vegetations in differrent condtions in the text.

8. **Ans. (c) Rheumatic carditis**

(Ref: Robbins 7th/593, 9/e 558, Harrison 17th/2095)

- **Aschoff's bodies are characteristic focal inflammatory lesion of acute rheumatic fever** *found in any of the three layers of the heart.*

9. **Ans. (b) Rupture of Chordae tendinae**

(Ref: Robbins 9/e 558-559, 7th/593-94, Harrison's 17th/2092)

Rupture of chordae tendinae is a feature of chronic rheumatic heart disease.

10. **Ans. (b) Major Jones' criteria**

(Ref: Robbins 9/e 559, 8th/566, Harrison 17th/2095)

ASO titre may be positive due to streptococcal infection even in normal people. In some individuals with rheumatic carditis, ASO titre may **not** be elevated. In PSGN, the titre of anti DNA se B antibody is elevated more commonly than ASLO.

11. **Ans. (c) Myxomatous degeneration**

(Ref: Robbins 7th/591-2,8th/563, 9/e 556, Harrison 17th/1472)

MVP/Myxomatous degeneration/Barlow's syndrome/ Floppy-valve syndrome

- Characteristic anatomic change in **myxomatous degeneration**Q is interchordial ballooning of the mitral leaflets. The affected leaflets are often enlarged, redundant, thick, and rubbery.
- **Annular dilation**Q is a characteristic finding. (it is rare in other causes of mitral insufficiency).
- There is reduction in the production of type III collagen and electron microscopy has revealed fragmentation of collagen fibrils.

12. **Ans. (c) Myocardial infarction**
(Ref: Harrison 17th/791, Harsh Mohan 6th/448, Robbins7th 596-7, 8th/567, 9/e 561)

Cardiac complications	Extra cardiac complications
• Valvular stenosis or insufficiency • Abscess on the myocardium **(ring abscess)** • Myocardial abscess • Suppurative pericarditis • Perforation, rupture and aneurysm of valve leaflets • Cardiac failure	• **Systemic emboli** from left side of heart affect spleen, brain and kidneys whereas those from right heart affect pulmonary abscess formation. • Antigen -antibody complexes cause focal (more commonly) and diffuse (less commonly) glomerulonephritis.

Harrison writes that "Emboli to a coronary artery may result in myocardial infarction; nevertheless embolic transmural infarcts are rare."

13. **Ans. (b) Epithelioid cell**
(Ref: Robbins 7th/593-4, 8th/565-6, 9/e 558)
Aschoff bodies consist of foci of swollen eosinophilic collagen surrounded by lymphocytes (primarily T cells), occasional plasma cells, and plump macrophages called **Anitschkow cells** (***pathognomonic for rheumatic fever***). These cells are also called "caterpillar cells". Some of the larger macrophages become multinucleated to form Aschoff giant cells.

14. **Ans. (a) Aschoff bodies; (b) Vegetation along the line of closure of valves** *(Ref: Robbins 7th/593-94, 9/e 558)*

15. **Ans. (d) Aschoff's nodule**
(Ref: Robbins 8th/565-566, 9/e 558)

16. **Ans. (b) Libman-Sacks endocarditis**
(Ref: Robbins 7th/597, 89, 9/e 562)
Vegetations in Libman Sack's endocarditis occur on surfaces of cusps. Both surfaces may be involved but, more commonly, the undersurface is affected.

17. **Ans. (a) Acute rheumatic fever**
(Ref: Robbin 7th/593, 9/e 558)

18. **Ans. (a) Acute rheumatic fever**
(Ref: Robbin 8th/565, 7th/593, 9/e 558)

19. **Ans. (b) Mycobacterium tuberculosis**
(Ref: Robbins 7th/607-609, 9/e 571)

- Mycobacterium tuberculosis causes involvement of pericardium (Caseous pericarditis). It is the commonest cause of **chronic constrictive pericarditis**Q.
- **Primary pericarditis** is unusual and is **almost always viral**Q **in origin**.

20. **Ans. (d) Hypertrophic cardiomyopathy**
(Ref: Robbins 9/e 569, 8th/576; 7th/604, 607)

21. **Ans. (a) Rheumatic heart disease** *(Ref: Robbins 9/e 554)*

22. **Ans. (c) Syphilis** *(Ref: Robbins 9/e p554-555)*

23. **Ans. (a) Myocardial infarction** *(Ref: Robbins 9/e p529)*

24. **Ans. (b) SLE** *(Ref: Robbins 9/e p562, 8th/220; 7th/598)*

25. **Ans. (b) TB** *(Ref: Harrison 17th/1493, Robbins 9/e p575)*

26. **Ans. (a) Acute rheumatic fever** *(Ref: Robbins 9/e p558)*

27. **Ans. (b) Aschoff's nodule** *(Ref: Robbins 9/e p558)*

28. **Ans. (a) lgM directed against lgG**
(Ref: Robbins 9/e p1210, 8th/1238)

29. **Ans. (d) Erythema nodosum** *(Ref: Robbins 9/e p559)*

30. **Ans. (b) Libman-Sacks endocarditis**
(Ref: Robbins 8/e p567, 9/e p562) ...Refer to the earlier question

31. **Ans. (c) Small or medium sized on either or both sides of valve** *(Ref: Robbins 9/e p560) ...see Table 9.1 in text*

32. **Ans. (c) Lungs** *(Ref: Robbins 8/e p 535, 9/e p529)*

33. **Ans. (b) Rheumatic endocarditis** *(Ref: Robbins 9/e p558)*

34. **Ans. (b) Fat deposition** *(Ref: Robbins 8/e p34)*
In a pattern of lipid deposition seen with prolonged moderate hypoxia, such as that produced by profound anemia, there is intracellular deposits of fat, which create grossly apparent bands of yellowed myocardium alternating with bands of darker, red-brown, uninvolved myocardium (**tigered effect**).

35. **Ans. (d) Lung** *(Ref: Robbins 9/e p561, 8/e p566, 7/e p597)*
- Mitral valve vegetations are associated with systemic embolisation which can affect brain, liver, spleen and kidney.
- ***Embolisation of the lung*** is associated with involvement of right heart (***tricuspid valve vegetation***) involvement.

36. **Ans. (b) Acute rheumatic fever... discussed in detail earlier** *(Ref: Robbins 8/e p565-566, 9/e 559)*

37. **Ans. (d) Tricuspid valve** *(Ref: Robbins 9/e p560)*

38. **Ans. (d) Aortic stenosis** *(Ref: Robbins 9th/555)*
The valve area is approximately 0.5 to 1 cm^2 in severe aortic stenosis whereas it is normally approximately 4 cm^2. The aortic stenosis leads to concentric left ventricular (pressure overload) hypertrophy. If untreated, most patients with aortic stenosis *will die within 5 years of developing angina, within 3 years of developing syncope, and within 2 years of CHF onset.*

39. **Ans. (c) Pulmonary** *(Ref: Robbins 9/e p559)*

40. **Ans. (c) Rheumatic endocarditis** *(Ref: Robbins 9th/ 560)*
Presence of vegetation along lines of closure of the valve is highly suggestive of this being a case of rheumatic heart disease. Readers are requested to see the figure given in Robbins.

41. **Ans. (b) 5′-nucleotidase**
(Ref: Robbins 9/e p547, Harrison 19/e p1997)

> • ***Alkaline phosphatase*** may be increased in ***congestive heart failure***.

42. **Ans. (c) Janeways lesion** *(Ref: Robbins 9/e p561)*
Janeway lesions are a feature of infective endocarditis.

43. **Ans. (c) Dystropin** *(Ref: Robbins 9/e p565)*

44. **Ans. (c) Trousseau syndrome** *(Ref: Robbins 9/e p562)*

> The pathogenesis of nonbacterial thrombotic endocarditis (NBTE) often involves a hypercoagulable state. When the hypercoagulability is the result of the procoagulant effects of circulating products of cancers the resulting cardiac valve vegetations may also be called marantic endocarditis. The pathophysiology of NBTE is similar to that of Trousseau's syndrome (migratory thrombophlebitis) which may also be induced by disseminated cancers like mucinous adenocarcinoma of the pancreas and adenocarcinoma of the lung which may relate to procoagulant effects of circulating mucin.

(Choice B) Cancer metastases to the heart usually involve the pericardium or myocardium. Valve metastases are less frequent and would probably have shown invasive characteristics on histological examination.

45. **Ans. (b) Presence of neutrophils** *(Ref: Robbins 9/e p544)*
As discussed in the text, granulation tissue appears between 7-10 days and collagen appears after 2 months. Between 3-7 dyas, neutrophils start disintegrating with early phagocytosis caused by macrophages. Presence of macrophages would have been a better answer but in the given question, presence of neutrophils is the best option.

46. **Ans. (d) These may result in aneurysm**
(Ref: Robbins 9/e p543, 7th/575)
Ventricular aneurysms result from transmural infarcts, which involve the whole thickness of myocardium from *epicardium to endocardium.* ***Subendocardial infarcts being limited to only the inner one-third or at most one*** half of the ventricular wall do not cause ventricular aneurysms. **Aneurysm** of the ventricular wall **most commonly** results from a **large transmural anteroseptal infarct**.

47. **Ans. (b) Necrotic myofibers with presence of neutrophils** *(Ref: Robbins 7th/578-581, 9/e p544)*
The patient in the question succumbed to myocardial infarction after about 28 hours of the attack. ***After twenty-four hours of the attack light microscopy shows coagulative necrosis of myofibrils with loss of nuclei and striations along with an interstitial infiltrate of neutrophils.*** *For details, see the table of morphological changes of MI in text.*

48. **Ans. (c) Nephrotic syndrome**
(Ref: Harrison 17th/272, Robbins 9/e p914)
- Nephrotic syndrome is a clinical complex characterized by proteinuria (> 3.5 g/day), hypoalbuminemia, edema and hyperlipidemia.
- A hypercoagulable state frequently accompanies severe nephrotic syndrome due to *urinary loss of AT-III, reduced serum levels of protein C and S, hyperfibrinogenimia and enhanced platelet aggregation.*
- Due to increased coagulation state, predisposition to CAD is present in patients with nephrotic syndrome.

Potential future questions

> Among hyperlipoproteinemias type II, III and IV are associated with increased risk of CAD whereas Type I and V are not associated with CAD.

49. **Ans. (c) Within 1 week**
(Ref: Robbins 7th/579, 9/e 544, Chandrasoma Taylor 3rd/364)

50. **Ans. (d) Myocardial infarction**
(Ref: Robbins 9/e 547, 8th/555, 7th/583, Harrison 17th/1534)
The preferred biomarkers for myocardial damage are cardiac-specific proteins, particularly Troponin-I (TnI) and Troponin-T.

51. **Ans. (b) Coagulative necrosis** *(Ref: Robbins 9/e 545)*

52. **Ans. (d) Troponin-I**
(Ref: Cardiovascular Imaging; Vol. 22, No. 2, April 2006, Robbins 9/th p547)
Hypothyroid patients have increased concentration of **CPK** that is mostly due to increased CPK MM. However CPK-MB has also been reported to increase above reference value in hypothyroid patients without myocardial damage. This may create confusion during the evaluation of myocardial injury in a hypothyroid patient presenting with chest pain.
Troponin I is considered superior, marker for the diagnosis of myocardial infarction in hypothyroid patient.

53. **Ans. (a) Troponin**
(Ref: Harrison 17th/1535, Robbins 9/e 547)
- Now Troponin is a better marker for diagnosis of reinfarction.

54. **Ans. (a) Waviness of the fibers** *(Ref: Robbins 9/e p544)*

55. **Ans. (c) Left anterior descending coronary artery**
(Ref: Robbins 9/e p542, 8th/551; 7th/577)

56. **Ans. (d) 3 months** *(Ref: Robbins 9/e p544)*

57. **Ans. (d) Autoimmune** *(Ref: Robbins 9/e p549)*

58. **Ans. (c) MM and MB** *(Ref: Robbins 8th/555, 9/e p547)*

59. **Ans. (a) CPK MB** *(Ref: Robbins 9/e p547)*

60. **Ans. (c) LDH** *(Ref: Robbins 8/e p555, 9/e p547)*

61. **Ans. (a) Troponin T** *(Ref: Robbins 8/e p555, 9/e p547)*

Enzyme	Initiation of rise	Peak	Return to baseline
CK-MB	2-4 hours	24 hours	48-72 hours
Troponin T and I (TnT, TnI)	2-4 hours	48 hours	7-10 days
AST/SGOT	In 12 hours	48 hours	4-5 days
LDH	24 hours	3-6 days	2 weeks

62. **Ans. (d) Free radicals** *(Ref: Robbins 8/e p553, 9/e p546)*

Restoration of blood flow to ischemic tissues can promote recovery of cells if they are reversibly injured. However, under certain circumstances, when blood flow is restored to cells that have been ischemic but have not died, injury is paradoxically exacerbated and proceeds at an accelerated pace. This process is called *ischemia-reperfusion injury*. The following mechanisms have been proposed for the reperfusion injury:

- New damage may be initiated during reoxygenation by increased generation of *reactive oxygen and nitrogen species* from parenchymal and endothelial cells and from infiltrating leukocytes.
- Ischemic injury is associated with *inflammation* as a result of the production of cytokines and increased expression of adhesion molecules by hypoxic parenchymal and endothelial cells, which recruit circulating neutrophils to reperfused tissue.
- Activation of the *complement system* may contribute to ischemia-reperfusion injury. Some IgM antibodies have a propensity to deposit in ischemic tissues, for unknown reasons, and when blood flow is resumed, complement proteins bind to the deposited antibodies, are activated, and cause more cell injury and inflammation.

63. **Ans. (c) Macrophages**
(Ref: Robbins 8/e p550, 9/e p544) ...see Table 9.2

64. **Ans. (c) Coxsackie virus** *(Ref: Robbins 7/e 610, 9/e p570)*

65. **Ans. (c) 1-3 days.... See the table in text or details**
(Ref: Robbins 9/e p544, 8/e p550, 7/e p579)

66. **Ans. (d) Brick red** *(Ref: Robbins 9th / 544)*

When tissue slices are dipped in a solution of triphenyltetrazolium chloride, the stain imparts a **brick-red color to intact, noninfarcted myocardium** where lactate dehydrogenase activity is preserved. Because dehydrogenases leak out through the damaged membranes of dead cells, an ***infarct appears as an unstained pale zone.***

67. **Ans. (c) 6 hours** *(Ref: Robbins 9th/544)*

Presence of a coagulative necrotic pattern along with widened space between dead fibers and wavy fiber appearance suggests this to a pattern of injury taking place around 6 hours.

68. **Ans. (a) Bronchial carcinoma** *(Ref: Robbins 9/e p574)*

69. **Ans. (a) Myxoma** *(Ref: Robbind 8/e p583, 9/e 575)*

- *Myxomas* are the most common primary tumor of the heart in adults.
- *Familial cardiac myxoma syndrome* (known as ***Carney syndrome***) is characterized by autosomal dominant transmission, multiple cardiac and often extracardiac (e.g. skin) myxomas, spotty pigmentation, and endocrine overactivity.

70. **Ans. (b) Left atrium** *(Ref: Robbins 9/e 575)*

Atrial myxoma is most commonly located on the **left atrium**. Other important points have discussed earlier.

71. **Ans. (d) Myxoma** *(Ref: Robbins 9/e p575, 8/e p583-4)*

72. **Ans. (c) Lower limb ischemia**
(Ref: Robbins 8th/499, 1140)

Direct quote from Robbins... *'Gangrene of the lower extremities as a result of advanced vascular disease is about 100 times more common in diabetics than in general population'.*

The risk of myocardial infarction (MI) is **twice** *in a diabetic as compared to a non diabetic* individual.

73. **Ans. (b) Atherosclerosis is less important in age more than 45 years age** *(Ref: Robbins 9/e p493, 8th/497)*

Risk factors for atherosclerosis

Modifiable	Non modifiable
• Hyperlipidemia • Hypertension • Cigarette smoking • Diabetes • C reactive protein	• Increasing age • Gender • Family history • Genetics

According to Robbins,

- Age is a dominant influence on atherosclerosis. Between ages 40 and 60, the incidence of myocardial infarction increases fivefold.
- Omega-3 fatty acids (abundant in fish oils) are beneficial, whereas (trans) unsaturated fats produced by artificial hydrogenation of polyunsaturated oils (used in baked goods and margarine) adversely affect cholesterol profiles.
- Cigarette smoking is a well-established risk factor in both men and women. Prolonged (years) smoking of one pack of cigarettes or more daily increases the death rate from ischemic heart disease by 200%. Smoking cessation reduces that risk substantially.
- C-reactive protein (CRP) is an acute-phase reactant synthesized primarily by the liver. When locally synthesized within atherosclerotic intima, it can also regulate local endothelial adhesion and thrombotic states. Most importantly, it strongly and independently predicts the risk of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals

74. **Ans. (c) Hyaline arteriosclerosis** *(Ref: Robbin's 9/e p490)*

Hyaline arteriosclerosis is characterized by the following:

- ***Pink, hyaline thickening*** of arteriolar walls (due to leaking of plasma proteins) associated with luminal narrowing.
- Seen in ***elderly***[Q], more commonly in ***benign hypertension***[Q], ***diabetes mellitus***[Q] ***(DM) and benign nephrosclerosis***[Q].

75. Ans. (a) Insulin deficiency *(Ref: Robbins 9/e p499)*

All the mentioned features in the question are the macrovascular complications of diabetes mellitus which is caused due to insulin deficiency.

76. Ans. (a) Atherosclerosis

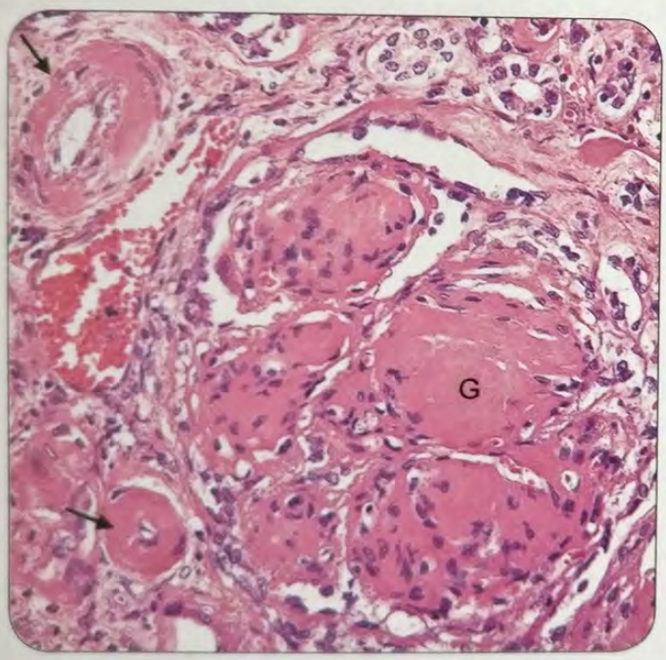
(Ref: Robbins 8th/507, Harrison 18th/2060-1)

Direct quote from Harrsion....*'atleast 90% of all abdominal aortic aneurysms >4.0 cm are related to atherosclerotic disease and most are present just below the renal arteries'.*

77. Ans. (a) Hyaline arteriosclerosis *(Ref: Robbins 9/e p490)*

Hyaline arteriosclerosis is characterized by the following:

- Pink, hyaline thickening of arteriolar walls (due to leaking of plasma proteins) associated with luminal narrowing.
- Seen in elderly, more commonly in benign hypertension, diabetes mellitus (DM) and benign nephrosclerosis.



Hyaline arteriolosclerosis affecting glomeruli (G)

78. Ans. (b) Hyaline arteriolosclerosis

(Ref: Robbins 7th/534, 8th/496, 949, 9/e p490)

Features of malignant hypertension

The characteristic features include:

1. Fibrinoid necrosis[Q] of the small vessels particularly the arterioles
2. Necrotizing arteriolitis[Q]: Presence of inflammatory cells in the vessel wall
3. Hyperplastic arteriosclerosis[Q]: Proliferation of the internal smooth muscle cells seen in the interlobular arteries giving **onion skin like appearance**[Q]

Renal involvement is called malignant nephrosclerosis having the features like

a. Kidneys have a typical "**flea bitten "appearance**[Q] (due to petechial hemorrhage on cortical surface)
b. Necrotizing glomerulonephritis: Necrotizing arteriolitis may involve the glomeruli also.

79. Ans. (c) Lipoprotein A *(Ref: Robbins 7th/520-521)*

Lp (a) has structural similarity with plasminogen. It interferes with formation of plasmin and hence, fibrinolysis. This contributes to atherosclerosis.

80. Ans. (b) Atherosclerosis

(Ref: Harrison 17th/1563, 18th/2060-1, Robbins 7th/531, 9/e p503)

81. Ans. (a) Heart

(Ref: Ultrastructural pathology/374, Robbins 8th/495-6)

Friends, trust me this seemed to be an easy one but as i found out to my surprise, the reference pages mentioned by all MCQ books including our competitors (whom we expect to copy this info as well as has happened so many times earlier !☺) give page number from Robbins which don't have this info! But I managed to find something worthy as follows:

Ultrastructural pathology by Cheville NF page 374 mentions that .... *'hyperplastic arteriosclerosis of the kidney has the most serious effects but this lesion is also found in the artereioles of the intestine , gall bladder and pancreas. "* I was not able to found anything relevant about pericardial fat. But after discussion with many senior faculty members, the answer of consensus is option 'a' i.e. Heart.

82. Ans. (a) Homocysteinemia; (c) Increased fibrinogen; (e) Increased plasminogen activator inhibitors.

(Ref: Robbins 7th/520, 8th/498, 9/e p492)

83. Ans. (a) Concentric hypertrophy of LV; (b) Increased heart size; (c) Increased size of the heart muscles; (d) Myohypertrophy: *(Ref: Robbins 7th/587, Harrison 17th/1552)*

Features of essential hypertensions are:

- Concentric hypertrophy of the left ventricles due to pressure overload of the heart.
- Increase in weight of heart (>500 gm) is disproportionate to the increase in overall size of heart.
- Thickening of the left ventricular wall increased the ratio of its wall thickness to radius.
- Microscopically the earliest changes of systemic hypertensive heart disease is an increased transverse myocytes diameter. In advanced stage the cellular and nuclear enlargement is prominent. Electron microscopy reveals increase in number of myofilaments comprising myofibrils, mitochondrial changes and multiple intercalated disks.
- Increase total RNA and ratio of RNA to DNA contents.

84. Ans. (c) Lipids in LDL get auto-oxidized
(Ref: Harrison 17th/1502 Robbins 7th/523, 9/e p496)

Scavenger receptors and not LDL receptors on macrophages result in uptake of oxidized LDL to form foam cells contributing to atherosclerosis.

85. Ans. (b) Pulmonary arterial trunk *(Ref: Robbins 9/e p498)*

86. Ans. (b) Hyaline arteriosclerosis *(Ref: Robbins 9/e p490)*

87. Ans. (a) Fibrinoid necrosis of arteriolar wall
(Ref: Robbins 7th/1007, 9/e p490)

Accelerated phase of hypertension is the other name for malignant hypertension.

88. Ans. (d) Abdominal aorta *(Ref: Robbins 9/e p502)*

89. Ans. (b) Media *(Ref: Robbins 9/e p491)*

90. Ans. (b) Flea bitten kidney *(Ref: Robbins 9/e p490)*
In malignant hypertension, on gross inspection the kidney size depends on the duration and severity of the hypertensive disease. Small, pinpoint petechial hemorrhages may appear on the cortical surface from rupture of arterioles or glomerular capillaries, giving the **kidney a peculiar "flea-bitten" appearance.**

Causes of contracted kidney

Symmetric	Asymmetric
• Chronic glomerulonephritis • Benign nephrosclerosis	• Chronic pyelonephritis
Causes of enlarged kidneys	
• Amyloidosis • Rapidly progressive glomerulonephritis (RPGN) • Myeloma kidney	• Diabetic renal disease [Kimmelstiel Wilson nodules are pathognomic] • Polycystic kidney disease • Bilateral obstruction (hydronephrosis)

91. Ans. (b) Left anterior descending coronary artery
(Ref: Robbins 8/e p551, 9/e p542)

The frequencies of involvement of each of the three main arterial trunks and the corresponding sites of myocardial lesions resulting in infarction (in the typical right dominant heart) are as follows: LAD >> RCA >> LCX.

92. Ans. (a) Hypertension *(Ref: Robbins 9/e p504) ...see text*

93. Ans. (a) Marfan syndrome *(Ref: Robbins 9/e p502)*
The vascular wall is weakened through loss of smooth muscle cells or the inappropriate synthesis of noncollagenous or nonelastic ECM. Atherosclerosis and hypertension induced ischemia is reflected in "degenerative changes" of the aorta, whereby smooth muscle cell loss leads to scarring (and loss of elastic fibers), inadequate ECM synthesis, and production of increasing amounts of amorphous ground substance (glycosaminoglycan). Histologically these changes are collectively called *cystic medial degeneration.* Though these are nonspecific, they can be seen with **Marfan disease**Q and **scurvy**Q

94. Ans. (a) Splenic
(Ref: Peripheral Vascular Interventions chapter 15, pg 263)

- The visceral arteries include the three main unpaired branches of the abdominal aorta namely celiac artery, superior mesenteric and inferior meseneteric arteries.

- The most common visceral vessel showing aneurysm formation is the splenic artery^{Q} followed by the hepatic artery.

95. Ans. (c) Monckeberg's sclerosis *(Ref: Robbins 9/e p491)*

- *Mönckeberg medial sclerosis* is characterized by **calcific deposits** in muscular arteries in persons **typically older than age 50.**
- The deposits may **undergo metaplastic change** into bone.
- Nevertheless, the lesions do not encroach on the vessel lumen and are usually **not clinically significant.**

96. Ans. (b) Heart *(Ref: Robbins 8/e p502, 9/e p498)*
Coronary arteries supply the heart. They are the second most common vessel (after abdominal aorta) to be affected in atherosclerosis.

97. Ans. (c) Atherosclerosis *(Ref: Robbins 9/e 502) ...see text*

98. Ans. (a) Syphilitic *(Ref: Robbins 8/e p507-508, 7/e p532)*
Direct lines... "The obliterative endarteritis characteristic of late-stage syphilis shows a predilection for small vessels, including those of the vasa vasorum of the thoracic aorta."
Atherosclerosis affects abdominal aorta most commonly. Traumatic aneurysm can affect any site of the aorta. Berry aneurysm affects the circle of Willis.

99. Ans (c) Chlamydia pneumoniae *(Ref: Robbins 9/e 496)*
Robbins.. "Herpes virus, cytomegalovirus and ***Chlamydia pneumoniae*** have all been detected in atherosclerotic plaques but not in normal arteries, and seroepidemiologic studies find increased antibody titers to *C. pneumoniae* in patients with more severe atherosclerosis".

100. Ans (c) Hyaline arteriosclerosis *(Ref: Robbins 9/e p490)*

101. Ans. (d) Hyperplastic arteriosclerosis
(Ref: Robbins 9/e p490, 8/e p496, 7/e p530)
Hyperplastic arteriosclerosis is associated with **malignant hypertension** in which concentric thickening of the walls and luminal narrowing leads to "**onion skin like lesions**".

102. Ans (a) SR-B1 *(Ref: Robbins 9/e p291-e-2)*
HDL cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class B1 (**SR-B1**), a cell surface receptor that mediates the selective transfer of lipids to cells.
Recent info... **SR-B1 is also useful for facilitating the entry of HCV in the host cells.**

103. Ans (d) syphilis *(Ref: Robbins 9/e p380)*

104. Ans. (a) Giant cell arteritis *(Ref: Robbins 9/e p508)*

105. **Ans. (d) Microscopic polyangiitis**
(Ref: Robbins 9/e p506, 8th/512, 515) ...see Table 9.3

106. **Ans. (a) Henoch-Schonlein Purpura**
(Ref: Robbins 8th/934, 9/e p926, Harrison 17th/2128, Wintrobes 12th/1343)

107. **Ans. (d) Microscopic polyangiitis** *(Ref: Robbins 9/e p510)*
Robbins clearly mentions that *"microscopic polyangiitis is characterized by segmental fibrinoid necrosis of the media with focal transmural necrotizing lesions; granulomatous inflammation is absent".*

108. **Ans. (d) Wegener's granulomatosis**
(Ref: Robbins 8th/516-517, 9/e p507)

109. **Ans. (c) Kawasaki's disease**
(Ref: Robbins 9/e p510, 8th/515, 7th/539, Harrison 17th/2130. 18th/2800)
Kawasaki's disease (**mucocutaneous lymph node syndrome**) is an arteritis that often involves the coronary arteries, usually in **young children** and infants (majority of the cases are seen in <5 years old). It is treated with intravenous immunoglobulin and aspirin. (For details, see text.)

110. **Ans. (b) Post-capillary venules**
(Ref: Harrison 17th/2128, 18th/2798, Robbins 8th/515, 9/e p510)
Direct quote from Harrison 18th/2798... *'**Post capillary venules are the most commonly involved vessels**; capillaries and arterioles may be involved less frequently'.*

111. **Ans. (c) Wegener's granulomatosis**
(Ref: Robbins illustrated 7th/541, 8th/516, 9/e p511-512)

112. **Ans. (a) Buerger's disease; (b) HSP; (d) Reiter's disease; (e) Behcet's syndrome.**
(Ref: Harrison' 17th/2119, 1485, Robbins' 7th/535, 537)

Vasculitis syndromes	
Primary vasculitis	**Secondary vasculitis syndrome**
• Wegener's granulomatosis • Churg-Strauss syndrome • PAN, HSP • Microscopic polyangitis • Giant cell arteritis, Takayasu's arteritis • Idiopathic cutaneous vasculitis • Essential mixed cryoglobulinemia • Behcet's syndrome, Cogan's syndrome • Kawasaki disease	• Drug induced vasculitis • Serum sickness • Infection • Malignancy • Rheumatic disease

113. **Ans. (a) Lung; (c) Kidney; (d) Upper respiratory tract; (e) Heart** *(Ref: Robbins 7th/541, 9/e p511)*

114. **Ans. (a) Involves lungs; (b) Involves nose; (c) Involves kidney; (d) Treated with cytotoxic agent and/or steroid.**
(Ref: Robbins 7th/541, 9/e p511, Harrison 17th/2121)
Wegener's granulomatosis is treated with steroids and cyclophosphamide. They dramatically ameliorate glomerular injury in pauci-immune glomerulonephritis.

115. **Ans. (c) Seen in Henoch-Schonlein purpura**
(Ref: Robbins 8th/920-921, 9/e p926)

116. **Ans. (a) Kawasaki's disease**
(Ref: Robbin 7th/537, 9/e p506) ...see text

117. **Ans. (a) Hypertension** *(Ref: Robbins 9/e p509-510)*
Polyarteritis Nodosa

- It is a systemic vasculitis manifested by transmural necrotizing inflammation of small or medium sized muscular arteries.
- *Renal artery* is most commonly involved whereas *Pulmonary circulation is spared.*
- Most common manifestations are malaise, fever of unknown cause, weight loss, hypertension (rapidly developing), abdominal pain, melena, diffuse muscular pains, and peripheral neuritis (predominantly motor).

118. **Ans. (c) Kawasaki disease**
(Ref: http://emedicine.medscape.com/article/1006838, Robbins 9/e p510)
Clinically, infantile polyarteritis nodosa (IPAN) often is part of the spectrum of Kawasaki disease (KD).

119. **Ans. (b) Lung and kidney** *(Ref: Robbins 9/e p511-512)*

120. **Ans. (a) Pulmonary artery** *(Ref: Robbins 9/e p 509-510)*

121. **Ans. (c) Wegener's granulomatosis**
(Ref: Robbins 9/e p511-512, 8th/516-517; 7 th/541)

122. **Ans. (b) Henoch-Schönlein purpura**
(Ref: Robbins 8th/920-921, 9/e p926)

123. **Ans. (c) Polyarteritis nodosa**
(Ref: Robbins 8/e p512, 9/e p506) ...see Table 9.3

124. **Ans. (c) Most commonly involved artery is abdominal aorta** *(Ref: Robins 8/e p512-3, 9/e p507-508) ...see text*

125. **Ans. (a) Lung** *(Ref: Robins 8/e p514-5, 9/e p509-510)*
Polyarteritis nodosa (PAN) is characterised by necrotizing inflammation typically involving renal arteries but **sparing pulmonary vessels.**

126. **Ans. (d) Involves large vessels** *(Ref: Robbins 9/e p511)*
Wegener's granulomatosis is a **small vessel** necrotizing vasculitis. *...for details see text*

127. **Ans. (a) No change** *(Ref: Robbins 8/e p518, 9/e p513)*
Structural changes in the arterial walls **are absent** ***except late in the course,*** when intimal thickening can appear.

128. **Ans. None or (c) 40-60%**
(Ref: Robbins 8/e p Heptinstall's Pathology of the Kidney, Volume 1 p463.)
I don't know why they frame these type of questions.

Heptinstall writes..."In different series, the degree if renal involvement in ***children*** with HSP (defined by the presence of hematuria) is ***20-56% (overall 32%)*** whereas in ***adults***, it is ***49-78% (overall 59%)***".
You may choose your answer friends.

129. Ans. (b)Takayasu arteritis

(Ref: Internet, Robins 9/e p508)

Takayasu arteritis is the choosen answer as it is associated with involvement of ***superior mesenteric artery***. So, it may be associated with abdominal angiitis.

130. Ans. (a) Carotid body tumour *(Ref: Robbins 8/e p522)*

Before we discuss the answer friends, a simple clarification that is to be kept in mind;
Glomus tumor (also known as a glomangioma) is a rare benign neoplasm arising from the ***glomus body*** and mainly found ***under the nail***, on the fingertip or in the foot. It **DOES NOTcontain glomus cells**.

- A glomus cell (type I) is a peripheral chemoreceptor mainly located in the carotid bodies and aortic bodies helping in regulation of the breathing.
- ***Neoplasms of glomus cells*** are known as ***paraganglioma.***
- The most common location of these tumors is **within the adrenal medulla**, where they give rise to pheochromocytomas.
- Approximately 70% of extra-adrenal paragangliomas occur in the head and neck region. Paragangliomas typically develop in two locations:
- **Paravertebral paraganglia** (e.g., organs of Zuckerkandl and, rarely, bladder). Such tumors have sympathetic connections and are **chromaffin-positive**, a stain that detects **catecholamines**.
- Paraganglia related to the great vessels of the head and neck, the so-called aorticopulmonary chain, including the ***carotid bodies*** (**most common**); aortic bodies; jugulotympanic ganglia; ganglion nodosum of the vagus nerve; and clusters located about the oral cavity, nose, nasopharynx, larynx, and orbit. These are innervated by the parasympathetic nervous system and **infrequently release catecholamines**

Important points about carotid body tumour

The **carotid body tumor** is a prototype of a **parasympathetic paraganglioma**.

Arisesclose to or envelops the bifurcation of the common carotid artery.

The microscopic features include presence of nests **(Zellballen)** of round to oval chief cells (neuroectodermal in origin) that are surrounded by delicate vascular septae.

The **chief cells** stain strongly for **neuroendocrine markers** such as chromogranin, synaptophysin, neuron-specific enolase, CD56, and CD57.

In addition, the supporting spindle-shaped stromal cells called ***sustentacular cells*** are positive for ***S-100 protein***.

131. Ans (a) Port wine stain *(Ref: Robbins 8/e p522, 9/e p516)*

Sturge–Weber syndrome is usually manifested at birth by a **port-wine stain** on the forehead and upper eyelid of one side of the face.

132. Ans (a) Bacterial infection

(Ref: Robbins 8/e p521, 9/e p516)

Pyogenic granuloma: Key points

- It is a **benign**[Q] tumor
- Type of **capillary hemangioma**[Q] which it **bleeds**[Q] easily and is often ulcerated.
- Is a rapidly growing pedunculated red nodule on the skin, or gingival or oral mucosa;
- 1/3rd of the lesions develop after trauma

Also know that;

- ***Pregnancy tumor (granuloma gravidarum)*** is a pyogenic granuloma that occurs infrequently (1% of patients) in the gingiva of pregnant women.
- These lesions may spontaneously regress post pregnancy) or undergo fibrosis;
- Some cases require surgical excision
- Recurrence is rare.

133. Ans. (c) Distal portion of digits *(Ref: Robbins 9/e p517)*

- *Glomus tumor* is a biologically **benign tumor**[Q] that arises from the modified smooth muscle cells of the glomus body
- *Glomus tumor* is a biologically **benign tumor**[Q] that arises from the modified smooth muscle cells of the glomus body
- **Glomus body** is a specialized arteriovenous anastomosis that is involved in **thermoregulation**[Q].
- It is an often exquisitely painful tumor
- Glomus tumors *are* ***most commonly found in the distal portion of the digits***[Q], especially under the fingernails.
- **Excision**[Q] is curative.

134. Ans. (a) Wegener's granulomatosis *(Robbins 9th/511-2)*

135. Ans. (b) Kawasaki disease *(Robbins 9th/510)*

136. Ans. (d) Polyarteritis nodosa *(Robbins 9th/509)*

137. Ans. (c) Cardiac involvement *(Robbins 9th/510)*

138. Ans. (b) Takayasu arteritis *(Robbins 9th/508)*

139. Ans. (b) Undergo spontaneous regression

(Robbins 9th/516)

Juvenile hemangiomas (*"strawberry hemangiomas"*) regress abut cavernous hemangiomas do not regress spontaneously.

140. Ans. (c) Thrombocytopenia *(Robbins 9th/510)*

ANNEXURE

Myocardial vessel spasm

1. Cardiac Raynaud

Excessive constriction of coronary arteries or myocardial arterioles may cause ischemia, and persistent vasospasm can even cause myocardial infarction. High levels of vasoactive mediators like endogenous epinephrine (in pheochromocytoma) or exogenous chemicals (cocaine or phenylephrine) can precipitate prolonged myocardial vessel contraction.

2. Takotsubo cardiomyopathy (broken heart syndrome)

Takotsubo cardiomyopathy is an ***ischemic dilated cardiomyopathy*** caused by ***emotional stress***.

3. Multifocal microinfarction

Small intramural vessel involvement is seen with microembolization, vasculitis, or vascular spasm, for example, due to endogenous catechols (epinephrine) or drugs (cocaine or ephedrine). This is called as Multifocal microinfarction. This may even lead to takotsubo cardiomyopathy.

CHAPTER 11

Respiratory System

Golden Points

- **Acinus** is the **functional unit** of the lung.
- **Clara cells** are seen in **Terminal bronchioles.**
- Bronchogenic (pulomonary) sequestration is seen in posterior basal segment of lower lobe of left lung. The sequestrated lobe of lung is supplied by aorta or its branches.
- Characteristic histological finding of **ARDS** (shock lung) is **Diffuse alveolar damage**.
- Part of airway involved in emphysema is distal to Terminal bronchioles.
- **Smoking** is the commonest cause of emphysema.
- Important points about asthma: hyper-responsive airways having Charcot-Leyden crystals, curschmann's spirals and creola bodies.
- Bronchiectasis (permanent dilation of airways) affects commonly lower lobe bronchi of left lung. It **does not** lead to lung **cancer**.
- **Hypersensitivity pneumonitis** is **type IV >>> type III** hypersensitivity reactions.
- Sarcoidosis is characterised by bilateral hilar lymphadenopathy (Potato nodes) with non-caseating granuloma.
- Good pasture syndrome is characterized by **focal** necrotizing hemorrhagic interstitial pneumonitis.
- Bacterial pneumonia is characterized by presence of alveolar exudates.
- Most common cause of lung abscess: Aspiration of oropharyngeal secretion.
- Most common lung carcinoma in India: Squamous cell carcinoma (associated with p53 gene mutation). Its histological marker is **cytokeratin**.
- Lung to lung metastasis is seen in adenocarcinoma in situ (Bronchiolo-alveolar carcinoma)
- Most common site of metastasis of lung carcinoma: Brain.
- Most common presentation of ***bronchial adenoma*** is **recurrent hemoptysis.**
- Pleural fibroma (benign mesothelioma) is characterized by: Intense fibrosis, CD34 positive, keratin negative.
- **Malignant mesothelioma** is associated with exposure to asbestos. Its characteristic microscopic finding includes **long-branching microvilli**.
- Most common mediastinal mass: Neurogenic tumors.
- **"Airway remodeling"** is associated with **bronchial asthma**.
- **Pulmonary hypertension** is defined as **a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest**.
- **Cough** is the most common symptom of the bronchogenic carcinoma.
- The **lung** is the **most common site** of **metastatic neoplasms**.
- The ***NAB2- STAT6* fusion gene** is virtually unique to **solitary fibrous tumor**.
- *In about 80% of mesotheliomas*, the most common is homozygous deletion of the tumor suppressor gene ***CDKN2A/INK4a***. The demonstration of this deletion (usually by **FISH**) involving chromosome 9p can be very helpful in distinguishing mesothelioma from reactive mesothelial proliferations.

ANATOMY OF RESPIRATORY TRACT

Trachea
↓
Principal Bronchi
↓
Bronchi
↓
Bronchiole
↓
Terminal Bronchiole
↓
Acinus [Respiratory Bronchiole
↓
Alveoli]

- *Acinus is the functional unit of lung* whereas alveoli are the chief sites of gaseous exchange.
- *Lobule is composed of 3-5 terminal bronchioles with their acini.*

Recent Exam Questions

- **Bronchioles DO NOT** have **cartilage** and **submucosal glands** in wall like bronchi[Q]
- **Terminal bronchiole** contain *maximum smooth muscle relative to the wall thickness*[Q]

- Alveoli are lined by type I pneumocytes (forming 95% of alveolar surface) and type II pneumocytes (responsible for secretion of surfactant and repair of alveoli after type I pneumocyte destruction). The alveolar wall has the presence of **pores of Kohn**[Q] for allowing the passage of bacteria and exudate between adjacent alveoli.
- The entire respiratory tract is lined by *pseudostratified, tall, ciliated columnar epithelial cells except vocal cords* (these have stratified squamous epithelium).

Broadly, the diseases of lung may be divided into infectious, obstructive, restrictive, vascular and neoplastic etiologies.

INFECTIVE LUNG DISEASES

1. Pneumonia

Infection of the lung parenchyma is called pneumonia. It can be of two types

Key Point

- Commonest cause of **community accquired pneumonia** is ***Streptococcus pneumoniae***
- Commonest cause of **nosocomial pneumonia** is ***Staphylococcus aureus***
- Most common cause of **atypical pneumonia** is ***Mycoplasma pneumoniae***).

Pneumonia

Typical pneumonia	Atypical pneumonia
• Infection caused by extracellular organisms mainly bacteria	• Infection caused by intracellular organisms like Mycoplasma, Chlamydia pneumoniae and viruses like RSV, influenza virus, rhinovirus.
• **Characterized by neutrophilic** infiltration and presence of **Intra-alveolar exudates** (leading to consolidation[Q]).	• **Characterized by lymphocytic** infiltration and presence of alveolar septal and interstitial inflammation with **absence of alveolar exudates**[Q].
• Clinical features include acute onset of high grade fever and mucopurulent cough which may also be associated with pleuritic pain.	• Clinical features include **fever, headache, dry cough and myalgia**. Productive Cough and pleural involvement is **uncommon**[Q].

Viral pneumonia result in interstitial infiltrates (therefore called interstitial pneumonia) and may result in variety of cytopathic effects. e.g. RSV shows bronchiolitis and multinucleate giant cells and CMV and herpes show inclusion bodies.

Furthermore, typical pneumonia can be of two types:

Typical pneumonia

Lobar pneumonia	Bronchopneumonia
• Consolidation of entire lobe usually caused by ***Streptococcus pneumoniae***.	• Patchy consolidation in the lobe of lung.
• Following 4 stages of inflammation are present. 1. **Congestion:** It is due to vasodilation. There is bacteria rich intra-alveolar fluid. 2. **Red hepatization:** Exudate is rich in RBC, neutrophils and fibrin[Q]. 3. **Gray hepatization:** Degradation of RBC and fibrinosuppurative exudates 4. **Resolution:** Enzymatic degradation of exudate and healing	• Usually **bilateral basal**[Q] in location due to gravitation of secretions.
	• Affects **extremes of age**[Q] (infants or old).
• Chest X-ray show opacification of the entire lobe.	• Chest X-ray shows patchy opacification of the lobe[Q].

2. Lung Abscess

- Local suppurative process within the lung associated with necrosis of the lung tissue is called lung abscess.
- It is most commonly caused by aspiration of infective material.
- Commonest etiological agent is Anaerobic bacteria of the oral cavity.Q

Recent Exam Questions

Timing of Stages of pneumonia
- Congestion: 1-2 days
- Red hepatization: 2-4 days
- Gray hepatization: 4-8 days
- Resolution: by 8-9 days

Causes of lung abscess

Aspiration	Post pneumonic infection	Post obstructive	Septic emboli	Miscellaneous
• Most common causeQ. • Right lower lobe is the most frequently affectedQ.	• Infection caused by Staph aureus, klebsiella or type 3 Pneumococcus • Usually basal, multiple and diffusely scattered.	• Due to primary or secondary cancer.		• Direct hematogenous spread to lung from infection in esophagus or pleural cavity.

Clinical features: Fever, productive cough with large amount of sputum, chest pain, weight loss and presence of clubbing of the fingers and toes.

Recent Exam Questions
- Commonest etiological agent of lung abscess is **Anaerobic bacteria**
- Commonest cause of lung abscess is **aspiration**

Characteristic histologic feature: Suppurative destruction of lung parenchyma within the central area of cavitation.

Complications include empyema, brain abscess or meningitis, pulmonary hemorrhage and **secondary amyloidosis**Q.

3. Tuberculosis (Koch's Disease)

Pulmonary tuberculosis is caused by **droplet infection** (coughing, sneezing etc) due to *Mycobacterium tuberculosis*. It is a strict aerobic bacteria for which the reservoir of infection is a human being with active tuberculosis. However, certain clinical conditions can increase the risk of tuberculosis like diabetes mellitus, Hodgkin's lymphoma, chronic lung disease (particularly silicosis), chronic renal failure, malnutrition, alcoholism, and immunosuppression.

Recent Exam Questions
- Pulmonary tuberculosis spread by **droplet infection.**
- The **reservoir** of infection is a ***human being with active tuberculosis.***
- **Acid-fastness** of the Mycobacterium is due to **mycolic acid**
- **Cord factor is a virulence factor** for Mycobacterium *tuberculosis*
- **Macrophages** are the primary cells infected by M. tuberculosis.

Concept

Infection with *M. tuberculosis* is different from *disease*. Infection is the *presence of organisms*, which may or may not cause clinically significant disease. In most of the people, primary tuberculosis is asymptomatic though it may be associated with fever and pleural effusion. Infection with *M. tuberculosis* typically leads to the development of delayed hypersensitivity to *M. tuberculosis* antigens, which can be detected by the **tuberculin (Mantoux) test**. A positive tuberculin test result signifies cell mediated hypersensitivity to tubercular antigens but ***does not differentiate*** between infection and disease.

False-negative Mantoux test	False-positive Mantoux test
• Sarcoidosis • Malnutrition • Hodgkin disease • Immunosuppression • Fulminant tuberculosis	• Infection by atypical mycobacteria • Previous vaccination with BCG

Key Point
- Both **ventilation** as well as **perfusion** per unit lung volume is **maximum at the base** of the lung.
- However **ventilation perfusion ratio** is **maximum** at the **apical regions** of the lungs

Pathogenesis

The bacteria enter macrophages by endocytosis and multiply there. The bacterial cell wall ***glycolipid lipoarabinomannan blocks the fusion of the phagosome and lysosome.*** After about 3 weeks of infection, the TH1 cells are stimulated by mycobacterial antigens and these cells differentiate into mature TH1cells by the action of IL-12.

Recent Exam Questions

Ghon's complex

- ***Subpleural lesion*** along with the ***draining lymphatics*** and the ***lymph nodes.***
- Located in lower part of the upper lobe or the upper part of the lower lobe.
- Fibrosed and calcified Ghon's focus is called as **Ranke complex.**

The mature TH1 cells in the lymph nodes and lung produce IFN-γ which activates macrophages leading to, oxidative damage to the mycobacteria. Activated macrophages produce TNF and recruit monocytes which then differentiate into the "epithelioid histiocytes", a characteristic feature of granulomatous inflammation. The immune response is usually accompanied by hypersensitivity and tissue destruction.

Clinical Features

Primary tuberculosis

- It *develops in a previously unexposed and unsensitized individual.* The source of the organism is usually exogenous. Most patients with primary tuberculosis develop **latent disease** while a minority develops progressive infection.
- Primary tuberculosis almost always begins in the lungs leading to formation of a subpleural lesion called Ghon's foccus. During the first few weeks, there is also lymphatic and hematogenous dissemination to other parts of the body.
- At times, occult hematogenous spread occurs in primary TB where the focus is then called Simon focus.
- In majority of the people, development of cell-mediated immunity controls the infection. The Ghon's complex undergoes progressive fibrosis and calcification (detected radiologically and called as **Ranke complex**[Q]).

Histologically

The sites of active disease show a characteristic granulomatous inflammatory reaction having the presence of *both caseating and non-caseating tubercles.* There is also presence of Langhans giant cells and lymphocytes.

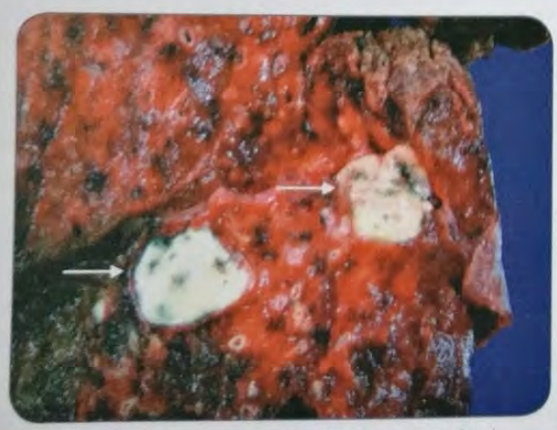


Fig. 1: Pulmonary TB with caseous foci.

Secondary tuberculosis

- *It is the pattern of disease that arises in a previously sensitized host.* It usually results from a reactivation of latent primary lesions after many years of an initial infection, particularly when host immunity is decreased or uncommonly may follow primary tuberculosis. The preexistence of hypersensitivity contributes to localization of the infection and increased incidence of cavitation. This can lead to erosion into an airway (leading to spread of bacilli during coughing).

Progressive pulmonary tuberculosis

It is seen in the *elderly* and the *immunosuppressed* individuals. The apical lesion enlarges with increase in the area of caseation. The erosion of blood vessels (particularly ***bronchial artery***[Q]) results in ***hemoptysis***. The pleural cavity is associated with pleural effusion or empyema. If the treatment is adequate, the disease may be controlled but if it is inadequate, the infection may disseminate through airways, lymphatics or the vascular system.

Miliary disease

It occurs when organisms drain through lymphatics and blood vessels to the different organs of the body resulting in small yellow-white consolidated lesions. Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis.

Recent Exam Questions

Secondary tuberculosis

- MC cause: reactivation of previous latent infection.
- **Infraclavicular lesion: Assman focus.**
- Supraclavicular lesion: Puhl focus.
- **Brain cortex: Rich focus.**
- Liver: Simmond focus.
- **Blood vessels: Weigart focus.**
- Apical lesion: Simon focus.

Concept

Immunocompromised people **do not** form the characteristic granulomas

Recent Exam Questions

- **Bronchial artery** is the source of hemoptysis in TB.
- *Infectious aneurysms* in a **pulmonary artery** secondary to pulmonary tuberculosis **(TB)** are referred to as **Rasmussen aneurysms.**
- The most frequent form of **extra pulmonary** tuberculosis is **lymphadenitis** usually in the cervical region and is known as "**scrofula**".

mportant radiological info

- Early **infraclavicular lesion - Assman Redeker** Simon[Q]
- In post primary stage (late dissemination), coarse granular dissemination is called Aschoff Puhl focus

Key Point

Clinical features in TB are drenching night sweats, fever, weight loss

The patients present with insidious onset of symptoms like low grade remittent fever usually associated with night sweats, productive cough, weight loss, hemoptysis, dyspnea and pleural effusion. The investigations usually reveal lymphocytosis and increased ESR (on hemogram), hilar lymphadenopathy and pleural effusion (on chest X ray), presence of acid fast bacilli with Ziehl Nielson staining. The treatment is provided with multiple drugs (for details, refer to *Review of Pharmacology* by the same authors).

Recent Exam Question

Most common cause of drug resistant tuberculosis is previous ATT.

Pulmonary diseases

Obstructive lung disease	Restrictive lung disease
• Characterized by increased resistance to airflow due to airway obstruction.	• Characterized by decreased expansion of the lung.
• Spirometry reveals $\frac{FEV_1}{FVC}$ **ratio is decreased**[Q].	• Spirometry reveals **reduced total lung capacity** and **vital capacity**[Q].
• Examples: Asthma, Emphysema, Chronic bronchitis, Bronchiectasis.	• Examples: 1. Chest wall disorder-polio, obesity kyphoscoliosis. 2. Interstitial/infiltrative disease: Pneumoconiosis, ARDS, Pulmonary fibrosis.

OBSTRUCTIVE LUNG DISEASES

1. Chronic Bronchitis

It is defined clinically as the presence of *productive cough for at least 3 months in at least 2 consecutive years* in absence of any other identifiable cause.

The most important initiating agent is *smoking*[Q] resulting in airway irritation leading to mucus hyper secretion; the latter may cause airway obstruction. Infection plays a secondary role particularly in maintaining chronic bronchitis and is also responsible for the acute exacerbations.

Key Point

Most important **initiating agent** in chronic bronchitis is **smoking**

Definition

Reid index is the ratio of the mucus gland layer thickness to the thickness of the wall between epithelium and cartilage.

- **Histologic features** include *chronic lymphocytic infiltration* of the airways and *submucosal gland hypertrophy*. There is also *increase in* **Reid index**[Q]. The bronchial epithelium may also have squamous metaplasia and dysplasia.

Recent Exam Question

- Normal Reid index is 0.4 whereas its value increases in chronic bronchitis

Clinical features: Late onset of dyspnea with productive cough (copious sputum), recurrent infections, hypoxemia and mild cyanosis (*BLUE BLOATERS*). Long standing chronic bronchitis can cause **cor pulmonale** (right sided heart failure due to pulmonary hypertension).

2. Emphysema

It is abnormal *permanent enlargement of the airspace distal to terminal* ***bronchioles*** and is associated with *destruction of their walls. Characteristically, there is loss or reduction of elastic recoil of the lung.*

- Most important etiological agent for emphysema is **smoking**[Q] which causes inflammation in airways resulting in increased neutrophils and macrophages. These inflammatory cells release elastase responsible for destruction of lung tissue resulting in emphysema.
- Normally, the pulmonary tissue destruction by elastase is prevented by the presence of anti-elastase activity which is primarily due to α_1-antitrypsin; α_1-AT (mainly) and serum α_1- macroglobulin). So, any increase in neutrophils (usually in smokers) or deficiency of α_1-AT would contribute to development of emphysema.

Recent Exam Questions

- Most important etiological agent for emphysema is **smoking.**
- **α1-AT deficiency** is associated with **panacinar emphysema.**

Emphysema

Centriacinar	Panacinar	Distal acinar/Paraseptal	Irregular
• Involvement of central part of acinus with **sparing of alveoli**[Q].	• Involvement of the **entire acinus**[Q].	• Distal part of acinus is affected with sparing of proximal part of acinus[Q].	• Irregular acinar involvement associated with fibrosis/scarring[Q].
• Seen in smokers[Q].	• Seen with α1-AT deficiency.	• Seen in **smokers**[Q].	
• Usually more severe in **upper lobes**[Q] (due to relative deficiency of serum α1-AT to this less perfused region).	• Occurs more severely in lower lobes at **base of lung**[Q] (due to lower lung distribution of neutrophils because of more perfusion of this region).	• Involvement of lung adjacent to pleura.	
• MC type of emphysema **seen clinically**.		• Associated with the development of **spontaneous pneumothorax**.	• Most common type of **emphysema histologically**[Q].

Mnemonic

emPhysema has letter P (and not B) so Pink Puffer.
chronic Bronchitis has letter B (and not P) so Blue Bloater.

Clinical features: Progressively increasing dyspnea, weight loss, late onset of cough with scanty sputum. The patient is non-cyanotic, uses accessory muscle of respiration and shows pursed lip breathing. (***PINK PUFFERS***).

Management: Cessation of smoking and use of bronchodilators is the mainstay of the management.

3. Asthma

Hyperactivity of the airways resulting in reversible bronchoconstriction and air flow obstruction on exposure to some external stimuli is called asthma.

Concept

Virus induced inflammation **lowers the threshold** of the subepithelial **vagal receptors** to irritants.

Pathogenesis: Primary exposure of an allergen causes T_{H2} *cell dominated* inflammatory response resulting in IgE production and eosinophil recruitment (called *sensitization*). Exposure to the same allergen causes cross linking of IgE bound to IgE receptors on mast cells in the airways which cause opening up of epithelial cells due to released mediators. Antigens then cause activation of mucosal mast cells and eosinophils and this along with neuronal reflexes (subepithelial vagal receptors) cause bronchospasm, increased vascular permeability and mucus production (**Acute or Immediate response**). Later on, leukocytic infiltration causes release of more mediators and damage to the epithelium (**Late Phase Reaction**). Eosinophils in airways release major basic protein which causes epithelial damage and more airway constriction.

Concept

Exercise causes loss of water and heat from the respiratory tract. The water loss causes **mucosal hyperosmolarity** which **stimulates release of mediators** from the mast cells. This explains the pathogenesis of exercise induced asthma

Leukotrienes C_4, D_4, E_4 and acetylcholine have definite role in bronchoconstriction whereas agents like histamine, PGD_2 and platelet activating factor (PAF) may also have role in the features of the disease. The following are the two variants of asthma.

Features	Extrinsic asthma	Intrinsic asthma
Pathogenesis	Type I hypersensitivity reaction due to exposure to an extrinsic antigen	Initiated by non-immune mechanisms with intrinsic body stimuli
Age on presentation	Child	Adult
Family history	Present[Q]	**Absent**[Q]
Prior allergic reaction/allergen exposure	Positive history of rhinitis, urticaria, eczema	Absent
Serum IgE levels	Increased[Q]	**Normal**[Q]
Skin test	Positive	Negative
Associated COPD	Rare	Usually present
Examples	Atopic/allergic asthma, Occupational asthma, Allergic bronchopulmonary aspergillosis	Drugs (most commonly aspirin), viral infections, cold exposure, exercise induced asthma

Concept

In **intrinsic asthma**, aspirin causes **shift** of the arachidonic acid metabolism **towards the lipoxygenase pathway** resulting in formation of the bronchoconstrictor leukotrienes.

IMPORTANT FACT

- **IL-13 gene polymorphism** is strongly associated with **bronchial asthma**.
- **ADAM-33** is another gene causing proliferation of smooth muscle cells and fibroblasts in bronchi resulting in **bronchial hyper-reactivity** and **subepithelial fibrosis**.
- ↑ **serum YKL-40** is co-related with **airway remodeling**, and **disease severity**.

Recent Exam Question

Differential of **asthma** from COPD is by **Reversibility of FEV1** using bronchodilators/ oral steroids

Clinical features: Acute asthmatic attack is characterized by wheezing, cough and severe dyspnea.

Morphology: The most stroking macroscopic finding is occlusion of the bronchi and bronchioles by mucus plugs. Histologically, there are numerous eosinophils, **Charcot leyden crystals**Q (composed of ***eosinophil membrane protein called as galectin-10***) and **Curschmann spirals**Q (whorls of shed airway epithelium). Structural changes in the bronchial wall called *"airway remodelling"* is characterized by presence of eosinophilic inflammation and edema of bronchial walls, increased size of submucosal glands, hypertrophy of bronchial wall smooth muscle and deposition of subepithelial collagen in the bronchial wall. Individual epithelial cells present in the sputum of the patients are called **Creola bodies**.

Management is done with bronchodilators and corticosteroids (for details, refer to the Review of Pharmacology by the same authors).

Mnemonic

3 **C's** of sputum findings in asthma;
- **C**harcot leyden crystals
- **C**urschmann spirals
- **C**reola bodies

4. Bronchiectasis

Abnormal permanent airway dilation resulting from chronic necrotizing infections is called bronchiectasis.

Causes

Bronchial obstruction	Congenital	Necrotizing pneumonias	Miscellaneous
• Tumor • Foreign body	• Cystic fibrosis • Kartagener syndromeQ.	• Mycobacterium • *Staph aureus* • Aspergillus • Influenza virus.	• SLE • Rheumatoid arthritis • Post transplantation.

Recent Exam Questions

Kartagener syndrome
- (Triad of Bronchiectasis + situs inversus + sinusitis).
- **Bronchiectasis** affects vertical air passages of the **lower lobes** bilaterally with involvement of **left side** more frequent than right.
- **High Resolution CT Scan (HRCT)** is the **best investigation** for the detection of bronchiectasis

Obstruction and infection are the chief contributors to the damage of airway wall associated with destruction of smooth muscle and elastic tissue fibrosis and further dilatation of bronchi.

Clinical features: Chronic cough, fever, foul smelling sputum production, recurrent pulmonary infections, sinusitis and immune deficiencies.

It usually affects vertical air passages of the *lower lobes* bilaterally with involvement of *left side*Q *more frequent* than right. The dilated bronchi can be followed directly out to the pleural surfaces. There is usually presence of inflammatory cells in the walls of bronchi and bronchioles which may also exhibit squamous metaplasia.

Recent Exam Questions
- Complications include ***massive hemoptysis, amyloidosis, visceral abscess*** and ***cor pulmonale***Q.
- Bronchiectasis is **NOT** a ***pre-malignant*** condition.

Fig. 2: Bronchiectasis: dilated bronchi reach pleural surface

RESTRICTIVE LUNG DISEASE

1. Interstitial Lung Disease

Interstitial lung disease (ILD) is a group of heterogeneous diseases characterized by *chronic inflammation and fibrosis of the interstitium and lung parenchyma*[Q]. The interstitium of the lung (supporting structure) is the area in and around the small blood vessels and alveoli where the exchange of oxygen and carbon dioxide takes place. Inflammation and scarring of the interstitium (and eventually extension into the alveoli) will disrupt normal gas exchange. Usually, patients present with *exertional dyspnea and non-productive cough.*

The chest X-ray shows reticular or reticulonodular pattern **("ground glass" appearance)**. Pulmonary function tests show evidence of intrapulmonary *restrictive pattern.*

Earliest manifestation of the disease is inflammation in the alveolar wall called **Alveolitis**. The inflammatory cells release chemical mediators resulting in injury to parenchymal cells and stimulation of fibrosis. In advanced stages of the disease, the gross destruction and scarring of the lung results in end stage disease or **honeycomb lung.**[Q]

ILD

Fibrosis	Granulomatous	Associated with smoking	Miscellaneous
• Idiopathic pulmonary fibrosis • Collagen vascular disease associated pulmonary fibrosis (SLE, RA, Scleroderma) • Pneumoconiosis • Drug reaction • Radiation pneumonitis • Fumes and gases (SO_2 etc.)	• Sarcoidosis • Hypersensitivity pneumonitis.	• Desquamative interstitial pneumonia	• Pulmonary alveolar proteinosis.

We shall focus on each of the chief subtypes of interstitial lung disease:

A. PNEUMOCONIOSIS

Non-neoplastic lung reaction (usually fibrosis) to inhalation of mineral dust, organic and inorganic particles and chemicals and vapors is called pneumoconiosis.

Key Point

The **most dangerous** particle size for causation of pneumoconiosis is **1-5 microns.**

These particles overwhelm the normal phagocytosis by alveolar macrophages to evoke fibroblast proliferation and collagen deposition. Some of the important pneumoconiosis includes:

Key Point

Dust cells are **alveolar macrophages** with *anthracotic* pigment.

(1) Coal worker's pneumoconiosis (Anthracosis)

It is due to inhalation of coal dust in coal miners and is usually present adjacent to respiratory bronchiole. It is categorized into:

Simple CWP:
(*i*) Coal macules (carbon-laden macrophages)
(*ii*) Coal nodules (*upper lobes more heavily involved*)
(*iii*) Centrilobular emphysema
Complicated CWP: Develops after many years
(*i*) Intense blackened scars larger than 2 cm in diameter
(*ii*) Center of lesion is often necrotic

Recent Exam Question

Caplan syndrome is the co existence of *pneumoconiosis* and cavitating *rheumatoid nodules*

(2) Silicosis (Grinder' disease)

- Nodular fibrosing disease[Q] due to inhalation of silica in workers engaged is sandblasting, hard rock mining, foundry work, glass and pottery making.
- *Most common chronic occupational disease* in the world[Q].
- Crystalline form of silica called *quartz is most commonly implicated in silicosis.*
- Co-inhalation of other mineral particles reduces[Q] the fibrogenic effect of silicosis.
- Involvement of upper lobes of the lung.[Q]
- Association with increased *susceptibility to tuberculosis*[Q].
- Chest X-ray shows presence of *Eggshell calcification*[Q] (thin sheet of calcification in the lymph node surrounding a zone lacking calcification).
- *Polarized microscopy* reveals presence of *birefringent silica particles*[Q].

(3) Asbestosis

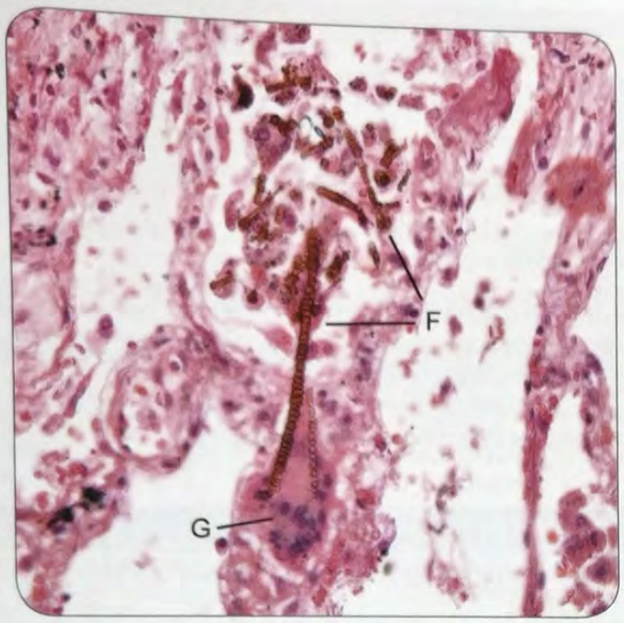


Fig. 3: Ferruginous Body (F) and foreign body giant cell (G) in Asbestosis

Key Point

The presence of asbestos bodies in or adjacent to the walls of fibrotic respiratory bronchioles is the hallmark of the disease.

- Diffuse interstitial fibrotic disease due to inhalation of asbestos particles in workers engaged in mining, pipes, brakes, insulation and boilers.
- Initially, involvement of **lower lobes** of the lung pleurally[Q].
- In contrast to other dusts, can also *act as a tumor initiator and tumor promoter*[Q].

Two types of fibers are:

- ***Serpentine*** *(curly and flexible fibres, chrysotile):* These account for **most of the asbestos** used in industry.
- ***Amphibole*** *(straight, stiff and brittle fibres, crocidolite, amosite, actinolyte):* These are **more pathogenic** than chrysotiles, particularly with respect to induction of malignant pleural tumors (mesotheliomas).

Key Point

Benign pleural plaques: most common lesions in asbestosis

Recent Exam Questions

- **Bronchogenic carcinoma: most common** asbestos related cancer.
- **Mesothelioma: most specific** asbestos related cancer.
- *Chronic asbestos* exposure causes ***adenocarcinoma*** more frequently than squamous cell carcinoma.

Lesions with asbestosis

Pleural plaque[Q]:

It is the most common manifestation of asbestos exposure and is composed of well circumscribed plaques of *dense collagen containing calcium.* They are usually asymptomatic and develop on anterior and posterolateral parts of parietal pleura and over the diaphragm.

Interstitial fibrosis

Pulmonary fibrosis with the presence of **asbestos body[Q]** (iron containing proteinaceous material coating asbestos fiber) and **ferruginous body[Q]** (iron protein complex coating other inorganic particles like talc, mica, fibre, glass and other less common materials in the lung). True asbestos bodies are clear whereas the core of these particles is dark).

Bronchogenic cancer (latent period is 10-30 years)

Most common cancer associated with asbestos[Q] whose risk is increased with concomitant smoking.

***Mesothelioma* (latent period is 25-45 years)**

Localization of asbestos fibres in the lung close to the mesothelial layers increases the risk of development of pleural and peritoneal mesothelioma. Concomitant smoking **does not** increase the risk of mesothelioma. It is the ***most specific*** cancer associated with asbestos inhalation.

Pleural effusion, laryngeal and colon cancers.

Recent Exam Questions

Other important pneumoconiosis

- Stannosis: Tin oxide (miners).
- Siderosis: Iron oxide (welders).
- **Byssinosis:** *cotton fibres* (textile workers).
- Baritosis: Barium sulfate (miners).

Clinical symptoms of pneumoconiosis include progressively increasing **dyspnea** (First symptom), productive cough, reduced exercise tolerance which may progress to respiratory failure, cor pulmonale and ultimately death.

B. SARCOIDOSIS

It is a systematic disease of unknown etiology characterized by the presence of *non-caseating granulomas* in many organs. It is seen more commonly in *females of 20-40 years* of age. It is associated with *HLA-A1 and HLA-B8.*

Key Point

Sarcoidosis shows presence of **noncaseating** *granulomas*

Concept

Sarcoidosis has **elevated ACE** levels. ACE enzyme is important even for distinguishing sarcoidosis from *bronchogenic carcinoma* as the *level* of the ACE enzyme in the latter would be *normal.*

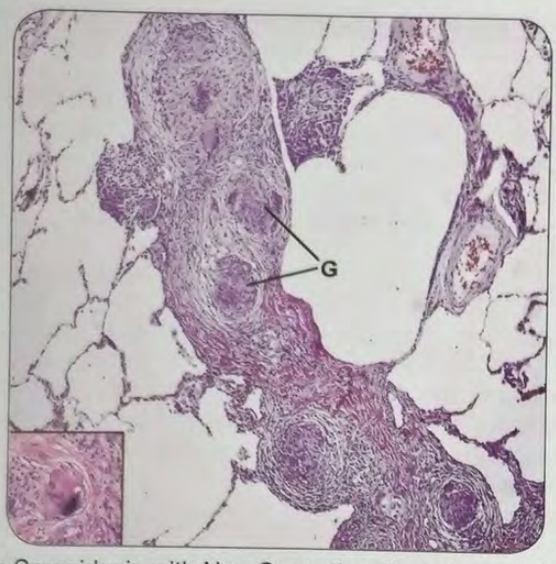


Fig. 4: Sarcoidosis with Non Caseating Granuloma (G); Inset shows Schaumann body.

Key Point

Sarcoidosis is a *diagnosis of exclusion;* rule out other granulomatous diseases.

Immunological abnormalities associated with sarcoidosis

- Intra-alveolar and interstitial *accumulation of CD_4 + T cells* resulting in CD_4:CD_8 T cell ratio ranging from 5:1 to 15:1[Q].
- Increased levels of IL-2 and IFN-γ causing *T-cell expansion and macrophage activation* respectively[Q].
- *Polyclonal hypergammaglobulinemia*[Q].
- *Anergy to skin antigens* like purified protein derivative (PPD)[Q].

Histologically, there is characteristically presence of *non-caseating granuloma*[Q] composed of aggregates of epithelioid cells and giant cells. There is also presence of *Schaumann bodies*[Q] (laminated concretions of calcium and protein) and *asteroid bodies*[Q] (stellate or star shaped inclusions in giant cells).

Organs Affected

Lungs

- ***Most common site*** of organ involvement
- There is presence of ***non-caseating granuloma*** in the bronchial submucosa.
- ***Bronchoalveolar lavage***[Q] shows ***CD_4:CD_8 T- lymphocytes ratio of > 2.5*** is seen.

Lymph nodes

- Involvement of hilar and mediastinal nodes is seen in almost all the cases.

Liver and spleen

- Splenomegaly may be seen with sparing of capsule. Scattered granulomas are seen more in portal triads as compared to globular parenchyma.

Contd...

Contd...

Bone marrow

- Favored site of localization having tendency to involve *phalangeal bones of hands and feet* showing small areas of bone resorption, bony shaft widening and new bone formation.

Skin

- Lesions include erythema nodosum, subcutaneous nodules, erythematous plaques and **lupus pernio**[Q].

Eye, lacrimal glands and salivary glands

- Unilateral or bilateral ocular involvement resulting in iritis, glaucoma or corneal opacity may occur.
- Causes lacrimal gland inflammation (causing ***dry eyes***[Q]) and salivary gland involvement (***dry mouth***[Q]).

Definition

Lofgren syndrome (has erythema nodosum, arthritis and hilar adenopathy).

Heerfordt Waldenstrom syndrome (fever, parotid enlargement, uveitis and facial palsy)

Clinical features include shortness of breath, cough, chest pain, hemoptysis, constitutional signs and symptoms (fever, fatigue, weight loss) or it may be discovered on routine X-ray as bilateral hilar lymphadenopathy. It can also manifest as Lofgren Syndrome and Heerfordt Waldenstrom Syndrome.

- Chest X-ray shows bilateral hilar and left paratracheal lymphadenopathy. There is **hypercalcemia**[Q] due to increased circulation of vitamin D by macrophages. **Elevated levels of ACE**[Q] (Angiotensin Converting Enzyme) are seen in the disease. These patients also demonstrate **skin anergy** and a **restrictive pattern** on pulmonary function tests.
- **Management:** It is done usually with corticosteroids.

C. PULMONARY ALVEOLAR PROTEINOSIS

Recent Exam Question

- **Autoantibodies against GM-CSF** is seen in ***pulmonary alveolar proteinosis***.

It is a rare disease in which phospholipids accumulate within alveolar spaces. This is a condition of unknown cause characterized by auto-antibodies against granulocyte macrophage-colony stimulating factor (GM-CSF).

Some (10%) PAP cases are congenital in nature secondary to mutations in the GM-CSF gene leading to reduced or absent SP-B and intra alveolar accumulation of SP-A and SP-C.

Secondary PAP is associated with immunodeficiency, hematopoietic disorders, malignancies, acute silicosis and other inhalational syndromes.

Clinical features: ***Progressive dyspnea*** is the usual presenting symptom. Chest X-ray shows bilateral alveolar infiltrates suggestive of pulmonary edema. **Bronchoalveolar lavage shows characteristic milky appearance and PAS-positive lipoproteinaceous material**. Lung biopsy reveals amorphous intra-alveolar phospholipids.

2. Adult Respiratory Distress Syndrome (ARDS)

- Also called as ***Shock lung***[Q], ***Diffuse alveolar damage***[Q] ***or Acute lung injury***[Q]
- Characterized by damage to alveolar cells and blood vessels resulting in oxygen refractory progressive respiratory insufficiency.

Conditions associated with ARDS

Infections	Physical factors	Chemical factors	Miscellaneous
• Septicemia • Aspiration • Pulmonary infections (TB, viral, mycoplasma, etc.)	• Drowning • Head injury • Radiation exposure • Fat embolism • Smoking • Irritant gases.	• Drugs like aspirin • Heroin/Methadone • Overdose of barbiturates • Hypersensitivity by organic solvents.	• Pancreatitis • Uremia • Multiple transfusion • DIC.

Recent Exam Questions

- **Sepsis** is most common cause of ARDS
- **Features of ARDS** severe hypoxemia, PA wedge pressure < 18 mm Hg, increased A-a (Alveolar-arterial) gradient.
- **Hyaline membrane** is made up of *fibrin* and *necrotic* cells.

Pathogenesis of ARDS

Etiological conditions
↓
Diffuse damage to alveolar capillary wall
↓
↑ Realease of cytokines like IL-8, IL-2, TNF
↓
Neutrophilic sequestration and activation
↓
Damage to type II pneumocytes
↓
Increased vascular permeability and alveolar exudate formation
↓
Decreased diffusion capacity and non-resolving continuous damage to pulmonary tissue

Morphological features include Interstitial and intra-alveolar edema with lining of alveoli with hyaline membrane composed of fibrin rich edema fluid and lipid remnants of epithelial cells. Later on, there is intra-alveolar fibrosis.

Clinical features include Progressively increasing dyspnea (difficulty in breathing), tachypnea resulting in respiratory failure, cyanosis and hypoxemia, chest x-ray shows bilateral diffuse infiltration **("white out" lung**[Q]**).** Management is done primarily with treatment of underlying cause and mechanical ventilation.

Neonatal RDS/Hyaline membrane disease (HMD)

Prematurity	Infants of diabetic mothers	Cesarean section

Key Point

Prevention of HMD

- Delay onset of labour.
- Give steroids to mother..

- Results from **surfactant deficiency** which is chemically composed of lecithin (dipalmitoylphosphatidylcholine; DPPC[Q]). Due to reduced surfactant, surface tension of alveoli increases. Increased alveolar surface tension causes atelectasis resulting in hypoxemia responsible for damage to endothelial and epithelial cells. The latter contributes to formation of hyaline membrane[Q] (fibrin + necrotic cells).

Key Point

Treatment of HMD

- Artificial surfactant.
- Oxygen using high frequency ventilation.

- Clinical features include normal infant at birth but within 30 minutes, there is development of progressively increasing respiratory effort and cyanosis. **Chest X-ray** demonstrates multiple reticulogranular densities (**"ground glass"** appearance[Q]).

VASCULAR LUNG DISEASES

1. Pulmonary Emboli and Pulmonary Infarction

Most (90-95%) of the pulmonary emboli arise from **deep vein thrombosis** (DVT) in the leg and *only 10% of pulmonary emboli cause infarction*. The infarcts occur in patients with underlying cardiopulmonary disease. It is a **wedge shaped hemorrhagic infarction**. The diagnosis of pulmonary embolism is made on ventilation/perfusion scan (V/Q lung scan) which shows a mismatch. The complications associated with this condition include pulmonary hypertension, cor pulmonale, pulmonary abscess and even sudden death.

Recent Exam Questions

- **Deep vein thrombosis** is the commonest cause of pulmonary thromboembolism.
- **Spiral CT scan** is the investigation of choice.

2. Pulmonary Hypertension

It is defined as increased pulmonary artery pressure, usually due to increased vascular resistance or blood flow. It is seen in association with:

- COPD and interstitial disease (hypoxia induced vasoconstriction is seen).
- Multiple ongoing pulmonary emboli.
- Mitral stenosis and left sided heart failure.
- Congenital heart disease with left to right shunts (ASD, VSD, PDA).
- Primary (idiopathic).

Key Point

Pulmonary hypertension is defined as a mean pulmonary artery pressure **greater than** or **equal to 25 mm Hg** at rest.

Recent Exam Question

Mutations in the **bone morphogenetic protein receptor type 2** (BMPR2) signaling pathway have been associated with **pulmonary hypertension**.

Pulmonary hypertension is characterised by increased medial hypertrophy and intimal fibrosis in small arteries.

The presence of plexogenic pulmonary arteriopathy may also be seen in primary pulmonary hypertension or congenital heart disease with left to right shunts.

3. Pulmonary Edema

It is defined as the fluid accumulation within the lungs usually due to disruption of starling forces or endothelial injury.

So, it can be due to:

1. Increased hydrostatic pressure as in left-sided heart failure, mitral valve stenosis, fluid overload, etc.
2. Decreased oncotic pressure as in nephrotic syndrome, or liver disease.
3. Increased capillary permeability as in infections, drugs (bleomycin, heroin), shock, radiation.

Recent Exam Question

Hemosiderin-laden macrophages are also known as **heart-failure cells**

The lungs are wet and heavy and the fluid accumulation is more in the lower lobes. Microscopically, there is presence of intra-alveolar fluid, engorged capillaries and *hemosiderin-laden macrophages (heart-failure cells)*.

NEOPLASTIC LUNG DISEASES

1. Bronchogenic Cancer

The lung is a common site of metastatic neoplasms. However, *bronchogenic cancer is the most common primary malignant tumor of the lung*. It is most frequently diagnosed major cancer in the world.

Key Point

Metastasis/Secondaries are the **commonest** malignant tumor of the lung.

Risk factors

Non-genetic	Genetic
• Tobacco smoking (contain chemicals like benzopyrene and polycyclic • Air pollution • Occupational exposure (asbestosis, uranium mining, radiation, etc.)	Mutations affecting • Tumor suppressor genes p53 and Rb gene • Oncogenes • K-ras – Adenocarcinoma • L-myc – Small cell carcinoma.

Histological variants of lung cancer

Squamous cell carcinoma	Adenocarcinoma	Small cell cancer or oat cancer	Large cell cancer
• MC type of lung cancer in smokers[Q].	• Overall MC type of cancer[Q].	• Associated with smoking	
• MC type in males[Q].	• MC type in non-smokers and females[Q].	• Commoner in smokers[Q].	
• Usually central in location (arise from the segmental bronchi)	• Usually peripheral in location (arise from terminal bronchiole)	• Central in location	• Peripheral in location.
• Shows highest frequency of p53 mutation[Q].	• Associated with K-ras mutation[Q].	• Immunohistochemistry shows high expression of **Bcl-2** gene[Q] in majority of tumors.	
• Intercellular bridges or junction is very specific. • Histologically, the tumor has presence of **keratinization**[Q].	• Glandular pattern of growth of the tumor is seen. • Cells are positive for **mucin,** thyroid transcription factor-1 **(TTF-1)**[Q] and **Napsin-A (sensitive as well as specific marker)**	• Cells have scanty cytoplasm, small nucleoli, granular chromatin **(salt and pepper pattern[Q])**. • **Azzopardl effect** (Basophilic staining of vascular walls) is frequently present. • Electron microscopy shows presence of neurosecretory granules chromogranin, synaptophysis and leu-7[Q].	• Cells have large nuclei, prominent nucleoli and a moderate amount of cytoplasm.
• Highest association with **cavitation** • **Has the** best prognosis		• Has **best response** to chemotherapy and radiotherapy. • Has the **worst prognosis**[Q]. • **Most aggressive** lung cancer[Q].	
• **Hypercalcemia**[Q] due to PTHrP is the MC paraneoplastic syndrome.		• Associated with maximum paraneoplastic syndrome[Q] (particularly **SIADH** and **Cushing syndrome**).	• Has **gynecomastia** as paraneoplastic syndrome[Q].

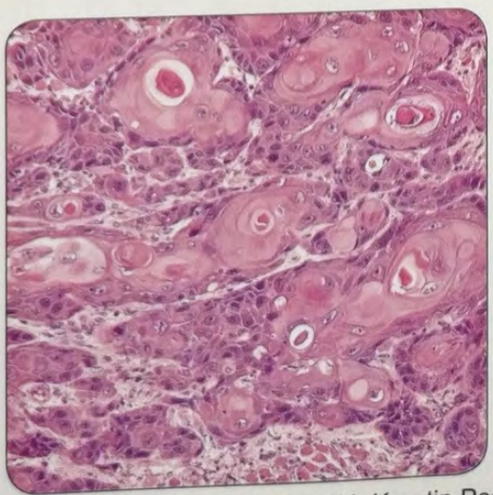


Fig. 5: Squamous Cell Cancer with Keratin Pearls

Recent Exam Questions

Bronchogenic cancer

- MC symptom: **Cough**
- MC site of spread: **Adrenals**
- **Clara** cell: ***adenocarcinoma insitu***
- Salt and pepper pattern: Small cell cancer.
- **Keratinization: Squamous** cell cancer.
- SVC syndrome: small cell cancer.
- **Adeno carcinoma insitu** (*earlier called as Bronchoalveolar carcinoma*) spreads by the ariways **(aerogenous spread)**. Due to this fact, the patient usually **dies by suffocation** (not by metastatic spread).

Horner syndrome

Horner syndrome[Q] is caused due to compression of sympathetic nerve plexus by an apical tumor called as *Pancoast tumor*[Q]. It is usually an **adenocarcinoma**. Its components are remembered by the **mnemonic: Punjabi MEAL (see box on the side)**.

Mnemonic

Horner syndrome

Punjabi	–	**P**tosis
M	–	**M**iosis
E	–	**E**nophthalmos
A	–	**A**nhidrosis
L	–	**L**oss of *ciliospinal reflex* (in this reflex, pinching of the skin on the nape of neck causes dilatation of the pupil of the same side)

Clinical features: ***Cough*** is the most common symptom in these patients which is followed by ***weight loss*** and ***dyspnea***. They also have anorexia, fatigue, hemoptysis, and chest pain.

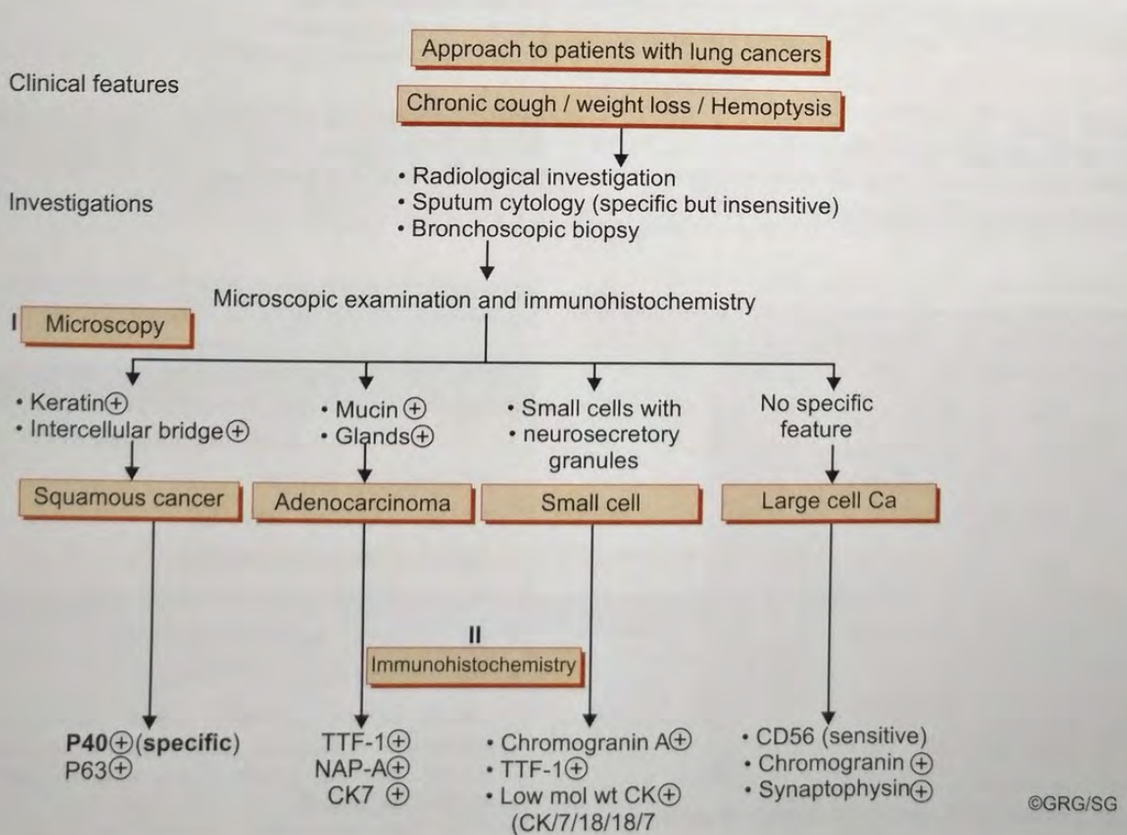
Metastasis of the cancer causes **involvement of adrenal (most commonly**[Q]) followed by liver, brain and bone. Intrathoracic spread of the cancer causes enlargement of lymph nodes (hilar, mediastinal, bronchial and tracheal), pleural involvement, hoarseness (recurrent laryngeal nerve invasion), dysphagia (esophageal obstruction), diaphragmatic paralysis (phrenic nerve paralysis), Horner syndrome and superior vena cava (SVC) syndrome.

Key Point

Diagnosis of bronchogenic cancer is usually made with **sputum cytology and fibreoptic bronchoscopy**

Important paraneoplastic syndromes associated with bronchogenic cancer include:

1. **Endocrinological syndrome**
   a. Cushing syndrome (Due to ACTH)
   b. Syndrome of inappropriate ADH secretion (SIADH) [Due to anti-diuretic hormone]
   c. Hypercalcemia: Due to parathyroid hormone related peptide (PTH related peptide).
   d. Hypocalcemia: Due to calcitonin
   e. Gynecomastia: Due to gonadotropins
2. **Lambert eaton syndrome:** Due to autoantibodies against neuronal calcium channel
3. **Acanthosis nigricans:** Hyperpigmentation of axillary region.
4. **Hypertrophic pulmonary osteoarthropathy** having clubbing and periosteal new born formation.



2. Solitary (Localized) Fibrous Tumor

It was earlier referred to as *'benign mesothelioma'*. It has got ***no relationship with asbestosis***[Q]. Microscopically, there is presence of whorls of reticulin and collagen fibers with interspersed spindle cells resembling fibroblasts. The tumor cells characteristically show immunostaining pattern of ***CD34(+) and keratin-negative***[Q].

Recent Exam Questions

Solitary (Localized) Fibrous Tumor

- Also called *benign mesothelioma.*
- **Not** related with asbestosis.
- Cells are **CD34(+)** and **keratin(–).**

3. Malignant Mesothelioma

It is a tumor arising from visceral or parietal pleura which is seen after prolonged duration (after a latent period of 25-45 years) of *asbestos inhalation*. It is *not associated with smoking*. Unlike bronchogenic cancer, it is less commonly associated with p53 mutation. It is associated with extensive pleural effusion and local invasion of thoracic structures. Microscopically, the tumor can have the following patterns:

1. *Sarcomatoid type*: Mesenchymal stromal cell type
2. *Epithelioid type*: Consists of cuboidal, columnar or flattened cell forming tubular or papillary structure resembling adenocarcinoma.
3. *Mixed type*: It contains both epithelioid and sarcomatoid patterns.

Key Point

- *Malignant Mesothelioma* is **not** associated with *smoking.*
- Cells are **CD34(–)** and **keratin(+)**

Difference between mesothelioma and adenocarcinoma

Epithelioid mesothelioma	Pulmonary adenocarcinoma
• Acid mucopolysaccharide staining (+)	• Acid mucopolysaccharide staining (–)
• *Keratin (+)*	• *Keratin (–)*
• **CEA (–)**	• **CEA (+)**
• *Electron microscopy* shows ***long***, *slender, numerous microvilli and tonofilaments*	• *Electron microscopy* shows **short microvilli** and *secretory rough endoplasmic reticulum*

Clinical features include chest pain, dyspnea and recurrent pleural effusions. Right lung is more commonly affected than left lung. It is **usually unilateral at presentation.** The lung is invaded directly, and there is often metastatic spread to the hilar lymph nodes and, eventually to the liver and other distant organs. It is associated with very poor prognosis.

Concept

The best marker to differentiate benign and malignant mesothelioma is p53. Its mutation is present in malignant mesothelioma and this mutation is absent in benign mesothelioma.

ATELECTASIS

Incomplete expansion of the lungs or the collapse of previously inflated lung is known as atelectasis.

1. **Resorption Atelectasis:**
   - Due to airway obstruction leading to resorption of oxygen trapped in the alveoli.
   - Causes mediastinal shift towards affected lung.
   - Associated with chronic bronchitis/asthma/aspiration of foreign body/secretions.
2. **Compression Atelectasis:**
   - Due to presence of fluid, blood, air or tumor in pleural space.
   - Causes mediastinal shift away from the affected lung.
   - Most commonly associated with cardiac failure[Q].
3. **Contraction Atelectasis:**
   - Fibrosis in the lung or pleura preventing full expansion of pulmonary tissue.
   - Only **irreversible** cause of atelectasis[Q].

Mediastinal tumors

Anterior Mediastinum	Middle Mediastinum	Posterior Mediastinum
• **Thymoma (commonest)**	• **Bronchogenic cyst** (commonest)	• **Neurogenic tumors** like schwannoma, neurofibroma (commonest)
• Teratoma	• Pericardial cyst	• Lymphoma
• Lymphoma	• Lymphoma	• Metastatic tumor (most are from the lung)
• Thyroid lesions		• Bronchogenic cyst
• Parathyroid tumors		• Gastroenteric hernia
• Metastatic carcinoma		

Multiple Choice Questions

INFECTIVE LUNG DISEASE: PNEUMONIA, TB, LUNG ABSCESS

1. **Infraclavicular lesion of tuberculosis is known as:** *(AIIMS May 2011)*
   (a) Gohn's focus
   (b) Puhl's focus
   (c) Assman's focus
   (d) Simmon's focus

2. **Pulmonary tuberculosis is more common in following associated diseases, except:** *(DPG 2011)*
   (a) Acquired immune deficiency syndrome
   (b) Diabetes
   (c) Chronic renal failure
   (d) Mitral stenosis

3. **All of the following features are seen in the viral pneumonia except:** *(AI 2005)*
   (a) Presence of interstitial inflammation
   (b) Predominance of alveolar exudate
   (c) Bronchiolitis
   (d) Multinucleate giant cells in the bronchiolar wall

4. **Atypical pneumonia can be caused by the following microbial agents except?** *(AI 2005)*
   (a) Mycoplasma pneumoniae
   (b) Legionella pneumophila
   (c) Human corona virus
   (d) Klebsiella pneumoniae

5. **In primary tuberculosis, all of the following may be seen except:** *(AI 2002)*
   (a) Cavitation
   (b) Caseation
   (c) Calcification
   (d) Langhans giant cell

6. **Lung granuloma with necrosis is seen in:**
   (a) PAN *(PGI June 01)*
   (b) TB
   (c) Histoplasmosis
   (d) Cryptococcosis
   (e) Wegener's granulomatosis

7. **Predisposing factors of lung abscess are:**
   (a) Altered sensorium *(PGI Dec 2003)*
   (b) Dental sepsis
   (c) Aggressive treatment of pneumonia
   (d) Subpulmonic effusion
   (e) Endobronchial obstruction

8. **Pulmonary, renal syndrome is seen in:**
   (a) Goodpasture syndrome *(PGI Dec 2003)*
   (b) Leptospirosis
   (c) Legionella
   (d) Wegener's granulomatosis
   (e) Hantan virus infection

9. **Lung granuloma found in A/E:** *(PGI June 2004)*
   (a) Berylliosis
   (b) Asbestosis
   (c) SLE
   (d) Sarcoidosis

10. **True about Ghon's focus:** *(PGI Dec 2004)*
    (a) Left apical parenchymal lesion
    (b) Right apical parenchymal lesion
    (c) Subpleural caseous lesion in right upper lobe
    (d) Subpleural caseous lesion just above or below interlobar fissure
    (e) Caseous hilar lymphadenopathy

11. **Which of these is seen in primary tuberculosis:**
    (a) Ghon's focus *(PGI Dec 2006)*
    (b) Pleural effusion
    (c) Miliary mottling
    (d) Fibrosis
    (e) Cavity

12. **Characteristic histopathological feature of pneumocystis carinii pneumonia:** *(PGI Dec 2000)*
    (a) Interstitial pneumonitis
    (b) Increased eosinophils
    (c) Foamy vacuolated exudates
    (d) Mononuclear cell in bronchoalveolar lavage
    (e) Neutrophil infiltration

13. **A 9-year-old girl Bandhini developed a 10 mm area of induration on the left forearm 72 hours after intradermal injection of 0.1 ml of purified protein derivative (PPD). Which of the following is most likely to be seen on the X-ray of this patient?**
    (a) Marked hilar adenopathy
    (b) Upper lobe calcifications
    (c) No abnormal findings
    (d) Reticulo-nodular densities

MOST RECENT QUESTIONS

14. **In the stage of Grey hepatisation, which of the following is a finding?**
    (a) WBC's fill the alveoli
    (b) RBC's fill the alveoli
    (c) Organisms fill the alveoli
    (d) Accumulation of fibrin

15. **Gray hepatization of lungs is seen on day:**
(a) 1 (b) 2-3
(c) 3-4 (d) 5-7

16. **Collapse of lung is called:**
(a) Emphysema (b) Bronchiactasis
(c) Atelectasis (d) Bronchitis

17. **Reactivated TB is most commonly located near:**
(a) Apex (b) Near bronchus
(c) Subpleurally (d) Base

18. **Maximum smooth muscle relative to wall thickness is seen in**
(a) Terminal bronchiole
(b) Trachea
(c) Bronchi
(d) Respiratory bronchioles

19. **The earliest feature of tuberculosis is:**
(a) Caseation
(b) Recruitment of lymphocytes
(c) Formation of giant cells (Langhans)
(d) Granuloma formation

20. **ESR is a very critical investigation is the diagnosis of TB. Which of the following is true about ESR in TB?**
(a) No change is ESR
(b) Confirms recovery from TB
(c) ESR is raised because of increased RBC aggregate
(d) ESR is raised due to decreased RBC size

21. **The alveoli are filled with exudates the air is displaced converting the lung into a solid organ this description suggests:**
(a) Chronic bronchitis (b) Bronchial asthma
(c) Bronchiectasis (d) Lobar pneumonia

22. **Azoospermia seen in which syndrome-**
(a) Kartagener syndrome
(b) Young syndrome
(c) Churg strauss syndrome
(d) Both a and b

OBSTRUCTIVE LUNG DISEASE: BRONCHITIS, ASTHMA, BRONCHIECTASIS, EMPHYSEMA

23. **Increased Reid's index is increased in which of the following?** *(AI 2012)*
(a) Bronchiectasis
(b) Bronchial asthma
(c) Chronic bronchitis
(d) Emphysema

24. **True about alpha-1 antitrypsin deficiency, is/are:** *(PGI June 01)*
(a) Autosomal dominant
(b) Pulmonary emphysema
(c) Diastase resistant hepatic cells
(d) Hepatic cells are orcein stain positive
(e) Associated with berry aneurysm

25. **Late response in bronchial asthma is due to:** *(UP 2003)*
(a) Mast cells
(b) Eosinophils
(c) Neutrophils
(d) Macrophages

26. **Charcot-Leyden crystals and Curschmann's spirals are seen in:** *(UP 2006)*
(a) Bronchial asthma
(b) Chronic bronchitis
(c) Bronchiectasis
(d) Emphysema

27. **Most common type of emphysema clinically is:** *(RJ 2006)*
(a) Panacinar
(b) Centriacinar
(c) Paraseptal
(d) Segmental

28. **In a heavy smoker with chronic bronchiolitis, which of the following is likely to be seen:** *(Kolkata 2003)*
(a) Centrilobular emphysema
(b) Panacinar emphysema
(c) Paraseptal emphysema
(d) None of the above

29. **A 30-year-old woman Chinamma has had increasing dyspnea with cough for the past week. Over the past 2 days she is having productive cough with copious sputum. On examination, she is afebrile but has extensive dullness to percussion over all the lung fields. Her chest X ray has B/L diffuse opacification. Electron microscopic examination of the biopsy tissue shows many lamellar bodies. The antibody is directed against which of the following substances in the pathogenesis of the above described condition?**
(a) CFTR
(b) Granulocyte – macrophage colony stimulating factor
(c) DNA topoisomerase 1
(d) Glomerular basement membrane

30. **A 50-year-old man Shahid K. John has had increasing dyspnea for the past 3 years with associated occasional cough but little sputum production. Auscultation reveals that his lungs are hyper-resonant and is associated with expiratory wheeze. Pulmonary function tests reveal increased total lung capacity (TLC) and slightly increased FVC. There is decreased FEV1 and FEV1/FVC ratio also. ABG analysis reveals pH of 7.35, pO_2 of 60 mm Hg and pCO_2 of 48 mm Hg. What is the most likely diagnosis?**
(a) Sarcoidosis
(b) Centriacinar emphysema
(c) Diffuse alveolar damage
(d) Chronic pulmonary embolism

31. **A 65-year-old smoker Sutta Ram with hemoptysis and weight loss undergoes a left upper lobectomy for squamous cell carcinoma. The uninvolved lung tissue**

shows destruction of the alveolar septae around the respiratory bronchioles, with marked enlargement of the airspaces. Anthracotic pigments deposited heavily in the walls of these tissues. These findings are most compatible with:
(a) Asthma (b) Chronic bronchitis
(c) Emphysema (d) Pulmonary hypertension

MOST RECENT QUESTIONS

32. Alpha-1-antitrypsin deficiency occurs in:
(a) Emphysema
(b) Bronchiectasis
(c) Empyema
(d) Bronchogenic carcinoma

33. Thickening of pulmonary membrane is seen in:
(a) Asthma (b) Emphysema
(c) Bronchitis (d) Bronchiectasis

34. Creola bodies are seen in:
(a) Bronchial asthma
(b) Chronic bronchitis
(c) Emphysema
(d) Bronchiectatsis

35. Distension of distant alveoli is seen in:
(a) Irregular emphysema
(b) Paraseptal emphysema
(c) Panacinar emphysema
(d) Centriacinar emphysema

RESTRICTIVE LUNG DISEASE: ILD, ARDS, PNEUMOCONIOSIS

36. Which of the following is the characteristic feature of adult respiratory distress syndrome? *(AI 2012)*
(a) Diffuse alveolar damage
(b) Interstitial tissue inflammation
(c) Alveolar exudates
(d) Interstitial fibrosis

37. All are true about phagocytosis except: *(AI 2011)*
(a) Size of the particle ingested is less than 0.5 micrometer
(b) Size of the particle ingested is more than 0.5 micrometer
(c) Combines with lysosome forming phagolysosome
(d) Amoeba and other unicellular organisms make their living out of it

38. The following does not occur with asbestosis: *(DPG 2011)*
(a) Methaemoglobinemia
(b) Pneumoconiosis
(c) Pleural mesothelioma
(d) Pleural calcification

39. Ferruginous bodies are seen in: *(AI 2008)*
(a) Silicosis (b) Byssinosis
(c) Asbestosis (d) Bagassosis

40. All of the following are seen in asbestosis except: *(AI 2002)*
(a) Diffuse alveolar damage
(b) Calcify pleural plaques
(c) Diffuse pulmonary interstitial fibrosis
(d) Mesothelioma

41. Which of the following is characteristically not associated with the development of interstitial lung disease? *(AIIMS May 2006)*
(a) Organic dusts
(b) Inorganic dusts
(c) Toxic gases, e.g. chlorine, sulphur dioxide
(d) Inhalation of tobacco smoke

42. All of the following features are seen in asbestosis except: *(AIIMS Nov 2002)*
(a) Diffuse pulmonary interstitial fibrosis
(b) Fibrous pleural thickening
(c) Emphysema
(d) Calcific pleural plaques

43. Asbestosis of the lung is associated with all of the following except: *(AIIMS May 2002)*
(a) Mesothelioma
(b) Progression of lesion even after stopping exposure to asbestos
(c) Nodular lesions involving upper lobe
(d) Asbestos bodies in sputum

44. Which of the following is associated with hypersensitive pneumonitis? *(AIIMS May 2002)*
(a) Silicosis (b) Asbestosis
(c) Byssinosis (d) Berylliosis

45. End stage lung disease is seen in: *(PGI June 2004)*
(a) Sarcoidosis
(b) Interstitial lung disease
(c) Langerhan's cell histiocytosis
(d) Aspergillosis
(e) Asbestosis

46. Features seen in bronchiolitis obliterans with organizing pneumonia include: *(PGI Dec 2001)*
(a) Polypoid plugs in bronchioles
(b) Ulceration and exudation of epithelium into the lumen
(c) Exudation of proteinaceous material in terminal airways
(d) Bronchoconstriction
(e) Response to steroids

47. Which of the following inhaled occupational pollutant produces extensive nodular pulmonary fibrosis? *(Delhi 2009 RP)*
(a) Silica
(b) Asbestos
(c) Wood dust
(d) Carbon

48. **Earliest lesion seen in asbestosis is:** *(Delhi PG-2007)*
(a) Pleural plaques
(b) Hilar lymphadenopathy
(c) Adenoma lung
(d) Mesothelioma

49. **Most dangerous particles causing pneumoconiosis are of size:** *(Delhi PG-2006)*
(a) 1-5 micron (b) < 1 micron
(c) 5-10 micron (d) 10-20 micron

50. **Asbestos exposure can cause all except:** *(Delhi PG-2006)*
(a) Arthralgia
(b) Mesothelioma
(c) Carcinoma larynx
(d) Bronchogenic carcinoma

51. **Predominant constituent of Hyaline membrane is:** *(Delhi PG-2005)*
(a) Albumi
(b) Anthracotic pigment
(c) Fibrin rich exudates
(d) None of the above

MOST RECENT QUESTIONS

52. **"Egg-shell calcifications" are seen in:**
(a) Silicosis (b) Berylliosis
(c) Asbestosis (d) Bronchial asthma

53. **Hyaline membrane disease is associated with:**
(a) Respiratory distress syndrome
(b) Bronchopulmonary dysplasia
(c) Sudden infant death syndrome
(d) Bronchiolitis obliterans

54. **Baggasosis is caused by:**
(a) Cotton dust (b) Sugarcane
(c) Asbestosis (d) None

55. **Which interstitial lung disease is caused by organic dust:**
(a) Silicosis (b) Asbestosis
(c) Byssinosis (d) Anthracosis

56. **Lower lung involvement is common in:**
(a) TB (b) Asbestosis
(c) Silicosis (d) All

57. **Pleural calcification is found in all of the following except:**
(a) Asbestosis
(b) Hemothorax
(c) Tuberculous pleural effusion
(d) Coal worker pneumoconiosis

58. **Caplan's syndrome is seen in:**
(a) COPD
(b) Pneumoconiosis
(c) Pulmonary edema
(d) Bronchial asthma

59. **Acute pulmonary sarcoidosis is least likely to be associated with:**
(a) Uveitis
(b) Pleural effusion
(c) Erythema nodosum
(d) Lymphadenopathy

60. **Which of the following would most likely be observed in the lung during an autopsy of a 2-week-old infant who died of neonatal respiratory distress syndrome?**
(a) Alveoli filled with neutrophils
(b) Dense fibrosis of the alveolar walls
(c) Enlarged air space
(d) Hyaline membranes and collapsed alveoli

61. **Pneumoconiosis is seen with which particle size?**
(a) 0.5-3 microns
(b) 3.5-6 microns
(c) 6.5-8 microns
(d) 10-20 microns

62. **Which of the following increases tuberculosis?**
(a) Asbestosis
(b) Sarcoidosis
(c) Silicosis
(d) Berylliosis

63. **The commonest cause of death in ARDS is:**
(a) Hypoxemia
(b) Hypotension
(c) Nonpulmonary organ failure
(d) Respiratory failure

64. **ARDS is due to a defect/damage in:**
(a) Type 1 pneumocytes
(b) Type 2 pneumocytes
(c) Clara cells
(d) Endothelial cells

65. **Which of the following is true regarding Non-specific interstitial pneumonia?**
(a) Honey combing on CT
(b) Predominant in males
(c) Affects elderly age group
(d) Good prognosis

66. **All are recognized causes of Adult Respiratory Distress Syndrome (ARDS), except:**
(a) Smoke inhalation
(b) Malignant hypertension
(c) Gastric aspiration
(d) Viral pneumonias

67. **Interstitial lung disease is seen in**
(a) Rheumatoid arthritis
(b) Sjogren syndrome
(c) SLE
(d) None

68. **Radiotherapy induced radiation pneumonitis is mediate by all of the following except?**
(a) TNF alpha
(b) PAF
(c) TGF-beta
(d) NF-kappa beta

VASCULAR LUNG DISEASE: INFARCT, PULMONARY EDEMA, PULMONARY HTN

69. **The percentage of pulmonary emboli, that proceed to infarction, is approximately:** *(AI 2006)*
(a) 0-5% (b) 5-15%
(c) 20-30% (d) 30-40%

70. **On sectioning of an organ at the time of autopsy, a focal, wedge-shaped firm area is seen accompanied by extensive hemorrhage, with a red appearance. The lesion has a base on the surface of the organ. This findings is typically of:** *(AIIMS May 2003)*
(a) Lung with pulmonary thromboembolism
(b) Heart with coronary thrombosis
(c) Liver with hypovolemic shock
(d) Kidney with septic embolus

71. **All are the histological features of pulmonary hypertension:** *(PGI June 2004)*
(a) Capillaritis of alveolar septa
(b) Saddle thrombi in pulmonary trunk
(c) Thrombi in pulmonary vasculature
(d) Veno-occlusive disease
(e) Thickened arterial wall

72. **Bilateral exudative pleural effusion is seen in:** *(PGI Dec 2006)*
(a) SLE
(b) Lymphoma
(c) CCF
(d) Nephrotic syndrome
(e) Ascites

73. **"Sudden cardio pulmonary collapse" occurring in pulmonary embolism is due to:** *(UP 2005)*
(a) Peripheral embolism of the vessels
(b) 60% pulmonary circulation is obstructed by emboli
(c) Multiple small thrombi causes impaction
(d) Organization of the clot

74. **Dr. Sushant Verma conducted a study in MAMC which included admitted patients hospitalized for more than 10 days and are bedridden for more than 7 days. On investigations, Dr. Verma finds that a small number of patients have abnormal ultrasound (suggestive of thrombosis in lower limbs), low pO_2 and pulmonary perfusion defects. Which of the following symptoms is most likely associated with these patients?**
(a) Cor pulmonale (b) Hemoptysis
(c) Dyspnea (d) No symptoms

MOST RECENT QUESTIONS

75. **Bronchogenic sequestration is seen in which lobe:**
(a) Left lower lobe
(b) Right upper lobe
(c) Left middle lobe
(d) Left upper lobe

76. **Which of the folloowing is not true about pulmonary embolus?**
(a) Saddle embolus may cause sudden death
(b) Most lesions affect are in the lower lobes
(c) Small arterioles are blocked
(d) Most of the emboli cause infarction

77. **Sequestrated lobe of lung is commonly supplied by which of the following vessels?**
(a) Pulmonary artery
(b) Intercostal artery
(c) Descending aorta
(d) Bronchial artery

LUNG MALIGNANCIES

78. **All are true regarding mesothelioma except:**
(a) Bilaterally symmetrical *(AIIMS May 2011)*
(b) Associated with asbestos exposure
(c) Histopathalogy shows biphasic pattern
(d) Occurs in late middle age

79. **A 67 yr male with history of chronic smoking hemoptysis with cough. Bronchoscopic biopsy from centrally located mass shows undifferentiated tumor histopathologically. Most useful I.H.C. (immunohistochemical) marker to make a proper diagnosis would be:** *(AIIMS Nov 2009)*
(a) Cytokeratin (b) Parvalbumin
(c) HMB-45 (d) Hep-par1

80. **Which of the following is a finding in biopsy of mesothelioma of pleura -** *(PGI Dec 01)*
(a) Myelin figures
(b) Desmosomes
(c) Weibel-Palade bodies
(d) Microvilli invasion
(e) Intense fibrosis

81. **Neuroendocrine lesions of lung are:** *(PGI June 2004)*
(a) Carcinoid hamartoma
(b) Alveolar carcinoma
(c) Hamartoma
(d) Asthma

82. **Hypersecretory granules are seen in which carcinoma of lung?:** *(PGI Dec 2006)*
(a) Adenocarcinoma
(b) Small cell carcinoma
(c) Large cell carcinoma
(d) Bronchoalveolar carcinoma
(e) Squamo us cell carcinoma

83. Most common site of metastasis in lung carcinoma is:
(a) Brain (b) Kidney *(RJ 2000)*
(c) Adrenal (d) Testes

84. True about oat cell carcinoma of lung is:
(a) Secrete ectopic hormone *(RJ 2001)*
(b) Variant of small cell carcinoma
(c) Cause SIADH
(d) All

85. A medical examination of a student reveals absence of cardiac sounds on left side of the chest but surprisingly the normal heart beat on the right side of the chest. The liver edge can be palpated on the left but not the right side of the abdomen. He also gives history of bronchiectasis and sinusitis. Which of the following should be suspected?
(a) Down syndrome
(b) Kartagener syndrome
(c) Kawasaki disease
(d) Marfan syndrome

86. Pleural mesothelioma is associated with:
(a) Asbestosis *(PGI Dec 2005)*
(b) Berylliosis
(c) Silicosis
(d) Berylliosis
(e) Baggasosis

MOST RECENT QUESTIONS

87. Which of the following can develop into lung cancer?
(a) Asbestosis
(b) Silicosis
(c) Byssinosis
(d) Anthracosis

88. Scar in lung tissue may get transformed into:
(a) Adenocarcinoma
(b) Oat cell carcinoma
(c) Squamous cell carcinoma
(d) Columnar cell carcinoma

89. APUD cells are seen in:
(a) Bronchial adenoma
(b) Bronchial carcinoid
(c) Hepatic adenoma
(d) Villous adenoma

90. All give rise to malignancy except:
(a) Cholelithiasis (b) Bronchiectasis
(c) Ulcerative colitis (d) Paget's disease

91. Indoor air pollution does not lead to:
(a) Chronic lung disease
(b) Impaired neurological development
(c) Pneumonia in child
(d) Adverse pregnancy outcome

92. Cavity formation is observed in one of the following bronchogenic carcinoma:
(a) Squamous cell
(b) Oat cell
(c) Adenocarcinoma
(d) Bronchoalveolar

93. Which of the following is having the minimal chances of causing a mesothelioma?
(a) Amphibole (b) Crysolite
(c) Amesolite (d) Tremolite

94. The most common lesions in the anterior mediastinum are all except:
(a) Thymomas
(b) Lymphomas
(c) Lymph node enlargement from metastasis
(d) Teratomatous neoplasms

95. In a 70-year-old man who was working in asbestos factory for 10-15 years. On routine X ray, a mass was seen in the right apical region of the lung. Biopsy was taken from the mass. Which of the following is seen on electron microscopic examination? *(AIIMS Nov 2013)*
(a) Numerous long slender microvilli
(b) Melanosomes
(c) Desmososmes with secretory endoplasmic reticulum
(d) Neurosecretory granules in the cytoplasm

96. Lung cancer most commonly associated with?
(a) Asbestosis
(b) Silicosis
(c) Berylliosis
(d) Coal worker pneumoconiosis

97. Least common cause of clubbing is:
(a) Adenocarcinoma
(b) Squamous cell cancer
(c) Small cell cancer
(d) Mesothelioma

98. Most common benign tumor of the lung is?
(a) Leiomyoma
(b) Hamartoma
(c) Papilloma
(d) Adenoma

Explanations

1. **Ans. (c) Assman's focus**
(Ref: Robbins 8th/370; OP Ghai 5th/2001-1, Radiology of chest diseases 2nd/77 Thieme)

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- Most common lesion of chronic pulmonary TB is called as Puhl lesion^{Q}.
- The infraclavicular lesion is called Assman Redeker Simon^{Q} focus.
- In post primary stage (late dissemination), coarse granular dissemination is called Aschoff Puhl focus.

2. **Ans. (d) Mitral stenosis** *(Ref: Robbins 8th/367-72)*
Disease states that increase the risk of tuberculosis are:

Diabetes mellitus	Chronic lung disease (particularly silicosis)	Malnutrition
Hodgkin's lymphoma	Chronic renal failure	Alcoholism
Immunosuppression (e.g. seen in AIDS)		

3. **Ans. (b) Predominance of alveolar exudate**
(Ref: Robbins 7th/751, 8th/713-4, 9th/704; Harrison's 17th/1620)

4. **Ans. (d) *Klebsiella pneumonia***
(Ref: Harrison 17th/838, Robbins 7th/751, 9/e p703-705)
Klebsiella pneumonia presents as typical ***air space pneumonia*** *with cough productive of purulent sputum.*
Causes of atypical pneumonias
- *Mycoplasma*
- *Chlamydia pneumonia*
- *Viral infections (Influenza, RSV, Adenovirus),*
- *Legionella*
- *Coxiella burnetti*
- *Pneumocystis carinii*

Mycoplasma^{Q} is the **commonest cause** of **atypical pneumonia.**

5. **Ans. (a) Cavitation**
(Ref: Robbins 7th/384–5, 9/e p373; Harrison 17th/1010)
- Cavitation is seen when there has been a previous sensitization of the host resulting in caseous necrotic material being present which is discharged through the cavities. So, it is associated with **secondary tuberculosis** more frequently.

Caseous granulomas with multinuclear giant cells are present in both primary and secondary tuberculosis.

6. **Ans. (b) TB; (c) Histoplasmosis; (d) Cryptococcosis; (e) Wegener's granulomatosis**
(Ref: Robbins' 7th/399, 754, 9/e p98,709)
Granuloma with necrosis is seen in following conditions
- Tuberculosis
- Histoplasmosis
- Wegener's granulomatosis
- Cryptococcosis
  - Classical PAN does not involve the pulmonary artery^{Q}.

7. **Ans. (a) Altered Sensorium; (b) Dental sepsis; (d) Subpulmonic effusion; (e) Endobronchial obstruction.**
(Ref: Robbins 7th/753, 8th/716-7, 9/e p708)
Predisposing factors of lung abscess
- **Aspiration** *of infective material:* Seen in alcoholics, during general anesthesia, sinusitis, gingivodental sepsis, coma, gastroesophageal reflux diseases.
- **Antecedent primary bacterial infection***:* Post pneumonic abscess.
- **Septic embolism**: Thrombophlebitis, bacterial endocarditis, IV drug abusers.
- **Carcinoma bronchus**: causing obstruction to bronchopulmonary segment.
- **Miscellaneous**: Direct spread of infection from suppuration of subphrenic space, pleural cavity, esophagus, spine, etc.

8. **Ans. (a) Goodpasture syndrome; (b) Leptospirosis; (d) Wegener's granulomatosis; (e) Hantana virus infection;**
(Ref: Harrison 17th 1793)
Pulmonary renal syndrome is seen in:

- **Goodpasture's syndrome:** Pulmonary hemorrhage and renal failure
- **Leptospirosis:** Renal and hepatic dysfunction, hemorrhagic pneumonia, bleeding diathesis
- Hantan virus also cause pulmonary renal syndrome.
- **Wegener's granulomatosis:** Lung and kidney involvement is common.

Note: Legionella does not affect kidneys. It causes atypical pneumonia, diarrhea and hyponatremia.

9. **Ans. (b) Asbestosis; (c) SLE**
(Ref: Crofton and Douglas 5th/979,1043, 579,1437,611, Robbins 9/e p693)

Causes of Granulomatous lung response

Known cause	Unknown cause
• Hypersensitivity pneumonitis • Inorganic dust: beryllium, silica • TB • Coccidiodomycosis • Schistosomiasis	• Sarcoidosis • Langerhan's cell granulomatosis • Granulomatous vasculitis • Wegener's granulomatosis • Churg-Strauss syndrome • Bronchocentric granulomatosis • Lymphomatoid granulomatosis

10. Ans. (d) Subpleural caseous lesion just above or below the interlobar fissure. *(Ref: Robbins 8th/370, 9/e p374)*

- Inhaled tubercle bacilli implanted in the distal air spaces of the *lower part of upper lobe or upper part of the lower lobe, close to the pleura* lead to formation of Ghon's focus.
- Primary complex or Ghon's complex of tuberculosis consists of 3 components
  - Pulmonary compound or Ghon's focus
  - Draining lymphatics
  - Caseating hilar lymph node
- Caseous hilar lymphadenopathy is associated with Ghon complex and not Ghon focus.

11. Ans. (a) Ghon's focus, (b) Pleural efffusion (d) Fibrosis *(Ref: Robbins 7th/384, 9/e p374-375)*

12. Ans. (a) Interstitial pneumonitis; (c) Foamy vacuolated exudates; (d) Mononuclear cell in bronchoalveolar lavage; (e) Neutrophil infiltration: *(Ref: Harrison' 17th/1267-8, 18th/1671)*

Pneumocystis carinii pneumonia

- On lung sections stained with H and E, the alveoli are filled with typical foamy, vacuolated exudates.
- Severe disease may include interstitial edema, fibrosis and hyaline membrane formation.
- The host inflammatory to lung injury results in increasing neutrophil count in bronchoalveolar lavage fluid, hypertrophy of alveolar type II cells and a mild mononuclear cell infiltrate.
- Malnourished infants display an intense plasma cell infiltrate.

13. Ans. (c) No abnormal findings *(Ref: Robbins 9/e p373)*

Most Mycobacterium tuberculosis infections are **asymptomatic and subclinical infections.**

- Calcifications and cavitation are more frequent after reinfection or reactivation of tuberculosis infections in adults.
- Lymphadenopathy or subpleural granuloma formation is more frequent in primary tuberculosis infections.
- A diffuse reticulo-nodular pattern is suggestive of miliary tuberculosis.

14. Ans. (d) Accumulation of fibrin *(Ref: Robbins 8/e p713, 9/e p704) ...see text*

15. Ans. (d) 5-7 *(Ref: Harsh Mohan 6/e p469) ...see text*

16. Ans. (c) Atelectasis *(Ref: Robins 9/e 670-671)*

Atelectasis refers either to **incomplete expansion of the lungs** (neonatal atelectasis) or to the **collapse of previously inflated lung**, producing areas of relatively airless pulmonary parenchyma.

Resorption Atelectasis	Compression Atelectasis	Contraction Atelectasis
• Due to airway obstruction leading to resorption of oxygen trapped in the alveoli.	• Due to presence of fluid, blood, air or tumor in pleural space.	• Fibrosis in the lung or pleura preventing full expansion of pulmonary tissue.
• Causes mediastinal shift **towards affected lung**.	• Causes mediastinal **shift away from the affected lung**.	• Only **irreversible** cause of atelectasis[Q].
• Associated with chronic bronchitis/ asthma/aspiration of foreign body/ secretions	• **Most commonly associated with cardiac failure[Q].**	

17. Ans. (a) Apex *(Ref: Robbins 9/e p373, 8/e p370, 7/e p383)*

- *Secondary pulmonary tuberculosis* classically involves the *apex of the upper lobes* of one or both lungs

18. Ans. (a) Terminal bronchiole *(Ref: Robbins 9/e p373)*

19. Ans. (b) Recruitment of lymphocytes *(Ref: Robbins 9/e p371-374, 8/e p74, 7/e p382)*

- *Macrophages are the primary cells infected by M. tuberculosis*. Early in infection, tuberculosis bacilli replicate essentially unchecked, while later in infection, the cell response stimulates macrophages to contain the proliferation of the bacteria.
- *About 3 weeks after infection*, a T-helper 1 (T_H1) response is mounted that activates macrophages to become bactericidal.
- The T_H1 response orchestrates the formation of granulomas and caseous necrosis. Macrophages activated by IFN-γ differentiate into the "epithelioid histiocytes" that characterize the granulomatous response, and may fuse to form giant cells.

20. Ans. (c) ESR is raised because of increased RBC aggregate *(Ref: Wintrobe's hematology 13/e p16-7)*

ESR is a non specific test which is used as an indicator of active disease. It increases in some disease states due to increase in plasma fibrinogen, immunoglobulins and other acute phase reactants. In addition, change in red cell shape and number affect ESR.

Decreased ESR: Sickle cell disease, polycythemia, and hereditary spherocytosis.

Increased ESR: Infections, anemia, liver disease, cancer, pregnancy, collagen vascular disease
So, in a patient with TB, ESR will increase due to aggregation of red cells called rouleaux whose formation is facilitated by fibrinogen. Since, it is non specific; it cannot conform recovery from TB.

Additonal info for AIIMS

- The ESR may be measured by Wintrobe or Westergren's tube but the readings need to be corrected for the patient anemia.
- However, a variant of ESR called zeta sedimentation rate is developed which produced reproducible results and doesnot require correction for anemia.

21. **Ans. (d) Lobar pneumonia** *(Ref: Robbins 9/e p704)*
    - *'Bacterial invasion of the lung parenchyma causes the alveoli to be filled with an inflammatory exudate, thus causing consolidation ("solidification") of the pulmonary tissue'.....Robbins definition of pneumonia*

22. **Ans. (b) Young syndrome** *(Ref: Robbins 9/e p683)*

- **Young syndrome** is characterized by ***bronchiectasis, rhinosinusitis*** and ***reduced fertility***.
- *Kartagener syndrome*, marked by situs inversus, bronchiectasis and sinusitis.

23. **Ans. (c) Chronic bronchitis** *(Ref: Robbins 9/e p679)*

24. **Ans. (b) Pulmonary emphysema; (c) Diastase resistant hepatic cells** *(Ref: Robbins 9/e p675-676)*
    - Alpha 1-anti-trypsin deficiency is an ***autosomal recessive*** disease marked by abnormally low serum levels of α1 AT enzyme resulting in ***panacinar emphysema***.
    - It is characterized by presence of round to oval, ***PAS positive and diastase resistant*** cytoplasmic ***inclusions in hepatocytes*** which on H and E stain acidophilic and indistinctly demarcated from surrounding cytoplasm.

25. **Ans. (b) Eosinophils** *(Ref: Robbins 9/e p680)*

26. **Ans. (a) Bronchial asthma** *(Ref: Robbins 9/e p682)*

27. **Ans. (b) Centriacinar** *(Ref: Robbins 9/e p675)*

28. **Ans. (a) Centrilobular emphysema** *(Ref: Robbins 9/e p675, 8th/684, 7th/719)*

29. **Ans. (b) Granulocyte-macrophage colony stimulating factor** *(Ref: Robbins 8th/705, 9/e p696)*

The patient in the stem of the question has the acquired from of pulmonary alveolar proteinosis (PAP).

CFTR gene mutations lead to cystic fibrosis and widespread bronchiectasis.

- Anti -DNA topoisomerase I antibodies are seen in diffuse scleroderma, which produces interstitial fibrosis.
- Anti - glomerular basement membrane antibody is present in Goodpasture's syndrome with extensive alveolar hemorrhage.

- **PAP** is associated with **impaired surfactant clearance** by alveolar macrophages.
- Microscopically there is accumulation of acellular surfactant in intra-alveolar and bronchiolar spaces.

30. **Ans. (b) Centriacinar emphysema** *(Ref: Robbins 8th/684-5, 9/e p675)*
The findings of Mr. John point to an obstructive lung disease like emphysema which occurs due to airway narrowing or even from loss of elastic recoil. So, emphysema is the most likely diagnosis.

- **Sarcoidosis** is a chronic **restrictive lung disease with all lung volumes decreased, low FVC, and normal FEV1/FVC ratio.**
- Diffuse alveolar damage is an acute restrictive lung disease.
- **Chronic pulmonary embolism does not affect FVC** because the airways are not affected. It is however associated with a ventilation/perfusion mismatch.

31. **Ans. (c) Emphysema** *(Ref: Robbins 9/e p675-676)*
Emphysema is a pulmonary disease characterized by enlargement of the alveolar airspaces due to destruction of the septae without consequent fibrosis. Pulmonary hypertension (choice D) affects neither the airways nor the alveoli. It causes involvement of pulmonary blood vessels.

32. **Ans. (a) Emphysema** *(Ref: Robbins 9/e p675)*
    - **Alpha 1 anti trypsin deficiency** is associated with **panacinar emphysema**.

33. **Ans (a) Asthma** *(Ref: Robbins 9th/ 682)*
Thickening of the airway wall is a feature of **airway remodeling** and is seen in **asthma**.

34. **Ans. (a) Bronchial asthma** *(Ref: Robbins 9/e p682)*

35. **Ans (b) Paraseptal emphysema** *(Ref: Robbins 9th/ 675)*
Paraseptal emphysema is synonymous as distal acinar emphysema. It is characterized by distension of the distal alveoli.

36. **Ans. (a) Diffuse alveolar damage** *(Ref: Robbins 9/e p672)*

37. **Ans. (a) Size of the particle ingested is less than 0.5 micrometer**
(Ref: Robbins 8th/53, Pharmaceutical Research, Vol. 25, No. 8, August 2008)
The article writes....Particles possessing diameters of 2-3 microns exhibits maximum phagocytosis and attachment.

38. **Ans. (a) Methaemoglobinemia** *(Ref: Harrison 17th/1612-3, Robbins 9/e p691)*

39. **Ans. (c) Asbestosis** *(Ref: Robbins 8th/700, 9/e p691)*
Robbins direct quote... *'inorganic particles may become coated with iron protein complexes and are called ferruginous bodies'*.
Asbestosis in its classical form is a diffuse fibrotic disease of the lung tissue. Typically, the fibrotic changes of

asbestosis are focal and are ***most prominent in the lower lung lobes***. The presence of asbestos bodies in or adjacent to the walls of fibrotic respiratory bronchioles is the hallmark of the disease. A characteristic of asbestos bodies is a core of asbestos coated by ferroprotein. (So, 'c' is the answer)

> Asbestos bodies are mimicked by "ferruginous bodies" which are formed on particles of talc, mica, fibre, glass and other less common materials in the lung. True asbestos bodies are clear whereas the core of these particles is dark.

40. Ans. (a) Diffuse alveolar damage *(Ref: Robbins 9/e p672)*
Diffuse alveolar damage is a characterstic feature of ARDS. As explained in the text, asbestos inhalation is associated with pleural plaque, interstitial fibrosis, bronchogenic cancer and mesothelioma.

41. Ans. NONE
(Ref: Harrison 17th/1643, Robbins 8th/694, 704, 9/e p685)
All the mentioned options are associated with interstitial lung disease. Following is a table adapted from Robbins and Harrison for a quick reference.

Causes of Interstitial Lung Disease (ILD)

Fibrosing	Granulomatous	Smoking related	Miscellaneous
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)	Sarcoidosis	Desquamative interstitial pneumonia	**Eosinophilic**
Associated with collagen vascular diseases, drugs and radiation	Hypersensitivity pneumonitis	Respiratory bronchiolitis-associated interstitial lung disease	**Pulmonary alveolar proteinosis**
Cryptogenic organizing pneumonia			
Nonspecific interstitial pneumonia			
Pneumoconiosis			

Directly quoting ***Pneumoconiosis*** as is given on page 696 of Robbins .... '***the pneumoconiosis was originally coined to describe the non-neoplastic lung reaction to inhalation of mineral dusts encountered in the work-place.*** **Now it also includes diseases induced by organic as well as inorganic particulates and chemical fumes and vapors**'. Presented underneath is an adapted classification from Robbins table 15-6;

Causes of pneumoconiosis

Mineral dusts	Coal dust, silica, asbestos, iron oxide, barium sulfate
Organic dusts inducing hypersensitivity pneumonitis	Moldy hay, bagasse, bird droppings
Chemical fumes and vapours	Sulfur dioxide, ammonia, benzene, insecticides
Organic dusts inducing asthma	Cotton, flax, hemp

As can be concluded from both the above tables, the answer should be none in the options provided. If the question would have been containing pneumoconiosis and NOT ILD, then smoking would have been the answer of choice.

42. Ans. (c) Emphysema *(Ref: Robbins 9/e p691)*

43. Ans. (c) Nodular lesions involving upper lobes
(Ref: Robbins 7th/734-6, 8th/700, 9/e p688)

- In asbestosis, there is presence of lesions affecting lower lobes or base of the lungs
- Nodular lesions involving upper lobes' is a feature of silicosis. The lesions continue to progress even after exposure to asbestos has stopped.

44. Ans. (c) Byssinosis *(Ref: Robbins 7/e p733, 9/3 p688)*

- **Hypersensitivity pneumonitis** (also called **allergic alveolitis**) describes a spectrum of immunologically mediated, predominantly interstitial lung disorders caused by intense, often prolonged exposure to **inhaled organic antigens**[Q]. It is a type *III + IV hypersensitivity reaction*.
- **Table 15-6** on page 697/8th Robbins mentions- **Byssinosis is an organic dust** *causing asthma*; rest of the options silicosis, asbestosis and berylliosis are given as examples of mineral dusts. So, they can be easily excluded. The best answer would therefore be option 'c' i.e. Byssinosis.

Other examples associated with hypersensitivity pneumonitis

Farmer's lung: Thermopohilic actionomycete or mouldy hay or grain dust*.
Pigeon breeder's lung: Proteins from serum, excreta or feathers of the birds.
Air conditioner lung (or Humidifier lung): Thermopohilic bacteria in heated water reservoirs.

45. Ans. (a) Sarcoidosis; (b) Interstitial lung disease; (c) Langerhan's cell histiocytosis (e) Asbestosis.

- Parenchymal causes of end stage lung disease:
- Emphysema
- Pneumoconiosis
- Bronchitis
- ARDS
- Asbestosis
- Interstitial lung disease.

- Pulmonary Langerhan's cell histiocytosis is a progressive disease, and can lead to end stage lung disease.
- Sarcoidosis of the lung is an interstitial lung disease; which may lead to progressive fibrosis and end stage lung disease.
- Aspergillosis causes extrinsic allergic alveolitis or hypersensitivity pneumonitis.

46. Ans. (a) Polypoid plugs in bronchioles; (c) Exudation of proteinaceous material in terminal airways; (d) Bronchoconstriction; (e) Response to steroids
(Ref: Robbins' 7th/731, 8th/696, 9/e p687; CMDT' 2010 243)

Cryptogenic organizing pneumonia (earlier called as Bronchiolitis obliterans with organizing pneumonia)

- Affects men and woman equally, around 50-70 years
- Etiology is **unknown**Q
- Clinical features- Dry cough and dyspnea
- Chest X-ray shows **subpleural and peribronchial**Q patchy area of airspace consolidation.
- Histopathology: there is presence of **polypoid plugs** of loose organizing connective tissue (called as Masson bodies)Q within alveolar ducts, alveoli and often bronchiolesQ (all are of same age)
- There is **no interstitial fibrosis or honey comb lung**Q.
- Treatment is done with **steroids**Q.

47. Ans. (a) Silica *(Ref: Robbins 8th/698-9, 9/e p690)*

48. Ans. (a) Pleural plaques *(Ref: Robbins 9/e p691)*

Pleural plaqueQ**:**
It is the most common manifestation of asbestos exposure composed of plaques of dense collagen containing calcium. They are usually asymptomatic and develop on anterior and posterolateral parts of parietal pleura and over the diaphragm.

49. Ans. (a) 1-5 micron *(Ref: Robbins 9/e p688)*

In pneumoconiosis, the most dangerous particles range from 1-5 micron in diameter, because they may reach the terminal small airways and air sacs and settle in their linings.

Note:
- The solubility and cytotoxicity of particles, modify the nature of pulmonary response.
- In general, the smaller the particle, the higher the surface area-to-mass ratio, and the more likely and more rapidly toxic levels will appear in the pulmonary fluids.
- Larger particles resist dissolution and so may persist within lung parenchyma for years.
- Larger particles tend to evoke fibrosing collagenous pneumoconiosis, such as characteristic of silicosis.

50. Ans. (a) Arthralgia *(Ref: Robbins 9/e p691)*

51. Ans. (c) Fibrin rich exudates *(Ref: Robbins 9/e p457)*

- The membranes (in hyaline membrane disease) are largely made up of fibrinogen and fibrin admixed with cell debris derived chiefly from necrotic type-II pneumocytes.
- There is a remarkable paucity of neutrophilic inflammatory reaction associated with these membranes.
- The lesions of hyaline membrane disease are never seen in still born infants or in live-born infants who die within a few hours of birth.

52. Ans. (a) Silicosis *(Ref: Robbins 9/e p690, 8th/699, 7th/734)*

53. Ans. (a) Respiratory distress syndrome
(Ref: Robbins 9/e p457, 8th/680, 7th/715)

54. Ans. (b) Sugarcane *(Ref: Robbins 9/e 688)*

55. Ans. (c) Byssinosis *(Ref: Robbins 9/e 688)*

56. Ans. (b) Asbestosis *(Ref: Robbins 9/e 691)*

57. Ans. (b) Hemothorax *(Ref: Robbins 8th/732, 9/e 722)*

58. Ans. (b) Pneumoconiosis *(Ref: Harrison 17th/1625,)*

59. Ans. (b) Pleural effusion *(Ref. Robbins 9/e 693)*

60. Ans. (d) Hyaline membranes and collapsed alveoli
(Ref: Robbins 8th/680, 9/e 457)

Neonatal respiratory distress syndrome is a disease of **immaturity**. The immature lung is not able to produce sufficient surfactant to prevent collapse of many alveoli. Severe diffuse damage to alveoli causes precipitation of protein ("**hyaline membranes**") adjacent to many alveolar walls.

Abundant neutrophils (choice A) are seen in pneumonia. Fibrosis (choice B) is a late, not early, feature of respiratory distress syndrome whereas the **air spaces are collapsed**, ***not enlarged*** (choice C), in this condition.

61. Ans (a) 0.5-3 microns *(Ref: Robbins 9th/ 688)*

62. Ans (c) Silicosis *(Ref: Robbins 9/e p 690)*

63. Ans (c) Nonpulmonary organ failure
(Ref: Robbins 9th/ 674)

In ARDS, most of the deaths are attributable to sepsis or multiorgan failure and, in some cases, direct lung injury.

64. Ans. (d) Endothelial cells *(Robbins 9th/672)*

ALI/ARDS is initiated by injury of pneumocytes and pulmonary endothelium, setting in motion a viscous cycle of increasing inflammation and pulmonary damage.

Endothelial activation is an important early event..... *Robbins 9th/672*

Also revise

The histologic manifestation of this disease is *diffuse alveolar damage* (DAD).

65. Ans. (d) Good prognosis *(Ref: Robbins 9th/686)*

Nonspecific interstitial pneumonia

- Nonspecific interstitial pneumonia may be idiopathic or associated with connective tissue disease.
- **Clinical features**
- Patients present with dyspnea and cough of several months' duration.
- More likely to be **female nonsmokers** in their sixth decade of life.

- High-resolution computed tomography scan: B/L, symmetric, predominantly lower lobe reticular opacities ***(honeycomb pattern is absent)***.
- Patients have a ***much better prognosis*** than those with usual interstitial pneumonia.
- Having 2 patterns: cellular and fibrosing patterns. Those having the cellular pattern are somewhat younger than those with the fibrosing pattern and have a better prognosis
- In cellular pattern, there is mild to moderate chronic interstitial inflammation, in a uniform or patchy distribution.
- In fibrosing pattern, there is diffuse or patchy interstitial fibrotic lesions of roughly the same stage of development ***(an important distinction from usual interstitial pneumonia)***
- Fibroblastic foci, **honeycombing, hyaline membranes** and **granulomas** are **absent**.

66. Ans (b) Malignant hypertension *(Ref: Robbins 9th/ 672)*

See the table of causes of acute respiratory distress syndrome. ARDS is associated with non cardiogenic pulmonary edema. Malignant hypertension will cause development of cardiogenic pulmonary edema.

The four most important causes of ARDS:

Sepsis, diffuse pulmonary infections, gastric aspiration and head injuries.

67. Ans (a) Rheumatoid arthritis *(Ref: Robbins 9e/ p687*

Interstitial lung disease is associated with rheumatoid arthritis.)

68. Ans (b) PAF *(Ref: Robbins 9th and multiple sources)*

69. Ans. (b) 5-15% *(Ref: Robbins 7th/742, 8th/706, 9/e 698)*

Robbins direct quote. *'Only about 10% of pulmonary artery emboli actually cause infarction'.*

70. Ans. (a) Lung with pulmonary thromboembolism *(Ref: Robbins 9/e p129-130, 8th/128, 7th/138)*

- The morphology is characteristically present as red (hemorrhagic) infarct. The red infarcts are seen in lung, liver and intestine.
- White infarcts are seen in brain, spleen, kidney and heart.

71. Ans. (c) Thrombi in pulmonary vasculature; (d) Vaso-occlusive disease; (e) Thickened arterial wall *(Ref: Robbins 8th/708, 9/e p699-700, Harsh Mohan 6th/466)*

In pulmonary hypertension pathological changes are seen from main pulmonary arteries to arterioles. They are:

Arterioles and small pulmonary arteries (most prominently affected)	Medium sized pulmonary arteries	Large pulmonary arteries
(i) Medial hypertrophy	(i) Medial hypertrophy; which is not marked in secondary pulmonary hypertension	(i) Atheromatous deposits
(ii) Thickening and reduplication of elastic lamina.	(ii) Concentric intimal thickening	
(iii) **Plexiform pulmonary arteriopathy** in which intraluminal tuft of capillary formation occurs in dilated thin walled arteriolar branches.	(iii) Adventitial fibrosis	
	(iv) Thickening and reduplication of elastic lamina.	

The presence of many organizing or recanalizing thrombi favors recurrent pulmonary emboli as the cause and the coexistence of diffuse pulmonary fibrosis or severe emphysema and chronic bronchitis points to chronic hypoxia as the initiating event.

72. Ans. (a) SLE; *(Ref: Harrison 17th/1660)*

Transudative and exudative pleural effusion (PE) are differentiated by measuring the LDH and protein level in the pleural fluid.

Exudative PE meets at least one of the following criteria:

1. Pleural fluid protein/serum protein > 0.5.
2. Pleural fluid LDH by serum LDH > 0.6.
3. Pleural fluid LDH more than 2/3rd of the normal upper limit of serum.

Transudative PE is caused by:

- CCF, cirrhosis, pulmonary embolism
- Nephrotic syndrome, peritoneal dialysis, superior vena cava obstruction
- Myxoedema

Causes of exudative pleural effusion			
Neoplastic disease	Pericardial disease	Asbestos exposure	Yellow nail syndrome
Hemothorax	Chylothorax	Uremia	Radiation therapy
Pulmonary emboli	Sarcoidosis	Meig's syndrome	Ovarian hyperstimulation syndrome
GI disease Esophageal perforation Pancreatic disease Intra-abdominal abscess Diaphragmatic hernia	**Collagen vascular disease** Rheumatoid pleuritis SLE Drug induced lupus Sjogren's syndrome Wegener's granulomatosis Churg Strauss syndrome	**Drugs** Nitrofurantoin Dantrolene Methysergide Bromocriptine Amiodarone Procarbazine	**Infections** Bacterial infections TB Fungal infections Viral infections Parasitic infections

73. **Ans. (b) 60% pulmonary circulation is obstructed by emboli** *(Ref: Robbins 9/e p127, 8th/126; 7th/136)*

74. **Ans. (d) No symptoms** *(Ref: Robbins 8th/698, 706-7)*
The stem of the question suggests that Dr. Verma's clinical study is being done on patients with pulmonary thromboembolism, and ***most pulmonary emboli are small and clinically silent***. Cor pulmonale may result from repeated embolization which is associated with reduction in the pulmonary vascular bed. Hemoptysis is a rare manifestation of pulmonary embolism. It occurs usually with hemorrhagic infarction of the lung. Dyspnea occurs with medium to large emboli.

75. **Ans. (a) Left lower lobe**
(Ref: Fetal and Neonatal Physiology 4/e p872; Robbins 9/e p670 8/e p679; www.uptodate.com)
*Pulmonary sequestration*can be either:
- *Extralobar sequestrations* are external to the lung and may be located anywhere in the thorax or mediastinum. They are seen in infants. They occur in the **lower left side of the thorax** between the left lower lobe ad the diaphragm.
- *Intralobar sequestrations* occur within the lung substance usually in older children and are often associated with recurrent localized infection or bronchiectasis. These are seen most commonly in the **posterior basal segment** of **left lower lobe**[Q] **(Ref.** Fetal and Neonatal Physiology**).**

76. **Ans. (d) Most of the emboli cause infarction**
(Ref: Robbins 8/e p706, 9/e p127)
- Large emboli lodge in the main pulmonary artery or its major branches or at the bifurcation as a ***saddle embolus***. It *may lead to sudden death.*
- *Smaller emboli travel out into the more peripheral vessels,* where they may cause hemorrhage or infarction. In patients with adequate cardiovascular function, the bronchial arterial supply can sustain the lung parenchyma. Hemorrhages may occur, but there is no infarction. The underlying pulmonary architecture is preserved, and resorption of the blood permits reconstitution of the preexisting architecture.

Also know: NEET points

- Only about **10%**[Q] **of emboli actually cause infarction**, which occurs when the circulation is already inadequate, as in patients with heart or lung disease.
- Pulmonaryinfarcts tend to be **uncommon** in the young.
- About 3/4[th]of all infarcts affect the **lower lobes**[Q]
- Inmore than half, multiple lesions occur.
- Typically, they extend to the periphery of the lung substance as a wedge with the **apex pointing toward the hilus**[Q] of the lung.

77. **Ans. (c) Descending aorta** *(Ref: Robbins 8/e p679, 9/e 670)*

- *Pulmonary sequestration* refers to the presence of a discrete mass of lung tissue *without normal connection to the airway system.*
- The blood supply to the **sequestered area** arises not from the pulmonary arteries but **from the aorta** or its branches

78. **Ans. (a) Bilaterally symmetrical**
(Ref: Robbins 8th/733-4, Malignant Pleural Mesothelioma 1st/65, DeVita's Cancer 8th/1840, 9/e p723-724)
Mesothelioma is an asbestos exposure releated tumor having Mean age of presentation as **50-70 years**. Microscopically it may have both epithelioid and sarcomatoid patterns **(biphasic pattern).**
Option 'a'.... 'Pleural mesotheliomas are ***more commonly right sided*** (R:L ratio is 3:2) may be because of greater size of right sided pleural cavity. Although **usually unilateral at presentation**, it is not infrequent to find histological evidence of mesothelioma in the contralateral pleura. Macroscopic evidence of **synchronous bilateral pleural tumors is rare'**.... *Malignant Pleural Mesothelioma* 1[st]/65.

79. **Ans. (a) Cytokeratin** *(Robbins 9/e p716)*
- The presence of chronic smoking, cough and hemoptysis in old man is a pointer towards a diagnosis

of *bronchogenic cancer*. The central location suggests the possibility of a *squamous cell cancer*.

- Robbins writes "***Histologically, this tumor is characterized by the presence of keratinization and/or intercellular bridges***".

Other options: HMB (melanoma), Hep par1 (liver cancer) and parvalbumin (schizophrenia).

80. Ans. (d) Microvilli invasion, (e) Intense fibrosis *(Ref: Robbins' 7th/768-9, 8th/734, 9/e p723-724)*

	Benign mesothelioma	Malignant mesothelioma
Nature	**Solitary** fibrous tumor	**Diffuse** thick and fleshy tumor
Prior asbestos exposure	**No**^{Q} relationship	**Definitive association**^{Q} is present
Microscopic feature	Whorls of reticulin and collagen fibers among which interspersed spindle cells resembling fibroblasts are present	**Epithelioid type:** cuboidal/columnar cells form tubular/ papillary structures **Sarcomatoid type:** appear as spindle cell carcinoma **Mixed type**
Immunotyping	Cells are CD34(+) and keratin (-)^{Q}	Cells are CD34(-) and keratin (+)^{Q}

81. Ans. (a) Carcinoid hamartoma *(Ref: Robbin 9/e p719)*

Neoplasms of neuroendocrine cells in the lung include:

- Benign tumorlets (small tumors in areas of scarring and inflammation)
- Carcinoid
- Small cell carcinoma
- Large cell neuroendocrine carcinoma of lung.

82. Ans. (b) Small cell carcinoma *(Ref: Robbins 9/e p717)*

- **Small cell carcinoma** of lung shows **dense core neurosecretory granules**. The granules are similar to those found in neuroendocrine argentaffin cells present along the bronchial epithelium.
- Some of these tumors secrete polypeptide hormones. Presence of neuroendocrine markers such as chromogranin, synaptophysin and Leu-7 is seen.
- *It also secretes PTH like substance.* They are most common pattern associated with ectopic hormone production.

83. Ans. (c) Adrenal *(Ref: Robbins 9/e p717, 8th/723, 7th/763)*

84. Ans. (d) All *(Ref: Robbins 9/e p717, 8th/728, 7th/762)*

85. Ans. (b) Kartagener syndrome *(Ref: Robbins 9/e p683)*

- **Isolated inversion of the heart (dextrocardia) is almost always associated with cardiac defects** that may include transposition of the atria and transposition of the great arteries.
- ***However, dextrocardia as part of situs inversus totalis***, with reversal of the thoracic and abdominal organs, is ***usually associated with a physiologically normal heart***. The cluster of situs inversus, sinusitis, and bronchiectasis is called **Kartagener syndrome**, which is caused by *defective ciliary function.*

Association of cardiac defects with syndromes

- Down syndrome - ostium primum type of atrial septal defect.
- Kawasaki disease- coronary artery aneurysms.
- **Marfan syndrome - aortic dissection.**
- Turner syndrome - coarctation of the aorta.

86. Ans. (a) Asbestosis *(Ref: Robbins 9/e p723)*

87. Ans. (a) Asbestosis *(Ref: Robbins 9/e p691)*

Direct lines.. "In contrast to other inorganic dusts, ***asbestos an also act as a tumour initiator and promoter***".

88. Ans. (a) Adenocarcinoma

(Ref: Robbins 9/e p714-715, 8/e p724, 7/e p760-761)

"**Peripheral adenocarcinomas** with a small central invasive component **associated with scarring** and a predominantly peripheral bronchioloalveolar growth pattern may have a better outcome than invasive carcinomas of the same size."..Robbins

89. Ans. (b) Bronchial carcinoid *(Ref: Robbins 9/e p719)*

Amine **P**recursor **U**ptake and **D**ecarboxylation (APUD) cells are also known as neuroendocrine cells. These cells are the cell of origin of the carcinoid tumour.

90. Ans. (b). Bronchiectasis *(Ref: Robbins 9/e p684)*

- Bronchiectasis cannot cause malignancy. The complications which may be associated with bronchiectasis are: Cor pulmonale, metastatic brain abscesses, and amyloidosis.
- To be considered bronchiectasis, **the dilation should be permanent**; reversible bronchial dilation often accompanies viral and bacterial pneumonia.

91. Ans. (b) Impaired neurological development

(Ref: Robbin 8/e p 403)

Concept: Please note friends that **impaired neurological development** can result from **lead** exposure but lead is an **outdoor air pollutant**.

Impaired lung function, lung inflammation, reduced exercise capacity; increased respiratory symptoms are associated with air pollution....

Indoor air pollution contributes to ***acute respiratory infections in young children, chronic lung disease*** and ***cancer in adults***, and ***adverse pregnancy outcomes*** (such as stillbirths) for women exposed during pregnancy. Acute respiratory infections, principally pneumonia, are the chief killers of young children....Park

92. **Ans. (a) Squamous cell** *(Ref: Robbins 9/e p716-717)*

Important points about Squamous cell carcinoma of lung

- MC type of lung cancer in **smokers**Q
- MC type in **males**Q
- Usually **central in location** (arise from the segmental bronchi)
- Intercellular bridges or junction is very specific.
- **Hypercalcemia**Q due to PTHrP is the MC paraneoplastic syndrome

93. **Ans (b) Crysolite** *(Ref: Robbins 9/e p 691)*

The serpentine chrysotile form accounts for 90% of the asbestos used in industry. Amphiboles even though less prevalent, are more pathogenic than chrysotiles with respect to induction of mesothelioma.

94. **Ans (c) Lymph node enlargement from metastasis** *(Ref: Robbins 9/e p 721)*

95. **Ans. (c) Desmososmes with secretory endoplasmic reticulum** *(Ref: Robbins 8/e p 669, Thurlbeck's Pathology of the Lung 3/e p428-435)*

Tough one friends....AIIMS guys laid the trap beautifully! Lets analyze the question...

The exposure to asbestos brings the first malignancy to our mind which is mesothelioma. However, this is not the answer for the current question because:

- Period of exposure is 10-15 years in question. However, as per Robbins.. *"there is a long latent period of* ***25 to 45 years*** *for the development of asbestos-related mesothelioma"*.
- More importantly, mesothelioma is a pleural tumor whereas the question clearly mentioned that the mass was seen in the right apical region. Considering that there is no history of smoking, this is more likely to an **adenocarcinoma** (and *not squamous cancer*) which is also the most common type of lung cancer associated with asbestos exposure.
- ***Desmososmes with secretory endoplasmic reticulum is a feature of electrom microscopic finding of adenocarcinoma*****.....** Thurlbeck's Pathology table 17-7

Type	Desmosomes/Tonofilament Bundles	Microvilli	Tight Junctions	Lumina	Secretory RER	Neuro-secretory Granules
Squamous carcinomas	Many, wellformed	+	–	–	–	–
Small cell carcinoma	Small, poorly formed	Rare	–	–	–	+
Adenocarcinoma	Many, small well formed	+	+	+	**Present**	–

For future AIIMS question!

- **Napsin A** is a **more sensitive and specific marker** than **TTF-1** for **adenocarcinoma of the lung.**

Features of mesothelioma

- On electron microscopy, the presence of long microvilli and abundant tonofilaments but absent microvillous rootlets and lamellar bodies.
- **Lack of staining for carcinoembryonic antigen** (it is *positive in adenocarcinoma*)
- Positive staining for **calretinin, Wilms tumor 1 (WT-1), cytokeratin 5/6**, and D2–40

96. **Ans: (a) Asbestosis** *(Ref: Robbins 9/e p713)*

97. **Ans (c) Small cell cancer.**

(Ref: Principles and practice of lung cancer page 348)

Clubbing is ***most common with adenocarcinoma*** and is least *common with small cell lung cancer*....direct quote

98. **Ans: (b) Hamartoma** *(Ref: Robbins 9/e p720)*

Lung hamartoma is a relatively common lesion that is usually discovered as an incidental, rounded radiopacity (coin lesion) on a routine chest film.

ANNEXURE

Acute lung injury (ALI)

- Acute lung injury (***ALI***) (also called ***noncardiogenic pulmonary edema***) is characterized by the abrupt onset of significant hypoxemia and bilateral pulmonary infiltrates in the absence of cardiac failure. Acute respiratory distress syndrome (ARDS) is a manifestation of severe ALI.
- It is associated with sepsis, severe trauma, or diffuse pulmonary infection.
- The histologic manifestation of these diseases is ***diffuse alveolar damage*** (DAD). There is also the presence of hyaline membranes lining alveolar walls.

Pulmonary Langerhans Cell Histiocytosis

- Pulmonary Langerhans cell histiocytosis is a rare reactive inflammatory disease characterized by focal collections of Langerhans cells (often accompanied by eosinophils). It results in scarring and the appearance of irregular cystic spaces.
- Langerhans cells are immature dendritic cells with grooved, indented nuclei and abundant cytoplasm. They are positive for S100, CD1a, and CD207 (langerin) and are negative for CD68.
- Most of the affected patients are relatively young adult smokers. It is associated with acquired activating mutations in the serine/threonine kinase BRAF.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a pulmonary disorder that primarily affects young woman of childbearing age. It is characterized by a proliferation of perivascular epithelioid cells that express markers of both melanocytes and smooth muscle cells. The proliferation distorts the involved lung, leading to cystic, emphysema-like dilation of terminal airspaces, thickening of the interstitium, and obstruction of lymphatic vessels. The condition is characterized by **TSC2 mutations**. The condition affects ***young women*** mainly and the presenting features include dyspnea or spontaneous pneumothorax. The condition is treated with lung transplantation.

Inflammatory myofibroblastic tumor (Recent AIIMS Topic)

- More common in children
- Equal male-to-female ratio
- Presenting symptoms include fever, cough, chest pain, and hemoptysis.
- Grossly, the lesion is firm, 3 to 10 cm in diameter, and grayish white.
- Microscopically, there is proliferation of spindle-shaped fibroblasts and myofibroblasts, lymphocytes, plasma cells, and peripheral fibrosis.
- Some of these tumors have **activating rearrangements of the anaplastic lymphoma kinase (*ALK*) gene** located on 2p23.

CHAPTER 12

Kidney and Urinary Bladder

Golden Points

- **Albumin** does not appear in the urine because of having a **negative charge** (and not size)
- Proteoglycan in the glomerular basement membrane responsible for charge dependent filtration.
- Inheritance of **ad**ult polycystic kidney disease is **A**utosomal **d**ominant affected by genes like PKD 1 (polycystin-1) and PKD 2 (polycystin) whereas inheritance of childhood polycystic kidney disease is Autosomal recessive.
- Hematuria of non-glomerular origin as in renal stones have isomorphic RBC. **Dysmorphic red cells** in urine are seen with **glomerular diseases**.
- Tamm Horsfall protein is produced by cells of the ascending limb of Loop of Henle.
- Commonest cause of **p**ediatric glomerulonephritis is **p**ost strepotocccal glomerulonephritis. It is a type III hypersensitivity reaction.
- **Crescent formation** (Fibrin + parietal epithelial cells + WBCs) is characteristic of **RPGN.** Number of crescents also decide the prognosis of the patient.
- Hallmark of Ig**A** nephropathy (commonest glomerulonephritis in **a**dults) is recurrent hematuria after 1–2 days of an upper respiratory tract infection and presence of **IgA mesangial deposits**.
- Nephrotic syndrome is characterised by massive proteinuria (> 3·5 gm/day), hypoalbuminemia, edema, hyperlipidemia and lipiduria. All protein are reduced in nephritic syndrome **except** fibrinogen.
- Most common cause of nephrotic syndrome in children (Minimal change disease), adults (focal segmental glomerulosclerosis) and elderly (Membranous glomerulopahy).
- Heymann rat glomerulonephritis true is Immune complex against Heymann antigen (megalin) and is a model for membranous glomerulopathy.
- Collapsing glomerulopathy (a variant of FSGS) is seen in AIDS patients.
- Subepithelial deposits are seen in: PSGN, membranous GN and RPGN.
- Subendothelial deposits are seen in: MPGN-type I, SLE (lupus nephritis class III & IV).
- Finnish type' of congenital nephrotic syndrome: NPHS-1 with mutation in 'Nephrin'.
- Steroid resistant congenital nephrotic syndrome: NPHS-2 with mutation in 'podocin'.'
- **Alport syndrome** is best diagnosed by **electron microscopy (basket weave appearance)**
- Renal lesions in diabetes mellitus: **basement membrane thickening *(commonest lesion)***, *nodular glomerulosclerosis* (**KW lesion;** most characteristic lesion). Renal changes are dependent mostly on **duration of the disease**.
- Commonest pathological renal finding in benign hypertension is: **Hyaline arteriosclerosis**.
- Renal lesions is **malignant hypertension** include ***fibrinoid necrosis*** (necrotizing arteriolitis), hyperplastic arteriolitis ***(Onion skin*** lesion) and ***flea bitten kidney.***
- Causes of renal papillary necrosis: Diabetes **(most common)**, obstructive uropathy, analgesic nephropathy and sickle cell disease.
- Pyelonephritis is most commonly caused by ***E. coli*** and its most predisposing factor is **vesico-ureteric reflux** (in chronic pyelonephritis)
- **Xanthogranulomatous pyelonephritis** is seen with **Proteus** (*most common*) and is characterised by the presence of **foam cells** (Xanthoma cells).
- **Fibronectin nephropathy** is inherited as an **Autosomal dominant** disease.
- Most common type of renal all carcinoma is **Clear cell carcinoma** having **chromosome 3** defects.
- **Sarcomatoid change** in the renal cancer has **poor prognosis**.
- **Chromophobe variant** of RCC is associated with **Hypodiploidy**
- ***Bilateral renal cell carcinoma*** is associated with: **Von-Hippel Lindau syndrome**.
- **Michaelis Gutmann bodies** are seen in **M**alakoplakia.
- Most common type of bladder cancer is the **transitional cell carcinoma** (TCC).
- Most common cause of **painless** hematuria: **urinary bladder cancer**
- Most common cause of ***painful*** hematuria: ***renal stones***.

Kidney is the organ of the body responsible for the removal of nitrogenous products from the blood.

SOME IMPORTANT DEFINITIONS:

1. **Azotemia** – It refers to an elevation of Blood Urea Nitrogen (BUN) and creatinine levels due to reduced glomerular filtration rate. It can be due to:
   a. *Pre-renal cause* – Associated with decreased perfusion as in shock, hemorrhage and heart failure.
   b. *Renal cause* – Due to intrinsic defect in the kidney.
   c. *Post renal cause* – Associated with obstruction to urine outflow.

   Patients **do not** require dialysis at this stage.
2. **Uremia** – Azotemia + Clinical signs and symptoms + Biochemical abnormalities
   – There is secondary presence of uremic gastroenteritis, peripheral neuropathy and uremic pericarditis. Patients require dialysis at this stage.

Definition

- **Azotemia** refers to an elevation of Blood Urea Nitrogen (BUN) and creatinine levels.
- **Uremia** = Azotemia + Clinical signs and symptoms + Biochemical abnormalities

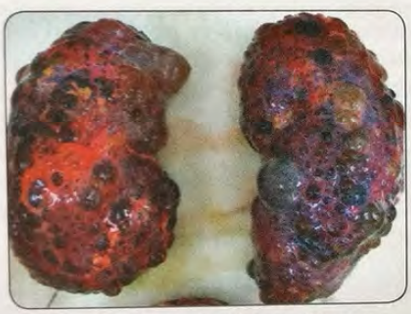


Fig. 1: Polycystic Kidney Disease

CYSTIC DISEASES OF THE KIDNEY

Polycystic Kidney Disease (PKD)

Adult PKD	Childhood PKD
• Autosomal dominant[Q] inheritance • Mutations in PKD1, PKD2 and PKD3 genes (PKD1 produces **Polycystin** protein[Q]). • Asymptomatic till middle age • Clinical features include hematuria, hypertension, UTI and renal stones. • Extrarenal manifestations 1. Cysts in other organs like **liver[Q] (most commonly)**, pancreas, spleen and ovary. 2. **Berry aneurysm[Q].** 3. **Colonic diverticula[Q].** 4. **Mitral valve prolapse and aortic regurgitation[Q].** • Grossly, bilaterally enlarged kidneys with multiple cysts containing serous or hemorrhagic fluid[Q].	• Autosomal recessive[Q] inheritance. • Mutation in PKHD1 gene which produces **fibrocystin** protein[Q]. • Presents in infancy with renal insufficiency. • Associated with multiple hepatic cysts and congenital hepatic fibrosis[Q]. • Grossly, bilaterally enlarged kidney with small cysts in cortex and medulla having their long axis at right angle to capsule.

Recent Exam Questions

- Major source of **renin** is ***JG cell of the kidney***[Q]
- Major source of erythropoietin is **Interstitial cells in peritubular capillaries and tubular epithelial cells**[Q]. It is also produced in *perisinusoidal cells in the liver*

Mnemonic

Genetics
ADult Polycystic Kidney Disease is **A**utosomal **D**ominant
Also; **Polycystic kidney** has *16 letters* and is due to a defect on chromosome **16**.

MNEMONIC FOR APKD:

1. **Clinical Features:** (11 B's)
   Signs: Bloody urine
   – Bilateral pain [vs. stones, which are usually unilateral pain]
   – Blood pressure up
   – Bigger kidneys
   Complications
   – Berry aneurysm
   – Biliary cysts
   – Bicuspid valve [prolapse and other problems]
   Accelerators:
   – Boys
   – Blacks
   – Blood pressure high.

GLOMERULAR DISEASES

PATHOGENESIS OF GLOMERULAR INJURY

a. In Situ **immune complex disease**
   1. ***Anti-GBM antibody induced nephritis***
      The antibodies are directed against intrinsic fixed antigens that are normal components of the glomerular basement membrane (GBM) proper resulting in a *diffuse linear pattern* of staining for the antibodies by immunofluorescence techniques. This is the model of anti-GBM disease (Goodpasture syndrome) which is caused by antibodies against non-collagenous domain of the *alpha 3 chain of collagen type IV*.
   2. ***Heymann nephritis***
      The antibodies are directed against intrinsic fixed antigen called *Heymann antigen* or *'megalin'* located on visceral epithelial cells resulting in complement activation and the formation of subepithelial deposits and a *granular pattern* of staining for the antibodies by immunofluorescence techniques.
   3. ***Antibodies against planted antigens***
      Antibodies can react with antigens that are not normally present in the glomerulus but are "planted" there. These antigens include cationic molecules like DNA, nuclear proteins, bacterial, viral and parasitic products and drugs. A *granular pattern* of staining is observed by immunofluorescence techniques.

Key Point

Heymann antigen or **'megalin'** is located on **visceral epithelial** cells

Concept

- **An**ionic antigens form sub**en**dothelial deposits.
- Cationic antigens form subepithelial deposits.
- Neutral antigens form mesangial deposits.

b. Circulating immune complex disease

The glomerular injury is caused by entrapment of circulating antigen-antibody complex within the glomeruli. This results in complement activation, leukocytic infiltration and proliferation of glomerular and mesangial cells. The endogenous antigens include DNA and tumor antigens whereas the exogenous antigens include infectious products. Electron microscopy reveals the presence of subendothelial deposits or subepithelial deposits. By immunofluorescence microscopy, the immune complexes can be seen as granular deposits along the basement membrane, in the mesangium or both.

Nephritic syndrome	Nephrotic syndrome
1. Proteinuria (1-2g/d)	1. Severe proteinuria (>3.5g/d)
2. Hematuria	2. Hypoalbuminemia (<3g/dl)
3. Hypertension	3. Edema
4. Azotemia, Oliguria	4. Hyperlipidemia, lipiduria

Key Point

Dehydration is the commonest cause of *primary renal vein thrombosis* in **children.**

Thrombotic and thromboembolic complications are common in nephrotic syndrome due to loss of anticoagulant factor (e.g. antithrombin III, protein C and S) combined with increased platelet activation. Renal vein thrombosis is most often a consequence of this hypercoagulative state specially in case of nephrotic syndrome associated with membranous nephropathy in adults. There is also increased synthesis of fibrinogen in the liver.

TERMINOLOGY IN GLOMERULAR DISEASES

Each region of a renal biopsy is assessed separately. By light microscopy, glomeruli **(at least 10 and ideally 20)** are reviewed individually for discrete lesions.

According to percentage of glomeruli affected

- *Focal* (Less than 50%)
- *Diffuse* (>50%)

Injury in each glomerular tuft can be

- *Segmental* (involving a portion of the tuft)
- *Global* (involving most of the glomerulus)

According to characteristic of lesion

- *Proliferative* when showing increased cellularity.
- *Endocapillary* (Proliferation of cells in the capillary tuft)

Contd...

Contd...

- *Extracapillary (Extension of proliferation* into Bowman's space)
- *Synechiae* (Epithelial podocytes attach to Bowman's capsule)
- *Crescents* (when fibrocellular/fibrin collections fill all or part of Bowman's space)
- *Sclerosis* (Acellular, amorphous accumulations of proteinaceous material throughout the tuft with loss of functional capillaries and normal mesangium)

Mnemonic

Nephritic syndrome

- MC cause in **P***ediatric* age group: ***P****ost Streptococcal GN*
- MC cause in **A***dults*: ***IgA*** *nephropathy*.

Recent Exam Question

Hematuria

- Presence of **> 3 RBCs**/high power field of centrifuged specimen is called hematuria.

NEPHRITIC SYNDROME

Acute Proliferative (Poststreptococcal) Glomerulonephritis

It is seen *1-4 weeks* after a **skin or pharyngeal infection** caused by *group A β hemolytic streptococci* (particularly *strains 12, 4 and 1*) usually in children. Activation of complement system results in consumption of complement proteins leading to *transiently low complement levels* (for 6-8 weeks). The antigen responsible for the development of this condition is a cytoplasmic antigen called **endostreptosin** and a cationic proteinase antigen called *nephritis strain associated protein* or **NSAP**[Q].

Key Point

Streptococcal **pyrogenic exotoxin B** (Spe B) is the principal antigenic determinant in most cases.

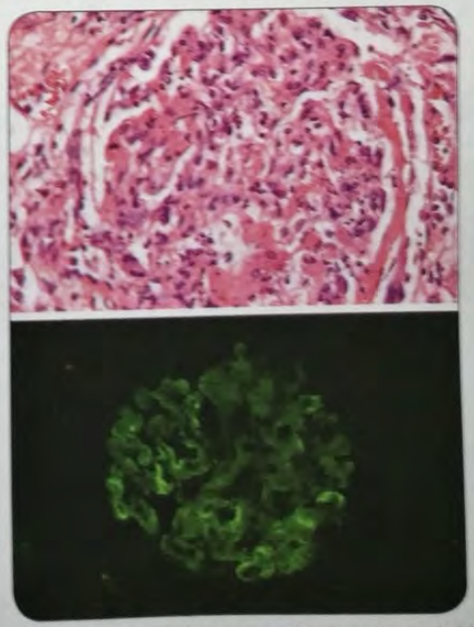


Fig. 2: Post Streptococcal Glomerulonephritis

Clinical features
Malaise, fever, nausea, oliguria and hematuria leading to smoky or cocoa colored urine, periorbital edema and mild to moderate hypertension.

Microscopic findings
Presence of hypercellular glomeruli due to leukocytic infiltration, proliferation of endothelial and mesangial cells. **Immunofluorescence** microscopy shows the presence of IgG, IgM and C3 deposits in the mesangium and along the basement membrane giving **'starry sky' appearance**.

Investigations
There is elevated levels of antistreptolysin O or ASO and anti DNAase antibodies[Q] (indicative of streptococcal infection) and ***transiently*** *reduced levels of serum C3.*

Management
It is done with fluid restriction. The majority of the patients recover and only a small fraction may progress to chronic glomerulonephritis.

RAPIDLY PROGRESSIVE (CRESCENTIC GLOMERULONEPHRITIS)

It is characterized by rapid and progressive loss of renal function associated with rapid development of renal failure in weeks or months.

It is of the following three types with the common feature of severe glomerular injury.

Key Point

Crescents are composed of **parietal cells**, **leukocytes** (macrophage) and **fibrin.**

Crescentic Glomerulonephritis

Type I RPGN (Anti-GBM antibody)	Type II RPGN (Immune complex)	Type III RPGN (Pauci immune)
• Idiopathic • Goodpasture's syndrome.	• Idiopathic • Post infectious • SLE, Henoch Schonlein Purpura.	• Idiopathic. • ANCA associated. • Wegener's granulomatosis. • Microscopic polyangiitis.
Immunofluorescence finding	***Immunofluorescence finding***	***Immunofluorescence finding***
• *Linear GBM deposits of IgG and C3*	• *"Lumpy bumpy" granular pattern of staining.*	• *No immunoglobulin or complement deposits in GBM.*

The characteristic histologic feature is the presence of glomerular **crescents (in > 50% of glomeruli seen on biopsy)** *which are composed of proliferation of parietal cells, leukocytic infiltration, and monocyte and macrophage movement in the urinary space.* The fibrin is prominent within the cellular layers of the crescents. Electron microscopy shows the presence of ruptures in the glomerular basement membrane and **subepithelial deposits**.

Clinical features include hematuria with RBC casts in the urine, subnephrotic proteinuria, hypertension and edema. The prognostic features are mentioned as follows:

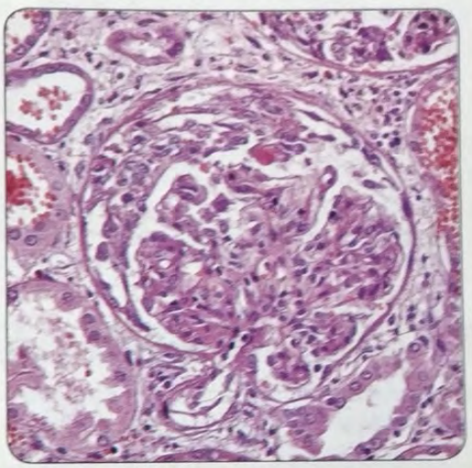


Fig. 3: Crescentic GN

Key Point

Prognosis in RPGN is related to the number of **crescents** as it correlates with oliguria.

Prognosis of RPGN

Poor prognostic factors	Good prognostic factors
• ***Oliguria*** and ***azotemia*** at presentation • ***More than 80% circumferential crescents*** have poor response to therapy • Glomerular tuft necrosis, global glomerular sclerosis, gaps in Bowman capsule and interstitial fibrosis	• *Pauci immune RPGN* has best prognosis • *Non- circumferential crescents in less than 50%* glomeruli have indolent course. • *Associated endocapillary proliferation* is a good prognostic factor

NEPHROTIC SYNDROME

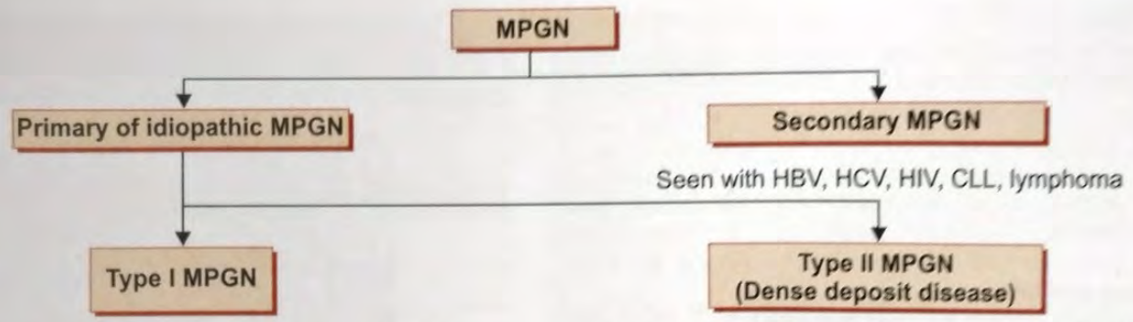
Membranoproliferative (Mesangiocapillary) Glomerulonephritis (MPGN)

It is characterized by the presence of basement membrane alterations, proliferation of glomerular cells (particularly in the mesangium) and leukocytic infiltration. These patients may have a nephritic or nephrotic picture.

Recent Exam Questions

Nephrotic syndrome

- MC **1° cause** in **children**: **minimal change disease**.
- MC **1° cause** in **Adults**: **focal segmental glomerulosclerosis**.
- MC **1° cause** in **Elderly**: **Membranous glomerulopathy**.
- MC **systemic** as well as **overall cause**: **diabetes mellitus**.



- Immune complexes in glomeruli cause activation of both classical and alternate complement pathway
- **Subendothelial** and mesangial immune complex deposits
- Granular pattern of C_3 with IgG, C_{1q} and C_4

- Immune complexes in glomeruli cause activation of alternate complement pathway
- Dense deposit in the glomerular basement membrane **(intramembranous deposits)**
- Granular and linear pattern of C_3 with absence IgG

NEET Booster!

Infection	Type of nephrotic syndrome
Syphilis	**MGN**
Schistosomiasis	*MGN*
HepB (children)	**MGN**
HepB (Adults)	*MPGN*
Toxoplasmosis	**MPGN**

- In type II MPGN, the serum of these patients contain C3 nephritic factor (C3NeF) which causes stabilization of alternate C3 convertase thereby causing persistent degradation of C3 and resulting hypocomplementemia.

Light microscopy shows the lobular appearance of glomeruli which are hypercellular (due to leukocytic infiltration and proliferation of capillary endothelial cells and mesangial cells). The GBM is thickened and the synthesis of new basement membrane causes **'tram-track'** or **'double contour'** appearance appreciated with silver or PAS stains.

Electron microscopically, type I MPGN is having the presence of subendothelial electron dense deposits. Immunofluorescence studies demonstrate the deposition of C_3, IgG and early complement proteins (C_{1q} and C_4) in the glomeruli. In type II disease, there is presence of dense deposits within the GBM, so it is also called as dense deposit disease. Immunofluorescence studies demonstrate the linear or granular deposition of C_3 whereas IgG and early complement proteins are absent. C_3 may also be present in mesangial rings.

Clinical presentation of the patient is nephrotic syndrome with the nephritic component of hematuria. There is high incidence of recurrence in transplant patients.

Secondary MPGN is invariably type I but the exact mechanism is unknown.

Recent Exam Question

Glomerular basement membrane **'tram-track'** or **'double contour'** appearance in MPGN.

Concept

Genetic Basis of Proteinuria

- **NPHS1 gene** encodes for the protein **nephrin** (component of podocyte foot process controlling glomerular permeability) and its mutation causes a hereditary form of **congenital** nephrotic syndrome **(Finnish type)**.
- **NPHS2 gene** encodes for the protein **podocin** (also a component of podocyte foot process) and its mutation results in the development of ***steroid resistant*** nephrotic syndrome of childhood onset or autosomal recessive focal segmental glomerulosclerosis (FSG).
- A mutation in the gene encoding podocyte actin-binding protein **(α-actinin 4)** results in **autosomal dominant** focal segmental glomerulosclerosis **(FSG)**.
- Mutations in gene encoding for **TRPC6** is implicated in *adult-onset* FSGS

Mnemonic

- **N**PHS1 contains 1, which suggest first letter (means **N**) that stands for **N**ephrin whereas N*P*HS2 contains 2, which suggest second letter (means ***P***) that stands for ***P***odocin.
- 1 comes first, so **NPHS1** mutations cause **congenital** nephrotic syndrome whereas 2 comes later, so *NPHS2* mutations cause *acquired* disease (steroid resistant nephrotic syndrome).

LIPOID NEPHROSIS (MINIMAL CHANGE DISEASE)

It is the ***commonest cause of nephrotic syndrome in the children*** (peak incidence in 2-6 years) characterized by the diffuse effacement of the foot processes of epithelial cells of the glomeruli which *appear normal by light microscopy*. So, the other name of the disease is minimal change disease.

There is absence of immune deposits but presence visceral epithelial injury due to abnormal secretion of mphokines by T cells resulting in the loss of glomerular olyanions responsible for low molecular weight proteinuria elective proteinuria). Mutation of the protein nephrin causes hereditary form of congenital nephrotic syndrome (*Finnish ype*[Q]).

Microscopy

Light microscopy shows the **normal glomeruli** with lipid accumulation in proximal tubular cells (lipoid nephrosis) whereas the **electron microscope** reveals the presence of *effacement of foot processes of podocytes*.

Clinical features

There is massive proteinuria particularly loss of albumin (highly selective proteinuria[Q]) in the absence of hypertension or hematuria.

Key Point

The patients with **lipoid nephrosis** have an **excellent response to steroids.**

MEMBRANOUS GLOMERULOPATHY (MGN)

It is a *common cause of nephritoc syndrome in the adults* characterized by the diffuse thickening of the glomerular capillary wall and accumulation of electron dense, immunoglobulin-containing deposits along the ***subepithelial side*** of the basement membrane. Its causes include:

Recent Exam Questions

Primary MGN

- Autoantibody formation against **phospholipase A2 receptor**.
- Associated with HLA-DQA1.
- *MCC of nephrotic syndrome* associated with **deep vein thrombosis**.
- **Spikes on basement membrane (on electron microscopy).**

Idiopathic	Secondary
• Seen in most of the patients (in 85% patients)	• Drugs (penicillamine, captopril, NSAIDs) • Malignancies like carcinoma of colon and lung, melanoma • Infections like hepatitis B and C, syphilis, malaria, schistosomiasis • Systemic diseases like SLE, diabetes mellitus, thyroiditis

The disease has resemblance to the *Heymann nephritis model*[Q] of glomerular injury mediated by immune complex formation against a visceral epithelial antigen called Heymann antigen or ***megalin***. The immune complex mediated formation of membrane attack complex C_{5b}-C_9 causes activation of glomerular epithelial and mesangial cells which release oxidants and proteases that cause vessel wall injury and protein leakage.

Microscopy

Light microscopy shows the diffuse membrane-like thickening of the glomerular capillary wall. Basement membrane projections as 'spikes'[Q] are seen on silver stains. **Electron microscopy** reveals effacement of the foot process of podocytes and presence of *subepithelial deposits.*

Immunofluorescence

It demonstrates the linear and granular deposition of C3 and IgG.

Clinical presentation

It is nephrotic syndrome with the excretion of higher weight globulins along with albumin (non selective proteinuria) which is poorly responsive to steroids.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

This is now the **commonest** cause of nephrotic syndrome and is characterized by the presence of focal (only some glomeruli are affected) and segmental (only a part of the glomerulus is affected) sclerosis of the glomeruli.

Recent Exam Questions

FSGS

- **MC** variant: **NOS** variant.
- **Worst** prognosis: **collapsing** variant.
- **Best** prognosis: **Glomerular tip** lesion variant

Key Point

Degeneration and focal ***disruption of the visceral epithelial cells*** is the hallmark feature of focal segmental glomerulosclerosis.

Causes

1. Idiopathic
2. Secondary:
   - Associated with loss of renal tissue as unilateral renal agenesis or advanced stages of **reflux nephropathy** or hypertensive nephropathy.
   - Associated with conditions like **Sickle cell** anemia, **HIV** infection, Heroin abuse, Obesity.
   - Inherited due to mutations in genes like nephrin, podocin and α-actinin 4.

Degeneration and focal disruption of the visceral epithelial cells is the hallmark feature of focal segmental glomerulosclerosis. *The hyalinosis and sclerosis are due to protein entrapment. Mutation of the protein* ***podocin*** *and* ***a-actinin*** *4 results in the development of autosomal* ***recessive*** *and autosomal* ***dominant*** *forms of focal segmental glomerulosclerosis respectively.*

Concept

HIVAN may present clinically with nephrotic range proteinuria but is **NOT** associated with Hypertension *(HTN), edema or hyperlipidemia.*

Recent Exam Questions

- **Collapsing glomerulopathy** is a variant of FSG is seen in **HIV associated nephropathy** it is characterised by hypertrophy and necrosis of glomeorular visceral epithelial cells.
- MC cause of *Collapsing glomerulopathy* in *Children* is *Cystinosis*.

Microscopy

Light microscopy reveals the focal segmental sclerosis and hyalinization of the glomeruli. **Electron microscopy** demonstrates the diffuse effacement of the podocytes, focal detachment of the epithelial cells and increased mesangial matrix in the sclerotic areas. Five mutually exclusive variants of FSGS may be distinguished by the pathological findings seen on renal biopsy

- Collapsing variant
- Glomerular tip lesion variant
- Cellular variant
- Perihilar variant
- Not otherwise specified variant (NOS) **(Commonest)**

Immunofluorescence

It demonstrates C3 and IgM deposits in the sclerotic areas and the mesangium.

It affects all age groups and is characterized by the clinical features of non-selective **proteinuria**, reduction in GFR and presence of hypertension and poor response to corticosteroids. There is high incidence of recurrence in transplant patients. Children have better prognosis than adults.

IgA NEPHROPATHY (BERGER DISEASE)

This is the *commonest glomerulonephritis* in the world. ♀ It is characterized by the presence of prominent IgA deposits in the mesangial regions and clinically by gross or microscopic hematuria. It can occur either alone or secondary to liver or intestinal disease.

Pathogenesis: The patient usually develops an initial respiratory or gastrointestinal infection resulting in increased synthesis of IgA1 which gets trapped in the mesangium. Here, these immunoglobulins cause activation of alternate pathway of complement system resulting in glomerular injury. Any liver disease causes reduced clearance of IgA whereas intestinal disease causes increased mucosal production of IgA.

Recent Exam Questions

BERGER DISEASE

- **MC glomerulonephritis** in **adults**.
- MC cause of **recurrent hematuria**.
- ↑↑ **IgA** in **mesangium**.
- Hematuria occurs **3-4 days after** throat infection.
- ↑ chance of **recurrence**.
- **Normal** complement levels.

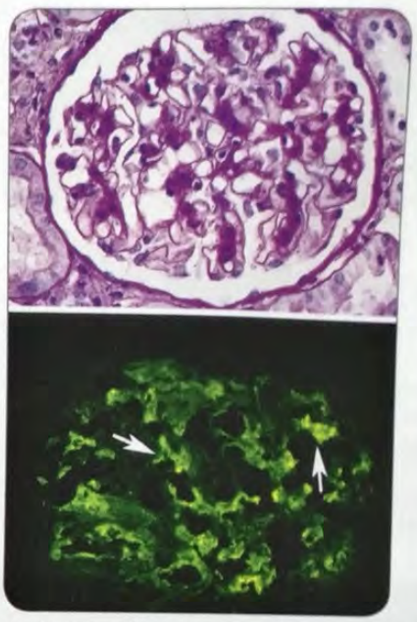


Fig. 4: Berger disease (IgA deposits in mesagium shown by arrows with immunofluorescence microscopy)

Microscopic examination reveals the mesangial widening and proliferation which on **immunofluorescence** reveals the presence of the mesangial deposition of IgA usually with C3 and properdin. Mesangioproliferative glomerulonephritis is seen more commonly than focal proliferative and crescentic (least) glomerulonephritis.

Clinical features: Any age group of the patients (more in children and young adults) may be affected who present with **gross hematuria 3-4 days after** an infection of the respiratory, GI or urinary tract. Almost 1/3rd of the patients have microscopic hematuria. This hematuria lasts for some days to subside and recur every few months. Recurrence of the disease in the transplanted kidneys is frequent.

Alport Syndrome

This is a nephritic disorder characterized by the involvement of the triad of **kidney, ear and eye**. There is a fundamental *defect in the α5-chain of collagen type IV* resulting in defective GBM synthesis responsible for the involvement of the organs where this collagen is found.

Microscopically

- **Light microscopy** glomerular involvement in the form of the presence of *foam cells* in the interstitial cells.

Electron microscopy (Diagnostic for this disorder♀)

- It shows the presence of irregular foci of thickening and ***thinning in the GBM*** with splitting and lamination of lamina densa called as ***"basket weave appearance"***. *Absence of α5 staining is seen even on skin biopsy apart from glomerular and tubular basement membrane.*

Clinical features

- **Males** in the age group of 5-20 years are more frequently affected presenting with gross or microscopic hematuria, nerve deafness and ocular features (posterior cataract, lens dislocation and corneal dystrophy).

Recent Exam Questions

Alport Syndrome

- **Earliest** feature: **hematuria**.
- MC **extrarenal** anomaly: **sensorineural deafness**.
- **Electron microscopy is diagnostic for Alport syndrome.** It shows ***"basket weave appearance"*** of the GBM.

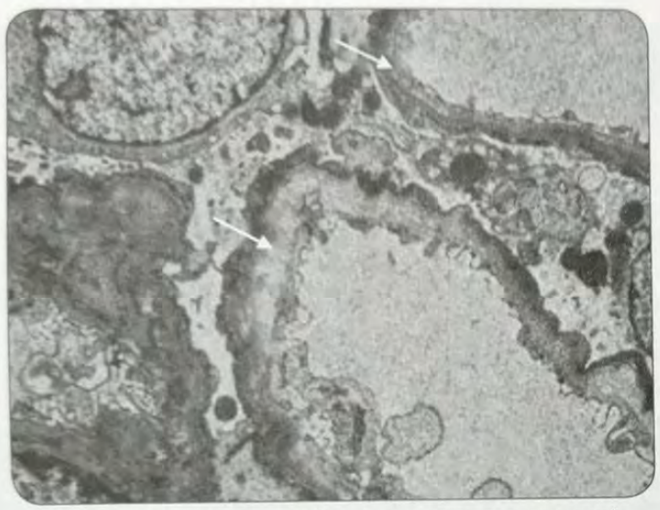


Fig. 5: Alport syndrome (basket weave appearance).

Thin Membrane Disease (Benign Familial Hematuria)

This is a disease characterized by the presence of familial asymptomatic hematuria and thinning of the basement membrane to 150-250 nm (normal GBM thickness is 300-400 nm). There is a defect in the α3 and α4 chains of collagen type IV.

Recent Exam Question

Thin basement membrane disease is the **most common** cause of **benign familial hematuria**.

Goodpasture Syndrome

It is an autoimmune disorder (**type II hypersensitivity reaction**) having the presence of antibodies against non-collagenous domain of α3 chain of collagen IV causing destruction of basement membrane in *renal glomeruli and pulmonary alveoli*.

The disease affects young men more commonly and is associated with smoking, viral infections or exposure to hydrocarbon solvents (workers in dry cleaning industry).

Histologically, the alveoli show focal necrosis, intra-alveolar hemorrhage, presence of hemosiderin laden macrophages and hypertrophy of type II Pneumocytes. The renal involvement is in the form of either focal proliferative or crescentic glomerulonephritis.

Immunofluorescence studies show linear deposits of immunoglobulins along alveolar septa and GBM.

Clinical features: *Interstitial hemorrhagic inflammation* leads to the predominant symptoms of hemoptysis and hematuria. Management is done by plasmapheresis.

Key Point

Uremia is the cause of death in Goodpasture Syndrome.

Concept

Goodpasture Syndrome and Goodpasture Disease are different!

Goodpasture syndrome	Goodpasture disease
• Affects young males • Lungs are affected • Poor prognosis	• Affects elderly **females** • Lungs are **not affected** • **Good prognosis**

SUMMARY OF GLOMERULAR DEPOSITS

Subepithelial	Subendothelial	Basement membrane	Mesangial
*Acute GN (like PSGN) *Membranous GN *Heymann GN *RPGN (some cases) *MPGN (Type I) rarely	*MPGN (Type I) *SLE *Acute GN	*MPGN (Type II) *Membranous Glomerulo-pathy	*IgA nephropathy *HSP *Anti-GBM diseases like RPGN and Goodpasture syndrome

Concept: Proliferative Glomerulonephritis

Glomerular lesions with increased cells in the tufts are often known as proliferative glomerulonephritis. It is seen in the following conditions:

- SLE (particularly class II, mesangial hypercellularity defined as >3 cells in mesangial regions)
- HIV
- Membranoproliferative glomerulonephritis
- Neoplasia (particularly CLL and MALT lymphoma)
- Post streptococcal glomerulonephritis.

CHRONIC GLOMERULONEPHRITIS

It is the final stage of many forms of glomerular disease and is characterized by progressive renal failure, uremia and ultimately death.

Clinical features include anemia, anorexia, malaise, proteinuria, hypertension and azotemia.

Grossly there is presence of *small, shrunken kidneys*. There is fine and symmetrical scars. Microscopically, there is hyalinization of glomeruli, interstitial fibrosis, atrophy of tubules, and a lymphocytic infiltrate. Management is done by dialysis and renal transplantation.

Key Point

The urinalysis in **Chronic Glomerulonephritis** shows **broad waxy casts**.

Diabetic Nephropathy

It is a disorder characterized by hyperglycemia resulting in formation of advanced glycosylation end products responsible for GBM thickening and increased mesangial matrix. There is also concomitant presence of hemodynamic changes resulting in glomerular hypertrophy with increased glomerular filtration area. Both of these contribute to the development of proteinuria.

Concept

In uncontrolled diabetes there is presence of glucosuria resulting in glycogen accumulation in Proximal Tubular cells (called as **Armani Ebstein** cells).

Morphological features include:

Capillary basement membrane thickening

It is the earliest morphological abnormality which is seen in *virtually all diabetics irrespective of proteinuria*. It is best detected with electron microscopy and is associated with thickening of the tubular basement membrane.

Diffuse mesangiosclerosis

There is *diffuse increase in the mesangial matrix* usually consisting of PAS positive material associated with GBM thickening.

Nodular glomerulosclerosis

It is a highly specific lesion of diabetes and is also known as intercapillary glomerulosclerosis or ***Kimmelsteil Wilson*** lesion. It consists of PAS positive nodules of matrix situated in the periphery of the glomeruli. It is associated with prominent accumulation of hyaline material in capillary loops and Bowman's capsule known as **"fibrin caps" and "capsular drops"** respectively.

There is also presence of ***hyalinizing arteriolar sclerosis*** (affects characteristically ***both*** ^{Q} ***afferent and efferent arterioles***), pyelonephritis and *papillary necrosis*.

Clinical features: The increased GFR is associated with **microalbuminuria.**It is very important clinical predictor of development of diabetic nephropathy later on. The protein excretion then reaches subnephrotic proteinuria followed by nephrotic proteinuria. Patients of type I diabetes may also have hypertension which further aggravates the renal disease.

Definition

Microalbuminuria means urinary excretion of **30-300 mg** of albumin per 24 hours.

Recent Exam Question

- **Liver-fatty acid binding protein (L-FABP)** is a **biomarker** of **chronic kidney disease** and **diabetic nephropathy**.

Differences between benign nephrosclerosis and malignant nephrosclerosis

Features	Benign nephrosclerosis	Malignant nephrosclerosis
Condition	Benign hypertension, DM, elderly age	Malignant hypertension

Contd...

Contd...

Features	Benign nephrosclerosis	Malignant nephrosclerosis
Gross appearance of kidneys	Leather grain appearance	Flea bitten appearance due to tiny petechial hemorrhage
	Small or reduced kidneys	Variable size of the kidney
Microscopy	1. Narrowing of the lumens of arterioles caused by thickening and hyalinization of the walls (hyaline arteriolosclerosis) 2. Fibroelastic hyperplasia of arteries and arterioles	(i) Hyperplastic arteriolitis (onion skinning) due to proliferation and elongation of smooth muscle cells. (ii) Necrotizing glomerulitis (neutrophils infiltration and thrombosed capillaries) (iii) Fibrinoid necrosis of arterioles (iv) Necrotizing arteriolitis
Activity of renin angiotensin system	Normal	↑ed
Proteinuria	Mild	Marked
Sign of malignant hypertension	Absent	Present such as retinopathy encephalopathy
Renal failure	Rare	More common

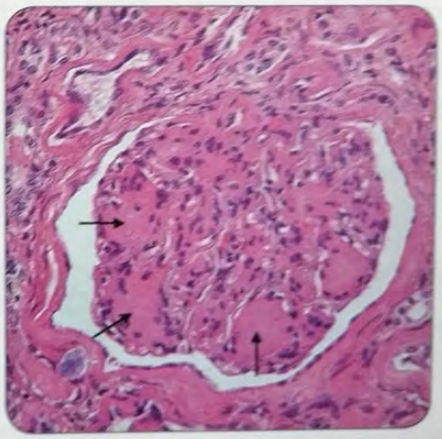


Fig. 6: Nodular Glomerulosclerosis in diabetes mellitus

Concept

Proteinuria in most adults with glomerular disease is non-selective, containing albumin and a mixture of other serum proteins while in children with minimal change disease; proteinuria is selective and largely composed of albumin.

TUBULAR DISEASES

Acute Tubular Necrosis (ATN)/Acute Kidney Injury (AKI)

- It is a disorder characterized by destruction of tubular epithelial cells resulting in loss of renal function. It is the *most common cause of acute renal failure* (ARF).

Recent Exam Questions

- **Acute Kidney Injury** is the **most common** cause of **acute renal failure** (ARF).
- In ARF, **24 hour urine output** is **less than 400 ml.**
- ↑ **kidney injury molecule-1 (KIM-1)** levels in urine are **sensitive** and **specific** for **acute kidney injury**.

NEET Booster!

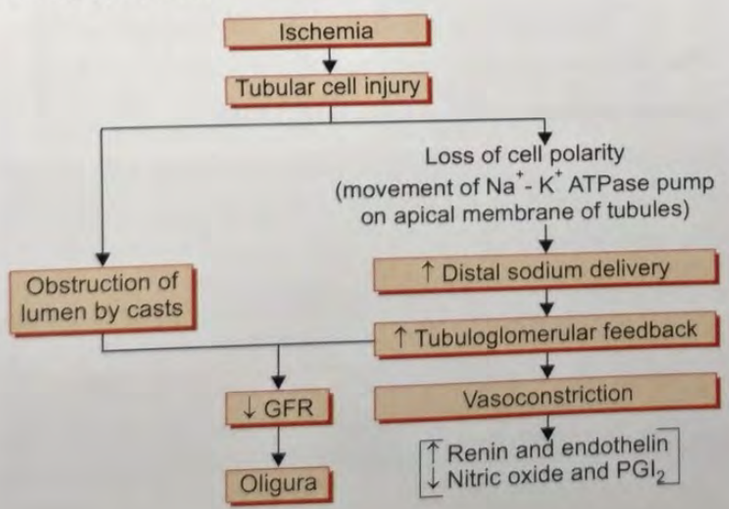
Poisoning	Features in tubular cells
Mercuric chloride	Large acidopathic inclusions[Q]
Carbon tetrachloride	Accumulation of neutral lipids[Q]
Ethylene glycol	Ballooning and vacuolar degeneration of PCT, Calcium oxalate crystals in tubular lumen[Q]

ATN

Ischemic ATN	Nephrotoxic ATN
• Most common cause of ATN[Q].	• Due to drugs (gentamicin, methicillin, radio contrast agents, organic solvents, ethylene glycol, phenol, pesticides, myoglobin).
• Due to decreased blood flow (in shock, hemorrhage, hypotension or dehydration).	• **Diffuse** necrosis of ***proximal convoluted*** tubular segments and ascending Henle's loop[Q] occur.
• Presence of **focal** tubular necrosis affecting **proximal straight** tubule and ascending limb of loop of Henle[Q].	

- In both ischemic and nephrotoxic ATN, there is rupture of tubular basement membranes *(tubulorrhexis)* and occlusions of lumen by a cast mostly seen in distal convoluted tubule and collecting ducts.

Pathogenesis of ATN



CLINICAL FEATURES OF ATN

1. **Initiation phase**–Lasts for about 36 hours and is characterized by slight decline in urine output with a rise in blood urea nitrogen (BUN).
2. **Maintenance phase**–Oliguria, salt and water overload, hyperkalemia, metabolic acidosis and rising BUN concentration.
3. **Recovery phase** – Steady increase in urine volume (up to 3L/d), hypokalemia and increased vulnerability to infections.

PYELONEPHRITIS

It is the infection involving the renal pelvis, tubules and interstitium. It can be of two types:

- *Acute Pyelonephritis* is the renal lesion associated with bacterial urinary tract infection (UTI)
- *Chronic pyelonephritis*, bacterial infection is associated with other factors including vesicoureteral reflex and obstruction.

Recent Exam Questions

- **Ascending infection is the most common route of pyelonephritis caused by most bacteria** *except TB which involves the kidney by hematogenous spread.*
- **WBC** casts are suggestive of renal involvement because *casts are formed only in tubules.*
- *E. coli* is the commonest bacteria causing UTI[Q] followed by Proteus, Klebsiella, Enterobacter and Strep. fecalis, etc.

Definition

Sterile pyuria is defined as 'white cells in the urine in the ***absence*** of significant bacterial growth'. Its important causes are:

- Recently treated UTI
- TB, fungal infection
- Perinephric abscess
- Chronic prostatitis
- Acute interstitial nephritis
- Chronic interstitial nephritis (including analgesic nephropathy)
- Chronic pyelonephritis

Key Point

In **chronic glomerulonephritis** kidneys are **diffusely** and **symmetrically scarred** whereas in **chronic pyelonephritis**; the kidneys are irregularly and **asymmetrically scarred**.

There is initial colonization of the distal urethra followed by movement in to the bladder due to frequent instrumentation or catheterization. Bladder dysfunction or outflow obstruction causes stasis of urine promoting the bacterial multiplication. From the bladder, it is the incompetence of the vesicoureteral valve allowing retrograde urine flow in to the ureters (vesicoureteral reflux). The infected urine enters the renal pelvis more commonly in the upper and lower poles of the kidney (intrarenal reflux).

Predisposing factors include Vesicourethral reflux, urethral instrumentation, diabetes mellitus, pregnancy, urinary obstruction, benign prostatic hypertrophy and other renal pathology.

Clinical features: Females more commonly affected than males (because of shorter urethra, hormonal changes favoring bacterial adhesion to mucosa, absence of antibacterial property as in prostatic fluid and urethral trauma during sexual intercourse). There is presence of fever with chills, dysuria (painful micturition), increased frequency and urgency along with costovertebral angle tenderness.

Urinalysis reveals presence of leukocytes particularly neutrophils (pyuria) and **WBC casts**Q suggestive of renal involvement (because casts are formed only in tubules).

Complications include papillary necrosis (usually bilateral), pyonephrosis and perinephric abscess.

Recent Exam Question

Urinary frequency is often the **earliest** symptom and may be the **only manifestation of renal tuberculosis.**

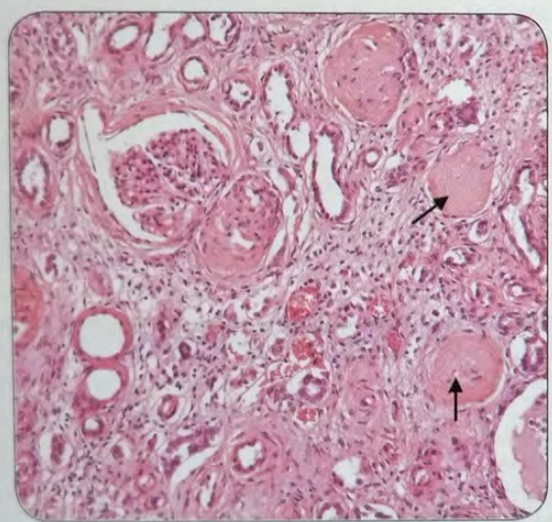


Fig. 7: Chronic glomerulonephritis having hyalinised glomeruli

Differences between chronic glomerulonephritis and chronic pyelonephritis

Traits	Chronic glomerulonephritis	Chronic pyelonephritis
Causes	Various glomerulonephritis	Reflux nephropathy or chronic obstructive pyelonephritis
Pathogenesis	End stage glomerular disease due to specific glomerulonephritis	Chronic tubulo-interstitial inflammation and scarring associated with renal disorder
Gross appearance of surface	Diffusely, granular, cortical surfaces	Depressed area on dilated and blunted calyx

Contd...

Contd...

Traits	Chronic glomerulonephritis	Chronic pyelonephritis
Scar	Fine and Symmetrical	Coarse and Asymmetrical
Glomeruli	Reduced in number with obliteration	Normal; may show periglomerular fibrosis
Tubules	Atrophied	Atrophy in some and hypertrophy in others filled with **colloid casts** (thyroidisation)
Renal pelvis and calyx	Normal	Dilated
Interstitial and periglomerular fibrosis	Mild	More marked
Clinical features	Insidious in onset Proteinuria, azotemia, hypertension, edema	May be asymptomatic or present with back pain, fever, polyuria, nocturia, pyuria, bacteriuria with gradual onset of hypertension and renal insufficiency

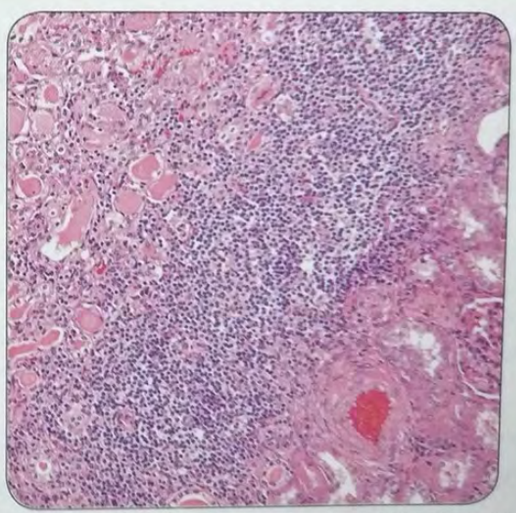


Fig. 8: Chronic pyelonephritis having thyroidisation of tubules

Xanthogranulomatous pyelonephritis (XPN)

Unusual *variant of chronic pyelonephritis*. Most cases occur in the setting of obstruction due to infected renal stones.

Grossly

- *Yellow, lobulated masses* diffusely replace the renal architecture.

Microscopically

- There is massive destruction of the kidney due to granulomatous tissue containing lipid-laden macrophages; the appearance may be *confused with renal malignancy*.

Contd...

Contd...

Clinical features

- It most often occurs in middle-aged women with a history of recurrent urinary tract infections.
- Typical presenting symptoms include flank pain, fever, malaise, anorexia and weight loss.
- A unilateral renal mass can usually be palpated on physical examination.

Diagnosis

- Examination of the urine confirms the presence of urinary tract infection. Urine culture typically demonstrates Enterobacteriaceae. The *most common organisms associated with XPN are E. coli, Proteus mirabilis, Pseudomonas, Streptococcus faecalis and Klebsiella.*

Key Point

Patients with calcium oxalate stone are advised to maintain a **low sodium, low protein but normal calcium** diet to reduce the recurrence renal stone.

Recent Exam Questions

- *Struvite (triple) stone*: **Coffin lid shaped**[Q].
- *Calcium oxalate:* **Needle shaped/ square envelope shape**[Q]

Recent Exam Questions

- *Cystine stone*: **Hexagonal**[Q]
- *Uric acid:* **diamond / barrel shape**[Q]

Renal Stones/Urinary Calculi

In the urinary tract, the *most common site of origin of stone is the kidney*. Males between the age group of 20-30 years are most commonly affected. Renal stones are formed either due to supersaturation of urine (constituent concentration exceeding the solubility) or deficiency of crystal formation inhibitors like pyrophosphate, diphosphonate, citrate, osteopontin and nephrocalcin.

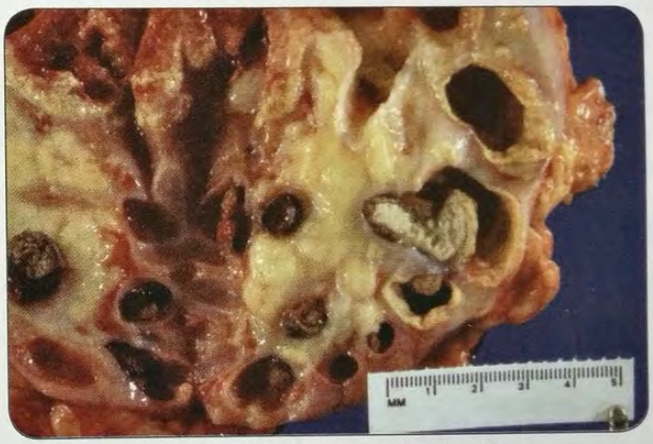
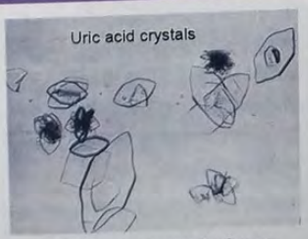


Fig. 9: Struvite stones or Triple stones

Renal stones

Calcium oxalate	Uric acid	Magnesium ammonium phosphate	Cystine
			
Square envelope shape	**Diamond / barrel shape**	**Coffin lid shape**	**Hexagonal shape**
• **Most common** stone[Q]. • **Idiopathic hypercalciuria** is the commonest cause[Q]. • Seen in acidic urine. • Also associated with hypocitraturia[Q]. • Radiopaque stone[Q].	• Seen with **hyperuricemia (gout, leukemias)**[Q]. • Seen in acidic urine (pH < 5.5)[Q]. • **Radiolucent stone**[Q].	• Also called **"struvite stones"** or **"triple stones"**[Q]. • Formed in **alkaline urine** particularly in infection with **proteus**[Q]. • Occupy large part of renal pelvis, so, called as **"staghorn calculi"**[Q].	• Due to genetic defect in the absorption of cystine resulting in **cystinuria**[Q]. • Formed in acidic urine • Change color from initial yellow to green on air exposure[Q].

Note: Uncommon renal stones can be composed of xanthine (due to xanthine oxidase deficiency), indinavir (in AIDS patients taking this drug) or triamterene (Patients on this antihypertensive medication). All these are radiolucent stones[Q].

Concept

Reasons why low calcium is avoided in patients with calcium oxalate are:

- ***Low calcium diet increases risk of stone formation*** by reducing calcium in the intestine to bind with oxalate thereby increasing oxalate levels in the urine.
- ***Low calcium increases the risk of reduced bone density.***

Stones are usually unilateral (80% of patients) and are deposited in renal pelvis and bladder. If the developing stone takes the shape of the pelvicalyceal system, it is called **staghorn calculi**.

Clinical symptoms include hematuria, urinary obstruction, renal colic (if they pass into the ureters) and increased chances of infection. Most of the renal stones are managed surgically.

URINARY CASTS

Hyaline casts

- This is a **normal constituent** of urine and has no attached significance.
- Tamm Horsfall protein is a protein secreted by epithelial cells of **loop of Henle**[Q].
- This protein may be exerted as Hyaline cast.
- May be seen in concentrated urine, febrile disease, after heavy exercise

RBC cast

Is suggestive of **glomerular injury**.[Q]

White cell casts

Are suggestive of interstitial injury and may be seen in interstitial nephritis. WBC cast with bacteria indicate **Pyelonephritis**.[Q]

Broad granular casts

Arise in the dilated tubules of enlarged nephrons that have undergone compensatory hypertrophy in response to reduced renal mass i.e. **chronic renal failure**.[Q]

Pigmented muddy brown granular casts

Are suggestive of ischemic or nephrotoxic injury i.e. Tubular Necrosis[Q].

Lipid cast

- Seen when there is fatty degeneration of the tubular epithelium.
- Also seen in nephrotic syndrome, lupus and toxic renal poisoning[Q].

RENAL TUMORS

Benign Tumors

- **Angiomyolipoma** – It is a hamartoma composed of fat, smooth muscle and blood vessels and is associated with tuberous sclerosis.
- **Oncocytoma** Tumor arising from intercalated cells of collecting ducts having large, eosinophilic cells which have numerous mitochondria. The cells have expression of carbonic anhydrase C and band 3 protein.

Wilms' Tumor (Nephroblastoma)

Wilms' tumor is the **most common primary renal tumor of childhood** in USA. This tumor's peak age is **2-5 years**. The risk of Wilms' tumor is increased in association with at least three recognizable groups of congenital malformations:

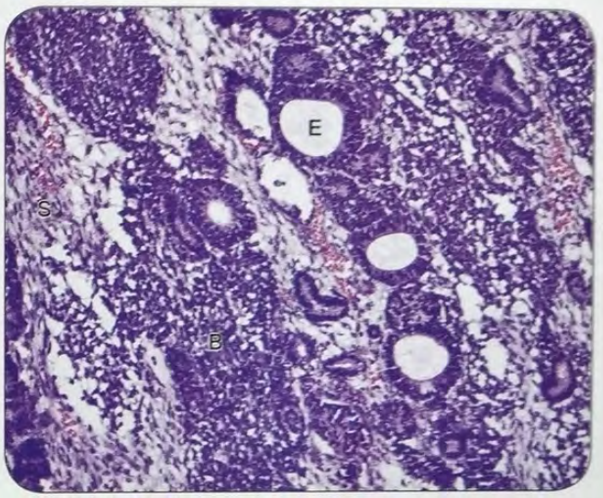


Fig. 10: Wilm Tumor: triphasic combination of blastemal (B), stromal (S), and epithelial (E) cells.

WAGR syndrome

It is characterized by 33% chance of developing **W**ilms' tumor, **A**niridia, **G**enital anomalies, and mental **R**etardation. Patients with WAGR syndrome carry constitutional (germline) deletions of two genes *WT1* and *PAX6* both located at chromosome **11p13**[Q].

Denys-Drash syndrome

It is characterized by *gonadal dysgenesis* (male pseudohermaphroditism) and *early-onset nephropathy* leading to renal failure. The characteristic glomerular lesion in these patients is a *diffuse mesangial sclerosis*. These patients also have germline abnormalities in *WT1*. In addition to Wilms' tumors these individuals are also at increased risk for developing germ-cell tumors called *gonadoblastomas*.

Beckwith-Wiedemann syndrome

It characterized by enlargement of body organs (organomegaly), macroglossia, hemihypertrophy, omphalocele and abnormal large cells in adrenal cortex (adrenal cytomegaly). The genetic locus involved in these patients is in band p15.5 of chromosome 11 called *"WT2"*. In addition to Wilms' tumors patients with Beckwith-Wiedemann syndrome are also *at increased risk for developing hepatoblastoma, adrenocortical tumors, rhabdomyosarcomas and pancreatic tumors*.

β catenin mutations are synergestically acting with WT1 mutations to cause cancer. Nephrogenic rest are precursor lesions of Wilms tumor.

MORPHOLOGY

Grossly, Wilms tumor tends to present as a large, solitary, well-circumscribed mass and on cut section, the tumor is soft, homogeneous, and tan to grey with occasional foci of hemorrhage, cyst formation, and necrosis.

Microscopically, Wilms' tumors are characterized by the *classic* ***triphasic*** *combination of blastemal, stromal, and epithelial cell types* (immature glomeruli and tubules) seen in majority of lesions.

The tumor usually presents as a large abdominal mass, which may extend across the midline and down into the pelvis. The patient may also present with fever and abdominal pain, with hematuria, or rarely, with intestinal obstruction as a result of pressure from the tumor.

The prognosis for Wilms tumor is generally very good, and excellent results are obtained with a combination of nephrectomy and chemotherapy.

Concept

- ***Anaplasia is an indicator of adverse prognosis*** because it is associated with p53 gene mutation and resistance to anti-cancer drugs.
- 11q/16q deletion or 1q gain of chromosome are also adverse factors
- If **nephrogenic rests** are present, it is associated with increased risk of **cancer** in **opposite kidney**.

Key Point

Triad of VHL syndrome = Cerebellar hemangioblastoma + Bilateral renal cell cancer + Retinal angiomatosis.

Renal Cell Carcinoma (Hypernephroma/Grawitz Tumor)

It is the **most common malignant cancer of the kidney** affecting the poles of the kidney (**more commonly upper pole**). Males are more frequently affected (M:F ratio is 2 to 3:1) in the age group of 6-7th decade.

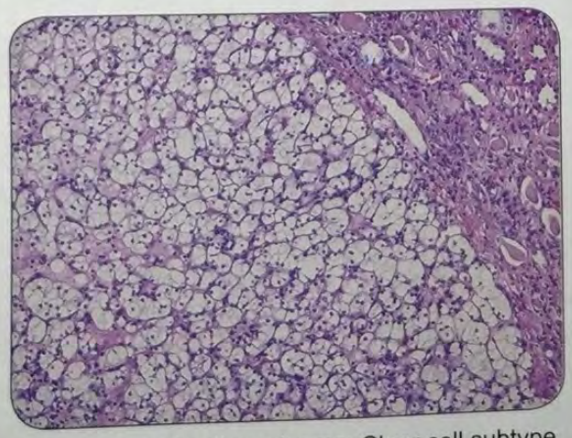


Fig. 11: Renal cell carcinoma: Clear cell subtype

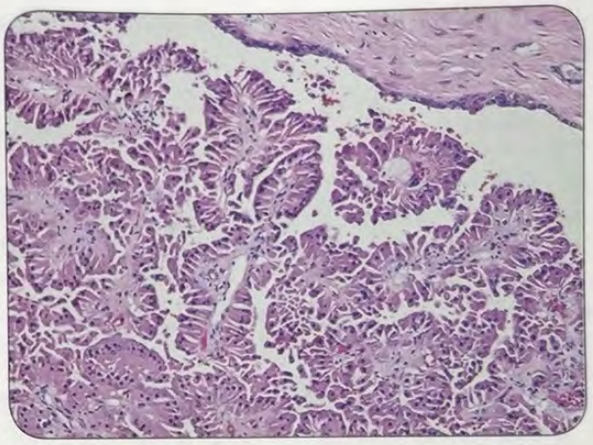


Fig. 12: Renal cell carcinoma: Papillary subtype

Recent Exam Question

- **Medullary cancer** of kidney is seen in **sickle cell trait** patients.

Risk factors

Nongenetic factors

- **Tobacco** (most important risk factor)[Q]
- Hypertension[Q]
- Obesity[Q]
- Tuberous sclerosis[Q]
- Estrogen therapy[Q]
- Asbestos exposure[Q]
- Chronic renal failure and acquired cystic disease[Q]
- Von Hippel Lindau syndrome

Genetic factors

- **Trisomy 7** shows increased expression of MET which is a proto-oncogene having tyrosine kinase receptor activity thereby resulting in development of **papillary type of renal cancer**.
- **t(X; 1)** causes translocation of PRCC gene to fuse with TFE-3 gene on X chromosome and fusion gene increases the risk of **papillary renal cell carcinoma** (PRCC) particularly in children.

- **Hereditary leiomyomatosis and renal cell cancer syndrome:** This autosomal dominant disease is caused by mutations of the *FH* gene, which expresses fumarate hydratase, and is characterized by *cutaneous and uterine leiomyomata and an aggressive type of papillary carcinoma* with increased propensity for metastatic spread.
- **Birt-Hogg-Dubé syndrome:** The autosomal dominant inheritance pattern of this disease is due to mutations involving the *BHD* gene, which expresses folliculin. The syndrome features a constellation of skin (fibrofolliculomas, trichodiscomas, and acrochordons), pulmonary (cysts or blebs), and renal tumors with varing histologies.
- ***Xp11 translocation carcinoma*** is a genetically distinct subtype of renal cell carcinoma. It often occurs in young patients and is defined by translocations of the *TFE3* gene located at Xp11.2 with other genes resulting in over expression of TFE3. The neoplastic cells consist of clear cytoplasm with a papillary architecture.

Renal cancer

Clear cell cancer
- ***Most common*** type[Q]
- Majority is sporadic (55% cases)
- **Deletion of** short arm ov chromosome 3 **(VHL gene)**[Q]
- Non papillary cells which have a clear or granular cytoplasm
- Arises from proximal tubular cells

Papillary cancer (chromophilic cancer)
- Renal cancer having papillary pattern of growth and presence of **psammoma bodies**[Q]
- Arises from distal convoluted tubules
- Are of two types

Sporadic	Familial
– **Trisomy 7, 16, 17**[Q]	– Trisomy 7[Q]
– Loss of Y patients	
– t(x;1) translocation in children	

Chromophobe cancer
- Cells having pale, eosinophilic cytoplasm with
- Presence of extreme **hypodiploidy**[Q] (due to loss of multiple chromosomes 1, 2, 6, 10, 13, 17, 21, Y)
- Arises from intercalated cell of collecting duct

Collecting duct carcinoma
- Also called **Bellini duct cancer**
- Least common renal cancer
- Arises from collecting duct cells in the medulla
- Cells have **prominent fibrotic stroma**[Q]

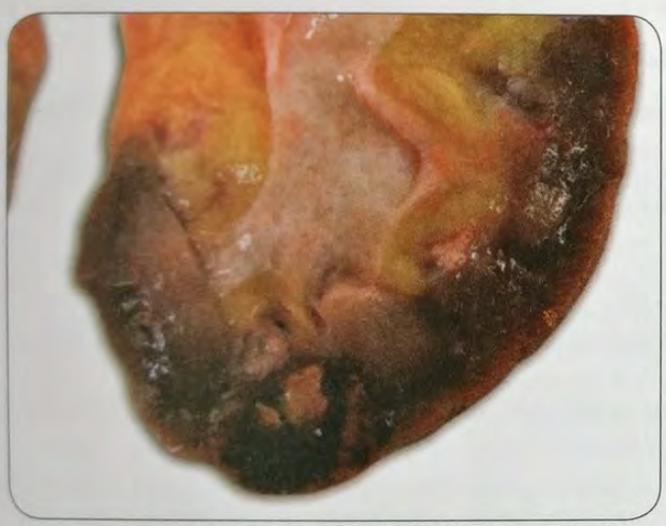


Fig. 13: Renal Cancer

Clinical features include the classical **triad**[Q] of *hematuria* (earliest and most common symptom[Q]; usually intermittent), *palpable mass and flank pain.*

Key Point

Sarcomatoid change in any renal cancer causes **worsening of prognosis**.

Paraneoplastic syndromes associated with RCC

- Elevation of erythrocyte sedimentation rate
- Polycythemia (Due to erythropoietin)
- Stauffer syndrome ***(non metastatic hepatic dysfunction)***
- Hypertension (Due to renin)
- Anemia and fever
- Hypercalcemia (Due to PTH related peptide)
- Cushing syndrome (Due to corticosteroid synthesis)
- Feminization or masculinization (Due to gonadotropin release)
- May also cause amyloidosis, eosinophilia or leukemoid reaction[Q]

Metastasis is usually by the hemotogenous route and the organs affected include **lungs**[Q] **(most common)**, bones, regional lymph nodes, liver, adrenals and brain.

Management: Partial/total nephrectomy is the **treatment of choice**.

Key Point

Papillary cancer is associated with a **strong tendency to invade the renal vein** and grow as solid column of cells. The tumor may *even extend to inferior vena cava and right side of the heart.*

URINARY BLADDER

It is the organ (lined by transitional epithelium) responsible for the collection of urine formed by the kidney and its removal by intermittent voiding.

Inflammation of urinary bladder is called **cystitis** and it is more common in females as compared to males. It is usually due to:

1. Bacterial cause: *E. coli, Proteus, Klebsiella, Mycobacterium tuberculosis*
2. Fungal cause: *Candida albicans,* seen with immunosuppression
3. Hemorrhagic cystitis: Due to cytotoxic antitumor drugs like cyclophosphamide and Adenovirus.
4. Radiation cystitis: Due to radiation exposure.

Clinical features:

1. ***Frequency*** – Requirement of urination every 15-20 minutes
2. ***Suprapubic pain*** – Pain in anatomical location of the bladder
3. ***Dysuria*** - Painful or burning sensation or urination

This triad may be associated with fever and malaise.

Special cystitis

Hunner ulcer	Malacoplakia
• Painful chronic cystitis associated with hemorrhagic inflammation and fibrosis of the layers of bladder wall[Q]. • Seen frequently in **females**. • Usually idiopathic but may be associated with **SLE**. • **Mast cells**[Q] are characteristically present.	• **Chronic bacterial cystitis** having presence of soft, yellow mucosal plaques. • Most commonly associated with ***E. coli*** or uncommonly **proteus**. • Microscopically, there is presence of infiltration with lymphocytes and abundant epithelioid histiocytes **(Von Hansemann Histiocytes)** having PAS positive granules and characteristics 3-10μ rounded intracytoplasmic inclusions (called **Michaelis-Gutmann** bodies)[Q] that contain iron (demonstrated by Prussian blue stain) **and calcium** (demonstrated by Von Kossa stain). • Similar lesions are also seen in colon, lungs, bones, kidneys and prostate, etc.

URINARY BLADDER NEOPLASMS

The urinary bladder cancers usually are of epithelial origin. The commonest histological variant is the transitional cell tumors (urothelial tumors).

Risk factors of urinary bladder cancers

Transitional cell cancers	Squamous cell cancer	Adenocarcinoma
• Cigarette smoking[Q]. • Industrial exposure to arylamines as 2-napthylamine, benzidine, aniline in textile workers, dye workers and leather workers[Q]. • Pelvic irradiation for other pelvic cancer[Q]. • Long term use of analgesics. • Exposure to drugs like cyclophosphamide[Q].	• Infection with ***Schistosoma haematobium***[Q]. • Chronic bladder infection and irradiation[Q]. • Diverticula in the bladder[Q].	• Usually arises from *urachal remnants*[Q] or in association with *intestinal metaplasia*[Q].

Genetic risk factors include:

- **9 p gene deletions-** Present in superficial papillary tumors.
- **17p gene deletion-** Invasive urothelial cancers.

9p and 9q have tumor suppressor gene, 17 p has the location of p53 (again tumor suppressor gene). So, any deletion of these genes increases the risk of bladder cancers.

CLINICAL FEATURES

Painless hematuria[Q] **(*most common symptom*)**, features of bladder irritability (frequency, urgency and dysuria) or uncommonly, hydronephrosis and pyelonephritis may also be seen.

The prognostic markers include grade of tumor, presence of lamina propria invasion and associated carcinoma *in situ*.

The worst prognosis is associated with tumor invading the muscularis mucosa (detrusor muscle)[Q].

Key Point

Involvement of the **detrusor muscle** is associated with the **worst prognosis**.

INVESTIGATIONS:

- ***Cystoscopy and biopsy***[Q] **(Best investigation)**
- Urine cytology of urine markers like telomerase, human complement factor H related protein, mucins, CEA, hyaluronic acid, hyaluronidase, fibrin-fibrinogen degradation products, nuclear matrix proteins and DNA content.

ISUP (International Society of Urological Pathology) Classification of Transitional Cell Tumors

- **Urothelial Papilloma** – Seen in young patients, finger like papillae covered with normal looking urothelium.
- **Urothelial neoplasm of low malignant potential** – Similar to papilloma but with thicker urothelium with diffuse nuclear enlargement.
- **Papillary urothelial carcinoma, low grade** – Almost always papillary having limited cell/nuclear pleomorphism and limited chromosomal/gene abnormalities.
- **Papillary urothelial carcinoma; high grade** – May be papillary/nodular or both having considerable anaplasia and high frequency of chromosomal/gene abnormalities.

Key Point

Mesenchymal tumors of urinary bladder

- MC benign tumor is Leiomyoma.
- MC sarcoma in infants/children: embryonal rhabdomyosarcoma.
- MC sarcoma in adults Leiomyosarcoma.

MANAGEMENT:

1. **Intravesical BCG**[Q]
   - Presence of lamina propria invasion
   - Carcinoma *in situ* (CIS)
2. **Radical cystectomy**
   - CIS refractory to BCG
   - Invasion of muscularis propria
   - CIS extending to prostatic urethra or down
3. **Chemotherapy (Mitomycin, thiotepa, etc.)**
   - Advanced bladder cancer

Multiple Choice Questions

KIDNEY: GENERAL ASPECTS, POLYCYSTIC KIDNEY DISEASE

1. A 28-year-old man has lenticonus and end stage renal disease now. His maternal uncle also died of the same illness. What is the most likely diagnosis?
(a) Autosomal dominant polycystic kidney disease
(b) Autosomal recessive polycystic kidney disease
(c) Oxalosis *(AIIMS Nov 2012)*
(d) Alport syndrome

2. Which one of the following is not associated with adult polycystic kidney disease? *(DPG 2011)*
(a) Autosomal dominant inheritance
(b) Mutations involving gene affecting cell-cell matrix interactions
(c) Intracranial berry aneurysm may be present
(d) Tricuspid valve prolapse

3. Which of the following is associated with adult polycystic kidney disease?
(a) Berry aneurysms of Circle of Willis
(b) Saccular aneurysms of aorta
(c) Fusiform aneurysms of aorta
(d) Leutic aneurysms

4. True about adult polycystic kidney disease is all, except: *(AIIMS Nov 2001)*
(a) Autosomal dominant inheritance
(b) Hypertension is rare
(c) Can be associated with cysts in liver, lungs and pancreas
(d) Pyelonephritis is common

5. True about autosomal dominant type of APKD:
(a) Small kidney *(PGI June 2004)*
(b) Bilateral medullary cysts
(c) Mutation of polycystin 1and 2 gene
(d) Renal transplantation is contraindicated
(e) Pathogenesis starts early and renal failure seen in middle life.

6. Chromosomes involved in adult polycystic kidney disease (APKD) are: *(PGI June 01)*
(a) 6 and 11 (b) 4 and 16
(c) 7 and 17 (d) 4 and 12
(e) 4 and 17

MOST RECENT QUESTIONS

7. Acquired cystic disease of kidney is associated with:
(a) Xanthogranulomatous pyelonephritis
(b) Dialysis
(c) Renal stones
(d) Renal dysplasia

8. Adult polycystic kidney disease is inherited by:
(a) Autosomal dominant
(b) Autosomal recessive
(c) X-linked
(d) Mitochondrial

9. Major cause of death in End Stage Renal Disease patients on display is which one of the following?
(a) Cardiovascular disease
(b) Infections
(c) Uremia
(d) Respiratory Failure

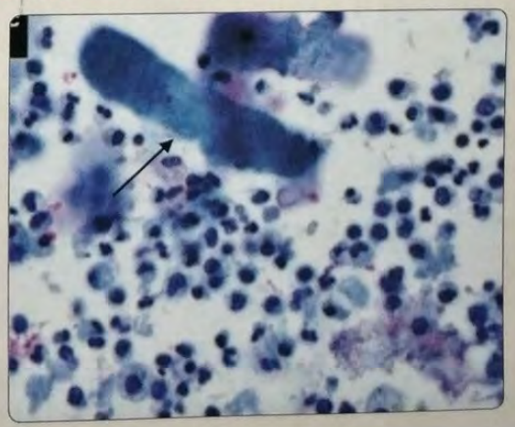
10. Podocytes are seen in:
(a) Proximal convoluted tubule
(b) Distal convoluted tubule
(c) Collecting tubule of the kidney
(d) Bowman's capsule

11. What is the minimum number of red blood cells per microliter of urine required for diagnosis of hematuria?
(a) 3 (b) 5
(c) 8 (d) 10

12. Polycystic kidney may be associated with cysts in all the sites, except:
(a) Lung (b) Liver
(c) Pancreas (d) Brain

13. What is oliguria
(a) Excretion of less than 300 ml in 24 hrs
(b) Excretion of less than 500 ml in 24 hrs
(c) Excretion of less than 300 ml in 12 hrs
(d) Excretion of less than 100 ml in 24 hrs

14. A postrenal transplant patient presented with decreased urine output. A urinalysis was done and the microscopic image is shown below. Identify the structure marked with an arrow: *(AIIMS Nov 2016)*



(a) Decoy cells
(b) Renal tubular epithelial cells
(c) Hyaline casts
(d) Clue cells

GLOMERULAR DISEASE: NEPHRITIC SYNDROME, NEPHROTIC SYNDROME, GLOMERULONEPHRITIS

15. In a specimen of kidney, fibrinoid necrosis is seen and onion peel appearance is also present. Most probable pathology is: *(AIIMS Nov 2012)*
(a) Hyaline degeneration
(b) Hyperplastic arteriosclerosis
(c) Glomerulosclerosis
(d) Fibrillary glomerulonephritis

16. Which of the following is the diagnosis for a condition having mutation in COL4A5 chain? *(AIIMS Nov 2012)*
(a) Alport's syndrome
(b) Good pasture's syndrome
(c) Thin membrane disease
(d) Nodular glomerulosclerosis

17. The most common gene defect in idiopathic steroid resistance nephrotic syndrome *(AIIMS Nov 2011)*
(a) ACE (b) NPHS 2
(c) HOX11 (d) PAX

18. A person with radiologically confirmed reflux nephropathy develops nephritic range proteinuria. Which of the following would be the most likely histological finding in this patient? *(AIIMS Nov 2011)*
(a) Focal segmental glomerulosclerosis
(b) Nodular glomerulosclerosis
(c) Membranous glomerulopathy
(d) Proliferative glomerulonephritis with crescents

19. A 7 yrs old girl is brought with complaints of generalised swelling of the body. Urinary examination reveals grade 3 proteinuria and the presence of hyaline and fatty casts. She has no history of hematuria. Which of the following statements about her condition is true? *(AIIMS May 2011)*
(a) IgA nephropathy is likely diagnosis
(b) Her C3 levels will be low
(c) No IgG deposits or C3 deposition on renal biopsy
(d) Alport syndrome is likely diagnosis

20. The pathological feature in Wegener's granulomatosis on renal biopsy is *(AIIMS Nov 2010)*
(a) Nodular glomerulosclerosis
(b) Focal necrotizing glomerulonephritis
(c) Granulomas in the vascular wall
(d) Granuloma of parenchyma of kidney

21. Fibronectin nephropathy has all of the following features except *(AIIMS Nov 2010)*
(a) Autosomal recessive inheritance
(b) Associated with mesangial expansion
(c) Glomeruli do not stain for immunoglobulin or complement
(d) PAS- positive amyloid negative deposits.

22. Pathological changes of diabetic nephropathy are all except: *(DPG 2011)*
(a) Fibrin caps and capsular drops
(b) Kimmelstein-Wilson lesion
(c) Basement membrane thickening
(d) Focal glomerular sclerosis

23. What is the cause of hypercoagulation in nephrotic syndrome: *(AI 2010)*
(a) Loss of antithrombin III (AT III)
(b) Decreased fibrinogen
(c) Decreased metabolism of vitamin K
(d) Increase in Protein C

24. Finnish type of nephrotic syndrome is associated with:
(a) Nephrin *(AI '09, '06)*
(b) Podocin
(c) Alpha actinin
(d) CD2 activated protein

25. Pauci-immune crescentic glomerulonephritis is associated with: *(AI 2009)*
(a) Microscopic polyangiitis
(b) SLE
(c) H S Purpura
(d) PAN

26. Most common mutation seen in congenital nephrotic syndrome is: *(AI 2008)*
(a) Nephrin
(b) Podocin
(c) α 4 actinin
(d) Megalin

27. Which of these does not cause crescentic glomerulonephritis? *(AI 2008)*
(a) Rapidly progressive glomerulonephritis
(b) Alport syndrome
(c) Goodpasture's syndrome
(d) Henoch-Schönlein purpura

28. All are non-proliferative glomerulonephritis, except:
(a) Membranous glomerulonephritis *(AI 2008)*
(b) Mesangiocapillary glomerulonephritis
(c) Diabetic glomerulosclerosis
(d) Amyloidosis

29. Kidney biopsy from a child with hemolytic uremic syndrome characteristically most likely presents features of: *(AI 2005)*
(a) Thrombotic microangiopathy
(b) Proliferative glomerulonephritis
(c) Focal segmental glomerulosclerosis
(d) Minimal change disease

30. Serum C3 is persistently low in the following except:
(a) Post streptococcal glomerulonephritis
(b) Membranoproliferative glomerulonephritis
(c) Lupus nephritis *(AI '04, DNB '07)*
(d) Glomerulonephritis related to bacterial endocarditis

31. All of the following are associated with low complement levels except: *(AI 2004)*
(a) Lupus nephritis
(b) Mesangiocapillary glomerulonephritis
(c) Diarrhea-associated hemolytic uremic syndrome
(d) Post-infections glomerulonephritis

32. All of the following are associated with low C3 level except: *(AI 2003)*
(a) Post streptococcal glomerulonephritis
(b) Membranoproliferative Glomerulonephritis
(c) Goodpasture's disease
(d) Systemic lupus erythematosus

33. Which of the following is not true about Berger's disease? *(AI 2003)*
(a) The pathological changes are proliferative and usually confined to mesangial cells; usually focal and segmental
(b) Hematuria may be gross or microscopic
(c) On immunofluorescence deposits contain with IgA and IgG
(d) Absence of associated proteinuria is pathognomic

34. Crescent formation is characteristic of which of the following glomerular disease: *(AI 2002)*
(a) Minimal change disease
(b) Rapidly progressive glomerulonephritis
(c) Focal and segmental glomerulosclerosis
(d) Rapidly non progressive glomerulonephritis

35. In Wegener's granulomatosis, kidney has which of the following lesions? *(AIIMS Nov 2009)*
(a) Glomerular granuloma
(b) Interstitial granuloma
(c) Crescentic glomerulonephritis
(d) Glomerulosclerosis

36. The Electron Microscopy is virtually diagnostic in renal biopsy study of: *(AIIMS May 2008)*
(a) Goodpasture's syndrome
(b) Churg-Strauss syndrome
(c) Alport syndrome
(d) Wegner's granulomatosis

37. Which type of FSGS has worst prognosis? *(AIIMS May 2008)*
(a) Tip variant (b) Collapsing
(c) NOS (d) Perihilar

38. Steroid resistant nephrotic syndrome is caused due to mutation in the gene encoding for? *(AIIMS May 2008, Nov 2006)*
(a) Nephrin
(b) Alpha-actinin-4
(c) Podocin
(d) Transient Receptor Potential 6

39. Which of the following is a feature of Collapsing glomerulopathy? *(AIIMS Nov '07)*
(a) Tuft necrosis
(b) Mesangiolysis
(c) Parietal epithelial proliferation
(d) Hypertrophy and necrosis of visceral epithelium

40. The most common gene defect in idiopathic steroid resistant nephrotic syndrome *(AIIMS May 2007)*
(a) ACE (b) NPHS 2
(c) HOX 11 (d) PAX

41. HIV associated nephropathy is a type of:
(a) Membranous glomerulonephritis *(AIIMS Nov 2004)*
(b) Immunotactoid glomerulopathy
(c) Collapsing glomerulopathy
(d) Fibrillary glomerulopathy

42. Mesangial deposits of monoclonal kappa/Lambda light chains in indicative of *(AIIMS May 2004)*
(a) Mesangioproliferative glomerulonephritis
(b) Focal and segmental glomerulosclerosis
(c) Kimmelstiel-Wilson lesions
(d) Amyloidosis

43. In renal disease, Albumin is first to appear in urine because *(AIIMS May 2004)*
(a) Of its high concentration in plasma
(b) Has molecular weight slightly greater than the molecules normally getting filtered
(c) High Albumin Globulin ratio
(d) Tubular epithelial cells are sensitive to albumin

44. A 7 year old boy presented with generalized edema. Urine examination revealed marked albuminuria. Serum biochemical examinations showed hypoalbuminemia with hyperlipidemia. Kidney biopsy was undertaken. On light microscopic examination, the kidney appeared normal. Electron microscopic examination is most likely to reveal: *(AIIMS Nov 2003)*
(a) Fusion of foot processes of the glomerular epithelial cells
(b) Rarefaction of glomerular basement membrane
(c) Deposition of electron dense material in the basement membrane
(d) Thin basement membrane

45. The prognosis of rapidly proliferating glomerulonephritis (Crescentic GN) depends upon
(a) Number of crescents *(AIIMS Nov 2001)*
(b) Size of crescents
(c) Shape of crescents
(d) Cellularity of crescents

46. True about light microscopy in minimal change disease is: *(AIIMS Nov 2001)*
(a) Loss of foot process seen
(b) Anti-GBM antibodies are seen
(c) IgA deposits seen
(d) No change seen

47. A child presented with edema, massive proteinuria and hyperlipidemia. True statment about this condition is:
(a) A type of focal segmental GN *(AIIMS Nov 2001)*
(b) IgA deposition on basement membrane
(c) Foot process of glomerular membrane normal
(d) Glomerular function is lost due to loss of polyanionic charge on both sites of glomerular foot process

48. Persistent low C3 complement level is not found in: *(AIIMS Nov 2006)*
(a) Post streptococcal glomerulonephritis
(b) Mesangiocapillary glomerulonephritis
(c) Cryoglobulinemia
(d) SLE

49. Low complement levels are seen in:
(a) PSGN *(PGI Dec 2006)*
(b) MPGN
(c) Goodpasture's syndrome
(d) Wegener's granulomatosis
(e) Infective endocarditis.

50. Subepithelial deposits in kidney are seen in:
(a) MPGN-1 *(PGI June 2001)*
(b) Goodpasture's syndrome
(c) PSGN
(d) Membranous GN
(e) RPGN

51. Nephrotic syndrome is characterized by: *(PGI Dec 2002)*
(a) Proteinuria (b) Hyperlipidemia
(c) Edema (d) Haematuria
(e) Lipiduria

52. In glomerular disease which of the following is mainly excreted in urine: *(PGI Dec 2003)*
(a) Albumin (b) Globulin
(c) Light chain (d) Heavy chain
(e) Tamm-Horsfall protein

53. Which of the following is included in definition of Nephrotic syndrome? *(PGI June 2004)*
(a) Microalbuminuria
(b) Massive Proteinuria
(c) Microscopic hematuria
(d) Edema
(e) Hyperlipidemia.

54. True about Heymann rat glomerulonephritis is: *(PGI Dec 2004)*
(a) Heymann antigen is called megalin
(b) Electron dense deposits in subendothelial space
(c) Electron dense deposits in mesangium
(d) Subepithelial aspect of basement membrane have deposits
(e) Antigen against bacterial and viral proteins

55. Malignant hypertension is associated with:
(a) RPGN *(PGI Dec 2004)*
(b) Malignant nephrosclerosis
(c) Membranous GN
(d) IgA nephropathy
(e) Acute pyelonephritis

56. Histology of Alport syndrome: *(PGI June 2005)*
(a) Foamy cells in interstitium
(b) Foamy cells in tubular epithelial cells
(c) Thickening of GBM > 100 nm
(d) Thinning of GBM < 100 nm
(e) Intimal proliferation.

57. RPGN is caused by: *(PGI June 2005)*
(a) FSGS
(b) Wegener's granulomatosis
(c) Goodpasture's syndrome
(d) PAN
(e) Microscopic polyangiitis

58. Post streptococcal glomerulonephritis is associated with: *(PGI Dec 2006)*
(a) Subepithelial deposit
(b) Nephritis along with acute renal failure
(c) Low complement levels
(d) HTN and proteinuria
(e) Normal complement levels

59. Pauci-immune glomerulonephritis is seen in:
(a) RPGN *(Delhi PG-2007)*
(b) IgA nephropathy
(c) Microscopic polyangiitis
(d) FSGS

60. Kimmelstiel Wilson lesions are characteristic of:
(a) Diabetic Nephropathy *(Delhi PG-2007)*
(b) Analgesic nephropathy
(c) RPGN
(d) Post streptococcal glomerulonephritis

61. Anti-glomerular basement membrane nephritis is seen in: *(Delhi PG-2005)*
(a) Goodpasture's syndrome
(b) SLE associated glomerulopathy
(c) MGN
(d) MPGN

62. Kimmelstiel Wilson disease is diagnostic of:
(a) Diabetic Glomerulosclerosis *(Delhi PG-2005)*
(b) Benign Hypertension
(c) Malignant Hypertension
(d) Amyloidosis

63. The following is not a feature of acute post streptococcal glomerulonephritis: *(Karnataka 2007)*
(a) Normal C3
(b) Hypertension
(c) Elevated blood urea and creatinine
(d) Increased ASO titre

64. **Visceral leishmaniasis causes** *(Karnataka 2005)*
(a) Membranous glomerulonephritis
(b) Mesangioproliferative glomerulonephritis
(c) Focal segmental glomerulonephritis
(d) Rapidly progressive glomerulonephritis

65. **Histological hallmark of rapidly progressive glomerulonephritis is** *(Karnataka 2004)*
(a) Crescents in most of the glomeruli
(b) Loss of foot processes of epithelial cells
(c) Subendothelial electron dense deposits
(d) The thickening of glomerular capillary wall

66. **ANCA is most specific and sensitive marker for**
(a) Idiopathic cresenteric glomerulonephritis *(UP 2000)*
(b) Post streptococcal glomerulonephritis
(c) Membranoproliferative glomerulonephritis
(d) Focal segmental glomerulosclerosis

67. **True about post streptococcal glomerulonephritis is:**
(a) Linear deposition *(UP 2001)*
(b) Diffuse involvement
(c) Tram track appearance
(d) Global sclerosis

68. **Most common in diabetic nephropathy is:**
(a) Diffuse glomerulosclerosis *(UP 2002)*
(b) Diffuse cortical sclerosis
(c) Nodular glomerulosclerosis
(d) Renal atherosclerosis

69. **Steroid responsive glomerulonephritis are all except:**
(a) Post streptococcal glomerulonephritis *(UP 2002)*
(b) Minimal change disease
(c) Membranoproliferative glomerulonephritis
(d) Focal segmental glomerulosclerosis

70. **All conditions lead to CRF except:** *(UP 2002)*
(a) Post streptococcal GN
(b) Membranoproliferative GN
(c) Minimal change GN
(d) Focal glomerulosclerosis

71. **Most characteristic finding in diabetic nephropathy is:**
(a) Diffuse glomerulosclerosis *(UP-2002, 2004)*
(b) Nodular glomerulosclerosis
(c) Diffuse cortical sclerosis
(d) Renal atherosclerosis

72. **All of the following are seen in Goodpasture's syndrome except:** *(PGI-1999)(UP 2004)*
(a) Cresenteric glomerulonephritis
(b) Hemorrhage inflammation
(c) Anti-GBM antibody
(d) Diffuse alveolar involvement

73. **All of the following are True about minimal change nephrotic disease except:** *(PGI-1999) (UP 2004)*
(a) Respond to steroids
(b) Selective proteinuria
(c) IgG deposition in mesangium
(d) Common in the age group of 2-9 years

MOST RECENT QUESTIONS

74. **IgA depositions in mesangial cells are seen in**
(a) Goodpasture's syndrome
(b) Berger disease
(c) Cresenteric glomerulonephritis
(d) Alport syndrome

75. **All are causes of rapidly progressive glomerulonephritis except:**
(a) SLE
(b) Polyarteritis nodosa
(c) Post streptococcal GN
(d) Rheumatoid arthritis

76. **The cause of edema in nephritic syndrome is:**
(a) Decrease in plasma protein concentration *(UP 2007)*
(b) Increase in plasma protein concentration
(c) Reduced plasma osmotic pressure
(d) Sodium and water retention

77. **Hall mark of the IgA nephropathy is:**
(a) Oedema
(b) Hematuria
(c) Hypertension
(d) Proteinuria

78. **Electron dense deposits in the region of hyalinosis and sclerosis, with diffuse loss of foot processes, seen in electron microscopy are features of:**
(a) Minimal change disease
(b) Membranous glomerulonephritis
(c) Membranoproliferative GN
(d) Focal segmental glomerulosclerosis

79. **In hemolytic uremic syndrome there is:**
(a) Thrombocytopenia + Renal failure
(b) Normal coagulative profile
(c) Microangiopathic hemolytic anemia
(d) All of the above

80. **Subepithelial deposits with 'M' spike is seen in:**
(a) Membranous glomerulonephritis
(b) Membranoproliferative glomerulonephritis
(c) Minimal change disease
(d) RPGN

81. **Crescentic glomerulonephritis with pauci-immune glomerulonephritis is associated with:**
(a) Post infectious glomerulonephritis
(b) Goodpasture's syndrome
(c) Wegener's glomerulonephritis
(d) Membranous glomerulonephritis

82. **Tram track appearance on histopathology of kidney is seen in:**
(a) Membranous nephropathy
(b) Membranoproliferative glomerulonephritis
(c) IgA nephropathy
(d) Crescentic glomerulonephritis

83. On electron microscopy, in most of the cases, characteristic splitting of GBM with subepithelial deposits in few cases is seen in:
(a) RPGN
(b) Membranous nephropathy
(c) FSGS
(d) Minimal change disease

84. An IV drug abuser Chulbul develops an aggressive form of nephrotic syndrome that does not respond to steroids. A renal biopsy is performed. Which of the following histological diagnoses will most likely be made from the biopsy tissue?
(a) Focal segmental glomerulosclerosis
(b) IgA nephropathy
(c) Membranous glomerulonephritis
(d) Membranoproliferative glomerulonephritis

85. Crescents are derived from which of the following?
(a) Epithelial cells + fibrin + macrophage
(b) Mesangial cell + fibrin + macrophage
(c) Tubular cell + mesangial cell + fibrin
(d) Neutrophil + tubular cell + fibrin

86. Flea bitten appearance of the kidney is seen in:
(a) Malignant hypertension
(b) Benign hypertension
(c) Chronic pyelonephritis
(d) Diabetes mellitus

87. All of the following decrease in Nephrotic syndrome except:
(a) Thyroxin (b) Transferrin
(c) Fibrinogen (d) Albumin

88. Most common cause of nephrotic syndrome in adults is:
(a) Membranous glomerulonephritis
(b) Minimal change disease
(c) Acute GN
(d) Focal segmental glomerulosclerosis

89. The crescent forming glomerulonephritis is:
(a) Acute GN
(b) Rapidly progressive glomerulonephritis
(c) Membranous GN
(d) Membranoproliferative GN

90. Most common cause of nephritic syndrome in adults is:
(a) Berger disease
(b) Focal segmental glomerulosclerosis
(c) Membranous glomerulonephritis
(d) Minimal change disease

91. Post streptococcal glomerulonephritis in children is diagnosed by:
(a) Heavy protienuria, high cholesterol, high ASO titre
(b) Heavy protienuria, hematuria, low ASO titre
(c) Mild proteinuria, hematuria, high ASO titre
(d) Mild protienuria, high cholesterol, normal ASO titre

92. IgA nephropathy is characterized by all of the following except:
(a) Hypertension
(b) Hematuria
(c) Nephritic syndrome
(d) Renal biopsy having thin basement membrane

93. Microalbuminuria is defined as protein levels of:
(a) 100-150 mg/d (b) 151-200 mg/d
(c) 30-300 mg/d (d) 301-600 mg/d

94. Type I membranoproliferative glomerulonephritis is commonly associated with all except:
(a) SLE
(b) Persistent hepatitis C infections
(c) Partial lipodystrophy
(d) Neoplastic diseases

95. RBC cast seen in:
(a) Minimal change disease
(b) Renal vein thrombosis
(c) Bladder schistomiasis
(d) Rapidly progressive glomerulonephritis

96. Most common glomerulonephritis associated with HIV is which of the following?
(a) Focal segmental glomerulonephritis
(b) Diffuse glomerulosclerosis
(c) Membrano-proliferative glomerulonephritis
(d) Crescentic glomerulonephritis

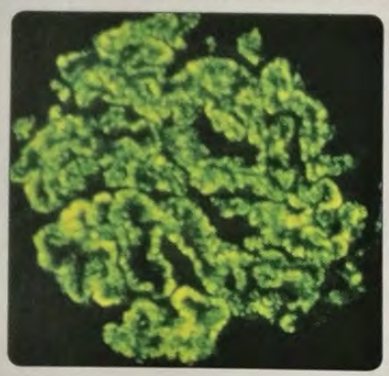
97. In which one of the primary glomerulonephritis the glomeruli are normal by light microscopy but shows loss of foot processes of the visceral epithelial cells and no deposits by electron microscopy
(a) Poststreptococcal glomerulonephritis
(b) Membrano-proliferative glomerulonephritis type I
(c) IgA nephropathy
(d) Minimal change disease

98. A 10-year-old child presented with edema and decreased urine output. On evaluation, serum albumin is 2.5 g/dL, S.Creatinine is 0.5 mg/dL, Urine protein is 3+ with no RBC or casts. The expected pathological change is:
(a) Interstitial nephritis
(b) Minimal change disease
(c) IgA nephropathy
(d) Membranous nephropathy

99. Which of the following is the commonest nephropathy seen in a patient with cancer?
(a) Minimal change disease
(b) IgA nephropathy
(c) Membranous glomerulopathy
(d) Focal segmental glomerulosclerosis

100. Most consistent feature of RPGN is: *(AIIMS Nov 2016)*
(a) IgA deposition
(b) Mesangial cell proliferation
(c) Crescent formation
(d) Loss of foot processes

101. The following is the FITC for IgG stained kidney specimen. What is this suggestive of?*(AIIMS May 2016)*



(a) SLE
(b) Berger's disease
(c) Membranous glomerulopathy
(d) Good Pasture Syndrome

102. Increased BP, proteinuria, urinary RBC casts are the features of which of the following type of glomerulonephritis?
(a) Membranous GN
(b) RPGN
(c) Minimal change disease
(d) Focal segmental glomerulosclerosis

103. True about Henoch Schonlein purpura is:
(a) Medium vessels vasculitis
(b) Renal symptoms start late in the disease
(c) IgA deposition in mesangium
(d) Low platelet count

104. Granular IgA deposits are seen in which of the following renal conditions?
(a) Minimal change disease
(b) Chronic pyelonephritis
(c) Haemolytic uremic syndrome
(d) Berger's nephropathy

105. IgA nephropathy is not associated with:
(a) Focal mesangial proliferation
(b) Gross hematuria within 1-2 days
(c) On immunofluorescence deposits contain both IgA and IgG
(d) Increased complement levels

106. Alport syndrome is characterized by all except:
(a) X-linked
(b) Cardiac hypertrophy
(c) Nerve deafness
(d) Glomerulonephritis

107. Characteristic feature of IgA nephropathy:
(a) More common in old age
(b) It is a type of membranoproliferative glomerulonephritis
(c) Serum complement level is normal
(d) Gross hematuria is present after 10 days

108. Which of the following is not seen in SLE affected kidneys?
(a) Focal glomerulonephritis
(b) Diffuse glomerulonephritis
(c) Membranous glomerulonephritis
(d) Lipoid nephrosis

TUBULAR DISEASE AND RENAL CALCULI

109. A lady presents with complaints of abdominal pain. Contrast enhanced CT scan shows bilateral papillary necrosis. Which of the following test shall not be done to investigate the cause of her papillary necrosis?
(a) Culture for bacteria *(AIIMS Nov 2011)*
(b) Sickling test
(c) Urine acidification
(d) Urine PCR for TB

110. Urine analysis of a patient with haematuria and hypercalciuria is most likely to reveal which of the following? *(AIIMS Nov 2011)*
(a) Isomorphic RBCs
(b) RBC casts
(c) Nephrotic range proteinuria
(d) Eosinophiluria

111. All of the following about xanthogranulomatous pyelonephritis are true except*(AI 2011, AIIMS May 2010)*
(a) On cut section yellowish nodules are seen
(b) Associated with tuberculosis.
(c) Foam cells are seen
(d) Giant cells are seen

112. In which of the following conditions bilateral contracted kidneys are characteristically seen?
(a) Amyloidosis *(AI 2005)*
(b) Diabetes mellitus
(c) Rapidly progressive glomerulonephritis
(d) Benign nephrosclerosis

113. Necrotizing papillitis may be seen in all of the following conditions except: *(AI 2002)*
(a) Sickle cell disease
(b) Tuberculous pyelonephritis
(c) Diabetes mellitus
(d) Analgesic nephropathy

114. Mercury affects which part of the kidney?
(a) PCT (b) DCT *(AIIMS May 2007)*
(c) Collecting duct (d) Loop of Henle

115. Nephrocalcinosis is seen in all except: *(AIIMS May 2007)*
(a) Sarcoidosis
(b) Distal RTA
(c) Milk alkali syndrome
(d) Medullary cystic kidney

116. Pulmonary, renal syndrome is seen in: *(PGI Dec 2003)*
(a) Goodpasture's syndrome
(b) Leptospirosis.
(c) Legionella.
(d) Wegener's granulomatosis.
(e) Hanta virus infection

117. Renal papillary necrosis is seen in: *(PGI June 2001)*
(a) Thalassemia
(b) DM
(c) Phenacetin abuse
(d) Alcoholism
(e) Cortical necrosis

118. Causes of Nephrocalcinosis are: *(PGI June 2001)*
(a) Hyperparathyroidism
(b) TB Kidney
(c) Hypercalcemia
(d) Glomerulonephritis
(e) MCD

119. Bilaterally enlarged kidneys are seen in: *(PGI Dec 2002)*
(a) Chronic glomerulonephritis
(b) Chronic pyelonephritis
(c) Benign nephrosclerosis
(d) Polycystic Kidney disease
(e) Amyloidosis

120. Hereditary nephritis is seen in: *(PGI Dec 2003)*
(a) Analgesic nephropathy
(b) Balkan nephropathy
(c) Alport's syndrome.
(d) Eosinophilic nephritis

121. Nephrocalcinosis is seen in: *(PGI June 2004)*
(a) Hypoparathyroidism
(b) Medullary sponge kidney
(c) DM
(d) RTA

122. Histology of acute rejection of renal transplant are: *(PGI June 2005)*
(a) Arteriolar hyalinosis
(b) Eosinophilic infiltration
(c) Glomerular vasodilatation
(d) Neutrophilic infiltration
(e) Necrotizing vasculitis.

123. Which of the following is seen in hemolytic uremic syndrome? *(Delhi PG-2007)*
(a) Spherocytes (b) Schistocytes
(c) Target cells (d) Heinz bodies

124. All are true about nephronophthisis except: *(Delhi PG-2006)*
(a) Interstitial fibrosis
(b) Cortical tubular hypertrophy
(c) Cysts in the medulla
(d) 20% cases are non-familial

125. Most common cause of papillary necrosis is: *(Delhi PG-2005)*
(a) Diabetes Mellitus
(b) Acute Pyelonephritis
(c) Sickle cell disease
(d) Analgesic Nephropathy

126. Renal calculi are commonly made up of *(Karnataka 2006)*
(a) Calcium oxalate
(b) Magnesium ammonium phosphate
(c) Uric acid
(d) Cystine

127. Salt losing nephritis is due to *(UP 2000)*
(a) Lupus nephritis
(b) Streptococcal infection
(c) Interstitial nephritis
(d) Goodpasture's syndrome

MOST RECENT QUESTIONS

128. Most common cause of renal papillary necrosis is:
(a) Analgesic nephropathy
(b) Sickle cell disease
(c) Diabetes mellitus
(d) Chronic pyelonephritis

129. Tubulointerstitial disease are all except:
(a) Hypokalemic nephropathy
(b) Lupus nephritis
(c) Hypercalcemic nephropathy
(d) Analgesic nephropathy

130. Renal pathology in SLE includes all except:
(a) Focal glomerulonephritis
(b) Diffuse glomerulonephritis
(c) Diffuse membranous glomerulonephritis
(d) Lipoid nephrosis

131. Pathologic feature of malignant hypertension is:
(a) Fibrinoid necrosis
(b) Papillary necrosis
(c) Hard exudate
(d) All

132. Contracted kidneys are seen in all of the following diseases except:
(a) Chronic glomerulonephritis
(b) Chronic renal failure
(c) Amyloidosis
(d) Analgesic nephropathy

133. Hematuria with dysmorphic RBC are seen in:
(a) Acute glomerulonephritis
(b) Renal TB
(c) Renal Calculi
(d) Chronic renal failure

134. **Birefringent crystals in urine is seen with:**
(a) Calcium oxalate stone (b) Uric acid stone
(c) Struvite stones (d) None

135. **Anti-GBM antibodies are seen in:**
(a) Goodpasture's syndrome
(b) RPGN
(c) Membranous GN
(d) Minimal change disease

136. **A 28 year young female Katrina present to your OPD with complaints of suprapubic pain, urinary frequency and dysuria. She also passed blood in last voided urine about 30 minutes ago. Her urinanalysis demonstrate the presence of pyuria but no white cell casts. On physical examination, she has suprapubic tenderness on palpation. Which of the following is the likely diagnosis in this patient?**
(a) Acute pyelonephritis
(b) Chronic pyelonephritis
(c) Cystitis
(d) Fanconi syndrome

137. **A 51-year-old man Sonu with a history of recurrent calcium-containing renal stones presents to the emergency room with excruciating flank pain and blood in the urine. This patient is likely to have which of the following underlying disorders?**
(a) Anemia of chronic disease
(b) Chronic Proteus infection
(c) Hyperparathyroidism
(d) Hyperaldosteronism

138. **Renal papillary necrosis is almost always associated with one of the following conditions:**
(a) Diabetes mellitus
(b) Analgesicnephropathy
(c) Chronic pyelonephritis
(d) Post streptococcal GN

139. **All are causes of granular contracted kidneys except:**
(a) Benign nephrosclerosis
(b) Diabetes mellitus
(c) Chronic Pyelonephritis
(d) Chronic glomerulonephritis

140. **Alports syndrome is inherited by al the following inheritances except**
(a) X linked (b) Codominant
(c) AD (d) AR

141. **Nephrocalcinosis is seen in which one of the following?**
(a) Hyperparathyroidism
(b) Diabetes mellitus
(c) Amyloidosis kidney
(d) End stage kidney

142. **Thimble bladder is typically seen in which one of the following?**
(a) Acute bacterial cystitis
(b) Tuberculous cystitis
(c) Bilharziasis
(d) Transitional cell carcinoma

143. **Periglomerular fibrosis is considered typical of:**
(a) Chronic pyelonephritis
(b) Chronic glomerulonephritis
(c) Arterionephrosclerosis
(d) Malignant hypertension

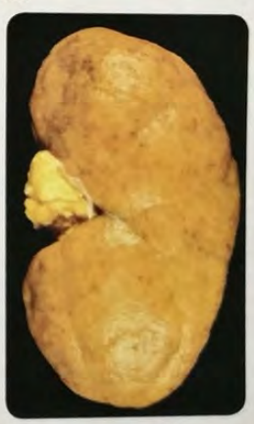
144. **Which of the following increases tuberculosis?**
(a) Asbestosis (b) Sarcoidosis
(c) Silicosis (d) Berylliosis

145. **Which one of the following statements is incorrect regarding uric acid stones?**
(a) They are radiolucent
(b) Crystals are hexagonal
(c) Formed in acidic urine
(d) Can be seen with normouricemia

146. **Characteristic histopathological feature of kidney in DM?**
(a) Nodular glomerulosclerosis
(b) Fibrin cap
(c) Papillary necrosis
(d) Diffuse glomerulosclerosis

147. **Marker of acute kidney injury includes all of the following except:**
(a) Cystatin C (b) N GAL
(c) KIM 1 (d) Micro RNA-122

148. **The resected specimen of a kidney is seen below. What is the diagnosis?** *(AIIMS May 2016)*



(a) Amyloidosis
(b) Acute post-streptococcal glomerulonephritis
(c) Flea bitten kidney of malignant hypertension
(d) Chronic glomerulonephritis

149. **Histological feature of acute pyelonephritis include all of the following except:**
(a) Interstitial suppurative inflammation
(b) Tubular necrosis
(c) Intratubular aggregates of neutrophils
(d) Hypercellular glomeruli

150. Renal papillary necrosis is seen in all except:
(a) Urinary tract infection
(b) Hypertension
(c) Diabetes mellitus
(d) Chronic alcohol use

151. Irregular scarred kidney with pelvic dilation is seen with:
(a) Chronic pyelonephritis
(b) Polycystic kidney
(c) Renal artery stenosis
(d) Tuberculosis of kidney

RENAL TUMOURS: RCC, WILM'S TUMOUR

152. Which of the following is not associated with renal cell carcinoma? *(AIIMS May 2011)*
(a) Polycythemia
(b) Amyloidosis
(c) Cushing's syndrome
(d) Hypertension

153. Wilm's tumor is associated with all of the following except *(AIIMS May 2010)*
(a) Hemihypertrophy
(b) Aniridia
(c) Hypertension
(d) Bilateral polycystic kidney

154. The cytogenetics of chromophilic renal cell carcinoma is characterized by: *(AI 2010)*
(a) Mutant VHL gene
(b) Loss of 3p
(c) Trisomy 7/17
(d) Loss of 5q 3

155. The most common histological variant of renal cell carcinoma is *(AIIMS Nov 2005)*
(a) Clear cell type (b) Chromophobe type
(c) Papillary type (d) Tubular type

MOST RECENT QUESTIONS

156. In which of the following conditions, Aniridia and Hemi-hypertrophy are most likely present
(a) Neuroblastoma
(b) Wilm's tumor
(c) Non-Hodgkin's lymphoma
(d) Germ cell tumor

157. In Wilm's tumor the following leads to emergence of resistance to chemotherapy:
(a) Nephrogenic rests
(b) Monophasic morphology
(c) Anaplasia
(d) Capsular infiltration

158. True statement regarding Wilm's tumour is:
(a) Common in adult
(b) Associated with deletion of chromosome 11p13
(c) Associated with MIC-2 genes
(d) Commonest presentation is hematuria

159. Most common histological type of renal cell carcinoma is:
(a) Clear cell (b) Medullary
(c) Papillary (d) Mixed type

160. Oncocytic carcinoma arises from:
(a) Perivascular tissue
(b) Glomerulus
(c) Loop of henle
(d) Collecting duct

161. Gene for Wilm's tumour is located on which of the following?
(a) Chromosome 1 (b) Chromosome 10
(c) Chromosome 11 (d) Chromosome 12

162. Most important prognostic factor of wilms tumour:
(a) Histopathology and ploidy of cells
(b) Tumour stage
(c) Age of patient
(d) Mutation of chromosome 1p

163. Deletion of short arm of chromosome 11 is seen in:
(a) Osteosarcoma (b) Meningioma
(c) Wilm's tumor (d) Colon Carcinoma

164. Percentage of renal vein involvement in renal cell carcinoma is:
(a) 2% (b) 8%
(c) 16% (d) 32%

165. All are true about renal cell cancer except:
(a) Invades renal vein
(b) Hematuria may occur
(c) Arises from proximal convoluted tubule
(d) More common in females

166. VHL syndrome is associated most commonly with which carcinoma?
(a) Lung carcinoma
(b) Renal cell carcinoma
(c) Endometrial carcinoma
(d) Hepatocellular carcinoma

167. Pseudohermaphroditism is seen with which tumor?
(a) RCC (b) Wilms tumor
(c) Carcinoma lung (d) HCC

URINARY BLADDER DISEASE

168. Michaelis Gutmann bodies are seen in
(a) Xanthogranulomatous pyelonephritis
(b) Malacoplakia
(c) Nail patella syndrome
(d) Tubercular cystitis

169. **Chronic urethral obstruction due to benign prostatic hyperplasia can lead to the following change in kidney parenchyma**
(a) Hyperplasia (b) Hypertrophy
(c) Atrophy (d) Dysplasia

MOST RECENT QUESTIONS

170. **Michaelis Guttmann bodies are present in:**
(a) Analgesic nephropathy
(b) Homman's ulcer
(c) Malacoplakia
(d) Erythroplasia

171. **Bence Jones proteins are:**
(a) Light chain (b) Heavy chain
(c) Medium chain (d) All

172. **Transitional cell carcinoma bladder is associated with which of the following?**
(a) Schistosomiasis (b) Ascariasis
(c) Malaria (d) Any of the above

173. **Metabolic complication in CRF include all of the following except**
(a) Hyperkalemia
(b) Hypophosphatemia
(c) Hypocalcemia
(d) Hypokalemia

174. **Mutation of which gene leads to urinary bladder carcinoma?**
(a) p53
(b) p7
(c) n-myc
(d) BRCA1

175. **Gene associated with superficial papillary urothelial neoplasm:**
(a) p53
(b) p16
(c) p7
(d) KRAS

176. **Schistosomiasis causes which type of bladder cancer:**
(a) Squamous cell carcinoma
(b) Transitional cell carcinoma
(c) Adenocarcinoma
(d) Both a and b

177. **Most common type of rhabdomyosarcoma is:**
(a) Pleomorphic
(b) Embryonal
(c) Alveolar
(d) Botryoid

Explanations

1. **Ans. (d) Alport's syndrome** *(Ref: Robbins 8th/931-2)*
Presentation of male patient with lenticonus and end stage renal disease with a family history of renal disease is highly suggestive of Alport syndrome.
   - AR polycystic kidney is ruled out because the age of presentation in ARPKD is childhood and most of the affected children do not survive beyond their childhood.
   - AD polycystic kidney is ruled out because there is no association of ADPKD with lenticonus as is mentioned in our question.

   > – *Alport syndrome is manifest by hematuria with progression to chronic renal failure, accompanied by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts, and corneal dystrophy.*

2. **Ans. (d) Tricuspid valve prolapse**
(Ref: Robbins 8th/959 9/e p947)
Mitral valve prolapse (and not tricuspid valve prolapse) and other cardiac valvular anomalies occur in 20% to 25% of patients.
Adult polycystic kidney disease (APKD) is a hereditary disorder characterized by multiple expanding cysts of both kidneys that ultimately destroy the renal parenchyma and cause renal failure. It is an *autosomal dominant* condition caused by mutation in PKD1 gene encoding for *polycystin-1*. This protein is present on distal tubular epithelial cells. It is involved in cell-cell and cell-matrix interactions. The *PKD2* gene product *polycystin-2* is localized to all segments of the renal tubules and may act as a Ca^{2+}-permeable cation channel for regulatoring intracellular Ca^{2+} levels.

3. **Ans. (a) Berry Aneurysm in Circle of Willis**
(Ref: Robbins 7th/964 9/e p947)

4. **Ans. (b) Hypertension is rare**
(Ref: Robbins 7th/964, 9/e p 947)
Hypertension is common in patients with autosomal dominant polycystic kidney disease. It is present in 75% of adult patients and 25% of children.

5. **Ans. (e) Pathogenesis starts early and renal failure seen in middle life** *(Ref: Robbins 9/e p947)*

6. **Ans. (b) 4 and 16.** *(Ref: Robbins 8th/960; 9/e p946)*

7. **Ans. (b) Dialysis**
(Ref: Robbins 9/e p949, 8th/960; 7th/962, 966)

8. **Ans. (a) Autosomal dominant..... Too obvious at this stage friend...For details, read text.**

9. **Ans. (a) Cardiovascular disease**
(Ref: Cambell's Urology, 8/e p346,349)
Principal causes of death in renal transplant patients (in decreasing order)
   - **Heart disease**[Q] • *Infection* • *Stroke*

10. **Ans. (d) Bowman's capsule** *(Ref: Robbins 9/e p900)*
Podocytes (or **visceral epithelial cells**) are cells in the Bowman's capsule in the kidneys that wrap around the capillaries of the glomerulus.

11. **Ans. (a) 3** *(Ref: Harrison 18/e p 339; CMDT 2014/e p879)*
The minimum number of red blood cells per microliter of urine required for diagnosis of hematuria is **>3 RBC/ HPF of centrifuged specimen.**
Persistent or significant hematuria (>3 RBCs/ HPF on three urinalyses, a single urinalysis with >100 RBCs, or gross hematuria) is associated with significant renal or urologic lesions…Harrison

12. **Ans. (d) Brain** *(Ref: Robbbins 9/e p947)*
About 40% have one to several cysts in the liver (polycystic liver disease) that are usually asymptomatic. Cysts occur much less frequently in the spleen, pancreas, and lungs.

13. **Ans. (b) Excretion of less than 500 ml in 24 hrs**
As per Harrison

   > - **Oliguria**[Q] refers to a **24-h urine output of <500 mL**[Q], and
   > - **Anuria**[Q] is the complete absence of urine formation **(<50 mL)**[Q].

14. **Ans. (c) Hyaline casts**
Hyaline cast are tubular structures made of solidified Tamm Horsfall mucoprotein. That's what the pointer has shown in the image.
Decoy cells are virally infected (polyoma and cytomegalovirus) epithelial cells found in the urine. They are seen in immunocompromised patients typically in transplant patients. These cells have *intracellular inclusion bodies.* This option confused most of the people.

15. **Ans. (b) Hyperplastic arteriosclerosis**
(Ref: Robbins 8th/950-951, 9/e p939)
Histological alterations characterizing blood vessels in malignant hypertension
   - **Fibrinoid necrosis of arterioles:**
   - **Onion-skinning** (due to concentrically arranged smooth muscle with collagen).
   - This condition, hyperplastic arteriolitis correlates with renal failure.

16. **Ans. (a) Alport's syndrome**
(Ref: Robbins 8th/931-2, 9/e p924)

COL4A5 chain represents the a5 chain of collagen type IV. It is associated with the development of Alport syndrome.

Genetic Mutation in Chain	Disease
Gene encoding α5 **chain** of collagen type IV	Alport syndrome
Gene encoding α4 **chain** of collagen type IV	**Benign familial hematuria/ Thin membrane disease**
Gene encoding α3 **chain** of collagen type IV	Goodpasture syndrome

17. Ans. (b) NPHS 2 *(Ref: Robbins 8th/927, 9/e p918)*

Gene	Chromosome	Protein	Location	Disease
NPHS 1	19q13	Nephrin	Slit diaphragm	Steroid sensitive/ Finnish type of nephrotic syndrome
NPHS 2	1q25	Podocin	Slit diaphragm	Steroid resistant nephrotic syndrome

18. Ans. (a) Focal segmental glomerulosclerosis
(Ref Robbins 8th/926, 9/e p918)

Direct quote Robbins 8th/926.... *'**Focal segmental glomerulosclerosis** occurs as a component of the adaptive response to loss of renal tissue in advanced stage of other renal disorders such as **reflux nephropathy, hypertensive nephropathy** and **unilateral renal agenesis**.'*

19. Ans. (c) No IgG deposits or C3 deposition on renal biopsy *(Ref: Robbin's 8th/925-6, 9/e 910)*

The clinical symptoms and the findings in the stem of the question (child with generalised swelling because of reduced serum protein secondary to massive proteinuria with urinary lipid casts) are suggestive of nephrotic syndrome. The commonest cause in a child of nephrotic syndrome is lipoid nephrosis or minimal change disease. So option 'a' and 'd' are ruled out. Both cause hematuria as a finding.

Electron microscopic examination in minimal change disease show the presence of effacement of foot processes of podocytes[Q].

20. Ans. (b) Focal necrotizing glomerulonephritis
(Ref: Robbins 9/e p511-512, 8th/516-7, 7th/541, Harrison 17th/2121-3)

- Robbins .....'The renal lesions range from a mild/ early disease, where glomeruli show acute focal necrosis with thrombosis of isolated glomerular capillary loops (focal and segmental necrotizing glomerulonephritis) whereas advanced glomerular lesions are characterized by diffuse necrosis and parietal cell proliferation to form crescents (crescentic glomerulonephritis)'.
- Direct quote from Harrison..... "Necrotizing vasculitis of small arteries and veins *with granuloma formation* is seen in pulmonary tissue whereas granuloma formation is *rarely seen* on *renal biopsy*".

21. Ans. (a) Autosomal recessive inheritance
(Ref: Heptinstall's pathology of kidney vol 1/931)

Fibronectin nephropathy is a disease with the following features:

- **Autosomal dominant**[Q] mode of inheritance.
- Presents with **proteinuria** (MC presentation) and slowly progressive **loss of renal function**.
- The **fibronectin levels** in serum are **normal**.
- **Light microscopy:** is glomerular enlargement and PAS (⊕), trichrome-positive but amyloid (–) mesangial deposits.
- Immunofluorescence microscopy: the glomeruli do **NOT** stain for **immunoglobulin** or **complement** components
- Electron microscopy: **large** (giant), **mesangial and subendothelial electron-dense deposits.**.

22. Ans. (d) Focal glomerular sclerosis
(Ref: Robbins 9/e p1118-1119, 8th/1141-1142)

Diabetes may cause nodular and diffuse glomerulosclerosis but not focal glomerular sclerosis.

23. Ans. (a) Loss of antithrombin III (AT III)
(Ref: Robbins 9/e p914, 8th/922, 7th/978 CMDT 2010)

Thrombotic and thromboembolic complications are common in nephrotic syndrome due to loss of anticoagulant factor (e.g. antithrombin III, protein C and S) combined with increased platelet activation. Renal vein thrombosis is most often a **consequence** of this hypercoagulative state. There is also **increased synthesis of fibrinogen** in the liver.

24. Ans. (a) Nephrin *(Ref: Robbins 9/e p918, 8th/927)*

25. Ans. (a) Microscopic polyangiitis
(Ref: Robbins 9/e p912, 8th/920)

Crescentic Glomerulonephritis

Type I RPGN (Anti-GBM antibody)	Type II RPGN (Immune complex)	Type III RPGN (Pauci immune)
• Idiopathic • Goodpasture's syndrome.	• Idiopathic • Post infectious • SLE, Henoch Schonlein Purpura.	• Idiopathic. • ANCA associated. • Wegener's granulomatosis. • Microscopic polyangiitis.
Immunofluorescence finding • *Linear GBM deposits of IgG and C3*	***Immunofluorescence finding*** • *"Lumpy bumpy" granular pattern of staining.*	***Immunofluorescence finding*** • *No immunoglobulin or complement deposits in GBM.*

26. Ans. (a) Nephrin
(Ref: Robbins 9/e p912, 8th/918, Nelson 17th/1757)

- Lipoid nephrosis or nephrotic syndrome is also called as minimal change disease. Congenital neph-

rotic syndrome occurs as a result of mutation in the **nephrin** gene. (Finnish type of nephrotic syndrome)

Also now

- Megalin in involved is the pathogenesis of membranous glomerulonephritis
- Podocin and α_4 actinin can also result in congenital nephrotic syndrome.

27. Ans. (b) Alport syndrome

(Ref: Robbins 9/e p912, 8th/920, 7th/523-4)

As discussed earlier, crescentic glomerulonephritis is the alternative name of RPGN.

Alport syndrome is a hereditary nephritis characterized by associated nerve deafness and eye disorders like lens dislocation, posterior cataracts and corneal dystrophy. Histologically foam cells (interstitial cells having fats and mucopolysaccharides) are seen.

28. Ans. (b) Mesangiocapillary GN

(Ref: Anderson 10th/2076; Robbins 7th/979)

Glomerular lesions with increased cells in the tufts are often known as proliferative glomerulonephritis.

Conditions with Proliferative Glomerulonephritis

- SLE (particularly class II, mesangial hypercellularity defined as >3 cells in mesangial regions)
- HIV
- Membranoproliferative/Mesangiocapillary glomerulonephritis
- Neoplasia (particularly CLL and MALT lymphoma)
- Post streptococcal glomerulonephritis

Rest all options are nonproliferative glomerulonephritis.

29. Ans. (a) Thrombotic microangiopathy

(Ref: Robbins 9/e p941, 8th/952, 7th/1009, 612, Harrison 17th/1813-4)

The term thrombotic microangiopathy encompasses a spectrum of clinical syndromes that include TTP and HUS.

Microthrombi are demonstrated in renal arterioles and capillaries. In HUS, microthrombi mainly contain fibrin whereas in TTP, these are composed of platelet aggregates, fibrin and VWF. More than 90% patients with HUS have significant renal failure whereas < 10% cases of classic TTP have anuria.

30. Ans. (a) Post streptococcal glomerulonephritis

(Ref: Robbins 9/e p918, 8th/919, Harrison's 17th/1786)

- Although all conditions mentioned in the question are associated with low complement levels. Persistently depressed levels' are not seen in post streptococcal glomerulonephritis.
- **In poststreptococcal glomerulonephritis:** serum C3 levels are depressed within 2 weeks, however, these usually return to normal levels within 6 to 8 weeks **(transient decrease of complement levels).**
- **Persistently depressed levels after this period should suggest another cause such as presence of C3 nephritic factor (Membranoproliferative glomerulonephritis).**

31. Ans. (c) Diarrhea associated hemolytic uremic syndrome *(Ref: Harrison 17th/1813-1814, 9/e p942)*

Nephritic syndrome associated with low C3

Immune complex glomerulonephritis	
• Post streptococcal glomerulonephritis	• Crescenteric glomerulonephritis
• Lupus nephritis	• Idiopathic proliferative glomerulonephritis
• Cryoglobulinemia	• Atheroembolic renal disease
• Bacterial endocarditis	• Sepsis
• Shunt nephritis	• Acute Pancreatitis/ advanced liver disease
• Membranoproliferative glomerulonephritis	

*Hemolytic uremic syndrome is associated with normal C3 levels.

32. Ans. (c) Goodpasture's disease

(Ref: Harrison's 17th/1788)

33. Ans. (d) Absence of associated proteinuria is pathognomic *(Ref: Robbin's 7th/986-988, 9/e p923)*

Berger's disease *(IgA nephropathy) is a frequent cause of gross or microscopic hematuria. Mild proteinuria is frequently present and occassionally nephrotic syndrome may develop.*

34. Ans. (b) Rapidly progressive glomerulonephritis

(Ref: Robbins 9/e p912, 8/e p920-921)

- Rapidly progressive glomerulonephritis, also known as crescentic glomerulonephritis is characterized by the presence of crescents in most of the glomeruli.
- Crescents are produced by proliferation of the ***parietal epithelial cells of Bowman's capsule and by infiltration of monocytes and macrophages.***

35. Ans. (c) Crescentic glomerulonephritis

(Ref: Robbins 9/e p912, 8th/516-7, 7th/541, Harrison 17th/2121-3)

Discussed earlier.

36. Ans. (c) Alport syndrome

(Ref: Robbins 9/e p924, 8th/932, 7th/988, Rubin pathology/361)

For Alport syndrome, Rubins mentions *'The* ***most diagnostic morphologic lesion*** *is seen* ***only by electron microscopy*** *as an irregularly thickened GBM, with splitting of the lamina densa into interlacing lamellae that surround electron-lucent areas'*

37. Ans. (b) Collapsing *(Ref: Robbin's 9th/p 920)*

- **Five mutually exclusive variants of focal segmental glomerulosclerosis (FSGS) may be distinguished by the pathological findings seen on renal biopsy**
  - Collapsing variant

- Glomerular tip lesion variant
- Cellular variant
- Perihilar variant
- Not otherwise specified variant (NOS)

- The **NOS** variant is the *most common* subtype and collapsing FSGS has worst prognosis.

38. Ans. (c) Podocin

(Ref: Robbins 9/e p918, 8th/927, 7th/983-4)

39. Ans. (d) Hypertrophy and necrosis of visceral epithelium *(Ref. Robbin's 9/e p920, 8th/926, 7th/983-4)*

Collapsing Glomerulopathy is characterised by

- A characteristic feature is proliferation and hypertrophy of glomerular visceral epithelial cells.
- The minimum diagnostic criteria for defining a collapsing variant of FSGS is the presence by light microscopy of at least one glomerulus showing segmental or global obliteration of the glomerular capillary lumen by wrinkling and collapse of glomerular basement membrane in association with hypertrophy and hyperplasia of overlying visceral epithelial cells.

40. Ans. (b) NPHS-2 *(Ref: Robbin 9/e p918)*

41. Ans. (c) Collapsing glomerulopathy

(Ref: Harrison 17th/1796, Robbins, 9/e p920, 8th/928, 7th/982- 3)

42. Ans. (d) Amyloidosis

(Ref: Robbins 9/e p926, 8th/252,610-1,927-8)

- Mesangial deposits of **monoclonal kappa/lambda** light chains suggest the diagnosis of **Amyloidosis.** In primary Amyloidosis **AL protein** is deposited in the organs, which is made of light chains (usually lambda type) of immunoglobulins. Renal amyloidosis is the **most common cause of death due to amyloidosis** (including both primary and secondary amyloidosis).

Other options:

- **Mesangioproliferative glomerulonephritis** shows mesangial deposits of IgG, IgA and C3.
- **Focal and segmental glomerulosclerosis** shows hyaline deposits of IgM, C3 and IgA and fibrinogen in juxtamedullary capillaries.
- In **Kimmelstiel-Wilson disease** (or nodular glomerulosclerosis), the hyaline masses are deposited in the mesangial core of the glomerular lobules consist of **lipids** and **fibrin**.

43. Ans. (b) Has molecular weight slightly greater than the molecules normally getting filtered

(Ref: Robbins 9/e p914, 8th/910, Harrison 18th/2334, Ganong 21st/709-10; Guyton 10th/373)

- There are **three main types of plasma proteins** which include Albumin, Globulin and Fibrinogen
- Normally, the glomerular filtration layer **does not** allow **any plasma protein** to pass through it. However, in any renal disease, it allows protein molecules to pass through it and **albumin** is the **first protein** to appear in the urine.
- The filtration of any substance through glomerular filtration layer depends on **two** factors as described below:

Size of the substance

The glomerular filtration layer is thick and porous membrane. *Any neutral substance* ≤ 4A *diameter freely filters through this layer. However,* the filterability of any neutral substance with diameter between 4 nm and 8 nm is *inversely proportional* to its size. The filterability of substances of diameter more than 8 nm is zero.

Charge of the substance

The **sialoproteins** contained in the glomerular filtration layer are **negatively charged** causing repulsion of *all negatively charged particles including proteins.* This explains the negligible filtration of **albumin anion** which has diameter of **7 nm**

In some renal diseases, the **anionic charge of the filtration membrane is lost** and this allows negatively charged particles of diameter **8 nm** to pass through it resulting in proteinuria. Albumin has a diameter of **7 nm** and it *starts appearing in urine as soon as the negative charge of filtration layer disappears.*

44. Ans. (a) Fusion of foot process of the glomerular epithelial cells *(Ref: Robbins 9/e p917, 8th/925)*

- The child is presenting with features likely of Nephrotic syndrome whose most frequent cause in children is minimal change disease or lipoid nephrosis.
- Light microscopy there is no abnormality whereas on electron microscopy there is fusion of foot processes of the glomerular epithelial cells with normal glomeruli.

45. Ans. (a) Number of crescents

(Ref: Robbins 6th/453, Essential of nephrology by K visweswaran 2nd/102)

As discussed in text the prognosis in RPGN is related to the number of crescents. However, this point is not mentioned in the 7th, 8th and 9th editions of Robbins.

Poor prognostic factors	Good prognostic factors
• ***Oliguria*** and ***azotemia*** at presentation • ***More than 80% circumferential crescents*** have poor response to therapy • Glomerular tuft necrosis, global glomerular sclerosis, gaps in Bowman capsule and interstitial fibrosis	• *Pauci immune RPGN* has best prognosis • *Non- circumferential crescents in less than 50%* glomeruli have indolent course. • *Associated endocapillary proliferation* is a good prognostic factor

Essential of nephrology writes that *'oliguria is related to crescent formation'*.

46. Ans. (d) No change seen

(Ref: Robbins 9/e p917, 7th/981-982)

47. Ans. (d) Glomerular function is lost due to loss of polyanionic charge on both sites of glomerular foot process.

(Ref: Harrison 17th/1790, Robbins 9/e p900)

As discussed earlier, *Glomerular barrier function* depends on the molecular size (the larger, the less permeable) and charge (the more cationic, the more permeable) is done. The anionic moieties present within the capillary wall including the acidic proteoglycans of the GBM and the sialoglycoproteins of epithelial and endothelial cells are responsible for the virtually complete exclusion of albumin (also having anionic charge) from the filtrate. In addition, the *visceral epithelial cell* (or podocyte) is important for the maintenance of glomerular barrier function. The slit diaphragm of the podocyte is composed of nephrin, actin and podocin, so, any defect in any of these is responsible for increased protein excretion from the kidney. In a patient of minimal change disease, there is presence of visceral epithelial injury leading to the loss of glomerular polyanions resulting in low molecular weight proteinuria (selective proteinuria).

Clarifying Option c; Foot process of the podocyte is effaced. However, it appears to be normal on light microscopy.

48. Ans. (a) Poststreptococcal glomerulonephritis

(Ref: Robbins 9/e p910, Harrison 17th/1786-1787)

49. Ans. (a) PSGN; (b) MPGN; (e) Infective endocarditis:

(Ref: Robbins 9/e p910, Harrison 17th/1788)

50. Ans. (a) MPGN-I; (c) PSGN; (d) Membranous GN; (e) RPGN *(Ref: Robbins 9/e p910, 7th-975)*

Summary of Glomerular Deposits

Subepithelial	Subendothelial	Basement membrane	Mesangial
• Acute GN (like PSGN) • Membranous GN • Heymann GN • RPGN (some cases) • MPGN (Type I) rarely	• MPGN (Type I) • SLE • Acute GN	• MPGN (Type II) • Membranous • Glomerulopathy	• IgA nephropathy • HSP • Anti-GBM diseases like • RPGN and Goodpasture syndrome

51. Ans. (a) Proteinuria; (b) Hyperlipidemia; (c) Edema; (e) Lipiduria

(Ref: Robbins 9/e p914, 8th/907, 7th/978)

52. Ans. (a) Albumin

(Ref: Robbins 9/e p914, 7th/958, Vasudevan-Sreekumari 4th/224)

Albuminuria is seen in nephrotic syndrome.

53. Ans. (b) Massive proteinuria; (d) Edema; (e) Hyperlipidemia. *(Ref: Robbins 7th/978, 9/e p914)*

54. Ans. (a) Heymann antigen is called megalin; (d) Subepithelial aspect of basement membrane has deposit.

(Ref: Robbins 7th/968 – 970, 9/e p903, 915)

- The Heymann model of rat glomerulonephritis is induced by immunizing rat with an **antigen containing preparation of proximal tubular brush border.**
- The rats develop antibodies to this antigen and a membranous glomerulopathy, resembling human membranous glomerulopathy. The **antigen is called megalin** and has homology to LDL receptor.
- On electron microscopy, the glomerulopathy is characterized by presence of numerous electron dense deposits along the **subepithelial** *aspect of basement membrane. Immunofluorescence microscopy shows granular deposits.*

55. Ans. (b) Malignant nephrosclerosis.

(Ref: Robbins 7th/1008, 9/e p939)

56. Ans. (a) Foamy cells in interstitium; (d) Thinning of GBM < 100 nm: *(Ref: Robbins 7th/988, 9/e p924)*

Histological characteristics of Alport's syndrome:

- Diffuse basement membrane thinning
- Vascular sclerosis
- Foam cells in interstitium
- Tubular atrophy
- In advanced stage there is focal or global glomerulosclerosis
- Interstitial fibrosis

On electron microscopy (diagnostic of this disorder), GBM shows

- Irregular foci of thickening alternating with thinning
- Pronounced splitting and lamination of lamina densa **(basket weave appearance)**[Q].
- Info: Immunohistochemistry shows failure to stain α-3, 4, 5 collagen.

57. Ans. (b) Wegener's granulomatosis (c) Goodpasture's syndrome (e) Microscopic polyangiitis

(Ref: Robbins 9/e p912, 7th/977)

58. Ans. (a) Subepithelial deposits; (b) Nephritis along with acute renal failure; (c) Low complement levels; (d) HTN and proteinuria: *(Ref: Robbins 9/e p910-911)*

59. **Ans. (c) Microscopic polyangiitis**
(Ref: Robbin 7th/540, 9/e p912, Harrison 17th/1789)

- In microscopic polyangiitis, there is a paucity of immunoglobulin demonstrable by immunofluorescence microscopy (pauci-immune injury). There are few or no immune deposits in this type of vasculitis.
- Pauci immune injury is also seen in Churg Strauss syndrome and Wegener granulomatosis.

60. **Ans. (a) Diabetic nephropathy** *(Ref: Robbin 9/e p1118)*

61. **Ans. (a) Goodpasture's syndrome**
(Ref: Robbins 7th/745-746, 9/e p912)

62. **Ans. (a) Diabetic glomerulosclerosis**
(Ref: Robbins 9/e p1118)

63. **Ans. (a) Normal C3** *(Ref: Robbins 9/e p910-911)*

64. **Ans. (b) Mesangioproliferative glomerulonephritis**
(Ref: Robbins 7th/403-405 , 9/e p393)

- Visceral leishmaniasis is caused by *L. donovani*
- Mucocutaneous leishmaniasis is caused by *L. braziliensis*.
- Visceral leishmaniasis is characterized by the clinical features of hepatosplenomegaly, lymphadenopathy, pancytopenia, fever and weight loss. There is hyperpigmentation of the skin, so it is also called as "Kala azar".
- In the renal involvement in this disease, there is presence of mesangioproliferative glomerulonephritis and in advanced cases, there is presence of amyloidosis.

65. **Ans. (a) Crescents in most of glomeruli**
(Ref: Robbins 975 7th/20-6, 9/e p910)

66. **Ans. (a) Idiopathic cresenteric glomerulonephritis**
(Ref: Robbins 9/e p910-911, 8th/920; 7th/977)

67. **Ans. (b) Diffuse involvement** *(Ref: Robbins 9/e p911)*

68. **Ans. (a) Diffuse glomerulosclerosis**
(Ref: Robbins 9/e p1118, 8th/934; 7th/990-992)

69. **Ans. (c) Membranoproliferative glomerulonephritis**
(Ref: Robbins 8th/929; 7th/985)

70. **Ans. (a) Poststreptococcal GN** *(Ref: Robbins 8th/920)*

71. **Ans. (b) Nodular glomerulosclerosis**
(Ref: Robbins 9/e p1118, 8th/934; 7th/991)

72. **Ans. (d) Diffuse alveolar involvement**
(Ref: Robbins 8th/709-710, 9/e p913)

73. **Ans. (c) IgG deposition in mesangium**
(Ref: Robbins 9/e p923, 8th/925-926; 7th/981)

74. **Ans. (b) Berger disease** *(Ref: Robbins 9/e p923)*

75. **Ans. (d) Rheumatoid arthritis** *(Ref: Robbins 9/e p912)*

76. **Ans. (d) Sodium and water retention**
(Ref: Robbins 9/e p922, 8th/407-408; 7th/522)

77. **Ans. (b) Hematuria** *(Ref: Robbins 9/e p923)*

78. **Ans. (d) Focal segmental glomerulosclerosis**
(Ref: Robbins 9/e p919, 8th/926, 7th/983)

79. **Ans. (d) All of the above** *(Ref: Robbins 9/e p942)*

80. **Ans. (a) Membranous glomerulonephritis**
(Ref: Robbins 9/e p915, 8th/918, 923; 7th/984,979-981)

81. **Ans. (c) Wegener's glomerulonephritis**
(Ref: Robbins 9/e p903, 8th/920; 7th/993,997)

82. **Ans. (b) Membranoproliferative glomerulonephritis**
(Ref: Robbins 9/e p920, 8th/929; 7th/984)

83. **Ans. (b) Membranous nephropathy**
(Ref: Robbins 9/e p915, 8th/918,920; 7th/975, 979)

84. **Ans. (a) Focal segmental glomerulosclerosis**
(Ref: Robbins 8th/928, 9/e p920)

There is a specific association between focal segmental glomerulosclerosis and both IV drug abuse and HIV nephropathy. This disorder usually presents as an aggressive form of nephrotic syndrome with poor prognosis and non responsive to steroid therapy (called as 'collapsing variant').

85. **Ans. (a) Epithelial cells + fibrin + macrophage**
(Ref: Robbins 8/e p921, 9/e p913)

Crescents are formed by proliferation of **parietal cells** and by **migration of monocytes and macrophages** into the urinary space. Neutrophils and lymphocytes may be present. **Fibrin strands** are frequently prominent **between the cellular layers in the crescents.** The escape of fibrinogen into Bowman space and its conversion to fibrin are an important contributor to crescent formation.

Rapidly progressive glomerulonephritis is characterized histologically by domination of distinctive **crescents**. It is also known as Crescentic glomerulonephritis. The crescents eventually obliterate Bowman space and compress the glomerular tuft. So, the prognosis is dependent on the number of crescents in the kidney biopsy.

86. **Ans. (a) Malignant hypertension**
(Ref: Robbins 8/e p950, 9/e p939)

Mnemonic for differential diagnosis of flea bitten kidney: We HaTe PSM

We - Wegener's granulomatosis
HaTe – **H**enoch Schonlein purpura; **H**US;**T**TP
P- Poststreptococcal glomerulonephritis (PSGN); **P**olyarteritis nodosa (PAN)
S-Subacute bacterial endocarditis (SABE)
M- Malignant hypertension

87. **Ans. (c) Fibrinogen**
(Ref: Robbins 8/e p922, Heptinstall's Pathology of the Kidney 6/e p131)

Direct quote from Heptinstall's Pathology.. "Many factors increase in nephrotic syndrome usually due to lowering of serum albumin to which they are usually bound. These factors include **fibrinogen**, factors **V, VII, VIII and von Willebrand factor**. On the other hand, substances like factors XI and XII, plasminogen an anti-thrombin III."

Thrombotic and thromboembolic complications are common in nephrotic syndrome due to loss of anticoagulant factor (e.g. antithrombin III, protein C and S) combined with increased platelet activation. Renal vein thrombosis is most often a **consequence** of this hypercoagulative state. There is also **increased synthesis of fibrinogen** in the liver.

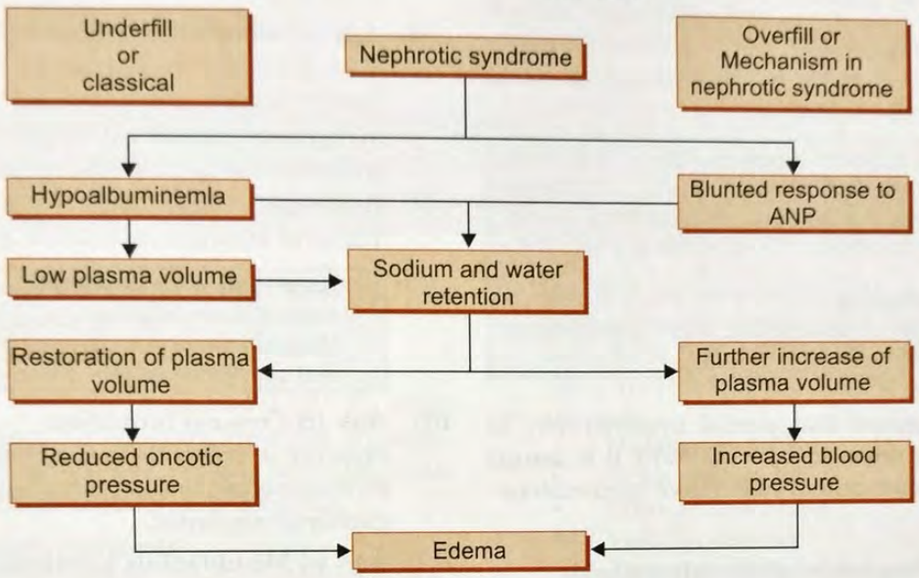


Figure: Mechanisms of edema formation in the nephrotic syndrome left. The classic view of edema formation, in which a low blood volume (underfill) serves as the signal for secondary renal sodium retention Right. The mechanism of edema formation in most patient with the nephrotic syndrome who have normal or slightly elevated blood volumes (overfill). The blunted response to atrial natriuretic peptide observed in patients with the nephrotic syndrome may be the stimulus for primary renal sodium retention that plays a central role in edema formation. ANP, atrial natriuretic peptide.

Edema in nephrotic syndrome is attributed to the following:

- **Underfill hypothesis/classical hypothesis:**
  - Seen in patients with low plasma volume
  - *Hypovolemia is the primary stimulus* leading to sodium and water retention leading to edema by alteration of Starling forces
- **Overfill hypothesis:**
  - Seen in patients with normal or increased plasma volume
  - Sodium retention is the primary mechanism leading to increased blood pressure and then alteration in Starling forces and edema formation.

88. Ans. (d) Focal segmental glomerulosclerosis
(Ref: Robbins 8/e p926, 9/e p 918)

Focal segmental glomerulosclerosis is the **commonest cause** of **nephrotic syndrome** in the **adults** in the World. It is characterized by

NEET Points to be brushed up!

- Associated with loss of renal tissue as **unilateral renal agenesis**[Q] or advanced stages of reflux nephropathy or hypertensive nephropathy.
- Also seen with with conditions like **Sickle cell anemia**[Q], **HIV infection**[Q], Heroin abuse, Obesity
- Degeneration and focal ***disruption of the visceral epithelial cells*** is the hallmark feature of focal segmental glomerulosclerosis.
- Is chief renal lesion in **HIV associated nephropathy** (especially **collapsing**[Q]variant)

89. Ans. (b) Rapidly progressive glomerulonephritis... discussed earlier *(Ref: Robbins 7/e p976-977, 9/e p912)*

90. Ans. (a) Berger disease *(Ref: Robbins 9/e p912-913)*

91. Ans. (c) Mild proteinuria, hematuria, high ASO titre
(Ref: Robbins 9/e p910-911)

In poststreptococcal glomerulonephritis, there elevated levels of antistreptolysin O or ASO and anti DNAase antibodies [Q] (indicative of streptococcal infection) and *reduced levels of serum C3*

92. Ans. (d) Renal biopsy having thin basement membrane
(Ref: Robbins 9/e p925)

Benign familial hematuria is common hereditary entity manifested clinically by familial asymptomatic hematuria—usually uncovered on routine urinalysis—and morphologically by diffuse thinning of the GBM to widths between 150 and 225 nm (compared with 300 to 400 nm in healthy adults).

93. **Ans. (c) 30-300 mg/d** *(Ref: Robbins 8/e p1145, 9/e p1120)*

- The **earliest manifestation** of diabetic nephropathy is the appearance of low amounts of albumin in the urine (**>30 mg/day, but <300 mg/day**), that is, *microalbuminuria*.
- Microalbuminuria is also a *marker for greatly increased cardiovascular morbidity and mortality* for persons with either type 1 or type 2 diabetes

94. **Ans. (c) Partial lipodystrophy** *(Ref: Robbins 9/e p 922)*
Secondary MPGN (invariably type I) is more common in adults and arises in the following:

- Chronic immune complex disorders, such as SLE; hepatitis B infection; hepatitis C infection, usually with cryoglobulinemia; endocarditis; infected ventriculoatrial shunts; chronic visceral abscesses; HIV infection; and schistosomiasis
- α1-Antitrypsin deficiency
- Malignant diseases particularly CLL which have formation of autoantibodies

Robbins 8th mentioned that partial lipodystrophy is associated with *C3 nephritic factor (C3NeF)*. It is associated with type II membranoproliferative glomerulonephritis.

95. **Ans. (d) Rapidly progressive glomerulonephritis** *(Ref: Robbins 9/e p912)*
RBC casts are a feature of glomerular damage. Normally < 3 RBC/HPF are going to leak. But in case of glomerular damage the number of RBC in the urine will exceed the limit mentioned above and these RBC get impinged on Tamm Horsfall protein. The resultant RBC casts can be seen under microscopic examination of urine.

96. **Ans. (a) Focal segmental glomerulonephritis** *(Ref: Robbins 9/e p919)*
A morphologic variant of FSGS is called collapsing glomerulopathy and is the most characteristic lesion of HIV-associated nephropathy.

97. **Ans. (d) Minimal change disease** *(Ref: Robbins 9/e p 917)*
The glomeruli are **normal** by light microscopy. By electron microscopy the GBM appears normal, and no electrondense material is deposited. The principal lesion is in the visceral epithelial cells, which show a ***uniform and diffuse effacement of foot processes.***

Foot process effacement is also present in other proteinuric states (e.g., membranous glomerulopathy, diabetic nephropathy); it is only when effacement is associated with normal glomeruli by light microscopy that the diagnosis of minimal-change disease can be made.

98. **Ans. (b) Minimal change disease** *(Ref: Robbins 9th/917)*

- Presence of edema, proteinuria (frothy urine in stem of question), hypoalbuminemia etc. is suggestive of **nephrotic syndrome**.
- **Minimal change disease** is the most frequent cause of nephrotic syndrome in children. There is commonly no hyper-tension or hematuria. The proteinuria usually is highly selective, most of the protein being albumin.
- No RBC casts in the urine is suggestive of absence of glomerulonephritis. So, options 'a' and 'c' are ruled out. Membranous nephropathy causes nephrotic syndrome in adults. The best answer therefore is option 'b'

99. **Ans. (c) Membranous glomerulopathy**
(Ref: Nephrol Dial Transplant (2001) 16: 13-14 Robbins 9th/832-3)
Malignancy associated nephropathy is a recognised entity for many years which usually presents as nephrotic syndrome.
The most common association are:

- **Solid tumors** cause nephrotic syndrome due to **membranous glomerulopathy**.
- **Hodgkin disease** cause nephrotic syndrome due to **minimal change disease**.

100. **Ans. (c) Crescent formation** *(Ref: Robbins 9/e p913)*
Presence of crescents in the glomeruli is the characteristic microscopic finding in patient of rapidly progressive glomerulonephritis.

101. **Ans. (c) Membranous glomerulopathy**
(Ref: Robbins 9/e p916)

Presence of granular IgG deposits along the glomerular basement membrane is associated with membranous glomerulopathy.

Berger's disease (IgA nephropathy) is associated with *linear Ig deposits* are seen.

102. **Ans. (b) RPGN** *(Ref: Robbins 9/e p912)*
The features are suggestive of nephritic syndrome and the only option associated with nephritic syndrome is RPGN.

103. **Ans. (c) IgA deposition in mesangium** *(Ref: Robbins 9/e p926)*

104. **Ans. (d) Berger's nephropathy** *(Ref: Robbins 9/e p923)*

105. **Ans. (d) Increased complement levels** *(Ref: Robbins 9/e p923)*

106. **Ans. (b) Cardiac hypertrophy** *(Ref: Robbins 9/e p924)*

107. **Ans. (c) Serum complement level is normal** *(Ref: Robbins 9/e p923)*

108. **Ans. (d) Lipoid nephrosis** *(Ref: Robbins 9/e p222-223)*

109. **Ans. (d) Urine PCR for TB**
(Ref: Robbins 9/e p943, 8th/947, Harrisons 18th/2372)

110. **Ans. (a) Isomorphic RBC**
(Ref: Paediatric Nephrology 5th/141, 190 by R.N. Srivastava, Arvind Bagga (senior faculty from AIIMS)

Approach to patient with hematuria to determine source of bleeding		
	Parenchymal Intrarenal	Collecting system Extrarenal
Appearance of urine	Tea colored	Bright red, blood clots
Pattern of hematuria	Total hematuria (throughout the stream)	Initial, terminal hematuria
Urinary symptoms	Painless	Dysuria, urgency, frequency
Associated features	Sore throat, HTN, edema	Fever, colicky pain
Family history	Deafness, renal failure	Renal stones, urinary infection
Proteinuria	High grade (urine protein: creatinine ratio >1)	Low grade
Other urinary findings	RBC casts (highly specific less sensitive)	Crystals
RBC morphology	Dysmorphic	Eumorphic

Page 141 mentions ...Eosinophiluria (>1% WBCs) is observed in acute interstitial nephritis.

111. Ans. (b) Associated with tuberculosis

(Ref: Robbins 8th/943, 9/e p934)

As discussed in text, Xanthogranulomatous pyelonephritis is associated with E. coli Proteus mirabilis, Pseudomonas, Streptococcus faecalis and Klebsiella.

112. Ans. (d) Benign Nephrosclerosis

(Ref: Robbins 9/e p938, 8th/949, 7th/992, 1006; Chandrasoma taylor 3rd/275)

Direct quote Robbins.. *'In benign nephrosclerosis, kidneys are either normal or moderately reduced in size on gross appearance. The loss of mass is due mainly to cortical scarring and shrinking'.*

Causes of contracted kidneys

Symmetric	Asymmetric
• Chronic glomerulonephritis • Benign nephrosclerosis	• Chronic pyelonephritis

Causes of enlarged kidneys

• Amyloidosis • Rapidly progressive glomerulonephritis (RPGN) • Myeloma kidney	• Diabetic renal disease [Kimmelstiel Wilson nodules are pathognomic] • Polycystic kidney disease • Bilateral obstruction (hydronephrosis)

Important info

Contracted kidneys:Less than 8 cm length of kidney is taken as chronic contracted kidney. Normal size corresponds to 3 times the length of L1 vertebrae *or 2/3rd of additive length of T11, T12 and L1 vertebrae.*

Note: In some patients of diabetes (especially in late stages), kidney may be reduced in size.

113. Ans. (b) Tuberculous pyelonephritis

(Ref: Robbins 7th/1004, 9/e p936, Harrison 17th/1825 - 1826)

Necrotizing papillitis is the other name of acute papillary necrosis. When infection of renal pyramids develop in association with vascular diseases of the kidney or with urinary tract obstruction, renal papillary necrosis is likely to result. In the given options, DM is the commonest and TB is the rarest cause of papillary necrosis

- Diabetes mellitus
- Sickle cell disease
- Chronic alcoholism
- Vascular disease
- Analgesic abuse nephropathy

114. Ans. (a) PCT *(Ref: Robbins 9/e p928, 8th/937-8, 7th/918)*

115. Ans. (d) Medullary cystic kidney

(Ref: Harrison 18th/2383, 16th/1807, Robbin's 9/e p948, 8th/947, 7th/1005)

Nephrocalcinosis is a diffuse deposition of calcium salts in the interstitium of the kidney.

Conditions associated with nephrocalcinosis are:

• Hyperoxaluria • Hyperparathyroidism • Prolonged immobilization • Hypervitaminosis D • Hypophosphatemic rickets • Excessive bone destruction in metastasis • Cortical necrosis malignancies (such as multiple myeloma) • Cushing syndrome	• Hyperthyroidism • Hyperuricosuria • Renal candidiasis • Excessive calcium intake (***milk alkali syndrome***) • ***Sarcoidosis*** • ***Renal tubular acidosis (distal)*** • *Medullary sponge kidney*

116. Ans. (a) Goodpasture's syndrome; (b) Leptospirosis; (d) Wegener's granulomatosis; (e) Hantan virus infection;

(Ref: Harrison 17th/1793)

Pulmonary renal syndrome is seen in

- Goodpasture's syndrome: pulmonary hemorrhage and renal failure
- Leptospirosis: Renal and hepatic dysfunction, Hemorrhagic pneumonia, bleeding diathesis
- Hantan virus also cause pulmonary renal syndrome.
- Wegener's granulomatosis: Lung and kidney involvement common.
- Other causes of pulmonary renal syndrome include Henoch Schonlein purpura, Churg Strauss vasculitis, microscopic polyangiitis and cryoglobulinemia.

Please note that Legionella does not affect kidneys. It causes atypical pneumonia, diarrhea and hyponatremia.*

117. Ans. (b) DM, (c) Phenacetin abuse, (d) Alcoholism
(Ref: Harrison 17th/1826, Robbins 9/e p936, 8th/947, 7th-1004)

Causes of papillary necrosis				
	Diabetes mellitus	Analgesic nephropathy	Sickle cell disease	Obstruction
M:F	1:3	1:5	1:1	9:1
Time course	10 years	7 years of abuse	Variable	Variable
Infection	80%	25%	+ or –	90%
Calcification	Rare	Frequent	Rare	Frequent
Number of papillae affected	Several; all of same stage	Almost all; all in different stages of necrosis	Few	Variable

118. Ans. (a) Hyperparathyroidism; (b) TB Kidney; (c) Hypercalcemia
(Ref: Harsh Mohan 6th/685, Robbins 9/e p937, 7th/1005)
Causes of Nephrocalcinosis

• Distal RTA	• Hyperparathyroidism	• Multiple myeloma
• Severe hypercalcemia	• Hypercalcemia	• Vitamin D intoxication
• Medullary sponge kidney	• TB kidney	• Metastatic bone disease

119. Ans. (d) Polycystic kidney disease; (e) Amyloidosis:
(Ref: Robbins 7th/964, 992, 989, 9/e 947)

Causes of bilaterally enlarged kidneys	Causes of small contracted kidney
• Polycystic kidney diseases • Amyloidosis of kidney • DM	• Benign nephrosclerosis • Chronic glomerulonephritis • Chronic Pyelonephritis

120. Ans. (c) Alport's syndrome
(Ref: Robbins 7th/988, 9/e p924, Harrison 17th/1794)
Hereditary Nephritis refers to a group of heterogenous hereditary familial diseases associated primarily with glomerular injury. These are: **Alport's syndrome** and **Thin membrane disease.**

121. Ans. (b) Medullary sponge kidney; (d) RTA
(Ref: Robbins 7th/1005, 9/e p937,948)

122. Ans. (d) Neutrophilic infiltration; (e) Necrotizing vasculitis: *(Ref: Robbins 7th/220)*
Acute rejection can be caused by either cellular or humoral mechanisms
The histologic features of **acute humoral rejection** (within days) in renal transplants are:
- Necrotizing vasculitis
- Endothelial cell necrosis
- Neutrophilic infiltration
- Deposition of immunoglobulins
- Complement and fibrin deposition and thrombosis.
- There is extensive necrosis of renal parenchyma.

In acute cellular rejection

- Extensive interstitial mononuclear cell infiltration
- Edema
- Interstitial hemorrhage is seen.

In hyper acute rejection (within minutes or hours)

- Fibrinoid reactions are seen.

In chronic rejection (over period of 4-6 months)

- Vascular changes consisting of dense, obliterative intimal fibrosis, principally in the cortical arteries seen. It clinically presents with progressive rise in serum creatinine.

123. Ans. (b) Schistocytes
(Ref: Harrison 17th/723, Robbin 9/e p644)
The presence of a severe hemolytic anemia with schistocytes or fragmented red blood cells in the peripheral blood smear is characteristic of microangiopathic hemolytic anemia such as in Hemolytic uremic syndrome and Thrombotic thrombocytopenic purpura.

124. Ans. (b) Cortical tubular hypertrophy
(Ref: Robbins 8th/959, 7th/966)
- Cortical tubulointerstitial damage occurs in nephronophthisis.

Nephronophthisis (Uremic Medullary Cystic Disease Complex)
- It is a group of progressive renal disorders that usually have onset in childhood.
- Common characteristic is the presence of a variable number of cysts in the medulla, usually concentrated at the corticomedullary junction.
- Cortical tubulointerstitial damage occurs.
- 4 variants of this disease are:
  - Sporadic/nonfamilial (20%)
  - Familial juvenile nephronophthisis (40-50% autosomal recessive).
  - Renal-retinal dysplasia (15% autosomal recessive)
  - Adult-onset medullary cystic disease (15% autosomal dominant).
- Affected children present first with polyuria and polydipsia which reflect a marked tubular defect in concentrating ability.
- Sodium wasting and tubular acidosis are also prominent.
- Renal failure occurs in a period of 5-10 years.
- In gross appearance, the kidneys are small, have contracted granular surfaces and show cysts in the

medulla, most prominently at the corticomedullary junction.
- Small cysts are also seen in the cortices and are lined by flattened or cuboidal epithelium.
- In the cortex, there is widespread atrophy and thickening of the basement membranes of proximal and distal tubules together with interstitial fibrosis.
- In general, glomerular structure is preserved.

125. Ans. (a) Diabetes mellitus *(Ref. Robbins 9/e p936)*

126. Ans. (a) Calcium oxalate *(Ref: Robbins 9/e p951)*

127. Ans. (c) Interstitial nephritis *(Ref: Robbins 9/e p930)*

128. Ans. (c) Diabetes mellitus *(Ref: Robbins 9/e p936)*

129. Ans. (b) Lupus nephritis *(Ref: Robbins 9/e p929)*

130. Ans. (d) Lipoid nephrosis *(Ref: Robbins 9/e p222-223)*

131. Ans. (a) Fibrinoid necrosis *(Ref: Robbins 9/e p939)*

132. Ans. (c) Amyloidosis *(Ref: Robbins 8th/254)*

133. Ans. (a) Acute glomerulonephritis *(Ref: Robbins 9/e p911)*

134. Ans. (a) Calcium oxalate stone *(Ref: Robbins 9/e p951)*

135. Ans. (a) Goodpasture's syndrome *(Ref: Robbins 9/e p912)*

136. Ans. (c) Cystitis *(Ref: Robbins 8th/974-5, 9/e p962)*

The clinical presentation of the patient in the stem of the question is of cystitis, which is characterized by pyuria and hematuria but absence of white cell casts in the urine.

Patients with acute pyelonephritis present with fever, leucocytosis, flank tenderness, urinary white cells, and white cell casts in the urine. Chronic pyelonephritis is almost always the result of chornic urinary tract obstruction and repeated bouts of acute inflammation in the kidneys.

137. Ans. (c) Hyperparathyroidism *(Ref: Robbins 9/e p951)*

The patient's history of recurrent urolithiasis with calcium-containing stones implies a disorder in the regulation of calcium concentration. Hyperparathyroidism is associated with increased parathormone (PTH) levels, which can produce hypercalcemia, hypercalciuria, and, ultimately, renal stones.

138. Ans. (a) Diabetes mellitus

(Ref: Robbins 8/e p947, 9/e p 936, Top 3 Differentials in Radiology: A Case Review Thieme pg 121)

The most common cause of papillary necrosis is **diabetes mellitus**Q.....Top 3 Differentials in Radiology

Encyclopedia of Imaging, Vol 2; pg 1192.. *"diabetes mellitus is the most common condition associated with renal papillary necrosis accounting for >50% of all cases."*

Clinical Pathology Oxford press pg220.. **"acute papillary necrosis** is most often a complication of acute pyelonephritis in **diabetes**. Chronic papillary necrosis is seen most often in association with analgesic nephropathy".

Conditions with papillary necrosis: Mnemonic is POST-CARDS

• **P**yelonephritis
• **O**bstruction of the urinary tract
• **S**ickle cell hemoglobinopathies, including sickle cell trait
• **T**uberculosis
• **C**irrhosis of the liver, **C**hronic alcoholism
• **A**nalgesic abuse
• **R**enal transplant rejection, **R**adiation
• **D**iabetes mellitus
• **S**ystemic vasculitis

139. Ans. (b) Diabetes mellitus

(Ref: Robbins 8/e p934, 7/e p991-992)

Causes of contracted kidneys

Symmetric	Asymmetric
• Chronic glomerulonephritis	• Chronic pyelonephritis
• Benign nephrosclerosis	
Causes of enlarged kidneys	
• Amyloidosis	• Diabetic renal disease [Kimmelstiel winos nodules are pathognomonic]
• Rapidly progressive glomerulonephritis (RPGN)	• Polycystic kidney disease
• Myeloma kidney	• Bilateral obstruction (hydronephrosis)

140. Ans. (b) Codominant *(Ref: Robbins 8/e p931-2, 9/e p924)*

Friends, read the following lines from Robbins carefully....

- *Alport syndrome* is manifested by *hematuria with progression to chronic renal failure, accompanied by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts, and corneal dystrophy.*
- The disease is inherited as an **X-linked trait** in approximately **85%** of cases. In this X-linked form, *males express the full syndrome and females are carriers* in whom manifestations of disease are typically limited to hematuria.
- **Autosomal recessive** and **autosomal dominant** pedigrees also exist, in which males and females are equally susceptible to the full syndrome

141. Ans. (a) Hyperparathyroidism *(Ref: Robbins 9/e p937)*

- Disorders ***characterized by hypercalcemia***, such as *hyperparathyroidism, multiple myeloma, vitamin D intoxication, metastatic bone disease, or excess calcium intake (milk-alkali syndrome)*, may induce the formation of calcium stones and deposition of calcium in the kidney (**nephrocalcinosis**).

142. **Ans. (b) Tuberculous cystitis** *(Ref: Bailey 25/e p1108)*

TB Urinary Bladder

- Bladder tuberculosis ***is almost always secondary to renal tuberculosis***[Q].
- The disease **starts at the ureteric opening**, the earliest evidence being pallor of the mucosa due to submucosal edema.
- Subsequently tiny white transluscent tubercles develop all over. Gradually these tubercles enlarge and may ulcerate (but **do not cause bladder perforation**[Q]).
- These tubercles lend **'cobblestone' appearance**[Q] **on cystoscopy**.
- There is considerable suhmucous fibrosis which causes diminished capacity of bladder. *Scarred & ftbrosed, small capacity bladder* is known as **thimble bladder**[Q].
- The fibrosis which usually starts around the ureter, contracts to cause a pull at the ureters. This either leads to a stricture or displaced, dilated and rigid wide mouthed ureter called as **golf hole ureters**[Q] (this almost always leads to *ureteral reflux*.)

143. **Ans. (a) Chronic pyelonephritis**

(Ref: Robbins 9/e p934, 8/e p943, 7/e p989)

In the morphology of chronic pyelonephritis, glomeruli may appear normal except for **periglomerular fibrosis.**

144. **Ans. (c) Silicosis** *(Ref: Robbins 9/e p690)*

145. **Ans. (b) Crystals are hexagonal** *(Ref: Robbins 9/e p 952)*

- Hexagonal stones are seen in cystine stones whereas uric acid stones are barrel or diamond shaped.
- Uric acid stones are common in individuals with hyperuricemia, such as patients with gout, and diseases involving rapid cell turnover, such as the leukemias.
- A tendency to excrete urine of pH below 5.5 may predispose to uric acid stones, because uric acid is insoluble in **acidic urine**. In contrast to the radiopaque calcium stones, ***uric acid stones are radiolucent***.

146. **Ans. (a) Nodular glomerulosclerosis**

(Ref: Harsh Mohan 6/e p678)

Nodular lesions of diabetic glomerulosclerosis are also called as *Kimmelstiel-Wilson (KW) lesions or intercapillary glomerulosclerosis.* These lesions are specific for type 1 diabetes.

147. **Ans. (d) Micro RNA-122** *(Ref: Harrison 18/e p2304-5)*

New question friends and highly likely to be repeated... see annexure.

148. **Ans. (c) Flea bitten kidney** *(Ref: Robbins 9th/947)*

Presence of a granular kidney with multiple haemorrhagic spots is suggestive of either of the following conditions:

- Malignant hypertension
- Wegener's granulomatosis
- Henoch Schonlein purpura
- Post streptococcal glomerulonephritis
- Polyarteritis nodosa
- Subacute infective endocarditis

149. **Ans. (d) Hypercellular glomeruli** *(Ref: Robbins 9/e p931)*

Hypercellular glomeruli are a feature of acute glomerulonephritis.

150. **Ans. (b) Hypertension** *(Ref: Robbins 9/e p932)*

Diabetes, analgesics, sickle cell disease and urinary tract infection are the main causes of sickle cell disease.

151. **Ans. (a) Chronic pyelonephritis** *(Ref: Robbins 9/e p933)*

152. **Ans. None or 'c' Cushing syndrome.**

(Ref: Robbins 8th/966, Kidney Cancer: Principles and Practice (2012) pg 71, Springer, Harrison 17th/592: 618)

Friends, ideal answer of this question would be none. Robbins 8th/966.... 'renal cell carcinomas produce a number of paraneoplastic syndromes, ascribed to abnormal hormone production, including polycythemia, hypercalcemia, hypertension, hepatic dysfunction, feminization or masculinization, Cushing syndrome, eosinophilia, leukemoid reactions, and amyloidosis.'

However, a table from Kidney Cancer: Principles and Practice is given underneath to help you decide the fact that if we have to compulsorily mark one option as the answer, then it has to be Cushing syndrome (option 'c') because it has the rarest incidence.

Paraneoplastic manifestations of renal cell cancer syndromes with their incidence

Paraneoplastic syndrome	Incidence
Endocrinological	
Hypercalcemia	13-20%
Hypertension	40%
Polycythemia	1-8%
Stauffer syndrome	3-20%
Elevated Alkaline	10%
phosphatase	2%
Cushing syndrome	-
Thrombocytosis	30%
Cachexia	
Non endocrine	3-8%
Amyloidosis	20%
Anemia	3%
Neuromyopathy	-
Vasculopathy	-
Nephropathy	20%
Fever	

Stauffer syndrome *is the name give to nonmetastatic hepatic dysfunction.*

153. **Ans. (d) Bilateral polycystic kidney**

(Ref: Robbins 8th/479-480, 9/e p479-480)

Wilm's tumor (Nephroblastoma) is the **most common primary renal tumor of childhood** in USA. It is associated with the following:

154. Ans. (c) Trisomy 7/17
(Ref: Robbins 8th/964-964, 9/e p953-954, Harrison 17th/592)
Friends, answer to the question is very easy for us to understand provided we are aware of the fact that chromophilic renal cell cancer is the other name of papillary renal cell cancer because 80% of chromophilic renal cell cancers show a tubulopapillary architecture. (source.... British Journal of Cancer 1996,74; 1605-1614.). As discussed in text, Papillary cancer is associated with trisomy 7, 16, 17.

155. Ans. (a) Clear cell type
(Ref: Robbins 7th/1016, 1017, 9/e p953)

156. Ans. (b) Wilm's tumor *(Ref. Robbins 8th/479, 9/e p479)*
Wilm's tumor is increased in WAGR syndrome, Dennys-Drash syndrome and Beckwith-wiedemann syndrome.
The features mentioned in the question point to a diagnosis of WAGR syndrome. The components of this syndrome are

W – Wilm's tumor
A – Aniridia
G – Genital anomalies
R – Mental retardation

157. Ans. (c) Anaplasia *(Ref: Robbins 8th/481, 9/e p481)*
5% of tumors reveal **anaplasia**, defined as the presence of cells with large, hyperchromatic, pleomorphic nuclei and abnormal mitoses and the presence of anaplasia correlates with underlying *p53* mutations and the emergence of resistance to chemotherapy.

158. Ans. (b) Associated with deletion of chromosome 11p13 *(Ref: Robbins 9/e p479, 8th/479-481; 7th/504-506)*

159. Ans. (a) Clear cell *(Ref: Robbins 9/e p953)*

160. Ans. (d) Collecting duct *(Ref: Robbins 8/e p964, 9/e p953)*

Oncocytoma

- Arises from the **intercalated cells of collecting ducts**[Q].
- Epithelial tumor composed of large **eosinophilic cells** having small, round, benign-appearing nuclei that have large nucleoli.
- *Ultrastructurally the eosinophilic cells have* ***numerous mitochondria***[Q].

161. Ans. (c) Chromosome 11 *(Ref: Robbins 9/e p479-480)*
Easiest way to remember that info..... count the number of letters in Wilms tumour..yea it is exactly 11...the location of both genes associated with Wilms tumour ☺
So, the two genes associated with Wilms tumour **WT1** gene (located on **chr 11p13**)and WT2 gene (located on **chr 11p15).**

162. Ans. (b) Tumour stage
(Ref: Robbins 8/e p, Rudolph Pediatrics; Robbins 9/e p481)
Also revise that anaplsia is an adverse prognostic factor because it increases the resistance to chemotherapy and increased chances of recurrence.

Good prognostic factors	Poor prognostic factors
• Age < 2 years • Early stage disease (stage I,II) • Favourable histology • Tumour < 500 gm	• Age > 2 years • Late stage disease (stage III,IV) • Anaplasia (unfavourable histology) • Tumour > 500 gms • Loss of genetic material on 11q,16q • Gain of material on 1q • Renal vessel and capsule invasion

163. Ans. (c) Wilm's tumor.... Discussed in a separate question *(Ref: Robbins 8/e p479-480, 9/e p479-480)*

164. Ans. (b) 8% *(Ref: Internet: multiple sources)*
Renal vein involvement is seen 4-9% of the patients of renal cell carcinoma.

165. Ans. (d) More common in females
(Ref: Robbins, 9/e p953)

166. Ans. (b) Renal cell carcinoma *(Ref: Robbins, 9/e p1134)*

167. Ans. (b) Wilms tumor *(Ref: Robbins, 9/e p480)*

168. Ans. (b) Malacoplakia *(Ref: Robbins, 9/e p963)*
Michaelis-Gutmann bodies are laminated mineralized concretions typically present within the macrophages resulting from deposition of calcium in enlarged lysosomes. It is seen in malacoplakia. Similar lesions are also seen in the colon, lungs, bones, kidneys, prostate, and epididymis. In this conditions, there is presence of PAS+ macrophages.

169. Ans. (c) Atrophy *(Ref: Robbins 7th/9, 1012, 9/e p950)*
Chronic urethral obstruction because of urinary calculi, prostatic hypertrophy, tumors, normal pregnancy, uterine prolapse or functional disorders cause **hydronephrosis** which by definition is used to describe *dilatation of renal pelvis* and calyces associated with *progressive atrophy of the kidney* due to obstruction to the outflow of urine.
Concept

Atrophy is shrinkage in size of the cell by loss of cell substance.*Atrophied cells are only decreased in size; they are not dead*

170. Ans. (c) Malacoplakia *(Ref: Robbins 9/e p963)*

171. Ans. (a) Light chain *(Ref: Robbins 9/e p937-938)*

172. Ans. (a) Schistosomiasis *(Ref: Robbins 9/e p965)*
Direct lines from Robbins...
Schistosoma haematobium infections in endemic areas like Egypt and Sudan are an established risk. The ova are deposited in the bladder wall and incite a brisk chronic inflammatory response that induces progressive mucosal squamous metaplasia and dysplasia and,

in some instances, neoplasia.

Most of these cancers are **squamous cell** carcinomas.

173. Ans. (b) Hypophosphatemia *(Ref: Harrison 18/e)*

- Hyponatremia
- Hyperkalemia
- **Hyperphosphatemia**

174. Ans. (a) p53 *(Ref: Robbins 9/e p965)*

Loss-of-function mutations in the TP53 and RB tumor suppressor genes are almost always seen in high-grade and, frequently, muscle invasive tumors.

175. Ans. (b) p16 *(Ref: Robbins 9/e p965)*

Particularly common (occurring in 30% to 60% of tumors) are losses of genetic material on **chromosome 9** (including monosomy or deletions of 9p and 9q). These abnormalities are often the only chromosomal changes present in **superficial noninvasive papillary tumors.** The 9p deletions (9p20) affects tumor suppressor gene CDKN2A, which encodes the cyclin-dependent kinase inhibitor p16/INK4a and ARF, a protein that augments p53 function.

176. Ans. (d) Both a and b *(Ref: Robbins 9/e p398, 965)*

There is an association between urinary schistosomiasis and squamous cell carcinoma (more commonly) as well as transitional cell cancer (less commonly) of the bladder.

177. Ans. (b) Embryonal *(Ref: Robbins 9/e p968)*

- **MC** sarcoma in **infancy** or childhood is ***embryonal rhabdomyosarcoma***. In some cases, it manifests as a polypoid grapelike mass (sarcoma botryoides).
- **MC** sarcoma in the bladder in **adults** is **leiomyosarcoma**

ANEXURE

Markers of Kidney Injury

Name of marker	Significance
Kidney injury molecule-1 (KIM-1) and Clusterin	• Type-1 cell membrane glycoprotein upregulated in de: differentiated proximal tubule epithelial cells • ***Elevated urinary levels are highly sensitive and specific for A***KI
Cystatin C	• Important extracellular inhibitor of cysteineproteases • Elevated urinary levels ***reflect tubular dysfunctio***n; high levels may predict poorer outcome
NGAL	• Expression upregulated in kidney proximal tubule cells and urine following ***ischemic or cisplatin induced renal injury*** • Found to be an early indicator of AKI following cardiopulmonary bypass
IL-18	• Constitutively expressed in distal tubules; strong immunoreactivity in proximal tubules with transplant rejection • Elevated urinary levels found to be ***early marker*** of AKI and ***independent predictor of mortalit***y in critically ill patients
Na^+/H^+ exchanger 3 (NHE 3)	• For ***discrimination between prerenal azotemia and AKI*** in ICU patients
L-FABP	Biomarker in **CKD and diabetic nephropathy**
Osteopontin	• Correlates with inflammation and tubulointerstitial fibrosis
β_2-Microglobulin	• Light chain of the MHC I molecule; • An ***early marker of tubular dysfunction***
α_1-Microglobulin	• Synthesized by the liver; tubular dysfunction marker
Microalbumin	Marker for monitoring progression of chronic kidney disease

NGAL is Neutrophil gelatinase associated lipocalin, Liver fatty acidbinding protein (L-FABP);

In addition, *N*-Acetyl--(D) glucosaminidase (NAG), Retinol-binding protein, Cysteine-rich protein CYR 61, Exosomal fetuin-A and enzymes like Alanine aminopeptidase (AAP), alkaline phosphatase (AP), Glutathione-S-transferase (α-GST) Glutamyl transpeptidase (γ-GT) are other markers of acute kidney injury (AKI).

CHAPTER 13

Gastrointestinal Tract

Golden Points

- Length of esophagus: 25 cm and it begins from lower border of cricoid cartilage.
- Tear in Mallory Weiss syndrome is located at the **gastro-esophageal junction.**
- Pathogenesis of Achalasia cardia: Neurogenic degeneration (causing absence of nerves). Pseudoachalasia is seen in cancer of the lower esophageal sphincter.
- Most common type of eosphageal carcinoma is squamous cell carcinoma and it affects the middle 1/3rd of the esophagus.
- Type **A** gastritis (**a**utoimmune gastritis) affects body of the stomach.
- Type **B** gastritis (bacterial cause; *H. pylori*). affects the **antrum**.
- Most common location of duodenal ulcer: Anterior wall of 1st part of duodenum.
- Most common type of gastric polyp: Hyperplastic (inflammatory) polyp.
- Gastric polyp with no malignant potential: Hyperplastic polyp.
- Most important risk factor for gastric carcinoma is **intestinal metaplasia** and its most common location is **antrum.**
- Type of gastric carcinoma with best prognosis: **Superficial spreading**.
- Gastric lymphoma is a B-cell non Hodgkin lymphoma called MALToma associated with H. pylori infection. It has lymphoepithelial lesion.
- GIST arises from Interstitial cell of Cajal having the most specific marker as DOG > c-Kit (CD117).
- Paneth cells contain zinc and provide mucosal immunity.
- Cereales to be avoided in Celiac sprue: Wheat, oat, barley, rye (rice and maize are safe).
- Most important association of celiac sprue (gluten sensitive enteropathy): HLA-DQ2 followed by HLA-DQ8.
- Maximum malignant potential: Familial adenomatous polyposis.
- Intestinal polyps with no malignant potential: Hyperplastic polyp, Juvenile polyp, Peutz Jegher syndrome.
- Protective against colorectal cancers: Vitamin A, C & E; omega-3 fatty acids (fish fat), aspirin, **high fibre diet**, folic acid, calcium, selenium.
- Most common location of colorectal cancer: ***Rectum followed by sigmoid colon***. The ascending or right colon cancer presents as a fungating/ ulcerative mass whereas descending/left colon cancer presents as a napkin-ring constriction.
- Single most important prognostic factor for colorectal cancer: Extent of tumor **(stage)**.
- Most common intestinal lymphoma: Diffuse large B-cell NHL.
- **Allgrove (triple A) syndrome**, an autosomal recessive disorder characterized by *achalasia, alacrima,* and *adrenocorticotrophic hormone-resistant adrenal insufficiency*.
- The most common cause of gastroesophageal reflux is ***transient lower esophageal sphincter relaxation***.
- ***Reflux of gastric contents*** into the lower esophagus is the most frequent cause of esophagitis.
- The malabsorptive diarrhea of Whipple disease is due to **impaired lymphatic transport**.
- ***Gastritis*** is a mucosal inflammatory process. When neutrophils are present, the lesion is referred to as acute gastritis. When inflammatory cells are rare or absent, it is termed as *gastropathy*.
- The ***most common cause of chronic gastritis*** is infection with the bacillus ***H. pylori***.
- ***Autoimmune gastritis*** is the most common cause of **diffuse atrophic gastritis**. It is the most common form of ***chronic gastritis in patients without H. pylori infection***.
- ***Carney triad***, a nonhereditary syndrome of unknown etiology is seen primarily in young females and includes ***gastric GIST, paraganglioma, and pulmonary chondroma***.
- ***Carney-Stratakis syndrome*** (different from Carney triad) is caused by loss of succinate dehydrogenase complex (SDH) function. It increases the risk of ***GIST and paraganglioma***.
- ***Celiac disease*** is associated with a higher incidence of other autoimmune diseases like including ***type 1 diabetes, thyroiditis, and Sjögren syndrome, IgA nephropathy***, and neurologic disorders, such as ***ataxia, autism, depression, epilepsy, Down syndrome, and Turner syndrome***.
- Individuals with celiac disease have a higher than normal rate of malignancy. The most common celiac disease-associated cancer is ***enteropathy-associated T-cell lymphoma***. The patients also have increased risk of small intestinal adenocarcinoma.

The normal layers present in the gastrointestinal tract are:

1. *Mucosa* consisting of epithelial layer, lamina propria and muscularis mucosae
2. *Submucosa* having submucosal glands and Meissner's plexus
3. *Muscularis propria* consisting of inner circular layer, outer longitudinal layer and having Auerbach's plexus in between these two layers.
4. *Serosa.*

Key Point

- Serosa is absent in the esophagus *except* for intra-abdominal portion.
- The **submucosa** is the **strongest** layer of the gut. Surgically, it provides strength to intestinal anastomosis

ESOPHAGUS

It is a muscular tube almost **25 cm in length in adults** (it is about 10 cm in a newborn) taking the food from the oral cavity into the stomach. The esophagus is having the following four constrictions in it:

- **Cricopharyngeus** constriction: present at 15 cm **(6 inches)** from the incisor teeth[Q].
- **Aortic arch constriction:** present at 22.5 cm **(9 inches)** from the incisor teeth[Q].
- **Left bronchus constriction:** present at 27.5 cm **(11 inches)** from the incisor teeth.[Q]
- **Diaphragmatic** and **lower esophageal sphincter** constriction: present at 40 cm **(16 inches)** from the incisor teeth[Q].

There is presence of a functional sphincter at the lower end of the esophagus (LES) which prevents the reflux of the gastric contents back into the esophagus.

Recent Exam Question

Calcifying epithelial odonto-genic tumor is called as **"Pindborg tumour".**

ACHALASIA CARDIA

It is a disease characterized by loss of ganglion cells in the Auerbach's plexus the cause of which may be unknown (**Primary achalasia**) or it may be due to secondary cause like **Chagas'** disease (caused by T. cruzi) or *Varicella zoster* infection. This result in the incomplete relaxation of the LES and its increased resting tone. There is selective loss of function of inhibitory neurons like those secreting vasoactive intestinal peptide and nitric oxide whereas *cholinergic innervation is intact.* It is characterized by the triad of *incomplete LES relaxation, increased LES tone and aperistalsis of the esophagus.*

Key Point

CCK test causes paradoxical increase in LES tone in achalasia cardia

Clinical features include ***progressive dysphagia*** (difficulty in swallowing increases with time as the disease progresses) for food though usually dysphagia is more for the liquid food as compared to solid food particles.

Key Point

The **gastric bubble** is usually **absent** in chest X-ray.

Screening test

Cholecystokinin[Q] (CCK) test: CCK normally causes a fall in the sphincter pressure (because of the relaxant effect of inhibitory neurotransmitters like VIP and nitric oxide) but in achalasia cardia it causes paradoxical increase in LES tone (loss of inhibitory neurons).

Diagnosis

- Barium swallow shows **'bird beak'[Q] or 'rat tail'[Q] appearance** of the esophagus (due to normal upper esophagus with tapering in the lower part).
- ***Manometry*** *is the most confirmatory investigation* [Q].

Treatment

It is medically managed with *botulinum toxin* but the treatment of choice is surgical excision of the muscle of the lower esophagus and cardia (*Heller myotomy*[Q]).

HIATAL HERNIA

It is characterized by the separation of the diaphragmatic crura and increased space between the muscular crura and the esophageal wall. It can be of two types:

1. **Sliding hernia** (95%): Characterized by upward dislocation of cardioesophageal junction. Esophagitis resulting from the reflux is commonly seen.
2. **Paraesophageal/Rolling hernia** (5%): A part of the stomach enters the thorax without any displacement of the cardioesophageal junction. Dysphagia is common and chest pain may also be present (usually relieved by a loud belch).

   Treatment is achieved only with surgical repair of the defect.

MALLORY-WEISS TEARS

Mallory-Weiss tears are mucosal tears in the *esophagogastric junction or the gastric cardiac mucosa* caused *due to vigorous vomiting usually seen in alcoholics.* In most of the cases (**90%**), the tear is present immediately **below the squamocolumnar junction at the cardia**[Q] whereas in 10% cases, it is present in the esophagus. These tears **never involve the muscular layer** of the esophagus whereas, in contrast, in **Boerhaave syndrome**, *rupture of all the esophageal layers* is seen including

the muscle layer. Most common location of the perforation in this syndrome is in *left posterolateral part* 3-5 cm above the gastroesophageal junction.

Key Point

Most of the cases (90%), the tear is present at the cardia.

ESOPHAGITIS

Inflammation of the esophageal mucosa is known as esophagitis and *reflux of the gastric contents into the lower esophagus* is its *most important cause*. *Gold standard* for the diagnosis of reflux esophagitis is *24 hours pH study*[Q]. The reflux is associated with obesity, alcohol intake, smoking, pregnancy and overeating.

BARRETT'S ESOPHAGUS

Barrett's esophagus is the **metaplastic change** in the esophageal lining in which the normal squamous epithelium is changed to columnar epithelium due to prolonged gastroesophageal reflux disease (GERD). It is classified as **long segment** (if **>3 cm** is involved) or **short segment** (if **<3 cm** is involved). Microscopically, esophageal squamous epithelium is replaced by columnar epithelium. *Definite diagnosis is made only when columnar mucosa contains the intestinal goblet cells*[Q].

Note: Barrett's ulcer is the ulcer in the columnar lined portion of Barrett's esophagus.

Key Point

Barrett's esophagus is the most important risk factor for the development of esophageal adenocarcinoma.

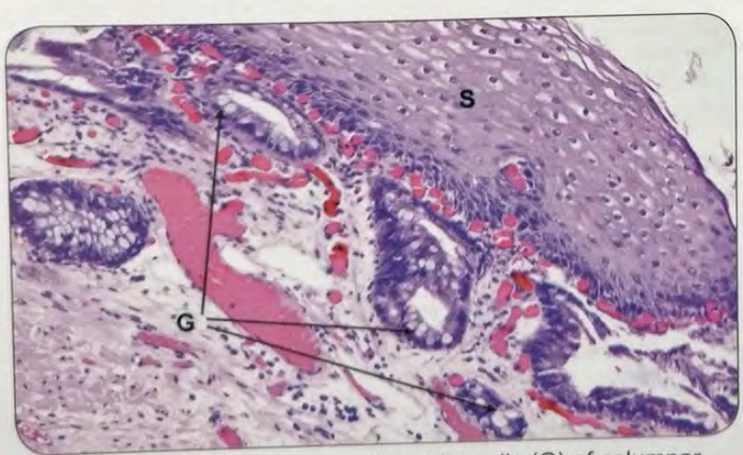


Fig. 1: Barret esopahgus with goblet cells (G) of columnar epithelium. **...(AIIMS Image)**

Concept

Intestinal goblet cells differ from normal mucus secreting foveolar cells of the stomach by the fact that in the former, there is presence of distinct mucous vacuoles (not present in gastric foveolar cells).

CARCINOMA OF THE ESOPHAGUS

It is a cancer affecting individuals of mid to late adulthood which is of two main types: **squamous cell cancer and adenocarcinoma.**

Key Point

- **Triad of Plummer Vinson syndrome = *iron deficiency anemia + esophageal webs + glossitis***
- The investigation of choice in esophageal cancer is **endoscopy and biopsy.**

Risk factors for squamous cell cancer

- Tobacco and alcohol consumption
- Hot beverages or food
- Longstanding esophagitis
- Achalasia
- *Plummer Vinson syndrome* (also known as *Patterson Kelly syndrome*)
- Ingestion of nitrites in diet
- Nutritional deficiency of vitamins A, vitamin C, riboflavin, zinc, molybdenum
- *Tylosis et palmaris* (hyperkeratosis and pitting of palms and soles)
- Longstanding celiac disease
- Other conditions like ectodermal dysplasia and epidermolysis bullosa
- ***Genetic alterations*** include amplification of cyclin D1, c-MYC and Epithelial Growth Factor Receptor (EGFR)

Most of the cancers are well differentiated and the morphological patterns include:

i. Exophytic protruding lesion in the lumen (60%)
ii. Flat, diffuse infiltrative form spreading in the esophageal wall (15%)
iii. Ulcerative lesion (25%)

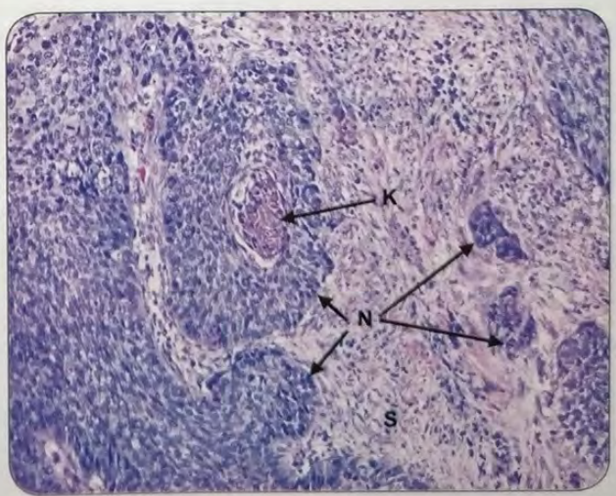


Fig. 2: Esophageal squamous cancer (N) with keratin pearl (K). **...(AIIMS Image)**

Risk factors for Adenocarcinoma

- Barrett's esophagus[Q] (*Most important*)
- Tobacco exposure

- Obesity
- *Genetic alterations* include over expression of p53, amplification of c-ERB-B2 and nuclear translocation of β-catenin (biomarkers of disease progression).

Microscopically, most of the cancers are mucin producing glandular tumors exhibiting intestinal type features. Multiple foci of dysplastic epithelium are present adjacent to the mucosa.

Key Point

Barium swallow in esophageal cancer shows **"rat tail"** appearance of the esophagus.

Clinical features include progressive dysphagia (more for solids as compared to liquids), weight loss, chest pain and vomiting. The lymph node metastasis is dependent on the anatomic site of the primary tumor.

- Cancer in the upper 1/3rd of the esophagus: metastasis to cervical lymph nodes.
- Cancer in the middle 1/3rd of the esophagus: metastasis to paratracheal, mediastinal and tracheobronchial lymph nodes.
- Cancer in the lower 1/3rd of the esophagus: metastasis to gastric and celiac lymph nodes.

Key Point

- MC type of esophageal cancer in India: ***Squamous cell cancer***Q
- MC type of esophageal cancer in upper 1/3rd of esophagus: ***Squamous cell cancer***Q
- MC type of esophageal cancer in middle 1/3rd of esophagus: ***Squamous cell cancer***Q
- MC type of esophageal cancer in lower 1/3rd of esophagus: ***Adenocarcinoma***Q.

Treatment: It is mainly surgical with **partial or total esophagectomy**.

STOMACH

CELLS AND THEIR SECRETIONS

Parietal (Oxyntic) cells	• **Secrete acid** (from the proton pump, H^+-K^+ ATPase) • **Secrete intrinsic factor** (required for vitamin B_{12} absorption)
Chief (Zymogenic) cells	• Secrete the **proenzymes pepsinogen I and II** (activated to pepsin)
Endocrine cells	• Secrete **gastrin in antrum** (by G cells), **histamine** in the body
Foveolar cells	• Secrete **mucin layer** over the mucosal cells

GASTRITIS

Gastritis is the inflammation of the gastric mucosa. It can either be acute gastritis or chronic gastritis.

Risk factors of acute gastritis

- Heavy smoking and alcohol consumption
- Excessive NSAID use (particularly aspirin)
- Uremia
- Ischemia and shock
- Stress (trauma, burns, surgery)
- Others (nasogastric intubation, distal gastrectomy, systemic infections)

Recent Exam Question

Humans are the **only** known host of *H.pylori*.

Microscopically

*Presence of neutrophils above the basement membrane in direct contact with the epithelial cells is indicative of active inflammation*Q.

Risk factors of chronic gastritis

- Chronic infection with *H. pylori*
- Autoimmune cause (pernicious anemia)
- Alcohol and smoking
- Radiation
- Antrectomy with gastroenterostomy
- Others (amyloidosis, graft-versus-host disease, uremia, Crohn's disease).

Key Point

- *H.pylori.* gastritis causes involvement of the **antrum**
- **Autoimmune** gastritis causes involvement of the **fundus** and **body.**

MICROSCOPICALLY

Chronic gastritis has the *presence of lymphocytes and plasma cells associated with intestinal metaplasia and mucosal atrophy.*

Chronic gastritis can be of the following **two types**:

1. **Associated with *H. pylori* (in 90% patients)**

H. pylori is a gram-negative flagellated bacteria producing enzymes like phospholipase and urease, adhesion molecules like BabA (responsible for enhanced binding in people having **blood group O**) and toxins like CagA and VacA. It causes gastritis in *two patterns*:

a. ***Antral predominant gastritis:*** Seen in individuals having *lower IL-1β* production and associated with *high acid production* and increased risk of *duodenal ulcer.*
b. ***Pangastritis followed by multifocal atrophic gastritis***— Seen in individuals having *higher IL-1β production* and *lower gastric acid production* and increased risk of *adenocarcinoma.*

Intraepithelial neutrophils and *subepithelial plasma cells* (meaning plasma cells in the lamina propria) are

characteristic of H. pylori gastritis. *H. pylori is also associated with peptic ulcer disease, gastric cancer and gastric mucosa associated lymphoma*[Q].

Recent Exam Question

Histology remains the gold standard for detection of *H. pylori*. The special stains used for H. pylori include **non-silver stains** (like Giemsa, Diff-Quick, Gimenez, Acridine orange) and **silver stains** (like Warthin-Starry, Steiner etc.) (*see* Figure 3)

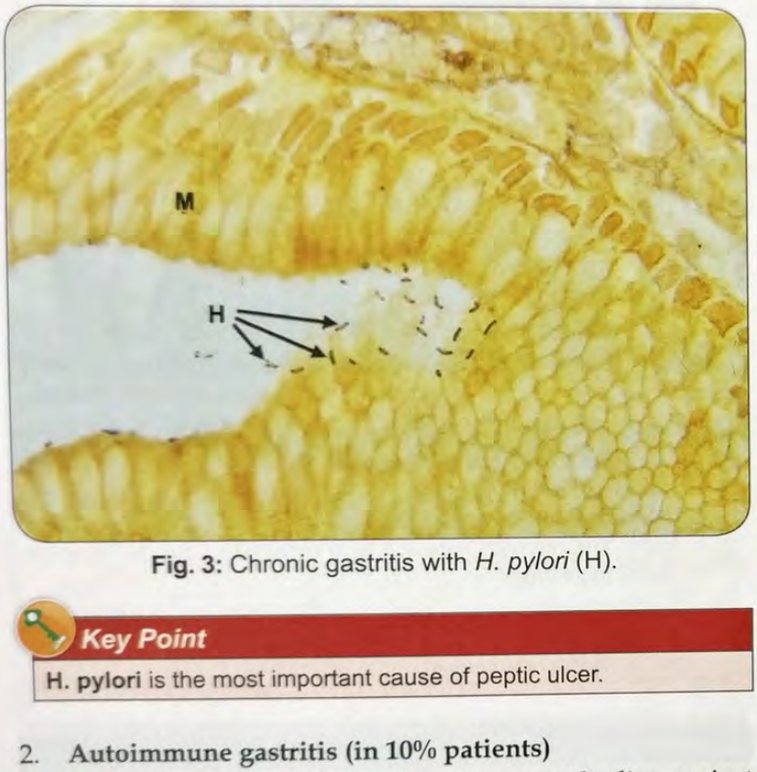


Fig. 3: Chronic gastritis with *H. pylori* (H).

Key Point

H. pylori is the most important cause of peptic ulcer.

2. **Autoimmune gastritis (in 10% patients)**
   It is caused due to formation of autoantibodies against the proton pump, gastrin receptor and intrinsic factor and is associated with pernicious anemia, Hashimoto's thyroiditis, Addison's disease, type 1 diabetes, gastric cancer and carcinoid tumor. This is particularly associated with damage to the *mucosa of the body and fundus with less involvement of the antrum*. Hyperplasia of gastrin producing G cells in the antral mucosa may result in gastric carcinoid tumor formation.

The **histologic features** of chronic gastritis include regenerative change, intestinal metaplasia (columnar absorptive cells and goblet cells of intestinal type), atrophy and dysplasia. In autoimmune gastritis, there is presence of inflammatory infiltrate having lymphocytes, macrophages in the deeper layers. *Plasma cells in the superficial lamina propria* are characteristically *absent*.

Clinical features include nausea, vomiting and epigastric pain. Autoimmune gastritis maybe associated with symptoms seen in pernicious anemia (beefy tongue, paresthesia, numbness, sensory ataxia, loss of vibration and position sense).

PEPTIC ULCER DISEASE

Any breach in the mucosa of the GIT that involves the submucosa or deeper due to exposure to gastric acid is called peptic ulcer. It is usually a chronic and ***solitary lesion less than 4 cm*** caused due to imbalance between gastroduodenal protective and damaging factors:

Damaging factors	Protective factors
• Gastric acid • Pepsin • Smoking, alcohol • Drugs like NSAIDs • H. pylori • Ischemia and shock • Delayed gastric emptying • Duodenal gastric reflux or gastric hyperacidity	• Mucus and bicarbonate secretion • Mucosal blood flow • Prostaglandin production • Epithelial regenerative capacity

The **location of the peptic ulcer** (in decreasing order of frequency) is:

- **Duodenum (first part)**[Q]
- Stomach **(lesser curvature near the junction of body and antrum**[Q]**)**
- Gastroesophageal junction in GERD or Barrett's esophagus
- Margins of jejunostomy
- Stomach, duodenum and/or jejunum of patients with Zollinger-Ellison syndrome
- In ileal Meckel's diverticulum containing ectopic gastric mucosa.

Males are more commonly affected than females

Duodenal ulcers are located near the pyloric ring and gastric ulcers are predominantly located near the lesser curvature and the antrum. More commonly, there is involvement of the *anterior wall of the duodenum* as compared to the posterior wall. Benign peptic ulcer is classically punched with margins of the ulcer usually at level with the surrounding mucosa whereas heaping up of the margins is more frequently associated with malignancy. Histologically the zones in peptic ulcer are:

i. Base and margins having necrotic fibrinoid debris
ii. Zone of neutrophil predominant infiltrate
iii. Base having active granulation tissue with mononuclear cells
iv. Zone of fibrous or collagenous scar

Clinical features include burning epigastric pain (usually getting worse at night), nausea, vomiting and bloating.

Recent Exam Question

Gastroduodenal artery is the source of the bleeding in **duodenal ulcer** whereas *left gastric artery* bleeds in *gastric ulcer.*

Complications of Peptic Ulcer

Bleeding

- Most frequent complication[Q]
- More common in posterior wall duodenal ulcers[Q]

Perforation

- Most common cause of death in peptic ulcer[Q]
- More common in anterior wall duodenal ulcers[Q]

Gastric outlet obstruction (GOO)

- Results in persistent vomiting leading to fluid and electrolyte imbalance (metabolic alkalosis due to loss of acid in vomitus)

Malignancy

- Associated with gastric ulcer but never with duodenal ulcer.

Duodenal and Gastric peptic ulcer

Features	Duodenal ulcer	Gastric ulcer
Site	1st part of duodenum	Along lesser curvature
Incidence	More common	Less common
Age	25 – 50 yrs, M>F	Beyond 6th decade, M>F
Etiology	Almost all patients have H. pylori infection	Less stronger association
Acid level	High	Usually normal; ↑ if hypergastrinemia
Pain after food intake	Relieved	Aggravated
Clinical features	Night pain and melena more common	No night pain, hematemesis more common
	No vomiting/no weight loss	Vomiting common/ weight loss is present
Complications	No malignant change	Malignant change present (though rarely)

Investigations

- **Screening test:** Serum ELISA for antibodies against *H. pylori*
- Urea breath test (radiolabeled urea is broken down to radiolabeled CO_2 by urease enzyme which is detected by breath analyzer, thus suggesting presence of *H. pylori* infection)
- **Gold standard:** Staining of *H. pylori* with silver stain or Warthin starry stain[Q]
- **Most specific investigation:** Culture of bacteria[Q] (done on Skirrow's medium)

Treatment: with "triple drug therapy"[Q] (combination of lansoprazole, clarithromycin and metronidazole) for 2 weeks.

Concept

Urea breath test is used to ensure the efficacy of the treatment for peptic ulcer disease.

Key Point

Menetrier disease: It is characterized by diffuse foveolar cell hyperplasia due to **excessive secretion of TGF-α.** It is associated with ***enlarged gastric rugae*** and ***protein losing enteropathy***.

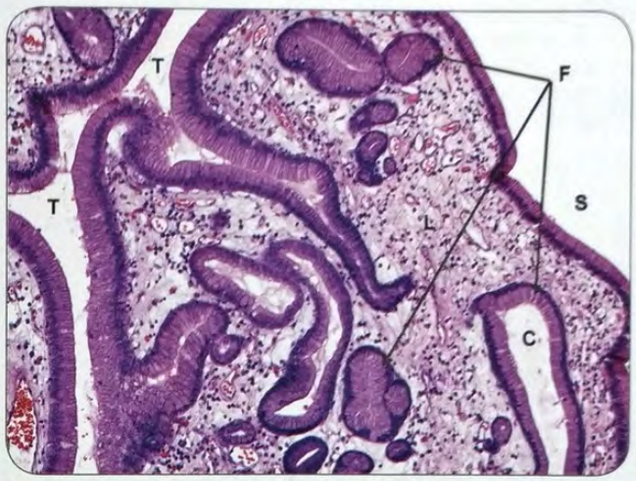


Fig. 4: Menetrier disease with foveolar cell hyperplasia (F).

Recent Exams Questions

- **Cushing ulcer** is seen in esophagus, stomach or the duodenum and is associated with *intracranial disease or head injury*. It is caused by gastric acid hypersecretion due to vagal nuclei stimulation.
- **Curling ulcer** is seen in proximal duodenum and is associated with *burns or trauma*. It is caused due to reduced blood supply and systemic acidosis in burns or trauma.

GASTRIC CANCER

Gastric cancer is the *most common gastric malignancy*. The risk factors for this cancer are:

Environmental factors	Genetic factors	Host factors
• H. pylori infection • Nitrites in diet • Nutritional (vitamins C, E) deficiency • Smoking	• Family history of gastric cancer • Blood group A • Hereditary nonpolyosis colon cancer syndrome (HNPCC) • Familial gastric cancer syndrome (*due to E-cadherin mutation*)	• Chronic gastritis • Intestinal metaplasia • Partial gastrectomy • Gastric adenoma • Barrett's esophagus • Menetrier disease

Classification of gastric cancer

1. **Based on Lauren's histological classification**
   i. *Intestinal type*: This is localized type of cancer composed of the neoplastic intestinal glands which exhibit an expanding sheet pattern of spread due to cohesion of the cells.

ii. *Diffuse type*: Poorly differentiated non-cohesive cells which do not form glands. The appearance of the cells is "**signet ring**" appearance[Q] (because mucin in the cell pushes the nucleus to the periphery). It is seen more frequently with *E-cadherin mutation*.

Concept

Infection with *H. pylori* is associated with *distal intestinal type* and **not** with diffuse, proximal carcinoma.

2. **Based on Depth of invasion**
   i. *Early gastric cancer*: Characterized by the involvement of ***mucosa and the submucosa*** irrespective of the involvement of perigastric lymph nodes and is associated with better prognosis.
   ii. *Late gastric cancer*: Characterized by the involvement of the ***muscle layer***[Q] of the stomach and is associated with poor prognosis.

Key Point

Diffuse involvement of the stomach in cancer is called **linitis plastica** or **"leather bottle"** appearance of the stomach. It is also seen in metastasis from cancers of breast and lung.

3. **Based on Macroscopic pattern**
   i. Protruding mass or *exophytic* (type I lesion)
   ii. *Flat* or depressed: No obvious mass in the mucosa (type II lesion)
   iii. *Excavated:* Erosion is present in stomach wall (type III lesion).

Recent Exam Question

H. pylori is a **Type 1 carcinogen** for **gastric cancer**.

Clinical Features

The most common location of the gastric cancer is the antrum of the stomach[Q]

Symptoms include postprandial heaviness in the abdomen (*earliest symptom*), weight loss (*most common symptom*), vomiting and anorexia.

Investigation of choice: Endoscopy with biopsy and brush cytology[Q].

Recent Exam Question

Metastasis to anterior left axillary lymph node is called as **Irish Nodes.**

Metastasis occurs to the liver (first organ to be affected) followed by lungs, bone, ovary (where it is known as **Krukenberg's tumor**), periumbilical lymph nodes (*Sister Mary Joseph nodule*), peritoneal cul-de-sac (Blumer's shelf palpable on rectal or vaginal examination) and left supraclavicular lymph node (*Virchow's lymph node*[Q]).

Treatment: Surgical resection is the only curative treatment in gastric cancer. Chemotherapy may be given in advanced cancers with ECF regime (Epirubacin, Cisplatin and 5-Fluorouracil).

GASTROINTESTINAL STROMAL TUMOR (GIST)

- Arise from pacemakers of the GIT known as *interstitial cells of Cajal*[Q].
- GIST is the **most common mesenchymal tumor**[Q] of the abdomen
- The most common location of the GIST is the **stomach**[Q]
- This is associated with patients having **neurofibromatosis-1**[Q].
- **Microscopically** the tumor may show either epithelioid cells, spindle cells or mixed (both the epithelioid cells and spindle cells).
- The useful diagnostic markers are DOG (detected on GIST) and **c-kit (CD117)**[Q].
- It is **best diagnosed** with**CT scan *with PET scan***[Q] (preferable) or CT scan.
- **Treatment**is done with **surgical resection** (localized tumors) and non-excisable tumors are managed with tyrosine kinase inhibitors called **imatinib mesylate**[Q] or sunitinib.

Recent Exam Question

Carney's triad is gastric GIST + paraganglioma + pulmonary chondroma.

INTESTINE

Infectious Diseases

The important causes of infections in the intestine are as follows:

I. *Enteric fever (typhoid)*
   It is caused because of infection with Salmonella species usually affecting the ileum and the colon.
   - It is associated with ulceration of the Peyer's patches in the terminal ileum and presence of **longitudinal ulcers**[Q] (oval ulcers with long axis along the long axis of the ileum). Microscopic examination reveals the presence of macrophages having bacteria and red blood cells (*erythrophagocytosis*[Q])
   - In the liver, the hepatocytes are replaced by an aggregation of macrophages called as "typhoid nodule"[Q]. Involvement of gallbladder results in development of chronic carrier state. Healing in ulcer is *uncommonly associated with fibrosis or stricture formation*.
   - Clinically, the patient develops ***step-ladder pyrexia, rose spots*** (erythematous macular lesions on chest and abdomen), abdominal pain, vomiting and diarrhea. ***Salmonella osteomyelitis*** is particularly common in patients having ***sickle cell disease***.

- Complications include hemorrhage and perforation.
- ***Blood culture*** is the mainstay of diagnosis and Widal test is use for measuring the antibody titer.
- Drug of choice for the treatment is ***ciprofloxacin/ ceftriaxone*** and for *carriers*, it is *ampicillin + probenecid*.

Recent Exams Questions

- **Erythrophagocytosis** is a characteristic feature of **enteric fever.**
- **Hemorrhage** occurs in **3rd week** of typhoid infection.

Key Point

Unlike typhoid, **stricture formation** is **common** in intestinal **tuberculosis.**

II. *Tuberculosis*: It can present itself in two of the following forms:

Primary infection

- Caused by infection due to *Mycobacterium bovis* (due to intake of infected/non pasteurised milk) and results in the development of hyperplastic tuberculosis. The infection is present in the lymphoid follicles of the intestine and associated with thickening and narrowing of the lumen of the intestine. It usually affects the *ileocecal region* and is associated with subacute intestinal obstruction. The mesenteric lymph nodes are enlarged; matted and caseous. This is known as **tabes mesenterica**.
- ***Clinical features*** of the patient include acute abdominal pain and intermittent diarrhea. Investigations show widening of the ileocecal angle (known as **"pulled up cecum"**) on barium radiography.

Secondary infection

- Caused by *Mycobacterium tuberculosis* secondary to swallowing of infected sputum in a patient of pulmonary tuberculosis. It is characterized by presence of the **transverse ulcers** in the intestine particularly the ileum.
- ***Clinical features*** of the patient include weight loss and intermittent diarrhea. Investigations show "*filling defect* in the ileum, cecum and ascending colon" on barium radiography. Complications include perforation of the intestine and fistula formation.

Treatment is by administration of antitubercular therapy (conservative management) or surgical resection of the affected part of the intestine (in case of obstruction or fistula formation).

III. *Amoebiasis*

It is caused by infection with an anaerobic protozoa *E. histolytica* and results in the development of **flask shaped ulcers**[Q] (ulcer with a broad base but narrow neck). The disease affects the cecum and ascending colon followed by sigmoid colon, rectum and appendix. The ulcers usually involve the mucosa and the submucosa (not the muscle layer) and have the presence of liquefactive necrosis. Liver is another important organ affected by the disease resulting in the development of hepatic abscess having necrotic material and hemorrhage (called as **"anchovy sauce pus"**[Q]). The invasive disease is diagnosed with ELISA.

Key Point

The drug of choice for amoebiasis is metronidazole.

Microbiology link!

- Rotavirus is the most common cause of diarrhea in children of age 6-24 months.
- *Giardia lamblia* is the most common pathogenic parasitic infection in the humans.
- Cholera is caused by *Vibrio cholerae* resulting in the passage of "rice water" stools.

PSEUDOMEMBRANOUS COLITIS

It is a condition most commonly caused by ***Clostridium difficile*** and is characterized by inflammation in the colon associated with the formation of a pseudomembrane (layer of inflammatory cells and necrotic material overlying the sites of mucosal injury). In normal individuals, the normal flora of the gut is responsible for the production of chemicals called bacteriocins in the intestine. On administration of broad spectrum antibiotics (***most commonly, IIIrd generation cephalosporins***), the normal bacteria are destroyed resulting in increased proliferation of the Clostridium bacteria which then produces large amounts of two toxins, toxin A and toxin B. These toxins induce cytokine production and host cell apoptosis resulting in diarrhea. The disease is diagnosed with the demonstration of ***C. difficile*** **cytotoxin in stool.**

Key Point

Treatment of Pseudomembranous colitis is done with either **metronidazole (drug of choice)** or vancomycin.

Malabsorption Syndromes

Defective absorption of fats, vitamins, proteins, carbohydrates and fats is called malabsorption. Its hallmark feature is steatorrhea and chronic diarrhea is the most common clinical presentation. The important causes are as follows:

1. ***Celiac Disease (Celiac Sprue or Gluten Sensitive Enteropathy or Non-troical sprue)***

   It is a disease characterized by increased sensitivity to a protein called **gluten** or its alcohol soluble fraction **α-gliadin**[Q] present in the grains like wheat, oat, barley and

rye resulting in a T-cell mediated chronic inflammatory reaction in the small intestine and impaired absorption. It is associated with **HLA-DQ2 or HLA-DQ8**. Clinical features include diarrhea, flatulence, weight loss and fatigue and a characteristic skin lesion called '*dermatitis herpetiformis*'.

Key Point

Dapsone is the drug of choice for dermatitis herpetiformis.

Biopsy of the intestine shows the diffuse enteritis (lymphocytes and plasma cells in lamina propria) with marked atrophy of the villi and elongated and hyperplastic crypts (**overall mucosal thickness is unaltered**Q). The disease also demonstrates the presence of antigliadin, **antiendomysial**Q **(most useful)** or antitransglutaminase antibodies Q (useful for screening test) whereas definitive diagnosis is made by the following three features:

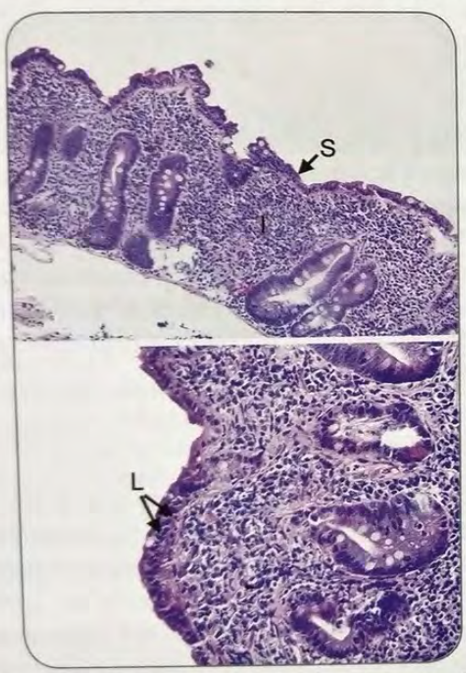


Fig. 5: Celiac disease having villous atrophy on surface (S) and presence of intra epithelial lymphocytes (L). **...(AIIMS Image)**

- Clinical documentation of malabsorption
- Demonstration of small intestinal lesion by biopsy
- Improvement in clinical features and mucosal histology on gluten withdrawal from the diet.

Treatment is intake of the ***gluten-free diet*** and substitution by rice, millet, tapioca, potato and maize in the diet.

2. ***Tropical Sprue (Post Infectious Sprue) is now called as Environmental Enteropathy***

It is a disease similar in features to celiac sprue but present in the tropical region. Though the exact cause is unknown, but bacterial overgrowth particularly *E. coli and Hemophilus* have been implicated. Biopsy of the intestine shows the diffuse enteritis with *atrophy of the villi*. Treatment is done with the help of antibiotics.

Concept

In tropical sprue, the features in the intestine **do not** reverse on gluten free diet.

Note:

- There is characteristically involvement of the **proximal intestine in celiac sprue** resulting in iron deficiency anemia whereas ***in tropical sprue, there is generalized involvement of the small intestine*** (resulting in megaloblastic anemia because B12 and folic acid are absorbed from the terminal ileum).
- Another important difference between the two is that ***tropical sprue is not associated with cancer development*** whereas **celiac sprue is associated with cancers** like non Hodgkin's lymphoma, small intestine adenocarcinoma and esophageal squamous cell cancer.

3. ***Whipple's Disease***
   - It is a systemic infectious disease caused by an actinomycete, *Tropheryma whippelii* affecting the triad of *small intestine, CNS and joints*Q. The bacteria characteristically proliferate inside the macrophages without getting destroyed.
   - The **hallmark feature** of the disease is *small intestinal mucosa having macrophages in the lamina propria* and these macrophages show the *presence of PAS positive, diastase resistant granules*Q *and rod shaped bacteria on electron microscopy*. There is mucosal edema, dilation of the lymphatics and involvement of mesenteric lymph nodes. The macrophages having the bacteria can also be found in the *joints, brain, cardiac valves etc with absence of inflammation* being a typical feature.
   - Clinical features include arthropathy (initial presentation), diarrhea, weight loss, hyperpigmentation and dementia. *The diarrhea is due to impaired lymphatic transport.*
   - Diagnosis is confirmed by identification of *T. whipplei* by polymerase chain reaction (PCR). Treatment is done with **cotrimoxazole** (*drug of choice*) for one year.

Concept

The presence of *T. whipplei* **outside of macrophages is more important** indicator of active disease than is their presence inside the macrophages.

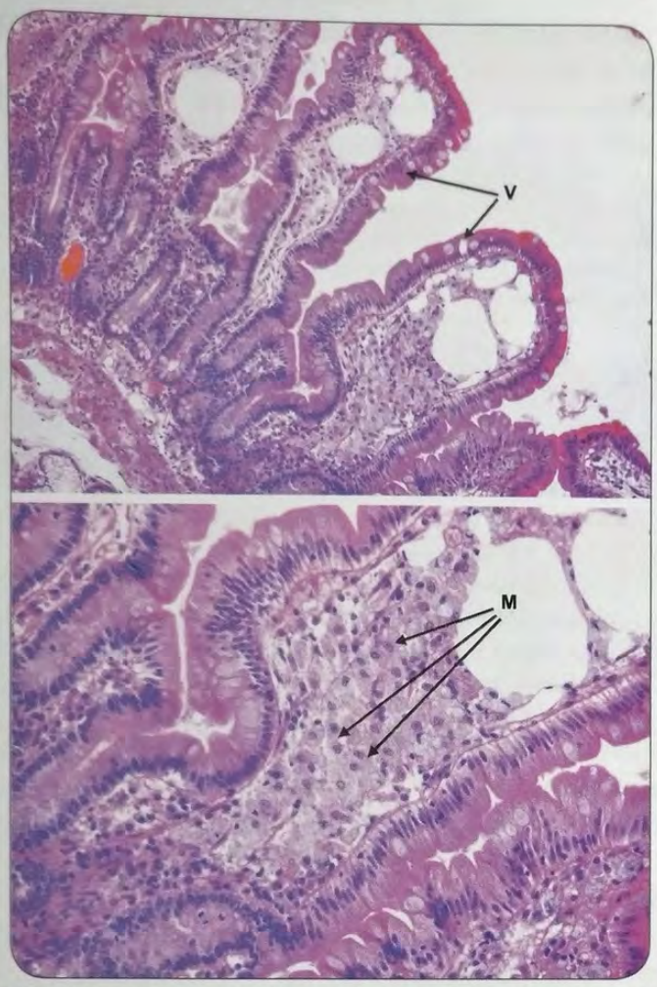


Fig. 6: Whipple's Disease: Several broad villi (V), abundant foamy macrophages (M).

Notes:

- Hallmark of Whipple's disease had been presence of PAS positive macrophages containing the characteristic small bacilli. But, similar picture (PAS +ve macrophages with bacilli) can also be seen with M. avium complex (cause of diarrhea in AIDS). However, these organisms are acid fast whereas Tropheryma is not.
- The organs in which these foamy macrophages can be seen are Liver, Small intestine, Lymph nodes, Heart, Eyes, CNS and synovial membranes of joints.

Disorders Associated with Abnormalities in Small-Bowel Biopsy Specimens

Biopsy has diagnostic value (Diffuse Lesions)	
Whipple's disease:	Lamina propria infiltrated with macrophages containing PAS-positive glycoproteins
Abetalipoproteinemia:	Villus structure normal; epithelial cells vacuolated due to excess fat
Agammaglobulinemia:	Flattened or absent villi; increased lymphocytic infiltration; absence of plasma cells
Mycobacterium avium complex	

Contd...

Contd...

Biopsy may have diagnostic value (Patchy lesions)	
Intestinal lymphoma:	Infiltration of lamina propria and submucosa with malignant cells
Intestinal lymphangiectasia:	Dilated lacteals and lymphatics in lamina propria; clubbed villi
Eosinophilic enteritis:	Diffuse or patchy eosinophilic infiltration in lamina propria and mucosa
Amyloidosis:	Presence of amyloid confirmed by special stains
Regional enteritis:	Noncaseating granulomas
Parasitic infestations:	Parasitic invasion of mucosa; adherence of trophozoites to mucosal surface, as in Giardiasis
Systemic mastocytosis:	Mast cell infiltration of lamina propria
Biopsy is abnormal but not diagnostic	
Celiac sprue	Collagenous sprue
Tropical sprue	
Folate deficiency	Vitamin B_{12} deficiency
Acute radiation enteritis	
Systemic scleroderma	Bacterial overgrowth syndromes

Inflammatory Bowel Disease (IBD)

It is a group of chronic inflammatory conditions as a result of unregulated and persistent activation of the immune system in genetically susceptible persons. It is primarily of two types: Crohn's disease and ulcerative colitis.

CROHN'S DISEASE

It is a chronic granulomatous disease which can affect any part of the gut from the esophagus to the large intestine but the *most commonly affected part is small intestine particularly the ileum*. So, it is also called as *"terminal ileitis" or "granulomatous colitis"*[Q]. It is associated with HLA-DR1/DQw5 and NOD2 genes and an abnormal T-cell response particularly, CD4+ T cells (T_H1 cells[Q]).

MORPHOLOGY

- The *earliest lesion* in Crohn's disease is the **aphthous ulcer**. Many such ulcers may fuse together to from *serpentine ulcers* arranged longitudinally.
- Grossly, involved bowel segment typically has a rigid, strictured or **thickened wall with creeping fat**[Q].
- Full thickness of the intestine is affected in the disease i.e. there is **transmural inflammation**[Q]. This causes weakness in the wall thereby leading to *fissure and fistula formation* in Crohn's disease. Fibrosis is also commoner in this type of IBD. *Perianal fistula is the most common fistula seen.*
- There is patchy involvement of the intestine which is known as presence of *"skip lesions"*. The intervening area

between two affected portions is absolutely normal. So, the mucosa appears to be irregular which is known as "**cobblestone mucosa**"Q

- There is a presence of **non-caseating**Q granulomas.
- Clinical features are intermittent attacks of abdominal pain, blood in stools, fever, steatorrhea and megaloblastic anemia (the last two features result because there is impairment in the absorption of bile acids and vitamin B_{12} respectively from the ileum).
- **Screening test** is *presence of ASCA* (**Anti-Saccharomyces cerevisae Antibody**Q). Antibody formation is common against cell wall of yeast, *Saccharomyces cerevisae* in patients of Crohn's disease. The investigation done in these patients to confirm the diagnosis is endoscopy and colonoscopy so that direct visualization of the lesions can be done and even a biopsy can be taken if needed.

Recent Exam Question

"Skip lesions" and **non-caseating granulomas** are characteristic features of Crohn's disease.

Key Point

Radiological appearance on barium meal follow-through is known as **"String Sign of Kantor"** because of the decreased lumen in the affected part of the intestine.

Important features of Crohn's disease

S	–	**S**kip lesions
I	–	**I**leum (MC affected site)
S	–	**S**accharomyces cerevisae antibody present
T	–	**T**ransmural involvement
E	–	**E**xtra fibrosis and fistula formation (as compared to ulcerative colitis)
R	–	**R**adiological sign- *String sign of Kantor*, **R**ectum is *usually spared*.

Key Point

Radiological appearance on barium meal follow-through is known as **"lead pipe" appearance.**

Mnemonic

The mnemonic for important features of Ulcerative colitis is **U**lcerative **COLITIS.**

ULCERATIVE COLITIS

It is a chronic inflammatory condition affecting the colon. It most commonly starts from the rectum and affects the superficial layers, the mucosa and the submucosaQ (*muscularis propria is rarely affected*). It is **associated with HLA-DR2,** polymorphism in IL-10 gene and an abnormal T-cell response particularly of CD4+ T cells (**TH2 cells**Q).

MORPHOLOGY

- The disease involves the entire colon (**pancolitis**)Q starting from the rectum (retrograde involvement). There is presence of regenerating mucosa which projects in the lumen and is called "**pseudopolyps**"Q
- In extreme cases, there is involvement of the nerve plexus in the muscularis layer resulting in decrease in the motility of the colon and increase in its size over a period of time giving rise to "**toxic megacolon**"Q
- The characteristic feature of the disease is **mucosal damage continuously** from the rectum and extending proximally. This may also lead to "*backwash ileitis*". This type of IBD is more commonly associated with progression to the development of cancer.
- There is **absence of granulomas**Q.
- Clinical features are intermittent attacks of abdominal pain, bloody mucoid stools and fever.
- There is presence of **p-ANCA**Q (perinuclear antineutrophil cytoplasmic antibodies).

Mnemonic

The mnemonic for important features of Crohn's disease is **SISTER**

Important features of ulcerative colitis

Ulcerative	–	**U**lcers in mucosa and submucosa (Muscle layer **not** effected)
C	–	**C**ontinuous retrograde involvement (No skip lesions)
O	–	**O**riginates in the rectum
L	–	**L**ead pipe appearance
I	–	**I**ncreased chances of cancer (More than that in Crohn's disease)
T	–	**T**oxic megacolon (Due to involvement of transverse colon)
I	–	**I**ncreased growth from the mucosa ("Pseudopolyps")
S	–	**S**ymptoms are severe (As compared to Crohn's disease)

- The extraintestinal manifestations in the IBD are *uveitis, iritis, ankylosing spondylitis, clubbing, migratory polyarthritis, sacroilitis, primary sclerosing cholangitis, pyoderma gangrenosum, erythema nodosum* etc.
- The disease is treated with sulfasalazine (5-aminosalicylic acid is the principal therapeutic moiety), infliximab (TNF-α antagonist) and steroids.
- IBD is a ***precancerous condition*** and can increase the risk of development of cancer of the colon.

Concept

Polymorphism of the **IL-23 receptor** is **protective** in both the types of inflammatory bowel disease.

Smoking is a strong exogenous risk factor for development of **CD** whereas smoking partly ***relieves symptoms in UC***.

CARCINOID TUMOR

Carcinoid tumor arises from the endocrine cells called as argentaffin tissue (also called as **Kulchitzsky cells** of crypts of Lieberkuhn) with the GIT and the lungs as the main sites of origin of this cancer. The clinical features are due to release of peptide and non-peptide hormones from these cells. The gastrointestinal carcinoid tumors can be of the following types:

1. Foregut carcinoid tumors: Arise from the esophagus, stomach and the duodenum proximal to the ligament of Treitz, these are usually benign.
2. Midgut carcinoid tumors: Arise from the jejunum and ileum; these are aggressive and metastasize frequently.
3. Hindgut carcinoid tumors: Arise from the appendix, colon and rectum; usually benign.

Mnemonic

Alphabet M: **M**idgut carcinoid tumors are **M**alignant tumors

Morphology

On section, the tumors show a characteristic solid, yellow tan appearance and on electron microscopy, the tumor cells show **dense core granules** in the cytoplasm which stain positively with *chromogranin A, neuron-specific enolase and synaptophysin*[Q] on immunocytochemistry.

Carcinoid syndrome is present in 1% patients of carcinoid tumor and it is due to excessive release of serotonin (5-HT)[Q] It is strongly associated with metastatic disease.

Cardiac lesions are present in 50% of the patients with the *carcinoid syndrome.* They consist of **fibrous intimal thickenings** on the inside surfaces of the cardiac chambers and valvular leaflets. And are located mainly in the **right ventricle, tricuspid and pulmonic valves**, and *occasionally in the major blood vessels.* The commonest cardiac manifestation is the ***tricuspid regurgitation*** (tricuspid stenosis is relatively uncommon) followed by pulmonary regurgitation.

Concept

The cardiac changes are **largely right sided** due to inactivation of both serotonin and bradykinin in the blood during passage through the lungs by the monoamine oxidase present in the pulmonary vascular endothelium.

Hepatic metastasis is usually present in this tumor. The **most sensitive screening test** for small intestine carcinoids is the **plasma level of chromogranin A**. The levels of 5-HT and its metabolite *5-hydroxyindoleacetic acid*[Q] (5-HIAA) is elevated in the urine.

Mnemonic

Clinical features of carcinoid syndrome are

S - **S**ystemic fibrosis (Affects cardiac valves, endocardium, retroperitoneal and pelvic fibrosis)
H - **H**epatomegaly (Because of metastasis)
I - **I**ntestinal hypermotility (Vomiting, diarrhea, cramps, nausea)
V - **V**asomotor symptoms like flushing and cyanosis of the skin
A - **A**sthma like features (Cough, wheezing, dyspnea)

POLYPS

Polyps are seen most commonly in colon but can also be seen in other parts of GIT.

Polyps

Non-inflammatory	Neoplastic polyps
• Inflammatory polyp • Hyperplastic polyps • Hamartomatous polyps: they of 2 types – Juvenile polyp (MC in rectum) – Peutz-jegher polyp (MC in jejunum)	• Adenomatous polyp – Tubular adenoma (most common) – Villous adenomas (maximum malignant potential) – Tubulovillous adenoma

Key Point

The **size of the adenoma** is the most important characteristic which correlates with the **risk of malignancy**.

Concept

- Dysplasia may be seen in a small number of juvenile polyps and the juvenile polyposis syndrome is associated with increased risk of colonic cancer.
- Peutz Jegher polyp is a benign polyp but Peutz-Jegher's syndrome is characterized by multiple hamartomatous polyps scattered throughout the GIT and melanotic mucosal and cutaneous pigmentation around the lips, oral mucosa, face, genitalia and palmar surface of the hands.

Adenomatous polyps are usually asymptomatic.

Key Point

Peutz-Jegher's syndrome is associated with *increased risk of developing carcinoma* of pancreas, colon, breast, uterus, lung and ovary. The GIT malignancy in these patients arises **independently** of the hamartomatous polyps.

Also Know

Hamartomatous polyps can occur sporadically or as a part of syndromes such as Juvenile polyposis, Peutz-Jegher syndrome, Cowden syndrome and Cronkhite-Canada syndrome. All these syndromes have autosomal dominant inheritance **except Cronkhite-Canada syndrome, which is a non-hereditary disorder.**

CARCINOMA OF THE COLON

The cancer of the colon is seen frequently in old age (peak age 60-79 years). It is an **adenocarcinoma** in almost all the patients. The risk factors for the colon cancer are:

A. GENETIC FACTORS

i. *Hereditary Non-polyposis Colon Cancer (HNPCC) syndrome* (also called as **Lynch syndrome**[Q])
It is an autosomal dominant condition characterized by the increased incidence of colon cancer and extraintestinal

cancer particularly the ovarian and endometrial cancer. The hallmark is the *mutation in the DNA repair genes (MSH2 and MLH1) leading to microsatellite instability*. Colon cancers in these patients affect ***right or ascending colon*** and occurs at **younger age (<50 years)**. The proximal colon tumors in HNPCC have a better prognosis than sporadic tumors from patients of similar age.

ii. ***Familial Adenomatous Polyposis (FAP)***

It is caused by the mutation of adenomatous polyposis coli (APC) gene present on the long arm of chromosome 5Q (5q21). Some FAP patients without APC mutation have a mutation in the nucleotide base excision repair gene called MUTYH. Colorectal carcinoma develop in 100% of untreated FAP patients **often before age 30**. As a result, prophylactic colectomy is the standard therapy in patients with APC mutations.

Subtypes of FAP

Classic FAP syndrome
• The patient has a large number of adenomatous polyps and retinal pigment epithelial hypertrophy. There should be a minimum of *100 polyps*Q to make a diagnosis of this syndrome. Most of the adenomatous polyps are tubular polyps.
Attenuated FAP syndrome
• The patient has a lower number of adenomatous polyps (around 30) which are located in proximal colon.
Gardener syndromeQ
• Intestinal polyps + epidermal cysts + fibromatosis + osteomas (of the mandible, long bones and skull).
Turcot syndromeQ
• Adenomatous colon polyposis + CNS tumors (medulloblastoma in 2/3rd and gliomas in 1/3rd patients).

iii. ***Mutations affecting p53 and K-RAS genes***

Concept

Prophylactic colectomy in FAP **does not** decrease risk for cancer due to adenomas at other sites specially ampulla of Vater and stomach.

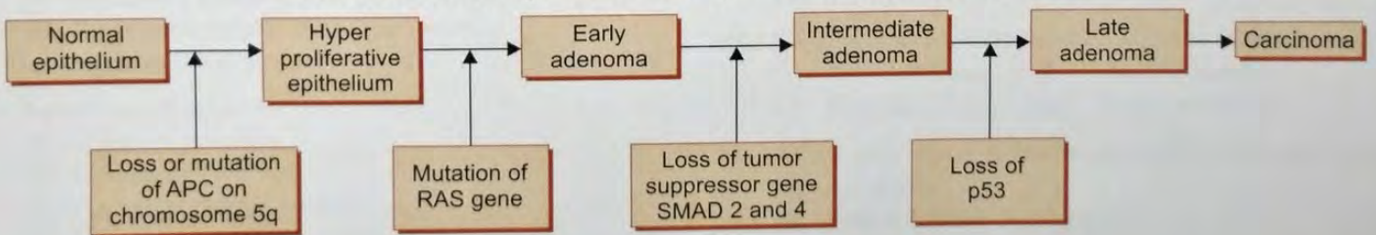
B. ENVIRONMENTAL FACTORS

Factors increasing risk	Factors decreasing risk
• Increased calorie intake and obesityQ • Decreased intake of micronutrients • Smoking and alcoholQ • Streptococcus bovis septicemia or endocarditis • UreterosigmoidostomyQ • Inflammatory bowel diseaseQ • Acromegaly • Pelvis irradiation	• Increased intake of dietary fiberQ • Intake of ω-3 fatty acids (fish)Q • NSAID use (especially Aspirin)Q • Intake of folic acid and calciumQ • Hormone replacement therapy

Molecular pathogenesis

1. **APC/β-catenin pathway** (also called *adenoma-carcinoma sequence*): Loss of tumor suppressor APC gene is followed by increased β-catenin transcriptional activity (normal APC protein degrades β-catenin) leading to localized colon epithelial proliferation and formation of small adenoma. This is followed by dysplastic change due to activating mutation in K-ras and inhibition of tumor suppressor genes like SMAD2, SMAD4 and p53 leads ultimately to cancer.
2. **Microsatellite instability pathway**: Genetic lesions in 90% cases involve **MSH2 and MLH1 genes** which are *DNA mismatch repair genes*. These genes correct any genetic disruption which may arise whenever the colonic cells are multiplying rapidly. Any mutation in these genes causes activation of BRAF and inhibition of BAX protein and TGF-β type II gene thereby increasing the chances of development of colonic cancer. Kras and p53 are not typically mutated.

Colon cancer exemplifies the concept of multi-step carcinogenesis



MORPHOLOGY

Most of the cancers arise from the **rectum**Q *followed by the sigmoid colon*. Microscopically, it is an adenocarcinoma and invasive cancers invoke a strong desmoplastic response. Cancers in the **anorectal region** are **squamous cell cancers**.

CLINICAL FEATURES OF COLORECTAL CARCINOMA

Features	Right sided/proximal	Left sided/distal
Sites in colon	Caecum and ascending colon	Descending colon and sigmoid colon

Contd...

Contd...

Features	Right sided/proximal	Left sided/distal
Gross appearance	Fungating/ulcerative type polypoid carcinoma Large cauliflower-like soft friable mass projecting into lumen	Obstructive type Carcinomatous ulcers have Napkin ring configuration
Infiltration	Absent	Present
Clinical features	Fatigue, weakness, Iron deficiency anemia, bleed readily	Occult bleeding change in bowel habits carmpy lower left quadrant discomfort, Melena, diarrhea, constipation
Diagnosis	Later	Early stage (theoretically) due to symptoms
Prognosis	Good	Poor

Metastasis occurs in order of preference, to regional lymph nodes, liver, lungs and bones.

Diagnosis

- **Tumor markers:** Colonic cancer is associated with the elevated levels of tumor markers CEA (carcinoembryonic antigen) and CA 19-9.
- **Colonoscopy** may also be done which helps in the direct visualization of the cancer and may also be used to take a biopsy. **Gross** appearance of the colon is called as **"napkin ring"[Q] appearance** (caused by annular and constricting lesions in distal colon).

Key Point

The **occult blood loss** in the stool can be detected with the help of **Guaiac test**.

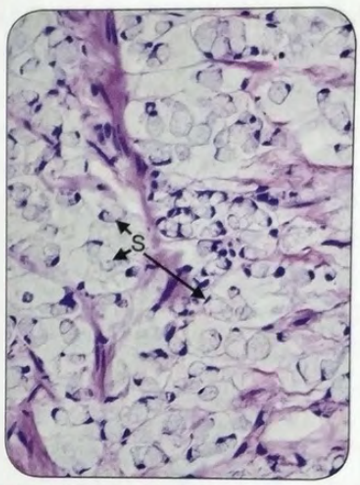


Fig. 7: Signet cell (S) in colon cancer.

Most important prognostic indicator of colon cancer is the **stage** which means the extent of tumor at the time of diagnosis. **Duke's staging** was used for colon cancer which has *now been replaced by the TNM staging.*

Key Point

Double contrast barium enema is the radiological investigation of choice which characteristically shows **"apple core" appearance** of the cancer.

TREATMENT

- ***Right colon cancer*** is surgically treated with ***resection and ileocolic anastomosis*** whereas for ***Left sided colon*** cancer, ***Hartman's procedure*** (surgical resection of the affected lesion and proximal diversion with the help of colostomy) is done.

Multiple Choice Questions

ESOPHAGUS

1. **Barrett's esophagus shows:** *(AIIMS May 2010)*
   (a) Intestinal dysplasia
   (b) Intestinal metaplasia
   (c) Columnar cell metaplasia
   (d) Columnar cell dysplasia

2. **Predisposing factor for esophageal cancer is all except:** *(AIIMS May 2009)*
   (a) Mediastinal fibrosis
   (b) Diverticula
   (c) Caustic alkali burn
   (d) HPV

3. **Most common cause of esophagitis is:** *(AIIMS May 2009)*
   (a) Smoking
   (b) Alcohol
   (c) Reflux disease
   (d) Increased intake of spices

4. **Best site for taking biopsy for viral esophagitis is:** *(AIIMS Nov 2001)*
   (a) Edge of ulcer
   (b) Base of ulcer
   (c) Adjacent indurated area around ulcer
   (d) Surrounding normal mucosa

5. **Which of the following viruses does not produce viral esophagitis?** *(Delhi PG 2009)*
   (a) Herpes (b) Adenovirus
   (c) Varicella (d) Cytomegalovirus

MOST RECENT QUESTIONS

6. **Which of the following is true about Barret's esophagus?**
   (a) Squamous to columnar metaplasia
   (b) Columnar to squamous metaplasia
   (c) Does not increase risk of malignancy
   (d) None of the above

7. **Barrett esophagus can result from:**
   (a) *H. pylori* infection
   (b) *H. simplex* infection
   (c) Gastroesophageal reflux
   (d) Varices

8. **Plummer-Vinson syndrome is characterized by all except:**
   (a) Glossitis
   (b) Esophageal webs
   (c) Megaloblastic anemia
   (d) Esophageal dysphagia

9. **Which of the following is true of Barrett esophagus?**
   (a) A biopsy will show a histologic finding of columnar to squamous metaplasia
   (b) It is a known precursor of carcinoma of the stomach
   (c) The most common location is the proximal (upper) third of the esophagus
   (d) It is a known precursor of adenocarcinoma of the esophagus

10. **A patient complains of pain in the upper portion of his neck on swallowing. He occasionally regurgitates undigested food shortly after eating. Which of the following is the most likely etiology of his problems?**
    (a) Mallory-Weiss tears
    (b) Zenker's diverticulum
    (c) Schatzki rings
    (d) Traction diverticula

11. **A female with chronic dysphagia undergoes an upper endoscopy that reveals massive dilation of the distal esophagus. The esophagus is kinked and tortuous and partly filled with undigested foods. What is the most likely diagnosis for this patient?**
    (a) Achalasia
    (b) Barrett's esophagus
    (c) Hiatal hernia
    (d) Plummer-Vinson syndrome

12. **Which of the following locations is most likely for the development of carcinoma in a man who has chronically chewed tobacco?**
    (a) Floor of the mouth
    (b) Lower lip
    (c) Tongue
    (d) Buccal mucosa

13. **Most common anatomical location of tongue cancer is:**
    (a) Anterior third (b) Lateral margin
    (c) Dorsum (d) Posterior third

14. **All are precancerous for carcinoma of esophagus except:**
    (a) Achalasia
    (b) Paterson-Kelly syndrome
    (c) Zenker diverticulum
    (d) Ectodermal dysplasia

15. **Most common antecedent of erythroplakia and leukoplakia is which of the following?**
    (a) Diphtheria (b) Tobacco use
    (c) Alcohol (d) Poor oral hygiene

16. **Lymphoid tissue is seen in which parotid tumor?**
(a) Pleomorphic adenoma
(b) Warthins tumor
(c) Adenoid cystic carcinoma
(d) Mucoepidermoid cancer

17. **False about pleomorphic adenoma is:**
(a) Large in size
(b) Encapsulated
(c) Commonly turns malignant
(d) Slow growing

STOMACH: GASTRITIS, PUD, GIST, GASTRIC CANCER

18. **A 50 years old male presents with obstructive symptoms. Biopsy of stomach reveals the likely diagnosis to be gastrointestinal stromal tumour (GIST). The most appropriate marker for this tumor would be which of the following?** *(AIIMS May 2011)*
(a) CD34 (b) CD117
(c) CD30 (d) CD10

19. **Sister Mary Joseph nodule is most commonly seen in with which of the following?** *(AIIMS May 2010)*
(a) Ovarian cancer (b) Stomach cancer
(c) Colon cancer (d) Pancreatic cancer

20. **Most appropriate marker of GIST:**
(a) CD117 *(AI 2010, AIIMS Nov 09)*
(b) CD 34
(c) CK
(d) Vimentin

21. **Which of the following is a specific marker for GIST?**
(a) CD 117 (b) CD34 *(AI 2009)*
(c) CD23 (d) S-100

22. **Which one of the following is the most significant risk factor for development of gastric carcinoma?** *(AI 2006)*
(a) Paneth cell metaplasia
(b) Pyloric metaplasia
(c) Intestinal metaplasia
(d) Ciliated metaplasia

23. **When carcinoma of stomach develops secondarily to pernicious anemia, it is usually situated in the:** *(AI 2006)*
(a) Prepyloric region (b) Pylorus
(c) Body (d) Fundus

24. **Sister Mary Joseph nodules are found in:**
(a) Gastric carcinoma *(AIIMS May 2009)*
(b) Pancreatic carcinoma
(c) Lung carcinoma
(d) Ovary carcinoma

25. **Gastrointestinal stromal malignancy arises from which of the following?** *(AIIMS May 2002)*
(a) Smooth muscle
(b) Nerve cells
(c) Interstitial cells of Cajal
(d) Vascular endothelium

26. **Histologic examination of the lesion in stomach reveal fat-laden cells, likely cause is:**
(a) Lymphoma *(AIIMS Nov 2001)*
(b) Postgastrectomy
(c) Signet-cell carcinoma stomach
(d) Atrophic gastritis

27. **The following have strong causal association with *H. pylori* infection except:** *(Karnataka 2008)*
(a) Chronic gastritis
(b) Peptic ulcer disease
(c) Gastric carcinoma
(d) Gastric adenoma

28. **In early gastric carcinoma malignancy is confined to:**
(a) Mucosa *(Karnataka 2004)*
(b) Mucosa and submucosa
(c) Gastric wall without lymph node metastasis
(d) Gastric glands

29. **In pernicious anemia, antibody is formed against:**
(a) G-cell *(Bihar 2006)*
(b) Parietal cell
(c) Stem cell
(d) All

30. **A 60 years old fashion photographer and smoker Alok Nath complaints of severe nausea, vomiting, early satiety, and a 10 kg weight loss over the past 5 months. His physical examination reveals the presence of mild muscle wasting. An upper GI endoscopy reveals the erosion of entire gastric mucosa. In addition, there is presence of erythematous cobblestone appearance of the mucosa. The stomach is also found to be shrunken and reduced in size. Upper gastrointestinal radiographs show that the stomach is small and shrunken. Which of the following is the likely microscopic finding in this man?**
(a) Early gastric carcinoma
(b) Gastrointestinal stromal tumor
(c) Signet ring cell adenocarcinoma
(d) Chronic atrophic gastritis

31. **A 56-year-old man with a history of glomerulonephritis is diagnosed with renal failure. The man subsequently complains of heartburn and nausea, and gives a history that he has been vomiting each morning for the last few days. Which of the following forms of gastritis would most likely be found in this patient?**
(a) Acute gastritis
(b) Chronic antral gastritis
(c) Lymphocytic gastritis
(d) Hypertrophic gastritis

32. **Which of the following conditions would mostly likely be associated with chronic gastritis (Type A) resulting from autoimmune destruction of parietal cells?**
(a) Decreased growth of luminal bacteria
(b) Decreased likelihood of developing gastric carcinoma
(c) Decreased plasma concentration of gastrin
(d) Increased production of macrocytic red blood cells

33. **Which of the following sites contains striated muscle that is not under voluntary control?**
(a) Bladder (b) Colon
(c) Esophagus (d) Gallbladder

34. **An old man being evaluated for abdominal pain and weight loss undergoes endoscopy showing a broad region of the gastric wall in which the rugae are flattened. Biopsy of this area shows infiltration by numerous polygonal tumor cells with small, dark, round or ovoid nuclei pushed to the margin of the cell by large, clear, cytoplasmic structures. These cells might be expected to have which of the following properties?**
(a) Keratohyalin granules observed by electron microscopy
(b) Melanosomes and premelanosomes by electron microscopy
(c) Positive staining for gastrin by light microscopy
(d) Positive staining for mucin by light microscopy

MOST RECENT QUESTIONS

35. **Which of the following is the most common site of mucosa associated lymphoid tissue?**
(a) Duodenum (b) Jejunum
(c) Ileum (d) Stomach

36. **One of the following can have malignant transformation:**
(a) Gastric ulcer (b) Duodenal ulcer
(c) Stomal ulcer (d) Stress ulcer

37. **Gastrointestinal stromal tumor originates in which of the following?**
(a) Parietal cells
(b) Chief cells
(c) Neuroendocrine cells
(d) Interstitial cells of Cajal

38. **Most common site of GIST is:**
(a) Ileum (b) Esophagus
(c) Colon (d) Stomach

39. **Which of the following is not true about GIST?**
(a) Stomach is the most common site
(b) High propensity of malignant change
(c) Associated with c-KIT mutation
(d) Histology shows spindle shaped cells

40. **Which of the following artery is responsible for duodenal ulcer hemorrhage?**
(a) Superior pancreaticoduodenal artery
(b) Inferior pancreaticodudenal artery
(c) Gastroduodenal artery
(d) Left gastric artery

41. **Krukenberg tumor associated mostly with which cancer?**
(a) Stomach (b) Brest
(c) Liver (d) Pancreas

42. **The best prognosis is gastric carcinoma is in type:**
(a) Linitis plastic
(b) Polypoidal growth
(c) Ulcerative
(d) Superficial spreading

43. **Most common association in MEN I is:**
(a) Gastrinoma
(b) Insulinoma
(c) Lipoma
(d) Glucagonoma

INTESTINE: INFECTIONS, MALABSORPTION DISEASES

44. **Which of the following is a histological feature of Whipple's disease?** *(AI 2008)*
(a) Infiltration of histiocytes in the lamina propria
(b) Granuloma in the lamina
(c) Macrophages with PAS (+) material inside the lamina propria
(d) Eosinophils in the lamina propria

45. **Gluten sensitive enteropathy is most strongly associated with:** *(AI 2003)*
(a) HLA-DQ2
(b) HLA-DR4
(c) HLA-DQ3
(d) Blood group 'B'

46. **In the intra-epithelial region of the mucosa of intestine the predominant cell population is that of:** *(AI 2002)*
(a) B cell (b) T-cells
(c) Plasma cells (d) Basophils

47. **Macrophages containing large quantities of undigested and partial digested bacteria in intestine are seen in:**
(a) Whipple's disease *(AI 2002)*
(b) Amyloidosis
(c) Immunoproliferative small intestinal disease
(d) *Vibrio cholerae* infection

48. **The histological features of celiac disease include all of the following, except:** *(AI 2002)*
(a) Crypt hyperplasia
(b) Increase in thickness of the mucosa
(c) Increase in intraepithelial lymphocytes
(d) Increase in inflammatory cells in lamina propria

49. Type of anemia caused by Ileocecal TB: *(AIIMS Nov 2009)*
(a) Iron – deficiency
(b) Megaloblastic
(c) Sideroblastic
(d) Normocytic Normochromic

50. The following cereals should be avoided in patients with celiac diseases, except: *(AIIMS Nov 2003)*
(a) Wheat (b) Barley
(c) Maize (d) Rye

51. Which of the following organs is not involved in Whipple's disease? *(Delhi PG 2009)*
(a) Heart (b) CNS
(c) Lungs (d) GI Tract

52. Morphological features of celiac disease include all except: *(Delhi PG 2009 RP)*
(a) Increase in intraepithelial lymphocytes
(b) Increase in crypt: villous ratio
(c) Distended macrophages with PAS positive granules in lamina propria
(d) Elongated hyperplastic and tortuous crypts

53. All are true about amoebic ulcer except: *(UP 2002)*
(a) Commonest site is ascending colon and cecum
(b) Flask shaped ulcer
(c) Perforation is common
(d) Paucity of inflammatory cells

54. Intestinal biopsy in not diagnostic in: *(UP 2002)*
(a) Abetalipoproteinemia
(b) Tropical sprue
(c) Agammaglobulinemia
(d) Intestinal lymphangiectasis

55. Transverse ulcers are seen in: *(UP 2004)*
(a) Typhoid (b) Tuberculosis
(c) Amoebiasis (d) Ulcerative colitis

56. Aphthous ulcers are also known as: *(UP 2007)*
(a) Canker sores (b) Marjolin's ulcer
(c) Curling's ulcer (d) Cushing's ulcer

57. All are complication of typhoid ulcers except: *(UP 2008)*
(a) Perforation (b) Stricture formation
(c) Hemorrhage (d) Sepsis

58. Which one of the following tumors is most commonly associated with pseudomyxoma peritonei? *(AP 2006)*
(a) Appendix (b) Gall bladder
(c) Stomach (d) Pancreas

59. All are true about typhoid ulcer except: *(Kolkata 2005)*
(a) Mainly affects ileum
(b) Multiple ulcer and transverse
(c) Perforation occurs at 3rd week
(d) Perforation treated by surgery

60. A patient who recently underwent a gastrectomy procedure complains of nausea, diarrhea, sweating, palpitations, and flushing soon after eating a meal. This patient should be instructed to:
(a) Eat less frequent, larger meals that are high in carbohydrates
(b) Eat more frequent, smaller meals that are high in fat
(c) Eat more frequent, larger meals that are high in protein
(d) Eat more frequent, smaller meals that are high in carbohydrates

61. A female patient has severe arthritis involving the lower back. Before making a diagnosis of ankylosing spondylitis, the patient should be questioned by the physician about which of the following diseases?
(a) Carcinoid syndrome
(b) Celiac disease
(c) Crohn's disease
(d) Whipple's disease

62. A patient with intestinal malabsorption is found to markedly improve when flour products (bread, noodles, etc.) are removed from his diet. At the height of the patient's disease, marked histologic changes would be seen at which of the following sites?
(a) Distal large bowel
(b) Distal small bowel
(c) Proximal small bowel
(d) Entire small bowel

63. A 25-year-old man presents to a rheumatologist with complaints of joint pain involving the large joints of the legs which exacerbates frequently accompanied by diarrhea. Which of the following gastrointestinal diseases is most likely to be implicated as the cause of the patient's joint problems?
(a) Amebic colitis
(b) Chronic appendicitis
(c) Diverticulosis
(d) Ulcerative colitis

MOST RECENT QUESTIONS

64. Based on epidemiological studies, which of the following has been found to be most protective against colon cancer?
(a) High fiber diet
(b) Low fat diet
(c) Low selenium diet
(d) Low protein diet

65. Purtscher's retinopathy is seen in:
(a) Meningitis
(b) Pancreatitis
(c) Uncontrolled hypertension
(d) Unilateral carotid artery occlusion

66. Usually, gall stones consists of these types, except:
(a) Oxalate (b) Bile salts
(c) Bile pigments (d) Cholesterol

67. Which of the following is the commonest site of intestinal tuberculosis?
(a) Stomach (b) Jejunum
(c) Ileum (d) Colon

68. The most common site for amoebiasis:
(a) Sigmoid colon (b) Transverse colon
(c) Cecum (d) Liver

69. Diverticulum most common site is:
(a) Sigmoid colon (b) Ileum
(c) Ascending colon (d) Transverse colon

70. Anti-gliadin antibodies are detectable in:
(a) Tropical sprue (b) Whipple's disease
(c) Celiac disease (d) Intestinal lymphoma

71. Which of the following is not associated with celiac sprue?
(a) Turner syndrome
(b) Down syndrome
(c) Klinefleter syndrome
(d) Type 1 diabetes

72. Paneth cells contain:
(a) Zinc (b) Copper
(c) Molybdenum (d) Selenium

73. Which is incorrect of typhoid ulcers?
(a) Hemorrhage is common
(b) Occurs on lymphoid aggregation
(c) Horizontal ulcers
(d) Longitudinal ulcers

74. Which of the following is not considered a pre-malignant lesion?
(a) Leukoplakia
(b) Erythroplakia
(c) Chronic hyperplastic candidiasis
(d) Oral lichen planus

75. Diagnosis of typhoid in first week is by:
(a) Widal test (b) Stool culture
(c) Urine culture (d) Blood culture

76. Perforation of typhoid ulcer usually occurs during which week?
(a) 1st (b) 2nd
(c) 3rd (d) 4th

77. Serum amylase level are raised in all of the following except:
(a) Duodeneal ulcer perforation
(b) Pancreatitis
(c) Appendicitis
(d) Small Bowel Strangulation

78. What is false about Meckel's diverticulitis?
(a) Present in 3% of the population
(b) Presents with periumbilical pain
(c) Remnant of proximal part of vitellointestinal duct
(d) Lies on the anti-mesenteric border

79. All are true about celiac disease except:
(a) Crypt hyperplasia
(b) Increase in thickness of the mucosa
(c) Increase in intraepithelial lymphocytes
(d) Increase in inflammatory cells in lamina propria

INTESTINE: IBD, POLYP, TUMORS

80. Most important prognostic factor for colorectal carcinoma is: *(AIIMS May 2011)*
(a) Site of lesion
(b) Tumour size and characteristics
(c) Age of patient
(d) Lymph node status

81. Which of the following is NOT true about FAP?
(a) AR inheritance *(AIIMS May 2011)*
(b) Screening done by sigmoidoscopy
(c) Polyps develop in early adulthood
(d) Epidermal cysts and osteomas may occur

82. In Peutz-Jeghers syndrome, polyps are mainly seen in:
(a) Rectum (b) Colon *(AIIMS May 2010)*
(c) Esophagus (d) Jejunum

83. Which of the following is not true about FAP? *(AIIMS May 2010, May 2011)*
(a) Autosomal recessive inheritance
(b) Screening done by sigmoidoscopy
(c) Polyps develop in early adulthood
(d) Epidermal cysts and osteomas may occur

84. Colon carcinoma is associated with all except:
(a) Rb *(AI 2009)*
(b) Mismatch repair genes
(c) APC
(d) β-catenin

85. In ulcerative colitis, which of the following is seen?
(a) Cryptitis *(AIIMS May 2008)*
(b) Crypt loss
(c) Crypt branching
(d) Proliferating mucosa

86. Which of the following would be the best morphological feature to distinguish ulcerative colitis from Crohn's disease? *(AIIMS May 2004)*
(a) Diffuse distribution of pseudopolyps
(b) Mucosal edema
(c) Crypt abscesses
(d) Lymphoid aggregates in the mucosa

87. Which of the following statements about Crohn's disease is incorrect? *(Delhi PG 2009)*
(a) Granulomas present frequently
(b) It is separate and distinct from ulcerative colitis
(c) Cigarette smoking is a risk factor
(d) Rectum spared in 50% patients with large bowel involvement

88. **Commonest endocrine tumour of pancreas artses from which of the following cells?** *(Karnataka 2009)*
(a) α cells (b) β cells
(c) Delta cells (d) VIPoma

89. **Skin lesions are seen in:** *(Karnataka 2006)*
(a) Ulcerative colitis (b) Crohn's disease
(c) Both (*a*) and (*b*) (d) None of the above

90. **Polyps in Peutz-Jegher's syndrome are:**
(a) Adenomatous polyps *(Karnataka 2004, 2008)*
(b) Hyperplastic polyps
(c) Hamartomatous polyps
(d) Pseudopolyps

91. **All are malignant in nature except:** *(UP 2000)*
(a) Juvenile polyp (b) Familial polyp
(c) Carcinoid tumor (d) Villous adenoma

92. **All are true about Crohn's disease except:**
(a) Rectal involvement is common *(UP 2001)*
(b) Granuloma formation
(c) Erythema nodosum
(d) Fistula formation

93. **Most common tumor of appendix is:** *(UP 2005)*
(a) Carcinoid tumor
(b) Pseudomyxoma-peritonitis
(c) Adenocarcinoma
(d) Mucocele

94. **Skip lesions are seen in:** *(UP 2005)*
(a) Ulcerative colitis
(b) Crohn's disease
(c) Carcinoid syndrome
(d) Whipple's disease

95. **Fistula is most common in:** *(UP 2007)*
(a) Crohn's disease
(b) Ulcerative colitis
(c) Infective enterocolitis
(d) Celiac sprue

96. **Most common site of carcinoid tumor is:** *(RJ 2000)*
(a) Stomach (b) Jejunum
(c) Distal ileum (d) Appendix

97. **Most common site of carcinoma pancreas is:** *(RJ 2000)*
(a) Head
(b) Body
(c) Tail
(d) Equal incidence at all sites

98. **Carcinoid tumor produces all except:** *(RJ 2003)*
(a) Flushing
(b) Diarrhea
(c) Bronchodilation
(d) Raynaud's phenomenon

99. **Which organ is always involved in ulcerative colitis?**
(a) Jejunum (b) Ileum *(RJ 2005)*
(c) Rectosigmoid (d) Duodenum

100. **Two identical specimen of the intestine obtained following colectomy shows on examination hemorrhagic cobblestone appearance; one of them however, shows longitudinal grooving. It is likely to be a specimen of:**
(a) Ulcerative colitis *(Kolkata 2002)*
(b) Ischemic colitis
(c) Multiple polyposis
(d) Crohn's disease

101. **Carcinoma of colon is associated with all except:**
(a) High fat diet *(Kolkata 2005)*
(b) High fiber diet
(c) Streptococcus bovis infection
(d) Ulcerative colitis

102. **Backwash ileitis is seen in:** *(Bihar 2006)*
(a) Crohn's disease (b) Ulcerative colitis
(c) Colonic carcinoma (d) Ileal polyp

103. **Granulomatous inflammation is found in:** *(Bihar 2006)*
(a) Crohn's disease (b) Ulcerative colitis
(c) Amoebiasis (d) Giardiasis

104. **Continuous involvement of colonic mucosa is seen in:**
(a) Ulcerative colitis *(Bihar 2006)*
(b) Crohn's disease
(c) Carcinoma colon
(d) Colonic polyp

105. **All are true about carcinoid syndrome except:**
(a) Wheezing *(Jharkhand 2006)*
(b) Pulmonary stenosis
(c) Flushing
(d) Splenomegaly

106. **A 24-year-old male Anil B. with a 4-year history of abdominal pain, periodic diarrhea, low-grade fever, and easy fatigability is found to have an enteroenteric fistula on contrast radiography. Colonoscopy shows "cobblestone" mucosa that has linear ulcerations with "skip areas" of normal bowel wall. Which of the following is the most likely explanation of fistula formation in this patient?**
(a) Intramural granulomas
(b) Transmural inflammation
(c) Marked lymphoid reaction
(d) Skip lesions of the intestinal wall

107. **A 51-year-young man Firdaus had been receiving antibiotics for severe folliculits. He develops fever, toxicity, and severe diarrhoea. Which of the following is the most likely diagnosis?**
(a) CMV infection
(b) Pseudomembranous colitis
(c) Ulcerative colitis
(d) Whipple disease

108. **A 50-year-old man Bhupi presents to his doctor with diarrhea, flushing and wheezing. Physical examination is significant for a grade II/VI diastolic murmur located**

at the right sternal border at the 4th intercostal space. Which of the following substances is most likely to be elevated in this patient's urine?
(a) 5-HIAA (b) HVA
(c) Phenylalanine (d) Selegiline

109. Biopsy of a small, rounded rectal polyp demonstrates glands and sawtooth crypts composed of a proliferation of goblet and columnar epithelial cells. No atypia is seen. This polyp is best classified as which of the following?
(a) Hyperplastic polyp
(b) Peutz-Jeghers polyp
(c) Tubular adenoma
(d) Tubulovillous adenoma

MOST RECENT QUESTIONS

110. True about ulcerative colitis, all except:
(a) Rectum involved (b) Pseudopolyps
(c) Pancolitis (d) Noncaseating granuloma

111. Which of the following is the most common location of carcinoid tumor?
(a) Pancreas
(b) Lung
(c) Gastrointestinal tract
(d) Gonads

112. Toxic megacolon is seen in:
(a) Chronic nonspecific ulcerative colitis
(b) Crohn's disease
(c) Colonic diverticulosis
(d) Hamartomatous polyp

113. Carcinoid tumour develops from:
(a) Hematopioetic cells
(b) Kulschitsky cells
(c) Neuroglial cells
(d) Chromaffin cell

114. Which of the following is not an etiological factor for pancreatitis?
(a) Abdominal trauma
(b) Hyperlipidemia
(c) Islet cell hyperplasia
(d) Germline mutations in the cationic trypsinogen gene

115. Pseudopolyps are seen in:
(a) Crohn's disease
(b) Ulcerative colitis
(c) Juvenile polyposis
(d) Tuberculosis

116. The highest malignant potential is seen in:
(a) Crohn's disease (b) Ulcerative colitis
(c) Familial polyposis (d) Infantile polyp

117. Commonest malignant small intestinal tumor:
(a) Adenocarcinoma (b) Lymphosarcoma
(c) Leiomyosarcoma (d) Carcinoid tumor

118. Most common site of carcinoma pancreas is:
(a) Head (b) Body
(c) Tail (d) None

119. Which of the following is the commonest cause of rectal bleeding in children?
(a) Peutz Jegers polyp
(b) Juvenile polyp
(c) Adenomatous polyp
(d) Inflammatory polyp

120. Which of the following type of anemia would be associated with carcinoma of the colon?
(a) Megaloblastic anemia
(b) Iron deficiency anemia
(c) Aplastic anemia
(d) Hemolytic anemia

121. Following statements regarding ulcerative colitis is:
(a) Smoking does not have a protective effect
(b) Smoking has a protective effect
(c) No relation with smoking
(d) Smoking causing relapses

122. Zollinger Ellison syndrome is not caused by tumors from:
(a) Pancreas (b) Ovary
(c) Colon (d) Duodenum

123. Crohn's disease is associated with:
(a) NOD2/CARD15 gene
(b) P53 gene
(c) Philadelphia chromosome
(d) BRCA1 gene

124. Which of the following is inheritance of Gardner syndrome?
(a) Autosomal recessive
(b) Autosomal dominant
(c) X linked dominant
(d) X linked recessive

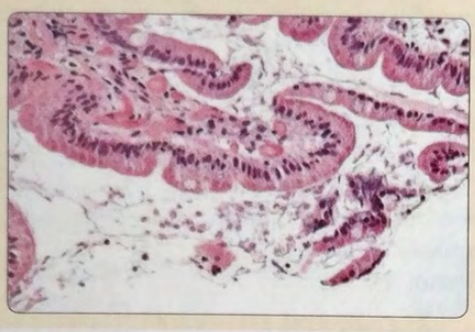
125. Osteomas, adenomatous polyps of intestine and periampullary carcinomas are seen in which oif the following conditions?
(a) Cowden syndrome
(b) Peutz Jegers syndrome
(c) FAP
(d) Gardener syndrome

126. A highly sensitive and specific marker for detecting intestinal inflammation in ulcerative colitis is:
(a) CRP (b) Fecal lactoferrin
(c) Fecal calprotectin (d) Leukocytosis

127. The minimum number of polyps necessary for a diagnosis of Familial Adenomatous Polyposis (FAP) is:
(a) 05 (b) 10
(c) 50 (d) 100

128. Antibody suggestive of diagnosis of ulcerative colitis:
(a) p-ANCA (b) c-ANCA
(c) A.M.A (d) A.N.A

129. A 32-year-old slum dweller presented with complaints of diarrhoea and a 2 kg weight loss since last 2 months. On examination, the patient has a dry tongue and poor skin turgor. An endoscopic biopsy from the gut reveals the following microscopic appearance. What is the likely diagnosis? *(AIIMS Nov 2016)*



(a) Whipple's disease
(b) *Entamoeba histolytica*
(c) *Helicobacter pylori*
(d) Giardiasis

130. Which of the following is false regarding carcinoid tumor?
(a) Neuroendocrine tumor
(b) Most common site lung
(c) Associated with serotonin production
(d) Potentially malignant tumor

131. Most common site for small intestinal carcinoma is:
(a) Duodenum
(b) Jejunum
(c) Ileum
(d) All are affected equally

Explanations

1. **Ans. (b) Intestinal metaplasia** *(Ref: Robbins 9/e 757)*
Direct quote from Robbins .... 'Barrett esophagus is a complication of chronic GERD that is characterized by intestinal metaplasia within the esophageal squamous mucosa'.

2. **Ans. (a) Mediastinal fibrosis** *(Ref: Robbins 9/e p758-759)*
   - **External beam irradiation** but **not mediastinal fibrosis** is a risk factor for esophageal cancer.
   - **HPV DNA** is found frequently in esophageal squmaous cell carcinoma in high incidence regions.. Robbins 7th/807
   - **Caustic ingestion, achalasia, bulimia, tylosis** (an inherited autosomal dominant trait), **Plummer-Vinson syndrome, external-beam radiation,** and **esophageal diverticula** all have known associations with squamous cell cancer..... ...Sabiston textbook of surgery 18th edn

3. **Ans. (c) Reflux disease** *(Ref: Robbins 8th/769, 9/e p755)*
Robbins clearly states that *"Reflux of gastric contents into the lower esophagus is the most important cause of esophagitis"*.

4. **Ans. (a) Edge of ulcer** *(Ref: Robbins 8th/768)*
   - *Herpes viruses* typically cause *punched-out ulcers*; the nuclear inclusions of herpes virus are found in a narrow rim of degenerating epithelial cells at the *margin of the ulcer*.
   - *CMV* causes linear ulceration of the esophageal mucosa; the histologic findings of CMV-associated change with both intranuclear and cytoplasmic inclusions are found in capillary endothelium and stromal cells in the *base of the ulcer*.

For diagnosis, the biopsy should be taken from edge of ulcer in HSV and base of ulcer in CMV.

So, friends both a and b options are correct. But as we have to choose only one, we will go for option (a) because Herpes simplex is the most common virus causing esophagitis.

5. **Ans. (b) Adenovirus**
(Ref: Robbins 8th/768, 9/e p754, Harrison 17th/1853)
Viruses that can cause esophagitis are: HSV-1, HSV-2, Varicella zoster virus, Cytomegalovirus and HIV For diagnosis, the biopsy should be taken from **edge of ulcer in HSV and base of ulcer in CMV**.
Findings in biopsy of edge of ulcer in HSV are:
   - Ballooning degeneration
   - Ground glass changes in nuclei
   - Cowdry type A intranuclear inclusion bodies.

6. **Ans. (a) Squamous to columnar metaplasia**
(Ref: Robbins 7th/804, 9/e p757)

7. **Ans. (c) Gastroesophageal reflux** *(Ref: Robbins 9/e p757)*

8. **Ans. (c) Megaloblastic anemia**

9. **Ans. (d) It is a known precursor of adenocarcinoma of the esophagus** *(Ref: Robbins 9/e p758, 8th/769-772)*
Barrett esophagus is columnar metaplasia of the esophageal squamous epithelium (squamous–to-columnar). The columnar epithelium is often of the intestinal type with goblet cells. Barrett esophagus is a complication of long-standing gastroesophageal reflux disease and is a precursor of esophageal adenocarcinoma. The most common location is in the distal (lower) third of the esophagus.

10. **Ans. (b) Zenker's diverticulum** *(Ref: Robbins 9/e p753)*
This is the classic presentation of ***Zenker's diverticulum***, which is a ***false diverticulum*** formed by herniation of the mucosa at a point of weakness at the junction of the pharynx and esophagus in the posterior hypopharyngeal wall. It is also associated with halitosis, and if the diverticulum fills completely with food, it can cause dysphagia or obstruction of the esophagus.

• Mallory-Weiss tears (option A) are mucosal tears at the gastroesophageal junction secondary to repeated, forceful vomiting. They are often seen in alcoholics. • Schatzki rings (option C) are mucosal rings found in the distal esophagus at the squamocolumnar junction. • In contrast to a Zenker's diverticulum, the usually asymptomatic traction diverticula (option D) are true diverticula involving all of the layers of the esophagus. They are typically caused by adherence of the esophagus to a scarred mediastinal structure.

11. **Ans. (a) Achalasia** *(Ref: Robbins 8th/768, 9/e p753)*

12. **Ans. (d) Buccal mucosa**
(Ref: Robbins 8th/811, 9/e p721-732)

13. **Ans. (b) Lateral margin**
   - The book mentions that '*60-70% arise from the lateral surface of the middle third of the tongue*'.
(Ref: Oral Cancer: Diagnosis, Management, and Rehabilitation p 100)

14. **Ans. (c) Zenker diverticulum** *(Ref: Robbins 9/e p 758-9)*

15. **Ans. (b) Tobacco use** *(Ref: Robbins 9/e p731)*

16. **Ans. (b) Warthins tumor** *(Ref: Robbins 9/e p745)*

17. **Ans. (c) Commonly turns malignant**
(Ref: Robbins 9/e p744)

A carcinoma arising in a pleomorphic adenoma is referred to variously as a *carcinoma ex pleomorphic adenoma or a malignant mixed tumor*. The incidence of malignant transformation increases with time, being about 2% for tumors present less than 5 years and almost 10% for those present for more than 15 years.

18. **Ans. (b) CD117** *(Ref Robbins 8th/789-790, 9/e p776)*
Direct quote Robbins... 'The most useful diagnostic marker for GIDT is c-kit^{9} (also known as CD117^{9})'.

19. **Ans. (b) Stomach Cancer** *(Ref: Robbins 8th/786, 9/e p776)*

20. **Ans. (a) CD117**
(Ref: Robbins 8th/789-790, 7th 826-827, Harrison 17th/573)
The most useful diagnostic marker is **c-kit (CD117)** detectable in 95% of the patients. Other markers like CD34 and vimentin can also be expressed by some tumor cells. **CD34** is also present on **pluripotent hematopoetic stem cell**.

21. **Ans. (a) CD117** *(Ref: Robbins 8th/790, 9/e p776)*

22. **Ans. (c) Intestinal metaplasia** *see text for details*
(Ref: Harrison 17th/572)

23. **Ans. (d) Fundus**
(Sleisenger & Fordtrans text book of Gastroinstestinal disease 7th/813)
Pernicious anemia is associated with autoimmune atrophic gastritis affecting the fundic glands. Intestinal metaplasia (premalignant for gastric carcinoma), is characteristically seen in this area of atrophic gastritis.
Atrophic glands with extensive intestinal metaplasia are most characteristically confined to the fundus in patients with pernicious anemia.

24. **Ans. (a) Gastric carcinoma** *(Ref: Robbins 8th/786)*

25. **Ans. (c) Interstitial cells of Cajal**
(Ref: Robbins 7th/826, 9/e p775)

26. **Ans. (d) Atrophic gastritis > (b) Postgastrectomy**
(Ref: Sternberg's diagnostic surgical pathology, Volume 2, page 1451, LWW, Biopsy interpretation of the gastrointestinal tract mucosa by EA Montgomery, Lippincott William Wilkins; 120, multiple journals)
Sternberg.. *'Multifocal atrophic gastritis with intestinal metaplasia is present commonly in postgastrectomy stomach.* It is not clear whether it is pre-existing (for which surgery was done) or develops after gastrectomy'.
Biopsy interpretation of the gastrointestinal tract mucosa... *'some authors have associated gastric xanthoma with atrophic gastritis'.*
Digestive Diseases and Sciences**, Vol. 31,1986,page 925-8* mentions... 'It says **xanthomatosis** is characterized by collections of lipid-laden macrophages, or foam cells, plaques or nodules in many tissues, most commonly the skin. Involvement can occur in all regions of the gastrointestinal tract, but is **most common in the stomach**. It is more common in patients with gastritis, gastric ulcer, and with duodeno-gastric reflux after gastric surgery and mucosal damage has been postulated to play an important role in its pathogenesis. There is *no documented relationship between degree of hyperlipidemia or hypercholesterolemia* and presence of gastric xanthomatosis. Rather, ***it is associated with atrophic gastritis.
Turkish Journal of gastroenterology.. 'Lipid islands are found in the stomach only when there are pathological changes such as chronic gastritis, intestinal metaplasia, ***atrophic gastritis***, gastric ulcer,and changes caused by bile reflux or **partial gastrectomy**'.

Clinical importance of knowing about gastric xanthoma

Atypical xanthoma cells can be easily confused with signet-ring adenocarcinoma cell. However, xanthoma cells are negative with periodic acid-Schiff (PAS) stain but show a positive reaction with Oil red 0 and weakly positive reaction with Masson trichrome. (Ref...Acta Cytol. 2006 Jan-Feb; 50(1):74-9).

Signet-ring adenocarcinoma cells showed a **strongly positive** reaction with **PAS stain, cytokeratin and mucicarmine.**

27. **Ans. (d) Gastric adenoma**
(Ref: Robbins 7th/817, 823, 826, 9/e p770)
- *H. pylori is also associated with peptic ulcer disease, gastric cancer and gastric mucosa associated lymphoma* (called MALToma or mucosa associated lymphoid tissue tumor)
- Gastric adenoma are polypoid lesions of the stomach found in the antrum most commonly.

28. **Ans. (b) Mucosa and submucosa**
(Ref: Robbins 7th/824, 825; fig/17-25, 9/e p771-772)
GASTRIC CARCINOMA
Classification – On the basis of

Depth of invasion	Macroscopic pattern	Histologic subtype
(a) **Early**-involving mucosa and submucosa (b) **Advanced**-extending into muscularis propria and beyond	1. Exophytic 2. Flat or depressed 3. Excavated	(a) Intestinal type (b) Diffuse type

29. **Ans. (b) Parietal cell**
(Ref: Robbins 8th/657; 7th/641, 9/e p765)

30. **Ans. (c) Signet ring cell adenocarcinoma**
(Ref: Robbins 8th/772)
The description is indicative of the presence of leather bottle appearance (linitis plastica) of diffuse gastric carcinoma. Microscopic examination reveals that in this cancer, diffuse infiltration of the stomach wall by gastric type mucus cells is present. The tumor cells have a signet ring appearance because the cytoplasmic mucin pushes the nucleus to one side.

- **Early gastric carcinoma** is confined to the **mucosa and submucosa**.
- **Gastrointestinal stromal tumors** tend to be **bulky masses**.
- In **chronic atrophic gastritis**, there is *no significant scarring or shrinkage* but **rugal folds are lost**.

Info

In the comparison of the whole GIT, granulomas are rarest in the stomach.

31. Ans. (a) Acute gastritis *(Ref: Robbins 8th/773, 9/e p763)*

Acute gastritis, characterized by patches of erythematous mucosa, sometimes with petechiae and ulceration, can be seen as a complication of a variety of other conditions (alcohol use, aspirin and other NSAIDs use, smoking, shock, steroid use, and uremia), which usually have in common disruption of the mucosal barrier of the stomach.

- Chronic antral (type B) gastritis (option B) is associated with Helicobacter pylori.
- Lymphocytic gastritis (option C) is thought to be a gastric manifestation of celiac sprue.
- Hypertrophic gastritis (Menetrier's disease; option D) is an idiopathic condition characterized by markedly enlarged mucosal folds.

32. Ans. (d) Increased production of macrocytic red blood cells *(Ref: Robbins 8th/778-779, 9/e p765)*

Autoimmune destruction of parietal cells would lead to decreased secretion of gastric acid and intrinsic factor followed by poor absorption of dietary vitamin B12 and then pernicious anemia. It is characterized by increased production of macrocytes (megaloblasts) by the bone marrow.

The luminal bacteria (option A) would most likely exhibit increased (not decreased) growth due to sterilizing action of the acid.

A decrease in acid secretion leads to increased secretion of gastrin by antral G cells because low gastric pH (less than 3) inhibits gastrin secretion via paracrine release of somatostatin from cells in the gastric mucosa that can sense the acidity. With decreased parietal cells, the pH of the gastric lumen would rise and remove this inhibitory component.

Because less acid would be delivered to the duodenum with parietal cell destruction, less secretin would be released into the blood.

33. Ans. (c) Esophagus *(Read explanation below)*

Striated (skeletal) muscle not under voluntary control is an unusual feature of the upper third of the esophagus. The middle third of the esophagus contains roughly half striated and half smooth muscle; the lower third contains only smooth muscle. All the other structures listed in the answer choices contain smooth muscle.

34. Ans. (d) Positive staining for mucin by light microscopy *(Ref: Robbins 8th/785)*

35. Ans. (c) Ileum *(Ref: Robbins 9th/772)*

Direct quote... "Although extranodal lymphomas can arise in virtually any tissue, they do so most commonly in the GI tract, particularly the stomach".

However, the question is regarding the most common site for MALT (and not MALToma) for which the answer is **ileum.**

36. Ans. (a) Gastric ulcer *(Ref: Bailey 25/e p1055, Robbin 9/e p767)*

Chronic duodenal ulcers are not associated with malignancy but, in contrast, gastric ulcers are.

- It is fundamental that any gastric ulcer should be regarded as being malignant, no matter how classically it resembles a benign gastric ulcer.
- *Stomal ulcers* occur *after a gastroenterostomy or a gastrectomy of the Billroth II type.* The ulcer is usually found on the jejunal side of the stoma.

37. Ans (d) Interstitial cells of Cajal *(Ref: Robbins 9/e p 775)*

38. Ans. (d) Stomach *(Ref: Robbins 8/e p789-90, 9/e p776)*

39. Ans. (b) High propensity of malignant change *(Ref: Robbins 8/e p789-90, 9/e p775-776)*

High-yield Imaging: Gastrointestinal p213

Direct quote from **High yield**.. "90% of stomach GISTs are found to be **benign**".

40. Ans (c) Gastroduodenal artery *(Ref: Robbins 9/e p767; Bailey 25/e p1064)*

41. Ans (a) Stomach *(Ref: Robbins 9/e p1034)*

42. Ans (d) Superficial spreading *(Ref: Robbins 9/e p772-3)*

43. Ans. (a) Gastrinoma *(Ref: Robbins 9/e p1136)*

Know the following about MEN-1-associated pancreatic endocrine tumors:

- **Pancreatic polypeptide** is the **most commonly** secreted product, however it is **non functional**.
- *In functional tumors,* ***gastrinomas are the commonest.***

44. Ans. (c) Macrophages with PAS (+) material inside the lamina propria *(Ref: Harrison 18th/2474, Robbins 9/e p792)*

- Hallmark of Whipple's disease had been presence of PAS positive macrophages containing the characteristic small bacilli.
- Just revise friends that the presence of *T. Whipplei* **outside of macrophages is more important** indicator of active disease than is their presence inside the macrophages.

45. Ans. (a) HLA-DQ2 *(Ref: Harrison's 17th/2051, Robbins 9/e p782)*

Celiac sprue is associated with HLA-DQ2. For other diseases associated with HLA; refer to the table in the chapter of Immunity (chap-6)

46. Ans. (b) T-cells *(Ref: Mucosal Immunology Elsevier, 3rd/565)*

Direct quote.. 'IEL are a distinctive population of T cells dispersed among the luminal epithelial cells. Particularly in the small intestine, there is a predominance of CD 8+T cells.

- Increase in IEL is defined as > 40 lymphocytes per 100 enterocytes.

47. **Ans. (a) Whipple's disease**
(Ref: Robbins 7th/884 9/e p792, Harrison 17th/1884)
The hallmark of Whipple's disease is a small intestinal mucosa laden with distended macrophages in the lamia propria. The macrophages contain periodic acid– Schiff (PAS) positive granules and small rod shaped bacilli)

48. **Ans. (b) Increase in thickness of the mucosa**
(Ref: Robbins 7th/843, 9/e p783, Harrison's 17th/1881)
- Characteristic **histological features** seen on duodenal/jejunal biopsy in celiac sprue are:

1. Absence or reduced height of villi, resulting in '**flat**' appearance.
2. Crypt cell hyperplasia compensate for villous atrophy and **mucosal thickness remain same**
3. Cuboidal appearance and nucleus that are no longer basally oriented and increased intraepithelial lymphocytes.
4. Increased lymphocytes and plasma cells in lamina propria.

- These features are **characteristic of celiac sprue but not diagnostic** because similar features can be seen in:

1. Tropical sprue, 2. Eosinophilic enteritis, 3. Milk-protein intolerance in children

- So, for establishing the diagnosis of celiac sprue, the **characteristic histological picture on small intestinal biopsy should also revert back to normal on gluten free diet.** Gluten free diet also reverses the symptoms as well as serological markers (anti-endomysial antibodies).

49. **Ans. (b) Megaloblastic**
(Ref: Harsh Mohan 6th/569-571, Harrison 17th/649)
In intestinal tuberculosis the ileocecal junction is the commonest site of involvement. Ileum is the physiological site for absorption of vitamin B_{12}. Also, TB is mentioned to be a cause of folic acid deficiency which is therefore going to result in megaloblastic anemia.

50. **Ans. (c) Maize** *(Ref: Robbin's 8th/796, 9/e p782)*
- It is a disease characterized by increased sensitivity to a protein called gliadin present in the grains like wheat; oat, barley and rye resulting in a T-cell mediated chronic inflammatory reaction in the small intestine and impaired absorption. It is associated with HLA-DQ2 or HLA-DQ8.

51. **Ans. (c) Lungs**
(Ref: Robbins 9/e p792, 8th/804, Harrison 17th/1884)
The organs in which these foamy macrophages can be seen are *Liver, Small intestine*, Lymph nodes, Heart, Eyes, *CNS* and *synovial membranes of joints.*

52. **Ans. (c) Distended macrophages with PAS positive granules in lamina propria** *(Ref: Robbins 9/e p792)*
It is feature of Whipple's disease.

53. **Ans. (c) Perforation is common** *(Ref: Robbins 9/e p795)*

54. **Ans. (b) Tropical sprue** *(Ref: Robbins 9/e p784)*

55. **Ans. (b) Tuberculosis** *(Ref: Robbins 9/e p376)*

56. **Ans. (a) Canker sores** *(Ref: Robbins 9/e p728)*

57. **Ans. (b) Stricture formation** *(Ref: Robbins 9/e p789)*

58. **Ans. (a) Appendix** *(Ref: Robbins 9/e p816)*

59. **Ans. (b) Multiple ulcer and transverse**
(Ref: Robbins 8th/801, 9/e p789)

60. **Ans. (b) Eat more frequent, smaller meals that are high in fat**
Read explanation below
The postgastrectomy symptoms in the given question is called the **dumping syndrome**. Since all or part of the stomach is removed, an ingested meal will be delivered to the small intestine more quickly than normal. The large increase in tonicity in the small intestine causes an osmotic fluid shift from the extracellular fluid (plasma) into the lumen of the gut. The increased distention of the small intestine increases motility through reflex mechanisms and causes diarrhea. The blood volume contraction and concomitant release of vasoactive substances such as bradykinin and/or vasoactive intestinal peptide can create hypotension and reflex tachycardia.

These patients should be instructed to eat more frequent, smaller meals to reduce the osmotic and/or carbohydrate load that is delivered to the small intestine. Furthermore, since fats are the slowest to be absorbed, a diet that is higher in fat will also reduce the problem of rapid absorption.

61. **Ans. (c) Crohn's disease** *(Ref: Robbins 9/e p799-800)*

62. **Ans. (c) Proximal small bowel**
(Ref: Robbins 8th/795-796, 9/e p782-783)
The patient has celiac disease, which is apparently an acquired hypersensitivity to the gluten (such as gliadin) in wheat. Unlike tropical sprue (which may be related to enterotoxigenic E. coli infection), which involves the entire small bowel, celiac sprue is usually limited to the proximal small bowel.

63. **Ans. (d) Ulcerative colitis** *(Ref: Robbins 9/e p800)*
The most frequent GIT disorder which can be associated with sacroiliitis (related to HLA-B27) or lower limb arthritis is the chronic inflammatory bowel diseases, ulcerative colitis and Crohn's disease. Other GI diseases associated with arthropathy include bypass surgery, Whipple's disease, Behcet's syndrome, and celiac disease.

Amebic colitis (choice A) is caused by ingestion of infectious cysts (typically from Entamoeba histolytica). Cecal amebiasis can resemble acute appendicitis.
Diverticulosis (choice C) is usually a disease of older adults. It is often asymptomatic unless inflammation supervenes.

64. Ans. (a) High fiber diet *(Ref Robbins 9/e p811)*

The dietary factors predisposing to a higher incidence of cancer are

- Excess dietary caloric intake relative to requirements,
- A low content of unabsorbable vegetable fiber,
- A corresponding high content of refined carbohydrates,
- Intake of red meat, and
- Decreased intake of protective micronutrients.

Concept

- **Reduced fiber content** leads to decreased stool bulk, increased fecal transit time in the bowel, and an altered bacterial flora of the intestine. Potentially toxic oxidative byproducts of carbohydrate degradation by bacteria are therefore present in higher concentrations in the stools and are held in contact with the colonic mucosa for longer periods of time.
- **High fat intake** (red meat) enhances the synthesis of cholesterol and bile acids by the liver, which may be converted into potential carcinogens by intestinal bacteria.
- Refined diets also contain less of vitamins A, C, and E, which may act as oxygen-radical scavengers.
- **NSAIDs** like aspirin are **protective in colon cancer** because they inhibit the COX-2 enzyme which is responsible for the proliferation of the colonic mucosa. The COX-2 expression is upregulated by TLR4 which recognizes lipopolyaccharides and is over-expressed in adenoma and carcinoma.

65. Ans (b) Pancreatitis

Purtscher's retinopathy is manifested by a sudden and severe loss of vision in a patient with acute pancreatitis. It is caused by occlusion of the posterior retinal artery with aggregated granulocytes. There are cotton-wool spots and hemorrhages confined to an area limited by the optic disc and macula.

66. Ans (a) Oxalate *(Ref: Robbins 9/e p876)*

There are two general classes of gallstones: cholesterol stones, containing more than 50% of crystalline cholesterol monohydrate, and pigment stones composed predominantly of bilirubin calcium salts.

67. Ans. (c) Ileum *(Ref: Robbins 8/e p372)*

Although any portion of the gastrointestinal tract may be affected, **the terminal ileum** and *the cecum* are the sites most commonly involved"... **Harrison 18th**

68. Ans. (c) Cecum *(Ref: Robbins 9/e p795)*

Amoebiasis is seen most frequently in the cecum and ascending colon.....Robbins

69. Ans. (a) sigmoid colon

(Ref: Robbins 8/e p814-5, 9/e p803, Bailey 25/e p1160)

- The condition is found in the **sigmoid colon** in 90% of cases.
- Interestingly in South-east Asia, **right-sided diverticular disease**Q is twice as common as the left.
- The main morbidity of the disease is due to **sepsis**Q.

70. Ans. (c) Celiac disease *(Ref: Robbins 9/e p783)*

- The **most sensitive tests** are the presence of **IgA antibodies to tissue transglutaminase or IgA or IgG antibodies to deamidated gliadin.**
- **Anti-endomysial antibodies** are **highly specific** but less sensitive than other antibodies.

71. Ans. (c) Klinefelter syndrome *(Robbins 9/e p782-783)*

Direct line... 'There is also an association of celiac disease with other immune diseases including ***type 1 diabetes, thyroiditis, and Sjögren syndrome, as well as ataxia, autism, depression, some forms of epilepsy, IgA nephropathy, Down syndrome*** and ***Turner syndrome***'

72. Ans. (a) Zinc *(Ref: Robbins 8/e p804)*

Paneth cells contain zinc along with lysozyme. They are involved in gut defence.

73. Ans. (c) Horizontal ulcers *(Ref: Bailey 25/e p1174)*

74. Ans. (d) Oral lichen planus *(Ref: Bailey 25/e p735)*

Conditions associated with malignant transformation

High-risk lesions	Medium-risk lesions	Low-risk/equivocal-risk lesions
*Erythroplakia *Speckled erythroplakia *Chronic hyperplastic candidiasis	*Oral submucous fibrosis *Syphilitic glossitis *Sideropenic dysphagia	*Oral lichen planus *Discoid lupus erythematosus *Discoid keratosis congenita

- In the Indian subcontinent oral submucous fibrosis is very common. This condition is characterized by limited opening of mouth and burning sensation on eating of spicy food.

75. Ans. (d) Blood culture....remember the acronym *BASU* **for blood, antibody, stool and urine for making the diagnosis in the 1st/2nd/3rd and 4th week respectively.**

76. Ans. (c) 3rd *(Ref: Bailey 25/e p1174)*

Perforation of a typhoid ulcer usually occurs **during the third week**Q and is occasionally the first sign of the disease.

77. Ans. (c) Appendicitis *(Ref: Bailey 25/e p1132)*

Causes of raised serum amylase level other than *acute pancreatitis*Q

- **Upper gastrointestinal tract perforation**[Q]
- **Mesenteric infarction**[Q]
- *Torsion of an intra-abdominal viscus*
- *Retroperitoneal haematoma*
- *Ectopic pregnancy*
- ***Macroamylasaemia***
- ***Renal failure***
- ***Salivary gland inflammation***

78. Ans. (a) Present in 3% of the population

(Ref: Robbins 9th/751)

Meckel diverticulum occurs as a result of failed involution of the vitelline duct, which connects the lumen of the developing gut to the yolk sac. This solitary diverticulum extends from the antimesenteric side of the bowel. The "rule of 2s" is often used to help remember characteristics of Meckel diverticula, which:

- Occur in approximately 2% of the population
- Are generally present within 2 feet (60 cm) of the ileocecal valve
- Are approximately 2 inches (5 cm) long
- Are twice as common in males
- Are most often symptomatic by age 2 (only approximately 4% are ever symptomatic).

79. Ans (b) Increase in thickness of the mucosa

(Ref: Robbins 9/e p783)

80. Ans. (d) Lymph node status *(Ref: Robbins 9/e p813)*

Direct quote Robbins .. 'the two most important prognostic factors are depth of invasion and the presence or absence of lymph node metastasis,

81. Ans. (a) AR inheritance

(Ref Robbins 8th/820-821, 9/e p809)

Prophylactic colectomy does not decrease risk for cancer due to adenomas at other sites specially ampulla of Vater and stomach.

82. Ans. (d) Jejunum *(Ref: Robbins 8th/817, 9/e p806)*

The polyps of Peutz-Jeghers syndrome are **most common in the small intestine**, although they may occur in the stomach and colon, and, with much lower frequency, in the bladder and lungs.

83. Ans. (a) Autosomal recessive inheritance

(Ref: Robbins 8th/820-821, , 9/e p809)

Familial polyposis syndrome (FAP) is an **autosomal dominant**[Q] disorder. It is caused by mutation in the adenomatous polyposis coli or APC gene on chromosome 5q21. Atleast 100 polyps are necessary for a diagnosis of FAP.

Option 'c'..Robbins clearly writes that colorectal carcinoma develop in 100% of untreated FAP patients often before age 30. As a result, prophylactic colectomy is the standard therapy in patients with APC mutations.

84. Ans. (a) Rb *(Ref: Robbins 8th/823-824, 9/e p811)*

Two distinct genetic pathways are described in adenocarcinoma of colon:

Adenoma-carcinoma sequence: It accounts for 80% of sporadic colon cancers. Mutation of APC gene occurs early or is inherited. Whenever second allele of APC is mutated or inactivated, β-catenin accumulates [APC protein degrades β-catenin]. Beta–catenin translocates to nucleus and activates genes like myc and cyclin D1.

Additional mutations occuring later are:

- Kras
- SMAD-2 and SMAD-4
- p53

Microsatellite instability pathway: Mutations in DNA mismatch repair genes (MSH2 and MLH1) results in expansion of microsatellites. This microsatellite instability may result in decreased functioning of TGF- β type II and bax proteins. Mutations in BRAF and epigenetic silencing of genes by hypermethylation may also occur. Kras and p53 are not typically mutated.

85. Ans. (a) Cryptitis

(Ref: Robbins 7th/849-850; 9/e 800, Harrison 17th/1888)

The pathology in ulcerative colitis typically involves distortion of crypt architecture, inflammation of crypts (cryptitis), frank crypt abscess, and hemorrhage or inflammatory cells in the lamina propria.

The **mnemonic** for important features is **U**lcerative **CO-LITIS** *(described in text)*.

86. Ans. (a) Diffuse distribution of pseudopolyps

(Ref: Harrison 17th/2077, Robbins 8th/807-13, 9/e p800)

- Pseudopolyps (inflammatory polyps) can be seen in both Crohn's disease and ulcerative colitis.
- Even Mucosal edema, crypt abscess and mucosal lymphoid aggregates are features common to both the types of inflammatory bowel disease.
- However, diffuse distribution of these polyps is observed only in ulcerative colitis because in Crohn's disease, there is presence of skip lesions in which there is presence of normal area adjacent to diseased segments of the intestine. So, patchy distribution of polyps is observed in Crohn's disease.

87. Ans. (d) Rectum spared in 50% patients with large bowel involvement

(Ref: Robbins 8th/810-2, 9/e p799, Harrison 17th/1888)

88. Ans. (b) β cells *(Ref: Robbins 7th/1205)*

89. Ans. (c) Both a and b *(Ref: Robbins 7th/849-851, 9/e p800)*

Please don't confuse 'skin lesions' with *'skip lesions'*, the latter are seen only in *Crohn's disease*.

90. Ans. (c) Hamartomatous polyp *(Ref: Robbins 9/e p806)*

- **Peutz-Jegher's polyps** are **hamartomatous polyps** that involve mucosal epithelium, lamina propria and muscularis mucosa. Peutz-Jegher's polyps are located usually in small intestine ***most commonly in jejunum.***
- When they occur in multiple numbers, condition is called **Peutz-Jegher's syndrome.** It is rare autosomal

dominant syndrome characterized by multiple hamartomatous polyps scattered throughout GIT, along with mucosal and cutaneous melanotic pigmentation along lips, face, genitalia and palms

Genetic basis of Peutz-Jegher's syndrome is mutation in gene STKII (LKB1) located on chromosome 19 which encodes protein with serine/threonine kinase activity.

91. Ans. (a) Juvenile polyp *(Ref: Robbins 9/e p805)*

92. Ans. (a) Rectal involvement is common
(Ref: Robbins 9/e p799, 8th/810-811; 7th/851)

93. Ans. (a) Carcinoid tumor *(Ref: Robbins 9/e p816)*

94. Ans. (b) Crohn's disease *(Ref: Robbins 9/e p799)*

95. Ans. (a) Crohn's disease *(Ref: Robbins 9/e p800)*

96. Ans. (c) Distal ileum *(Ref: Robbins 9/e p774)*

97. Ans. (a) Head *(Ref: Robbins 9/e p893)*

98. Ans. (c) Bronchodilation *(Ref: Robbins 9/e p774)*

99. Ans. (c) Rectosigmoid *(Ref: Robbins 9/e p800)*

100. Ans. (d) Crohn's disease *(Ref: Robbins 9/e 799)*

101. Ans. (b) High fiber diet *(Ref: Robbins 8th/811)*

102. Ans. (b) Ulcerative colitis *(Ref: Robbins 9/e 800)*

103. Ans. (a) Crohn's disease *(Ref: Robbins 9/e p799)*

104. Ans. (a) Ulcerative colitis *(Ref: Robbins 9/e p800)*

105. Ans. (d) Splenomegaly *(Ref: Robbins 9/e p774)*

106. Ans. (b) Transmural inflammation
(Ref: Robbins 9/e p799-800, 8th/810)

The typical presentation of Crohn's disease is abdominal pain and diarrhea in a 20-30-year-old patient. Weight loss, fatigability, low grade fever, and aphthous ulcers of the oral mucosa are also common.

Transmural inflammation explains the two most common complications of Crohn's disease: strictures, and fistulas. Chronic inflammation causes edema and fibrosis leading to narrowing of the intestinal lumen (strictures). Necrosis of the intestinal wall causes ulcer formation. Ulcers can penetrate the entire thickness of the affected intestinal wall, leading to the formation of a fistula.

> Please contrast with ulcerative colitis in which only the mucosa and submucosa are inflammed, so, strictures and fistulas are not common.

- **(Choices a and d)** Intramural granulomas and skip lesions are commonly found in Crohn's disease. They do not, however, predispose to fistula formation.
- **(Choice c)** A chronic inflammatory infiltration that consists predominantly of monocytes and lymphocytes is characteristic of Crohn's disease. However, it is not the composition of the inflammatory infiltrate, rather the fistula's depth that is responsible for fistula formation.

107. Ans. (b) Pseudomembranous colitis
(Ref: Robbins 9/e p791, 8th/803)

108. Ans. (a) 5-HIAA *(Ref: Robbins 9/e p774, 8th/788-789)*

109. Ans. (a) Hyperplastic polyp *(Ref: Robbins 9/e p804)*

This is a hyperplastic polyp; these polyps comprise 90% of all colonic polyps and have no malignant potential.

Peutz-Jeghers polyps (choice 'b') also have no malignant potential, but tend to be larger and have a complex branching pattern.

Tubular adenomas and tubulovillous adenomas, (choices c and d) are all true neoplastic polyps containing dysplastic epithelium; the malignant potential of these polyps increases with size and the percentage of the polyp which has a villous configuration.

110. Ans. (d) Noncaseating granuloma *(Ref: Robbins 9/e p799)*

111. Ans. (c) Gastrointestinal tract
(Ref: Robbins 9/e p774, 8/e p788 , Harrison 18/e p)

Direct quote from Harrison.. "The **GI tract** is the **most common** site for these tumors, accounting for 64%, with the respiratory tract a distant second at 28%."

112. Ans. (a) Chronic nonspecific ulcerative colitis
(Ref: Robbins 9/e p800, 8/e p812)

In **ulcerative colitis**, inflammation and inflammatory mediators can damage the muscularis propria and disturb neuromuscular function leading to colonic dilation and **toxic megacolon**, which carries a significant risk of perforation

113. Ans. (b) Kulschitsky cells *(Ref: Robbins 9/e p774)*

Carcinoid tumour arises from the neuroendocrine cells called **Kulschitsky cells**. These cells are also called as **Enterochromaffin (EC) cells**and are present in gastrointestinal tract and the respiratory tract.

114. Ans. (c) Islet cell hyperplasia *(Ref. Robbins 9th/884)*

Etiological factors in acute pancreatitis

Metabolic
Alcoholism Hyperlipoprotelnemia Hypercalcemia Drugs (e.g., azathioprine)
Genetics
Mutations in genes encoding trypsin, trypsin regulators, or proteins that regulate calium metabolism
Mechanical
Gallstones Trauma Iatrogenic injury • Operative injury • Endoscopic procedures with dye injection
Vasular
Shock Atheroembolism Vasculitis
Infections
Mumps

115. Ans. (b) Ulcerative colitis *(Ref: Robbins 9/e p800)*
Though pseudopolyps may be seen in both Crohn's disease and ulcerative colitis, it is more common in ulcerative colitis.

116. Ans. (c) Familial polyposis *(Ref: Robbins 9/e p809)*
Direct line.. *"Colorectal cancer develops in 100% of untreated FAP patients often before the age of 30".*

117. Ans. (a) Adenocarcinoma
- **Small intestinal adenocarcinomas**[Q] and carcinoids have roughly equal incidence, followed in order by lymphomas and sarcomas. However, other texts mention that adenocarcinomas are common. So, its he answer of consensus here.
- Most common **benign** small intestinal tumor is **adenoma**[Q]. It is located most commonly **near Ampulla of Vater**[Q].

118. Ans. (a) Head *(Ref: Robbins 9/e p893)*

Carcinoma of the pancreas

- More than 85% of pancreatic cancers are **ductal adenocarcinomas**[Q].
- Ductal adenocarcinomas arise most commonly in the **head of the gland**[Q].
- **Painless jaundice**[Q] secondary to obstruction of the distal bile duct is the most common symptom.
- The jaundice may be associated with nausea and epigastric discomfort.
- On examination, there may be evidence of jaundice, weight loss, a palpable liver and **a palpable gallbladder**[Q]
- If there is a genuine suspicion of a tumour in the head of the pancreas, the preferred test is a **contrast-enhanced CT scan**[Q]
- The standard resection for a tumour of the pancreatic head or the ampulla is a **pylorus-preserving pancreatoduodenectomy**[Q]. This is considered better than the earlier performed **Whipple procedure**.

119. Ans. (b) Juvenile polyp *(Ref: Robbin 8/e p 816-7)*
- *Juvenile polyps* are focal malformations of the mucosal epithelium and lamina propria.
- The vast majority of juvenile polyps occur in ***children less than 5 years***[Q] of age.
- *The majority of juvenile polyps are located in the* ***rectum***[Q] and **most present with rectal bleeding.**[Q]

120. Ans (b) Iron deficiency anemia *(Ref: Robbins 9/e p 813)*
The underlying cause of iron deficiency anemia in an older man or postmenopausal woman is GI cancer until proven otherwise.

121. Ans. (b) Smoking has a protective effect
(Ref: Robbins 9/e p 800)

122. Ans (c) Colon
(Ref: Robbins 9/e p 769; Harrison 18/e p 2455-6)
- Zollinger-Ellison syndrome is caused by gastrin-secreting tumors. These gastrinomas are most commonly found in the small intestine or pancreas.
- The extrapancreatic sites of these tumors are ***duodenum*** (*most common extrapancreatic site*), stomach, bones, ovaries, heart, liver, and lymph nodes.

Also revise!

Gastrinoma triangle (confluence of the cystic and common bile ducts superiorly, junction of the second and third portions of the duodenum inferiorly, and junction of the neck and body of the pancreas medially).

123. Ans (a) NOD2/CARD15 gene *(Ref: Robbins 9/e p 797)*
One of genes ***most strongly associated with Crohn's disease is NOD2*** (nucleotide oligomerization binding domain 2), which encodes an intracellular protein that binds to bacterial peptidoglycans and activates signaling events, including the NF-κB pathway.

124. Ans. (b) Autosomal dominant *(Ref: Robbins 9/e p809)*
Familial Adenomatous Polyposis is caused by the mutation of adenomatous polyposis coli (APC) gene present on the long arm of chromosome 5[Q] (5q21). It is inherited as an autosomal dominant disorder.

125. Ans. (d) Gardener syndrome *(Ref: Robbins 9/e p809)*

126. Ans. (b) Fecal lactoferrin *(Ref: Harrison 18/e)*
In ulcerative colitis, active disease can be associated with a rise in acute-phase reactants C-reactive protein (CRP), platelet count, erythrocyte sedimentation rate (ESR), and a decrease in hemoglobin.
Direct line… ***"Fecal lactoferrin is a highly sensitive and specific marker for detecting intestinal inflammation".***

Other options:

- Fecal calprotectin levels correlate well with histologic inflammation, predict relapses, and detect pouchitis.
- Leukocytosis may be present but is not a specific indicator of disease activity.

Fecal lactoferrin is a marker of fecal leukocytes and is more sensitive and is available in latex agglutination and enzyme-linked immunosorbent assay formats.

127. Ans. (d) 100 *(Ref: Robbins 9/e p809)*

128. Ans. (a) p-ANCA *(Ref: Robbins 9/e p860)*
p-ANCA is also called now by the name of anti myeloperoxidase (MPO-ANCA). It is directed against a lysosomal granule constituent and is seen in the following conditions:

- Ulcerative colitis
- Churg-Strauss syndrome
- Primary sclerosing cholangitis
- Microscopic polyangiitis
- Focal necrotising and crescentic glomerulonephritis
- Rheumatoid arthritis

129. Ans. (d) Giardiasis *(Ref: Robbins 9th/795)*
Giardia lamblia are the most common parasitic pathogen in humans and are spread by fecally contaminated water

or food. It can be identified in duodenal biopsies based on their characteristic pear shape and the presence of two equally sized nuclei. Despite large numbers of trophozoites, which are tightly bound to the brush border of villous enterocytes, there is no invasion and small intestinal morphology may be normal (as seen in the figure). However, villous blunting with increased numbers of intraepithelial lymphocytes and mixed lamina propria inflammatory infiltrates can develop in patients with heavy infections.

130. Ans. (b) Most common site lung

(Ref: Robbins 9/e p773-4)

Commonest site for the carcinoid tumor is the gastrointestinal tract.

131. Ans. (a) Duodenum *(Ref: Robbins 9/e p734)*

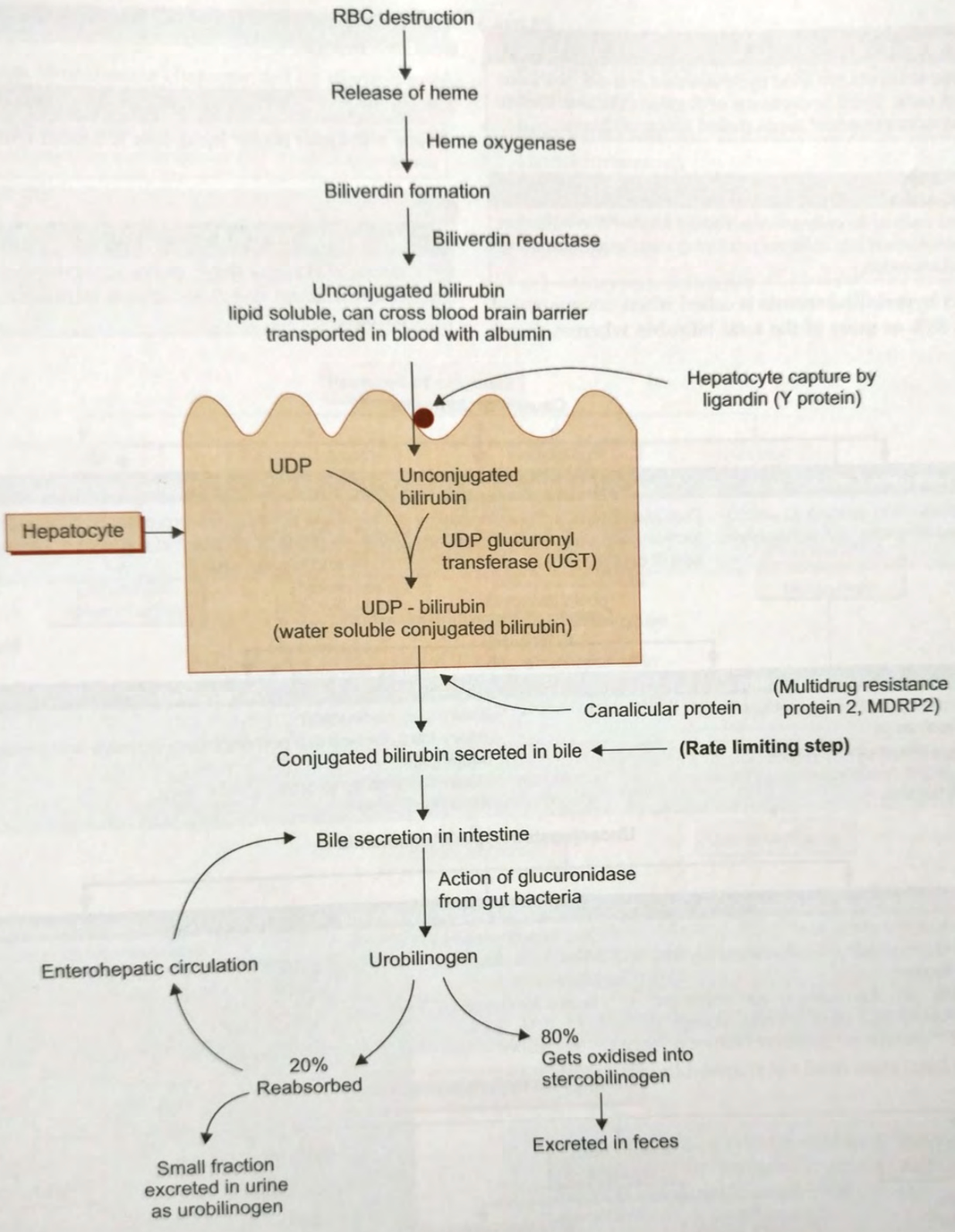
- **50%** of the small bowel adenocarcinomas occur in the **duodenum**. It is also good to know that **Periampullary region** is the location of more than 50% adenocarcinomas

CHAPTER 14

Liver

Golden Points

- Canals of herring and Von Meyenburg complexes are seen in the liver.
- Hexagonal lobule is a vital anatomical microstructure in the liver.
- Centrilobular necrosis is seen in hypovolemia, carbon tetrachloride and halothane toxicity whereas yellow fever causes mid zonal necrosis.
- Inherited causes of unconjugated hyperbilirubinemia: Gilbert syndrome, Crigler-Najjar syndrome.
- Inherited causes of conjugated hyperbilirubinemia: Rotor syndrome, Dubin-Johnson syndrome.
- Bilirubin has affinity for elastin and so, jaundice is observed in skin and sclera.
- Acute hepatitis has the microscopic findings like focal or centrilobular nerosis, ballooning degeneration, acidophilic degeneration (Councilman bodies) and interface hepatitis.
- Chronic (active) hepatitis has the findings like Piecemeal necrosis, bridging necrosis, portal fibrosis and interface hepatitis.
- Mallory bodies have Cytokeratin/keratin intermediate filament and are seen in causes Alcoholism, liver cancer, Indian childhood cirrhosis, primary biliary cirrhosis, Wilson's disease and alpha 1 antitrypsin deficiency.
- Fatty liver is due to accumulation of: Triglyceride
- Most common cause of fatty liver (***triglyceride accumulation***) is **Alcoholism**.
- Major source of collagen in liver in cirrhosis: Ito cells (perisinusoidal stellate cells).
- Non-cirrhotic portal fibrosis is characterised by fibrosis in portal and periportal area only (bridging fibrosis is absent); it has a young patient with hematemesis (variceal bleeding) and splenomegaly in absence of hepatomegaly as clinical findings.
- **Hemochromatosis** is a disorder of iron metabolism characterised by **triad of Micronodular cirrhosis, diabetes mellitus and skin pigmentation**.
- Organ **not** showing iron deposition in hemochromatosis: gonads (Testis/ovary).
- Angiosarcoma of liver is associated with exposure to either **Arsenic, vinyl chloride or thorotrast**.
- **Cavernous hemangioma** is the most common **benign tumor** of liver.
- Hepatocellular carcinoma is the most common primary malignant tumor of liver.
- **Fibrolamellar type** of HCC has: best prognosis, equal sex incidence and non association with HBV/cirrhosis. It has normal AFP levels.
- **AFP** is the best/ definitive marker for **hepatoblastoma**.
- Primary biliary cirrhosis has the presence of Antimitochondrial antibodies.
- 'Comet tail artefact' with thickening of gallbladder wall: Adenomyomatosis.
- Primary sclerosing cholangitis is associated most commonly with: IBD (UC > CD).
- **'Onion skin' fibrosis of bile duct** is seen in: **Primary sclerosing cholangitis**.
- **'Klastkin' tumors** are: ***Cholangiocarcinomas*** located at the **junction** of *right and left hepatic ducts.*



Key Point

The adult liver is an important organ of the body weighing around 1.5 kg and supplied by portal vein (60% of blood flow) and hepatic artery (40% of blood flow). It is responsible for plasma protein synthesis and metabolism of endogenous waste products and xenobiotics.

Key Point

The functional unit of the liver is a hexagonal lobule having hepatic vein at its centre and portal tract (composed of hepatic artery, portal vein and bile duct) at its periphery.

Jaundice is characterized by hyperbilirubinemia and yellowing of the skin and sclera (due to elastin fibers).

Key Point

The hepatic sinusoids are lined by fenestrated and discontinuous endothelial cells. There is presence of Kupffer cells and stellate cells in the extra sinusoidal space (called *space of Disse*).

Key Point

The *stellate cells or Ito cells are required for vitamin A metabolism and get transformed into collagen producing myofibroblasts during hepatic inflammation.*

Indirect hyperbilirubinemia is called when unconjugated bilirubin is 85% or more of the total bilirubin whereas direct hyperbilirubinemia corresponds to conjugated bilirubin more than 15% of total.

Key Point

Type II Criggler Najjar Syndrome is treated with **phenobarbitone.**

Mnemonic

- **G**ilbert and **C**riggler **N**ajjar: **G**lucuronide **C**onjugation **N**ot present
- **D**ubin Johnson and **R**otor: **D**efect in **R**emoving conjugated bilirubin

Causes of Jaundice

Prehepatic Cause	Hepatic Cause	Posthepatic Cause
↑ Bilirubin production leading to unconjugated hyperbilirubinemia e.g. hemolytic anemia.	Due to defect in hepatocyte leading to defective conjugation or decreased excretion of conjugated bilirubin.	Due to impaired excretion of conjugated bilirubin as a result of obstruction e.g. stone, cancer of pancreas and bile duct etc.

Causes of Hyperbilirubinemia

Unconjugated	Conjugated
• Physiological jaundice of newborn • Hemolytic anemia • Diffuse hepatocellular disease • Criggler Najjar syndrome • Gilbert syndrome	• Biliary tract obstruction • Biliary tract disease like primary biliary cirrhosis and primary sclerosing cholangitis • Dubin Johnson syndrome • Rotor syndrome

Unconjugated Hyperbilirubinemia

Physiological Jaundice	Criggler Najjar Syndrome	Gilbert Syndrome
• Due to immaturity of the liver • Increased changes with prematurity and **erythroblastosis fetalis**[Q]. • May result in kernicterus (unconjugated bilirubin crosses BBB causing brain damage[Q])	• Due to decreased UGT activity • Type I → **Absence** of UGT enzyme; 100% fatal • Type II **Reduced** UGT activity.	• Decreased bilirubin glucuronidation • Jaundice associated with stress like **illness, fasting** or **exercise**[Q].

Conjugated hyperbilirubinemia

Biliary tract obstruction
- Stones
- Stricture
- Cancers
- Fluke (Clonorchis sinensis)

Biliary tract Disease

Primary biliary cirrhosis
- Autoimmune liver disease having inflammation of **intrahepatic bile duct**[Q]
- F > M; 30-65 years

Primary sclerosing cholangitis
- Chronic liver disease having segmental inflammation of **extrahepatic**[Q] **bile ducts**
- M > F; 20-40 years
- Usually associated with ulcerative colitis[Q]

Dubin Johnson syndrome
- Defective canalicular protein[Q]
- Pigmented liver present (pigment is **epinephrine** not bilirubin[Q])

Rotor syndrome
- Defect in bilirubin excretion
- **Non pigmented liver**[Q]

CIRRHOSIS

It is the end stage liver disease characterized by disruption of the liver architecture by fibrotic bands that divide the liver into nodules of regenerating liver parenchyma. It can be *micronodular* (if nodule is <3 mm) or *macronodular* (>3 mm) or mixed.

Key Point

Most common cause of cirrhosis is **alcoholic liver disease**. ***Non-alcoholic fatty liver disease*** is the most common cause of ***cryptogenic cirrhosis***.

CAUSES

- **Alcoholic liver disease** (*most common cause*[Q])
- Viral hepatitis
- Biliary tract disease
- Hemochromatosis
- Cryptogenic/idiopathic (**non alcoholic fatty liver disease** is its ***commonest cause***)
- Wilson disease
- α-1-antitrypsin deficiency

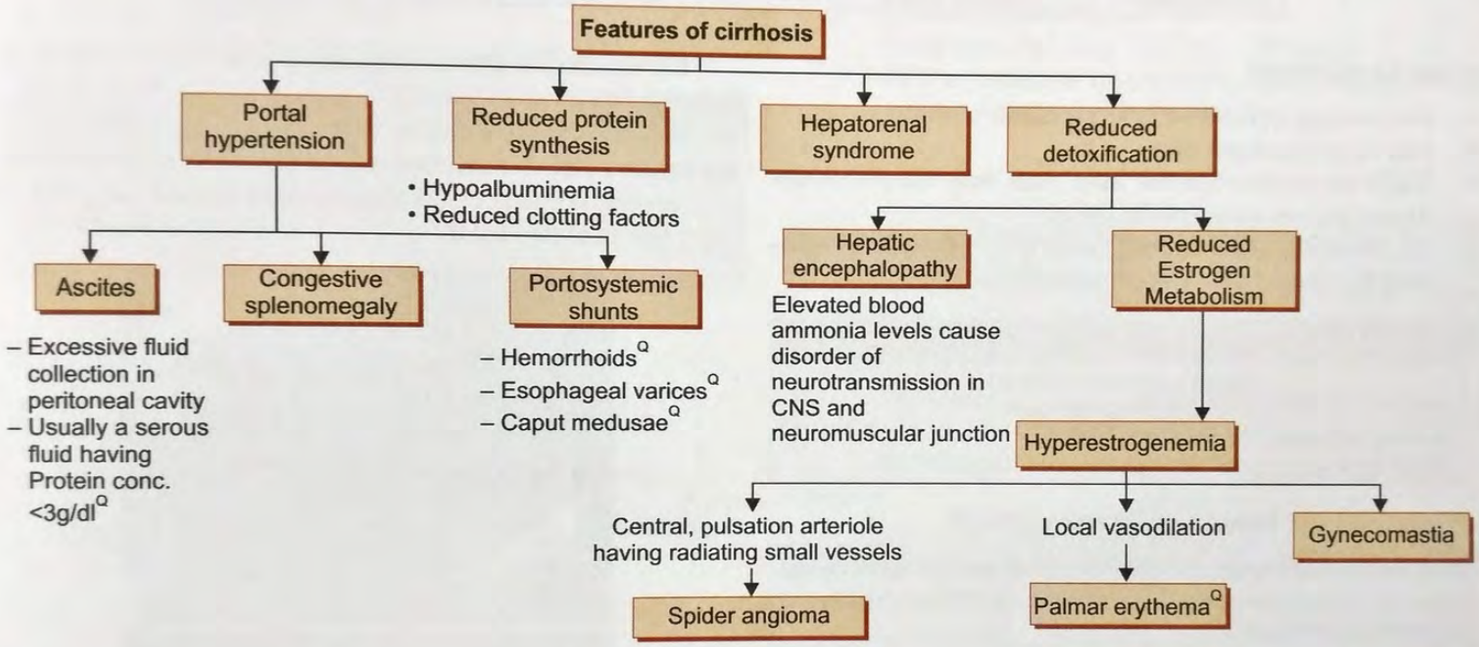


Fig. 1: Liver cirrhosis

Key Point

The **fibrosis** is produced by the **hepatic stellate cell or Ito cell** and there is deposition of primarily **type I and type III collagen** in the lobule.

Non-Cirrhotic Portal Fibrosis (NCPF)/Idiopathic Portal Hypertension (IPH)

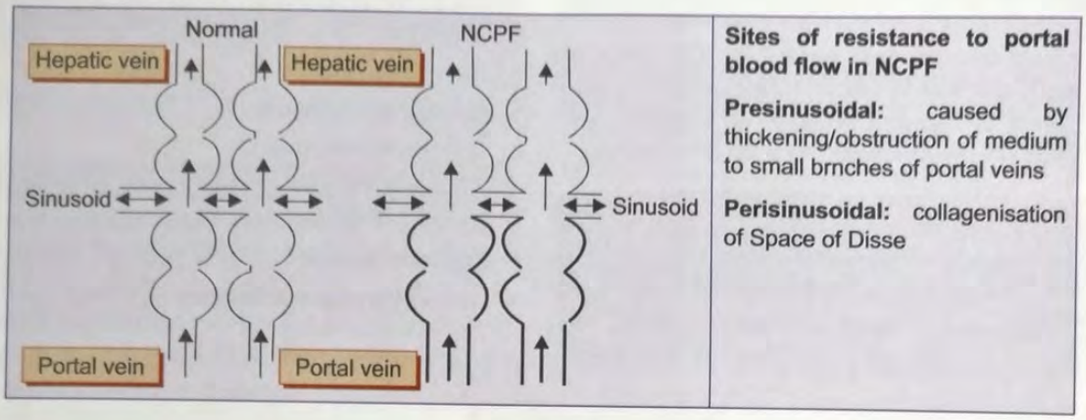
It is a condition characterized by portal hypertension and moderate portal fibrosis without cirrhosis. Though the exact etiology is unknown, it has been associated with the following:

- **Infections:** sepsis, diarrhea in children, bacterial infections
- **Immunological mechanisms:** associated with HLA DR-3
- **Chemical exposure:** ***arsenic***, vinyl chloride, copper sulfate, hypervitaminosis A, drugs (steroid)

Histopathological Features

Intimal fibroelastosis of medium sized portal veins (Obliterative portovenopathy of liver): characteristic finding. Other findings include: *portal fibrosis* (intra portal but **not bridging fibrosis**), portal vein sclerosis, portal tract edema and *lymphocytic infilteration*, pseudolobulation, and atrophy of liver parenchyma with no regenerative capacity.

FIGURE EXPLAINING THE PATHOGENESIS OF NCPF



CLINICAL FEATURES

- Presentation in the *3rd-4th decade* of life
- Low socioeconomic strata
- Slight sex preponderance ***M>F*** (this may vary however depending on geographical areas)
- **GI bleeding** (***commonest symptom***), **massive splenomegaly** with **normal liver function tests.**

Key Point

Most common cause of Portal hypertension
Adults: Cirrhosis *followed by NCPF*
Children: Extra hepatic portal vein obstruction **(EHPVO).**

Clinical significance of NCPF

Massive splenomegaly and **emergence of new aberrant blood vessels** is **most commonly** associated with NCPF out of all causes of portal hypertension.

INFECTIOUS DISORDERS OF LIVER

Hepatitis

ACUTE HEPATITIS

1. Swelling of the hepatocytes called *"Ballooning"*.
2. Presence of apoptotic hepatocytes giving rise to *Councilman bodies*. Apoptosis of a single hepatocyte is called **'spotty necrosis'**.
3. Disruption of lobular architecture of the liver.
4. Necrosis connecting portal to portal, portal to central, central to central regions of adjacent lobules is called **bridging necrosis**
5. Infiltration of portal tract with inflammatory cells.
6. Spilling of inflammatory cells in the adjacent parenchyma causing necrosis of adjacent cells (**Interface hepatitis** or **piecemeal necrosis**).

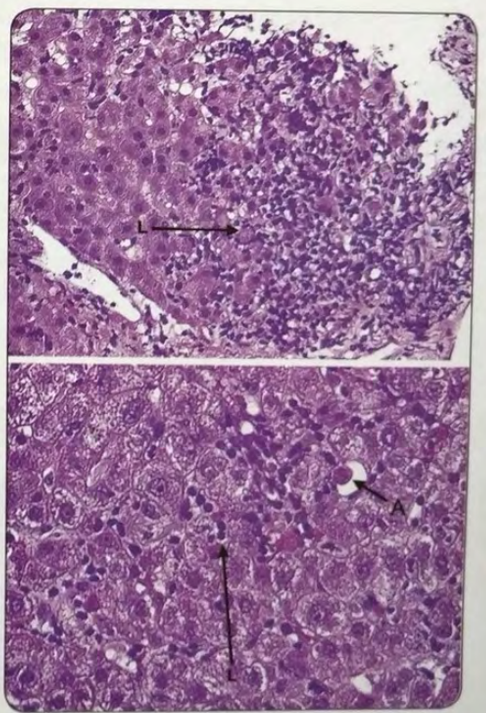


Fig. 2: Active hepatitis having lymphocytic infiltration (L) and apoptotic cells (A)

CHRONIC HEPATITIS

Older classification of chronic hepatitic

Chronic persistant Hepatitis	Chronic active hepatitis	Chronic lobular hepatitis
• Inflammation limited to portal tracts • Lobular structure of liver is preserved	• Inflammation involving both parenchyma and portal tracts • Associated with ***"piecemeal necrosis"*** and ***"bridging necrosis"*** • Lobular structure not preserved.	• Inflammation limited to the lobules

Latest classification of hepatitis is based on

1. *Cause* (Viral hepatitis, autoimmune hepatitis, drug associated hepatitis, etc.)
2. *Histological activity or grade*
   - Grading is based on necrosis and inflammation which include assessment of the following factors:
   - Periportal necrosis including piecemeal necrosis and bridging necrosis
   - Portal inflammation
   - Intralobular necrosis
   - Fibrosis
3. *Degree of progression or stage*
   Staging is done based on the degree of fibrosis

Absent	Mild	Moderate	Severe	Cirrhosis
0	1 (Fibrosis confined to portal tracts with portal expansion)	2 (Portal and periportal fibrosis)	3 (Bridging fibrosis)	4 (Cirrhosis)

VIRAL HEPATITIS

1. **Hepatitis A virus (Infectious Hepatitis)**
   - It is a benign and self-limiting disease.
   - Incubation period of HAV is 2-6 weeks.
   - It **does not** cause chronic hepatitis or carrier state in hepatitis.
   - HAV is an unenveloped, single stranded RNA virus belonging to Picornavirus family.
   - **Feco-oral route** is the predominant route of spread.
   - HAV is present in stools 2-3 weeks before and 1 week after onset of jaundice.
   - IgM antibody appearing in blood with onset of symptoms is a marker of acute infection whereas IgG antibody provides life long immunity.
2. **Hepatitis B virus (Serum Hepatitis)**
   - It can cause acute hepatitis, non-progressive chronic hepatitis, progressive chronic hepatitis leading to cirrhosis, fulminant hepatitis, carrier state and hepatocellular carcinoma.
   - Incubation Period of HBV is 30-180 days.
   - HBV is present in all physiologic and pathologic body fluids, ***except in stools*** (unlike HAV).

Mode of Infection

- Blood products, needle sticks etc. (30%)
- Sexual transmission
- Vertical transmission is responsible for development of carrier state
- The virus is a double stranded DNA belonging to Hepadnaviridae family.
- It is a spherical, double layered 'Dane particle' 42 mm in size.

Genome

The genome of the virus has several genes coding for different proteins or enzymes. These include:

'S' gene	'C' gene	'P' gene	'X' gene
• Codes for envelope protein, **HBs Ag**[Q] (surface antigen)	• Codes for 2 nucleocapsid proteins: • **HBc Ag:**[Q] Intracellular nucleocapsid core antigen • **HBe Ag:**[Q] Nucleocapsid protein with a core and precore region.	• Codes for **DNA polymerase** having **reverse transcriptase activity**[Q]	• Codes for **HBx protein**[Q] required for viral replication and transcriptional activator of viral and host genes. • Particularly important in the development of **hepatocellular carcinoma**[Q].

- The precore region directs the release of HBeAg towards secretion in the blood. Uncommonly, mutated strains called ***precore mutants*** of HBV emerge that do not produce HBeAg but are replication competent and express HBcAg. In these patients, the HBeAg may be undetectable despite the presence of HBV viral load. A **mutation in the core promoter region** can also lead to an HBeAg negative phenotype. Clinically both these conditions are characterized by the presence of elevated liver enzymes and active viral multiplication is indicated only by the high levels of DNA polymerase.

PHASE OF INFECTIONS

There is an *initial proliferative phase* in which the viral DNA is present in an episomal form leading to the formation of complete virion with associated antigens. This is followed by expression of viral antigens with MHC class I molecules resulting in CD8+ T cells activation and destruction of infected hepatocytes. There is presence of an *integrative phase* in which the viral DNA is incorporated into host DNA. This usually occurs in hepatocytes not destroyed by immune response.

Definition

Carrier state is defined by the presence of **HBs Ag** in the serum for **6 months or longer** after initial detection.

Sequential Appearance of Hepatitis B Markers and Significance

HBs Ag ↓	• Present in *acute disease*[Q] • Continued presence indicates chronic disease or carrier state
HBe Ag ***HBV DNA*** ***DNA polymerase***	• Seen with active viral replication and denotes *high infectivity*[Q]
↓ ***IgM anti HBc*** ↓	• Antibody detectable shortly before onset of symptoms • *Marker of window period*[Q] • *IgM anti HBc is indicator of recent disease whereas IgG anti HBc is seen with chronic infection or prior infection*
Anti HBe Ab ↓	• Detected after HBe Ag disappears and denotes *low infectivity*[Q]
IgG anti HBs	• Appears after disappearance of HBs Ag • Provides protection against Hepatitis B and *indicates immunity*[Q] • Seen in prior infection and in vaccinated persons[Q]

Key Point

HBc Ag never appears in the blood.

Concept

An important mutation seen in HBV is ***"escape mutants"*** due to amino acid substitution causing a conformational change in HBsAg resulting in ***loss of neutralizing activity by anti-HBs***. It is seen in association with active and passive immunization and in liver transplant patients. In both these conditions, there is increased concentration of anti HBs leading to mutation in the virus so that it can escape from the protective effect of anti-HBs.

NUTSHELL OF HEPATITIS B SEROLOGY

	HBsAg	IgM anti HBc	IgG anti HBc	IgG anti HBs
Acute HBV infection	+	+	–	–
Window period	–	+	–	–
Chronic infection	+	+/-	+	–
Prior infection	–	–	+	+
Immunization	–	–	–	+

Recent Exam Question

Most useful indicator of **prior infection** with HBV is **Anti HBc Ag**

In addition: Remember that the presence of HBeAg denotes high infectivity and its absence denotes low infectivity.

Immunology concept

Immunization for HBV is based on the fact that anti HBs Ab is protective in nature. So, vaccination with non- infectious HBsAg still retaining its immunogenic potential is done.

Key Point

Microscopically, **HBs Ag** is responsible for **"ground glass" hepatocytes** whereas *'HBc Ag"* gives *"sanded nuclei"* appearance.

3. **Hepatitis C virus (Transfusion Associated Hepatitis)**
   - HCV is a single stranded RNA virus belonging to Flaviviridae family.
   - Incubation Period is 2-26 weeks.
   - Acute HCV infection is generally undetectable clinically whereas chronic disease occurs in majority of infected individuals.
   - Spread of the virus is through inoculation and blood transfusion (more frequently) and less commonly through sexual and vertical transmission.
   - Acute illness is usually asymptomatic/mild.
   - Initially, there is IgM anti-HCV followed by the presence of IgG anti-HCV antibodies.
   - Chronic infection is associated with episodic elevations in serum transaminases with intervening normal period associated with persistence of HCV RNA in the blood.

Key Point

Focal macrovesicular fatty changes indicates **HCV** infection
Panlobular micro and macrovesicular steatosis indicates ***Alcohol*** as the etiology
Bile duct damage and lymphoid aggregates in portal tract are indicative of ***chronic HCV infection***.

Note: Antibody against HCV is IgG anti-HCV which does not provide effective immunity because the virus demonstrates genomic instability and antigenic variability.

4. **Hepatitis D virus (Delta Agent)**
   - It is a single stranded RNA virus.
   - Replication is defective and can cause infection only when encapsulated by HBs Ag.
   - So, it can cause infection in 2 conditions:

- **Acute coinfection**: In which there is simultaneous exposure to both HBV and HDV. However, HBV must establish first. This is associated with 90% chances of recovery and only rare chances of development of chronic hepatitis.
- **Super infection**: In which chronic carriers of HBV get infected with HDV. This is associated with majority developing chronic hepatitis.

The serology shows the presence of *IgM Anti HDV* which is the *most reliable marker of recent infection*.

5. **Hepatitis E virus**

- It is a single stranded RNA unenveloped **enterically transmitted** virus accounting for more than 50% of cases of acute hepatitis in India.
- Incubation period is 2-8 weeks.
- It causes sporadic infection in young to middle aged adults (rare in children).
- The **disease is self limiting** (*not associated with chronic disease*).
- The serology shows the HEV RNA and presence of virions in stool and the liver even before onset of clinical illness.
- IgM anti-HEV IgG anti HEV followed by is seen in 2-4 weeks.

Key Point

HEV is associated with high mortality in pregnancy.

6. **Hepatitis G virus**

It is a single stranded RNA virus transmitted by the parenteral route i.e. by the contaminated blood or blood products and possibly by the sexual route. In up to 75% of infections, HGV is cleared from the plasma and the infection becomes chronic in the remaining 25%. The site of HGV replication is *mononuclear cells*, so, it does not cause any rise in serum amino transferases and is **non pathogenic**. It co-infects patients with HIV and the dual infection is protective against HIV disease.

Clinicopathologic Syndromes

1. **Acute asymptomatic infection with recovery:**
This is identified incidentally with the help of elevated serum transaminases or the presence of antiviral antibodies

2. **Acute viral hepatitis:** It has got 4 phases:

Incubation period
Peak infectivity during last days of incubation period and early days of acute symptoms.
Symptomatic pre-icteric phase
Nonspecific, constitutional symptoms, malaise, general fatigability, nausea, and loss of appetite.
Symptomatic icteric phase
Caused mainly by conjugated hyperbilirubinemia, dark urine and light stools
Convalescence
Recovery due to T cell activity against infected hepatocytes.

3. **Chronic viral hepatitis:** Symptomatic, biochemical or serologic evidence of continuing or relapsing disease for *> 6 months* with histologic documentation of inflammation and necrosis. Chronic hepatitis constitutes a "Carrier State". Healthy carriers are individuals having the virus without adverse effects. Vertical transmission with HBV produces carrier in 90-95% cases. The most common symptom is fatigue; less common symptoms are malaise, loss of appetite, and occasionally mild jaundice.
4. **Fulminat hepatitis:** Progression of hepatic insufficiency *from onset* of symptoms *to hepatic encephalopathy* within 2-3 *weeks*, is called *fulminant hepatic failure*. The progression in upto 3 months is called subfulminant failure.

ALCOHOLIC LIVER DISEASE

Mnemonic

Conditions where Mallory Hyaline bodies are seen (Mnemonic: New Indian WATCH)

New - **N**on-alcoholic fatty liver disease (NAFLD)
Indian - **I**ndian childhood cirrhosis
W - **W**ilson's disease
A - α_1- **A**T deficiency; **A**lcoholic Liver Disease
T - **T**umor of liver (Hepatocellular carcinoma)
C - **C**hronic cholestatic conditions
H - **H**epatic or Primary Biliary cirrhosis (it is **not** seen in Secondary biliary cirrhosis)

Alcoholic liver disease

Hepatic steatosis	Alcoholic hepatitis	Alcoholic cirrhosis
• Also called fatty liver • Characterized by the presence of small (microvesicular) or large (macrovesicular) lipid droplets inside the hepatocytes • Initial centrilobular involvement followed by entire lobule involved • Reversible if there is abstinence from alcohol.	• Having hepatocyte swelling and necrosis **(ballooning degeneration)** • Neutrophilic infiltration in lobule • Perivenular and periportal fibrosis (due to ito cell in space of sisse) • Some hepatocytes show the presence of eosinophilic, cytokeratin filaments called **'Mallory Hyaline bodies'**.	• Irreversible form of alcoholic liver disease • Initially, liver is enlarged and later there is presence of micronodules and macronodules • Later, the whole liver has tough, pale scar tissue **(Laennec Cirrhosis)**.

Non Alcoholic Fatty Liver Disease (NAFLD)

- It is a condition that resembles alcohol-induced liver disease but occurs in patients who are not heavy drinkers. Men and women are equally affected.

Association

- Strong association with **obesity**[Q], **dyslipidemia**[Q], **hyperinsulinemia**[Q] **and insulin resistance**[Q].

Spectrum of disease

- NAFLD includes simple hepatic steatosis, steatosis with non specific inflammation and non-alcoholic steatohepatitis (NASH). Some patients may develop cirrhosis. Patients are largely asymptomatic, with abnormalities only in biochemical laboratory tests.

Clinical Significance

- NAFL is now the ***most common cause of "cryptogenic" cirrhosis***[Q]. It also contributes to the progression of other liver diseases like hepatitis C viral infection.

Diagnosis

- NAFL is a diagnosis of exclusion (excessive alcohol intake has to be excluded).
- ***Liver biopsy***[Q] is the most important diagnostic tool for NASH. It is also associated with AST/ALT ratio less than 1 (in alcoholic steatohepattis the same ratio is >2.0).

Clinically

- The patients are asymptomatic with elevated enzyme levels. **Cardiovascular disease**[Q] is a frequent cause of death.

HEMOCHROMATOSIS

In normal hepatocytes, HFE protein, hemojuvelin and transferrin receptor 1 and 2 regulate the formation of hepcidin. As we know hepcidin causes ferroportin degradation, it leads to reduced iron absorption though intestinal cells. Mutation in the proteins like HFE, HJV and TFR1/2 reduce hepcidin synthesis thereby leading to increased iron absorption and systemic iron overload.

- It is characterized by **excessive accumulation of iron** in the body.
- It **is an autosomal recessive** disorder most commonly caused by **mutations in HFE gene** located at **6p**21.3.
- It is more common in males characterized by the triad of
  ***Micronodular cirrhosis**
  ***Diabetes mellitus and**
  ***Skin pigmentation**
- Most of the cells of the body have increased amounts of hemosiderin in them but skin pigmentation is primarily due to increased intracellular **melanin**.
- **Inflammation** is characteristically **absent**
- Deposition of hemosiderin in the joint synovial lining can result in acute synovitis and pseudogout.
- Derangement of the hypothalamo-pituitary axis results in hypogonadism (loss of libido and impotence in male and amenorrhea in the female).
- Treatment is removal of excessive iron and it is accomplished by weekly or twice weekly **phlebotomy**.
- Chelating agents like ***desferrioxamine*** are indicated only when anemia or hypoproteinemia is severe enough to preclude phlebotomy.
- Cardiac failure and **hepatocellular carcinoma** are the most common causes of death.

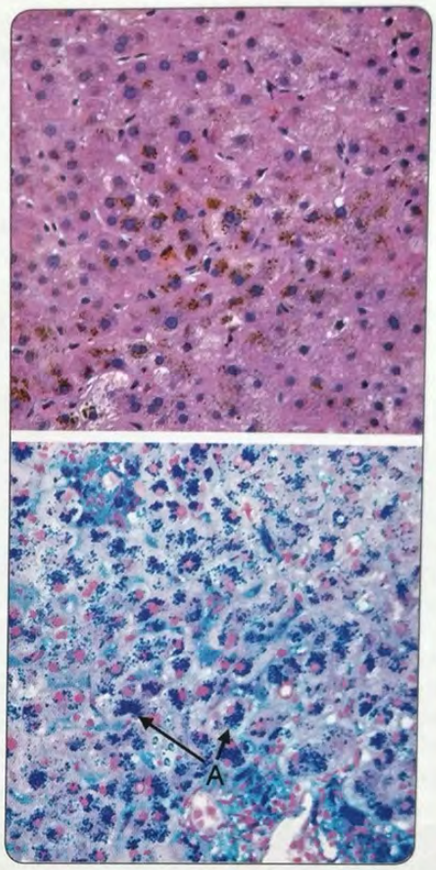


Fig. 3: Hereditary hemochromatosis with Prussian Blue reaction having inclusions

WILSON DISEASE

Normally in the body, copper is absorbed in the proximal small intestins and it binds to apoceruloplamin to form ceruloplasmin which is then secreted in the blood. Circulating ceruloplasmin is degraded in the liver and the released copper is excreted in the bile.

Wilson disease is an ***autosomal*** recessive ***disorder*** caused by mutation of the ***ATP7B gene*** located on **chromosome 13**. The deficiency of the ATP7B protein leads to:

- Reduced copper transport in the bile
- Reduced ceruloplasmin formation and its secretion in the blood.

The net result is copper overload in the liver which then spills in the systemic circulation affecting organs like red cells, liver, brain and eye. The average of onset of symptoms is 11.4 years. Patients may present as a liver disease (mild to cirrhosis like), neurological symptoms (movement disorders, dystonia, mood liability, psychiatric symptoms and even hemolytic anemia. Eyes may have the presence of **Kayser-Fleischer rings** (green to brown deposits of copper in Descemet membrane in the limbus of the cornea).

Diagnosis is made by the presence of

- Decrease in serum ceruloplasmin,
- An increase in hepatic copper content (the **most sensitive** and accurate test), and
- Increased urinary excretion of copper (the **most specific** screening test).

Treatment is done by copper chelation therapy (trientine or penicillamine) or zinc therapy (zinc inhibits absorption of copper in the intestine).

NODULAR HYPERPLASIAS

These are represented by two conditions: **Focal nodular hyperplasia** and **Nodular regenerative hyperplasia.**

Focal nodular hyperplasia

- Presents as a spontaneous mass lesion
- Most frequently in **young** to middle-aged adults
- **Female** preponderance
- Associated with long term use of **anabolic hormones** or **contraceptives**
- Typically, there is a **central** grey-white, depressed **stellate scar** from which fibrous septa radiate to the periphery. The central scar contains large vessels, usually arterial, that typically exhibit fibromuscular hyperplasia with eccentric or concentric narrowing of the lumen.

Nodular regenerative hyperplasia

- Associated with the development of **portal hypertension** and its clinical manifestations.
- Occurs in conditions affecting intra hepatic blood flow like **rheumatoid arthritis (most commonly)**, Felty syndrome, myeloproliferative disorders, hyperviscosity syndromes, solid organ (particularly renal and liver) transplantation, bone marrow transplantation, **HIV infection** (Robbins), vasculitic conditions and **drugs (anabolic steroids and cytotoxics).**
- Characteristically, there is **absence of fibrosis** in this condition.

Hepatic Tumors

Hepatic tumors

Benign	Malignant
• Cavernous hemangioma – *Most common benign lesion of liver* • Liver cell adenoma (hepatic adenoma) – Seen in young females – Associated with oral contraceptive intake – Microscopically, the cells have clear cytoplasm and the portal tracts are absent.	• Hepatoblastoma – *Most common liver tumor of young children* – Activation of Wnt/β catein signaling pathway causes carcinogenesis • Angiosarcoma – Associated with previous exposure to arsenic vinyl chloride or thorotrast • Hepatocellular carcinoma • Cholangiocarcinoma

HEPATOCELLULAR CARCINOMA (HCC)

It is the *most common primary malignant tumor of the liver.* It usually affects old patients with a M:F ratio of 3:1.

Risk factors for development of HCC

- Chronic Hepatitis (Hepatitis B, Hepatitis C)
- Alcoholism
- Aflatoxins (due to *Aspergillus flavus* infection of peanuts, grains)
- Tyrosinemia
- Hereditary hemochromatosis

Key Point

Hep–par 1 or hepatocyte paraffin 1 is specific for hepatocyte mitochondria and is considered the **most specific** and **sensitive marker** of normal and neoplastic hepatocytes. It has been used in diagnosing hepatocellular carcinomas.

Pathogenesis: HBV has the presence of HBX protein which causes activation of host cell proto-oncogenes and disruption of cell cycle control. Aflatoxins cause mutations in proto-oncogenes or p53 (tumor suppressor gene).

Concept

The staining for **Glypican-3** is used to distinguish early hepatocellular carcinoma from a dysplastic nodule. Other tests cannot be used because the levels of serum α-fetoprotein are inconclusive in this condition.

Clinical features include malaise, upper abdominal pain, weight loss and fatigue. Laboratory investigations show elevation of serum α-fetoprotein (AFP). AFP elevation can also be seen in yolk sac tumors, cirrhosis, massive liver necrosis, chronic hepatitis, normal pregnancy, fetal distress or death, fetal neural tube defects (anencephaly and spina bifida).

Histologically, HCC can present as a unifocal mass, multifocal mass or diffuse infiltrative cancer involving the entire liver. All the three variants have a strong *tendency for vascular invasion* and intrahepatic metastasis. These can involve portal vein or inferior vena cava extending upto right side of the heart. There is presence of Mallory Hyaline bodies (eosinophilic intracytoplasmic inclusions of keratin filaments).

Key Point

The tumor marker of fibrolamellar variant of hepatocellular carcinoma is ***Neurotensin***.

Distinguishing features of Fibrolamellar cancer (from hepatocellular cancer)

- Seen in **young adults** (20-40 years).
- **Equal incidence in males and females**, [In India, however, females > males]
- **No association** with HBV or cirrhosis risk factors.
- Has **better prognosis**.
- **No elevation of serum AFP** levels.
- Microscopic examination shows well differentiated cells separated by dense collagen bands.
- Fibrolamellar variant usually affects **left lobe** of the liver more commonly.
- It spreads by ***lymphatic route***.

Key Point

The marker of choice for differentiating between hepatocellular cancer and its fibrolamellar variant is ***AFP***.

Metastasis from HCC takes place to:

1. Contiguous spread through hepatic vessels – *"Satellite nodules"*
2. Lungs
3. Perihilar, peri-pancreatic and para-aortic lymph nodes.

Cholangiocarcinoma

Recent Exam Question

Klatskin tumors are located at ***junction of right and left hepatic ducts***. They are the commonest sub type of **cholangiocarcinoma**.

Cholangiocarcinoma (CC)

CC typically refers to mucin-producing adenocarcinomas that arise from the bile ducts.

Classification

Extrahepatic- 90%
- Perihilar-60%
- Distal bile duct – 20 to 30%

Intra-hepatic – 10%.

Risk factors (Mnemonic: All have alphabet **'C')**

Genetic predisposition

There is ***over expression of IL-6*** and ***K-RAS and reduced expression of p53***.

Clinical features

Painless jaundice, often with pruritus or weight loss, and acholic stools.

Microscopically

It is an *adenocarcinoma associated with dense collagenous stroma* (desmoplastic reaction). The differentiated bile duct epithelial cells do not produce bile, so, this cancer is **rarely bile stained**.

Diagnosis

- Percutaneous biopsy for peripheral liver lesions.
- Endoscopic retrograde cholangiopancreatography (ERCP) for central lesions.

Tumor markers

- Tumors stain **positively** for **cytokeratin 7, 8, and 19** and ***negatively for cytokeratin 20***.
- **CEA, CA 19-9,** and **CA-125** are non specific and are **useful for following response to therapy**.

Metastasis

Spread of the cancer takes place to lungs, vertebrae, adrenals, brain and regional lymph nodes.

Mnemonic

All risk factors of **cholangio-carcinoma** start with **alphabet 'C'**
- Primary sclerosing **C**holangitis
- Liver flukes like **C***lonorchis sinensis and Opisthorchis viverrini*
- Cause of chronic biliary inflammation and injury (**C**holedocholithiasis)
- **C**ontrat material: thorotrast
- **C**hronic alcoholic liver disease
- **C**ongenital fibropolycystic diease (**C**holedochal cysts, **C**aroli's disease)

METASTATIC TUMORS

Secondary liver cancers are more common than primary liver cancers. The common primary sites include breast, colon and lung. The metastatic nodules have central necrosis and umbilication.

Multiple Choice Questions

BILIRUBIN METABOLISM, HYPERBILIRUBINEMIAS

1. **Which of the following condition is associated with unconjugated hyperbilirubinemia?** *(DPG 2011)*
   (a) Dubin-Johnson syndrome
   (b) Rotor syndrome
   (c) Gilbert syndrome
   (d) Gall stones

2. **A patient with unconjugated bilirubinemia has increased excretion of urobilinogen in his urine. This can be seen in all of the following conditions, except:**
   (a) G6 PD deficiency *(AI 2010)*
   (b) Hemolytic anemia
   (c) Hereditary spherocytosis
   (d) Biliary cirrhosis

3. **In post-hepatic jaundice, the concentration of conjugated bilirubin in the blood is higher than that of unconjugated bilirubin because:** *(AIIMS Nov 2002)*
   (a) There is an increased rate of destruction of red blood cells
   (b) The unconjugated bilirubin is trapped by the bile stone produced in the bile duct.
   (c) The conjugation process of bilirubin in liver remains operative without any interference.
   (d) The UDP glucuronyl transferase activity is increased manifold in obstructive jaundice

4. **Function of hepatic stellate cells is/are:**
   (a) Formation of sinusoids *(PGI June 2001)*
   (b) Vitamin A storage
   (c) Increases blood perfusion
   (d) Phagocytosis

5. **Which of the following diseases is not a cause of indirect hyperbilirubinemia?** *(Delhi PG 2009)*
   (a) Rotor's syndrome
   (b) Criggler Najjar syndrome
   (c) Gilbert syndrome
   (d) Hereditary spherocytosis

6. **In unconjugated hyperbilirubinemia, the fraction of unconjugated bilirubin to total bilirubin exceeds:**
   (a) 0.65 (b) 0.50 *(UP 2002)*
   (c) 0.35 (d) 0.80

7. **A 40 years old woman Hema Thapar presents with generalized pruritus for last 4 months which is not relieved by various lotions available in the market. On physical examination is unremarkable but her blood sample is sent to the laboratory. Her reports are as follows:**
   - Total serum bilirubin of 2.0 mg/dL
   - Direct bilirubin of 1.4 mg/dL
   - SGOT 58 U/L
   - SGPT 52U/L
   - Alkaline phosphate is 300U/L
   - Total protein is 7.2 g/dL with serum albumin of 3.5 g/dL
   - Total cholesterol of 350 mg/dL.

   Which of the following serologic test findings is most likely to be positive in this patient?
   (a) Anti-parietal cell antibody
   (b) Antimitochondrial antibody
   (c) Anti-centromere antibody
   (d) Anti ribonucleoprotein antibody

MOST RECENT QUESTIONS

8. **Which of the following is not a function of liver?**
   (a) Production of vitamin K
   (b) Production of albumin
   (c) Detoxification of ammonia
   (d) Metabolism of drugs

9. **Primary biliary cirrhosis is positive for:**
   (a) p-ANCA
   (b) Anti nuclear antibody
   (c) Anti-microsomal antibody
   (d) Anti-mitochondrial antibody

10. **Complete deficiency of UDP glucoronyl transferase (UGT) is seen in:**
    (a) Criggler–Najjar Type I
    (b) Criggler–Najjar Type II
    (c) Gilbert's syndrome
    (d) Dubin-Jhonson syndrome

CIRRHOSIS, NCPF

11. **A 30 years old man Surajmal visits his physician because he noticed the development of yellowish skin during last 5 days. His physical examination has absence of abdominal pain or tenderness. His blood reports are as follows: Haemoglobin 11.5 g/dL, MCV 94 μm^3, platelet count 1,80,000/mm^3, WBC count 6930/mm^3, albumin 3.7 g/dL, total protein 5.6 g/dL, total bilirubin 8.2 mg/dL, direct bilirubin, 0.5 mg/dL, AST, 45 U/L, ALT 32 U/L, and alkaline phosphatase, 340 U/L. What of the following is the most likely diagnosis?**
    (a) Cholelithiasis
    (b) HAV infection

(c) Micronodular cirrhosis
(d) Hemolytic anemia

12. **Which one of the following is not a feature of liver histology in *Non cirrhotic portal fibrosis*?** *(AI 05, DPG '10)*
(a) Fibrosis in and around the portal tracts
(b) Thrombosis of the medium and small portal vein branches
(c) Non specific inflammatory cell infiltrates in the portal tracts
(d) Bridging fibrosis

13. **'Nutmeg liver' is seen in:** *(Karnataka 2005)*
(a) Portal cirrhosis
(b) Biliary cirrhosis
(c) Chronic venous congestion of liver
(d) Fatty liver

MOST RECENT QUESTIONS

14. **In cirrhosis of liver collagen is laid down by:**
(a) Hepatocytes
(b) Hepatic stellate cells
(c) Biliary epithelial cells
(d) Kupffer cells

15. **With the known finding of significantly increased serum ammonia, which of the following physical findings may be expected in a patient of hepatic failure?**
(a) Capillary telangiectasias
(b) Asterixis
(c) Caput medusae
(d) Gynecomastia

16. **A 42-year-old woman with polycythemia vera develops progressive severe ascites and tender hepatomegaly over a period of several months. Liver function tests are near normal. Which of the following tests would be most likely to establish the probable diagnosis?**
(a) Endoscopic retrograde cholangiopancreatography
(b) Hepatic venography
(c) Serum alpha fetoprotein
(d) Serum iron

17. **Micronodular cirrhosis is seen in all except:**
(a) Alcoholic cirrhosis
(b) Viral hepatitis
(c) Budd-Chiari syndrome
(d) Indian childhood cirrhosis

18. **Commonest site of varices in portal hypertension is:**
(a) Esophagus (b) Anal canal
(c) Periumbilical (d) Liver

19. **A 50-year-old chronic alcoholic with jaundice and ascites secondary to known cirrhosis becomes disoriented and confused. Asterixis (flapping tremor) can be demonstrated. Which of the following is not associated with the development of ascites?**
(a) Hypoalbuminemia
(b) Increased hepatic lymph formation
(c) Increased portal venous pressure
(d) Portal-systemic venous shunting

20. **Nutmeg liver is seen in which of the following conditions?**
(a) Right sided heart failure
(b) Left sided heart failure
(c) Increased pulmonary pressure
(d) Decreased pulmonary pressure

21. **Nutmeg liver is seen in:**
(a) Right sided heart failure
(b) Left sided heart failure
(c) Increased pulmonary pressure
(d) Decreased pulmonary pressure

22. **Fibrosis associated with liver cirrhosis is mediated by:**
(a) MCP-1 (b) PDGF
(c) ICAM-1 (d) IFN-gamma

HEPATITIS

23. **A 20 year old man with HBs Ag +ve, HbeAg –ve with SGOT and SGPT raised 5 times the normal value. The HBV DNA copies are 1,00,000/ml. Which is the likely diagnosis?** *(AI 2010)*
(a) Wild type HBV (b) Surface mutant HBV
(c) PreCore mutant HBV (d) Inactive HBV carrier

24. **Which one of the following diseases characteristically causes fatty change in liver?** *(AI 2005)*
(a) Hepatitis B virus infection
(b) Wilson's disease
(c) Hepatitis C infection
(d) Chronic alcoholism

25. **Councilman bodies are seen in:** *(AIIMS Nov 2007)*
(a) Wilson disease (b) Alcoholic hepatitis
(c) Acute viral hepatitis (d) Auto immune hepatitis

26. **In Chronic Viral Hepatitis:** *(AIIMS May 2004)*
(a) Hepatitis A virus infection is a common cause in children
(b) Morphological classification into Chronic Active Hepatitis and Chronic Persistent Hepatitis are important
(c) Fatty change is pathognomic of Hepatitis C virus infection
(d) Grading refers to the extent of necrosis and inflammation

27. **The liver biopsy in acute hepatitis due to hepatitis B virus is likely to show all of the following, except:**
(a) Ballooning change of hepatocytes
(b) Ground glass hepatocytes *(AIIMS May 2004)*
(c) Focal or spotty necrosis
(d) Acidophil bodies

28. All are correctly matched except: *(PGI June 2006)*
(a) Hepatitis B - Ground glass hepatocytes
(b) Reye's syndrome - Ground glass hepatocytes
(c) Alcohol - Mallory bodies
(d) Wilson disease - Mallory bodies
(e) Acute hepatitis - councilman bodies

29. Centrilobular necrosis of liver occurs in: *(UP 2000)*
(a) Phosphorus (b) Phenol
(c) Arsenic (d) Mercury

30. Most common pathological change seen in acute viral hepatitis is: *(UP 2002)*
(a) Ballooning degeneration
(b) Neutrophilic infiltration
(c) Piece meal necrosis
(d) Periportal fatty change

31. Steatosis is NOT seen in: *(UP 2004)*
(a) Hepatitis-B infection
(b) Hepatitis-C infection
(c) Alcoholic person
(d) Protein malnutrition

32. Piece meal necrosis is seen in: *(RJ 2001)*
(a) Alcoholic hepatitis
(b) Toxic hepatitis
(c) Chronic active hepatitis
(d) Malignancy

33. In pregnancy, which viral infection has maximum mortality? *(RJ 2003)*
(a) Hepatitis A Virus
(b) Hepatitis B Virus
(c) Hepatitis C Virus
(d) Hepatitis E Virus.

34. Hepatitis B virus is not associated with: *(RJ 2004)*
(a) Fulminant hepatitis
(b) Chronic active hepatitis
(c) Hepatocellular carcinoma
(d) Cholangiocarcinoma

35. Piece meal necrosis is pathognomic of: *(RJ 2006)*
(a) Alcoholic Liver disease
(b) Chronic active hepatitis
(c) Toxic hepatitis
(d) Wilson disease

36. Hepatitis E is transmitted by: *(AP 2004)*
(a) Blood
(b) Feco-oral
(c) Venereal
(d) All of the above

37. Incubation period of hepatitis B is: *(Bihar 2004)*
(a) 6 weeks to 6 months
(b) 6 days to 6 weeks
(c) 6 months to 6 years
(d) More than 6 years

38. Indicator of active multiplication of hepatitis B virus is: *(Bihar 2004)*
(a) HBs Ag (b) HBc Ag
(c) Hbe Ag (d) Anti-HBs Ab

39. Chronic carrier stage is not found in: *(RJ 2003)*
(a) Hepatitis B Virus
(b) Hepatitis C Virus
(c) Both a and b
(d) Hepatitis A Virus

40. A 30 year old woman Aishwarya goes to her gynecologist Dr. Harmeet for a pre-pregnancy examination. Routine prenatal laboratory testing demonstrates normal hematological profile with controlled sugar as well negative TORCH infections. She normal liver function tests with the following profile: HBsAg negative, anti-HBcAg (-), anti- HBeAg (-), HBV DNA polymerase (-) but anti- HBsAg is positive. Which of the following likely represents the status of the patient?
(a) Hepatitis B carrier
(b) Recently infected with hepatitis B
(c) Immunized against hepatitis B
(d) Infected with hepatitis B and highly transmissible

41. An eminent hepatobiliary expert Dr. Sarin conducts a study in hepatitis B patients for which the patients are followed for almost a decade. Their detailed history regarding the mode of transmission of HBV is taken. A battery of tests including periodic serologic testing for HBs Ag, anti HBs and anti-HBc, and serum levels of bilirubin, SOT, SGPT, alkaline phosphatase, and prothrombin time is conducted. Dr. Sarin finds that a particular group of patients happen to be chronic carriers of HBV. This finding is most likely to be associated with which of the following modes of transmission of HBV?
(a) Blood transfusion
(b) Heterosexual transmission
(c) Vertical transmission during childbirth
(d) Needle stick injury

42. A 34-year-old man Bholu presents to his physician with loss of appetite, nausea and vomiting, and fatigue. Laboratory examination confirms the diagnosis of hepatitis B, and the man becomes icteric 2 weeks later. This patient may also be particularly vulnerable to the development of which of the following disorders?
(a) Berry aneurysm
(b) Coronary artery aneurysm
(c) Polyarteritis nodosa
(d) Giant cell arteritis

43. After passing his physical exam, a young army recruit gives urine and blood samples for further testing. Serum analysis yields elevated ALT, HBsAg, Anti-HBc, HBeAg, and bilirubin. All other values are normal.

Which of the following is the hepatitis B status of this recruit?

(a) Asymptomatic carrier
(b) Chronic active carrier
(c) Fulminant hepatitis B
(d) Recovered from acute self-limited HBV

MOST RECENT QUESTIONS

44. Which of the following is not a part of HELLP syndrome?

(a) Hemolysis
(b) Elevated liver enzymes
(c) Thrombocytopenia
(d) Retroplacental hemorrhage

45. Nurse got a needle prick injury. Which of the following suggests active phase of hepatitis?

(a) IgM anti HBc
(b) IgG anti HBc
(c) IgG anti HBs
(d) IgM anti Hbe

46. Maximum ground appearance change is associated with:

(a) Hep A (b) Hep B
(c) Hep C (d) Hep E

ALCOHOLIC LIVER DISEASE, NODULAR HYPERPLASIA

47. In a chronic alcoholic all the following may be seen in the liver except: *(AI 2002)*

(a) Fatty degeneration
(b) Chronic hepatitis
(c) Granuloma formation
(d) Cholestatic hepatitis

48. Nodular regenerative changes in liver most commonly occur in: *(AIIMS May 2009)*

(a) Drugs induced hepatitis
(b) Alcoholic hepatitis
(c) Hepatitis B
(d) Autoimmune hepatitis

49. Mallory hyaline is seen in: *(PGI Dec 2000)*

(a) Alcoholic liver disease
(b) Hepatocellular carcinoma
(c) Wilson's disease
(d) I.C.C. (Indian childhood cirrhosis)
(e) Biliary cirrhosis

50. All of the following are true except: *(DPG &AIIMS Nov 10)*

(a) LKM 1 – Autoimmune hepatitis
(b) LKM 2– Drug induced
(c) LKM 1– Chronic hepatitis C
(d) LKM 2– Chronic hepatitis D

51. A chronic alcoholic has an elevated serum alpha fetoprotein levels. Which of the following neoplasms is most likely seen? *(Delhi PG 09 RP)*

(a) Prostatic adenocarcinoma
(b) Multiple myeloma
(c) Hepatocellular carcinoma
(d) Glioblastoma multiforme

52. Mallory's hyaline is seen in: *(Delhi PG 2009 RP)*

(a) Hepatitis C infection
(b) Amoebic liver abscess
(c) Indian childhood cirrhosis
(d) Autoimmune hepatitis

53. Mallory hyaline body is seen in all except:

(a) Indian childhood cirrhosis *(Delhi PG-2007)*
(b) Alcoholism
(c) Secondary biliary cirrhosis
(d) α-1 antitrypsin deficiency

54. Mallory bodies are composed of: **(Karnataka 2009)**

(a) Fat droplets
(b) Mitochondria
(c) Lysosomal enzymes
(d) Intermediate filaments

55. Alcoholic hyaline seen in alcoholic liver disease is composed of: *(UP 2007)*

(a) Lipofuschin
(b) Eosinophilic intracytoplasmic inclusions
(c) Basophilic intracytoplasmic inclusions
(d) Hemazoin

56. In Alcoholic liver disease, which of the following pigments is deposited in the hepatocytes? *(UP 2008)*

(a) Hemosiderin (b) Hemoglobin
(c) Lipofuschin (d) Melanin

57. Mallory bodies are seen in: *(RJ 2006)*

(a) Viral hepatitis
(b) Toxic hepatitis
(c) Alcoholic hepatitis
(d) All

58. Mallory bodies are seen in all except: *(AP 2004)*

(a) Alcoholic cirrhosis (b) Biliary cirrhosis
(c) Cardiac cirrhosis (d) Wilson disease

59. A 46-year-old man, Sushil who has a long history of excessive drinking presents with signs of alcoholic hepatitis. Microscopic examination of a biopsy of this patient's liver reveals irregular eosinophilic hyaline inclusions within the cytoplasm of the hepatocytes. These eosinophilic inclusions are composed of which of the following substances?

(a) Immunoglobulin
(b) Excess plasma proteins
(c) Prekeratin intermediate filaments
(d) Basement membrane material
(e) Lipofuscin

MOST RECENT QUESTIONS

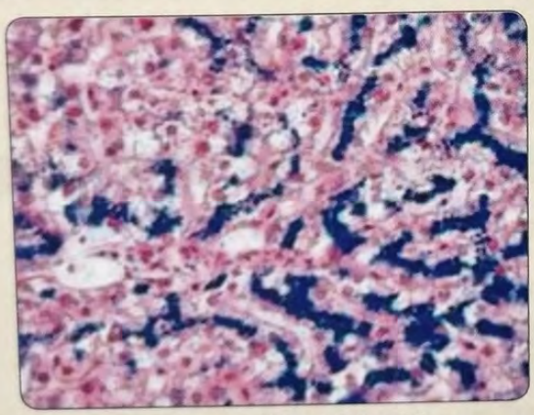
60. Which of the following may not cause microvesicular steatosis?
(a) Alcoholic fatty liver
(b) Tetracycline toxicity
(c) Acute fatty liver of pregnancy
(d) Reye's syndrome

61. The following are true attributes of hepatitis B infection except:
(a) Infants develop chronic infections
(b) HBc Ag in serum is indicative of active infection
(c) Can cause hepatocellular cancer
(d) Interferons are used for treatment

62. Mallory bodies contain:
(a) Vimentin (b) Cytokeratin
(c) Keratin (d) Collagen

63. Which of the following is not associated with Mallory hyaline bodies?
(a) Alcoholic liver disease
(b) Primary biliary cirrhosis
(c) Secondary biliary cirrhosis
(d) Indian childhood cirrhosis

64. Given below is the histopathology of liver biopsy of a patient with hemochromatosis. Which of the following stain has been used? *(AIIMS Nov 2016)*



(a) Prussian blue (b) Alcian blue
(c) Von kossa (d) Crystal violet

HEPATIC TUMOURS

65. Which of the following most significantly increases the risk of hepatocellular cancer? *(AIIMS May 2012)*
(a) Hep A (b) Hep B
(c) CMV (d) EBV

66. True about Fibrolamellar carcinoma of Liver is all, except: *(AIIMS Nov 2001)*
(a) Females do not increased incidence than males
(b) Has good prognosis
(c) Not associated with liver cirrhosis
(d) Serum AFP levels are usually > 1000 mg/litre

67. Which of the following is not correct about fibrolamellar variant of hepatocellular carcinoma? *(Delhi PG 2009 RP)*
(a) Occurs in young males and females
(b) Hepatitis B virus is an important risk factor
(c) Often has a better prognosis
(d) Is a hard scirrhous tumor

68. Most common primary malignant tumour of liver in adult is: *(UP 2002)*
(a) Squamous cell carcinoma
(b) Hepatoblastoma
(c) Hepatocellular carcinoma
(d) Hepatoma

69. Which is not correct about hepatocellular carcinoma?
(a) More in females *(Jharkhand 2004)*
(b) Rise of AFP noted
(c) Has stronger propensity to invade vascular channels.
(d) Chronic HBV has high rate of hepatocellular carcinoma

70. A young woman Ms Shaano who is otherwise normal goes for an annual examination in a nursing home. Her blood investigations reveal hemoglobin is 15 gm/dl, TLC is 7,000/mm^3, ESR is 12 mm/hr. Her kidney and liver function tests are also normal. She undergoes a radiological scanning too. Dr. Sethi, the radiologist describes her findings to be normal except a mass in the right lobe of the liver. A biopsy is taken which confirms the diagnosis of a liver adenoma. Which of the following is likely to be associated with this lesion?
(a) Polycythemia vera
(b) Hepatitis B
(c) Oral contraceptives
(d) Polyvinyl chloride

MOST RECENT QUESTIONS

71. Thorium induced tumor:
(a) Angiosarcoma of liver
(b) Renal cell carcinoma
(c) Lymphoma
(d) Astrocytoma

72. Commonest benign tumor of liver is:
(a) Hamartoma
(b) Hemangioma
(c) Adenoma
(d) Nodular focal hyperplasia

73. Which of the following organ has the presence of infarct of Zahn?
(a) Kidney (b) Heart
(c) Liver (d) Spleen

74. Solution currently used for liver preservation for transplant is:
(a) UW solution
(b) IGL solution
(c) Kyoto ET solution
(d) Ross Marshal Citrate solution

75 Most common malignant mesenchymal tumor of liver is:
(a) HCC (b) Cholangiocarcinoma
(c) Angiosarcoma (d) Hepatoblastoma

BILIARY TRACT DISORDER

76. Most common site of Cholangiocarcinoma is?
(a) Distal biliary tree *(AIIMS Nov 2008)*
(b) Hilum
(c) Intrahepatic biliary duct
(d) Multifocal

77. Cholangiocarcinoma of liver is caused by: *(UP 2008)*
(a) *Hepatitis B* infection
(b) Cirrhosis of liver
(c) Antitrypsin deficiency
(d) *Clonorchis sinensis* infection

78. Most common bile duct tumor is: *(RJ 2000)*
(a) Adenocarcinoma
(b) Squamous cell cancer
(c) Transitional cell carcinoma
(d) All

79. A 50-year-old male film actor Sallu Kahn looses weight rapidly for one of his forthcoming films. He experiences occasional abdominal discomfort few days after that and guided by his physician, he undergoes a radiological scan (HIDA scan) is shown to have slow and incomplete gallbladder emptying in response to cholecystokinin stimulation. This patient is likely to develop which of the following?
(a) Black pigment stones
(b) Brown pigment stones
(c) Biliary sludge
(d) Phospholipid stones

80. A middle aged woman comes to the emergency room complaining of severe, right-sided abdominal pain, fever, and chills for the past several hours. She has a history of gallstones and her family doctor recommended a cholecystectomy after a similar episode several months ago. Upon examination, she has a temperature of 102.7°F (39.3°C), is tender in the right upper quadrant, and is visibly jaundiced. Her white blood count is 18,000/mm^3. In which of the following locations is a gallstone most likely lodged in this patient?
(a) Common bile duct
(b) Cystic duct
(c) Fundus of gallbladder
(d) Proximal duodenum

MOST RECENT QUESTIONS

81. All of the following are risk factors for carcinoma gallbladder, except:
(a) Typhoid carriers
(b) Adenomatous gall bladder polyps
(c) Choledochal cysts
(d) Oral contraceptives

82. Focal diffuse gall bladder wall thickening with comet tail reverberation artifacts on USG are seen in:
(a) Adenomyomatosis of gallbladder
(b) Carcinoma gallbladder
(c) Adenomatous Polyps
(d) Xanthogranulomatous gallbladder

83. Onion skin fibrosis of the common bile duct is:
(a) Primary biliary cirrhosis
(b) Primary sclerosing cholangitis
(c) Extrahepatic biliary fibrosis
(d) Congenital hepatic fibrosis

84. Which is risk factor for cholangiocarcinoma:
(a) Obesity
(b) Primary sclerosing cholangitis
(c) Salmonella carrier state
(d) HBV infection

85. Klatskin tumor is:
(a) Nodular type of cholangiocarcinoma
(b) Fibrolamellar hepatocellular carcinoma
(c) Gall bladder carcinoma
(d) Hepatocellular carcinoma

MISCELLANEOUS

86. True about hemochromatosis is: *(AI 2009)*
(a) Complete penetrance
(b) Autosomal recessive
(c) Phlebotomy leads to cure
(d) More common in females

87. All are seen in hemochromatosis except: *(AI 2008)*
(a) Hypogonadism
(b) Arthropathy
(c) Bronze diabetes
(d) Desferrioxamine is the treatment of choice

88. Liver granulomas may be associated with all of the following except: *(AI 2002)*
(a) Candida (b) Halothane
(c) Sarcoidosis (d) Hepatic metastasis

89. Histological finding in Reye's syndrome is:
(a) Budding and branching of mitochondria
(b) Swelling of endoplasmic reticulum
(c) Para-nuclear micro-dense deposits
(d) Glycogen depletion

90. Finding on histopathological examination of liver in case of malaria is: *(AIIMS May 2007)*
(a) Microabscess formation
(b) Kupffer's cell hyperplasia with macrophage infiltration around periportal area laden with pigments.
(c) Non caseating granuloma
(d) Non specific finding of neutrophilic infiltration

91. Pigmentation in the liver is caused by all except: *(PGI Dec 01)*
(a) Lipofuscin
(b) Pseudomelanin
(c) Wilson's disease
(d) Malarial pigment
(e) Bile pigment

92. True statements about α-l antitrypsin deficiency is:
(a) Autosomal dominant disease *(PGI June 2003)*
(b) Emphysema
(c) Fibrosis of portal tract
(d) Diastase resistant positive hepatocytes
(e) Orcein positive granules

93. "Kayser-Fleischer ring" is seen in: *(UP 2007)*
(a) Wilson's disease
(b) α-1 antitrypsin deficiency
(c) Hemochromatosis
(d) Primary biliary cirrhosis

94. All are true about Wilson's disease except: *(RJ 2000,2004,2006)*
(a) ↑Liver Cu (b) ↑Urine Cu
(c) ↑Ceruloplasmin (d) ↑Serum Cu

95. α-1 antitrypsin deficiency causes: *(AP 2000)*
(a) Congenital cystic fibrosis
(b) Neonatal hepatitis
(c) Pulmonary fibrosis
(d) All of the above

96. Centrilobular necrosis is seen in: *(Kolkata 2005)*
(a) CCl_4 (b) White phosphorus
(c) Yellow fever (d) Eclampsia

97. A retired man Pradyuman R complains of vague abdominal pain since last 6 months. One fine day, he experienced acute chest pain with dyspnea. He was rushed to the emergency of Gangaram Hospital where his chest and abdomen CT scans demonstrate a pulmonary embolus. The radiologist Dr. Sandeep Goel also notices a 7.5 cm mass in the body of the pancreas. His blood investigations reveal elevated levels of CEA and CA 19-9. Which of the following genetic mutations is likely to be associated with this pancreatic mass?
(a) BRCA -2 (b) K-RAS
(c) PRSS1 (d) SPINK1

MOST RECENT QUESTIONS

98. Copper is mainly transported by:
(a) Albumin (b) Haptoglobin
(c) Ceruloplasmin (d) Globulin

99. Liver in hemochromatosis is stained by which of the following stain?
(a) Perls iron stain (b) Alcian blue
(c) Congo Red (d) Masson trichome

100. Bronze diabetes is seen in:
(a) Wilson's disease (b) Sarcoidosis
(c) Lead intoxication (d) Hemochromatosis

101. Gene of Wilsons disease is:
(a) ATP 7A (b) ATP 7B
(c) ADP 7A (d) ADP 7B

102. True about Wilson's disease is:
(a) Increased serum ceruloplasmin
(b) Coomb's positive hemolytic anemia
(c) Sensory deficit
(d) Autosomal recessive

103. Gene for Wilson is present on which of the following chromosome?
(a) 10 (b) 13
(c) 15 (d) 17

Explanations

1. **Ans. (c) Gilbert syndrome**

(Ref: Harrison 17th/1929, 9/e p854)

2. **Ans. (d) Biliary cirrhosis**

(Ref: Robbins 8th/868, 9/e p853-854)

Biliary cirrhosis is characterized by conjugated hyperbilirubinemia. Rest all the mentioned options cause unconjugated hyperbilirubinemia.

3. **Ans. (c) The conjugation process of bilirubin in liver remains operative without any interference**

(Ref: Harrison 17th/262-3, Ganong 22nd/503, 9/e p853)

Post hepatic jaundice is due to impaired excretion of conjugated bilirubin as a result of obstruction. However, the process of conjugation is not interfered with.

4. **Ans. (b) Vitamin A storage**

(Ref: Robbins' 7th/878, 9/e p436)

The hepatic stellate cells (also called Ito cells) are of mesenchymal origin, found in space of Disse. The stellate cells play a role in the storage and metabolism of vitamin A and are transformed into collagen producing myofibroblasts when there is inflammation and cause fibrosis of liver.

5. **Ans. (a) Rotor's syndrome**

(Ref: Robbins 9/e p854, 8th/841, Harrison 17th/26)

6. **Ans. (d) 0.80**

(Ref: Robbins 9/e p853, Harrison 17th/262)

Indirect hyperbilirubinemia is called when unconjugated bilirubin is 85% or more of the total bilirubin whereas direct hyperbilirubinemia corresponds to conjugated bilirubin more than 15% of total.

7. **Ans. (b) Antimitochondrial antibody**

(Ref: Robbins 8th/867, 9th/858)

The findings in the stem of the question are suggestive of clinical condition of primary biliary cirrhosis. It is seen in middle aged women in which the jaundice may progress due to progressive intrahepatic destruction. In these patients, there is presence of anti mitochondrial antibodies.

Other options

- Anti parietal antibodies are seen in pernicious anemia.
- Anti-centromere antibody is seen in systemic sclerosis.
- Anti-ribonucleoprotein antibody is seen in different connective tissue disorders.

The following disorders present with insidious onset of features of obstructive jaundice like pruritus, jaundice, malaise dark urine, light stools and hepatosplenomegaly.

Features of the Bile Duct Disorders

	Primary Biliary Cirrhosis	Secondary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Cause	Possibly autoimmune	Biliary atresia, gallstones, stricture, cancer of pancreatic head	Autoimmune; usually associated with inflammatory bowel disease
Sex predilection	Female to male: 6:1	None	Female to male: 1:2
Distribution	Intrahepatic bile duct obstruction	Extrahepatic bile duct obstruction	Extra + intra hepatic duct affected
Lab. findings	Same as secondary biliary cirrhosis with elevated serum IgM antimitochondrial antibody	↑conjugated bilirubin, ↑serum alkaline phosphatase with increased cholesterol	Same as secondary biliary cirrhosis with hypergammaglobulinemia (↑IgM), atypical p-ANCA (+)
Histological findings	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts	Bile stasis in bile ducts, bile ductules proliferation with surrounding neutrophils, portal tract edema	Periductal portal tract fibrosis (onion skin fibrosis), segmental stenosis of extra and intrahepatic bile ducts

An important feature is Atypical p-ANCA (+) is seen with primary sclerosing cholangitis but that this antibody is directed against a nuclear envelope protein and not myeloperoxidase seen with typical p-ANCA antibodies.

8. **Ans. (a) Production of vitamin K**

(Ref: Robbins 9/e p 822)

- Vitamin K is produced by the bacteria of gut and is used by liver for gamma carboxylation of factor 2/7/9/10.
- Liver produces albumin which falls in liver cirrhosis producing ascites/edema
- Ammonia is combined with carbon dioxide to produce urea which in turn is excreted by the liver.
- The cytochrome p450 is responsible for metabolism of drugs.

9. **Ans. (d) Anti-mitochondrial antibody**

(Ref: Robbins 8/e p867, 9/e p858)

Friends, please do not get confused between options "b" and "d".

- **Antimicrosomal antibodies** are autoantibodies, directed against the microsomes (in particular peroxidase) of the thyroid cells leading to thyroiditis, tissue damage, and disruption of thyroid function. It is associated with autoimmune conditions like **Hashimoto's thyroiditis** and **Grave's disease**.

- Anti-mitochondrial antibody is seen in primary biliary cirrhosis.

Key points for primary biliary cirrhosis

- Non-suppurative, inflammatory destruction of medium-sized ***intrahepatic*** [Q] ***bile ducts***.
- Female to male ratio 6 : 1
- Serum *alkaline phosphatase and cholesterol are almost always elevated*[Q], even at onset; hyperbilirubinemia is a late development and usually signifies incipient hepatic decompensation.
- ***Antimitochondrial*** **antibodies**[Q] are present in 90% to 95% of patients.
- Associated with *increased risk to develop hepatocellular carcinomas*[Q].
- The major cause of death is **liver failure**[Q],

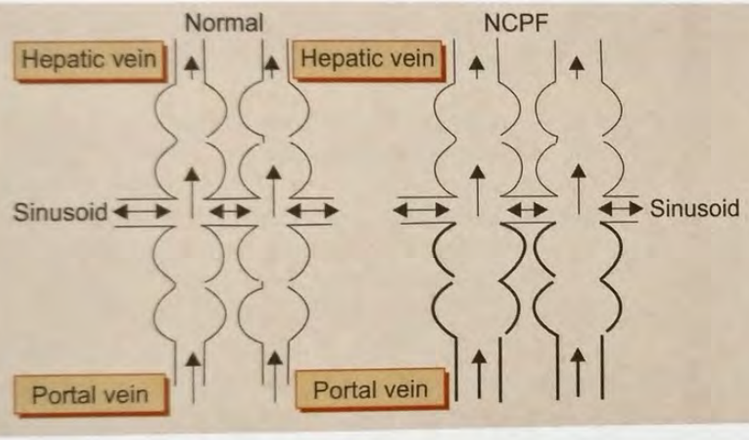
10. Ans. (a) Criggler–Najjar Type I *(Ref: Robbins 9/e p853)*

11. Ans. (d) Hemolytic anemia
(Ref: Robbins 8th/840-1, 9/e p853)

The patient has unconjugated hyperbilirubinemia which can result in the given options from hemolytic anemia.
Option (a), Cholelithiasis results in conjugated hyperbilirubinemia.
Option (c) and (d), hepatitis and micronodular cirrhosis can present with both unconjugated and conjugated hyperbilirubinemia though conjugated bilirubin predominates.

12. Ans. (d) Bridging fibrosis
(Ref: Tropical Hepato-Gastroenterology by Tandon Elsevier 1st/391, Histopathology of the liver in non-cirrhotic portal hypertension of unknown etiology Histopathology 1996;28:195–204 by Nakanuma Y et al., Non-cirrhotic portalfibrosis: current concept and management by Sarin SK, Kapoor D in J Gastroenterol Hepatol 2002; 17:526-534)

The Following is a Figure explaining the pathogenesis of NCPF along with Histologically findings in NCPF



- **Portal fibrosis** (intra portal but not bridging fibrosis)
- Portal vein sclerosis
- Subcapsular scarring
- Pseudolobulation
- Portal tract edema and lymphocytic infilteration
- *Intimal fibroelastosis of medium sized portal veins*; **obliterative portal venopathy (characteristic lesion)**
- Sclerosis and obliteration of portal vein radicals
- Atrophy of liver parenchyma with no regenerative capacity
- Collagen deposition in the space of Disse

So, the answer is clear from the above mentioned features given collectively in all the references mentioned above. Bridging fibrosis is not seen in NCPF.

13. Ans. (c) Chronic venous congestion of liver
(Ref: Robbins 7th/122-3, 9/e p864)

Congestion is a passive process resulting from impaired outflow from a tissue. In long standing or chronic venous congestion, the stasis results in chronic hypoxia resulting in parenchymal cell death. The central part of hepatic lobule is red brown and slightly depressed (due to loss of cells) and is accentuated against surrounding zone of uncongested tan liver. This is called **nutmeg liver**. Microscopically, there is presence of *hemosiderin laden macrophages*.
In severe cases (as with heart failure); there may be presence of hepatic fibrosis which is called *cardiac cirrhosis*.

14. Ans. (b) Hepatic stellate cells
(Ref: Robbins 9/e p822, 8th/837; 7th/883)

15. Ans. (b) Asterixis *(Ref: Robbins 8th/836, 9/e p826)*

- Asterixis is a flapping tremor of the hands associated with hepatic encephalopathy. Failure of the liver to detoxify metabolites absorbed from the gastrointestinal tract results in accumulation of nitrogenous wastes that are neurotoxic.
- Disturbed mental status is also attributed to production of false neurotransmitters, increased CNS sensitivity to GABA, reduced activity of urea cycle enzymes due to zinc deficiency and swelling of astrocytes. Ref 2013 **(CMDT)**.
- Caput medusa results from dilation of the periumbilical venous collaterals as a result of portal hypertension and opening of portal-caval anastomoses. Other findings like palmar erythema, capillary telangiectasias, and gynecomastia results from the inability of the liver to metabolize estrogen leading to hyperestrinism.

16. Ans. (b) Hepatic venography
(Ref: Robbins 8th/872-873, 9/e p863-864)

The clinical presentation is most consistent with **Budd-Chiari syndrome** (hepatic vein obstruction), which may occur as a complication of thrombogenic and myeloproliferative disorders including polycythemia vera. The presentation in the question is the most common. **Hepatic venography is the best technique** of those listed to demonstrate the occlusion of the hepatic venous system.

- Endoscopic retrograde cholangiopancreatography (choice A) is most useful in demonstrating lesions of the biliary tree.
- Serum alpha fetoprotein (choice C) is a marker for hepatocellular carcinoma.
- Serum iron studies (choice D) are useful when considering hemochromatosis as a cause of cirrhosis.

17. Ans. (b) Viral hepatitis

(Ref: Clinical Hepatology: Principles and Practice of Hepatobiliary Diseases: Volume 2 Springer publications p952)

- Common causes of **micronodular cirrhosis** (nodules **<3 mm in diameter**) Alcohol, Metabolic, Hemachromatosis, Wilson's Disease, Indian childhood cirrhosis, chronic venous outflow tract obstruction, bile duct obstruction
- Common causes of macronodular cirrhosis (nodules **>3 mm in diameter**) Viruses, Toxins, Poisoning

Budd-Chiari syndrome is characterized by the obstruction of two or more major hepatic veins produce liver enlargement, pain, and ascites. So, it is a cause of hepatic venous outflow obstruction.

18. Ans. (a) Esophagus *(Ref: Robbins 9/e p830)*

19. Ans. (d) Portal-systemic venous shunting

(Ref: Robbins 8th/839, 9/e p830, Harrison 18th/2600)

Portal-systemic venous shunting leads to encephalopathy in end-stage cirrhosis. It is also contributing to other features like esophageal varices, rectal haemorrhoids, and distention of periumbilical venous collaterals. Other factors like hypoalbuminemia, increased hepatic lymph formation and increased portal venous pressure mentioned as the options contribute to the development of ascites, but not to encephalopathy.

20. Ans. (a) Right sided heart failure *(Ref: Robbins 9/e p864)*

- *Right-sided cardiac decompensation leads to passive congestion of the liver.* In long standing or chronic venous congestion, the central part of hepatic lobule is red brown and slightly depressed (due to loss of cells) and is accentuated against surrounding zone of uncongested tan liver. This is called **nutmeg liver.**
- In severe cases this is called as ***cardiac sclerosis*** *or* ***cardiac cirrhosis***.

21. Ans. (a) Right sided heart failure explained earlier *(Ref: Robbins 9/e p864)*

22. Ans. (b) PDGF *(Ref: Robbins 9/e p823)*

In the pathogenesis of cirrhosis, proliferation of hepatic stellate cells and their activation into myofibroblasts is initiated by a series of changes that include an increase in the *expression of platelet-derived growth factor receptor β (PDGFR-β) in the stellate cells.*

23. Ans. (c) preCore mutant HBV

(Ref: Robbins 8th/846, Harrison 17th/1935-6)

The precore region directs the release of HBeAg towards secretion in the blood. Uncommonly, mutated strains called **precore mutants** of HBV emerge that do not produce HBeAg but are replication competent and express HBcAg. In these patients, the HBeAg may be undetectable despite the presence of HBV viral load. Another **mutation in the core promoter region** can also lead to an HBeAg negative phenotype. Clinically both these conditions are characterized by the presence of elevated liver enzymes and active viral multiplication is indicated only by the high levels of DNA polymerase.

Additional info

Another important mutation seen in HBV is **"escape mutants"** due to amino acid substitution causing a conformational change in HBs Ag resulting in **loss of neutralizing activity by anti-HBs.** It is seen in association with active and passive immunization and in liver transplant patients. In both these conditions, there is increased concentration of anti HBs leading to mutation in the virus so that it can escape from the protective effect of anti-HBs.

24. Ans. (d) Chronic alcoholism

(Ref: Robbins 7th/903-4, 9/e p 842, Harrisons 17th/1982)

Alcoholic liver disease (ALD) is the most common cause of fatty liver. So, Fatty liver is characteristically seen in chronic alcoholism. However, now many other causes of fatty liver have also been elucidated known as Non-Alcoholic fatty liver disease (NAFLD) or Non-alcoholic steatohepatitis (NASH). These are explained in the chapter review.

- Sternberg 4th mentions *"although fatty change has been reported as a common feature of hepatits C, the degree of fatty changes is usually minimal and* ***absence is not unusual.***"

25. Ans. (c) Acute viral hepatitis

(Ref: Robbin's 7th/899, 9/e p823; Harrison 17th/1929)

Councilman bodies are feature of acute hepatitis. These are associated with the cellular phenomers of opposit.

26. Ans. (d) Grading refers to the extent of necrosis and inflammation

(Ref: Harrison 17th/1955), Sternberg's diagnostic surgical pathology 4th/1682

The new classification system of **hepatitis** is based on **its etiology, grade or stage.** Grading refers to the assessment of necroinflammatory activity whereas the staging refers to degree of progression.

Concept

Regarding option 'c', Sternberg writes clearly 'although fatty change has been reported as a common feature of hepatits C, the degree of fatty changes is usually minimal and absence is not unusual. Fatty change due to virus is most likely associated with genotype 3. Biopsy in hepatitis B and C is done for purpose of staging and grading and not for diagnosis'.

27. Ans. (b) Ground glass hepatocytes

(Ref: Harrison 17th/1727; Robbins 7th/899, 8th/851, 9/e p837)

Ground glass hepatocytes are large hepatocytes containing surface antigen. Their cytoplasm is ground glass in

appearance. These cells are a feature of chronic hepatitis and not acute hepatitis.

28. Ans. (b) Reye's syndrome – ground glass appearance of hepatocytes. *(Ref: Robbins 9/e p841, H Mohan 6th-602)*

- In *acute hepatitis B*, hepatocytes show *ground glass appearance.*
- In Reye's syndrome, hepatocytes show microvesicular fatty change.
- Mallory bodies are seen in alcoholic hepatitis, primary biliary cirrhosis, non-alcoholic fatty liver disease, Wilson's disease, chronic cholestatic jaundice and hepatocellular carcinoma.

29. Ans. (b) Phenol *(Ref: Robbins 7th/903)*

30. Ans. (a) Ballooning degeneration *(Ref: Robbins 9/e p838)*

31. Ans. (a) Hepatitis-B infection *(Ref: Robbins 9/e p841-842)*

32. Ans. (c) Chronic active hepatitis *(Ref: Robbins 8th/852-3)*

33. Ans. (d) Hepatitis E Virus *(Ref: Robbins 9/e p835)*

34. Ans. (d) Cholangiocarcinoma *(Ref: Robbins 9/e p833)*

35. Ans. (b) Chronic active hepatitis *(Ref: Robbins 8th/851-2)*

36. Ans. (b) Feco-oral *(Ref: Robbins 9/e p835)*

37. Ans. (a) 6 weeks to 6 months *(Ref: Robbins 9/e p831-832)*

38. Ans. (c) HBeAg *(Ref: Robbins 9/e p832, 8th/846; 7th/893)*

39. Ans. (d) Hepatitis A Virus *(Ref: Robbins 9/e p831)*

40. Ans. (c) Immunized against hepatitis B
(Ref: Robbins 9/e 832-833, 8th/846, Harrison 18th/2550)

Ms Aishwarya is positive only for the antibody to the hepatitis B antigen. This is suggestive of her being vaccinated for hepatitis B virus (HBV). The vaccine consists of recombinantly produced HBV surface antigen (HBsAg) alone and the antibodies to this protein provide immunity.

HBsAg would be seen in the serum within the first 3-4 months after initial infection. Antibodies to the core protein (anit-HBcAg) appear during acute illness and between the disappearance of HBsAg and the appearance of anti-HBsAg, the "window period." Anti-HBeAg appears during the window period as well. HBeAg and HBV DNA polymerase are the indices of infectivity.

Nutshell of Hepatitis B Serology

	HBs Ag	IgM anti HBc	IgG anti HBc	IgG anti HBs
Acute HBV infection	+	+	–	–
Window period	–	+	–	–
Chronic infection	+	+/-	+	–
Prior infection	–	–	+	+
Immunization	–	–	–	+

Also know: The presence of HBe Ag denotes high infectivity and its absence denotes low infectivity.

41. Ans. (c) Vertical transmission during childbirth
(Ref: Robbins 8th/845, 9/e p832)

Hepatitis B infection is not commonly transmitted through blood transfusion now (due to mandatory screening of blood and its products), heterosexual transmission and needle stick injury (much more chances in comparison to HIV and HCV).

Important concept

- In adults, the viral hepatitis develops because they are immunocompetent, so, HBV induced T cells induce apoptosis of infected liver cells.
- Vertical transmission during childbirth is responsible for HBV chronic carrier stage. This is attributed to the fact that unlike the adults, the immune responses in the neonatal period are not fully developed thereby preventing the development of hepatitis.
- **Clinical significance** of high carrier rate is **increased risk of development of hepatocellular cancer.**

42. Ans. (c) Polyarteritis nodosa *(Ref: Robbins 9/e p509)*

Thirty percent of patients with polyarteritis nodosa have hepatitis B antigenemia. Polyarteritis is a systemic necrotizing vasculitis that can be difficult to diagnose, since the vascular involvement is typically widely scattered, and the specific symptoms depend on the specific vessels (small- to medium-sized arteries) involved. Patients typically present with low-grade fever, weakness, and weight loss. Abdominal pain, hematuria, renal failure, hypertension, and leukocytosis may occur. The disease is frequently fatal if untreated.

43. Ans. (b) Chronic active carrier *(Ref: Robbins 9/e 837)*

The presence of elevated ALT, HBsAg, anti-HBc, HBeAg, and bilirubin all point to active hepatitis B.

- An asymptomatic carrier (choice A) does not have elevated ALT and bilirubin.
- The absence of findings on physical examination rules out fulminant hepatitis B (choice C).
- Recovery from acute self-limited HBV (choice D) is associated with the presence of anti-HBs and the decrease in HBsAg and HBeAg.

44. Ans. (d) Retroplacental hemorrhage *(Robbins 9th/ 866)*

The subclinical hepatic disease may be the primary manifestation of preeclampsia, as part of a syndrome of ***h***emolysis, ***e***levated ***l***iver enzymes, and ***l***ow ***p***latelets, dubbed the ***HELLP syndrome.***

45. Ans. (b) IgM anti HBc *(Ref: Robbins 9th/833)*

IgM anti-HBc antibody becomes detectable in serum ***shortly before*** the onset of symptoms, concurrent with the *onset of elevated serum aminotransferase levels* (indicative of hepatocyte destruction).

46. Ans. (b) Hep B *(Ref: Robbins 9/e p837)*

In chronic hepatitis B, **"ground-glass"** hepatocytes (cells with endoplasmic reticulum swollen by **$HBsAg^{Q}$**) are a diagnostic hallmark.

47. Ans. (c) Granuloma formation
(Ref: Robbins 7th/94 - 905, 9/e 842 Harrison - 17th/1970)

Spectrum of alcoholic liver disease includes:

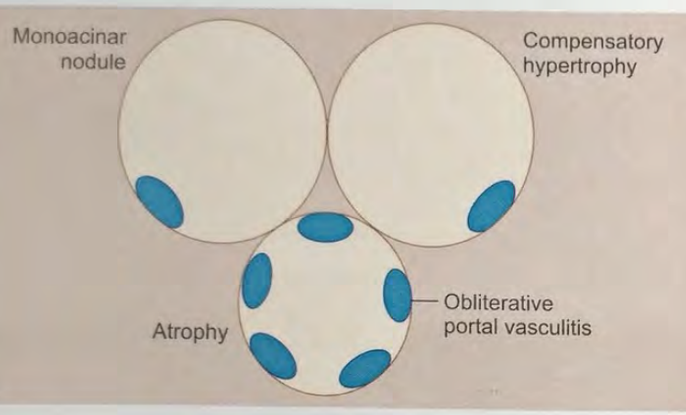
- **Fatty Liver (Hepatic steatosis)**
- **Alcoholic hepatitis** - Hallmark of alcoholic hepatitis is hepatocyte injury characterized by ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate and fibrosis in the perivenular and perisinusoidal space of Disse. Mallory bodies may also be present.
- **Alcoholic Cirrhosis**

Granuloma is **not** seen in alcoholic liver disease.

48. Ans. (a) Drugs induced hepatitis

(Ref: Robbins 8th/876, Diseases of the liver and biliary system by Sheila Sherlock, Sheila Sherlock (Dame.), James S. Dooley Blackwell Science 11th/530)

Nodular regenerative hyperplasia: summary from Robbins and Sherlock



- Associated with the development of portal hypertension and its clinical manifestations.
- Occurs in conditions affecting intra hepatic blood flow like **rheumatoid arthritis (most commonly)**, Felty syndrome, myeloproliferative disorders, hyperviscosity syndromes, solid organ (particularly renal and liver) transplantation, bone marrow transplantation, **HIV infection** (Robbins), vasculitic conditions and **drugs (anabolic steroids and cytotoxics).**
- Characteristically, there is absence of fibrosis in this condition.

49. Ans. (a) Alcoholic liver disease; (b) Hepatocellular carcinoma; (c) Wilson's disease; (d) ICC (Indian childhood cirrhosis); (e) Biliary cirrhosis

(Ref: Robbins' 7th/905, 9/e p843)

Mallory bodies- scattered hepatocytes accumulate tangled skeins of cytokeratin intermediate filaments and other proteins, visible as eosinophilic cytoplasmic inclusions in degenerating hepatocytes.

50. Ans. (d) LKM 2- Chronic hepatitis D

(Ref: Harrison 17th/1956, 1968 CMDT/595-600, Robbin 839-840)

LKM stand for liver kidney microsomal antibodies

Type of LKM antibody	Associated conditions
Anti LKM 1 antibodies	Chronic hepatitis C, Autoimmune hepatitis type 2
Anti LKM 2 antibodies	Drug induced hepatitis
Anti LKM 3 antibodies	Chronic hepatitis D, type 2 autoimmune hepatitis (rarely)

51. Ans. (c) Hepatocellular carcinoma

(Ref: Robbins 8th/879-880, 9/e p873)

Elevated levels of serum α-fetoprotein are found in 50 to 75% of patients with HCC.

False-positive results are encountered with yolk-sac tumors and many non-neoplastic conditions, including cirrhosis, massive liver necrosis, chronic hepatitis, normal pregnancy, fetal distress or death, and fetal neural tube defects such as anencephaly and spina bifida.

Concept

The staining for Glypican-3 is used to distinguish early hepatocellular carcinoma from a dysplastic nodule. Other tests cannot be used because the levels of serum α-fetoprotein are inconclusive in this condition.

52. Ans. (c) Indian childhood cirrhosis

(Ref: Harsh Mohan 6th/621-622)

53. Ans. (c) Secondary biliary cirrhosis

(Ref: Robbin 7th/904, 9/e p843)

54. Ans. (d) Intermediate filaments *(Ref: Robbins 9/e p843)*

Scattered hepatocytes accumulate tangled skeins of cytokeratin intermediate filaments and other proteins, visible as eosinophilic cytoplasmic inclusions in degenerating hepatocytes called as **Mallory bodies.** These inclusions are a characteristic but not specific feature of alcoholic liver disease.

55. Ans. (b) Eosinophilic intracytoplasmic inclusions

(Ref: Robbins 8th/858; 7th/612, 9/e p843)

56. Ans. (a) Hemosiderin *(Ref: Robbins 8th/857; 7th/905)*

57. Ans. (c) Alcoholic hepatitis

(Ref: Robbins 9/e p843, 8th/858, 7th/905)

58. Ans. (c) Cardiac cirrhosis *(Ref: Robbins 9/e p843)*

59. Ans. (c) Prekeratin intermediate filaments;

(Ref: Robbins 7th/34, 37- 41, 423, 905 9/e p843)

- Hyaline is a nonspecific term that is used to describe any material, inside or outside the cell, that stains a red homogeneous color with the routine H&E stain.

- Alcoholic hyaline inclusions (Mallory bodies) are irregular eosinophilic hyaline inclusions that are found within the cytoplasm of hepatocytes. These are composed of pre-keratin intermediate filaments. They are a nonspecific finding and can be found in patients with several diseases other than alcoholic hepatitis, such as Wilson's disease, and in patients who have undergone bypass operations for morbid obesity.

Other options

- **Immunoglobulins** may form intracytoplasmic or extracellular oval hyaline bodies called **Russell bodies**.
- Excess plasma proteins may form hyaline droplets in proximal renal tubular epithelial cells or hyaline membranes in the alveoli of the lungs.
- The hyaline found in the walls of arterioles of kidneys in patients with benign nephrosclerosis is composed of basement membranes and precipitated plasma proteins.

60. Ans. (a) Alcoholic fatty liver
(Ref: Robbins 9/e p830, 841, 8/e p857-8, Schiffs Diseases of the Liver)

Steatosis is considered to be microvesiuclar when multiple small cytoplasmic vacuoles tend to leave the nucleus centrally placed. In contrast, macrovesicular steatosis has a single large fat vacuole which displaces the nucleus to the periphery.

Causes of Microvasicular steatosis
• Reye syndrome, acute fatty liver of pregnancy, drugs (tetracycline, valproate, aspirin, nucleoside analogs of anti HIV drugs)
Causes of Macrovasicular steatosis
• Malnutrition, diabetes, obesity, malabsorption, steroid therapy, some metabolic diseases

Alcohol intake can be associated with both microvesicular (initially) and macrovesicular steatosis (later on continued drinking).

61. Ans (b) HBc Ag in serum is indicative of active infection *(Ref: Robbins 9/e p833)*

HBe Ag and *not HBc Ag* in serum is *indicative of active infection.*

- Persistence of HBeAg is an important indicator of continued viral replication, infectivity, and probable progression to chronic hepatitis.

62. Ans. (b) Cytokeratin *(Ref: Robbins 8/e p858, 9/e p843)*

Mallory bodies are visible as eosinophilic cytoplasmic clumps in hepatocytes. They are composed of tangled skeins of **cytokeratin intermediate filaments**[Q] such as cytokeratin 8 and 18, in complex with other proteins such as ubiquitin.

63. Ans. (c) Secondary biliary cirrhosis *(Ref: Robbins 9/e 843, 8/e 858, 7/e p905)*

Mallory Hyaline bodies are seen in conditions memorized by Mnemonic: New Indian WATCH.

64. Ans. (a) Prussian blue *(Ref: Robbins 9/e p849)*

Hemochromatosis is characterized by excess of iron deposition in different tissues. This can be demonstrated with the help of Prussian blue stain (Perls reaction).

65. Ans. (b) Hep B *(Ref: Robbins 8th/878-9, 9/e p870)*

Risk factors for development of hepatocellular cancer (HCC)

- Chronic Hepatitis (Hepatitis B, Hepatitis C)
- Alcoholism
- Aflatoxins (due to *Aspergillus flavus* infection of peanuts, grains)
- Tyrosinemia
- Hereditary hemochromatosis

66. Ans. (d) Serum AFP levels are usually greater than 1000 mg/liter *(Ref: Robbins 7th/925, 9/e p873)*

As discussed in text fibrolammelar cancer is not associated with elevated AFP levels.

67. Ans. (b) Hepatitis B is an important risk factor *(Ref: Robbins 8th/879, 9/e p873)*

68. Ans. (c) Hepatocellular carcinoma *(Ref: Robbins 8th/878; 7th/922-4, 9/e p869)*

69. Ans. (a) More in females *(Ref: Robbins 9/e p873)*

70. Ans. (c) Oral contraceptives *(Ref: Robbins 8th/877, 9/e p868)*

Liver adenomas are benign liver tumors commonly associated with ***oral contraceptive*** use in young women (usually 3-4th decade of life). They may resemble hepatocellular carcinoma. If they are subscapular, they can rupture, causing intra-abdominal haemorrhage leading to acute abdominal pain.

- **Hepatitis B** may lead to **hepatocellular carcinoma**.
- **Polycythemia vera** is associated with **thrombosis of the hepatic veins**.
- **Polyvinyl chloride, thorotrast** (a contrast material) and **arsenic** are the risk factors for development of **angiosarcoma of the liver**. Immunohistochemical staining of these ***tumor cells is positive for*** the **CD 31** cell marker.

71. Ans. (a) Angiosarcoma of liver *(Ref: Robbins 8/e p877, 9/e p875)*

Angiosarcoma of the liver is a highly aggressive tumor which is associated with exposure to:

- **Vinyl chloride**[Q],
- **Arsenic**[Q], or
- **Thorotrast**[Q],

Thorotrast is a suspension containing particles of the radioactive compound thorium dioxide. It emits **alpha particles** due to which it has been found to be extremely carcinogenic.

72. **Ans. (b) Hemangioma**
(Ref: Robbins 9/e p867, 8/e p876, 7/e p922)
- Cavernous hemangiomas are the most common benign liver tumours.

73. **Ans. (c) Liver** *(Ref: Robbins 9/e p863)*
Intrahepatic portal vein radicles may be obstructed by acute thrombosis. The thrombosis does not cause ischemic infarction but instead results in a sharply demarcated area of red-blue discoloration called *infarct of Zahn*. There is no necrosis, only severe hepatocellular atrophy and marked stasis in distended sinusoids.

74. **Ans. (a) UW solution** *(Ref: Transplantation E-Book/99)*
University of Wisconsin **(UW) solution** has been known as the **standard solution** for liver graft preservation.

75. **Ans. (c) Angiosarcoma** *(Ref: Robbins 9/e p875)*
Angiosarcoma of the liver resembles those occurring elsewhere and has historical associations with **vinyl chloride, arsenic, or Thorotrast.**

76. **Ans. (b) Hilum**
(Ref: Robbins 9/e 874, 8th/880, Harrison 17th/585)
The commonest location of the cholangiocarcinoma is at the hilum. Klatskin tumors are located at the junction of the right and the left hepatic ducts.

77. **Ans. (d) *Clonorchis sinensis* infection**
(Ref: Robbins 9/e p874, 8th/880; 7th/671)

78. **Ans. (a) Adenocarcinoma**
(Ref: Robbins 9/e p874, 8th/888, 7th/926-927)

79. **Ans. (c) Biliary sludge**
(Ref: Robbins 9/e p876, 8th/882-4. Harrison 18th/2617-9)
The demonstration of slow or incomplete gallbladder emptying in response to cholecystokinin stimulation is called gallbladder hypomotility. This is usually associated with ***risk factors*** like ***pregnancy, rapid weight loss prolonged use of total parenteral nutrition or octreotide, and high spinal cord injuries.***
Gallbladder hypomotility frequently results in the formation of biliary sludge, which results from bile precipitation. Biliary sludge typically contains cholesterol monohydrate crystals, calcium bilirubinate, and mucus and is a known precursor to stone formation. Complications such as acute cholecystitis occur in up to 20% of patients with biliary sludge.
- (Choice b) **Brown pigment** stones are most likely to arise in cases of **biliary tract infection**.
- (Choice a) **Black pigment stones** are most likely to arise in cases of **intravascular hemolysis.**
- (Choice d) Gallstones **do not** typically ***contain phospholipid*** as a primary ingredient.

Concept

Gallbladder hypomotility often results in bile precipitation and the formation of biliary sludge.

80. **Ans. (a) Common bile duct**
(Ref: Robbins 9/e p877, 8th/887)
The patient is probably suffering from choledocholithiasis, a condition in which a gallstone becomes lodged in the common bile duct.
She is displaying **"Charcot's triad" (fever, jaundice, and right upper quadrant pain)**, which is indicative of cholangitis (infection of the biliary tree proximal to an obstruction such as a gallstone or malignancy).
The important point in this case is the fact that the patient is jaundiced, eliminating all options other than a stone in the common bile duct. Stones within the cystic duct (option B) or gallbladder (option C) or small intestine (options D) do not cause jaundice.

81. **Ans. (d) Oral contraceptives**
(Ref: Robbins 9/e p879, 8/e p888, Cancer Nursing: Principles and Practice 7/e p1317)
Risk factors of gall bladder cancer
- Gallstones: most important risk factor associated with gallbladder carcinoma.
- Gholedochal cyst
- Carcinogens and chemicals including nitrosamines, rubber and textile industries
- Rubber plant workers
- Obesity
- Estrogen
- Typhoid carrier
- Porcelain gall bladder (calcification of the gallbladder wall)
- Gall bladder polyps
- Anomalous pancreatobiliary duct junction

Also know
- Only 0.5% of patients with gallstones develop gallbladder cancer after twenty or more years
- In Asia, where pyogenic and parasitic diseases of the biliary tree are common, the coexistence of gallstones in gallbladder cancer is much lower.

82. **Ans. (a) Adenomyomatosis of gallbladder**
(Ref: Learning Ultrasound Imaging p9, Harrison 17/e 1998)
Focal diffuse gall bladder wall thickening with comet tail reverberation artifacts on USG is a diagnostic finding of Adenomyomatosis of gall bladder.

83. **Ans. (b) Primary sclerosing cholangitis**
(Ref: Robbins 9/e p860)

84. **Ans. (b) Primary sclerosing cholangitis**
(Ref: Robbins 8/e p880)

Risk factors (Mnemonic: All have alphabet **'C')**

- Primary sclerosing **C**holangitis
- Liver flukes like **C***lonorchis sinensis and Opisthorchis viverrini*
- Cause of chronic biliary inflammation and injury (**C**holedocholithiasis)
- **C**ontrat material: thorotrast
- Chronic alcoholic liver disease
- **C**ongenital fibropolycystic diease (**C**holedochal cysts, **C**aroli's disease)

85. Ans. (a) Nodular type of cholangiocarcinoma

(Ref: Robbins 9/e p874, 8/e p880)

- *According to their localization,* cholangiocarcinomas (CCAs) *are classified into intrahepatic and extrahepatic forms.*
- Eighty to 90% of the tumors are **extrahepatic**Q.
- The extrahepatic forms include perihilar tumors known as ***Klatskin tumors***Q, which are located at the **junction of the right and left hepatic ducts**Q forming the common hepatic duct, and distal bile duct tumors.
- Most extrahepatic CCAs appear as **firm, gray nodules**Q within the bile duct wall
- Klatskin tumors generally have slower growth than other CCAs, show ***prominent fibrosis***, and *infrequently involve distal metastases.*

86. Ans. (b) Autosomal recessive

(Ref: Robbins 9/e p847-849, 8th/861, Harrison 18th/3166)

87. Ans. (d) Desferrioxamine is the treatment of choice

(Ref: Harrison 18th/3166; Robbins 7th/615-7, 9/e p849)

- *Desferrioxamine* is the drug of choice.
- The treatment of choice is phlebotomy at regular intervals.

88. Ans. (d) Hepatic Metastasis

(Ref: Harrison's 17th/1983; Oxford Texbook of Pathology by McGeel 1312t, Robbins 9/e p841)

Causes of Hepatic Granulomas

Systemic disease	Infections	Drugs
• ***Sarcoidosis***	- Tuberculosis	• Sulfonamides
• Hodgkin's and Non-Hodgkin's lymphoma	- MAC, Leprosy	• Isoniazid
	- Brucellosis	• Allopurinol
	- EBV, CMV, Chicken pox	• Methyldopa
• Primary biliary cirrhosis	- Histoplasmosis, ***Candidiasis***	• Quinidine
• Berylliosis	- Schistosomiasis	• Phenylbutazone
• Crohn's disease	- Q fever	• ***Halothane***
• Wegener's granulomatosis	- Syphilis	
• Idiopathic		

89. Ans. (d) Glycogen depletion

(Ref: OP Ghai 6th/524; 7th/543, CPDT 18th/662-3)

Reye's Syndrome/Jamshedpur Fever

- Described as a diffuse fatty infiltration of the liver, kidney and cerebral edema with diffuse mitochondrial injury.
- An acute self-limiting metabolic insult resulting in generalized mitochondrial dysfunction due to inhibition of fatty acid β-oxidation due to:
  - Salicylates
  - Inborn error of coenzyme A dehydrogenase
  - Varicella or Influenza B viral infections
  - Contamination of food with aflatoxin
  - Usually observed from 2 month - 15 years of age.

Clinical features

- Child presents with *vomiting, anorexia, listlessness followed by altered sensorium, irregular breathing, seizures* and coma.
- Hepatomegaly is present in 50% cases. Jaundice and focal neurological signs are absent.

Diagnosis

- Liver biopsy shows fatty change and glycogen depletion but no NECROSIS of liver cells.
- Liver is showing **fatty change,** so these lipids can be stained with *Oil Red – O.*

90. Ans. (b) Kupffer's cell hyperplasia with macrophage infiltration around periportal area laden with pigments

(Ref: Robbins 7th/402, 9/e p391-392)

- In severe infections with ***Plasmodium falciparum,*** the vital organs are ***packed with erythrocytes*** containing mature form of the parasite. There is abundant ***intra and extraerythrocytic*** pigment and organs such as ***liver, spleen*** and ***placenta*** may be grey black in color.

Liver and spleen in severe malaria

Liver

- Liver is generally enlarged and may be black from malarial pigment.
- There is congestion of the centrilobular capillaries with sinusoidal dilatation and Kupffer cell hyperplasia
- The Kupffer cells are heavily laden with malarial pigment, parasites and cellular debris.
- Sequestration of parasitized erythrocytes is associated with variable cloudy swelling of the hepatocytes and perivenous ischemic change and sometimes centrizonal necrosis.
- Hepatic glycogen is often present despite hypoglycemia.

Spleen

- The spleen is often dark or black from malarial pigment enlarged, soft and friable.
- It is full of erythrocytes containing mature and immature parasites.
- There is evidence of reticular hyperplasia and architectural reorganization.
- The soft and acutely enlarged spleen of acute lethal infections **contrasts** with the *hard fibrous enlargement* associated with **repeated malaria**.

Also know

Durck's granuloma is pathognomic of malignant cerebral malaria.

91. Ans. None

(Ref: Harsh Mohan 6th/628; Robbins' 39, 910, 914)

Pigmentation in liver is caused by:

1. Lipofuscin: It is an insoluble pigment known as lipochrome and 'wear and tear' pigment. It is seen in cells undergoing low, regressive changes and is particularly prominent in liver and heart of ageing patient or patients with severe malnutrition and cancer cachexia.
2. Pseudomelanin: After death, a dark greenish or blackish discoloration of the surface of the abdominal viscera results from the action of sulfated hydrogen upon the iron of disintegrated hemoglobin. Liver is also pigmented.
3. Wilson's disease: Copper is usually deposited in periportal hepatocytes in the form of reddish granules in cytoplasm or reddish cytoplasmic coloration stained by rubeanic acid or rhodamine stain for copper or orcein stain for copper associated protein. Copper also gets deposited in chronic obstructive cholestasis.
4. Malarial pigment: Liver colour varies from dark chocolate red to slate-grey even black depending upon the stage of congestion.
5. In biliary cirrhosis liver is enlarged and greenish-yellow in colour due to cholestasis. So liver is pigmented due to bile.

92. Ans. (b) Emphysema; (c) Fibrosis of portal tact; (d) Diastase resistance positive hepatocytes

(Ref: Robbins 7th/911-2, 9/e p850-851)

- This is **an autosomal recessive** disease characterized by deficiency of α_1-antitrypsin (important protease inhibitor).
- There is **portal tract fibrosis**Q in neonatal hepatitis. About 10%-20% of newborn with α_1-antitrypsin deficiency develop neonatal hepatitis and cholestasis.
- Hepatocellular carcinoma develops in 2-3 % α_1 - antitrypsin deficiency in adults.
- The treatment and cure, for severe hepatic disease is *orthotopic liver transplantation*.
- Most important treatment for pulmonary disease is to avoid cigarette smoking because it accelerates the development of **emphysema**.

93. Ans. (a) Wilson's disease

(Ref: Robbins 9/e p850, 8th/864, 7th/911)

94. Ans. (c) ↑Ceruloplasmin *(Ref: Robbins 8th/863-4, 9/e p849-850, Harrison 17th/1492)*

95. Ans. (b) Neonatal hepatitis

(Ref: Robbins 9/e p851, 8th/865-6; 7th/492,719)

96. Ans. (a) CCl_4 *(Ref: Robbins 8th/872, 7th/882)*

97. Ans. (b) K-RAS *(Ref: Robbins 8th/900-2, 9/e p892)*

Presence of pulmonary thromboembolism with a pancreatic mass in an old man suggests a diagnosis of pancreatic cancer with Trosseau syndrome. This is also supported with elevated serum levels of tumor markers like CEA and CA 19-9.

The ***K-RAS* gene (chromosome 12p**Q**)** is the **most frequently altered oncogene** in **pancreatic cancer**. This oncogene is activated by point mutation in 80% to 90% of pancreatic cancers.

Other options

- BRCA 2 mutation may be associated with some pancreatic cancers but usually there is a history of other cancers like breast cancer, prostate cancer (in males) and breast and ovarian cancers (in females).
- **PRSS1** mutation is also associated with **pancreatic cancer** but this is usually a cancer starting early in life secondary hereditary pancreatitis.
- **SPINK1** is only associated with **hereditary pancreatitis** but **not pancreatic cancer.**

98. Ans. (c) Ceruloplasmin

(Ref: Robbins 8/e p863, 9/e p849-850)

Wilson disease is an autosomal recessive disorder caused by mutation of the ***ATP7B* gene**Q, resulting in impaired copper excretion into bile and a failure to incorporate copper into ***ceruloplasmin***Q.

99. Ans. (a) Perls iron stain *(Ref: Robbins 8/e p862, 9/e p849)*

In the liver, iron becomes evident as golden yellow **hemosiderin granules** in the cytoplasm of periportal hepatocytes which stain blue with **Prussian blue stain**. The last mentioned stain is also called as Perls iron stain.

100. Ans. (d) Hemochromatosis

(Ref: Robbins 8/e p862, 9/e p849)

In hemochromatosis, there is iron deposited in different tissues in the form of hemosiderin. This deposition along with **increased epidermal melanin** production leads to a characteristic slate-gray color to the skin. The development of diabetes in these patients is therefore termed as **bronze diabetes**.

101. Ans. (b) ATP 7B.. see above explanation.....

(Ref: Robbins 8/e p863, 9/e p849)

102. Ans. (d) Autosomal recessive *(Ref: Robbins 9/e p849-50)*

Wilson disease is an **autosomal recessive** disorder caused by mutation of the **ATP7B gene** located on long arm of **chromosome 13**, resulting in impaired copper excretion into bile and a failure to incorporate copper into ceruloplasmin. This causes copper accumulation in the liver and a decrease in circulating ceruloplasmin.

Spillage of non–ceruloplasmin-bound copper from the liver into the circulation causes hemolysis and pathologic changes at other sites such as the brain, corneas, kidneys, bones, joints, and parathyroids. Concomitantly, urinary excretion of copper markedly increases from its normal miniscule levels.

Diagnosis: It is based on

- *A decrease in serum ceruloplasmin*
- *Increase in hepatic copper content (the most sensitive and accurate test)*
- *Increased urinary excretion of copper (the most specific screening test)*

103. Ans. (b) 13 *(Ref: Robbins 9/e p849-50)*

ANNEXURE

Precursor Lesions of Hepatocellular and Cholangiocarcinoma

	Hepatocellular Cancer					Cholangiocarcinoma		
	Hepatocellular Adenoma	Small Cell Change	Large Cell Change	Low Grade Dysplastic Nodule	High Grade Dysplastic Nodule	BilIN-3	Mucinous Cystic Neoplasm	Intraductal Papillary Biliary Neoplasia
Focality in liver	Single or multiple (adenomatosis)	Diffuse	Diffuse	Single or multiple	Single or multiple	Diffuse or multifocal	Single	Focal or diffuse
Premalignant	Yes	Yes	In some HBV*	Uncertain*	Yes	Yes	Yes	Yes
Association with cirrhosis	Rare	Common	Comon	Usual	Usual	Sometimes	No	No
Commonly associated diseases	NAFLD, Sex hormone exposures Glycogen storage diseases	HBV, HCV, Alcohol, NAFLD, A1AT, HH, PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH, PBC	PSC, Hepatolithiasis Liver flukes	None	None
Occurrence without identified predisposing condition	Occasional	No	No	No	No	Yes	Yes	Yes
Need for surveillance cancer screening	± depending on presence of predisposing condition	Yes	Yes	Yes	Yes	Yes	No	Yes

*While these are not certain to be directly premalignant, they are always at least an indication of increased risk for malignancy in the liver as a whole. BilIN-3, Bliary intraepithelial neoplasia, high grade; NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; hepatitis C virus; A1AT, α_1 –antitrypsin deficiency; HH, hereditary hemochromatosis PBC, primary biliary cirrhosis, PSC, primary sclerosis cholangitis.

CHAPTER 15

Genital System and Breast

Golden Points

- Breast lesions not involving terminal duct lobules unit (TDLU): Nipple adenoma and syringoma.
- Non-proliferative breast lesions (no risk of malignancy): Duct ectasia, cysts; apocrine metaplasia, adenosis, fibroadenoma without atypia, mild hyperplasia.
- Proliferative lesions without atypia (slight risk of malignancy): Moderate to florid hyperplasia, sclerosing adenosis, papilloma, fibroadenoma with complex features.
- Proliferative lesion with atypia (moderate risk of malignancy): Atypical epithelial hyperplasia.
- Most common gene involved in breast cancer **(overall): p53** whereas the commonest gene involved in ***familial breast cancer*** is ***BRCA-1***. Subtypes of breast carcinoma with BRCA-1 mutation are Medullary and mucinous carcinomas.
- DCIS which can present as *palpable mass*: ***Comedocarcinoma*** (it is a carcinoma ***in situ***)
- **Most common** breast cancer: **Invasive ductal carcinoma**.
- **Bilateral** breast cancer: **Lobular carcinoma** .
- Histologic hallmark of lobular carcinoma: Pattern of single infiltrating tumor cells often only one cell in width or in loose clusters or sheets.
- **Paget cells** are: Large cells with clear cytoplasm and prominent nucleus.
- Carcinoma of penis is extremely rare in people having circumcision (Jews and Muslims)
- Most common testicular tumor Seminoma.
- Most common testicular tumor in infant and young children: Yolk sac tumor.\
- Most common testicular tumor in elderly is lymphoma.
- Microscopic feature of seminoma: Sheets of uniform cells with lymphocytic infiltration.
- Seminoma is positive for: Placental alkaline phosphatase, keratin, only in 7% cases HCG.
- Yolk sac (endodermal sinus) tumor is, positive for: AFP, α-1 antitrypsin and has presence of Schiller-Duval' bodies (glomeruloid structures).
- Common sites for extragonadal germ cell tumors: Mediastinum (M/C,) retroperitoneum (2nd most common), sacrococcygeal region, pineal gland.
- **Sarcoma botryoides** is seen in infant and children (< 5 years). It shows the presence of **Tennis racket cells**
- Most common ovarian tumor: Surface epithelial tumors specially serous tumors like serous cystadenoma/ cystadenocarcinoma. Reinke crystalloids are seen in: Hilus cell tumor/pure Leydig (interstitial) cell tumor.
- Psammoma bodies are seen in: Serous cystadenoma.
- Call-Exner bodies are seen in: Granulosa-theca cell tumor.
- **Rokitansky's protuberance** is seen in: Mature (benign) teratoma/**dermoid cyst.**
- Largest ovarian tumor: Mucinous cystadenoma (also causes Pseudomyxoma peritonei)
- **Krukenberg's tumor** of ovary is produced by: Carcinoma of breast (**most commonly**) and GIT, like stomach, pancreas, colon, gallbladder (**not by liver**).

MALE GENITAL TRACT

Key Point

Hypospadias

- *Urethral opening* located on *ventral (inferior) surface* of the penis.
- Results from failure of urethral folds to close.

Penis

- Congenital malformations affecting the penis are *abnormal locations of urethral openings and phimosis*. These abnormal locations may produce obstruction of urinary tract infection or infertility.
- **Phimosis** occurs when the orifice of the prepuce (foreskin) is too small to permit normal retraction. It may be due to abnormal development or more commonly due to inflammatory scarring. It interferes with cleanliness and favors the development of secondary infections and possibly carcinoma.
- **Paraphimosis** is inability to roll back the prepuce after forcible retraction over glans penis. It is extremely painful and may cause obstruction of urinary tract (cause of acute urinary retention) or blood flow (may lead to necrosis of penis).
- **Balanoposthitis** is a non-specific infection of glans and prepuce. It is mostly caused by Candida, anerobic bacteria and Gardernella.

Key Point

Epispadias

- *Urethral opening* located on *ventral (inferior) surface* of the penis.
- Results from faulty position of genital tubercle.
- It is ***associated with exstrophy of urinary bladder and undescended testes***.

Tumors of penis may be benign [condyloma acuminata] or malignant [carcinoma in-situ and invasive carcinoma].

- **Condyloma acuminatum** is a benign tumor caused by human papilloma virus (HPV), most commonly type 6 and sometimes type 11. **Koilocytosis** is a characteristic of infection with HPV. It is seen in condyloma as well as carcinoma.

Definition

Koilocytosis is clear vacuolization of superficial, prickle cell layers of epithelial cells associated with **HPV infection**.

- **Carcinoma in-situ** refers to epithelial lesions in which cytological changes of malignancy are confined to epithelium, with no evidence of local invasion or metastasis. These are considered as **pre-cancerous lesions**. In about 80% of cases, these lesions are associated with HPV-16. **Bowen disease, Erythroplasia of Queyrat** (a variant of Bowen's disease) **and Bowenoid papulosis** are examples of carcinoma in-situ. Bowen disease may transform into invasive squamous cell carcinoma in 10% patients and is associated with occurrence of visceral cancers in about one thirds of patients. In contrast, *bowenoid papulosis never develops into invasive carcinoma* and many times, it spontaneously regresses.
- **Squamous cell carcinoma** is associated with cigarette smoking and infection with HPV-16 (more commonly) and HPV-18. Mostly, squamous cell carcinoma invades tissue as finger like projections (papillary) of atypical squamous epithelial cells. These show varying degree of differentiation. A variant of squamous cell carcinoma is **verrucous carcinoma** [also known as Giant condyloma or **Buschke-Lowenstein tumor**] which invades the underlying tissue along a broad front (in contrast, papillary carcinoma invades as finger like projections).

Recent Exam Questions

- **Squamous cell carcinoma's** risk is **reduced by circumcision**; therefore it is rare in Jews and Muslims.
- **Buschke-Lowenstein tumor** is a **well differentiated** variant of squamous cell carcinoma.

TESTIS AND EPIDIDYMIS

Key Point

Increased risk of malignancy ***(most commonly seminoma)*** occurs with undescended testes (more for abdominal than for inguinal).

- **Cryptorchidism** (undescended testes) is found in 1% of 1-year-old boys and is mostly unilateral (Right > Left). Testicular descent has two phases; transabdominal and inguino-scrotal. Transabdominal phase is controlled by Mullerian-inhibiting substance whereas inguinoscrotal phase is androgen dependent (mediated by androgen induced release of CGRP from genitofemoral nerve). Grossly, testis is small, brown and atrophic. Microscopically, tubules are atrophic with thickened basement membranes. **Leydig cells are spared and appear to be prominent**. Occasionally, proliferation of Sertoli cells may also be seen. Smaller but definite risk of malignancy is present for contralateral, correctly placed testis. Persistently undescended testes require orchiopexy (placement in scrotal sac) preferably before 2 years before histological deterioration sets in. Orchiopexy does not guarantee fertility.

Concept

The **risk of malignancy** is **NOT REDUCED** by orchiopexy.

Note: Cryptorchidism is *associated with trisomy 13* and genitourinary malformations like *hypospadias* or in-utero *exposure of DES*.

Recent Exams Questions

- **Superficial inguinal pouch** is the *most common site* of **ectopic testis**.
- Gonorrhea and tuberculosis almost invariably arise in epididymis whereas **syphilis affects the testis first.**

- **Ectopic testes** is the deviation of testes from normal path of descent. Gubernaculum testis has five tails (namely scrotal, pubic, perineal, inguinal and femoral). Normally scrotal tail is strongest, so testes descend to scrotum. If other accessory tails become strong, testis may drain toward that tail. Difference of ectopic testis from undescended testis is that former is fully developed and hence has **normal spermatogenesis** whereas latter lacks spermatogenesis.
- **Scrotal swelling** may occur due to inflammation, abnormality of blood vessels, cysts or tumors of testes or epididymis.

Key Point

Prehan sign: Manually lifting of scrotal sac causes:
- ↑ pain in torsion:
- ↓ pain in orchitis.

- Non-specific inflammations in a sexually active young patient **(< 35 years)** is mostly caused by *Chlamydia trachomatis* and *Neisseria gonorrhea* whereas most common culprit in men **older than 35 years** *are E. coli and pseudomonas.*
- Twisting of spermatic cord resulting in cut-off of the venous drainage and arterial supply to testis may result in **TORSION.** Neonatal torsion lacks any associated anatomical defect whereas adult torsion results from a bilateral anatomical defect in which testes have increased mobility [**bell-clapper abnormality**]. If untwisted within 6 hours, testes may remain viable. To prevent subsequent torsion, contralateral normal testis is fixed to scrotum [orchiopexy].

Concept

Transillumination is helpful in differentiation of cysts (which transilluminate) and tumors (which do not).

Inguino-scrotal ultrasound is used to confirm the diagnosis.

Note: Doppler flow studies and testicular scintigraphy are useful if testicular torsion is expected clinically.

- **Benign scrotal cysts** may form from abnormalities of tunica vaginalis. Processus vaginalis is an outpouching of the peritoneum that enters into the scrotum. When testis reaches the scrotum, proximal portion of processus vaginalis obliterates whereas distal portion persists and forms tunica vaginalis. Cysts involving tunica vaginalis can be **hydrocele** [contain clear fluid], **hematocele** [results from hemorrhage into a hydrocele], **chylocele** [accumulation of lymph in tunica due to elephantiasis) or **spermatocele** (cystic enlargement of efferent ducts or rete testis with numerous spermatocytes present]. **Varicocele** results from dilatation of testicular veins in pampiniform plexus. It is associated with oligospermia (< 20 million spermatozoa/ml of semen) and is most common cause of infertility. Left side is affected more commonly.
- **Sertoli cell only syndrome** also known as **Del-Castillo's syndrome** is a condition in which seminiferous tubules are lined by only Sertoli cells.

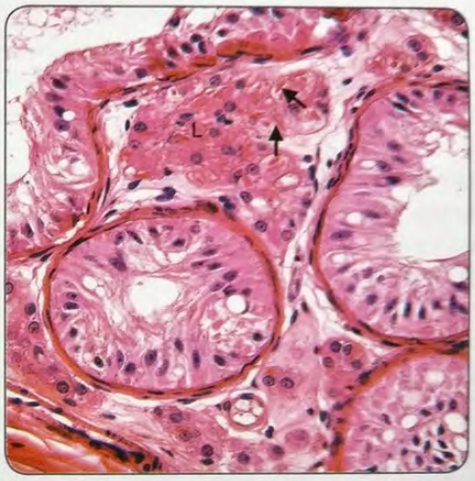


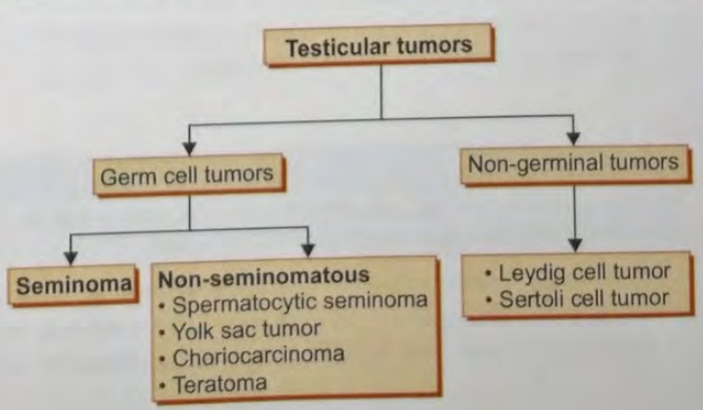
Fig. 1: Sertoli Only syndrome; Reinke crystals (arrows) in Leydig cells (L)

Recent Exam Questions

Sertoli cell only syndrome:
- Absence of germ cells
- ***Results in infertility*** due to absence of spermatogenesis.

Key Point

Seminomas are the most common type of *germ cell tumors* (50%).



Recent Exam Questions

- **Yolk sac tumor** is the commonest testicular tumor in **infants and children** up to 3 years of age.
- **Seminoma** is commonest testicular tumor in **young adults**.
- **Lymphoma** is commonest testicular tumor in **elderly**.

Testicular Germ Cell Tumors

Most of these arise from *intratubular germ cell neoplasia* (ITGCN) except **spermatocytic seminoma** and **teratoma.**

Key Point

Testicular Germ Cell Tumors
Most of these arise from intra tubular germ cell neoplasia (ITGCN) **except *spermatocytic seminoma*** and ***teratoma***.

Predisposing factors for germ cell tumors are:

- Cryptorchidism [abdominal > inguinal]
- Testicular dysgenesis [feminization and Klinefelter]
- Siblings of affected person (have tenfold higher risk)
- Isochromosome of short arm of chromosome 12, **i (12p) is seen in all germ cell tumors [both testicular as well as ovarian]**

Key Point

Seminomas almost never occur in infants.

Clinically germ cell tumors of testes can be divided into seminoma and non-seminomatous germ cell tumors (NSGCT).

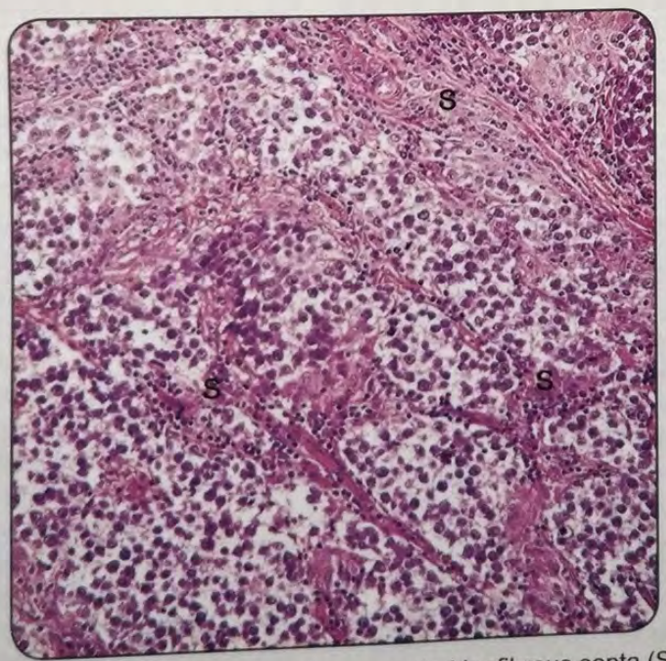


Fig. 2: Seminoma: Clear cell surrounded by fibrous septa (S)

SEMINOMATOUS GERM CELL TUMORS

- **Seminomas** are characterized by *large cells with distinct cell membranes and clear cytoplasm, large central nucleus with prominent one or two nucleoli. Cytoplasm contains glycogen.* Classical seminomas **do not contain alpha fetoprotein (AFP)**. Human chorionic gonadotropin (hCG) is present in 15% of seminomas that contain syncytiotrophoblasts. **Spermatocytic seminoma** is a distinctive tumor characterized by being found in *old age and having excellent prognosis* [do not metastasize]. Histologically, it is characterized by maturation of tumor cells, some of which resemble secondary spermatocytes. **Spermatocytic seminoma** is seen only in testis. There is **no ovarian counterpart**.

Key Point

Counterpart of seminoma in ovary is dysgerminoma.

NON-SEMINOMATOUS GERM CELL TUMORS

These may be embryonal carcinoma, yolk sac tumors, choriocarcinoma or teratoma.

- **Choriocarcinomas** have a mixture of malignant cytotrophoblasts and syncytiotrophoblasts. These are most aggressive variants. **Malignant teratomas** have tissue derived from all three germ layers with scattered immature neural elements. In children, differentiated mature teratomas are considered benign whereas in post-pubertal males, all teratomas are regarded as malignant.

Key Point

Pure choriocarcinoma is most aggressive testicular tumor.

Key Point

Yolk sac tumor are characterized by **elevated AFP** and *choriocarcinoma* by *elevated hCG*. AFP is never elevated in seminoma.

- **Embryonal cell carcinomas** present as sheets of undifferentiated cells. Focal glandular differentiation may be present. Elevated AFP and hCG is seen in this tumor.
- **Yolk sac tumor or infantile embryonal carcinoma or endodermal sinus tumor** are the *most common testicular tumor in infants and children up to 3 years of age*. These have very good prognosis. Half of tumors show **Schiller-Duval bodies or glomeruloid structures** [structures resembling endodermal sinuses]. Presence of **AFP** is highly characteristic of **yolk sac tumors.**

Concept

Biopsy of testicular neoplasm is associated with risk of tumor spillage, therefore radical orchiectomy should be done on presumption of malignancy.

Seminoma	NSGCT
1. *Radiosensitive*	Radio resistant
2. *Localized to testes for long duration (70% present in stage 1)*	Early dissemination (60% present in stage II & III)
3. *Metastasis first to lymph nodes*	Early hematogenous metastasis
4. *Tunica albuginea spared*	Tunica breached mostly

Key Point

Extragonadal site of germ cell tumors include **mediastinum (commonest)**, retroperitoneum and pineal gland.

Important points about germ cell tumors

- Painless enlargement of testis is a characteristic feature.
- Lymphatic spread is common to all testicular tumors. Retroperitoneal nodes are first involved.
- Hematogenous spread is primarily to lungs.

Key Point

Rod shaped **crystalloids of Reinke** are seen in about 25% of **Leydig cell tumors.**

Non-Germinal Tumors

- **Leydig cell tumors** are derived from stroma and Sertoli cell tumors from sex cords. *Sertoli cell tumors* are also known as *Androblastoma*. Both these tumors are benign.
- **Gonadoblastoma** contains a **mixture** of germ cells and gonadal stromal elements.

Lymphomas are most common testicular neoplasms in men over the age of 60 years. The prognosis is extremely poor. These are most common cause of bilateral testicular tumors.

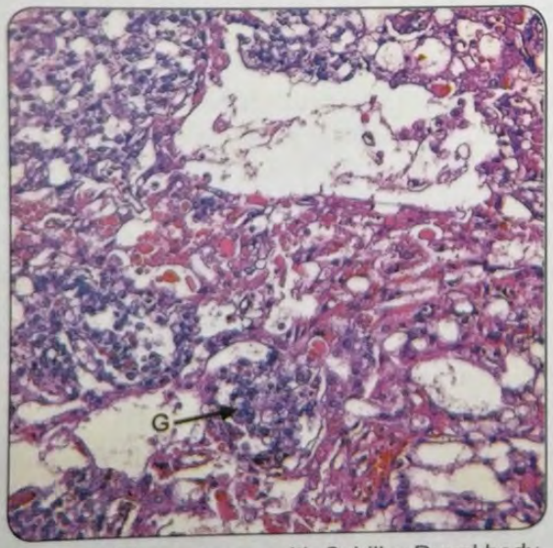


Fig. 3: Yolk sac tumor with Schiller Duval body (Glomeruloid structure; G)

PROSTATE

In a normal adult prostate weighs about 20 g. It is divided into peripheral, central, transitional zones and the region of anterior fibromuscular stroma. Prostate is a **combined tubuloalveolar organ**. Characteristically, the glands are lined by *two layer of cells*, basal layer of cuboidal cells covered by a layer of columnar secretory cells. Three important conditions of prostate are inflammations, hyperplasia and tumors.

Key Point

BPH mostly originates from *transitional zone* of prostate whereas **carcinoma** mostly arises from **peripheral zone**.

Inflammation of prostate (prostatitis)

It is characterized by finding at least **15 leukocytes per high power field** in prostatic secretions.

- Acute prostatitis present with sudden onset of fever, chills and dysuria. It is mostly caused by *E. coli*
- Chronic bacterial prostatitis is associated with recurrent UTI.
- Chronic abacterial prostatitis is associated with infections with Chlamydia or Ureaplasma.
- Granulomatous prostatitis is mostly caused by intravesical administration of BCG (used for treatment of superficial bladder carcinoma).

Malacoplakia is a granulomatous disease with defective intracellular lysosomal digestion of bacteria. It is mostly caused by E. coli. Sharply demarcated spherical structures with concentric owl eye (known as *Michaelis-Guttmann bodies*) are seen histologically.

Concept

BHP is NOT a premalignant condition.

5-α-reductase inhibitors (e.g. **finasteride**) and α_{1A} receptor antagonists (e.g. **tamsulosin**) can be used for treatment of BPH.

Nodular hyperplasia

It is also known as *benign prostatic hyperplasia* (BPH). Clinical symptoms are urinary frequency, nocturia, difficulty in starting or stopping urination, dribbling and dysuria. Histologically, nodules are composed of hyperplastic stromal cells and hyperplastic glands. **Glands consist of two layer of cells; cuboidal and columnar [in carcinoma single layers of cells are present in glands]** with intervening stroma. Histological signs of malignancy are absent. Development of BHP is associated with advanced age and high testosterone levels. Dihydrotestosterone (DHT) is produced from testosterone with the help of an enzyme, 5α-reductase type 2. DHT is the main substance responsible for prostatic growth. In addition to mechanical effects of enlarged prostate, clinical symptoms are also due to smooth muscle mediated contraction of prostate by α_{1A} receptors.

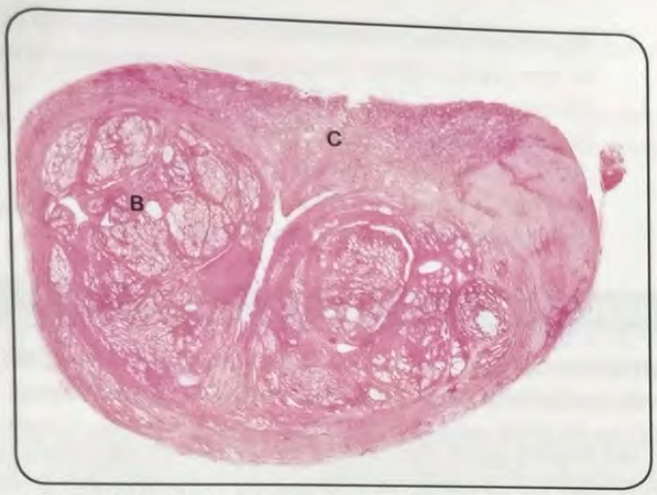


Fig. 4: Prostate showing benign hyperplasia (B) and carcinoma (C)

Note: In some cases, nodular enlargement may project up into the floor of urethra as a hemispherical mass, which is termed as "median lobe hypertrophy".

Key Point

Most of the prostatic carcinomas are acinar adenocarcinoma and arise in peripheral zone, classically in a posterior location.

Tumors

Adenocarcinoma of prostate is most common form of cancer in men. Advancing age, race (more in American blacks, least in Asians), dietary factors (increases with more fat consumption, decreases with lycopene, vitamin A, vitamin E, selenium and soy products), androgens and genetic factors are implicated in pathogenesis of prostate cancer. *Genetic factors include germ line mutations of BRCA2 tumor suppressor gene, chromosomal re-arrangements that juxtapose ERG or ETV1 next to androgen regulated TMPRSS2 promoter and epigenetic alterations like hypermethylation of glutathione 5-transferase (GSTP1) gene causing down regulation of GSTP1 expression.* Local extension most commonly involves seminal vesicles and later base of bladder; **Fascia of Denonvilliers prevents the backward extension of the tumor**. Hematogenous spread occur chiefly to bones (**osteoblastic secondaries**) *most commonly to lumbar spine.* Lymphatic spread occurs initially to obturator nodes. Histologically, most lesions are adenocarcinomas characterized by small **glands that appear "back to back" without intervening stroma** or that appear to be infiltrating beyond the normal prostate lobules.

Concept

Feature that differentiate benign and malignant prostate gland is that benign glands contain basal cells [two layered; basal cells and columnar cells] that are absent in cancer [single layered cells].

Most ***prostate cancers*** arise peripherally, away from urethra; therefore ***urinary symptoms occur late.*** Osteoblastic secondaries in bone are virtually diagnostic of prostate cancer.

Key Point

Gleason score is used for **Grading** of prostate cancer.

Grading of prostate cancer

Grade 1 is well differentiated and Grade 5 shows no glandular differentiation. Grade 2, 3 and 4 are in-between. Most tumors contain more than one pattern, so primary grade is assigned to dominant pattern and secondary grade to subdominant pattern. Combined Gleason score is derived by addition of these two grades. Tumors with only one pattern are assumed to have both primary and secondary grade as same. Thus Gleason score for these is double the grade. Score of 2-4 are considered well-differentiated, 5-6 as moderately differentiated, 7 moderate to poorly differentiated and 8-10 high grade cancers. Grading is of particular importance in prostatic cancer, as it is the best marker, along with stage, for predicting prognosis.

Key Point

Minimum Gleason score is 2 (1 + 1) and is most differentiated whereas **maximum score is 10** (5 + 5), least differentiated.

Major role of transrectal ultrasonography (TRUS) in prostate cancer is in guiding the placement of needle biopsies to thoroughly sample the gland. Transperineal or transrectal biopsy is required for diagnosis.

Key Point

PSA is organ specific but not cancer specific because it may be elevated in BHP, prostatitis, infarct, ejaculation, etc. apart from prostatic cancer.

Prostate specific antigen (PSA): 20-40% patients with prostate cancer have PSA value of 4 ng/ml or less and so, four different refinements in PSA value can be utilized.

a. *PSA density:* It is the ratio of serum PSA value and volume of prostate. It reflects PSA produced per gram of prostate tissue. Upper normal limit is 0.15.
b. *Age specific reference range*

Age	Upper normal value
40-49 years	2.5 ng/ml
50-59 years	3.5 ng/ml
60-69 years	3.5 ng/ml
70-79 years	6.5 ng/ml

Key Point

PSA velocity of *0.75 ng/ml/year best distinguishes* between cancer and benign lesions.

c. *PSA velocity:* It is rate of change of PSA with time. At least 3 PSA measurements should be taken over a period of 1.5 to 2 years.
d. *Percentage of free PSA:* It is calculated as

Free PSA/Total PSA × 100

It is more valuable, when total PSA is in 'gray zone' of 4 to 10 ng/ml. Free PSA less than 10% indicates high risk of carcinoma whereas value > 25% indicates lower risk.

FEMALE GENITAL TRACT

Embryology

The paired genital ducts consist of the mesonephric (Wolffian) duct, which extends from the mesonephros to the cloaca, and the paramesonephric (Mullerian) duct, which runs parallel and lateral to the Wolffian duct.

Key Point

Mesonephric ducts in males: develop into the *vas deferens, epididymis, and seminal vesicles.*

Mesonephric ducts in females: Gartner duct cysts *in the vagina.*

- The **mesonephric ducts in males**, if stimulated by testosterone (secreted by the Leydig cells), develop into the *vas deferens, epididymis, and seminal vesicles*. In contrast, because normal females do not secrete testosterone, the Wolffian ducts regress and form vestigial structures. They may, however, form mesonephric cysts in the cervix or vulva, or they may form Gartner duct cysts in the vagina. The cranial group of mesonephric tubules (the epoophoron) remains as vestigial structures in the broad ligament above the ovary, while the caudal group of mesonephric tubules (the paroophoron) forms vestigial structures in the broad ligament beside the ovary.
- The **paramesonephric ducts in the female** form the *fallopian tubes, the uterus, the uppermost vaginal wall, and the hydatid of Morgagni.* The lower portion of the vagina and the vestibule develop from the urogenital sinus. Males secrete Mullerian-inhibiting factor (MIF) from the Sertoli cells of the testes, which causes regression of the Mullerian ducts. This results in the formation of the vestigial appendix testis.

Key Point

Paramesonephric ducts in the female: form the *fallopian tubes, the uterus, the uppermost vaginal wall, and the hydatid of Morgagni.*

- Several **abnormalities** result from abnormal embryonic development of the Mullerian ducts.
  - **Uterine agenesis** may result from abnormal development or fusion of these paired paramesonephric ducts. Developmental failure of the inferior portions of the Mullerian ducts results in a **double uterus,** while failure of the superior portions to fuse (incomplete fusion) may form a **bicornuate uterus.**
  - Retarded growth of one of the paramesonephric ducts along with incomplete fusion to the other paramesonephric ducts results in the formation of a **bicornuate uterus with a rudimentary horn.**

GENITAL CYSTS

Obstruction of the ducts of any of the glands found within the female genitalia may cause the formation of a genital cyst.

- **Bartholin's cyst:** The paired Bartholin's glands, which are analogous to the bulbourethral glands of the male, are located in the lateral wall of the vestibule. If these are obstructed, a cyst may form that is usually lined with transitional epithelium.
- **Gartner's duct cysts:** These are derived from Wolffian (mesonephric) duct remnants and are located in the lateral walls of the vagina.
- **Mesonephric cysts:** Cysts derived from the same Wolffian duct may also be found on the lateral aspect of the vulva and are called mesonephric cysts.
- **Nabothian cysts:** Obstruction of the ducts of the mucous glands in the endocervix may result in small mucous (Nabothian) cysts.
- **Epithelial inclusion cysts:** Cysts may also be found within the skin of the vulva. These cysts, which contain white, cheesy material, are called keratinous (epithelial inclusion) cysts. Clinically they are referred to as sebaceous cysts, which is a misnomer.
- **Follicular cysts:** These are benign cysts of the ovary.

Definition

Chocolate cysts: These refer to cystic areas of endometriosis that include hemorrhages and blood clots.

DISEASES OF VULVA

1. Leukoplakia

Several pathologic conditions are associated with the formation of white plaques on the vulva, which are clinically referred to as leukoplakia.

- **Lichen sclerosis** is seen histologically as atrophy of the epidermis with underlying dermal fibrosis.

Key Point

The *male counterpart of lichen sclerosis*, called ***balanitis xerotica obliterans***, is found on the penis.

The **four cardinal histologic features** are:

- Atrophy (thinning) of the epidermis, with disappearance of the rete pegs
- Hydropic degeneration of the basal cells
- Replacement of the underlying dermis by dense collagenous fibrous tissue
- A monoclonal bandlike lymphocytic infiltrate

- Loss of pigment in the epidermis (**vitiligo**) can also produce leukoplakia.
- Inflammatory skin diseases, squamous hyperplasia and vulvar intraepithelial neoplasia can also present with leukoplakia.

2. Benign Tumors

a. Papillary Hidradenoma

Hidradenomas consist of tubular ducts lined by a single or double layer of nonciliated columnar cells, with a layer of flattened "myoepithelial cells" underlying the epithelium. These myoepithelial elements are characteristic of sweat glands and sweat gland tumors. It is identical in appearance to intraductal papillomas of the breast.

Key Point

Koilocytotic atypia (nuclear atypia and perinuclear vacuolization) caused by HPV is considered a viral "cytopathic" effect.

b. Condyloma Acuminatum

Condylomata acuminata are sexually transmitted, benign tumors that have a distinctly verrucous gross appearance. Condylomata are caused by HPV, principally types 6 and 11. It is not considered to be precancerous lesions.

Key Point

Most (85%) of the malignant tumors of vulva are squamous cell carcinomas.

3. Premalignant and Malignant Neoplasms

i. Squamous cell carcinoma

It may be *associated with high-risk HPV or with squamous cell hyperplasia and lichen sclerosus.*

- Rare variants of squamous cell carcinoma include *verrucous carcinomas*, which are fungating tumors resembling condyloma acuminatum, and *basal cell carcinomas*, which are identical to their counterparts on the skin. Neither tumor is associated with papillomaviruses.

Concept

Paget's disease of the vulva (extramammary Paget's disease) is similar to Paget's disease of the nipple except that *100% of cases of Paget's disease of the nipple are associated with an underlying ductal carcinoma* of the breast, while ***vulvar lesions are most commonly confined to the skin.***

ii. Paget's disease

- It manifests grossly as pruritic, red, crusted, sharply demarcated map-like areas.
- Histologically, it reveals single anaplastic tumor cells infiltrating the epidermis. These cells are characterized by having **clear spaces ("halos")** between them and the adjacent epithelial cells. These malignant cells stain positively with PAS or mucicarmine stains.

iii. Malignant melanoma

Malignant melanoma of the vulva may resemble Paget's disease, however, these malignant cells **stain positively with a melanin stain or S100** immunoperoxidase stain.

DISEASES OF VAGINA

1. Adenocarcinoma

- The tumors are most often located on the anterior wall of the vagina, usually in the upper third.
- These are often composed of vacuolated, glycogen-containing cells, hence the term clear cell carcinoma. These cancers can also arise in the cervix.
- A probable precursor of the tumor is **vaginal adenosis**, a condition in which glandular columnar epithelium of Müllerian type either appears beneath the squamous epithelium or replaces it.

Key Point

Clear cell adenocarcinomas are seen in young ***women whose mothers*** had been treated with ***diethylstilbestrol (DES) during pregnancy***

2. Embryonal rhabdomyosarcoma or sarcoma botryoides

- It is an uncommon vaginal tumor most frequently found in infants and in children **younger than 5 years** of age.
- The tumor consists predominantly of malignant embryonal rhabdomyoblasts and is thus a type of rhabdomyosarcoma.
- These tumors have the appearance and consistency of **grapelike clusters** (hence the designation botryoides, meaning grapelike).

Key Point

Sarcoma botryoides or Embryonal rhabdomyosarcoma

- Tumor cells have "**tennis racket" appearance on light microscopy.**

DISEASES OF CERVIX

1. Cervicitis

- **Acute cervicitis** is characterized by acute inflammatory cells, erosion, and reactive or reparative epithelial change.
- **Chronic cervicitis** includes inflammation, usually mononuclear, with lymphocytes, macrophages, and plasma cells.
- HSV is most strongly associated with epithelial ulcers (often with intranuclear inclusions in epithelial cells) and a lymphocytic infiltrate, and *C. trachomatis* with lymphoid germinal centers and a prominent plasmacytic infiltrate. Epithelial spongiosis is associated with *T. vaginalis* infection.

2. Intraepithelial and Invasive Squamous Neoplasia

a. *Cervical Intraepithelial Neoplasia (CIN)*

CIN can be divided into three grades; CIN I, CIN II and CIN III

- **CIN I:** These lesions are on the extreme low end of the spectrum and are often indistinguishable histologically from condylomata acuminata. These have a low rate of progression to cancer.
- **CIN II:** These consist of the appearance of atypical cells in the lower layers of the squamous epithelium but nonetheless with persistent (but abnormal) differentiation toward the prickle and keratinizing cell layers.
- **CIN III:** As the lesion evolves, there is progressive loss of differentiation accompanied by greater atypia in more layers of the epithelium, until it is totally replaced by immature atypical cells, exhibiting no surface differentiation (CIN III).

b. *Squamous Cell Carcinoma*

- Invasive cervical carcinoma manifests in three somewhat distinctive patterns: fungating (or exophytic), ulcerating, and infiltrative cancers. The most common variant is the fungating tumor, which produces an obviously neoplastic mass that projects above the surrounding mucosa.
- On histologic examination, a small subset of tumors (less than 5%) are poorly differentiated small cell squamous or, more rarely, small cell undifferentiated carcinomas (neuroendocrine or oat cell carcinomas). The latter closely resemble oat cell carcinomas of the lung and have an unusually poor prognosis owing to early spread by lymphatics and systemic spread. These tumors are also frequently associated with a specific high-risk HPV, type 18.

Key Point

Risk factors for cervical neoplasia

- Early age at first intercourse
- Multiple sexual partners
- Increased parity
- A male partner with multiple previous sexual partners
- Presence of a cancer-associated HPV
- Exposure to oral contraceptives and nicotine
- Genital infections (chlamydia)
- Persistent detection of a high viral load of high-risk HPV.
- Certain HLA and viral subtypes

Clear cell adenocarcinomas of the cervix in DES-exposed women are similar to those occurring in the vagina.

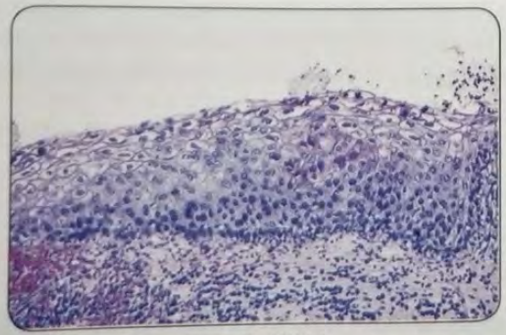


Fig. 5: CIN I

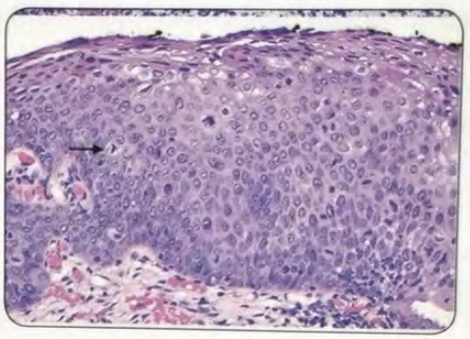


Fig. 6: CIN II

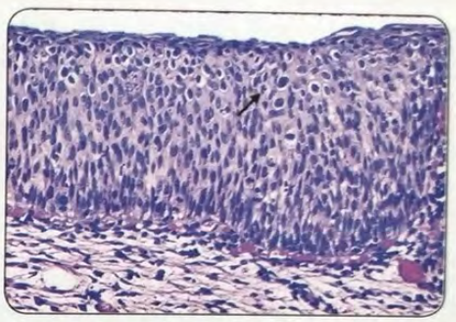


Fig. 7: CIN III

DISEASES OF UTERUS

1. Endometritis

- The endometrium and myometrium are relatively resistant to infections. Therefore, inflammation of the endometrium (endometritis) is rare.
- **Acute endometritis** is usually caused by bacterial infection following delivery or miscarriage and is characterized by the presence of **neutrophils** in non-menstrual endometrium.
- The histologic diagnosis of **chronic endometritis** depends on finding **plasma cells** within the endometrium. All it takes is one plasma cell to make the diagnosis.
- Chronic endometritis may be seen in patients with intrauterine devices (IUDs), pelvic inflammatory disease (PID), retained products of conception (postpartum), or tuberculosis.

Key Point

About 95% of squamous carcinomas are composed of relatively large cells, either keratinizing (well-differentiated) or nonkeratinizing (moderately differentiated) patterns.

Definition

Presence of *benign endometrial glands* surrounded by endometrial stroma **within the myometrium** (conventionally atleast 2.5 mm below the endomyometrial junction), is called **adenomyosis.**

Ectopic endometrial tissue **outside of the uterus** is called **endometriosis**

2. Endometriosis and Adenomyosis

- Adenomyosis is thought to result from the abnormal down growth of the endometrium into the myometrium. Symptoms produced by adenomyosis include *menorrhagia, colicky dysmenorrhea, dyspareunia, and pelvic pain.*
- Endometriosis is thought to possibly arise from metaplasia of celomic epithelium into endometrial tissue or implantation of normal fragments of menstrual endometrium either via the fallopian tubes or via the blood vessels. Histologically, it reveals endometrial glands, stroma, and hemosiderin pigment (from the cyclic bleeding). Repeated cyclic bleeding in patients with endometriosis can lead to the formation of cysts (3-5 cm diameter) that contain areas of new and old hemorrhages.

Recent Exam Question

Cysts containing blood clots in **endometriosis** are called as **"chocolate cysts.**

- Sites of endometriosis include the ovary, uterine ligaments (associated with dyspareunia), the rectovaginal pouch (associated with pain on defecation and low back pain), the fallopian tubes (associated with peritubular adhesions, infertility, and ectopic pregnancies), the urinary bladder (associated with hematuria), the GI tract (associated with pain, adhesions, bleeding and obstruction), and the vagina (associated with bleeding).

Key Point

Most common site of endometriois is **ovary.**

3. Menstrual abnormalities

With normal menstruation about 30 to 40 ml of blood is lost. Amount greater than 80 ml lost on a continued basis are considered to be abnormal.

Key Point

Postmenopausal bleeding occurs **more than 1 year** *after the normal cessation of menses at menopause.*

- **Menorrhagia** refers to excessive bleeding at the time of menstruation, either in the number of days or the amount of blood. A submucosal leiomyoma could produce menorrhagia.
- **Metrorrhagia** refers to bleeding that occurs at ***irregular intervals.***
- **Menometrorrhagia** refers to ***excessive*** bleeding that occurs at ***irregular intervals***. Causes of metro or menometrorrhagia include cervical polyps, cervical carcinoma, endometrial carcinoma, or exogenous estrogens.
- **Oligomenorrhea** refers to infrequent bleeding that occurs at ***intervals greater than 35 days.*** Causes include polycystic ovarian syndrome and too low a total body weight.
- **Polymenorrhea** refers to ***frequent***, ***regular*** menses that are ***less than 22 days*** apart. It is commonly associated with anovulatory cycles, which can occur at menarche.

Key Point

Dysmenorrhea refers to **painful menses**. It is associated with increased levels of **prostaglandin F** in the menstrual fluid.

4. Dysfunctional uterine bleeding (DUB)

DUB is defined as abnormal uterine bleeding that is due to a **functional abnormality** rather than an organic lesion of the uterus.

The three main categories of DUB are:

- Anovulatory cycles (the most common form),
- Inadequate luteal phase
- Irregular shedding.

Key Point

DUB: *Abnormal uterine bleeding* due to a **functional abnormality; NO organic lesion** of the uterus.

Anovulatory cycles consist of *persistence of the Graffian follicle without ovulation*. This results in continous and excess estrogen production without the normal postovulatory rise in progesterone levels. With no progesterone production, no secretory endometrium is formed. Instead, biopsies reveal proliferative endometrium with mild hyperplasia. The mucosa becomes too thick and is sloughed off, resulting in the abnormal bleeding.

If there is ovulation but the functioning of the corpus luteum is inadequate, then the levels of progesterone are decreased, resulting in asynchrony between the chronologic dates and the histologic appearance of the secretory endometrium. This is referred to as an inadequate luteal phase (luteal phase defect).

Key Point

Avovulatory cycles characteristically occur at **menarche and menopause;** are also associated with **polycystic ovary (Stein-Leventhal) syndrome.**

The luteal phase defect is an important cause of infertility. Biopsies are usually performed several days after the predicted time of ovulation. If the histologic dating of the endometrium lags 4 or more days behind the chronologic date predicted by menstrual history, the diagnosis of luteal phase defect can be made. Clinically, these patients exhibit low serum progesterone, FSH, and LH levels.

Prolonged functioning of the corpus luteum (**persistent luteal phase** with continued progesterone production) results in prolonged heavy bleeding at the time of menses. Histologically, there is a combination of secretory glands mixed with proliferative glands (irregular shedding). Clinically, these patients have regular periods, but the menstrual bleeding is excessive and prolonged (lasting 10 to 14 days).

5. Endometrial hyperplasia (Endometrial Intraepithelial Neoplasia)

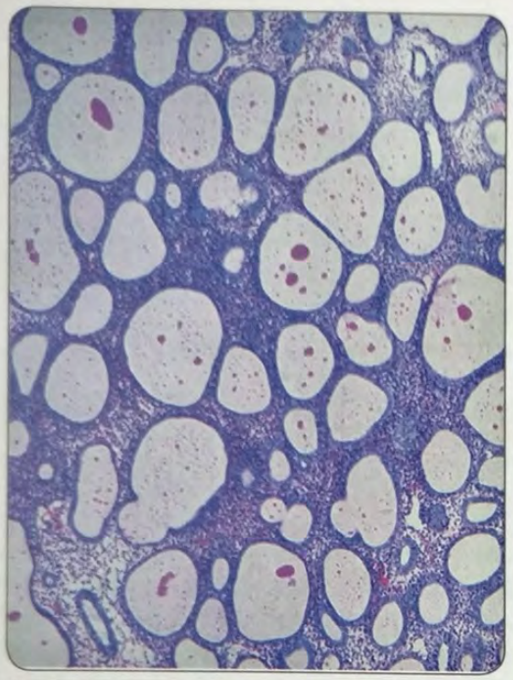


Fig. 8: Endometrial hyperplasia without atypia

It is related to excess estrogens and is important clinically because of its relation to the development of endometrial adenocarcinoma. The types of endometrial hyperplasia include simple hyperplasia and complex hyperplasias.

Note: The shift in gland morphology from benign to precancerous is often highlighted by a loss of PTEN gene expression.

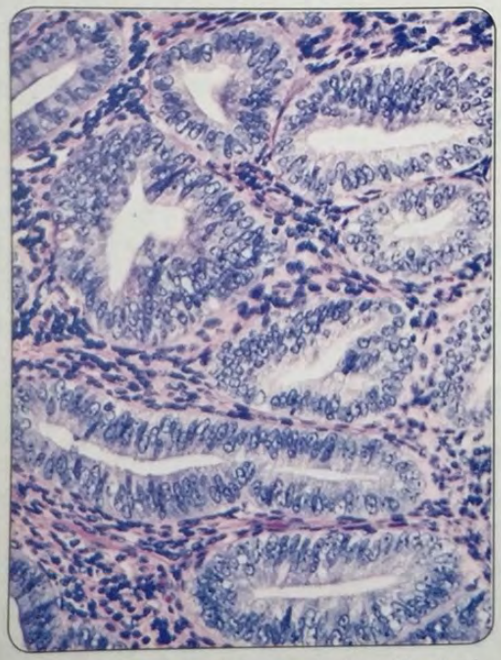


Fig. 9: Endometrial hyperplasia with atypia

Mnemonic

Endometrial cancer risk factors (Mnemonic: ***ENDOMET***rial)

E	**E**lderly
N	**N**ulliparity
D	**D**iabetes
O	**O**besity
M	**M**enstrual irregularity
E	**E**strogen therapy
T	**T**ension (hypertension)

Characteristis of type I and Type II endometerial carcinoma

Charateristics	Type I	Type II
Age	55-65 year	65-75 year
Clinical setting	Unopposed estrogen obesity hypertension diabetes	Atrophy thin physique
Morphology	Endometroid	Serous clear cell mixed mullerian tumor
Precursor	Hyperplasia	Serous endometrial intraepithelial carcinomas
Mutated genes/genetic abnormalities	PTEN ARIDA (regulator of chromatin) PIK3CA (PI3K) KRAS FGF2 (growth factor) MSI* CTNNB1 (Wnt signating) TP53	TP53 Aneuploidy PIK3CA (PI3K) FBXW7 (regulator of MYC, cyclin E) CHD4 (regulator of chromatin) PPP2R1A (PP2A)
Behavior	Indolent Spreads via lymphatics	Aggressive Intraperitoneal and lymphatic spread

(MSI: Microsatellite instability; CTNNB1: Beta-cetanin gene).

6. Endometrial carcinoma

- Endometrial carcinomas that are associated with hyperplasia tend either to be well-differentiated, mimicking normal endometrial glands (*endometrioid*) in histologic appearance, or to display altered differentiation (mucinous, tubal, squamous differentiation).
- Endometrial cancer not associated with pre-existing hyperplasia are generally more poorly differentiated, including tumors that resemble subtypes of ovarian carcinomas (papillary *serous carcinomas*). Overall, these tumors have a **poorer prognosis** than estrogen-related cancers do. In contrast to endometrioid tumors, serous subtypes infrequently display microsatellite instability and are linked to **mutation of** p53.

- ***Histologically most of the endometrial carcinomas are adenocarcinomas.***
- If there are areas of *squamous differentiation* within these tumors, they are called *adenoacanthomas*.
- If there are areas of ***malignant squamous differentiation***, they are called ***adenosquamous carcinomas***.

7. Tumors of the Endometrium with Stromal Differentiation

a. *Carcinosarcomas or malignant mixed Müllerian tumors*
Carcinosarcomas consist of endometrial adenocarcinomas in which malignant stromal differentiation takes place. The stroma tends to differentiate into a variety of malignant mesodermal components, including muscle, cartilage, and even osteoid. On histology, the tumors consist of adenocarcinoma mixed with the stromal (sarcoma) elements Sarcomatous components may mimic extrauterine tissues (i.e., striated muscle cells, cartilage, adipose tissue, and bone).

b. *Adenosarcomas*
It consists of malignant appearing stroma, which coexists with benign but abnormally shaped endometrial glands.

c. *Stromal Tumors*
The endometrial stroma occasionally gives rise to neoplasms that may resemble normal stromal cells. Stromal neoplasms may be benign stromal nodules or endometrial stromal sarcomas.

8. Tumors of Myometrium

- **Fibroids (Leiomyoma)** of the uterus arise in the myometrium, submucosally, subserosally, and mid-wall, both singly and several at a time. They are benign smooth-muscle tumors that are sharply circumscribed, firm, gray-white, and **whorled** on cut section.
- Their malignant counterpart, **leiomyosarcoma** of the uterus, is quite rare in the *de novo* state and arises even more rarely from an antecedent leiomyoma.

Concept

Mitoses are the most important criteria in assessing malignancy in smooth-muscle tumors of the uterus.

DISEASES OF OVARIES

1. Stein-Leventhal syndrome/Polycystic ovarian disease (PCOD)

- The symptoms of patients with this syndrome are related to *increased androgen production*, which causes hirsutism, and decreased ovarian follicle maturation, which can lead to amenorrhea.
- The cause of this syndrome is thought to be the abnormal secretion of gonadotropins by the pituitary. *Increased secretion of LH* stimulates the thecal cells to secrete excess amounts of androgens, which are converted to estrone by the peripheral aromatization of androgens by the adrenal gland. Excess estrogens in turn increase the levels of gonadotropin-releasing hormone (GnRH) but decrease the levels of FSH. The GnRH increases the levels of LH, which then stimulate the thecal cells of the ovary to secrete more androgens, and the hormonal cycle begins again.

Key Point

PCOD patients typically have **excess androgens** (androstenedione), **increased estrogen** levels, **increased LH levels,** *increased GnRH* levels, and ***decreased FSH*** levels (with a **high LH/FSH ratio**).

Concept

PCOD is associated with *increased risk of developing endometrial hyperplasia and endometrial carcinoma* because of the excess estrogen production.

The ovaries in these patients are enlarged and show thick capsules, hyperplastic ovarian stroma, and numerous follicular cysts, which are lined by a hyperplastic theca interna. Because these patients do not ovulate, there is a markedly decreased number of corpora lutea, which, in turn, results in decreased progesterone levels.

2. Ovarian tumors

Ovarian neoplasms may be divided into four main categories; epithelial tumors, sex cord-stromal tumors, Germ cell tumors and metastases.

Mnemonic:

WHO classification of ovarian tumors

1. Surface Epithelial Tumors		2. Germ Cell Tumors	
My	Mucinous	Doctor	Dysgerminoma
Servant	Serous	Examined	Endodermal Sinus tumor
Began	Brenner	The	Teratoma
Experiencing	Endometrioid	Ovaries	Ovarian choriocarcinoma
Cancer	Clear		
3. Sex cord Stromal Tumors		**4. Metastatic**	
She	Sertoli-Leydig	Killed:	Krukenberg
Felt	Fibroma-thecoma		
Grim	Granulosa theca		

A. Surface Epithelial Tumors

These are derived from the surface celomic epithelium, which embryonically gives rise to the Mullerian epithelium. Therefore, these ovarian epithelial tumors may recapitulate the histology of organs derived from the Mullerian epithelium.

Key Point

Surface epithelial tumors are the **most common tumors of ovary**.

a. **Serous ovarian tumors**
These are composed to ciliated columnar serous epithelial cells, which are similar to the *lining cells of the fallopian tubes.*
- They commonly involve the *surface of ovary.*

- Bilaterality is common, occurring in 20% of benign cystadenomas, 30% of borderline tumors, and approximately 66% of cystadenocarcinomas.
- Concentric calcifications (psammoma bodies) characterize serous tumors, although they are not specific for neoplasia when they are found alone.

Key Point

Serous cystadenocarcinomas account for approximately 40% of all cancers of the ovary and are the **most common malignant ovarian tumors.**

b. **Mucinous ovarian tumors**
Benign mucinous tumors are characterized by a lining of tall columnar epithelial cells with apical mucin and the absence of cilia, akin to *benign cervical or intestinal epithelia.* In gross appearance, the mucinous tumors differ from the serous variety in several ways:

- They are characterized by more cysts of variable size and a rarity of surface involvement.
- They are less frequently bilateral.
- Mucinous tumors tend to produce larger cystic masses, and some have been recorded with weights of more than 25 kg.

Key Point

Serous tumors are also the **most common bilateral tumors of the ovaries**.

- One group of typically benign or borderline mucinous tumors arises in endometriosis and is termed "Müllerian mucinous" cystadenoma, resembling endometrial or cervical epithelium. These tumors are uncommonly malignant.
- The second, more common group includes tumors exhibiting abundant gland-like or papillary growth with nuclear atypia and stratification and is strikingly similar to tubular adenomas or villous adenomas of the intestine. These tumors are presumed precursors to most cystadenocarcinomas. Cystadenocarcinomas contain more solid growth with conspicuous epithelial cell atypia and stratification, loss of gland architecture, and necrosis, and are similar to colonic cancer in appearance.
- Pseudomyxoma peritonei refers to the formation of multiple mucinous masses within the peritoneum. This condition results from the spread of mucinous tumors, either from metastasis or rupture of an ovarian mucinous cyst.

Key Point

Most cases of **Pseudomyxoma peritonei** result from spread of a mucinous tumor located in the appendix (mucocele).

c. **Endometrioid ovarian tumors**
These are composed of nonciliated columnar cells, which are *similar to the epithelial cells of the endocervical glands.*

d. **Clear cell carcinoma of the ovary**
It is similar histologically to clear cell carcinoma of the kidney, or more accurately, the clear cell variant of endometrial adenocarcinoma or the glycogen-rich cells associated with pregnancy.

Key Point

Meig's syndrome = *ovarian fibroma + ascites + hydrothorax.* (usually right sided).

e. **Brenner tumor**
It is similar to the *transitional lining of the renal pelvis or bladder.* This ovarian tumor is associated with benign mucinous cystadenomas of the ovary. Most Brenner tumors are benign, but borderline (proliferative Brenner tumor) and malignant counterparts have been reported.

f. **Cystadenofibromas**
These are variants in which there is more pronounced proliferation of the fibrous stroma that underlies the columnar lining epithelium. They may be composed of mucinous, serous, endometrioid, and transitional (Brenner tumors) epithelium.

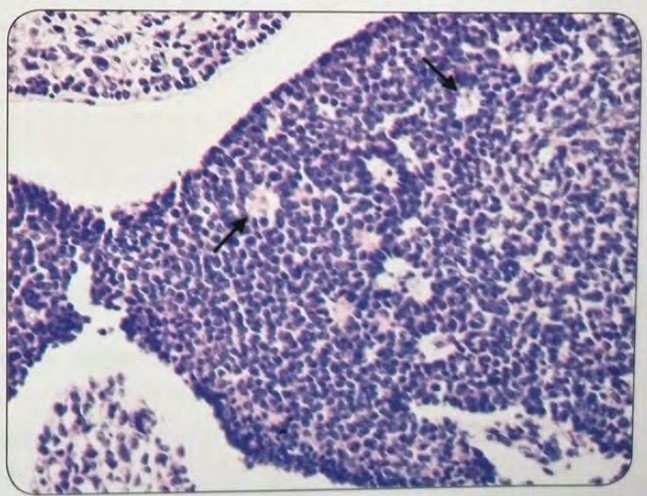


Fig. 10: Granulosa cell tumor with Call-exner Body

B. Sex-Cord Stromal Tumors

Examples of ovarian stromal tumors include thecomas, fibromas, granulosa cell tumors, and Sertoli-Leydig cell tumors.

- **Thecomas** are composed of *spindle-shaped cells with vacuolated cytoplasm.* They are vacuolated because of *steroid hormone (estrogen) production,* which can be stained with an Oil Red O stain.

- **Fibromas** are also composed of *spindle-shaped cells, but they do not produce steroid hormones* and are Oil Red O-negative.
- **Granulosa cell tumor**: These are the most common type of ovarian tumor that is composed of cells that *stain positively with inhibin*. Histologically, the cells may form Call-Exner bodies, which are gland-like structures formed by the tumor cells aligning themselves around a central space that is filled with acidophilic material. The tumor cells may secrete estrogens and cause precocious sexual development in girls or increase the risk for endometrial hyperplasia and carcinoma in women. Less commonly granulosa cell tumors can secrete androgens and produce masculinization.

Concept

Granulosa cell tumor: *Stain positively with inhibin;* **Call-Exner bodies are present.**

Sertoli-Leydig tumors: May *stain positively with inhibin*, but **Call-Exner bodies are NOT present.**

- **Sertoli-Leydig tumors (Androblastomas)**: These also may secrete androgens and produce virilization in women. The tumor cells may *stain positively with inhibin, but Call-Exner bodies are not present*. Granulosa cell tumors vary in their clinical behavior, but they are considered to be potentially malignant.
- **Hilus cell tumors (Pure Leydig cell tumor):** The ovarian hilum normally contains clusters of polygonal cells arranged around vessels (hilar cells). *Hilus cell tumors* are rare tumors derived from these cells and are *mostly unilateral*. These are characterized histologically by large lipid-laden cells with distinct borders. Typically, patients with hilus cell tumors present with evidence of masculinization, hirsutism, voice changes, and clitoral enlargement. True hilus cell tumors are almost always benign.

Recent Exam Question

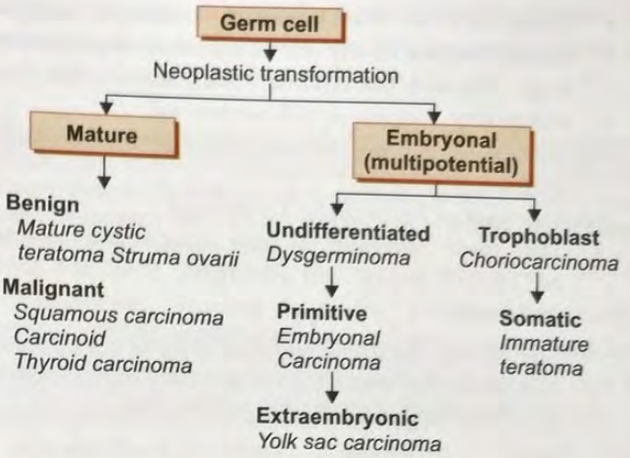
Reinke crystalloids is a typical cytoplasmic structure characteristic of **Leydig cells** is usually present.

- **Small cell carcinoma** of the ovary is the another tumor of possible stromal origin. These malignant tumors occur predominantly in young women and may be associated with hypercalcemia.

C. Germ Cell Tumors

Concept

Most consistent lab finding in Hilus cell tumors is *an elevated 17-ketosteroid excretion level unresponsive to cortisone suppression.*



a. **Teratomas:** These are divided into three categories: mature (benign), immature (malignant), monodermal or highly specialized.

Mature (Benign) Teratomas:

- Cystic teratomas are usually found in young women during the active reproductive years.
  - Characteristically, they are unilocular cysts containing hair and cheesy sebaceous material.
  - Within the wall, it is common to find tooth structures and areas of calcification.

Key Point

Most **benign teratomas** are cystic and are known as **dermoid cysts; they arise from** the ectodermal differentiation of **totipotential cells.**

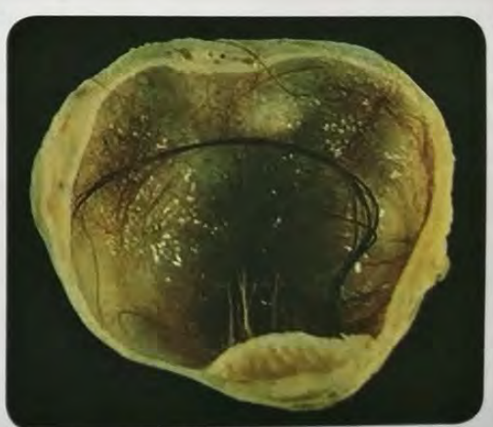


Fig. 11: Dermoid cyst

- On histologic examination, the cyst wall is composed of stratified squamous epithelium with underlying sebaceous glands, hair shafts, and other skin adnexal structures.
- In most cases, structures from other germ layers can be identified, such as cartilage, bone, thyroid tissue, and other organoid formations.

- About 1% of the dermoids undergo malignant transformation of any one of the component elements (e.g., thyroid carcinoma, melanoma, but most commonly, squamous cell carcinoma).
- These tumors arise from an ovum after the first meiotic division.

Monodermal or Specialized Teratomas:

- The most common of the specialized teratoma are struma ovarii and carcinoid. They are always unilateral.
  - Struma ovarii is composed entirely of mature thyroid tissue. Interestingly, these thyroidal neoplasms may hyperfunction, causing hyperthyroidism.

Key Point

The karyotype of all benign ovarian teratomas is 46, XX.

- The **ovarian carcinoid** presumably arises from intestinal epithelium in a teratoma and may result in carcinoid syndrome. Primary ovarian carcinoid can be distinguished from metastatic intestinal carcinoid, the latter virtually always bilateral.
- Even more rare is the **strumal carcinoid**, a combination of struma ovarii and carcinoid in the same ovary.

Immature Malignant Teratomas:

- These are rare tumors that differ from benign teratomas in that the component tissue resembles that observed in the fetus or embryo rather than in the adult.
- The tumor is found chiefly in prepubertal adolescents and young women, the mean age being 18 years.
- On microscopic examination, there are varying amounts of immature tissue differentiating toward cartilage, glands, bone, muscle, nerve, and others.

b. **Dysgerminoma**

- It is the **ovarian counterpart of the seminoma** of the testis.
- Similar to the seminoma, it is composed of large vesicular cells having a clear cytoplasm, well-defined cell boundaries, and centrally placed regular nuclei.
- Most of these tumors have no endocrine function. A few produce elevated levels of chorionic gonadotropin and may have syncytiotrophoblastic giant cells on histologic examination.
- These are **usually unilateral** (80% to 90%) and solid.

Key Point

All **dysgerminomas** are **malignant.**
These neoplasms are **extremely radiosensitive.**

- On histologic examination, the dysgerminoma cells are dispersed in sheets or cords separated by scant fibrous stroma. As in the seminoma, the fibrous stroma is infiltrated with mature lymphocytes and occasional granulomas.

c. **Endodermal Sinus (Yolk Sac) Tumor**

- It is the second most common malignant tumor of germ cell origin.
- It is thought to be derived from differentiation of malignant germ cells toward extraembryonic yolk sac structure.
- Similar to the yolk sac, the tumor is rich in *a-fetoprotein and a1-antitrypsin.*

Key Point

Characteristic histologic feature of **yolk sac tumor** is a glomerulus-like structure composed of a central blood vessel enveloped by germ cells within a space lined by germ cells (**Schiller-Duval body**).

d. **Choriocarcinoma**

- More commonly of placental origin, the choriocarcinoma, similar to the endodermal sinus tumor, is an example of extraembryonic differentiation of malignant germ cells.
- Most ovarian choriocarcinomas exist in combination with other germ cell tumors, and pure choriocarcinomas are extremely rare.
- Like all choriocarcinomas, they elaborate high levels of chorionic gonadotropins that are sometimes helpful in establishing the diagnosis or detecting recurrences.

Concept

In contrast to choriocarcinomas arising in placental tissue, those arising in the ovary are generally unresponsive to chemotherapy and are often fatal.

e. **Other Germ Cell Tumors**

- These include **embryonal carcinoma** (another highly malignant tumor of primitive embryonal elements, histologically similar to tumors arising in the testes), **polyembryoma** (a malignant tumor containing so-called embryoid bodies) and **mixed germ cell tumors** (containing various combinations of dysgerminoma, teratoma, endodermal sinus tumor, and choriocarcinoma).

Key Point

Krukenberg tumors are often found in **both ovaries.**

Gonadoblastoma is an uncommon tumor thought to be composed of germ cells and sex cord-stroma derivatives. It occurs in individuals with abnormal sexual development and in gonads of indeterminate nature. Eighty per cent of patients are phenotypic females, and 20% are phenotypic males with undescended testicles and female internal secondary organs. On microscopic examination, the tumor consists of nests of a mixture of germ cells and sex cord derivatives resembling immature Sertoli and granulosa cells. A coexistent dysgerminoma occurs in 50% of the cases. The prognosis is excellent.

D. Metastatic tumors of ovary

- The most common "metastatic" tumors of the ovary are probably derived from tumors of Mullerian origin: the uterus, fallopian tube, contralateral ovary, or pelvic peritoneum.
- The most common extramullerian primaries are the breast and gastrointestinal tract, including colon, stomach, biliary tract, and pancreas.
- Also included in this group are the rare cases of pseudomyxoma peritonei, derived from appendiceal tumors.
- **Krukenberg tumor** classically refers to a metastatic ovarian malignancy whose primary site arose in the gastrointestinal tract or breast. Microscopically, they are characterized by appearance of **mucin-secreting signet-ring cells** in the tissue of the ovary; when the primary tumor is discovered, the same signet-ring cells are typically found. Carcinomas of colon, appendix, and breast (mainly invasive lobular carcinoma) are the next most common primary sites. Rare cases of Krukenberg tumor originating from carcinomas of the gallbladder, biliary tract, pancreas, small intestine, ampulla of Vater, cervix, and urinary bladder/urachus have been reported

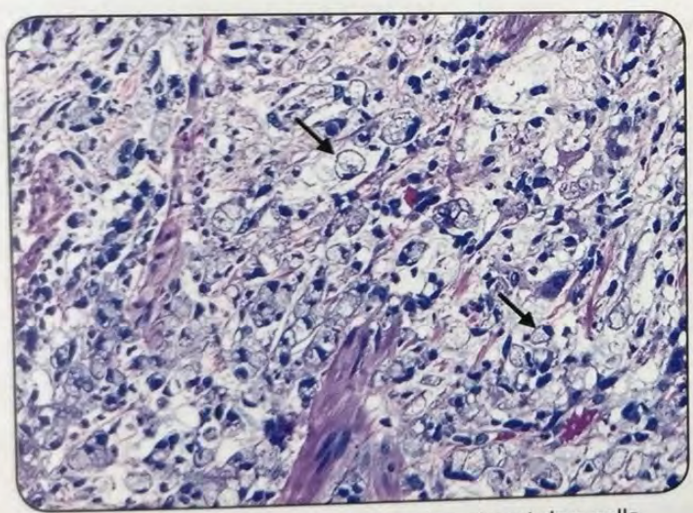


Fig. 12: Krukenberg tumor having signet ring cells

Key Point

Stomach is the primary site in most of the cases of Krukenberg tumor.

SECONDARY AMENORRHEA

Secondary amenorrhea refers to absent menses for 3 months in a woman who had previously had menses. Causes of secondary amenorrhea include pregnancy (the most common cause), hypothalamic/pituitary abnormalities, ovarian disorders, and end organ (uterine) disease. The remainder of the disorders causing secondary amenorrhea can be differentiated by examining gonadotropin (FSH and LH) levels along with the results of a progesterone challenge test.

Concept

Pregnancy can be **diagnosed** by obtaining a clinical history along with a pregnancy test that determines serum or urine beta-human chorionic gonadotropin **(beta-hCG) levels**.

- Withdrawal bleeding following progesterone administration indicates that the endometrial mucosa had been primed with estrogen, which, in turn, indicates that the hypothalamus/pituitary axis and ovaries are normal.
- **Hypothalamic/pituitary disorders**, which are characterized by decreased FSH and LH levels, include functional gonadotropin deficiencies, such as can be seen in patients with a weight loss syndrome. In these patients, markedly decreased body weight (> 15% below ideal weight) causes decreased secretion of GnRH from the hypothalamus. Decreased gonadotropin levels decrease estrogen levels, which results in amenorrhea and an increased risk for osteoporosis. Because of the decreased estrogen levels, progesterone challenge does not result in withdrawal bleeding.
- **Ovarian conditions**, such as surgical removal of the ovaries, would most likely produce elevated gonadotropin levels due to the lack of negative feedback from estrogen and progesterone. Because of the decreased estrogen levels, a progesterone challenge would not result in withdrawal bleeding.
- **Uterine (end organ) disorders** are characterized by normal FSH and LH levels. An example is Asherman's syndrome. (Describe alongside) A patient with Asherman's syndrome would have no response to progesterone.

Key Point

Asherman's syndrome is a clinical condition caused by numerous aggressive dilatation and curettage of the endometrium for menorrhagia leading to removal of the stratum basalis. It is also associated with absence of the glandular epithelium.

GESTATIONAL TROPHOBLASTIC DISEASES

The diseases in this category include; benign hydatidiform mole (partial and complete), invasive mole, placental site trophoblastic tumor and choriocarcinoma.

1. **Hydatidiform mole**: Both partial and complete, are composed of *avascular, grape-like structures* that do not invade the myometrium.

Differentiating features between partial and complete mole

- In complete (classic) moles, all the chorionic villi are abnormal and fetal parts are not found. In partial moles, only some of the villi are abnormal and fetal parts may be seen.
- Complete moles have a 46, XX diploid pattern and arise from the paternal chromosomes of a single sperm by a process called androgenesis. In contrast, partial moles have a triploid or a tetraploid karyotype and arise from the fertilization of a single egg by two sperm.
- Another way to differentiate these two disorders is to use immunostaining for p57, which is a gene that is paternally imprinted (inactivated). Because the complete mole arises only from paternal chromosomes, immunostaining for p57 will be negative.

Concept

It is important to differentiate between partial and complete mole these two disorders because about **2% of complete moles may develop into chriocarcinoma,** but *partial moles are rarely followed by malignancy*

2. **Invasive moles**: This is defined as a mole that penetrates and may even perforate the uterine wall. There is invasion of the myometrium by hydropic chorionic villi, accompanied by proliferation of both cytotrophoblast and syncytiotrophoblast. Hydropic villi may embolize to distant sites, such as lungs and brain, but do not grow in these organs as true metastases.
3. **Placental site trophoblastic tumor**: In contrast to syncytial cytotrophoblast, which is present on the chorionic villi, intermediate trophoblast is found in the implantation site and placental membranes. Intermediate trophoblasts may give rise to *placental site trophoblastic tumors* (PSTTs). PSTTs comprise less than 2% of gestational trophoblastic neoplasms and present as neoplastic polygonal cells infiltrating the endomyometrium. PSTTs may be preceded by a normal pregnancy (one-half), spontaneous abortion (one-sixth), or hydatidiform mole (one-fifth). Distinction of PSTTs from normal exaggerated placental implantation site trophoblast may be difficult and can be achieved by using biomarkers (Mel-Cam and Ki-67) that detect increased proliferation in the trophoblastic cells.
4. **Gestational choriocarcinomas:** These are composed of malignant proliferations of both cytotrophoblasts and syncytiotrophoblasts without the formation of villi, can arise from either normal or abnormal pregnancies: 50% arise in hydatidiform moles, 25% in cases of previous abortion, 22% in normal pregnancies, and the rest in ectopic pregnancies or teratomas. Both hydatidiform moles and choriocarcinomas have high levels of human chorionic gonadotropin (hCG); the levels are extremely high in choriocarcinoma unless considerable tumor necrosis is present.

BREAST

Pain (mastalgia or mastodynia) is the most common breast symptom.

Key Point

DCIS is the most common malignancy associated with calcifications

Discrete *palpable masses* are the second most common breast symptom. A breast mass usually does not become palpable until it is about 2 cm in diameter. Approximately 50% of carcinomas arise in the upper outer quadrant, 10% in each of the remaining quadrants, and about 20% in the central or subareolar region.

Nipple discharge is a less common presenting symptom but is of concern when it is spontaneous and unilateral. Bloody or serous discharges are most commonly associated with benign lesions but, rarely, can be due to a malignancy. The most common etiologies for discharge are a solitary large duct papilloma, cysts, or carcinoma.

The principal mammographic signs of breast carcinoma are densities and calcifications:

- Densities. Most neoplasms grow as solid masses and are radiologically denser than the intermingled connective and adipose tissue of the normal breast. Mammography can detect masses before they become palpable. The most common lesions that are detected as densities are invasive carcinomas, fibroadenomas, and cysts. Ductal carcinoma in situ (DCIS, or carcinoma limited to the ductal system) rarely presents as a density.
- Calcifications. Calcifications are associated with secretory material, necrotic debris, and hyalinized stroma. Calcifications associated with malignancy are commonly small, irregular, numerous, and clustered or linear and branching.

INFLAMMATIONS

Acute Mastitis

Almost all cases of acute mastitis occur during lactation usually caused by *Staphylococcus aureus.*

Periductal Mastitis/Zuska disease

This condition is also known by the names of recurrent subareolar abscess or squamous metaplasia of lactiferous ducts. Both women, as well as men, present with a painful erythematous subareolar mass. The main histologic feature is keratinizing squamous epithelium extending to an abnormal depth into the orifices of the nipple ducts.

Key Point

More than 90% of patients with **periductal mastitis** are **smokers**.

Mammary Duct Ectasia

This disorder tends to occur in the fifth or sixth decade of life, usually in multiparous women, and, unlike periductal mastitis, is not associated with cigarette smoking.
Patients present with a poorly defined palpable periareolar mass, sometimes with skin retraction, often accompanied by thick, white nipple secretions. This lesion is characterized chiefly by dilation of ducts, inspissation of breast secretions, and a marked periductal and interstitial chronic granulomatous inflammatory reaction.

Fat Necrosis

Fat necrosis can present as a painless palpable mass, skin thickening or retraction, a mammographic density, or mammographic calcifications.

BENIGN EPITHELIAL LESIONS

Nonproliferative Breast Changes (Fibrocystic Changes)

Three principal patterns of morphologic change:
1. Cyst formation, often with apocrine metaplasia;
2. Fibrosis; and
3. Adenosis

Cysts: Small cysts form by the dilation and unfolding of lobules. When cystic lobules coalesce, larger cysts are formed. Unopened cysts are brown to blue (blue-dome cysts) owing to the contained semitranslucent, turbid fluid. Cysts are lined either by a flattened atrophic epithelium or by cells altered by apocrine metaplasia. Metaplastic cells have an abundant granular, eosinophilic cytoplasm, with round nuclei, resembling the apocrine epithelium of sweat glands.

Concept

"Milk of calcium" is a term radiologists use to describe calcifications in large cysts that look as if they are lining the bottom of a rounded cyst on mammography.

Fibrosis: Cysts frequently rupture, with release of secretory material into the adjacent stroma. The resulting chronic inflammation and fibrous scarring contribute to the palpable firmness of the breast.

Adenosis: Adenosis is defined as an increase in the number of acini per lobule.

The acini are often enlarged (blunt duct adenosis) and are not distorted as is seen in sclerosing adenosis.

Proliferative Breast Disease without Atypia

This group of disorders is characterized by proliferation of ductal epithelium and/or stroma without cellular abnormalities suggestive of malignancy. The following entities are included in this category: (1) moderate or florid epithelial hyperplasia, (2) sclerosing adenosis, (3) complex sclerosing lesions, (4) papillomas, and (5) fibroadenoma with complex features.

Epithelial Hyperplasia
- In the normal breast, only myoepithelial cells and a single layer of luminal cells are present above the basement membrane. Epithelial hyperplasia is defined by the presence of more than two cell layers.

Sclerosing Adenosis
- The number of acini per terminal duct is increased to at least twice the number found in uninvolved lobules. The normal lobular arrangement is maintained. The acini are compressed and distorted in the central portions of the lesion but characteristically dilated at the periphery. Myoepithelial cells are usually prominent.

Complex Sclerosing Lesion (Radial Scar)
- Radial scars are stellate lesions characterized by a central nidus of entrapped glands in a hyalinized stroma.

Papillomas
- Papillomas are composed of multiple branching fibrovascular cores, each having a connective tissue axis lined by luminal and myoepithelial cells. Growth occurs within a dilated duct.
- Small duct papillomas have been shown to be a component of proliferative breast disease and increase the risk of subsequent carcinoma.

Proliferative Breast Disease with Atypia

Proliferative disease with atypia *includes atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH).*

- **ADH** is recognized by its histologic resemblance to ductal carcinoma in situ, including a monomorphic cell population, regular cell placement, and round lumina. However, the lesions are characteristically limited in extent, and the cells are not completely monomorphic in type or they fail to completely fill ductal spaces.
- **ALH** refers to a proliferation of cells identical to those of LCIS (described later), but the cells do not fill or distend more than 50% of the acini within a lobule.

Concept

Atypical hyperplasia is a cellular proliferation resembling ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) but lacking sufficient qualitative or quantitative features for a diagnosis of carcinoma in situ.

Non-proliferative changes do not increase the risk of cancer. Proliferative disease is associated with a mild increase in risk. Proliferative disease with atypia (ADH and ALH) confers a moderate increase in risk.

CARCINOMA OF THE BREAST

Carcinoma is the most common malignancy of the breast, and breast cancer is the most common non-skin malignancy in women.

Key Point

Breast cancer is the ***most common*** malignancy in women in **India**

PROGNOSTIC FACTORS

Major

- Invasive carcinoma has worse prognosis than in-situ carcinoma
- Distant metastasis indicates bad prognosis.
- Axillary lymph node involvement is associated with worse prognosis.
- Tumor Size: Less than 1 cm good prognosis, more than 2 cm bad prognosis.
- Local invasion into skeletal muscle carries poor prognosis.
- Inflammatory carcinoma has poor prognosis.

Minor

- **Histological type:** Invasive ductal carcinoma (no special type; NST) carries poor prognosis. Special types have good prognosis except medullary.
- **Nottingham histological score (Scarff-Bloom-Richardson grade):** Grade 1 good prognosis, grade 3 poor
- **Estrogen and Progesterone receptor** positivity indicates good response to antiestrogen therapy.
- **HER2/neu overexpression:** Poor prognosis
- **Lymphovascular invasion:** poor prognosis
- High proliferative rate indicates worse prognosis
- **Aneuploidy** indicates bad prognosis
- *The major risk factors for the development of breast cancer are hormonal and genetic (family history).* Breast carcinomas can, therefore, be divided into sporadic cases, possibly related to hormonal exposure, and hereditary cases, associated with family history or germ-line mutations.

Key Point

Axillary lymph node status is the ***most important prognostic factor for invasive carcinoma*** *in the absence of distant metastases.*

Key Point

Triple assessment in breast cancer = *clinical examination + radiological examination (mammography) + FNAC.*

Hereditary Breast Cancer

Mutated *BRCA1* also markedly increases the risk of developing ovarian carcinoma, which is as high as 20 to 40%. *BRCA2* confers a smaller risk for ovarian carcinoma (10 to 20%) but is associated more frequently with male breast cancer. *BRCA1* and *BRCA2* carriers are also susceptible to other cancers, such as colon, prostate, and pancreas, but to a lesser extent. BRCA1-associated breast cancers are commonly poorly differentiated, have medullary features and do not express hormone receptors or HER2/neu (so called, *triple negative phenotype*). Their gene profile signature is similar to basal-like breast cancers. These are frequently associated with loss of inactive X-chromosome and reduplication of active X, resulting in absence of Barr body. BRCA2 are also poorly differentiated but are more commonly estrogen receptor positive.

Key Point

In comparison to BRCA1, **BRCA2** is associated more frequently with **male breast cancer**.

Sporadic Breast Cancer

The major risk factors for sporadic breast cancer are related to hormone exposure: gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. The majority of these cancers occur in postmenopausal women and overexpress estrogen receptors (ER).

CLASSIFICATION OF BREAST CARCINOMA

Almost all breast malignancies are adenocarcinomas, all other types (i.e., squamous cell carcinomas, phyllodes tumors, sarcomas, and lymphomas) making up fewer than 5% of the total.

Recent Exams Questions

Molecular classification of breast cancer is based on **gene expression profiling** which major ***relative level of mRNA expression***

Defining Features	ER-positive, HER2-negative		HER2-Positive (ER-Positive or Negative)	ER-Negative HER2-Negative
Frequency	-40-55% (Low proliferation)	10% (High proliferation)	-20%	-15%
Included special histologic types	Well or moderately differentiated lobular, tubular, mucinous	Poorly differentiated lobular	Some apocrine	Medullary, adenoid cystic, secretory, metaplastic
Typical patient groups	Older women, men, cancers detected by mammographic screening	**BRCA2** mutation carriers	**Young women, non-white** women, TP53 mutation carriers (ER positive)	**Young women, BRCA1** mutation carriers, African and American and Hispanic women
Metastatic pattern	Bone (70%) more common than visceral (25%) or brain (>10%)	Bone (80%) more common than visceral(30%) or brain (>10%)	Bone (70%), visceral (30%) and brain(30%) are all common	Bone (40%), visceral (35%) and brain (25%) are all common
Relapse Pattern	Late, >10 years, long survival possible with metastases	Intermediate	Usually short, <10 years, survival with metastases rare	Usually short, <5years, survival with metastases rare
Complete response to chemotherapy	<10%	-10%	ER Positive- 15% ER Negative- 30%	-30%

Carcinomas are divided into in situ carcinomas and invasive carcinomas.

Noninvasive carcinomas (carinoma in situ) may be located within the ducts (intraductal carcinoma) or within the lobules (lobular carcinoma in situ). There are several variants of intraductal carcinoma, including comedocarcinoma, cribriform carcinoma, and intraductal papillary carcinoma. Comedocarcinoma grows as a solid intraductal sheet of cells with a central area of necrosis, that commonly undergoes calcification. It is frequently associated with the erb B2/neu oncogene and a poor prognosis. Cribriform carcinoma is characterized by round, ductlike structures within the solid intraductal sheet of epithelial cells, while intraductal papillary carcinoma has a predominant papillary pattern.

Infiltration of the nipple by large cells with clear cytoplasm is diagnostic of Paget's disease. These cells are usually found both singly and in small clusters in the epidermis. Paget's disease is always associated with (in fact, it begins with) an underlying intraductal carcinoma that extends to infiltrate the skin of nipple and areola. **Paget cells** may resemble the cells of superficial spreading melanoma, but they are *PAS-positive and diastase-resistant* (*mucopolysaccharide-or mucin-positive*), unlike melanoma cells.

Concept

Paget cells may resemble the cells of superficial spreading melanoma, but they are *PAS-positive and diastase-resistant (mucopolysaccharide-or mucin-positive)*, unlike melanoma cells.

INVASIVE (INFILTRATING) CARCINOMA

Invasive breast carcinoma is divided into two main types:

- No- special type carcinoma **[Intraductal]**
- **Special carcinoma**
  - Lobular
  - Cribriform
  - Colloid
  - Medullary
  - Papillary
  - Metaplastic

Key Point

Intraductal carcinoma is most common carcinoma of breast and carries poor prognosis.

Invasive carcinomas of no special type include the majority of carcinomas (70 to 80%) that cannot be classified as any other subtype.

Key Point

Special type carcinomas carry good prognosis but inflammatory carcinoma has poor prognosis.

Invasive Carcinoma, No Special Type (NST; Invasive Ductal Carcinoma)

On gross examination, most carcinomas are firm to hard and have an irregular border. Within the center of the carcinoma, there are small pinpoint foci or streaks of chalky white elastotic stroma and occasionally small foci of calcification. There is a characteristic grating sound (similar to cutting a water chestnut) when cut or scraped. Five major patterns of gene expression in the NST group are noted:

- **Luminal A (40-55%):** ER positive and HER2/neu negative. These are generally slow growing and respond to hormonal treatments.
- **Luminal B (15-20%):** Triple positive cancers i.e. ER, PR and HER2/neu positive. These are of higher grade and more likely to have lymph node metastasis.
- **Normal breast-like (6-10%):** Well-differentiated ER positive and HER2/neu negative.
- **Basal-like (13-25%):** Triple negative cancers i.e. ER, PR and HER2/neu negative. Express markers of typical myoepithelial cells (e.g. basal keratins, P-cadherin, p63 or laminin), progenitor cells or putative stem cells (cytokeratin 5 and 6). Members of this group include medullary carcinoma, metaplastic carcinoma (e.g. spindle cell carcinoma or matrix producing carcinoma) and carcinomas with a central fibrotic focus. Many cancers in women with BRCA-1 mutations are of this type.
- HER2 positive (7-12%): ER negative but overexpress HER2/neu. In more than 90%, it is due to amplification of the segment of DNA on chromosome 17q21.

Lobular Carcinoma

Lobular carcinoma (invasive) of breast is one of the very few carcinomas which are **seen bilaterally**. Histologic hallmark is the presence of dyscohesive infiltrating tumor cells, often arranged in *single file* or in loose clusters or sheets. *Tubule formation is absent.* Signet ring cells containing intracytoplasmic mucin droplets are common. It metastasizes frequently to peritoneum, retroperitoneum, leptomeninges, GIT and ovaries. The incidence of this carcinoma is increasing among postmenopausal females presumably because of increasing use of HRT.

Key Point

Lobular carcinoma (invasive) of breast occurs **bilaterally.**

Medullary Carcinoma

The tumor has a soft, fleshy consistency (*medulla* is Latin for "marrow") and is well-circumscribed. The carcinoma is characterized by

Concept

Both lobular carcinoma of breast and signet ring carcinoma of GIT are characterized by the loss of E-cadherin.

- Solid, syncytium-like sheets (occupying more than 75% of the tumor) of large cells with vesicular, pleomorphic nuclei, containing prominent nucleoli
- Frequent mitotic figures
- A moderate to marked lymphoplasmacytic infiltrate surrounding and within the tumor
- A pushing (non-infiltrative) border.

Medullary carcinomas have slightly better prognosis than do NST carcinomas, despite the almost universal presence of poor prognostic factors. These show overexpression of E-cadherin and basal like gene expression.

Mucinous (Colloid) Carcinoma

The tumor cells are seen as clusters and small islands of cells within large lakes of mucin that push into the adjacent stroma.

Tubular Carcinoma

These tumors consist exclusively of well-formed tubules. However, a myoepithelial cell layer is absent, and tumor cells are in direct contact with stroma.

Invasive Papillary Carcinoma

Invasive carcinomas with a papillary architecture are rare and represent 1% or fewer of all invasive cancers. Papillary architecture is more commonly seen in DCIS.

Metaplastic Carcinoma

"Metaplastic carcinoma" includes a wide variety of rare types of breast cancer (<1% of all cases), including conventional adenocarcinomas with a chondroid stroma, squamous cell carcinomas, and carcinomas with a prominent spindle cell component that might be difficult to distinguish from sarcomas. Some of these carcinomas express genes in common with myoepithelial cells and likely to arise from this cell type.

Multiple Choice Questions

MALE GENITAL TRACT

1. Alpha fetoprotein is *Not* raised in which testicular tumors? *(AI 2010)*
(a) Choriocarcinoma
(b) Teratocarcinoma
(c) Yolk sac tumor
(d) Embryonal cell carcinoma

2. Which one of the following is not used as a tumor marker in testicular tumors? *(AI 2005) (DNB 2007)*
(a) AFP (b) LDH *(Kolkata 2008)*
(c) hCG (d) CEA

3. All of the following statements about Gleason grading system are true except: *(AIIMS Nov 2008)*
(a) Score range from 1 to 10
(b) High score is associated with bad prognosis
(c) Helps in grading of tumor
(d) Helps decide treatment modality

4. Infertility is a common feature in "Sertoli cell only" syndrome because: *(AIIMS May 2003)*
(a) Too many Sertoli cells inhibit spermatogenesis via inhibin
(b) Proper blood testis barrier is not established
(c) There is no germ cell in this condition
(d) Sufficient numbers of spermatozoa are not produced

5. Predisposing factors for germ cell tumor are:
(a) Cryptorchidism *(PGI Dec 2002)*
(b) Testicular feminizing syndrome
(c) Klinefelter's syndrome
(d) Smoking
(e) Right side more common than left side.

6. In the testis intratubular germ cell neoplasia is seen in all, except: *(Delhi 2009 RP)*
(a) Seminomas
(b) Spermatocytic seminoma
(c) Yolk sac tumor of testis
(d) Embryonal carcinoma

7. Condyloma are mostly caused by HPV types:
(a) 11 and 13 (b) 6 and 11 *(Delhi PG-2006)*
(c) 6 and 13 (d) 30 and 33

8. Which one of the following is not used as a tumor marker in testicular tumors? *(DNB- 2007)*
(a) AFP (b) LDH
(c) hCG (d) CEA

9. Gleason's classification is used for: *(UP 2008)*
(a) Carcinoma breast
(b) Carcinoma prostate
(c) Carcinoma pancreas
(d) Carcinoma rectum

10. Which of the following is not a malignant tumor of germ cell origin? *(AP 2002)*
(a) Mature teratoma
(b) Choriocarcinoma
(c) Dysgerminoma
(d) Embryonal carcinoma

11. Metastasis is least common with: *(AP 2007)*
(a) Embryonal cell carcinoma
(b) Endodermal sinus tumor
(c) Teratocarcinoma
(d) Spermatocytic seminoma

12. A 25-year-old man, Ramesh presents with a testicular mass and is found to have high serum levels of α-fetoprotein (AFP). Microscopic examination of a biopsy from this mass reveals sheets of undifferentiated cells along with focal primitive glandular differentiation. The tumor cells have large and hyperchromatic nuclei. Further workup fails to reveal the presence of any metastatic disease as the tumor is confined within the testis. Based on all of these findings, which of the following best characterizes this tumor?

Tumor Aggressiveness	Grade	Stage
(a) Benign	Low	Low
(b) Benign	Low	High
(c) Malignant	Low	Low
(d) Malignant	High	Low
(e) Malignant	High	High

13. In which of the following respects do a seminoma involving the testis and a dysgerminoma involving the ovary differ most significantly?
(a) Most common age of presentation
(b) Number of mitoses
(c) Potential to contain foci of more aggressive tumors
(d) Ultrastructural appearance

14. A 10-year-old child develops a testicular mass and undergoes orchiectomy. On cut section, the mass shows a variety of appearances and colors. Histologically, many different tissues are seen, including cartilage, thyroid, and neural tissue. A small focus of clear-cut squamous cell carcinoma is seen. Which of the following is the most appropriate classification for this tumor?

(a) Dermoid cyst
(b) Teratoma with malignant transformation
(c) Immature teratoma
(d) Solid mature teratoma

MOST RECENT QUESTIONS

15. Benign hyperplasia of prostate first develops in:
(a) Central zone
(b) Peripharal zone
(c) Periurethral transition zone
(d) Any of the above

16. The commonest site for extragonadal germ cell tumour is:
(a) Pineal gland
(b) Mediastinum
(c) Retroperitoneum
(d) Sacrococyygeal region

17. Which one of the following is not used as a tumor marker in testicular tumors?
(a) AFP (b) LDH
(c) HCG (d) CEA

18. All of the following genes are associated with seminoma except:
(a) PLAP (b) C-KIT
(c) OCT-4 (d) CDK-4

FEMALE GENITAL TRACT

19. The cytogenicity of solid tumors is not easily assessed especially in carcinoma cervix because
(a) Metaphase is distinct *(AIIMS Nov 2010)*
(b) Due to contamination with infectious agents
(c) High mitotic rate
(d) Deficient tissue sample

20. With regard to the malignant behavior of leiomyosarcoma, the most important criterion is:
(a) Blood vessel penetration by tumor cells *(AI 2006)*
(b) Tumor cells in lymphatic channels
(c) Lymphocyte infiltration
(d) The number of mitoses per high power field

21. All are true about polycystic ovarian disease except:
(a) Persistently elevated LH *(AIIMS Nov 2008)*
(b) Increased LH/FSH ratio
(c) Increased DHEAS
(d) Increased prolactin

22. Sections from a solid-cystic unilateral ovarian tumor in a 30-year old female show a tumor composed of diffuse sheets of small cells with doubtful nuclear grooving and scanty cytoplasm. No Call-Exner bodies are seen. The ideal immunohistochemistry panel would include: *(AIIMS May 2006)*
(a) Vimentin, epithelial membrane antigen, inhibin, CD99
(b) Desmin, S-100 protein, smooth muscle antigen, cytokeratin
(c) Chromogranin, CD45, CD99, CD20
(d) CD3, Chromogranin, CD 45, Synaptophysin

23. An ovarian neoplasm in a 14-year old girl is most likely to be: *(Delhi 2009)*
(a) Germ cell tumor
(b) Epithelial tumor
(c) Sertoli-Leydig cell tumor
(d) Granulosa cell tumor

24. The incidence of bilaterality in a dermoid cyst is approximately: *(Delhi 2009)*
(a) 10% (b) 30%
(c) 50% (d) 70%

25. The risk of sarcoma developing in a fibroid uterus is approximately: *(Delhi 2009)*
(a) < 1% (b) 10%
(c) 30% (d) 50%

26. Uterine leiomyoma is least likely to undergo:
(a) Malignant change *(Delhi PG-2005)*
(b) Hyaline change
(c) Calcification
(d) Red degeneration

27. Carcinosarcoma occurs in: *(UP 2003)*
(a) Uterus (b) Liver
(c) Breast (d) Lungs

28. Schiller–Duval bodies are seen in: *(UP 2005, 2007)*
(a) Teratoma
(b) Seminoma
(c) Yolk-Sac tumor
(d) Choriocarcinoma

29. Call-Exner bodies are seen in: *(UP 2007)*
(a) Mature teratoma
(b) Endodermal sinus tumor
(c) Granulosa cell tumor
(d) Sertoli Leydig cell tumor

30. Hormone produced by endodermal sinus tumor is
(a) AFP (b) Alpha1 antitrypsin
(c) Both (d) hCG *(RJ 2002)*

31. Choriocarcinoma is characterized by all except: *(AP 2004)*
(a) Primarily trophoblastic tumor
(b) It can occur following hydatidiform mole
(c) Villi present
(d) It can metastasize to lungs

32. Call-Exner bodies are characteristic feature of *(AP 2005)*
(a) Granulosa theca cell tumor
(b) Brenner tumor
(c) Dysgerminoma
(d) Endodermal sinus tumor

33. Tennis Racquet cells are seen in : *(AP 2007)*
(a) Rhabdomyoma
(b) Rhabdomyosarcoma
(c) Histiocytoma
(d) Eosinophilic granuloma

34. A 30-year-old woman Shagun visits her gynecologist for a surgery. After laparotomy, a mass is removed which on microscopic examination demonstrates a cystic cavity filled with hair and keratin debris, and the wall contains skin, adnexal tissue, thyroid tissue, and neural tissue. All of the tissues are similar to those normally found, and no malignant changes are seen. Which of the following is the most likely diagnosis?
(a) Immature teratoma
(b) Leiomyoma
(c) Leiomyosarcoma
(d) Mature teratoma

35. Bilateral ovarian masses are identified on pelvic examination of a 40-year-old woman for which she undergoes total abdominal hysterectomy. Pathologic examination demonstrates papillary carcinoma producing serous fluid. Which of the following tumor markers would be most useful in monitoring for recurrence?
(a) Alpha-fetoprotein (b) Bombesin
(c) CA-125 (d) PSA

MOST RECENT QUESTIONS

36. A patient with chronic pelvic pain undergoes a hysterectomy. The resected uterus is filled with nodules composed of benign smooth muscle cells. Which of the following terms best describes these nodules?
(a) Angiosarcoma (b) Leiomyoma
(c) Leiomyosarcoma (d) Rhabdomyoma

37. Endodermal sinus tumor is characterized by:
(a) Call Exner body
(b) Psammoma body
(c) Schiller duval body
(d) Homer wright body

38. An adenofibroma of the ovary in which the epithelial component consists of the nests of transitional cells is called:
(a) Thecoma
(b) Brenner tumour
(c) Serous cystadenoma
(d) Granulose cell tumor

39. A lady with abdominal mass was investigated. On surgery, she was found to have bilateral ovarian masses with smooth surface. On microscopy they revealed mucin secreting cells with signet ring shape. What is the most likely diagnosis?
(a) Dysgerminoma
(b) Krukenberg tumor
(c) Mucinous adenocarcinoma of the ovaries
(d) Dermoid cyst

40. Most common subtype of endometrial carcinoma on histopathology is:
(a) Clear cell
(b) Adenocarcinoma
(c) Squamous cell carcinoma
(d) Transistional cell carcinoma

41. All are true about condylomata acuminata except which tumor?
(a) Caused by HPV
(b) Sexually transmitted
(c) Progresses to malignancy
(d) Occurs in genitalia

42. Risk factor for endometrial carcinoma is all except:
(a) Obesity (b) Smoking
(c) Infertility (d) Tamoxifen

43. Most common ovarian tumor:
a. Fibroma
b. Teratoma
c. Mucinous cystadenoma
d. Serous cystadenoma

BREAST TISSUE

44. Lesions affecting the teminal duct lobulat unit (TDLU) in breast are all except *(DPG 2011)*
(a) Nipple adenoma
(b) Blunt duct adenosis
(c) Intraductal papilloma
(d) Fibroadenoma

45. Dimorphic carcinoma is:
(a) Follicular carcinoma thyroid
(b) Papillary carcinoma thyroid
(c) Papillary carcinoma breast
(d) Gastric adenocarcinoma

46. The type of mammary ductal carcinoma in situ (DCIS) most likely to result in a palpable abnormality in the breast is: *(AI 2006)*
(a) Apocrine DCIS
(b) Neuroendocrine DCIS
(c) Will-differentiated DCIS
(d) Comedo DCIS

47. BRCA 1 gene is located on: *(AIIMS Nov 2008)*
(a) Chromosome 13 (b) Chromosome 11
(c) Chromosome 17 (d) Chromosome 22

48. Increased susceptibility to breast cancer is likely to be associated with a mutation in the following gene:
(a) p53 (b) BRCA-1 *(AIIMS Nov 2004)*
(c) Retinoblastoma (Rb) (d) H-Ras

49. A female patient presented with a firm mass of 2 × 2 cm in the upper outer quadrant of the breast. She gives a family history of ovarian carcinoma. The investigation that needs to be done to assess for mutations is:
(a) p53 (b) BRCA-2 *(AIIMS May 2002)*
(c) Her 2/Neu gene (d) C-myc gene

50. Bilateral breast carcinoma is: *(PGI June 2002)*
(a) Scirrhous carcinoma (b) Medullary carcinoma
(c) Lobular carcinoma (d) Ductal carcinoma
(e) Paget's carcinoma

51. Rare histological variants of carcinoma breast with better prognosis include all except: *(Delhi 2009)*
(a) Colloid carcinoma
(b) Medullary carcinoma
(c) Inflammatory carcinoma
(d) Tubular carcinoma

52. Tumor marker useful in the diagnosis of the cancer of the breast is: *(Karnataka 2005)*
(a) CEA (b) AFP
(c) CA-125 (d) CA-15-3

MOST RECENT QUESTIONS

53. Histologic hallmark of Paget's disease of nipple is:
(a) Caseous necrosis
(b) Infiltration of the epidermis by malignant cells
(c) Atypical lobular hyperplasia
(d) Desmoplasia

54. BRCA-1 gene lies on chromosome:
(a) 17 (b) 18
(c) 20 (d) 21

55. Commonest carcinoma of the breast with multifocal origin is: *(UP 2001)*
(a) Scirrhous carcinoma (b) Adenocystic carcinoma
(c) Lobular carcinoma (d) Ductal carcinoma

56. Which of the following breast tumors is bilateral?
(a) Colloid carcinoma
(b) Invasive ductal carcinoma
(c) Invasive lobular carcinoma
(d) Medullary carcinoma

57. Indian file pattern is seen in histopathological examination of:
(a) Infiltrating duct carcinoma
(b) Fibroadenoma
(c) Fibro carcinoma
(d) Lobular carcinoma

58. Fleshy, soft lymphatic infiltration of skin in breast cancer appears as:
(a) Puckering (b) Peau 'd orange
(c) Cancer encurasse (d) All of the above

59. A 54-year-old female Shanti presents for an annual exam. Her right breast is swollen, red, and tender. The physician palpates a firm area in the breast and suspects inflammatory breast cancer. Which of the following best describes the histological changes observed in this disorder?
(a) Acute inflammation in breast carcinoma
(b) Chronic inflammation in breast carcinoma
(c) Dermal lymphatic invasion by cancer cells
(d) Epidermal invasion by cancer cells

60. BRCA-1 gene lies on chromosome:
(a) 17 (b) 18
(c) 20 (d) 21

61. Paget's disease of the nipple is:
(a) Infection (b) Dermatisis
(c) Neoplasia (d) Hypopigmentation

62. Molecular classification of breast cancer is based on which of the following?
(a) Gene expression profiling
(b) Expression of hormone receptors like ER,PR, and HER-2 neu
(c) Histology
(d) Response to chemotherapy

63. HER-2/neu gene causes breast carcinoma due to:
(a) Overexpression (b) Suppression
(c) Mutation (d) Translocation

64. BRCA 1 responsible which type breast cancer?
(a) Medullary (b) Lobular
(c) Colloid (d) Secretory

65. Which antigen is not of prognostic significance in carcinoma breast?
(a) Her 2 neu receptor
(b) Epithelial membrane antigen
(c) Estrogen receptor
(d) Progesterone receptor

66. Infiltrative lobular breast carcinoma is associated with which of the following pattern of arrangement of cells?
(a) Pin wheel pattern
(b) Pleomorphic cells in sheets
(c) Cribiform pattern
(d) Single file pattern

CONCEPTUAL QUESTIONS

1-3. Will have two statements, assertion and reason. Read both of them carefully and answer according to these options.
(a) Both assertion and reason are true and reason is correct explanation of assertion.
(b) Both assertion and reason are true and reason is not the correct explanation of assertion.
(c) Assertion is true and reason is false.
(d) Both assertion and reason are false.

1. **Assertion:** Stromal cells are responsible for androgen dependent prostatic growth
Reason: Stromal cells have 5α reductase activity which produces testosterone in prostate.
2. **Assertion:** Struma ovarii is mature teratoma
Reason: It is responsible for production of the gonadotropins
3. **Assertion:** Seminoma is germ cell tumor with good prognosis.
Reason: The tumor cells rarely have areas of necrosis and hemorrhage

Explanations

1. **Ans. (a) Choriocarcinoma**

(Ref: Robbins 9/e p978, 8th/327, 989-991, 7th/339)

AFP is a marker of hepatocellular cancer and non-seminomatous germ cell tumors of testes.

Non-seminomatous germ cell tumors may be embryonal carcinoma, yolk sac tumors, choriocarcinoma or teratoma.

- **Embryonal cell carcinomas** and Yolk **sac tumor** have elevated AFP levels.
- **Dorland's** dictionary 27th edition writes that **Teratocarcinoma** refers to a germ cell tumor that is a mixture of teratoma with embryonal carcinoma, or with choriocarcinoma, or with both. So, it may be having elevated levels of AFP.
- **Choriocarcinomas** have elevated levels of hCG which can be readily demonstrated in the cytoplasm of syncytiotrophoblastic cells.

2. **Ans. (d) CEA**

(Ref: Robbins 7th/1045, 9/e p979, Harrison 17th/602)

3. **Ans. (a) Score range from 1 to 10**

(Ref: Schwartz 8th/1216, Robbins 9/e 987)

- A **Gleason score** is given to prostate cancer based upon its microscopic appearance. Cancers with a higher Gleason score are more aggressive and have a worse prognosis. Most tumors contain more than 1 pattern.
- The pathologist assigns a *grade* to the most common tumor, and a second *grade* to the next most common tumor. The two *grades* are added together to get a Gleason *score*. For example, if the most common tumor was grade 3, and the next most common tumor was grade 4, the Gleason *score* would be 3 + 4 = 7.
- The Gleason *grade* ranges from 1 to 5, with 5 having the worst prognosis. The Gleason *score* ranges from 2 to 10, with 10 having the worst prognosis.
- It should be noted that for Gleason score 7, a Gleason 4 + 3 is a more aggressive cancer than a Gleason 3 + 4. Also, there is not really any difference between the aggressiveness of a Gleason score 9 or 10 tumour.
- **Gleason scores are associated with the following features:**

  - **Grade 1**: The cancerous prostate closely resembles normal prostate tissue. The glands are small, well-formed, and closely packed
  - **Grade 2**: The tissue still has well-formed glands, but they are larger and have more tissue between them.
  - **Grade 3**: The tissue still has recognizable glands, but the cells are darker. At high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.
  - **Grade 4:** The tissue has few recognizable glands. Many cells are invading the surrounding tissue.
  - **Grade 5:** The tissue does not have recognizable glands. There are often just sheets of cells throughout the surrounding tissue

The Gleason score is used to help evaluate the prognosis of men with prostate cancer. Together with other parameters, the Gleason score is incorporated into a strategy of prostate cancer staging which predicts prognosis and helps guide therapy.

4. **Ans. (c) There is no germ cells in this condition**

(Ref: Anderson 10th 2177)

'Sertoli cell only' syndrome also called as Germ cell aplasia has small seminiferous tubules. In this condition seminiferous tubules are smaller than normal and are lined by a single layer of Sertoli cells and no germ cells. Without germ cell, spermatogenesis does not take place resulting in infertility.

5. **Ans. (a) Cryptorchidism ; (b) Testicular feminising syndrome; (c) Klinefelter syndrome; (e) Rt. side has more common flow than Lt. side**

(Ref: Robbins' 7th/1041, 9/e p975, Harrison' 16th/550)

The predisposing factors of germ cell tumors of testes are:

- Cryptorchidism
- Testicular feminization syndrome
- Klinefelter syndrome
- Excess 12P copy number either in the term of i(l2P) or increased 12P an aberrantly banded marker chromosome.
- Prior germ cell tumor
- Strong family history of germ cell tumor

6. **Ans. (b) Spermatocytic seminoma**

(Ref: Robbins 8th/988, 9/e p975,)

Most testicular germ cell tumors originate from intratubular germ cell neoplasia (ITGCN).

ITGCN is seen adjacent to all germ cell tumors in adults except for spermatocytic seminoma and epidermoid and dermoid cysts. With rare exceptions, it is also not seen in pediatric tumors (teratomas, yolk sac tumors… Robbins 7th edition page 1096)

So, obviously friends, if we have to choose between options b and c, we would prefer option b as the answer.

ITCGN is seen with a high frequency in the following conditions:

- Cryptorchidism
- Prior germ cell tumors
- Strong family history of germ cell tumor
- Androgen insensitivity syndrome
- Gonadal dysgenesis syndrome.

Untreated ITGCN progresses to invasive germ cell tumor in approximately 50% of cases over 5 years of follow-up.

7. **Ans. (b) 6 and 11** *(Ref: Robbins 7th/1035, 9/e p970)*
   - Condyloma are most commonly caused by HPV types 6 and 11.
   - Condyloma acuminatum is a benign tumor caused by human papilloma virus (HPV).
   - It is related to the common wart (verruca vulgaris) and may occur on any moist mucocutaneous surface of the external genitalia in either sex.
   - Also, HPV and associated diseases are sexually transmitted.
   - On the penis, these lesions occur most often about the coronal sulcus and inner surface of the prepuce.
   - They consist of single or multiple sessile or pedunculated, red papillary excrescences that vary from 1 mm to several mm in diameter.
   - Histologically a branching, villous, papillary connective tissue stroma is covered by a thickened hyperplastic
   - Epithelium that may have considerable superficial hyperkeratosis and thickening of the underlying epidermis (acanthosis).
     - The normal orderly maturation of the epithelial cells is preserved.
     - Clear vacuolization of the prickle cells (Koilocytosis), characteristic of HPV infection, is noted in these lesions.
     - The basement membrane is intact, and there is no evidence of invasion of the underlying stroma.
     - Condyloma acuminata tend to recur but do not evolve into invasive cancers.

8. **Ans. (d) CEA** *(Ref: Robbins 8th/327, 9/e p979)*

9. **Ans. (b) Carcinoma prostate** *(Ref: Robbins 9/e p987)*

10. **Ans. (a) Mature teratoma (Mature teratoma is a benign tumour)** *(Ref: Robbins 9/e p979, 8th/1047; 7th/1093,1096)*

11. **Ans. (b) Endodermal sinus tumor** *(Ref: Robbins 9/e p977)*

12. **Ans. (d)** *(Ref: Robbins 7th/335, 1043, 9/e p977, Chandrasoma/307-308)*
    - An embryonal carcinoma is testicular malignancy that secretes alpha-fetoprotein (α-AFP) and is composed of undifferentiated cells along with primitive glandular differentiation. Once the diagnosis of malignancy is established, prognosis for the patient is estimated through the process of grading and staging.
    - It is important to understand the difference between these two terms. First of all, note that these terms are applied only to malignant neoplasms. Basically, **grading is done histologically, while staging is done clinically**.
    - Lower grades, such as grades I and II, are more differentiated, less aggressive and have a better prognosis, while higher grades, such as grades III and IV, are less differentiated, more aggressive and have a worse prognosis. Tumors composed of malignant cells that appear primitive or undifferentiated are classified as high grade tumors.
    - In contrast to grading, the staging of cancers is based on the size of the primary lesion, the presence of lymph node metastases, and the presence of blood-borne metastases. Two main staging systems are Union International Centre le Cancer (UICC) and American Joint Committee (AJC), UICC classification is called the TNM classification. AJC staging system generally divides cancers into stages 0 through IV. Lower stage tumors are smaller, localized, and have a better prognosis, while higher stage tumors are larger, widespread, and have worse prognosis.

13. **Ans. (a) Most common age of presentation**
    (Ref: Robbins 8th/988, 1049, 9/e p976, 1030)
    - Seminomas and dysgerminomas are very similar tumors but differ in two significant respects: the most common age of presentation in men is in the fourth decade, while in women, it is in the third decade. Also, seminomas are relatively common in men (30% of testicular germ cell tumors), while dysgerminomas are rare in women (1% of ovarian tumors).
    - Both of these tumors are composed of sheets of uniform polyhedral cells with intervening fibrous septa of connective tissue, lymphocytes, and multinucleated giant cells. The number of mitoses (choice B) per high-power field and ultrastructural appearance (choice D) do not differ greatly between the two tumors.
    - These tumors in pure form are very radiosensitive but can be much more aggressive (choice C) if foci of other germ cell tumors (notably embryonal carcinoma, choriocarcinoma, and yolk sac tumors) are present.

14. **Ans. (b) Teratoma with malignant transformation**
    (Ref: Robbins 8th/991, 9/e p978)
    - This is teratoma with malignant transformation. The possibility of malignant transformation is the reason why mature teratomas with very well differentiated tissues should be completely excised. Malignant transformation is more common in teratomas in adults than in children or babies.
    - Dermoid cyst (choice A) is a cystic form of mature teratoma, usually found in the ovaries.

- Immature teratoma (choice C), while clinically malignant, shows embryonal tissues and often displays no clear-cut cytological evidence of malignancy.
- Solid mature teratoma (choice D) without the added descriptor "with malignant transformation" is by definition a benign tumor. Careful extensive sampling is required to exclude minute foci of cancerous transformation.

15. Ans. (c) Periurethral transition zone
(Ref: Robbins 9/e p982)

16. Ans. (b) Mediastinum
(Ref: Robbins 9/e p475; Harsh Mohan 6/e p703)

17. Ans. (d) CEA *(Ref: Robbins 8/e 327, 9/e p979)*
Carcino embryonic antigen is increased in cancers of the pancreas and colon.

18. Ans. (d) CDK-4 *(Ref: Robbins 9/e p976)*

Seminomas contain *iso chromosome 12p* and express *OCT3/4 and NANOG*. Approximately 25% of these tumors have KIT activating mutations.

19. Ans. (b) Due to contamination with infectious agents
(Ref: Enzinger and Weiss Soft Tissue Tumors, 5th/73, Wintrobes Hematology, 12th/50-60)

- Cytogenetics is the study of chromosome structure which can be done with techniques like karyotyping or molecular techniques (FISH, spectral karyotyping/multicolor FISH, comparative genomic hybridization). These techniques needs metaphase (more commonly) but can be applied to interphase also. Cytogenetics is easy if the metaphase is distinct. So, culture is often done in solid tumors to get the cells in metaphase.
- Cytogenetics is also easier if mitotic rate is high.

The problems with cytogenetics are:

- Unpredictable growth of the neoplastic cells in tissue culture
- Overgrowth of neoplastic cells by reactive non-neoplastic cells
- Contamination of tumor cultures by bacteria or fungi
- Predominance of nonviable tumor (necrotic sample)

Deficient tissue sampling like sampling from non-representative areas or the necrotic areas will impair the results in most of the solid tumors but the commonest problem with cancer of the cervix is the high contamination rate. So, option 'B' is better than option 'D'.

20. Ans. (d) The number of mitoses per high power field
(Ref: Robbins 7th/1090, 9/e p1021)

- The most important criterion for distinction of leiomyosarcoma from leiomyoma (malignant transformation) is the number of mitoses present.
- Ten high power fields (hpf) are examined. If > 10 mitoses are seen, it signifies malignancy. If cellular atypia is also present, ≥ 5 mitoses are enough to make a diagnosis of leiomyosarcoma.

21. Ans. (d) Increased Prolactin
(Ref: Shaw 13th/353, 9/e p1022)

The diagnosis of polycystic ovarian syndrome (PCOS) is straightforward using the **Rotterdam criteria**, even when the syndrome is associated with a wide range of symptoms.

Standard diagnostic assessments

- History-taking, specifically for menstrual pattern, obesity, hirsutism, and the absence of breast discharge. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% CI 62.7-88.0%) and a specificity of 93.8% (95% CI 82.8-98.7%).
- Gynecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In normal menstrual cycle, one egg is released from a dominant follicle - essentially a cyst that bursts to release the egg. After ovulation the follicle remnant is transformed into a progesterone producing corpus luteum, which shrinks and disappears after approximately 12-14 days. In PCOS, there is a so called "follicular arrest", i.e. several follicles develop to a size of 5-7 mm, but not further. No single follicle reach the preovulatory size (16 mm or more). According to the Rotterdam criteria, **12 or more small follicles** should be seen in an ovary on ultrasound examination. The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'. The numerous follicles contribute to the increased size of the ovaries, that is, 1.5 to 3 times larger than normal.
- Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary.
- Serum (blood) levels of androgens (male hormones), including androstenedione, testosterone and dehydroepiandrosterone sulfate may be elevated: free testosterone is more sensitive than total. Free testosterone is reflected as the ratio of testosterone to sex hormone-binding globulin (SHBG).
- Some other blood tests are suggestive but not diagnostic. The ratio of LH (Luteinizing hormone) to FSH (Follicle stimulating hormone) is greater than 1:1, as tested on Day 3 of the menstrual cycle. The pattern is not very specific and was present in less than 50% in one study. There are often low levels of sex hormone binding globulin, particularly among obese women.

22. Ans. (a) Vimentin, epithelial membrane antigen, inhibin, CD99
(Ref. Sternberg Pathology/2581, 2583, 2543, 2579, 2652 Ackerman's Pathology/1694, 1675, 1681, 687)

The specimen in the given question is most likely to be of granulosa cell tumor of ovary:

The features pointing toward this diagnosis are:

- Unilateral tumor
- Solid and cystic areas
- Small cells arranged in sheets
- Nuclear grooving
- Scant cytoplasm

The only point against this diagnosis is absence of Call-Exner bodies, but note that these structures if found are diagnostic of Granulosa cell tumors but these are not prerequisite for diagnosis.

Vimentin, EMA, inhibin and CD99 all are the markers of granulosa cell tumors.

23. Ans. (a) Germ cell tumor

(Ref: Robbins 8th/1047-1049, 9/e p1029, Harrison 17th/606, 604)

- Epithelial tumors of ovary usually occur in old age
- Germ cell tumors of ovary generally occur in younger women. About 75% of these occur in women <30 years old
- Stromal tumors (like Sertoli Leydig tumors and granulosa cell tumors) occur in all ages.
- *Granulosa- theca cell tumors are mostly seen in post-menopausal women.*
  - Robbins/1050
- Sertoli-Leydig cell tumors occur in women of all ages, although the peak incidence is in second and third decade *(Ref: Robbins/1051)*

Thus, we are left with two options: Germ cell tumors and Sertoli Leydig cell tumors. But, if we see the frequency of tumors; germ cell tumors have 15-20% whereas all sex-cord stromal tumors (Sertoli Leydig is one of them) together constitute only 5-10% of ovarian neoplasms
Thus, a 14-year-old girl is most likely to have germ cell tumor.

Important Points about Ovarian Neoplasms

- These may develop from epithelial cells (like serous, mucinous, Brenner tumor, etc), germ cells (like granulose cell tumor, Sertoli-Leydig cell tumors, etc).
- *Most common* ovarian neoplasms are *epithelial tumors*
- *Most common* malignant *ovarian neoplasms are epithelial tumors.*
  Two types of autosomal dominant familial cancers have been identified:
  - *Breast/ovarian cancer syndrome:* Due to mutations in BRCA1 or BRCA2 genes.
  - *Lynch type II syndrome:* Results due to mutations in mismatch repair genes. This is associated with Non-polyposis colorectal cancer, endometrial and ovarian cancer.
- CA-125 is marker of epithelial ovarian cancers
- Dysgerminoma is ovarian counterpart of seminoma and is highly sensitive to radiation therapy

24. Ans. (a) 10% *(Ref: Robbins 8th/1047, 9/e p1029)*

- Germ cell tumors constitutes 15-20% of all ovarian tumors
- Most are benign cystic teratoma, also known as dermoid cyst.
- *Benign teratomas are bilateral in 0-15% of cases* — Robbins 1047

25. Ans. (a) < 1% *(Ref: Robbins 8th/1037, 9/e p1020)*

- Fibroid is the term used for uterine leiomyoma. *Malignant transformation (leiomyosarcoma) within a leiomyoma is extremely rare*
  -- Robbins/1037
- Fibroids are most common tumor in women
- They have characteristic whorled pattern of smooth muscle bundles on cut section as well as histologically
- Differences between leiomyoma and leiomyosarcoma is mainly based on number of mitoses
- If $\geq$10 mitoses per high power field are present or $\geq$ 5 mitoses with nuclear atypia are present, it indicates malignancy

26. Ans. (a) Malignant change

(Ref: Shaw's 13th/341, Robbins 9/e p1020)

Secondary changes (degenerations) in uterine leiomyoma:

- **Atrophy:** It can be:
  - After menopause
  - After delivery

  Tumour becomes firmer and more fibrotic. It is due to diminished blood supply.
- **Calcareous degeneration:** Phosphates and carbonates of lime are deposited in the periphery along the course of the vessels.
  - *'Womb-stones' in graveyard:* In old patients with long-standing myomas.
- **Red (Carneous) degeneration:** It is more common during pregnancy. The myoma becomes tense and tender and causes severe abdominal pain with constitutional upset and fever. The tumour itself assumes a peculiar purple-red color and develops a fishy odour.
  - Although the patient is febrile with moderate leucocytosis and raised ESR, the condition is an aseptic one.
  - It needs to be differentiated from–
    - Appendicitis
    - Twisted ovarian cyst
    - Pyelitis
    - Accidental hemorrhage
- **Sarcomatous change:** It is extremely rare. Incidence is no more than 0.5% of all myomas.
  - Intramural and submucous tumors have a higher potential than sub-serous.
  - It is rare for malignant change to develop in a women under the age of 40.
  - It is highly malignant and spreads through blood.

- **Other complications:**
  - Torsion
  - Inversion
  - Capsular hemorrhage
  - Infection
  - Associated endometrial carcinoma

27. **Ans. (a) Uterus**
(Ref: Robbins 9/e p1018, 8th/1035; 7th/1088)

28. **Ans. (c) Yolk-Sac tumour**
(Ref: Robbins 8th/1049, 9/e p1031)

29. **Ans. (c) Granulosa cell tumour**
(Ref: Robbins 8th/1050, 9/e p1032)

30. **Ans. (c) Both** *(Ref: Robbins 8th/1049, 9/e p1031)*

31. **Ans. (c) Villi present** *(Ref: Robbins 7th/1113, 9/e p1041)*

32. **Ans. (a) Granulosa theca cell tumor**
(Ref: Robbins 9/e p1032, 8th/1050; 7th/1102)

33. **Ans. (b) Rhabdomyosarcoma**
(Ref: Robbins 9/e p1001, 8th/1017)

34. **Ans. (d) Mature teratoma**
(Ref: Robbins 9/e p1029, 8th/1047-1048)
The lesion is a mature teratoma. Teratomas located in the ovary and containing a hair and keratin filled cyst are sometimes called dermoid cysts. They contain cells of a variety of types, often including skin, skin adnexal structures (hair follicles, sweat glands, sebaceous glands), connective tissues, neural tissue, muscle, and thyroid tissue. If immature tissues such as primitive neuroepithelial cells or developing skeletal muscle cells are seen, the lesion is considered potentially malignant and classified as an immature teratoma (option A).

35. **Ans. (c) CA-125** *(Ref: Robbins 9/e p1029, 8th/327)*
- The tumors are serous papillary cystadenocarcinomas of the ovaries. These tumors express CA-125 and are apparently derived from the surface epithelium of the ovaries.
- Bombesin (choice B) is a marker for neuroblastoma, small cell carcinoma, gastric carcinoma, and pancreatic carcinoma.

36. **Ans. (b) Leiomyoma** *(Ref: Robbins 8th/327, 9/e p1020)*

37. **Ans. (c) Schiller duval body** *(Ref: Robbins 9/e p977)*

38. **Ans. (b) Brenner tumour** *(Ref: Robbins 9/e p1028)*
Transitional cell tumors contain neoplastic epithelial cells resembling urothelium and are usually benign. They comprise roughly 10% of ovarian epithelial tumors and are also referred to as Brenner tumors

39. **Ans. (b) Krukenberg tumor** *(Ref: Robbins 9th/1034)*
- A classic metastatic **gastrointestinal carcinoma** involving the ovaries is termed **Krukenberg tumor**, characterized by **bilateral metastases** composed of ***mucin-producing***, **signet-ring cancer cells**, most often of gastric origin.

40. **Ans. (b) Adenocarcinoma** *(Ref: Robbins 9/e p1013)*

41. **Ans. (c) Progresses to malignancy**
(Ref: Robbins 9/e p970)
- Condyloma acuminatum is a **benign *sexually transmitted wart*** caused by human papillomavirus.
- It is related to the common wart and may occur on any moist mucocutaneous surface of the **external genitals** in either sex.
- Cytoplasmic vacuolization of the squamous cells called as **koilocytosis** is characteristic of HPV infection.
- It tends to recur but only rarely progress into in situ or invasive cancers.

42. **Ans. (b) Smoking** *(Ref: Robbins 9/e p1014)*

43. **Ans. (d) Serous cystadenoma** *(Ref: Robbins 9/e p1024)*

44. **Ans. (c) Intraductal papilloma**
(Ref: Pathology and Genetics of tumours of breast and female genital organs/81, Robbin 9/e p1044)
Successive branching of the large ducts eventually leads to the terminal duct lobular unit (TDLU).
- All breast cancers whether ductal or lobular originate from terminal duct lobular unit (TDLU).
- Most of the benign breast diseases also originate from TDLU except intraductal papilloma, 90% of which occurs in large ducts in the central portion of breast.

45. **Ans. (c) Papillary carcinoma breast**
(Ref: Rossen Breast Pathology 390)
Dimorphic papillary carcinoma is a term that has been used to refer to papillary carcinomas that have 2 types of neoplastic cells, with a second population of cells showing pale cytoplasm. So, morphologically the cells appear to have diverse origins but expression of immunohistochemical markers is useful for confirming the diagnosis.

46. **Ans. (d) Comedo DCIS** *(Ref: Robbins 9/e p1057)*
- **DCIS most frequently presents as mammographic calcifications. Less typically DCIS may present as a vaguely palpable mass. This is most likely with Comedocarcinomas.**
- **Most of the breast malignancies are adenocarcinomas. These can be** *divided into insitu carcinomas and invasive carcinomas.*
- **Carcinoma in situ** refers to a neoplastic population of cells limited to ducts and lobules by the basement membrane. It does not invade into lymphatics and blood vessels and cannot metastasize.
- **Invasive carcinoma** (synonymous with "infiltrating" carcinoma) has invaded beyond the basement membrane into stroma. Here, the cells might also invade into the vasculature and thereby reach regional lymph nodes and distant sites. Even the smallest invasive breast carcinomas have some capacity to metastasize.
- All carcinomas are thought to arise from the terminal duct lobular unit, and the terms "ductal" and "lobular" do not imply a site or cell type of origin.

47. Ans. (c) Chromosome 17

(Ref: Harrison 17th/563, Robbin 9/e p1054)

- Tumor-suppressor gene, *BRCA-1*, has been identified at the chromosomal locus 17q21; this gene encodes a zinc finger protein, and the product therefore may function as a transcription factor. The gene appears to be involved in gene repair.
- *BRCA-2*, which has been localized to chromosome 13q12, is also associated with an increased incidence of breast cancer in men and women.

48. Ans. (a) p53

(Ref: Robbins 7th/286, 300, 302, 8th/290-291, 9/e p1054, Harrison 16th/516, 517; 17th/563)

Breast cancer can be either familial (associated with germline mutation) or sporadic (associated with somatic mutation).

The **familial breast cancer** is caused due to mutation in the following 4 genes:

- **p53** tumor suppressor gene (called Li Fraumeni syndrome having multiple malignancies like breast cancer, osteogenic sarcoma etc.)
- **PTEN gene**: Gene on chromosome 10q associated with epithelial cancers of breast, endometrium and thyroid.
- **BRCA1 gene**: Located on 17q: females having mutant gene have increased incidence of breast and ovarian cancer whereas males having mutant gene have high incidence of breast and prostate cancer.
- **BRCA2 gene**: Located on chromosome 13q is associated with increased incidence of breast cancer in men and women.

Sporadic breast cancer is associated with mutation in *p53 gene* (p53 defect is present in 40% of human breast cancer as an acquired defect) and *PTEN gene*.

Since, incidence of sporadic cancer is much more than familial cancer, so the most important gene mutation increasing susceptibility to breast cancer should be answered as p53.

49. Ans. (b) BRCA2 *(Ref: Harrison 17th/604, 9/e p1054)*

In women with hereditary breast/ovarian cancer, there can be two susceptibility loci:

- *BRCA1* located on chromosome 17q12-21, and
- *BRCA2* located on 13q12-13.

Both these are tumor-suppressor genes which produce nuclear proteins that interact with RAD 51 affecting genomic integrity.

The cumulative risk of ovarian cancer with critical mutations of *BRCA1* or - *BRCA2* is 25%. Men in such families have an increased risk of prostate cancer.

50. Ans. (c) Lobular Ca *(Ref: Robbins 9/e p1065)*

- Lobular carcinoma (invasive) of breast is one of the very few carcinomas which are seen bilaterally.
- Lobular carcinoma in situ in 20-40% cases is bilateral.
- Histologic hallmark is pattern of single infiltrating tumor cells often only one cell in width or in loose clusters or sheets.
- Signet ring cells common.
- Metastasize frequently to peritoneum, retroperitoneum, leptomeninges, GIT and ovaries.
- The incidence of this carcinoma is increasing among postmenopausal females presumably because of increasing use of HRT.

51. Ans. (c) Inflammatory carcinoma

(Ref: Robbins 8th/1083)

52. Ans. (d) CA 15-3

(Ref: Robbins 7th/339, 9/e p337, Anderson pathology 144-152)

53. Ans. (b) Infiltration of the epidermis by malignant cells

(Ref: Robbins 7th/1140, 9/e p1057)

54. Ans. (a) 17 *(Ref: Robbins 8th/275-276, 9/e p1054)*

55. Ans. (d) Ductal carcinoma *(Ref: Robbins 9/e p1057)*

56. Ans. (c) Invasive lobular carcinoma

(Ref: Robbins 8th/1082; 7th/1142, 9/e p1059)

57. Ans. (d) Lobular carcinoma

(Ref: Harsh Mohan 6th/762-763)

58. Ans. (b) Peau 'd orange

(Ref: Robbins 9/e p1067, 8th/1083; 7th/122,1140,1142)

59. Ans. (c) Dermal lymphatic invasion by cancer cells

(Ref: Robbins 8th/1089, 9/e p1067)

- Inflammatory breast cancer is a pattern of invasive breast cancer in which the neoplastic cells infiltrate widely through the breast tissue. The cancer involves dermal lymphatics and therefore has a high incidence of systemic metastasis and a poor prognosis. If the lymphatics become blocked, then the area of skin may develop lymphedema and "peau d'orange," or orange peel appearance. The overlying skin in inflammatory breast cancer is usually swollen, red, and tender.
- Acute inflammation (option A) is associated with secondary infection or abscess whereas chronic inflammation in breast cancer (option B) is a non-specific finding. In medullary breast cancer, a type of invasive ductal carcinoma, there are a large number of lymphocytes around the tumor and a desmoplastic reaction is often absent in the surrounding tissue.
- Epidermal invasion by cancer cells (option D) is a poor prognostic indicator. Intraepidermal malignant cells are called Paget cells. Paget's disease of the nipple is a type of ductal carcinoma that arises in large ducts and spreads intraepidermally to the skin of the nipple and areola. There is usually an underlying ductal carcinoma.

60. Ans. (a) 17 *(Ref: Robbins 8/e p275-276, 9/e p1054)*

61. Ans. (c) Neoplasia *(Ref: Robbins 9/e p1057)*

Paget disease of the nipple is a rare manifestation of breast cancer (1% to 4% of cases) that presents as a unilateral erythematous eruption with a scale crust. Pruritus is common, and the lesion may be mistaken for eczema.

62. Ans. (a) Gene expression profiling

(Ref: Robbins 9th/1061)

Invasive carcinomas can be divided based on molecular and morphologic characteristics into several clinically important subgroups. Breast carcinomas have a wide variety of morphologic appearances. One third can be classified morphologically into special histologic types, some of which are strongly associated with clinically relevant biologic characteristics. The remainder are grouped together and called "ductal" or no special type (NST).

> Recent detailed description of ***genomic alterations and gene and protein expression*** in large cohorts of breast cancers has provided a framework for a **molecular classification** for this group of breast cancers.....*Robbins 9th/ 1060*

Gene expression profiling measures relative levels of mRNA expression...*figure 23.20 Robbins*

63. Ans. (a) Overexpression *(Ref: Robbins 9/e p284)*

HER-2/neu gene is a proto-oncogene whose **amplification/overexpression** cause breast carcinoma.

64. Ans. (a) Medullary *(Ref: Robbins 9/e 1055)*

BRCA1-associated breast cancers are commonly poorly differentiated, have "medullary features" (a syncytial growth pattern with pushing margins and a lymphocytic response).

65. Ans. (b) Epithelial membrane antigen

(Ref: Robbins 9/e 1067)

66. Ans. (d) Single file pattern *(Ref: Robbins 9/e 1065)*

The histologic hallmark is the presence of discohesive infiltrating tumor cells, often including signet-ring cells containing intracytoplasmic mucin droplets. This is called as single file pattern.

EXPLANATIONS TO CONCEPTUAL QUESTIONS

Explanations(1-3): ***While solving assertion reason type of questions, we can use a particular method.***

1. First of all, read both assertion (A) and reason (R) carefully and independently analyse whether they are true or false.
2. If A is false, the answere will directly be (d) i.e. both A and R are false. You can note that all other options (i.e. a, b or c) consider A to be true.
3. If A is true, answer can be (a), (b) or (c), Now look at R. If R is false, answer will be (c)
4. If both A and R are ture, then we have to know whether R is correctly explaining A [answer is (a)] or it is not the explanation of assertion [answer is (b)]

1. Ans. (c) Assertion is true and reason is false.

(Ref: Robbins 8th/995, 9/e p983)

Stromal cells are responsible for androgen dependent prostatic growth. The main hormone responsible for androgen dependent prostatic growth is **dihydrotestosterone** (and not testosterone) because stromal cells have type 2 5α reductase enzyme which converts testosterone into dihydrotestosterone. DHT is more potent than testosterone because it binds more strongly to the androgen receptor.

> - **FGF-7**[Q] (fibroblast growth factor-7) is the most important factor mediating **paracrine** regulation of androgen dependent growth.
> - **Type 1** [Q] 5α **reductase** enzyme is minimally present in prostate and is mainly located mainly in **liver and skin**[Q].

2. Ans. (c) Assertion is true and reason is false.

(Ref: Robbins 8th/1048, 9/e p1030)

Struma ovarii is mature teratoma which is composed of **functioning thyroid tissue**. It is therefore responsible for production of the **thyroid hormones** (and not gonadotropins).

3. Ans. (b) Both assertion and reason are true and reason is not the correct explanation of assertion.

(Ref: Robbins 8th/988-9, 9/e p976)

Seminoma is a germ cell tumor with a good prognosis because it is an extremely radiosensitive and chemosensitive tumor. These tumors histologically have necrosis and hemorrhage only rarely.

Features	Seminoma	Non –seminoma
Localization	Localized to testes for long time	Metastasize early
Stage	70% patients present in stage I	60% in stage II and III
Metastasis	Mainly lymph node: hematogenous spread later	Hematogenous spread more frequent
Necrosis and hemorrhage	Rare	Common
Radiation sensitivity	Radiosensitive	Radioresistant
General behavior	Less aggressive	More aggressive
Prognosis	Good	Bad

CHAPTER 16

Central Nervous System

Golden Points

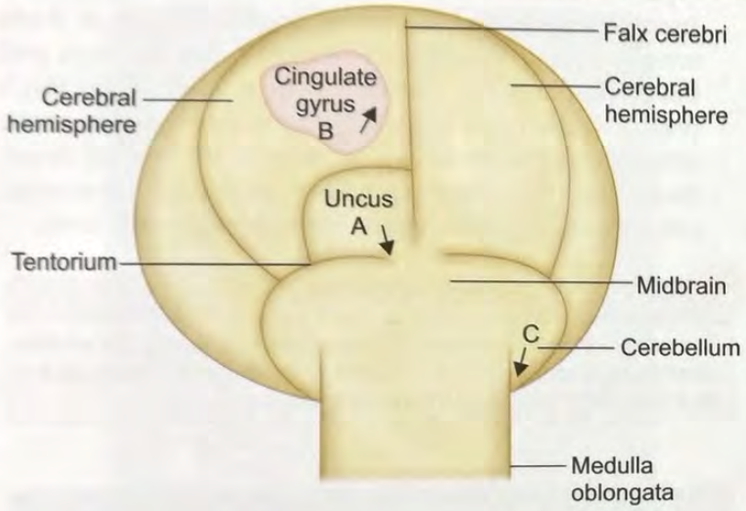
- Functions of different cells in the brain include Gitter cells or microglia (phagocytic cells), neuroglia or astrocytes (tissue repair in brain) and oligodendrocytes (myelination).
- Maximum decrease in CSF chloride: TB meningitis.
- Vasculitis is typically absent in HIV encephalitis.
- Rabies encephalitis is characterized by Brainstem encephalitis and histologicaly by intra-neuronal Negri bodies.
- Key words with Alzheimer disease: Meyernet nucleus involvement, cortical atrophy, neuritic (senile) plaque, neurofibrillary tangles, amyloid angiopathy and Hirano bodies. Grossly, there is atrophy of parietal and temporal lobe.
- Hydrocephalus ex vacuo is seen in: Alzheimer disease, Pick disease.
- Most common cause of intracerebral (intraparenchymal) hemorrhage: Hypertension.
- Most common cause of subarachnoid hemorrhage: Trauma (most common) followed by Berry aneurysm
- Most common cause of subdural hematoma: Traumatic rupture of bridging veins
- Most common cause of epidural hematoma: Injury to middle meningeal artery.
- Dandy Walker syndrome can be differentiated from Aqueductal stenosis by: Posterior fossa volume.
- Ash leaf macules are characteristic of: Boumeville's disease (tuberous sclerosis).
- Tectal breaking is seen in: Arnold chiary malformation.
- Most common nerve from which schwannomas arise is 8th cranial nerve whereas commonest nerve from which schwannomas arise in neck is 10th cranial nerve (vagus).
- Brain tumor arising from arachnoid villi: Meningioma.
- Medulloblastoma (arising mostly from cerebellum) commonly metastatizes to other parts of brain and spine (via CSF).
- Spongiform degeneration of cerebral cortex is characteristic: Creutzfeldt Jakob disease.
- Intranuclear inculsions of oligodendrocytes are seen in: Progressive multifocal leukoencephalopathy.
- Onion bulb appearance on nerve biopsy is seen in: Chronic inflammatory demyelinating polyneuropathy (CIDP).

CEREBRAL HERNIATION

The cranial cavity is separated into compartments by infoldings of the dura. The two cerebral hemispheres are separated by the falx, and the anterior and posterior fossae by the tentorium. Herniation refers to displacement of brain tissue into a compartment that it normally does not occupy. These are of three main types: transtentorial, transfalcine (subfalcine) and tonsillar (foraminal).

Key Point

The **most common** herniations are **Transtentorial herniation**.



Transtentorial Herniation

The most common herniations are from the supratentorial to the infratentorial compartments through the tentorial opening, hence *transtentorial*. These may be divided into temporal (Uncal) or central herniations.

- **Uncal transtentorial herniation** refers to impaction of the anterior medial temporal gyrus (the uncus) into the tentorial opening just anterior to and adjacent to the midbrain. The displaced brain tissue compresses the third nerve and results in ***mydriasis and ophthalmoplegia (pupil point down and out) of the ipsilateral pupil.***
- **Central transtentorial herniation** denotes a symmetric downward movement of the thalamic medial structures through the tentorial opening with compression of the upper midbrain. Miotic pupils and drowsiness are the heralding signs.

Recent Exam Question

Uncal transtentorial herniation: *compression of IIIrd cranial nerve; eye deviated down and out; mydriasis.*

Transfalcine Herniations

These are caused by herniation of the medial aspect of the cerebral hemisphere (cingulate gyrus) under the falx, which may compress the anterior cerebral artery.

Concept

Tonsillar herniation may also occur if a lumbar puncture is performed in a patient with increased intracranial pressure. Therefore, **before** *performing a lumbar puncture,* the patient should be *checked for the presence of* ***papilledema.***

Tonsillar Herniation

Masses in the cerebellum may cause tonsillar herniation, in which the cerebellar tonsils are herniated into the foramen magnum. This may compress the medulla and respiratory centers, causing death.

DEVELOPMENTAL ABNORMALITIES OF THE BRAIN

Developmental abnormalities of the brain include the **Arnold-Chiari malformation**, the **Dandy-Walker malformation**, and the **Phakomatoses**, which include tuberous sclerosis, neurofibromatosis, von Hippel-Lindau disease, and Sturge-Weber syndrome.

Mnemonic

Dandy	**D**ilated 4th ventricle
Walker	**W**ater on the brain (hydrocephalus)
Syndrome	**S**mall or absent vermis

- **Dandy-Walker malformation** has severe hypoplasia or absence of the cerebellar vermis. There is cystic distention of the roof of the fourth ventricle, hydrocephalus, and possibly agenesis of the corpus callosum.

Recent Exam Question

Triad of tuberous sclerosis: Seizures+mental retardation+ congenital white spots or macules (leukoderma).

- **Arnold-Chiari malformation** consists of herniation of the cerebellum and fourth ventricle into the foramen magnum, flattening of the base of the skull, and spina bifida with meningomyelocele. Newborns with this disorder are at risk of developing hydrocephalus within the first few days of delivery secondary to stenosis of the cerebral aqueduct.
- **Tuberous sclerosis** may show characteristic firm, white nodules (tubers) in the cortex and subependymal nodules of gliosis protruding into the ventricles (**"candle drippings"**) Facial angiofibromas (*adenoma sebaceum*) may also occur.
- **von Hippel-Lindau** disease shows multiple benign and malignant neoplasms including hemangioblastomas of the retina, cerebellum, and medulla oblongata; angiomas of the kidney and liver; and renal cell carcinomas.
- **Sturge-Weber syndrome** is a non-familial congenital disorder, display angiomas of the brain, leptomeninges, and ipsilateral face, which are called port-wine stains (nevus flammeus).

- **Syringomyelia**: Bilateral loss of pain and temperature sensations in both arms is most likely to be caused by syringomyelia, which is a chronic myelopathy that results from formation of a cavity (syrinx) involving the central gray matter of the spinal cord. This is the location where pain fibers cross to join the contralateral spinothalamic tract. Interruption of the lateral spinothalamic tracts results in segmental sensory dissociation with loss of pain and temperature sense, but preservation of the sense of touch and pressure or vibration, usually over the neck, shoulders, and arms. Other features of syringomyelia include wasting of the small intrinsic hand muscles (claw hand) and thoracic scoliosis. The cause of syringomyelia is unknown, although one type is associated with a Chiari malformation with obstruction at the foramen magnum.

Key Point

The most common location of a syrinx is the **cervical region** and so, the loss of pain and temperature sensation **affects both arms**.

NEURAL TUBE DEFECTS

These are caused by defective closure of the neural tube. These defects may occur anywhere along the extent of the neural tube and are classified as either caudal or cranial defects. Failure of development of the cranial end of the neural tube results in anencephaly, while failure of development of the caudal end of the neural tube results in spina bifida.

- Anencephaly, which is not compatible with life, is characterized by the absence of the forebrain. Instead, there is a mass of disorganized glial tissue with vessels in this area called a cerebrovasculosa. Ultrasound examination will reveal an abnormal shape to the head of the fetus with an absence of the skull.

Concept

Neural tube defects are associated with **increased** maternal serum levels of **α-fetoprotein (AFP)**, which is a glycoprotein synthesized by the yolk sac and the fetal liver. Increased serum levels are also associated with yolk sac tumors of the testes and liver cell carcinomas (note that **decreased AFP is associated with Down syndrome**).

- Spina bifida can be spina bifida occulta which results due to failure of closure of vertebral arches posteriorly. It is a mild disorder with normal meninges and spinal cord. If meninges also herniate out, it is known as meningocele whereas protruding out of both meninges as well as spinal cord is called meningomyelocele.

Key Point

Maternal folate level must be adequate **BEFORE** pregnancy to decrease the risk of neural tube defects.

- Neural tube defects are associated with maternal obesity and decreased folate during pregnancy (folate supplementation in diet decreases the incidence of these development defects).

CEREBRAL HEMORRHAGE

It can be epidural, subarachnoid, subdural and intraparenchymal.

- **Epidural hemorrhage**: It results from hemorrhages into the potential space between the dura and the bone of the skull. These hemorrhages result from severe trauma that typically causes a skull fracture. The hemorrhage results from rupture of one of the meningeal arteries, as these arteries supply the dura and run between the dura and the skull. Since the bleeding is of arterial origin (high pressure), it is rapid and the symptoms are rapid in onset, although the patient may be normal for several hours (lucid interval). Bleeding causes increased intracranial pressure and can lead to tentorial herniation and death.

Key Point

The artery involved in **epidural hemorrhage** is usually the **middle meningeal artery,** which is a branch of the maxillary artery, as the skull fracture is usually in the **temporal area**.

Recent Exam Question

Excluding trauma, *Berry aneurysm is the commonest cause of subarachnoid hemorrhage.*

- **Subarachnoid hemorrhage:** It is much less common than hypertensive intracerebral hemorrhage. It most often results from the rupture of a berry aneurysm. These aneurysms are Saccular aneurysms that result from congenital defects in the media of arteries. They are typically located at the bifurcations of arteries. They are not the result of atherosclerosis. Instead, berry aneurysms are called congenital, although the aneurysm itself is not present at birth. The chance of rupture of berry aneurysms increases with age (rupture is rare in childhood). Rupture causes marked bleeding into the subarachnoid space and produces severe headaches, typically described as the "worst headache ever". Additional symptoms include vomiting, pain and stiffness of the neck (due to meningeal irritation caused by the blood), and papilledema. Death may follow rapidly.

Key Point

Berry aneurysms are most commonly found in the **circle of Willis,** typically either at the junction of the anterior communicating artery with the anterior cerebral artery or at the junction of the middle cerebral artery and the posterior communicating artery.

- **Subdural hemorrhage:** The space beneath the inner surface of the dura mater and the outer arachnoid layer of the leptomeninges is also a potential space.

Recent Exam Question

Subdural hemorrhage most commonly occurs due to **rupture of bridging veins.**

CEREBRAL ISCHEMIA

Decreased brain perfusion may be generalized (global) or localized.

Global ischemia results from generalized decreased blood flow, such as with shock, cardiac arrest, or hypoxic episodes (e.g. near drowning or carbon monoxide poisoning).

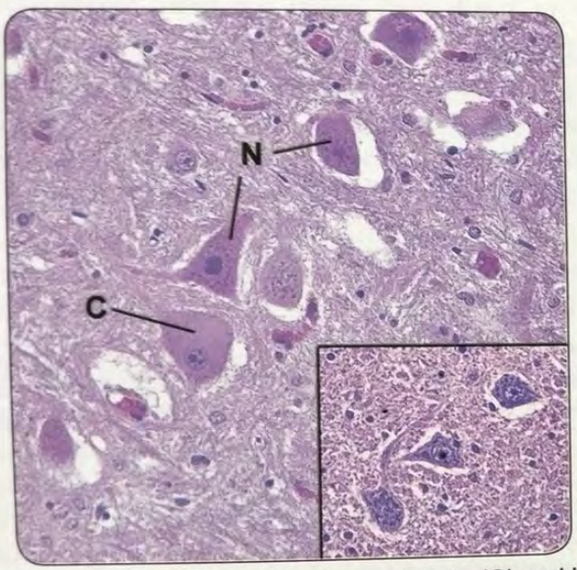


Fig. 1: Neuronal injury showing chromatolysis (C) and injured eosinophilic neurons (N)

- The gross changes produced by global hypoxia include watershed (border zone) infarcts, which typically occur at the border of areas supplied by the anterior and middle cerebral arteries, and laminar necrosis, which is related to the short, penetrating vessels originating from pial arteries.

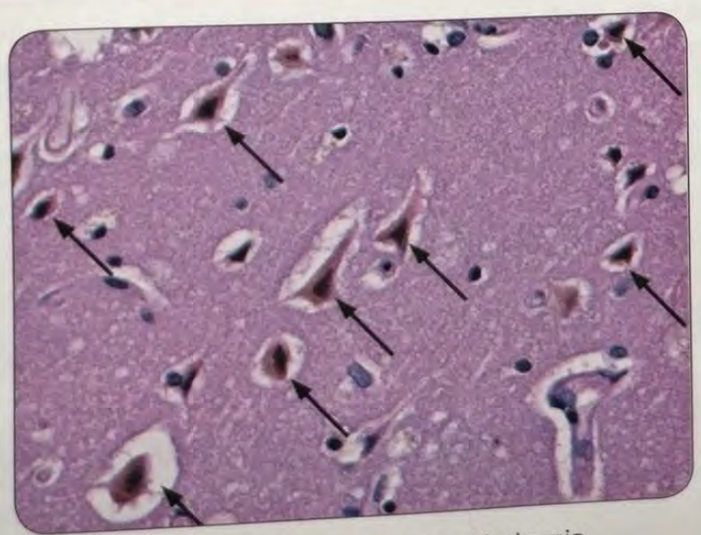


Fig. 2: Red neurons on global ischemia

- The microscopic changes produced by global hypoxia are grouped into three categories. The earliest histologic changes, occurring in the first 24 h, include the formation of *red neurons (acute neuronal injury)*, characterized by eosinophilia of the cytoplasm of the neurons, and followed in time by pyknosis and karyorrhexis. Subacute changes occur at 24 h to 2 weeks. These include tissue necrosis, vascular proliferation, and reactive gliosis.

Key Point

The **Purkinje cells of the cerebellum** and the **pyramidal neurons of Sommer's sector in the hippocampus** are particularly sensitive to ischemic damage.

INTRACRANIAL ANEURYSMS

- **Charcot-Bouchard aneurysms**: It results from weakening of the wall of cerebral artery by lipohyalinosis (deposition of lipids and hyaline material) caused by hypertension. Hypertensive hemorrhage shows a *predilection for the distribution of the lenticulostriate arteries (branch of middle cerebral artery)* with small (lacunar) hemorrhages, or large hemorrhages obliterating the corpus striatum, including the putamen and internal capsule. Hypertensive hemorrhages also commonly occur in cerebellum and pons and are often fatal.
- **Berry aneurysms** (small saccular aneurysms) are the result of congenital defects in the **media of blood vessels** and are located at the bifurcations of arteries.
- **Atherosclerotic aneurysms** are fusiform (spindle-shaped) aneurysms usually located in the major cerebral vessels. They rarely rupture, but may become thrombosed.
- **Mycotic (septic) aneurysms** result from septic emboli, most commonly from subacute bacterial endocarditis.

CNS INFECTIONS

- Meningoencephalitis caused by HIV (human immunodeficiency virus) is characterized by microglial nodules within the brain that are composed of mononuclear cells, microglia, and scattered multinucleated giant cells.
- Herpes simplex virus produces characteristic Cowdry type A intranuclear inclusions in neurons and glial cells.
- Rabies form characteristic inclusions within neurons called Negri bodies. Rabies, caused by a single-stranded RNA rhabdovirus, is transmitted by the bite of a rabid animal, usually a dog, and travels to the brain via peripheral nerves. Symptoms caused by destruction of neurons in the brainstem include irritability, difficulty in swallowing and spasms of the throat (these two resulting in "hydrophobia"), seizures, and delirium. The illness is almost uniformly fatal.
- Enlarged cells (cytomegaly) with intranuclear and intracytoplasmic inclusions are seen with cytomegalovirus infection.

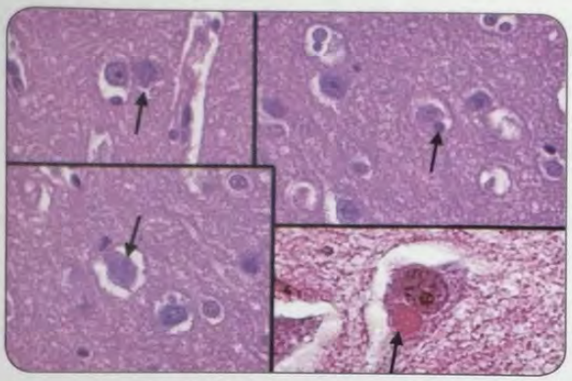


Fig. 3: Negri body in rabies

Progressive multifocal leukoencephalopathy (PML): It is a demyelinating disease of the central nervous system that results from infection of oligodendrocytes by the **JC polyomavirus**. Signs and symptoms of PML are varied but include dementia and ataxia along with abnormal vision and speech. PML occurs as a terminal complication in immunosuppressed individuals, especially individuals with AIDS.

Key Point

The pathognomonic feature of **PML** is the **oligodendrocytes** in areas of demyelination, which have a **"ground-glass"** appearance of their nuclei due to infection with the viral particles.

Neurosyphilis: Neurosyphilis, a tertiary stage of syphilis, includes syphilitic meningitis, paretic neurosyphilis, and tabes dorsalis.

- Syphilitic meningitis is characterized by perivascular infiltrates of lymphocytes and plasma cells that cause obliterative endarteritis and meningeal fibrosis.
- *Tabes dorsalis* is the result of degeneration of the posterior columns of the spinal cord. This is caused by compression atrophy of the posterior spinal sensory nerves, which produces impaired joint position sensation, ataxia, loss of pain sensation (leading to joint damage, i.e. *Charcot joints*), and *Argyll Robertson pupils* (pupils that react to accommodation but not to light).

Mnemonic

DORSALIS
D Dorsal column degeneration
O Orthopedic pain (Charcot joints)
R Reflexes decreased (deep tendon)
S Shooting pain
A Argyll-Robertson pupils
L Locomotor ataxia
I Impaired proprioception
S Syphilis

Prion diseases: The spongiform encephalopathies include Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), fatal familial insomnia, and kuru. Microscopically, there is characteristic spongiform change in the gray matter ("cluster of grapes" vacuolation) without inflammation.

All of the spongiform encephalopathies are associated with abnormal forms of a prion protein (PrP). Disease results from alternate folding of the normal α-helix (called PrP^{c}) to an abnormal β-pleated sheet form (called PrP^{sc}). This conformational change can occur spontaneously at a very slow rate. Once formed, however, PrP^{sc} can combine with PrP^{c} to much more quickly form many more PrP^{sc} particles, which can "crystallize" and form plaques. PrP^{c} can also form PrP^{sc} at much higher rates if mutations are present in PrP^{c}, which can result from mutations in the gene that codes for PrP^{c} called PRNP. Mutations in this gene have been identified in patients with the familial forms of CJD, GSS, and fatal familial insomnia.

Note: *SOD1 mutations are seen with amyotrophic lateral sclerosis (ALS), FGFR3 mutations with achondroplasia, UBE3A mutations with Angelman's syndrome, and PTEN mutations with endometrial and prostate cancers.*

CSF Findings in CNS Infections

Parameters	Normal values	Bacterial meningitis	Tuberculous meningitis	Viral meningitis
Pressure	50-180 mm water	Raised	Raised	Raised
Gross appearance	Clear and colorless	Turbid	Clear (may clot)	Clear
Protein	20 – 50 mg/dL	High	Very High	Slightly high
Glucose	40-70 mg/dL	Very low	Low	Normal
Chloride	116 – 122 µg/dL	Low	Very low	Normal
Cells	< 5/microlitre	Neutrophils	Pleocytosis	Lymphocytosis

Meningitis [inflammation of the arachnoid and the cerebrospinal fluid (CSF)] may be classified as acute pyogenic, aseptic, or chronic. The etiology and CSF findings vary in these three groups.

Key Point

- In **bacterial meningitis**, majority of organisms originate in **nasopharynx** whereas
- ***Viral meningitis*** is most often transmitted by ***fecal-oral route***.

- The CSF in acute pyogenic meningitis, which is usually caused by bacteria, is grossly cloudy (not bloody, which is suggestive of a subarachnoid hemorrhage) and displays increased pressure, increased neurophils, increased protein, and decreased glucose.
- With chronic meningitis, such as that caused by *Mycobacterium tuberculosis*, the CSF is clear grossly, with only a slight increase in leukocytes (either mononuclear cells or a mixed infiltrate), a markedly increased protein level, increased pressure, and moderately decreased or normal amounts of sugar.
- **Brain abscesses and subdural empyemas,** which are parameningeal infections rather than direct meningeal infections, cause increased CSF pressure (more marked with abscess because of mass effect) along with increased inflammatory cells (lymphocytes and polymorphonuclear cells) and increased protein but a normal glucose level. The *CSF is clear.*
- Encephalitis, also not a direct infection of the meninges, results in clear CSF, increased pressure, increased protein, normal glucose, and possibly increased lymphocytes.

Key Point

Meningitis
↑ CSF protein (viral, bacterial, fungal)
↓ CSF glucose (bacterial, fungal)

DEMYELINATING DISORDERS

Multiple Sclerosis

In primary CNS demyelination there is loss of myelin sheaths with relative preservation of axons. Primary demyelination is seen predominately in multiple sclerosis, in the perivenous encephalomyelopathies, and in progressive multifocal leukoencephalopathy (PML). Multiple sclerosis (MS), a disease of unknown etiology, causes disseminated but focal plaques of primary demyelination anywhere in the CNS, but often in the white matter near the angles of the lateral ventricles. It primarily affects young adults between 20 and 40 years of age, with the onset of symptoms such as abnormalities of vision, tremors, paresthesias, and incoordination. The course is typically remitting and relapsing. Early findings include weakness of the lower extremities and visual abnormalities with retrobulbar pain.

Key Point

Multiple sclerosis is the most common demyelinating disease.

Apart from the Charcot triad, another pathognomonic feature in MS is **internuclear ophthalmoplegia** (INO), also known as the **MLF syndrome**, which results from demyelination of the *medial longitudinal fasciculus*. It results in medial rectus palsy in attempted lateral gaze and monocular nystagmus in abducting eye with convergence.

Examination of the CSF in patients with MS reveals increased T lymphocytes, increased protein, and normal glucose. *Protein electrophoresis of the CSF reveals oligoclonal bands* (individual monoclonal spikes), although this latter finding is not specific for MS.

Key Point

The **classic (Charcot) triad** in patients with MS consists of **scanning speech, intension tremor,** and **Nystagmus** (***mnemonic is SIN***).

Neuromyelitis Optica (also known as Devic disease)

It is characterized by the development of synchronous bilateral optic neuritis and spinal cord demyelination.

DEGENERATIVE DISORDERS

The degenerative diseases of the CNS are diseases that affect the gray matter and are characterized by the progressive loss of neurons in specific areas of the brain.

Alzheimer's Disease

Alzheimer's disease (AD) is the **most common cause** of dementia in elderly (followed by vascular multi-infact dementia and diffuse Lewy body disease). AD often begins insidiously with impairment of memory and progresses to dementia. Histologically, AD is characterized by numerous neurofibrillary tangles and senile plaques with a central core of amyloid alpha-protein. Both tangles and plaques are found to a lesser extent in other conditions, for example, neurofibrillary tangles in Down syndrome. Silver stains demonstrate tangles and plaques and Congo red shows amyloid deposition in plaques and vascular walls (**amyloid angiopathy**). In AD there are also numerous **Hirano bodies,** and granulovacuolar degeneration is found in more than 10% of the neurons of the hippocampus. Grossly, brain atrophy (narrowed gyri and widened sulci) is predominant in the frontal and superior temporal lobes.

Key Point

AD: ↑ density of **NF tangles** and senile (neuritic) plaques in the brain.
NF tangles: hyperphosphorylated **tau protein** in neuron.

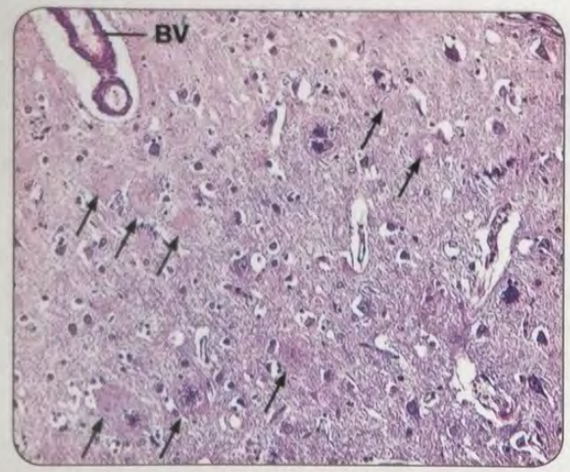


Fig. 4: Alzheimer disease, senile plaques

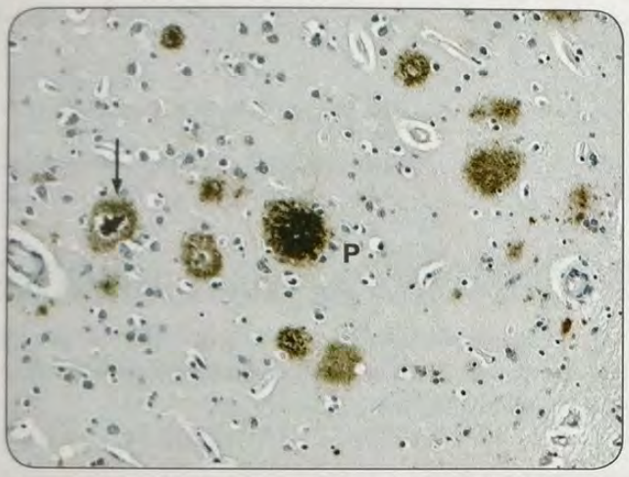


Fig. 5: Alzheimer disease, Tau protein

The etiology of AD is not well understood, but it is clear that there are multiple etiologic pathways to this disease state. Alzheimer's disease has been linked to abnormalities involving four specific genes. Cleavage of the beta-amyloid precursor protein (beta-APP) by alpha-secretase precludes beta-A formation; but cleavage of beta-APP by beta-secretase (BACE-1) or gamma-secretase produces fragments that tend to aggregate into the pathogenic amyloid fibrils. Beta-amyloid deposition is necessary but not sufficient for the development of Alzheimer's disease. Early-onset familial Alzheimer's is also related to **mutations in presenilins**. The presenilin 1 (PS1) gene is located on *chromosome 14*, while the presenilin 2 **(PS2) gene** is located on *chromosome 1*.

Key Point

Age is the main risk factor for AD

Concept

The gene for beta-amyloid (A-beta) is located on chromosome 21 and so, the high incidence of Alzheimer's disease is seen in individuals with **trisomy 21 (Down Syndrome).**

Parkinson's Disease

It is characterized by a mask-like facial expression, coarse tremors, slowness of voluntary movements, and muscular rigidity, there is degeneration and loss of pigmented cells in the substantia nigra, resulting in a decrease in dopamine synthesis. The decreased synthesis of dopamine by neurons originating in the substantia nigra leads to decreased amounts and functioning of dopamine in the striatum. This results in decreased dopamine inhibition and a relative increase in acetylcholine function, which is excitatory in the straitum. The effect of this excitation, however, is to increase the functioning of GABA neurons, which are inhibitory. The result, therefore, is increased inhibition or decreased movement. The severity of the motor syndrome correlates with the degree of dopamine deficiency.

Recent Exam Questions

- **Idiopathic Parkinson's disease** is the *most common cause of parkinsonism.*
- **Lewy bodies** (eosinophilic intracytoplasmic inclusions) are found in the surviving neurons of the **substantia nigra** in **PD**.

Lewy Body Disorders

Lewy bodies are intracytoplasmic eosinophilic inclusions that are composed of fine filaments, which are densely packed in the core but loose at their rim. These filaments are composed of neurofilament antigens, parkin, and ubiquitin, but the major component of the Lewy body is alpha-synuclein. The histologic presence of Lewy bodies can be seen in several disorders (Lewy body disorders) that differ in the location where the Lewy bodies are found.

- In **classic Parkinson's disease**, Lewy bodies are found in the ***nigrostriatal system*** (producing extrapyramidal movement disorder).
- In **Lewy body dementia**, Lewy bodies are found in the ***cerebral cortex*** (producing dementia; this is the third most common cause of dementia).
- In **Shy-Dragger syndrome**, Lewy bodies are found in ***sympathetic neurons in the spinal cord*** (causing *autonomic dysfunction*, including orthostatic hypotension, impotence, abnormal sweat and salivary gland secretion, and pupillary abnormalities).

Concept

Unlike Parkinson's disease, how-ever, no mutations in the gene that codes for alpha-synuclein have been found with the Shy-Drager syndrome.

Huntington's Disease: (HD)

It is characterized by choreiform movements and progressive dementia that appear after the age of 30. It is an **autosomal dominant** disorder that results from an abnormal gene (showing CAG repeats) on **chromosome**-4. Choreiform

movements and progressive dementia appear after the age of 30. There is degeneration of *GABA neurons* in the striatum, which leads to decreased function (decreased inhibition) and increased movement.

Note: Huntington's disease is one of four diseases that are characterized by long repeating sequences of three nucleotides (the other diseases being fragile X syndrome, myotonic dystrophy, and spinal and bulbar muscular atrophy).

Key Point

HD involves the extrapyramidal system and atrophy of the **caudate nuclei and putamen.**

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as **Lou Gehrig's disease**, is a degenerative disorder of motor neurons, principally the anterior horn cells of the spinal cord, the motor nuclei of the brainstem, and the upper motor neurons of the cerebral cortex. Clinically, this disease is a combination of lower motor neuron (LMN) disease with weakness and fasciculations and upper motor neuron (UMN) disease with spasticity and hyperreflexia. Early symptoms include weakness and cramping and then muscle atrophy and fasciculations. Reflexes are hyperactive in upper and lower extremities, and a positive extensor plantar (Babinski) reflex develops because of the loss of upper motor neurons. The clinical course is rapid, and death may result from respiratory complications.

Recent Exam Questions

- The **triad** of *atrophic weakness of hands and forearms, slight spasticity of the legs, and generalized hyperreflexia—**in the absence of sensory changes*** suggests the diagnosis of ALS.
- **Riluzole** *(NMDA antagonist)* and **baclofen** are used for the treatment of ALS.

TUMORS

CNS tumors can be gliomas, neuronal tumors, poorly differentiated neoplasms, meningiomas and metastatic tumors.

Key Point

Metastatic tumors are most common intra—cranial tumors.

1. Gliomas: These are most common group of primary brain tumors. These include astrocytoma, oligodendroglioma and ependymoma.
   a. **Astrocytoma**
   It is the **most common primary brain tumors in adults** and range from low grade to very high grade (glioblastoma multiforme). These grades of astrocytomas include:

Key Point

Astrocytoma is the *most common* **primary** *brain tumors* in **adults**

Grade I: The least aggressive and histologically difficult to differentiate from reactive astrocytosis.
Grade II: Some plemorphism microscopically.
Grade III: Anaplastic astrocytoma, characterized histologically by increased pleomorphism and prominent mitoses.
Grade IV: Glioblastoma multiforme. A highly malignant tumor characterized histologically by endothelial proliferation and serpentine areas of necrosis surrounded by peripheral palisading of tumor cells. It frequently crosses the midline (**"butterfly tumor"**).

Key Point

Glioblastoma multiforme: *high grade astrocytoma with **worst prognosis.***

Progression of low grade astrocytoma to a higher grade (secondary glioblastoma multiforme) is associated with several genetic abnormalities, such as disruption of the p16/CDKNZA gene or overexpression of PDGF-A and its receptor.

b. **Oligodendroglioma**
These most commonly involve the cerebrum (hemispheres) in adults, are slow-growing tumors that have a high recurrence rate. Some oligodendrogliomas do proliferate in a rapid and aggressive fashion and may be associated with a malignant astrocytoma component. Histologically, oligodendrogliomas consist of sheets of cells with clear halos (**"fried-egg" appearance**) and various amounts of calcification (which can be seen on x-ray). Cytogenetic abnormalities have therapeutic significance for this type of tumor, as only tumors with deletion involving 19q or 1p respond to chemotherapy.

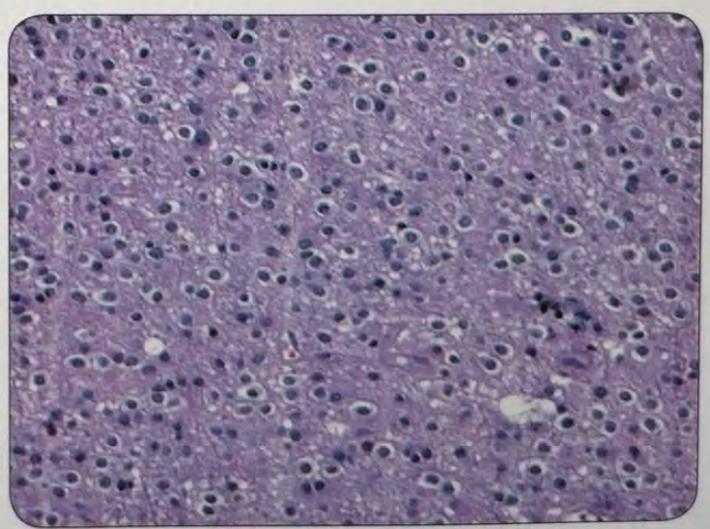


Fig. 6: Fried Egg appearance in oligodendroglioma

c. **Ependymoma**
These most often arise next to the ependyma-lined ventricular system, including central canal of spinal cord. Spinal cord ependymoma frequently occur in setting of neurofibromatosis type 2.

Recent Exam Questions

MC Site of Ependymoma
- In ***children***: typically near ***fourth ventricle*** whereas
- In ***adults***: ***spinal cord***.

2. **Neuronal tumors**
The most common CNS tumor containing mature appearing neurons (ganglion cells) is ganglioglioma. These are most commonly found in temporal lobe and frequently contain ganglion cells with binucleated forms.
3. **Poorly differentiated neoplasms**
Most common among these is medulloblastoma. Others include atypical tetroid/rhabdoid tumor.
a. **Medulloblastoma**
Primitive neuroectodermal tumors (PNETs) are a type of malignant embryonal tumor that can be found at sites within or outside of the central nervous system. An example of a PNET located outside of the CNS is Ewing's sarcoma of bone. PNETs of the CNS can be divided into supratentorial tumors (sPNET) and infratentorial tumors (iPNET). The latter are also called as medulloblastoma and they usually arise in the midline of the cerebellum (the vermis) but in adults, where the incidence is much less than in children, they are more apt to arise in the cerebellar hemispheres in a lateral position. In about one-third of cases, these show rosette formation centered by neurofibrillary material. Medulloblastomas grow by local invasive growth and may block cerebrospinal fluid circulation (CSF block) via compression of the fourth ventricle.

Key Point

Medulloblastoma is the most common tumor located in the posterior fossa of a child.

4. **Meningioma**
A tumor that is attached to the dura is most likely to be a meningioma. This type of tumor arises from the arachnoid villi of the brain or spinal cord. Although they usually occur during middle or later life, a small number occur in persons 20 to 40 years of age. They commonly arise along the venous sinuses (parasagittal, sphenoid wings, and olfactory groove).

Note: Both oligodendroglioma and craniopharyngioma show calcification fairly frequently, oligodendroglioma is often located in the frontal lobe, whereas **craniopharyngioma** occurs around the third ventricle and demonstrates *suprasellar calcification*.

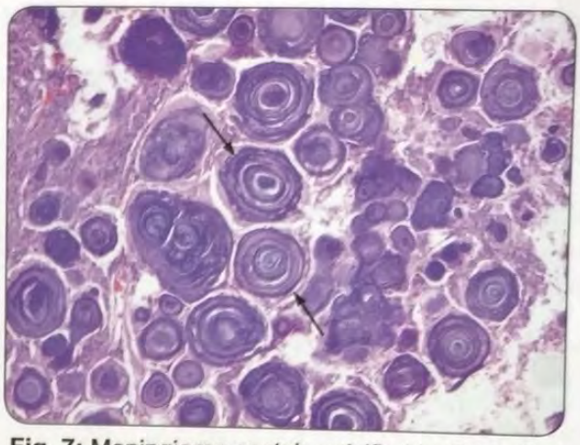


Fig. 7: Meningioma contain calcified bodies called psammoma bodies

Recent Exam Questions

- Deletion of region 12 on chromosome 22 is the most common cytogenetic abnormality of meningiomas.
- Duplication of the long arm of chromosome 17 is the most common genetic abnormality seen in medulloblastomas.

5. **Metastatic tumors**
These are *most common intra – cranial tumors*. Five most common sites are
Lung
Breast
Skin (melanoma)
Kidney
GIT

Key Point

Lung cancer is the most common cancer causing metastasis to the brain.

Choriocarcinoma has high likelihood of metastasizing to brain whereas *prostatic carcinoma almost never grow in the brain.*

CNS Tumors and Age

The location of a tumor and the age of the patient are both very important in the differential diagnosis of tumors of the central nervous system. Astrocytomas occur predominantly in the cerebral hemispheres in adult life and old age, in the cerebellum and pons in childhood, and in the spinal cord in young adult. The pilocytic astrocytoma is a subtype that is the most common brain tumor in children, and therefore it is also called a juvenile pilocytic astrocytoma. It is characterized by its location in the cerebellum and better prognosis. Meningiomas, found within the meninges, have their peak incidence in the fourth and fifth decades. The highly malignant glioblastoma multiforme is also found primarily in adults. Oligodendrogliomas also involve the cerebrum in adults. Ependymomas are found most frequently in the fourth ventricle, while the choroid plexus papilloma, a variant

of the ependymoma, is found most commonly in the lateral ventricles of young boys. The medulloblastoma is a tumor that arises exclusively in the cerebellum and has its highest incidence toward the end of the first decade. In children medulloblastomas are located in the midline, while in adults they are found in more lateral locations.

PERIPHERAL NERVE SHEATH TUMOR

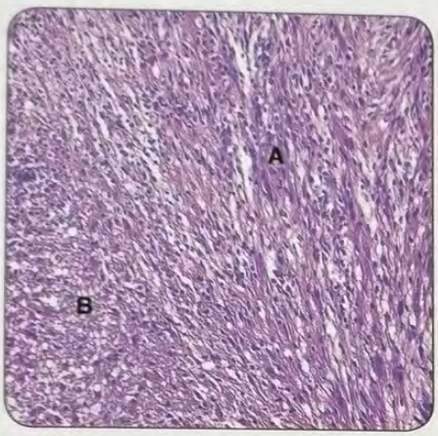


Fig. 8: Schwannoma Antoni A and Antoni B areas

Schwannomas

These are benign tumors that generally appear as extremely cellular spindle cell neoplasms, sometimes with metaplastic elements of bone, cartilage, and skeletal muscle. Schwannomas (neurilemomas) are single, encapsulated tumors of nerve sheaths, usually benign, occurring on peripheral, spinal, or cranial nerves.

Acoustic neuromas typically located at the cerebellopontine angle or in the internal acoustic meatus. Initially, when they are small, these tumors produce symptoms by compressing CN VIII and CN VII (facial). CN VIII symptoms include unilateral tinnitus (ringing in the ear), unilateral hearing loss, and vertigo (dizziness). Involvement of the facial nerve produces facial weakness and loss of corneal reflex. Histologically, an acoustic neuroma consists of cellular areas **(Antoni A)** and loose edematous areas **(Antoni B)**. **Verocay bodies** (foci of palisaded nuclei) may be found in the more cellular areas.

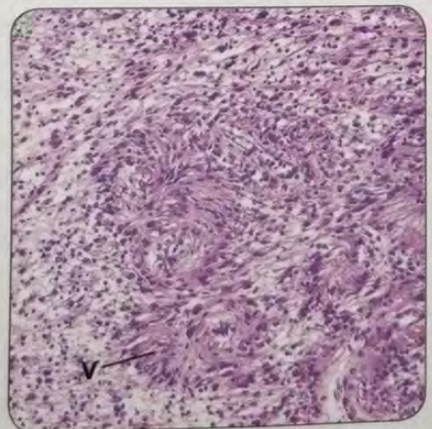


Fig. 9: Schwannoma with Verrocay Body (V)

Key Point

The **acoustic neuroma** is an example of a Schwannoma that arises from the **vestibulocochlear nerve (CN VIII).**

Familial Tumor Syndromes

a. **Tuberous sclerosis**

Tuberous sclerosis is an autosomal dominant syndrome characterized by the **clinical triad of angiofibromas ("adenoma sebaceum"), seizures, and mental retardation**. Patients develop hamartomas in the central nervous system including "tubers", which are film areas with haphazardly arranged neurons and glia with stout processes. The syndrome is associated with the development of several different types of tumors, including subepedymal giant cell tumor, rhabdomyoma of the heart, and angiomyolipoma of the kidney. Mutations at several loci have been associated with tuberous sclerosis including the TSC1 locus, which codes for hamartin, and the TSC2 locus, which codes for tuberin. These two proteins inhibit mTOR, which is the mammalian target of rapamycin. mTOR plays a central role in the regulation of cell growth.

Note: Dysregulation of mTOR activity is associated with several hamartoma syndromes, including the tuberous sclerosis, von Hippel-Lindau syndrome, Peutz-Jegher's syndrome, and the PTEN-related hamartoma syndromes.

Key Point

- Clinical triad of tuberous sclerosis is angiofibromas ("adenoma sebaceum"), seizures, and mental retardation.
- ***Rhabdomyoma of the heart*** is highly predictive of tuberous sclerosis.

b. **von Hippel-Lindau disease**

In this rare autosomal dominant disorder, multiple benign, and malignant neoplasms occur. These include hemangioblastomas of retina and brain (cerebellum and medulla oblongata), angiomas of kidney and liver, and renal cell carcinomas (multiple and bilateral) in 25 to 50% of cases.

c. **Neurofibromatosis type 1**

Classic neurofibromatosis (NF-1) is an autosomal dominant disorder. It is characterized by **cafe-au-lait skin macules, axillary freckling, multiple neurofibromas, plexiform neurofibromas, and Lisch nodules** (pigmented iris hamartomas). Lisch nodules are found in 95% of patients after age 6. There is increased risk of developing meningiomas or even pheochromocytoma. A major complication of NF-1 is the malignant transformation of a neurofibroma to a neurofibrosarcoma. The gene for the classic form (NF-1) is lcoated on chromosome 17. It encodes for neurofibromin, a protein that regulates the function of p21 oncoprotein.

Key Point

Hamartomas of the iris are not present in central or acoustic neurofibromatosis (NF-2), though both types of neurofibromatosis produce cafe-au-lait macules and neurofibromas.

d. **Neurofibromatosis type 2**

Central neurofibromatosis (NF-2) is an autosomal-dominant disorder in which patients develop a range of tumors, most commonly **bilateral VIII nerve schwannomas and multiple meningiomas**. Gliomas, typically ependymomas of the spinal cord, also occur in these patients. Many individuals with NF2 also have non-neoplastic lesions, which include nodular ingrowth of Schwann cells into the spinal cord (schwannosis), meningioangiomatosis (a proliferation of meningeal cells and blood vessels that grows into the brain), and glial hamartia (microscopic nodular collections of glial cells at abnormal locations, often in the superficial and deep layers of cerebral cortex). The ***NF2* gene is located on chromosome 22 and encodes for merlin**.

Key Point

Only the central, or acoustic, form produces bilateral acoustic neuromas; the classic form may produce unilateral acoustic neuroma.

Multiple Choice Questions

DEVELOPMENTAL DEFECTS, CEREBRAL HEMORRHAGE, ANEURYSM

1. **Cervical syringomyelia all are seen except:**
   (a) Burning sensation in hands *(AIIMS Nov 2012)*
   (b) Hypertrophy of abductor pollicis brevis
   (c) Extensor plantar response is present
   (d) Absent biceps reflex.

2. **The best described etiology for Berry aneurysm is which of the following?** *(AIIMS May 2011)*
   (a) Degeneration of internal elastic lamina
   (b) Degeneration of tunica media
   (c) Defect in muscular layer
   (d) Low grade inflammation in the vessel wall

MOST RECENT QUESTIONS

3. **The defect in Berry aneurysm is:**
   (a) Degeneration of internal elastic lamina
   (b) Degeneration of media
   (c) Deposition of mucoid material in media
   (d) Low grade inflammation of vessel wall

4. **Which of the following would distinguish hydrocephalus due to aqueductal stenosis when compared to that due to Dandy walker malformation?**
   (a) Third ventricle size
   (b) Posterior fossa volume
   (c) Lateral ventricular size
   (d) Head circumference

5. **Most common site for berry aneurysm is:**
   (a) Basilar artery
   (b) Anterior communicating artery
   (c) Posterior communicating artery
   (d) Posterior cerebral artery

6. **Middle meningeal vessel damage results in:**
   (a) Subdural hemorrhage
   (b) Extradural hemorrhage
   (c) Subarachnoid hemorrhage
   (d) Intracerebral hemorrhage

7. **Hypertensive hemorrhage is most commonly seen in :**
   (a) Basal ganglia
   (b) Thalamus
   (c) Brain stem
   (d) Cerebrum

CNS INFECTIONS, DEMYELINATING DISEASE

8. **Enzymes found in CSF:** *(AIIMS Nov 2012)*
   (a) GGT+ALP
   (b) ALP+CK-MB
   (c) CK+LDH
   (d) Deaminase and Peroxidase

9. **A 17-year-old female presents with a history of fever and headache and now develops altered sensorium. CT scan shows basal exudates with meningeal enhancement. The CSF is most likely to show:** *(AIIMS Nov 2011)*
   (a) Lymphocytic pleocytosis, low sugar, low protein
   (b) Polymorphonuclear pleocytosis, normal sugar, high protein
   (c) Lymphocytic pleocytosis, low sugar, high protein
   (d) Lymphocytic pleocytosis, normal sugar, high protein

10. **Inclusion body in oligodendroglia is a feature of which of the following?** *(AIIMS Nov 2010)*
    (a) Progressive multifocal leucoencephalopathy
    (b) Japanese encephalitis
    (c) Polio
    (d) CJD

11. **Which of the following is not a Prion disease?**
    (a) Creutzfeldt-Jakob disease *(DPG 2011)*
    (b) Fatal familial insomnia
    (c) Gerstmann-Straussler-Scheinker syndrome
    (d) Parkinson's disease

12. **All of the following diseases show abnormal folding of proteins except:** *(AIIMS Nov 2008)*
    (a) Creutzfeldt-Jakob disease
    (b) Prion disease
    (c) Multiple sclerosis
    (d) Amyloidosis

13. **Prion includes:** *(AIIMS Nov 2007)*
    (a) DNA and RNA
    (b) Only RNA
    (c) Proteins
    (d) Only DNA

14. **Pathologic features of brain in AIDS are all, except:**
    (a) Perivascular giant cell invasion *(AIIMS Nov 2001)*
    (b) Microglial nodules
    (c) Vasculitis
    (d) Temporal lobe infarction

15. **Febrile response in CNS is mediated by:** *(PGI Dec 2003)*
    (a) Bacterial toxin (b) IL-1
    (c) IL-6 (d) Interferon
    (e) Tumor Necrosis Factor

16. **Cerebral infarction is caused by:** *(PGI June 01)*
    (a) Toxoplasma (b) Cryptococcus
    (c) Aspergillus (d) Mucor
    (e) Histoplasma

17. **Complications of tubercular meningitis are:** *(PGI Dec 2000)*
    (a) Endarteritis
    (b) Hydrocephalus
    (c) Deafness
    (d) Venous sinus infarct

18. **The pathogenesis of cerebral malaria includes:** *(PGI Dec 2000)*
    (a) Cytoadhesion
    (b) Sequestration of cerebral vessels by RBCs
    (c) Reticulocytopenia
    (d) Also caused by P. vivax
    (e) Sporozoites are sequestrated in blood

19. **Brain infarct is seen in:** *(PGI Dec 2003)*
    (a) TB (b) Cryptococcosis
    (c) Aspergillosis (d) Toxoplasmosis
    (e) Rabies

MOST RECENT QUESTIONS

20. **Commonest cause of cerebral infarction is:**
    (a) Arterial thrombosis
    (b) Arteritis
    (c) Venous thrombosis
    (d) Embolism

21. **Albumino-cytologic dissociation occurs in cases of:**
    (a) Guillain-Barré syndrome
    (b) TB meningitis
    (c) Motor neuron disease
    (d) Demyelinating disorder

22. **Most common type of pathological changes seen in Rabies are:**
    (a) Meningitis
    (b) Cranial arteritis
    (c) Ventriculitis
    (d) Brain stem encephalitis

23. **What is the histological appearance of brain in Creutzfeldt-Jakob disease?**
    (a) Neuronophagia
    (b) Spongiform change in brain
    (c) Microabscesses
    (d) Demyelination

24. **Perivascular lymphocytes and microglial nodules are seen in:**
    (a) Multiple sclerosis
    (b) CMV meningitis
    (c) Bacterial meningitis
    (d) HIV encephalitis

25. **Albumino-cytologic dissociation occurs in cases of:**
    (a) Guillain Barre syndrome
    (b) TB meningitis
    (c) Motor neuron disease
    (d) Demyelinating disorder

26. **Dissociated sensory loss is seen in:**
    (a) Syringomyelia
    (b) Vitamin B12 deficiency
    (c) Transverse myelitis
    (d) Pellagra

27. **Locomotor ataxia, a late manifestation of syphilis due to parenchymatous involvement of the spinal cord is called:**
    (a) General paralysis of insane
    (b) Tabes dorsalis
    (c) Meningovascular syphilis
    (d) Syphilitic amyotrophy

28. **All of the following are seen in thymoma except:**
    (a) Hypogamma globulinemia
    (b) Hyperalbuminemia
    (c) Red cell aplasia
    (d) Myasthenia Gravis

29. **Spongiform degeneration of cerebral cortex occurs in which of the following?**
    (a) Subacute sclerosing panencephalitis
    (b) Fatal familial insomnia
    (c) Creutzfeldt-Jakob disease
    (d) Cerebral toxoplasmosis

30. **Which of the following is true about multiple sclerosis?**
    (a) Affects white matter
    (b) Affects gray matter
    (c) Rarest demyelinating disorder
    (d) Affects males more than females

ALZHEIMER DISEASE, PARKINSON DISEASE AND OTHER DEGENERATIVE DISEASE

31. **Disease or infarction of neurological tissue causes it to be replaced by:** *(AI 2002)*
    (a) Fluid
    (b) Neuroglia
    (c) Proliferation of adjacent nerve cells
    (d) Blood vessel

32. **Nucleus involved in Alzheimer's disease is:** *(Delhi PG-2005)*
    (a) Nucleus Basalis of Meynert
    (b) Superior salivary nucleus
    (c) Ventromedial nucleus of thalamus
    (d) All of the above

33. **Damage to nervous tissue is repaired by:**
    (a) Neuroglia (b) Fibroblasts *(DNB- 2001,2005)*
    (c) Axons (d) Microglia

MOST RECENT QUESTIONS

34. The following is not a feature of Alzheimer's disease: *(DNB- 2007)*
(a) Neurofibrillary tangles
(b) Senile (neuritic) plaques
(c) Amyloid angiopathy
(d) Lewy bodies

35. Neurofibrillary tangles are seen in:
(a) Parkinsonism
(b) Alzheimer's disease
(c) Multiple sclerosis
(d) Perivenous encephalomyelitis

36. Dementia in an old man with senile plaques is usually associated with:
(a) Alzheimer's disease
(b) Picks disease
(c) Parkinson's disease
(d) All of the above

37. The following is not a feature of Alzheimer's disease:
(a) Neurofibrillary tangles
(b) Senile (neuritic) plaques
(c) Amyloid angiopathy
(d) Lewy bodies

38. Which of the following is incorrect about neuroblastoma?
(a) Most common abdominal tumor in infants
(b) X-ray abdomen shows calcification
(c) Can show spontaneous regression
(d) Urine contains 5H.I.A.A

39. Commonest cause of cerebral infarction is:
(a) Arterial thrombosis
(b) Arteritis
(c) Venous thrombosis
(d) Embolism

40. Damage to nervous tissue is repaired by:
(a) Neuroglia (b) Fibroblasts
(c) Axons (d) Microglia

41. Tau protein are associated with all except:
(a) Parkinsonism
(b) Alzheimer's disease
(c) Frontotemporal lobar degeneration
(d) Huntington's disease

42. Alzheimer's disease associated chromosome is:
(a) 2 (b) 6
(c) 12 (d) 19

CNS TUMORS

43. Which of the following receptor on neuronal membrane that induces development of glioma? *(AIIMS Nov 2012)*
(a) CD45 (b) CD133
(c) CD33 (d) CD24

44. Pituitary adenomas are regarded as macroadenomas when their size is: *(AI 2012)*
(a) > 1 cm (b) > 1.5 cm
(c) > 2 cm (d) > 2.5 cm

45. Which is not a neuronal tumor? *(AI 2011)*
(a) Ependymoma (b) Neuroblastoma
(c) Gangliocytoma (d) Ganglioglioma

46. Which of the following brain tumors does not spread via CSF? *(DPG 2011)*
(a) Germ cell tumors (b) Medulloblastoma
(c) CNS Lymphoma (d) Craniopharyngioma

47. A metastatic carcinoma in the brain of an adult, most often comes from a primary in the: *(AIIMS Nov 2005)*
(a) Stomach (b) Ovary
(c) Oral cavity (d) Lung

48. Which of the following is true about Medulloblastoma? *(PGI Dec 2005)*
(a) Radiosensitive tumor
(b) Spreads through CSF
(c) Surgical treatment not done
(d) Occurs in young age group

MOST RECENT QUESTIONS

49. Commonest type of intracranial tumor is:
(a) Astrocytoma (b) Medulloblastoma
(c) Meningioma (d) Secondaries

50. Most common CNS tumor is:
(a) Astrocytoma (b) Meduloblastoma
(c) Meningioma (d) Oligodendroma

51. Glial fibrillary proteins are present in:
(a) Astrocytoma (b) Meduloblastoma
(c) Ependymoma (d) All

52. Enamel like superstructure is seen in which CNS lesion?
(a) Craniopharyngioma
(b) Pituitary tumour
(c) Astrocytoma
(d) Glioma

53. Pseudorosettes are seen in all except:
(a) Neuroblastoma (b) Retinoblastoma
(c) Medulloblastoma (d) Thecoma

54. Most common intracranial malignancy is:
(a) Glioblastoma multiforme
(b) Ependymoma
(c) Choroid angioma
(d) Pinealoma

55. Worst prognosis meningioma is:
(a) Syncytial (b) Fibroblastic
(c) Anaplastic (d) Atypical

56. **Which of the following is affected in patients with Alzheimer's disease?**
   (a) Parietal and frontal lobe
   (b) Parietal and temporal lobe
   (c) Temporal and occipital lobe
   (d) Parietal and occipital lobe

57. **Lewy bodies are found in the substantia nigra neurons in:**
   (a) Alzheimer disease
   (b) Parkinson disease
   (c) Huntington disease
   (d) Pick disease

58. **Tuberous sclerosis is associated with all except:**
   (a) Ash leaf macule
   (b) Shagreen patch
   (c) Schwannoma
   (d) Adenoma sebaceum

59. **Which of the following is seen in schwannnoma?** *(AIIMS Nov 14)*
   (a) Spindle cells
   (b) Storiform pattern
   (c) Target cells
   (d) Antoni A and B pattern

60. **Most common site for medulloblastoma is:**
   (a) Medulla (b) Cerebellum
   (c) Cerebrum (d) Pineal gland

61. **Medulloblastoma most common metastasis is to:**
   (a) Lung (b) Liver
   (c) Spleen (d) CNS

62. **Rosenthal fibres are seen in which of the following tumors?**
   (a) Pilocytic astrocytoma
   (b) Glioblastoma
   (c) Medulloblastoma
   (d) Ependymoma

63. **Most common cerebellar tumor in children:**
   (a) Medulloblastoma (b) Ependymoma
   (c) Astrocytoma (d) PNET

64. **Commonest type of intracranial tumor is:**
   (a) Astrocytoma (b) Medulloblastoma
   (c) Meningioma (d) Secondaries

65. **Verocay bodies are seen in:** *(AIIMS May' 14)*
   (a) Meningioma (b) Hemangioma
   (c) Glioma (d) Schwannoma

66. **Most common tumor of head which undergoes calcification is:**
   (a) Ependymoma
   (b) Medulloblastoma
   (c) Oligodendroglioma
   (d) Glioblastoma multiformae

67. **Which chromosome mutation is associated with medulloblastoma?**
   (a) Chromosome 16
   (b) Chromosome 17
   (c) Chromosome 18
   (d) Chromosome 19

ASSERTION AND REASON QUESTIONS

1-5. Will have two statements, assertion and reason. Read both of them carefully and answer according to these options.
   (a) Both assertion and reason are true and reason is correct explanation of assertion.
   (b) Both assertion and reason are true and reason is not the correct explanation of assertion.
   (c) Assertion is true and reason is false.
   (d) Both assertion and reason are false.

1. **Assertion:** Berry aneurysm is the commonest cause of subarachnoid hemorrhage
   Reason: Rupture of the aneurysm occurs commonly in childhood
2. **Assertion:** B12 deficiency causes subacute combined degeneration of the spinal cord
   Reason: B12 deficiency causes degeneration of both the ascending and descending tracts of the spinal cord
3. **Assertion:** Alzheimer's disease is associated with Down syndrome
   Reason: Beta amyloid gene is located on chromosome 21
4. **Assertion:** Shy-Dragger syndrome is characterized by autonomic dysfunction
   Reason: Lewy bodies are found in nigrostriatal neurons
5. **Assertion:** Huntington's disease is characterized by chorea and dementia
   Reason: Degeneration of GABA neurons in the striatum leads to decreased function (decreased inhibition) and increased movement.

Explanations

1. Ans. (b) Hypertrophy of abductor pollicis brevis

(Ref: Robbins 8th/1286, 9/e p1258)

Atrophy and ***not hypertrophy*** of the abductor pollicis brevis is a feature of syringomyelia.

Syringomyelia

- It is a chronic myelopathy that results from formation of a cavity (syrinx) involving the central gray matter of the spinal cord. The cause of syringomyelia is unknown, although one type is associated with a Chiari malformation with obstruction at the foramen magnum.
- Since the gray matter is the location where pain fibers cross to join the contralateral spinothalamic tract, the interruption of the lateral spinothalamic tracts results in *segmental sensory dissociation with loss of pain and temperature sense*, but *preservation of the sense of touch and pressure or vibration*, usually over the neck, shoulders, and arms.
- The most common location of a syrinx is the cervicothoracic region and therefore, ***the loss of pain and temperature sensation affects both arms***.
- Other features of syringomyelia include ***wasting of the small intrinsic hand muscles (claw hand) and thoracic scoliosis***. This is accompanied by areflexic weakness in the upper limbs. As the cavity enlarges, spasticity and weakness of the legs, bladder and bowel dysfunction as well as Horner syndrome appear due to compression of the long tracts.
- ***The diagnosis of syringomyelia is best made with MRI of the spine (cervical region should be examined first)***

2. Ans. (b) Degeneration of tunica media

(Ref: Robbins 8th/1297-8, 9/e p1270)

Direct quote from Robbins... 'the berry aneurysms develop over time ***because of an underlying defect in the media of the vessel"***.

Concept

It is different from other causes of aneurysm (atherosclerosis, trauma, infections) which cause **only cerebral infarction** and not subarachnoid hemorrhage.

Salient points about Berry aneurysm (saccular aneurysm)

Saccular aneurysm is the most common type of **intracranial aneurysm**.

Risk factors

Smoking and **hypertension** are the important risk factors for Berry aneurysm. They are **not the result of atherosclerosis** (which is a disease of intima).

Berry aneurysms are called congenital, although the aneurysm itself is not present at birth.

Contd...

Contd...

Location

Commonest location is in the circle of Willis, typically at the junction of the anterior communicating artery with the anterior cerebral artery[a].

It is also present at the junction of the middle cerebral artery and the posterior communicating artery.

Clinically

It is responsible for a clinically significant *subarachnoid hemorrhage*. In fact, excluding trauma, berry aneurysm is the commonest cause of subarachnoid hemorrhage.

The chance of rupture of berry aneurysms increases with age (rupture is rare in childhood). Rupture causes marked bleeding into the subarachnoid space and produces severe headaches, typically described as the "worst headache ever".

3. Ans. (b) Degeneration of media

(Ref: Robbins 8th/1297-8, 9/e p1270)

Direct quote from Robbins... 'the berry aneurysms develop over time because of an underlying defect in the media of the vessel".

Concept

It is different from other causes of aneurysm (atherosclerosis, trauma, infections) which cause **only cerebral infarction** and not subarachnoid hemorrhage.

4. Ans. (b) Posterior fossa volume

(Ref: Robbin's illustrated 6th/27691, 9/e p1255)

The basics of CSF production and drainage

CSF production (Occurs by choroid plexus of lateral and IIIrd ventricle)
↓
Foramen of Monro
↓
Third ventricle
↓
Aqueduct of Sylvius
↓
Fourth ventricle
↓
Foramen of Magendie and Lushka
↓
Subarachnoid space (It is absorbed here, by arachnoid villi)

Both Aqueductal stenosis and Dandy Walker syndrome cause non-communicating hydrocephalus but the site of obstruction is different.

- Let us see the causes of hydrocephalus in aqueductal stenosis and Dandy-Walker malformation.

Aqueductal stenosis

- In aqueductal stenosis the aqueduct connecting the 3rd and 4th ventricle is stenosed which leads to hydrocephalus with the dilatation of ventricular system prior to the aqueduct, i.e. lateral ventricles and third ventricle.

Dandy Walker Malformation

- In Dandy Walker malformation there is cystic dilatation of the fourth ventricle in the posterior fossa with obstruction at the formation of Lushka and Magendie.
- So the ventricular system in this condition will also be dilated as in aqueductal stenosis but here the posterior fossa is also enlarged (in contrast to normal posterior fossa size in aqueductal stenosis). i.e.

5. **Ans. (b) Anterior communicating artery**
(Ref: Robbins 9/e p1270, 8th/1297; 7th/1367)

6. **Ans. (b) Extradural hemorrhage** *(Ref: Robbins 9th/1261)*

7. **Ans. (a) Basal ganglia** *(Ref: Robbins 9th/1268)*
Direct quote ... "Hypertensive intraparenchymal hemorrhage may originate in the putamen (50% to 60% of cases), thalamus, pons, cerebellar hemispheres (rarely), and other regions of the brain". Putamen is a part of basal ganglia, hence, the answer here.

8. **Ans. (c) CK + LDH** *(Ref: Chatterjee Shinde 8th/730)*
The following enzymes are present in the CSF:

Aspartate transaminase (AST): 5- 12 units/ml. Its value increases in abscess, cerebral hemorrhage and infarction and in primary or metastatic malignant disease. It may increase in some patients with multiple sclerosis.

Lactate dehydrogenase (LDH): normal value is 5- 40IU/l. Its value increases in abscess, cerebral hemorrhage and infarction and in metastatic malignant disease.
Increase in LDH4 isoenzyme of CSF is seen in tuberculous meningitis.

Creatine kinase (CK): CK-BB is present in the brain. Its value increases in associated with meningitis, cerebral hemorrhage and infarction.
>30 units/ml is suggestive of tubercular meningitis and <30 units/ml is suggestive of pyogenic meningitis.

In MI, lDH1 increases but in heart failure, LDH 5 increases because right sided heart failure causing hepatic congestion and release of LDH5 from them. ....Dinesh Puri 3rd/122-3

9. **Ans. (c) Lymphocytic pleocytosis, low sugar, high protein**
(Ref: Harrison 18th/3426, Harsh Mohan 6th/appendix)
CT scan shows ***basal exudates with meningeal enhancement*** is highly suggestive of ***tuberculous meningitis***. For CSF changes in CNS infection see text.

10. **Ans. (a) Progressive multifocal leukoencephalopathy (PML)** *(Ref: Robbins 8th/1305, 9/e p1278)*
Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that results from infection of oligodendrocytes by the JC polyomavirus. It occurs almost exclusively in immunocompromised individuals as in HIV due to reactivation of the virus.

Microscopic examination shows lesions in the white matter which is an area of demyelination, in the center of which are scattered lipid-laden macrophages and a reduced number of axons. At the edge of the lesion are greatly **enlarged oligodendrocyte nuclei whose chromatin is replaced by glassy amphophilic viral inclusion**.....Robbins

Significance of microscopic findings in PML

In PML, the virus also **infects astrocytes**, leading to **bizarre giant forms** with irregular, hyperchromatic, sometimes multiple nuclei **that can be mistaken for tumor.**

OTHER OPTIONS

- In acute cases of ***Polio***, there is mononuclear cell perivascular cuffs and neuronophagia of the ***anterior horn motor neurons of the spinal cord***.
- In ***CJD***, microscopically, there is characteristic ***spongiform change in the gray matter*** ("cluster of grapes" vacuolation) ***without inflammation***.

11. **Ans. (d) Parkinson's disease**
(Ref: Harrison 17th/2647, Robbins 8th/1308, 9/e p1281)
Prion's disease of humans include:
- Iatrogenic Creutzfeldt-Jakob disease
- Sporadic Creutzfeldt-Jakob disease
- Variant Creutzfeldt-Jakob disease
- Fatal Familial Insomnia
- Gerstmann-Straussler-Scheinker syndrome
- Sporadic Fatal Insomnia
- Kuru

12. **Ans. (c) Multiple sclerosis**
(Ref: Harrison 17th/2647; Robbins 9/e p57, 1283-1284)
Disorders caused by misfolding of proteins are
- Amyloidosis
- Alzheimer's disease and other neurodegenerative diseases
- Transmissible prion diseases like CJD
- Some genetic diseases caused by mutations that lead to misfolding of protein and loss of function, such as certain of the cystic fibrosis mutations.

Prions are infectious proteins that cause degeneration of the central nervous system (CNS). Prion diseases are disorders of protein conformation, the most common of which in humans is called Creutzfeldt-Jakob disease (CJD). CJD typically presents with dementia and myoclonus, is relentlessly progressive, and generally causes death within a year of onset.

Four new concepts have emerged from studies of prions:

- Prions are the only known infectious pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny.
- Prion diseases may manifest as infectious, genetic, and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations.

- Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^{C}.
- PrP^{Sc} can exist in a variety of different conformations, each of which seems to specify a particular disease phenotype. How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^{C} during Prion replication to produce nascent PrP^{Sc} with the same conformation is unknown. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be deposited.

13. Ans. (c) Proteins

(Ref: Harrison 17th/2646; 16th/2495, 9/e p1281)

- *Prions* are infectious proteins that cause degeneration of the central nervous system (CNS). Prion diseases are disorders of protein conformation, the most common of which in humans is called Creutzfeldt-Jakob disease (CJD).
- In mammals, prions reproduce by binding to the normal, cellular isoform of the *pr*ion *p*rotein (PrP^{C}) and stimulating conversion of PrP^{C} into the disease-causing isoform (PrP^{Sc}). PrP^{C} is rich in alpha-helix and has little beta-structure, while PrP^{Sc} has less alpha-helix and a high amount of beta-structure. This **alpha-to-beta structural transition** in the prion protein (PrP) is the fundamental event underlying prion diseases.

- Prions are the only known infectious pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny.

14. Ans. (c) Vasculitis

(Ref: Anderson10th/2728, Robbins 9/e p1278)

Anderson clearly mentioned that "Unlike most other encephalitides, HIV does not seem to infect neurons and perivasculitis is conspicuously absent"

"Characteristic multinuclear Giant Cells of Macrophage origin are seen in white matter of frontal and temporal lobes particularly in perivascular location"

Feature of CNS involvement in AIDS

- Diffuse and focal spongiform changes
- Vacuolar myelopathy of posterior column of spinal cord
- Major cells affected are macrophages and monocytes
- Most characteristics finding is chronic inflammatory reaction with widely distributed infiltrates of microglial nodules

15. Correct answer: (a) Bacterial toxin; (b) IL-l; (d) Interferon; (e) Tumor necrosis factor (TNF).

(Ref: Robbins 7th/84, Harrison 16th/106)

Fever is produced in response to substances called pyrogens that act by stimulating prostaglandin synthesis in the vascular and perivascular cells of hypothalamus.

They can be classified as

- Exogenous pyrogens → Lipopolysaccharides (bacterial toxin) stimulate WBCs to release endogenous pyrogens.
- Endogenous pyrogens → IL-1 (α, β) and TNF-α, IL-6, Ciliary neurotropic factor and interferons that increase the enzyme (cyclooxygenase) that converts arachidonic acid into prostaglandins.

NSAIDs reduce fever by inhibiting cyclooxygenase.

16. Ans. (a) Toxoplasma; (c) Aspergillus; (d) Mucor

(Ref: Robbins 7th/1363, 1378)

Arteritis of small and large vessels causes cerebral infarcts.

Causes of cerebral infarction:

- Syphilis
- Tuberculosis
- Infectious vasculitis in setting of immunosuppression
- Toxoplasmosis
- Aspergillosis
- CMV encephalitis
- Mucormycosis

17. Ans. (a) Endarteritis; (b) Hydrocephalus

(Ref: Robbins 9/e p1274, 7th/1371, OPG' 6th/520-22)

Most serious complication of chronic tubercular meningitis

- Arachnoid fibrosis → Hydrocephalous
- Obliterative endarteritis → Arterial occlusion and infarction of underlying brain.
- Spinal roots may also be affected.
- Calcification
- Tuberculomas

18. Ans. (a) Cytoadhesin ; (b) Sequestration of cerebral vessels by RBCs *(Ref: Harrison 16th/1222, Robbins 9/e p391)*

Cerebral malaria is caused by *P. falciparum.*

Pathophysiology of cerebral malaria

Cytoadhesion: On the surface of infected RBC appears an antigen called $PfEMP_1$ (*P. falciparum* erythrocyte membrane protein-I). Due to this antigen infected RBCs adheres in the blood vessels.

Sequestration: It is the key events of falciparum pathology. Brain capillaries especially capillaries of white matter of brain are plugged with parasitized RBCs which terminally leads to thrombosis. Three receptors for parasitized RBC have been identified (ICAM - 1, CD_{36}, thrombospondin). These cause focal cerebral damage.

Rosetting occurs in middle of a sexual life cycle. It is seen in cerebral malaria in brain capillaries.

19. Ans. (a) TB; (c) Aspergillosis; (d) Toxoplasmosis.

(Ref: Robbins' 7th/1363, 1378)

20. Ans. (a) Arterial thrombosis *(Ref: Robbins 9/e p1263)*

21. Ans. (a) Guillain-Barré syndrome

(Ref: Harrison 17th/2667, Robbin 9/e p1231)

22. Ans. (d) Brain stem encephalitis

(Ref: Robbins 9/e p1277, 8th/1304-1305; 7th/1375)

23. Ans. (b) Spongiform change in brain....see earlier explanation. *(Ref: Robbins 9/e p1282)*

24. **Ans. (d) HIV encephalitis** *(Ref: Robbins 9/e p1278)*
    - HIV encephalitis is ***best characterized*** microscopically as a chronic inflammatory reaction with widely distributed infiltrates of **microglial nodules.**
    - The microglial nodules are also found in the vicinity of small blood vessels, which show abnormally prominent endothelial cells and ***perivascular foamy or pigment-laden macrophages***. These changes occur especially in the subcortical white matter, diencephalon, and brainstem.
    - An important component of the microglial nodule is the macrophage-derived **multinucleated giant cell.**

25. **Ans. (a) Guillain-Barré Syndrome**
    (Ref: Robbins 8/e p1262, 9/e p1231, Harrison 17/e p2667)
    In patients with Guillanin Barre syndrome, there is elevation of the CSF protein due to inflammation and altered permeability of the microcirculation within the spinal roots as they traverse the subarachnoid space. Inflammatory cells are contained within the roots, however, and there is little to no CSF pleocytosis. This is termed as albumin-cytological dissociation.

26. **Ans. (a) Syringomyelia** *(Ref: Robbins 9th/1258)*

27. **Ans. (b) Tabes dorsalis** *(Ref: Robbins 9th/1275)*
    - Tabes dorsalis is the result of damage to the sensory axons in the dorsal roots. This causes impaired joint position sense and ataxia (locomotor ataxia); loss of pain sensation, leading to skin and joint damage (Charcot joints); other sensory disturbances like the characteristic "lightning pains"; and absence of deep tendon reflexes.
    - Meningovascular neurosyphilis is chronic meningitis involving the base of the brain. It may be associated with obliterative endarteritis (Heubner arteritis) accompanied by a distinctive perivascular inflammatory reaction. Cerebral gummas (plasma cell-rich mass lesions) may also be present.
    - General paresis of the insane is caused by the invasion of the brain by T. pallidum. It manifests as progressive cognitive impairment associated with mood alterations (including delusions of grandeur) terminating in severe dementia.
    - Syphilitic amyotrophy presents with painless and progressive weakness.

28. **Ans. (b) Hyperalbuminemia** *(Ref: Robbins 9/e p627)*
    Direct lines..."In addition to myasthenia gravis, other associated autoimmune disorders with thymoma include *hypogammaglobulinemia, pure red cell aplasia, Graves' disease, pernicious anemia, dermatomyositis-polymyositis, and Cushing syndrome*".

29. **Ans. (c) Creutzfeldt-Jakob disease (CJD)**
    (Ref: Robbins 9/e p1282)
    - In CJD, on microscopic examination, the pathognomonic finding is a **spongiform *transformation of the cerebral cortex*** and, often, deep gray-matter structures (caudate, putamen).
    - This multifocal process results in the uneven formation of small, apparently empty, microscopic vacuoles of varying sizes within the neuropil and sometimes in the perikaryon of neurons.
    - In advanced cases there is severe neuronal loss, reactive gliosis, and sometimes expansion of the vacuolated areas into cystlike spaces ("status spongiosus").
    - ***No inflammatory infiltrate is present.***

30. **Ans. (a) Affects white matter** *(Ref: Robbins 9/e p1283)*

31. **Ans. (b) Neuroglia** *(Ref: Robbins 7th/1349, 9/e p1252)*
    - **Neuroglia** (astrocytes) are the principal cells in the central nervous system responsible for reaction to injury repair and scar formation in the brain. They perform **function similar to fibroblasts** in the CNS.
    - **Gliosis** is the most important histopathological indicator of CNS injury. Astrocytes participate in this process by undergoing both hypertrophy and hyperplasia.
    - *Neuroglial cells can be ectodermal in origin (e.g. astrocytes and oligodendrocytes) or derived from mesoderm (microglia).*
    - Microglia resemble macrophages and act as scavenger cells whereas oligodendrocytes help in myelin formation [similar to Schwann cells in PNS]

32. **Ans. (a) Nucleus basalis of Meynert**
    (Ref: Harrison 16th/2395, Robbins 9/e p1290)
    - The brain of Alzheimer's disease patients shows severe neuronal loss in the *nucleus basalis of Meynert,* the major source of cholinergic input to cerebral cortex.
    - The major microscopic abnormalities of Alzheimer's disease are:
      - Neurofibrillary tangles, neuropil threads
      - Senile (Neuritic) plaques
      - Amyloid angiopathy
      - Granulovacuolar degeneration
    - A dominant component of the plaque core is Aβ, a peptide of approximately 40-43 amino acid residues derived from a larger molecule, amyloid precursor protein (APP).
    - Although neurofibrillary tangles are characteristic of Alzheimer's disease, they are not specific to this condition.
    - **Hirano bodies:** Found especially in Alzheimer's disease, are elongated, glassy, eosinophilic bodies consisting of paracrystalline arrays of beaded filaments with actin as their major component.

33. **Ans. (a) Neuroglia** *(Ref: Robbins 8th/1282, 9/e p1252)*

34. **Ans. (d) Lewy bodies** *(Ref: Robbins 9/e p1290)*

35. **Ans. (b) Alzheimer's disease** *(Ref: Robbins 8th/1314)*

36. **Ans. (a) Alzheimer's disease** *(Ref: Robbins, 9/e p1290)*

37. **Ans. (d) Lewy bodies** *(Ref: Robbins 9/e p1290)*

The following are the histopathological features of Alzheimer's disease:

- Neuritic plaques : diagnostic feature
- Neurofibrillary tangles : diagnostic feature
- Cerebral amyloid angiopathy (CAA)
- Hirano bodies

38. Ans. (d) Urine contains 5H.I.A.A *(Ref: Robbins 9th/478)*

- Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy.
- About 90% of neuroblastomas, regardless of location, produce catecholamines, which are an important diagnostic feature (i.e., elevated blood levels of catecholamines and elevated urine levels of the metabolites vanillylmandelic acid and homovanillic acid.
- Increased urinary 5HIAA is a feature of carcinoid tumour and not neuroblastoma.

39. Ans. (a) Arterial thrombosis

(Ref: Robbins 8/e p1291-1292)

The majority of thrombotic occlusions are due to atherosclerosis. The most common sites of primary thrombosis causing cerebral infarction are the carotid bifurcation, the origin of the middle cerebral artery, and either end of the basilar artery…. Robbins

40. Ans. (d) Neuroglia *(Ref: Robbins 8/e p1282, 9/e p1252)*

"Gliosis is the most important histopathological indicator of CNS injury regardless of its etiology and is characterized by both hypertrophy and hyperplasia." The chief cell involved in this reaction is an astrocyte. Please remember that the oligodendrocytes and the ependyma do not participate in active response to injury.

In contrast, microglia are the fixed macrophage system in the CNS.

41. Ans. (d) Huntington's disease *(Ref: Robbins 9/e p1288)*

Relationship between proteins and neurodegenerative diseases

Protein	Diseases with inclusions
Aβ	Alzheimer disease
Tau	Alzheimer disease
	Frontotemporal lobar degeneration
	Parkinson disease (with LRRK2 mutations)
	Progressive supranuclear palsy
	Corticobasal degeneration
TPD-43	Frontotemporal lobar degeneration
	Amyotrophic lateral sclerosis
FUS	Frontotemporal lobar degeneration
	Amyotrophic lateral sclerosis
α-synuclein	Parkinson disease
	Multiple system atrophy
Polyglutamine aggregates	Huntington disease
	Some forms of spinocerebellar ataxia

42. Ans. (d) 19 *(Ref: Robbins 9/e p1289)*

- In **familial Alzheimer disease and Down syndrome**, the gene encoding APP on **chromosome 21** is involved.
- The genetic locus on **chromosome 19** that encodes **apolipoprotein E (ApoE)** has a strong influence on the risk of developing AD.

43. Ans. (b) CD133 *(Ref: Wintrobe's 12th/2559)*

- CD 133 is used as a marker for leukemia and glioblastoma stem cell. It is also used for identifying immature leukemic stem cell in AML and pro B leukemia.
- CD 45 is required for lymphocyte activation. Its deficiency causes Severe Combined Immunodeficiency disease (SCID).

44. Ans. (a) > 1 cm *(Ref: Robbins 8th/1100, 9/e p1075)*

Pituitary adenomas are designated as the following:

- *Microadenomas* if they are less than 1 cm in diameter and
- *Macroadenomas* if they exceed 1 cm in diameter

The **most common** cause of ***hyperpituitarism*** is an ***adenoma arising in the anterior lobe.***

45. Ans. (a) Ependymoma *(Ref: Robbins 8th/1330, 9/e p1306)*

The four major classes of brain tumors are:

1. Gliomas
Astrocytoma
• Pleomorphic xanthoastrocytoma
• Brainstem glioma
• Pilocytic astrocytoma
• Fibrillary (diffuse) astrocytomas
• Glioblastoma
Oligodendroglioma
Ependymoma
2. Neuronal tumors
Ganglion cell tumors
Gangliocytoma
Ganglioglioma
Dysembryoplastic neuroepithelial tumor
Cerebral neuroblastomas
3. Poorly differentiated neoplasms
4. Meningiomas

46. Ans. (d) Craniopharyngioma *(Ref: Robbins 9/e p1082)*

Brain tumors spreading via CSF are

- Ependymoma
- Medulloblastoma
- Choroid plexus carcinoma
- Astrocytoma
- Germinoma
- Pineoblastoma
- CNS Lymphoma

47. Ans. (d) Lung *(Ref: Robbins 8th/1339, 9/e p1315)*

48. **Ans. (a) Radiosensitive tumor; (b) Spreads through CSF; (d) Occurs in young age group.**
(Ref: Robbins 7th/1407; 9/e p1312 Harrison 16th/2455)

Medulloblastoma:

- The tumor occurs predominantly in children and exclusively in cerebellum (infratentorial tumor).
- Histopathological hallmark is Homer-Wright rosettes.
- Dissemination of tumor occurs through CSF.
- The tumor is highly malignant.
- It is a radiosensitive tumor. Radiotherapy improves the survival in children.
- Cranio-spinal irradiation (CSI) reduces the recurrence from CSF dissemination.

49. **Ans. (d) Secondaries** *(Ref: Robbins 8th/1339, 9/e p1315)*

50. **Ans. (a) Astrocytoma** *(Ref: Robbins 8th/1330, 9/e p1306)*

51. **Ans. (a) Astrocytoma** *(Ref: Robbins 8th/1330, 9/e p1253)*

52. **Ans. (a) Craniopharyngioma** *(Ref: Robbins 9/e p1082)*

53. **Ans. (d). Thecoma** *(Ref: Robbins 8th/1051; 7th/1442)*

54. **Ans. (a) Glioblastoma multiforme**
(Ref: Robbins 8th/1330-1331, 9/e p1308)

55. **Ans. (c) Anaplastic** *(Ref: Robbins 9/e p1315)*

56. **Ans. (b) Parietal and temporal lobe**
(Ref: Robbin 8/e p1314)

Grossly, the brain shows a variable degree of **cortical atrophy** marked by widening of the cerebral sulci that is most pronounced in the ***frontal, temporal, and parietal lobes.. (Ref: Robbind 8/e p 1314***

- *Hippocampus and other medial temporal lobe* structures are the ***earliest*** and ***most severely*** affected in Alzheimer's disease.
- Bradley's Neurology mentions that.. "***cortical atrophy is most pronounced in the temporal and parietal lobe*** with the *frontal lobe involvement being later* in the disease".

57. **Ans. (b) Parkinson disease** *(Ref: Robbins 9th/1294)*

58. **Ans. (c) Schwannoma** *(Ref: Robbins 9th/1316-7)*

- Tuberous sclerosis is an autosomal dominant syndrome characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Elsewhere in the body, renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangioleiomyomatosis and cardiac rhabdomyomas develop over childhood and adolescence. Cysts may be found at various sites, including the liver, kidneys, and pancreas.
- Cutaneous lesions include angiofibromas, localized leathery thickenings (shagreen patches), hypopigmented areas (ash-leaf patches), sebaceous adenomas and subungual fibromas.

59. **Ans. (d) Antoni A and B pattern**
(Ref: Robbins 9th/1247)

These are benign tumors that exhibit Schwann cell differentiation and often arise directly from peripheral nerves. They are a component of neurofibromatosis -2 (NF2). Microscopically, they are comprised of an admixture of dense and loose areas referred to as **Antoni A** and **Antoni B** areas, respectively.
The dense eosinophilic Antoni A areas often contain spindle cells arranged into cellular intersecting fascicles. Palisading of nuclei is common and "nuclear-free zones" that lie between the regions of nuclear palisading are termed **Verocay bodies.**

Also know!

- The Schwann cell tumors have a uniform immunoreactivity for S-100.
- Schwannomas may recur locally if incompletely resected, but ***malignant transformation is extremely rare***.

Storiform pattern is seen in ***dermatofibrosarcoma protuberans.*** This is composed of closely packed fibroblasts arranged radially.

60. **Ans. (b) Cerebellum** *(Ref: Robbins 8/e p1336, 9/e p1312)*
Medulloblastoma

- In **children**, the location is in the **midline of the cerebellum**, but *lateral locations are more often found in adults.*
- Medulloblastomas are the ***most common malignant brain tumor of childhood***
- 5% of children have it in association with **Gorlin syndrome**[Q] (the *most common of the inherited disorders* due to mutations in the patched-1; PTCH-1 gene.
- Histologically, there is presence of **Homer-Wright rosettes**[Q].
- ***Dissemination through the CSF is a common complication***[Q], presenting as nodular masses elsewhere in the CNS, including metastases to the cauda equina that are termed **drop metastases**[Q].

61. **Ans. (d) CNS……explained earlier**
(Ref: Robbins 9/e p1312)

62. **Ans. (a) Pilocytic astrocytoma** *(Ref: Robbins 9/e p1309)*
On microscopic examination of ***pilocytic astrocytoma,*** the tumor is composed of bipolar cells with long, thin *"hairlike" processes* that are **GFAP-positive** and form dense fibrillary meshworks; **Rosenthal fibers** and *eosinophilic granular bodies,* are often present.

63. **Ans. (c) Astrocytoma** *(Ref: Robbins 8/e)*

64. **Ans. (d) Secondaries** *(Ref: Robbins 8/e p1339, 9/e p1315)*

- Metastatic lesions, mostly carcinomas, account for approximately a quarter to half of intra-cranial tumors in hospitalized patients.
- The meninges are also a frequent site of involvement by metastatic disease.

65. **Ans. (d) Schwannoma** *(Robbins 9/e p1247)*

Schwannomas are well-circumscribed, encapsulated masses that abut the associated nerve without invading it. Microscopically, they are comprised of an admixture of dense and loose areas referred to as **Antoni A** and **Antoni B** areas, respectively.

- *The dense eosinophilic Antoni A* areas often contain spindle cells arranged into cellular intersecting fascicles. Palisading of nuclei is common and "nuclear-free zones" that lie between the regions of nuclear palisading are termed **Verocay bodies.**
- In the loose, hypocellular **Antoni B** areas the spindle cells are spread apart by a prominent myxoid extracellular matrix that may be associated with microcyst formation.

66. **Ans. (c) Oligodendroglioma** *(Robbins 9/e p1310, Neuroradiology/565)*

67. **Ans. (b) Chromosome 17** *(Robbins 9/e p1312)*

EXPLANATIONS TO ASSERTION AND REASON QUESTIONS

Explanations (1-5): While solving assertion reason type of questions, we can use a particular method.

- **First of all, read both assertion (A) and reason (R) carefully and independently analyse whether they are true or false.**
- **If A is false, the answer will directly be (d) i.e. both A and R are false. You can note that all other options (i.e. a, b or c) consider A to be true.**
- **If A is true, answer can be (a), (b) or (c), Now look at R. If R is false, answer will be (c)**
- **If both A and R are ture, then we have to know whether R is correctly explaining A [answer is (a)] or it is not the explanation of assertion [answer is (b)]**

1. **Ans. (d) Both assertion and reason are false.** *(Ref: Robbins 8th/1297, 9/e p1270)*

Already explained in text and answer 3.

2. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.** *(Ref: Robbins 8th/1321, 9/e p1304)*

Vitamin B_{12} deficiency leads to a swelling of myelin layers, producing vacuoles that begin segmentally at the mid-thoracic level of the spinal cord in the early stages. With time, axons in both the ascending tracts of the posterior columns and the descending pyramidal tracts degenerate. This is called as *subacute combined degeneration of the spinal cord.*

Concept

Though isolated involvement of descending or ascending tracts may be a feature of many spinal cord diseases, the combined degeneration of both ascending and descending tracts of the spinal cord is characteristic of vitamin B_{12} deficiency.

3. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.** *(Ref: Robbins 8th/1314, 9/e p1288)*

The gene for **amyloid precursor protein** (APP) is located on **chromosome 21**. APP gene mutation causes increased generation of Aβ. Alzheimer disease is associated with trisomy 21. This is related to a gene dosage effect with increased production of APP and subsequently Aβ.
Other genes linked to early-onset familial Alzheimer disease are:

Chromosomes **14**^{q} and **1**^{q} as these two chromosomes encode highly related intracellular proteins, **presenilin-1 (PS1)** and **presenilin-2 (PS2)**.

4. **Ans. (b) Both assertion and reason are true and reason is not the correct explanation of assertion.** *(Ref:Robbins 8th/1319-1321)*

Shy-Dragger syndrome is characterized by autonomic dysfunction including orthostatic hypotension, impotence, abnormal sweat and salivary gland secretion, and pupillary abnormalities. The Lewy bodies are found in sympathetic neurons in the spinal cord.

- Lewy bodies in the nigrostriatal neurons produce extrapyramidal symptoms and are a feature of **classic Parkinson's disease.**
- Lewy bodies in the *cerebral cortex* produce dementia and are a feature of **Lewy body dementia.**

Concept

Unlike Parkinson's disease, however, no mutations in the gene coding for alpha-synuclein has been found with the Shy-Drager syndrome.

5. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.** *(Ref: Robbins 8th/1322, 9/e p1297)*

Huntington's disease has already been explained in the text.

CHAPTER 17

Endocrine System

Golden Points

- **Microadenoma** of the pituitary is **< 1 cm** whereas *macroadenoma are > 1 cm.*
- Normal weight of thyroid gland: 15–25 gm.
- Commonest cause of hyperthyroidism is Graves' disease. Hyperthyroidism has proximal muscular weakness (and not Distal muscle weakness).
- The commonest cause of hypothyroidism is Hashimoto thyroiditis. It is also associated with Type I DM, autoimmune adrenalitis, SLE, myasthenia gravis and Sjogren syndrome.
- **Orphan Annie eye nuclei** is characteristic of **papillary thyroid carcinoma.**
- **Hurthle cells** are seen in: ***Follicular carcinoma, follicular adenoma, Hashmoto thyroiditis***.
- FNAC is not diagnostic in follicular thyroid carcinoma. The follicular adenoma is differentiated from follicular carcinoma by the capsular invasion or vascular invasion.
- Struma ovarii is the ectopic mature thyroid tissue in an ovarian tumor.
- Crooke's hyaline change is seen in pituitary gland of individuals having Cushing's syndrome.
- Most common cause of Adrenocortical insufficiency (Addison's disease) is Autoimmune adrenalitis (World) but **tuberculosis** (in **India**).
- **Zellballen pattern** (nest of cells) is seen in **Pheochromocytoma** and paraganglioma.
- **M**alignancy of **pheochromocytoma** is confirmed by **Metastasis**.
- Ultrastructural finding of paraganglioma: Dense core granule (neurosecretory granule).
- Most common cause of asymptomatic hypercalcemia is Parathyroid adenoma whereas the symptomatic hypercalcemia is associated with Malignancy.
- Diagnostic feature of malignancy in parathyroid tumor: **Metastasis.**

PANCREAS

The endocrine pancreas consists of the islets of Langerhans, which contain four major cell types-β, α, δ, and PP (pancreatic polypeptide) cells.

Key Point

Amylin reduces food intake and weight gain by acting on central neurons in the hypothalamus.

Cell	Hormone secreted
β cell	Insulin, Amylin
α cell	Glucagon
δ cells	Somatostatin
PP cells	*Pancreatic polypeptide* (vasoactive intestinal peptide, VIP)

Diabetes Mellitus

Diabetes mellitus is a *group of metabolic disorders having the feature of hyperglycemia* which results from either defect in insulin secretion, insulin action, or both. The diagnosis of diabetes is established by elevation of plasma glucose by any one of three criteria:

- A *random plasma glucose* concentration of *200 mg/dL or higher*, with classical signs and symptoms
- A *fasting glucose* concentration of *126 mg/dL or higher* on more than one occasion, or
- An abnormal oral glucose tolerance test (OGTT), in which the glucose concentration is 200 mg/dL or higher 2 hours after a standard carbohydrate load (75 gm of glucose).
- A level of glycated hemoglobin *(HbA1c) > 6.5 g/dL* (accepted as an additional criteria for the diagnosis of DM by American Diabetic Association.

Definition

Glysosylated hemoglobin A1C (HbA1C) is formed due to non enzymatic attachment of glucose with globin component of hemoglobin. It is used for diagnosis as well as a marker of glucose control in diabetics.

Its *target level during the treatment* of DM is **<7%.**

Apart from over diabetics, the following types of individuals are there:

- *Euglycemic* individuals: serum fasting glucose values less than 110 mg/dL, or less than 140 mg/dL following an OGTT
- *Impaired glucose tolerance*: serum fasting glucose greater than 110 but less than 126 mg/dL, or OGTT values of greater than 140 but less than 200 mg/dL. It is associated with increased risk of progressing to diabetes.

Key Point

The **most important stimulus** that triggers **insulin synthesis** and release is **glucose itself.**

The insulin gene is expressed in the β cells of the pancreatic islets. Preproinsulin synthesized in the rough endoplasmic reticulum is delivered to the Golgi apparatus where it is converted to insulin and a cleavage peptide, C-peptide.

Concept

Since both insulin and C-peptide are secreted in equal amounts equimolar quantities after physiologic stimulation, **C-peptide levels** are used a ***marker for endogenous insulin secretion.***

The vast majority of cases of diabetes fall into one of two broad classes:

- ***Type 1 diabetes:*** it is characterized by an ***absolute deficiency of insulin*** secretion caused by pancreatic β-cell destruction, usually resulting from an autoimmune attack.
- ***Type 2 diabetes:*** it is caused by a "***relative insulin deficiency***" due to combination of peripheral resistance to insulin action and an inadequate compensatory response of insulin secretion by the pancreatic β cells.

PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

The following are the risk factors for the development of type 1 DM:

Key Point

The presence of **islet cell antibodies** is used as a **predictive marker for type 1 DM**. There is characteristically presence of **insulitis** in these patients.

1. **Genetic factors**: these could affect
   HLA genes (***commonest locus*** being affected is on ***chromosome 6p21(HLA D)*** like HLA DR3/DR4 with DQ8 haplotype
   The non HLA genes like that for insulin or polymorphism in CD25 (normally regulated the function of T cells)
2. **Environmental factors**: viral infections like coxsackie B, mumps, rubella or cytomegalovirus.

Key Point

The genetic factors are much more important in type 2 DM than in type 1 DM.

The *failure of self tolerance in T cells* is the main defect in type 1 DM. The autoreactive Tcells (TH1 cells and CD8+ cytotoxic T cells) get activated and cause β cell injury resulting in the reduction of β cell mass. *Autoantibodies* against a variety of β-cell antigens, including insulin, islet cell autoantigen 512 and glutamic acid decarboxylase are also found in the patients.

Key Point

The presence of **islet amyloid protein (amylin)** is a characteristic feature of long standing **type 2 DM.** There is **no insulitis in type 2 DM** (which is characteristically seen in type 1 DM).

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

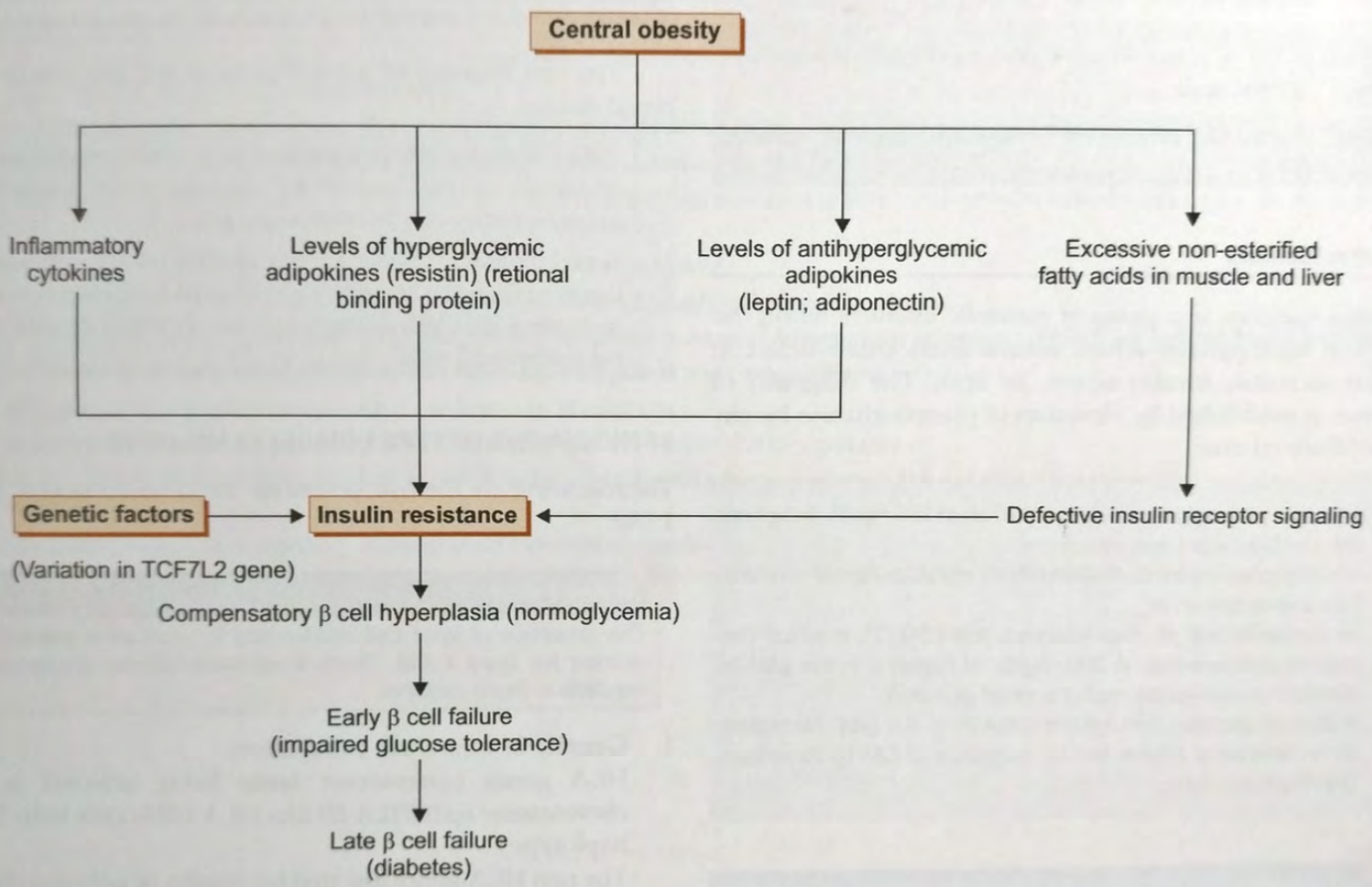
The disease is characterized by the following metabolic defects:

- **Insulin resistance:** it is defined as resistance to the effects of insulin on glucose uptake, metabolism, or storage. It is a characteristic feature of most individuals with type 2 diabetes.
- **β-cell dysfunction:** inadequate insulin secretion in the presence of insulin resistance and hyperglycemia

There is *no autoimmune basis* of type 2 DM. The insulin resistance is being contributed maximally by the ***loss of sensitivity in the hepatocytes.***

Key Point

Obesity is the most important risk factor **insulin resistance.**



Key Point

50% of carriers of **Glucokinase mutations** develop **Gestational diabetes mellitus.**

Patients with lipoatrophic diabetes have hyperglycemia with loss of adipose tissue.

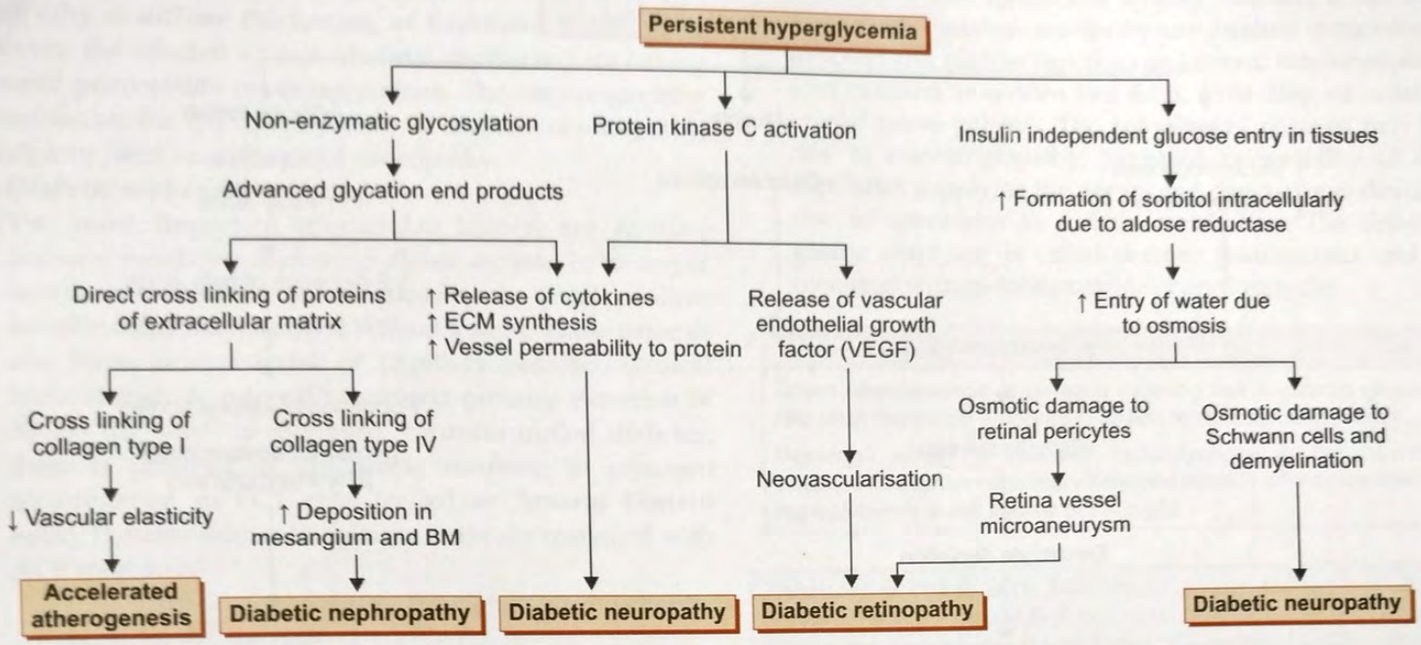
*An increase in the number of and size of islets is characteristic of non diabetic infants of diabetic mothers.

MONOGENIC FORMS OF DIABETES

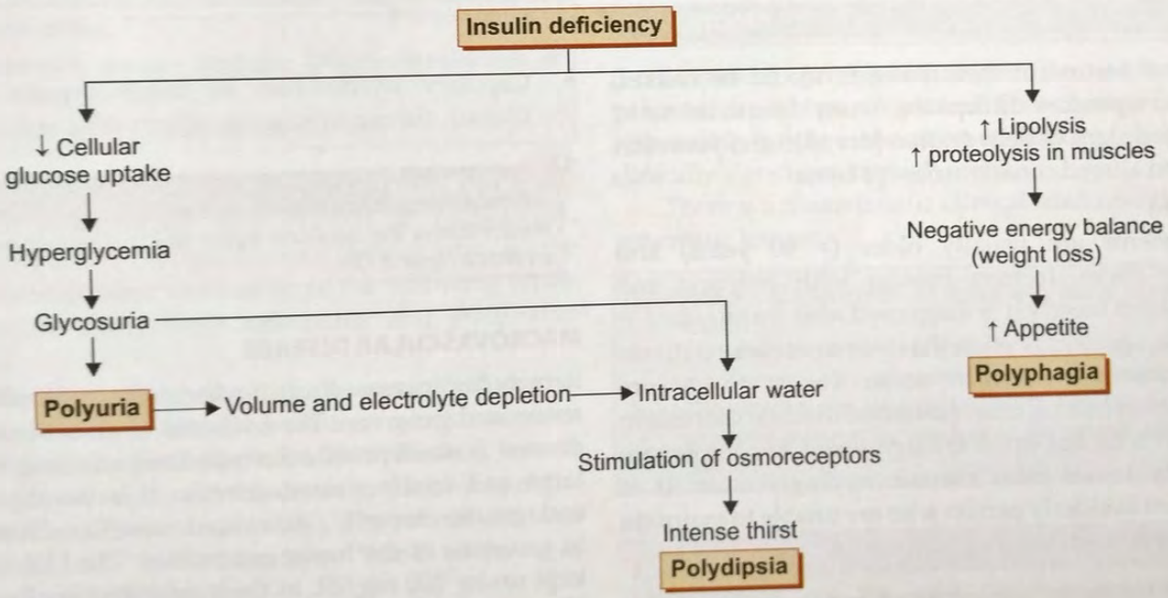
The monogenic forms of diabetes can be due to the following causes:

Primary defect in β-cell function	Defect in insulin-insulin receptor signaling
• Autosomal-dominant inheritance with high penetrance • Early onset (usually before age 25) • Absence of obesity • Lack of islet cell autoantibodies	• Type A insulin resistance (severe insulin resistance + hyperinsulinemia + DM) • Lipoatrophic diabetes (insulin resistance + hypertriglyceridemia + DM + acanthosis nigricans + hepatic steatosis)

Pathogenesis of Complications of DM



CLINICAL FEATURES OF DM



Concept

'Honeymoon period' is the *symptom free interval period* in a patient of DM in which the individual is asymptomatic. It is ***due to the β reserve cell mass*** in the pancreatic islets

Key Point

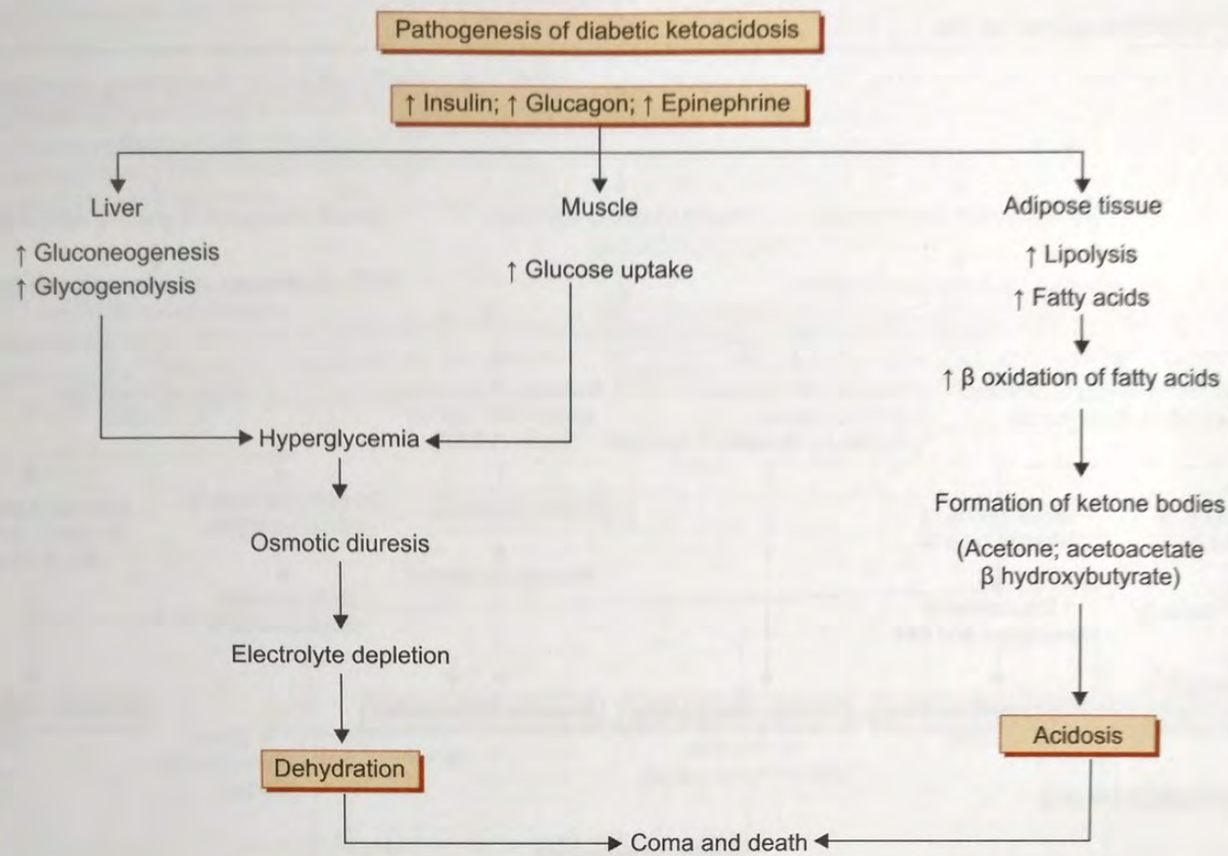
The **paradoxical combination** of **weight loss and polyphagia** should make the physician suspicious of **DM**

Recent information

A family of proteins called *sirtuins*, identified to be involved in aging are now implicated in diabetes. Sirt-1 improves glucose tolerance, enhance β cell insulin secretion, and increase production of adiponectin.

Acute Complications of DM

1. Type 1 DM
   Diabetic ketoacidosis is an important complication seen in type 1 diabetics. It is usually precipitated by inadequate insulin therapy, intercurrent infection, emotional stress and excessive alcohol intake.



The clinical feature of these patients would be nausea, vomiting, respiratory difficulties, 'fruity' breath odour of acetone, and signs of dehydration (dry skin and poor skin turgor) and altered consciousness to coma.

2. **Type 2 DM**
These patients are usually older (> 40 years) and frequently obese. It may present with polyuria and polydipsia but mostly it is diagnosed *after routine blood or urine testing*. A complication that is seen in these patients is ***hyperosmolar nonketotic coma*** due to the severe dehydration resulting from sustained osmotic diuresis in patients who do not drink enough water to compensate for urinary losses from chronic hyperglycemia. It is usually seen in elderly person who are unable to maintain adequate water intake.

Concept

Type 2 DM patients **don't develop ketoacidosis** and its symptoms (nausea, vomiting, respiratory difficulties) because of elevated portal insulin levels. The **'fat sparing' effect of insulin** prevents the formation of ketone bodies by inhibiting the fatty acid oxidation in the liver.

CHRONIC COMPLICATIONS OF DM

The long-standing diabetes may involve:

- Both large- and medium-sized muscular arteries *(macrovascular disease)*
- Capillary dysfunction in target organs *(microvascular disease)*: *diabetic retinopathy, nephropathy,* and *neuropathy.*

Key Point

Metformin is the *only oral agent* which ***reduces macrovascular events*** in type 2 DM.

MACROVASCULAR DISEASE

It includes increased cardiovascular complications like MI, stroke and gangrene. The ***hallmark*** of diabetic macrovascular disease is ***accelerated atherosclerosis*** affecting the aorta and large and medium-sized arteries. It is having earlier onset and greater severity. Advanced vascular disease can lead to gangrene of the lower extremities. The LDL cholesterol is kept under 100 mg/dL in these patients usually with statins. The vascular lesion in diabetics is **Hyaline arteriolosclerosis** (amorphous, hyaline thickening of the wall of the arterioles causing narrowing of the lumen).

Key Point

MI is the *most common cause of death* in diabetics.

Renal atherosclerosis and arteriolosclerosis is due to macrovascular disease in diabetics.

A characteristic feature of renal involvement in diabetics is **Hyaline arteriolosclerosis affecting both the afferent as well as the efferent arterioles.**

MICROVASCULAR DISEASE

The most consistent morphologic feature of diabetic microangiopathy is **diffuse thickening of basement membranes.** However, the affected vessels (diabetic capillaries) are having increased permeability to plasma proteins. The microangiopathy is responsible for the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.

1. ***Diabetic nephropathy***

   The most important glomerular lesions are *capillary basement membrane thickening; diffuse increase in mesangial matrix,* and nodular glomerulosclerosis (PAS positive nodules called ***Kimmelsteil Wilson*** lesion). These patients also have increased risk of papillary necrosis. Clinical features include **microalbuminuria** (urinary excretion of 30-300 mg/day^{Q} of albumin). In uncontrolled diabetes, there is presence of glucosuria resulting in glycogen accumulation in PCT cells (called as **Armani Ebstein cells**). Patients with microalbuminuria are managed with ACE inhibitors.

   (See diabetic nephropathy for details in the chapter on kidney).

Key Point

Diabetic nephropathy

Most characteristic lesion: Nodular Glomerulosclerosis or Kimmelsteil Wilson lesion

Most common lesion: Diffuse Glomerulosclerosis

2. ***Diabetic retinopathy***

   The ocular involvement may present as retinopathy, cataract formation, or glaucoma. Retinopathy is the most common pattern and can be of the following types: *nonproliferative (background) retinopathy* and *proliferative retinopathy.*

   Nonproliferative retinopathy includes intraretinal or preretinal hemorrhages, retinal exudates, microaneurysms (saccular dilations of retinal choroidal capillaries), venous dilations, edema, and, most importantly, thickening of the retinal capillaries (microangiopathy). The retinal exudates can be either "soft" (microinfarcts) or "hard" (deposits of plasma proteins and lipids).

   Proliferative retinopathy includes the process of neovascularization and fibrosis. Macular involvement can cause blindness whereas vitreous hemorrhages can result from retinal detachment. It is managed with laser photocoagulation.

Key Point

Peripheral, symmetric neuro-pathy of the *lower extremities* is the commonest pattern in **diabetic neuropathy.**

3. ***Diabetic Neuropathy***

   DM can affect both the central and peripheral nervous systems. The ***most frequent*** pattern of involvement is a ***peripheral, symmetric neuropathy*** of the lower extremities that affects both motor and sensory function. It can also manifest as *autonomic neuropathy* (can produce disturbances in bowel and bladder function) and *diabetic mononeuropathy* (can manifest as sudden foot drop, wrist drop, or isolated cranial nerve palsies). The neurological changes may be due to microangiopathy, increased permeability of the capillaries supplying the nerves and direct axonal damage due to alterations in sorbitol metabolism. The delayed gastric emptying is called diabetic gastroparesis and is managed with metoclopramide or erythromycin.

Concept

Dawn phenomenon is an early morning rise in plasma glucose *requiring increased amounts of insulin* to maintain euglycemia.

Somogyi effect is *rebound hyperglycemia* in the morning because of counter-regulatory hormone release *after an episode of hypoglycemia in the middle of the night.*

Treatment of DM is done with insulin and/or anti-hyperglycemic agents. The latter include Sulfonylureas; (Glipizide, Glibenclamide), Biguanides (metformin), Meglitinides (Repaglinide), Glucosidase inhibitor (Acarbose) and DPP-4 inhibitors (Vildagliptin).

INSULINOMA

β-cell tumors (insulinomas) are the most common of pancreatic endocrine neoplasms. These benign tumors may be responsible for the elaboration of sufficient insulin to induce clinically significant hypoglycemia.

There is a characteristic **clinical triad** resulting from these pancreatic lesions:

1. *Attacks of hypoglycemia* occur with *blood glucose levels below 50 mg/dl*
2. The attacks consist principally of such central nervous system manifestations as confusion, stupor, and loss of consciousness
3. The attacks are precipitated by fasting or exercise and are promptly *relieved by feeding or parenteral administration of glucose.*

Key Point

Insulinomas are the *most common pancreatic endocrine neoplasms;* characterized by the presence of **Whipple's triad.**

Hyperinsulinism may also be caused by *diffuse hyperplasia of the islets* which is usually seen in neonates and infants.

Definition

Nesidioblastosis is diffuse islet hyperplasia and is seen with maternal diabetes and Beckwith-Wiedemann syndrome.

The critical laboratory findings in insulinomas are high circulating levels of insulin and a high insulin-glucose ratio. Surgical removal of the tumor is usually followed by prompt reversal of the hypoglycemia.

THYROID GLAND

It is a gland (weighing 15-20 g) responsible for the secretion of the thyroid hormones (T_3 and T_4) and calcitonin. Thyroid hormones are required for the development of brain and maintenance of basal metabolic rate whereas calcitonin is involved in calcium homeostasis. The two types of disorders associated with this gland are hyperthyroidism and hypothyroidism.

Key Point

Graves' disease is the commonest cause of thyrotoxicosis

HYPERTHYROIDISM

It is a state of ***hyperfunctioning of the thyroid gland*** characterized by elevated levels of free T_3 and T_4 and associated with increased sympathetic activity. It should be differentiated from thyrotoxicosis which is a ***hypermetabolic state due to elevated levels of free T_3 and T_4*** (so, thyrotoxicosis includes hyperthyroidism as well as other causes). The causes for this condition include

Definition

Thyrotoxicosis factitia is Exogenous thyroid hormone induced hyperthyroidism

1. Diffuse toxic hyperplasia (Graves' disease) (Accounts for 85% of cases)
2. Toxic multinodular goiter
3. Toxic adenoma
4. Uncommon causes:
   - Acute or subacute thyroiditis
   - Hyperfunctioning thyroid carcinoma
   - TSH secreting pituitary adenoma
   - Struma ovarii
   - Iatrogenic hyperthyroidism
   - Thyrotoxicosis factitia

Key Point

The **cardiac manifestations** are *the earliest and most consistent* feature of hyperthyroidism.

Clinical features: The salient features include tachycardia, palpitations, diaphoresis (increased sweating), heat intolerance, tremors, diarrhea and weight loss despite a good appetite.

Key Point

Serum TSH is best screening test for thyroid dysfunction.

The diagnosis is made using serum TSH. It is the most useful screening test as its level may be altered in patients with even subclinical hyperthyroidism. **In primary hyperthyroidism**, serum *TSH is low* and free T_4 is increased whereas in **secondary** (due to increased TSH secretion from the pituitary) and **tertiary** (due to increased thyrotropin releasing hormone or TRH secretion from the hypothalamus) **hyperthyroidism**, serum *TSH is high.*

HYPOTHYROIDISM

It is caused due to decreased secretion of the thyroid hormones either due to a **primary** defect in the thyroid (*most common*^{Q}) or a **secondary** (TSH deficiency) or rarely a **tertiary** (TRH deficiency) cause. This can result in *cretinism in children and myxedema (or Gull disease) in adults.* The clinical features of the disease include lethargy, sensitivity to cold, reduced cardiac output, constipation, *myxedema* [due to accumulation of glycoaminoglycans, proteoglycans and water resulting in deep voice, macroglossia (enlarged tongue) and non- pitting edema of hands and feet] and menorrhagia (increased menstrual blood loss).

Key Point

Autoimmune hypothyroidism is the commonest cause of hypothyroidism in iodine sufficient areas of the world.

The diagnosis is made using *serum TSH. It is the most useful screening test. Serum TSH is elevated in primary hypothyroidism and it is reduced in secondary and tertiary hypothyroidism.*

THYROIDITIS

It is defined as the inflammation of the thyroid gland which may be associated with illness and severe thyroid pain (as in infectious thyroiditis or subacute granulomatous thyroiditis) or can be painless (subacute lymphocytic thyroiditis or Reidel thyroiditis). The important types of thyroiditis include:

Key Point

Primary hypothyroidism: ↓ serum T_4; ↑ **serum TSH.**

Secondary hypothyroidism: ↓ serum T_4; ↓ **serum TSH.**

Hashimoto Thyroiditis (Chronic Lymphocytic Thyroiditis)

It is a chronic inflammation with lymphocytic infiltration of the thyroid gland (the latter responsible for the term *'struma lymphomatosa'*). It is more commonly seen in **females** (F: M ratio is 10:1) of the age group of 45-65 years. This condition is associated with HLA-DR5, HLA-DR3 and chromosomal defects like Turner and Down syndrome. Increased susceptibility to Hashimoto's thyroiditis has been associated with polymorphisms of cytotoxic T lymphocyte associated antigen-4 (CTLA4) and protein tyrosine phosphatase-22 (PTPN 22).

Key Point

Hashimoto Thyroiditis: *Auto-immune thyroiditis*

Most common type of thyroiditis^{Q} and the *most common cause of hypothyroidism* in areas having sufficient iodine levels.

Pathogenesis: There is replacement of the thyroid cells with lymphocytic infiltration and fibrosis. There is presence of antithyroid antibodies (anti-TSH receptor antibodies, anti-thyroglobulin and anti-thyroid peroxidase antibodies) in the serum of the affected patients.

Morphology: The thyroid gland is diffusely enlarged with *intact capsule*. There is presence of *well developed germinal centers* and extensive infiltration of parenchyma by mononuclear inflammatory cells like lymphocytes and plasma cells. The thyroid follicles are atrophic and lined by epithelial cells having abundant eosinophilic and granular cytoplasm called **Hurthle cells.**Q

Clinical features: It is characterized by the presence of *painless enlargement* of the thyroid gland and a gradual loss of thyroid function (though initially, thyroid follicular disruption may cause transient hyperthyroidism). The disorder is *associated with autoimmune diseases* (like SLE, Sjögren syndrome, myasthenia gravis) and there is *increased risk of* development of *B-cell non-Hodgkin lymphoma*.

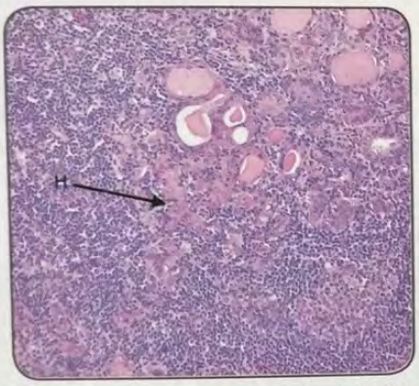


Fig. 1: Hashimoto thyroiditis showing Hurthle cell (H)

Subacute Lymphocytic Thyroiditis (or Silent/Painless Thyroiditis or Postpartum Thyroiditis)

It is a *self limiting*Q episode of thyrotoxicosis seen commonly in middle aged females especially in postpartum period. It is associated with HLA DR-3 and HLA DR-5 and is autoimmune in etiology. Painless and post-partum thyroiditis are variants of Hashimoto's thyroiditis.

Concept

The fibrosis does not extend beyond capsule (which is the main differentiating feature from Reidel thyroiditis

Morphology: The thyroid gland has lymphocytic infiltration with hyperplastic germinal centers and patchy collapse of thyroid follicles.

Clinical features are *painless enlargement of the thyroid* and *transient hyperthyroidism* (lasting about 2-8 weeks). Investigations reveal elevated levels of T_3 and T_4 and reduced TSH.

Key Point

Subacute painless lymphocytic thyroiditis: develops post partum and progression to hypothyroidism.
There is absence of Hurthle cells and fibrosis (differentiating feature from Hashimoto thyroiditis).

Subacute Thyroiditis (Granulomatous Thyroiditis or De Quervain Thyroiditis)

It is a disorder seen commonly in females (Female: Male ratio is 3 to 5:1) of the age group 30-50 years. It is more commonly seen in summer, is *preceded by a viral infection* (caused by coxsackie virus, mumps, measles, adenovirus etc.) and is **associated with HLA-B5.**

Pathogenesis: It results due to virus induced host tissue damage or direct viral damage.

Key Point

Subacute Granulomatous Thyroiditis: Most common cause of **painful thyroid;** *virus induced;* **NO** *cervical lymphadenopathy*

Morphology: The thyroid gland is diffusely enlarged with *intact capsule*. There is presence of patchy changes. In the initial stages, there is active inflammation characterized by disruption of follicles by neutrophils (forming micro abscess), lymphocytes, histiocytes, plasma cells and multi-nucleated giant cells which is followed by fibrosis.

Clinical features are *pain in neck, sore throat*, fever, fatigue, anorexia, myalgia, enlarged thyroid and the presence of **transient hyperthyroidism** which usually diminishes in 2-6 weeks. It may be followed by asymptomatic hypothyroidism but recovery is seen in most of the patients. Almost all patients have high T_3 and T_4 and low TSH initially which recovers in 6-8 weeks after the disease completes the course.

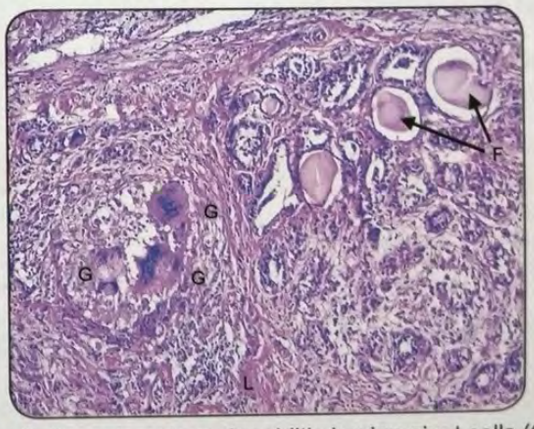


Fig. 2: Granulomatous thyroiditis having giant cells (G), lymphocyte (L) and colloid filled follicles (F)

Reidel's Thyroiditis (or Fibrous Thyroiditis/Invasive Thyroiditis)

It is an idiopathic rare disorder characterised by the *destruction of the thyroid gland by dense fibrosis*. Fibrosis *of the surrounding structures like trachea and esophagus can also occur*. It is more commonly seen in females of middle age and is associated with retroperitoneal and mediastinal fibrosis.

Key Point

Reidel's Thyroiditis: Fibrous tissue replacement of gland and surrounding tissue.

GRAVES' DISEASE

It is the *commonest cause*[Q] of endogenous hyperthyroidism characterized by the **triad** of *hyperthyroidism* due to hyperfunctional diffuse enlargement of gland, *infiltrative ophthalmopathy* and localized, infiltrative *dermopathy* (also called as *pretibial myxedema*). The disorder is more common in females of the age group of 20-40 years. It is associated with polymorphisms in HLA B8, HLA DR3, CTLA4 and PTPN-22.

Key Point

Triad of Graves' Disease = hyperthyroidism + infiltrative ophthalmopathy + localized, infiltrative dermopathy (pretibial myxedema)

Pathogenesis: It is an autoimmune disease most commonly due to formation of **antibodies to TSH receptors** (called TSI or LATS meaning *Thyroid Stimulating Immunoglobulin* and *Long Acting Thyroid Stimulator* respectively). The other antibodies found in this condition include **TGI** (Thyroid Growth stimulating Immunoglobulin) and **TBII** (TSH Binding Inhibitor Immunoglobulin), the latter sometimes responsible for *paradoxical hypothyroidism* seen in some of these patients. The anti-TSH antibodies stimulate the TSH receptor in this condition in contrast to Hashimoto's thyroiditis in which the antibodies inhibit the receptor.

Definition

Thyroid acropachy is digital swelling and clubbing of fingers in Graves disease.

Morphology: The thyroid gland is symmetrically enlarged with diffuse hypertrophy and hyperplasia. The capsule is intact.

Concept

In Graves disease, there is crowding of cells with **papillae formation without fibrovascular core** (presence of the latter is the differentiating feature of papillary thyroid cancer).

Clinical features as described above include **hyperthyroidism**, **ophthalmopathy** (due to increased volume of extraocular muscle and retro-orbital connective tissue *as a result of expression of TSH receptor by orbital fibroblasts*) and localized, **infiltrative dermopathy** (most commonly in skin overlying shin). Investigations reveal increased levels of T_3 and T_4 with reduced TSH levels. There is a diffuse increase in the uptake of radioactive iodine.

DIFFUSE AND MULTINODULAR GOITER

Goiter is enlargement of the thyroid gland. Both diffuse and multinodular goiter are caused due to impaired synthesis of thyroid hormones most commonly due to dietary iodine deficiency. This results in increased secretion of TSH leading to hypertrophy and hyperplasia of the thyroid gland. The degree of enlargement is proportional to the level and duration of thyroid hormone deficiency. Usually, the enlargement takes place to maintain a euthyroid state but may also be associated with hyperthyroid state.

Diffuse Non-toxic Goiter (Colloid Goiter or Simple Goiter)

In this condition, the thyroid shows no nodules and there are colloid filled follicles (so, the other name is colloid goiter). It can be **endemic** (when >10% of population is affected usually due to low dietary iodine intake) or **sporadic** (seen more commonly in females during puberty; usually due to enzyme defects affecting thyroid hormone synthesis or ingestion of *Goitrogens* which are substances interfering with thyroid hormone synthesis like calcium, cabbage, cauliflower, turnip, cassava, etc.)

Key Point

In Toxic multinodular goiter: one or more nodules becom TSH independent.

Exophthalmos and pretibial myxedema are **NOT** seen in toxic multinodular goiter

Histologically, there can be two stages: *initial hyperplastic stage* having diffuse, symmetrically enlarged gland with thyroid follicular hyperplasia and *later, the stage of colloid involution*.

MULTINODULAR GOITER (MNG)

This is a condition resulting from recurrent episodes of hyperplasia and involution resulting in *irregular enlargement* of thyroid gland. *The differential sensitivity of follicular cells for TSH results in multinodular goiter*. Grossly, there is presence of enlarged multinodular thyroid with presence of hemorrhage, fibrosis, calcification and cystic change.

Key Point

Presence of a hyper functioning nodule developing in MNG called as **Plummer Syndrome**.

Clinical features are due to mass effect (enlarged thyroid causing compression of esophagus, trachea, etc.) or cosmetic effect.

SOLITARY THYROID NODULE (STN)

It is a clinical entity seen more commonly in females. STN is *more likely to be neoplastic in* the presence of certain risk factor (mentioned alongside).

Mnemonic

Factors ↑ risk of neoplasia in STN
(MY SR is Cool)

- **M**ale patients
- **Y**oung patients
- **S**olitary as compared to multiple nodules
- **R**adiation exposure to head and neck is present
- **C**old nodule on radioactive scan (nodules taking less amount of radioactive iodine in imaging studies)

THYROID ADENOMA

These are solitary masses of the thyroid tissue composed of follicular epithelium and are therefore, called as follicular adenomas. They are formed due to chronic overactivation of cAMP pathway (due to somatic mutation of the TSH receptor or the α subunit of Gs receptor). They are usually asymptomatic and present as *'cold' nodules* on radio imaging scans.

Concept

(Presence of **intact capsule** distinguishes a **benign follicular adenoma** from *follicular carcinoma* because in the latter the *capsule is **NOT** intact*).

Morphologically, these are solitary, spherical lesions having an *intact capsule* Usually, the cells form uniform appearing follicles containing colloid but they can have the following subtypes:

- Follicular or simple colloid
- Microfollicular: Seen in fetal life
- Hurthle cell (oxyphil, oncocytic) adenoma: Cells have eosinophilic, granular cytoplasm
- Atypical adenoma: Increased variation in cellular and nuclear morphology
- Clear cell follicular adenoma: Cells have clear cytoplasm.

THYROID CARCINOMAS

It is a cancer seen more commonly in females in early and middle adult life. The four histological types of thyroid cancers are:

1. Papillary cancer
2. Follicular cancer
3. Medullary cancer
4. Anaplastic cancer

Risk Factors for Thyroid Cancers

- **Papillary cancer**: It is associated with mutation in either tyrosine kinase receptors **RET** or **NTRK1** (Neurotrophic Tyrosine Kinase Receptor 1) or **BRAF oncogene**. RET is located on chromosome10 and translocation with chromosome 17 causes formation of a fusion gene ret/PTC (ret/papillary thyroid cancer) which is responsible for increased tyrosine kinase activity of cells resulting in papillary thyroid cancer. This cancer is also seen after exposure to **ionizing radiation** during first two decades of life.
- **Follicular cancer**: It is associated with mutation in RAS oncogenes particularly **N-RAS**. A specific translocation associated with follicular cancer is **t(2;3)** resulting in PAX8-PPARγ1fusion. PPAR is peroxisome proliferator-activated receptor required for terminal differentiation of the cell whereas PAX8 is a homeobox gene required for thyroid development.
- **Medullary cancer**: It is the only thyroid cancer to **arise from parafollicular 'C' cells**. It is associated with **mutation in RET proto-oncogene** resulting in constitutional activation of the receptor.
- Remember that ret/PPTC is NOT seen in medullary carcinoma of thyroid.
- **Anaplastic cancer**: It is associated with mutation in the **p53** tumor suppressor gene.

Key Point

All thyroid cancers arise from *follicular epithelium* **except** medullary cancer (arises from "C" cells)

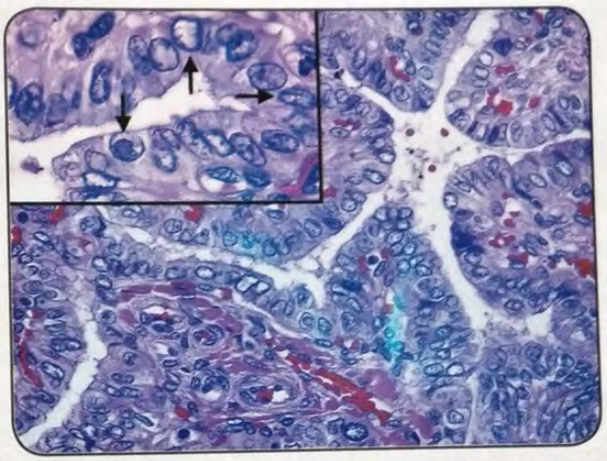


Fig. 3: Papillary thyroid cancer with characteristic nuclear features Inset: clear nucleus, nuclear grooving and intranuclear inclusions

SALIENT FEATURES OF THYROID CANCERS

PAPILLARY CARCINOMA

- It is the *commonest type* of thyroid cancer[Q]
- Seen in 20-40 years old age group
- Spread is by *lymphatic route*[Q]
- *Carries excellent prognosis*[Q]
- **Microscopically** there is presence of **papillae with fibrovascular stalk**, calcified structures called **Psammoma bodies**[Q] and cancer cells have diagnostic nuclear features like presence of fine chromatin leading to 'ground glass' or '**Orphan Annie eye' nuclei**[Q], intranuclear inclusions (called '**pseudoinclusions**') or intranuclear longitudinal grooves.
- The variants include encapsulated variant (good prognosis), follicular variant (poor prognosis) and tall cell variant (poorest prognosis).

Mnemonic

Papillary Thyroid tumor (6Ps)

Popular (Most common)
Palpable Lymph nodes (Spreads by lymphatics)
Positive I (131) uptake
Positive Prognosis (Excellent prognosis)
Post radiation in head and neck (cause)
Psammoma bodies

FOLLICULAR CARCINOMA

- It is the 2nd most common form of thyroid cancer
- Seen in women of older age (40-50 yrs.)

- *Vascular invasion is common* (less lymphatic spread) to bone, lung, liver etc.
- **Microscopically**, there is presence of cells forming small follicles having colloid with *NO* Psammoma bodies. Uncommonly, cells have abundant , eosinophilic cytoplasm called as *Hurthle cells*[Q]
- Differentiation from follicular adenoma is based on the *presence of capsular invasion preferably* and vascular invasion [Q] (capsular vessel invasion).

Mnemonic

Follicular carcinoma (4Fs)

Female
Faraway metastasis
Favorable prognosis
Flow in blood (vascular invasions are common)

MEDULLARY CARCINOMA

- Arises from *parafollicular cells/C cells and secretes calcitonin*[Q]
- *Sporadic in 80%* of cases
- *Associated with multiple endocrine neoplasia II (MEN) syndromes*[Q]
- **Only** thyroid cancer *associated with amyloidosis*[Q]
- ***Unilateral in sporadic** cases and bilateral and multicentric in familial cases*
- **Microscopically**, there is presence of polygonal, **spindle cells** in amyloid stroma. Familial cancers characteristically show the presence of multicentric C-cell hyperplasia.

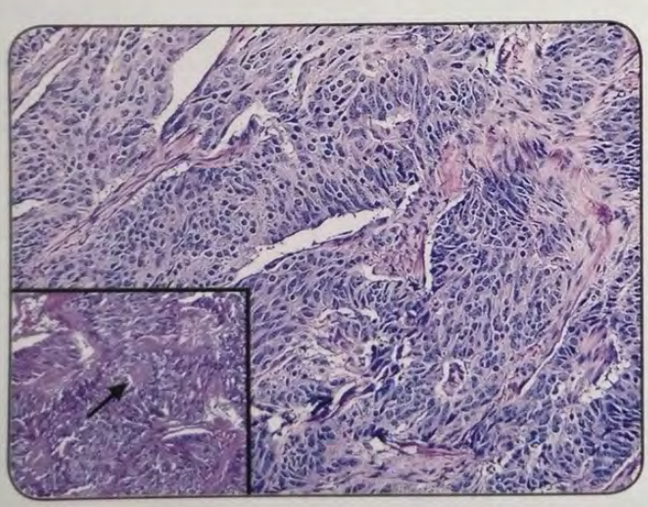


Fig. 4: Medullary thyroid cancer with fibrils of pink and waxy amyloid (arrow)

ANAPLASTIC CARCINOMA

- Undifferentiated thyroid cancer
- Have the *worst prognosis*[Q]
- Seen mostly in elderly female patients
- 50% patients give a history of presence of multinodular goiter[Q]
- **Microscopically**, there is presence of highly anaplastic cells which can either be giant cells, spindle cells, mixed giant and spindle cells or small cells.

Mnemonic

Medullary carcinoma (3Ms)

MEN association (associated with MEN IIa and MEN IIb)
Median node dissection
a**M**yloid (associated with amyloidosis)

Quick revision of frequently asked MCQ's from thyroid cancers:

- Most common thyroid carcinoma -Papillary[Q]
- Least common thyroid carcinoma -Anaplastic[Q]
- Least malignant -Papillary[Q]
- Most malignant -Anaplastic[Q]
- Most common cancer after radiation -Papillary[Q]
- Cancer developing in Hashimoto's thyroiditis -Lymphoma[Q]
- Thyroid cancer developing in long standing multinodular goiter -Follicular, Anaplastic (rare)
- Type of thyroid cancer in MEN syndrome -Medullary[Q]
- Thyroid cancer associated with amyloidosis -Medullary[Q]
- Psammoma bodies seen in -Papillary[Q]
- Orphan-Annie Eyed Nuclei seen in -Papillary[Q]
- Thyroid Ca associated with dystrophic calcification -Papillary[Q]
- Carcinoma derived from 'C' cell of thyroid -Medullary[Q]
- Carcinoma developing in thyroglossal tract -Papillary[Q]

PARATHYROID GLAND

These are four glands situated near the thyroid gland and are composed of **chief cells** (containing PTH granules) and **oxyphil cells** (containing glycogen).

PTH secretion is responsible for elevating serum calcium level and increasing phosphate excretion in the urine. *Malignancy is the most common cause of clinically apparent hypercalcemia,* while primary hyperparathyroidism is the commonest cause of asymptomatic hypercalcemia. Increased calcium levels associated with malignancies can be because of osteolytic metastasis and secretion of a PTH related peptide (PTHrP).

Key Point

The parathyroid gland activity is controlled by the concentration of **free calcium** in the body.

HYPERPARATHYROIDISM

Hyperparathyroidism can be primary (due to autonomous, spontaneous overproduction of PTH) or secondary. Rarely it can be tertiary.

Primary Hyperparathyroidism; 1° HPTH

It is the most important cause of asymptomatic hypercalcemia and can be due to a parathyroid adenoma, primary hyperplasia or parathyroid malignancy. Hyperparathyroidism can be familial or sporadic. The important *molecular defects associated with sporadic hyperparathyroidism include:*

Key Point

Parathyroid adenoma is the *commonest cause* of **Primary HPTH**

1. *PRAD 1 proto-oncogene on chromosome 11 causes over-expression of cyclin D1 resulting in proliferation of the parathyroid cells.*
2. *MEN I suppressor gene* on 11 q 13.

The **genetic syndromes associated with familial hyperparathyroidism** include

Key Point

Best intial screening test for Primary Hyperparathyroidism: intact serum PTH levels.

1. Multiple endocrine neoplasia I and II (**MEN-I and II**), the genes for which are located on chromosome 11q and 10 q respectively.
2. Familial hypocalciuric hypercalcemia (**FHH**) gene results in reduced sensitivity to extracellular calcium and is responsible for increased secretion of PTH.

Morphology

Adenoma: There is presence of solitary nodule with shrunken glands outside the adenoma.
Primary hyperplasia: There is asymmetric involvement of all four glands with the presence of chief cells.
Parathyroid carcinoma: Involvement of a single gland.

Concept

Invasion of surrounding tissue or metastasis is the only reliable criteria for diagnosis of malignancy.

Clinical features: Usually asymptomatic, the only indicator for diagnosis is increased serum calcium and PTH. Symptomatic patients may have nephrolithiasis (urinary tract stones) or nephrocalcinosis (calcification of renal interstitium and tubules), osteoporosis, *osteitis fibrosa cystica* (bone marrow having foci of fibrosis, hemorrhage and cyst formation), metastatic calcification (in blood vessels, stomach and myocardium) and neurological changes like depression, lethargy, etc.

Key Point

Clinical features of Primary Hyperparathyroidism; 1° HPTH: "Stones, bones, abdominal groans, and psychic moans"

SECONDARY HYPERPARATHYROIDISM

It is seen in renal failure (most common cause), vitamin D insufficiency, steatorrhea and nutritional deficiency. The hypocalcemia due to any of these causes stimulates the secretion of PTH.

Key Point

Renal failure is most common cause of **Secondary HPTH**

Morphology shows the presence of hyperplastic parathyroid glands.

Clinical features are similar to primary hyperparathyroidism. There is also presence of **calciphylaxis** (*vascular calcification causing organ ischemia*). Investigations reveal reduced serum calcium and increased PTH levels.

TERTIARY HYPERPARATHYROIDISM

Autonomous *excessive parathyroid activity even when serum calcium is increased* is called as tertiary hyperparathyroidism which is usually managed by parathyroidectomy.

Key Point

Surgical removal of the parathyroid gland is the commonest cause of **hypoparathyroidism.**

HYPOPARATHYROIDISM

It is seen due to surgical removal (*commonest cause*^{Q}), congenital absence (as in DiGeorge syndrome; failure of development of 3rd and 4th pharyngeal pouch leading to absence of thyroid and parathyroid glands) or is idiopathic.

Concept

Hyperventilation worsens the symptoms because the alkalosis decreases free calcium levels.

Clinical features are due to hypocalcemia and the hallmark is tetany characterised by neuromuscular hyperexcitability, cataract, hypotension, QT prolongation on ECG, tingling in circumoral region and hands and feet. Investigations demonstrate the presence of *Chvostek sign* (percussion of facial nerve over ear causes contraction of facial muscles and upper lip) and *Trousseau sign* (inflation of blood pressure cuff more than the systolic blood pressure for around 3 minutes causes flexion at metacarpophalangeal joint with extension at interphalangeal joint). Diagnosis is made by low serum calcium levels.

PITUITARY GLAND

It is a gland weighing 0.5g, present in sella turcica. It has two distinct lobes; anterior lobe and posterior lobe (stores oxytocin and antidiuretic hormone or vasopressin).

HYPERPITUITARISM

It can be caused due to **adenoma** arising from the anterior lobe (*commonest cause*), hyperplasia and carcinoma.The majority of the adenomas are monoclonal in origin or can be associated with MEN I. Histologically; the adenomas are composed of polygonal cells with little reticulin or connective tissue. The common pituitary tumors include the following:

Recent Exam Question

Depending on the size, adenoma can be **macrodenoma (> 1cm)** or *microadenoma (< 1 cm)*.

- **Prolactinoma**: It is the *most common pituitary tumor*. Small microadenomas secrete large amount of prolactin responsible for the clinical features of *amenorrhea, galactorrhea and infertility*. Since men will obviously not have amenorrhea and females are detected early due to menstrual problems, so, microadenomas are commoner in females.

Any mass in suprasellar compartment may disturb the normal inhibitory influence of the hypothalamus on prolactin secretion resulting in hyperprolactinemia. This is called **stalk effect.**

Concept

The absence of reticulin network and presence of cellular monomorphism differentiates pituitary adenoma from non-neoplastic anterior pituitary parenchyma.

- **Growth hormone adenoma**: It is the second most common type of pituitary adenoma. Almost 40% of the patients have persistent GH activity resulting in hypersecretion of insulin like growth factor I (or IGF-I or somatomedin C) causing *gigantism in children and acromegaly in adults*. Gigantism is characterized by features of tall stature and long extremities whereas acromegaly has features of prominent jaw (prognathism), flat, broad forehead, enlarged hands and feet and enlargement of internal organs like heart, spleen, kidney etc.
- Other pituitary tumors include corticotroph cell adenoma producing ACTH (causing Cushing disease), thyrotrope adenoma secreting TSH (causing hyperthyroidism), gonadotrope adenoma secreting FSH and LH.

Key Point

The best **initial** investigation is measurement of **serum IGF-I levels** (which would be elevated) and the ***confirmatory test*** is *failure to suppresss GH production in response to an oral load of glucose.*

HYPOPITUITARISM

It is usually seen when *more than 75% of* parenchyma is lost. GH and gonadotropins (FSH, LH) are typically lost early as compared to other hormones. The causes of hypopituitarism include:

Key Point

Pituitary adenoma is the commonest cause of **panhypopituitarism**

- Compression of the normal pituitary tissue by tumors or cysts
- Pituitary surgery or radiation exposure
- Pituitary apoplexy (acute hemorrhagic infarction of a pre-existing pituitary adenoma)
- Ischemic necrosis
- Sheehan syndrome (postpartum pituitary necrosis due to obstetric hemorrhage or shock)
- Empty sella syndrome.

Definition

Sheehan syndrome is ***post-partum*** pituitary necrosis due to obstetric hemorrhage or shock

Clinical features depend upon the hormone whose function is lost for example, there can be growth failure (due to GH deficiency), loss of libido, amenorrhea, infertility (due to gonadotropin deficiency), hypothyroidism and hypoadrenalism. Loss of melanocyte stimulating hormone (MSH) may cause pallor of the skin.

POSTERIOR PITUITARY SYNDROMES

- **Diabetes insipidus**: It is caused due to deficiency of ADH or vasopressin resulting in polyuria, polydipsia, hypernatremia and hyperosmolality (due to excessive renal loss of free water) and dehydration.
- **Syndrome of inappropriate ADH secretion (SIADH)**: Excessive production of ADH can cause oliguria, retention of water, hyponatremia and cerebral edema. The causes of SIADH include ***ectopic ADH secretion by small cell lung cancer (commonest)***, injury to hypothalamus or pituitary or both by head trauma and drugs (like vincristine).

Concept

In **Primary empty sella syndrome,** the herniation of the arachnoid mater and CSF from the defect in diaphragmatic sella causes pituitary compression whereas in **secondary empty sella**, surgical removal of adenoma results in hypopituitarism

ADRENAL CORTEX

Adrenal gland is divided into adrenal cortex and adrenal medulla. The cortex is further subdivided into the following three parts from outside to inside responsible for the secretion of the hormones mentioned in front of them.

- Zona glomerulosa - Mineralocorticoids
- Zona fasciculata - Glucocorticoids
- Zona reticularis – Sex steroids

Mnemonic

GFR
Layers of adrenal cortex from outside to inside: **G**lomerulosa, **F**asciculata and **R**eticularis

So, Hyperadrenalism can have 3 distinctive patterns:
1. Cushing syndrome:Excess of glucocorticoids
2. Hyperaldosteronism: Excess of mineralocorticoids
3. Adrenogenital syndrome: Excess of sex steroids (androgens)

Key Point

Administration of **exogenous corticosteroids** is the commonest cause of **Cushing syndrome.**

CUSHING SYNDROME

It has four important causes
1. *Primary hypersecretion* due to increased ACTH (also called **Cushing disease**), seen in women of 20–30 years due to an ACTH producing microadenoma.
2. *Adrenal over-secretion* due to adenomas or carcinomas (adrenal Cushing syndrome): There is no effect of ACTH, so, also known as ACTH independent Cushing syndrome.
3. Secretion of *Ectopic ACTH*: Small cell cancer of the lung, carcinoid tumors.
4. Administration of *exogenous corticosteroids*

Concept

- Pituitary Cushing: ↑ ACTH, ↑ Cortisol
- Adrenal Cushing: ↓ ACTH, ↑ Cortisol
- Ectopic Cushing: ↑↑ ACTH, ↑ Cortisol

Morphology:

In **adrenal gland**, there can be presence of:
1. Cortical atrophy- Seen with exogenous glucocorticoids which cause feedback inhibition of ACTH leading to cortical atrophy except in *zona glomerulosa* (it *functions independent of ACTH*).
2. Diffuse hyperplasia
3. Nodular hyperplasia

Key Point

In Cushing Syndrome, there is presence of light basophilic material due to accumulation of *intermediate keratin* filaments in the cytoplasm called as **Crooke hyaline change** in the **pituitary**.

Diagnosis

There is an increased 24 hour free cortisol level in the urine with loss of normal diurnal pattern of cortisol secretion. For differentiating between the causes of Cushing syndrome, we use ***dexamethasone suppression test.*** (*See **Review of Pharmacology*** Chapter-6 *by the same authors* for details)

ADRENOGENITAL SYNDROME

It is an adrenal disorder due to excessive production of androgens resulting in virilization. It can be caused either by an adrenocortical carcinoma or more commonly congenital adrenal hyperplasia (CAH). CAH represents a group of autosomal-recessive inherited metabolic errors in which there is deficiency of the enzyme/s necessary for synthesis of cortisol. Steroidogenesis channeled into other pathways lead to increased production of androgens, which accounts for virilization. Cortisol deficiency induced increased secretion of ACTH results in adrenal hyperplasia. CAH can manifest as the following three syndromes:
1. *Salt wasting syndrome* – Total absence of 21-α hydroxylase.
2. *Simple virilising adrenogenitalism* – Presents as genital ambiguity due to partial deficiency of 21 α hydroxylase.
3. *Non classic adrenogenitalism* – Asymptomatic or may manifest as hirsutism.

Key Point

Almost 90% of cases of CAH are due to **21 α hydroxylase deficiency** leading to defective conversion of progesterone to 11-deoxycorticosterone.

Morphology

Adrenals are hyperplastic bilaterally with nodular cortex that is brown (as there is absence of lipid).

CLINICAL FEATURES

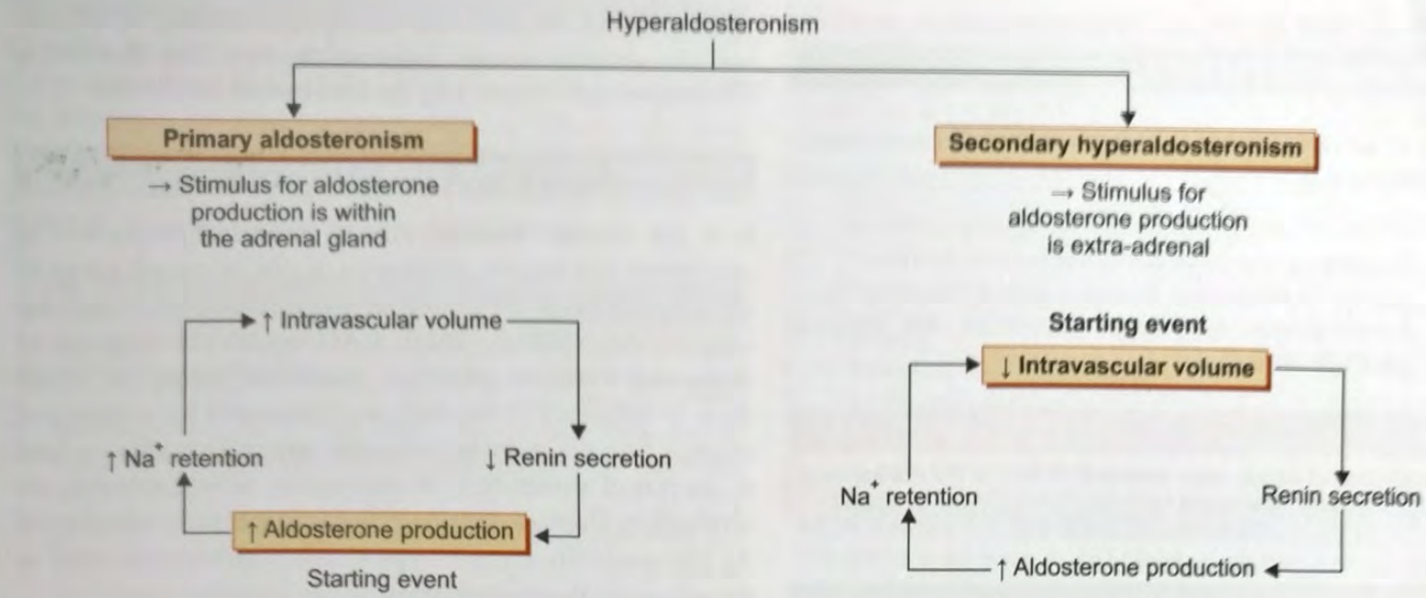
In 21-α hydroxylase deficiency, excessive androgenic activity causes signs of **masculinization** in females which may range from clitoral hypertrophy and pseudohermaphroditism in infants, to oligomenorrhea, hirsutism, and acne in post pubertal females. In males, androgen excess is associated with enlargement of the external genitalia and precocious puberty in prepubertal patients and oligospermia in older males.

HYPERALDOSTERONISM

The condition is characterized by elevated aldosterone levels leading to retention of sodium and excretion of potassium and hydrogen ions.

Key Point

Primary aldosteronism: *Diastolic hypertension* is ***present*** and there is ↓ **renin** secretion



Causes	Causes
• Adrenocortical adenoma (Conn syndrome): - Commonest cause[Q] • Primary adrenocortical hyperplasia → Due to overactivity of aldosterone synthase gene, CYP11B2 • Glucocorticoid remediable hyper aldosteronism due to fusion between CYP11B1 (11β hydroxylase) and CYP11B2 (Aldosterone synthetase) genes	• Decreased renal perfusion • Hypovolemia and edema (CHF and cirrhosis) • Pregnancy

Key Point

Secondary aldosteronism: *Diastolic hypertension* is ***absent*** and there is ↑ **renin** secretion

Concept

The **adjacent adrenal cortex** in **adenoma producing aldosterone is not atrophic** *(it is atrophic in adenoma causing Cushing syndrome).*

Key Point

Abrupt withdrawal of corticosteriods is the most common cause of **acute adrenocortical insufficiency**.

Morphology: Adrenal adenomas are usually *unilateral (more common on the left* as compared to right). The aldosterone producing adenoma has the presence of eosinophilic laminated cytoplasmic inclusions called as *'spironolactone bodies'* seen after treatment with spironolactone.

Clinical features include hypokalemia induced polyuria, polydipsia and muscle weakness. There may be associated metabolic alkalosis because of excessive aldosterone secretion. Edema is uncommon in primary hyperaldosteronism because of **'escape effect'**.

Key Point

TB is the most common cause of **Addison's disease in India**

ADRENAL INSUFFICIENCY

It can be due to **primary** adrenocortical insufficiency (primary hypoadrenalism) or ACTH deficiency induced reduced adrenal stimulation (**secondary** hypoadrenalism).

Concept

In **secondary adrenocortical insufficiency disease**, the *hyperpigmentation* of primary Addison disease **is lacking** because melanotropic hormone levels are low.

1. **Primary acute adrenocortical insufficiency**: It can be seen after stress, sudden withdrawal of steroids or massive adrenal hemorrhage. If the acute adrenal insufficiency is associated with *bilateral hemorrhagic infarction* of the adrenal glands associated with a *Neisseria infection* (septicemia) in a child, it can result in disseminated intravascular coagulation and rapidly developing hypotension and shock in the patient which is called **Waterhouse-Friedrichsen Syndrome**. The hemorrhage in this condition usually begins in the medulla and then involves the cortex.
2. **Primary chronic adrenocortical insufficiency (Addison disease):** It is a slow and progressive disease resulting from adrenocortical hypofunction. Idiopathic atrophy (by autoimmune mechanism) is the commonest cause of adrenal destruction. Autoimmune adrenalitis is associated with Autoimmune Polyendocrine Syndrome (APS) 1 and 2. The loss of adrenal cortex can also be due to tuberculosis, sarcoidosis, AIDS, hemorrhage, trauma and metastatic involvement.

Clinical features include initial manifestations of *progressive weakness and easy fatigability, gastrointestinal* disturbances like anorexia, nausea, vomiting, weight loss and diarrhea. In patients with primary adrenal disease, increased circulating levels of ACTH precursor hormone stimulate melanocytes, with resultant *hyperpigmentation* of the skin particularly of sun-exposed areas and at pressure points, such as neck, elbows, knees, and knuckles.

3. **Secondary adrenocortical insufficiency**: It occurs secondary to any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or irradiation. Further, in adrenal insufficiency secondary to pituitary malfunction, marked hyponatremia and hyperkalemia are not seen.

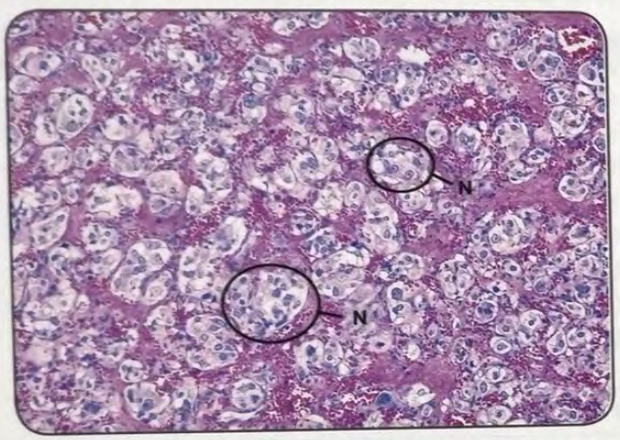


Fig. 5: Zellbalen (solid tumor nests; N) in Pheochromocytoma

Recent Exam Question

Zellballen pattern is a feature of the **carotid body tumor** which is a prototype of **parasympathetic paraganglioma.**

ADRENAL MEDULLA

The adrenal medulla is composed of neuroendocrine cells called chromaffin cells and their supporting cells called sustentacular cells. The organ is responsible for the secretion of epinephrine and nor-epinephrine and is controlled by the autonomic nervous system.

Key Point

Pheochromocytoma is 'rule of 10's' tumor.

PHEOCHROMOCYTOMA

It is a tumor of the adrenal medulla which produces catecholamines. The patients usually have severe headache, anxiety, increased sweating, tachycardia, palpitations and hypertensive episodes. The tumor is associated with a '**rule of 10's**' consisting of

- 10% are *bilateral*[Q]
- 10% are *extra-adrenal*[Q]
- 10% are *malignant*[Q]
- 10% occur in *children*[Q]
- 10% are not associated with hypertension[Q]

The tumor morphology shows the presence of small or large tumors that have yellow tan color that turns brown on incubation. There is presence of nests of chief or chromaffin cells with sustentacular cells (called **zellballen**[Q]) with abundant cytoplasm which contains catecholamine granules. The nuclei of the cells have **'salt and pepper'** appearance of the chromatin. The ***immunomarkers*** for this tumor include ***chromogranin and synaptophysin in chief cells and S-100 for sustentacular cells.***

Mnemonic

MEN III has three M
Medullary thyroid carcinoma
Medulla of adrenal (pheochro-mocytoma)
Mucosal neuroma

MEN II has two M (and one P)
Medullary thyroid carcinoma
Medulla of adrenal (pheochromo-cytoma)
Parathyroid hyperplasia

MEN I has three P
Pituiatry tumors
Pancreas tumors (insulinoma, gastrinoma)
Parathyroid tumors (hyperplasia)

Recent Exam Question

MEN 4 (12p13): CDKN1B; no common mutations identified to date

- Parathyroid adenoma
- Pituitary adenoma
- Reproductive organ tumors (e.g. testicular cancer, neuroendocrine cervical carcinoma)
- ?Adrenal + renal tumors

The definitive diagnosis of malignancy is based *exclusively on the presence of metastasis.*[Q]

The investigations reveal the presence of elevated urinary excretion of free catecholamines and their metabolites such as vanillylmandelic acid (VMA) and metanephrines.

Familial syndrome associated with pheochromocytoma

MEN IIA[Q]	MEN IIB / MEN III[Q]	Sturge-Weber syndrome[Q]	Von Hippel Lindau syndrome[Q]	Von Recklinghausen syndrome[Q]
• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia	• Medullary thyroid cancer • Pheochromocytoma • Mucosal neuromas marfanoid features	• Pheochromocytoma • Cavernous hemangioma of Vth cranial nerve distribution	• Pheochromocytoma • Renal cell cancer • Cerebellar hemangioblastoma • Angiomatosis • Renal, hepatic, pancreatic and epididymal cysts	• Pheochromocytoma • Neurofibromatosis • Cafe au lait skin spots[Q] • Schwannoma, glioma; meningiomas

Multiple Choice Questions

PANCREAS

1. **Amylin is secreted by which group of cells of pancreas?** *(All India 2012)*
   (a) Alpha cells
   (b) Beta cells
   (c) D cells
   (d) PP cells (Pancreatic polypeptide)

2. **Diabetes is diagnosed by which of the following criteria?** *(AIIMS Nov 2011)*
   (a) The level of fasting glucose is ≥ 100 mg/dL and that of postprandial glucose is ≥ 140 mg/dL
   (b) The level of fasting glucose is > 125 mg/dL and that of post prandial glucose is > 199 mg/dL
   (c) The level of plasma insulin is ≥ 6 IU/dL
   (d) The HbA1c level is ≥ 5.5%

3. **All statements are true about Nesidioblastosis except?** *(AI 2011)*
   (a) Hypoglycemic episodes are seen
   (b) Occurs more commonly in adults than in children
   (c) Histopathology shows hyperplasia of Islet cells
   (d) Diazoxide is used in treatment

4. **Insulin increases glucose entry into skeletal muscle, adipose tissues and liver cells by:** *(DPG 2011)*
   (a) Increasing the number of glucose transporter GLUT2 in all these tissues
   (b) Increasing the number of GLUT4 in muscle and adipose tissue and glucokinase in liver cells
   (c) Increasing the number of GLUT3 in skeletal muscle and adipose tissues and GLUT4 in liver cells
   (d) Increasing the number of GLUT1 in muscle, GLUT3 in adipose tissues and GLUT4 in liver cells

5. **The term fetal adenoma is used for:** *(UP 2003)*
   (a) Hepatoma liver
   (b) Fibroadenoma breast
   (c) Follicular adenoma of thyroid
   (d) Craniopharyngioma

6. **Which of the following is used to measure control of blood sugar in diabetes mellitus?** *(UP 2005)*
   (a) HbA (b) HbS
   (c) HbA2 (d) HbA 1C

7. **Two diabetic patients are seen by an endocrinologist, Dr. Saket. The first patient is a 16-year-old boy Raju who 2 years previously had presented with polyuria and polydipsia. The second patient is a 65-year-old woman Antara whose diabetes was identified by the presence of hyperglycemia on a routine blood glucose screen 10 years previously. Compared to Antara, Raju is more likely to**
   (a) Not have the HLA-DR3 or HLA-DR4 allele
   (b) Become euglycemic with oral hypoglycemic agents
   (c) Develop ketoacidosis
   (d) Have relatively high endogenous insulin levels

8. **A 62 year-old woman Omvati with advanced, metastatic lung cancer develops profound fatigue and weakness and alternating diarrhea and constipation. Physical examination demonstrates hyperpigmentation of skin, even in areas protected from the sun. Tumor involvement of which endocrine organ is most strongly suggested by this patient's presentation?**
   (a) Adrenal gland
   (b) Endocrine pancreas
   (c) Ovaries
   (d) Pituitary gland

MOST RECENT QUESTIONS

9. **Mauriac's syndrome is characterized by all except**
   (a) Diabetes (b) Obesity
   (c) Dwarfism (d) Cardiomegaly

10. **Necrobiosis lipoidica is seen in**
    (a) Diabetes insipidus
    (b) Lyme disease
    (c) Diabetes mellitus
    (d) Symmonds disease

11. **Insulin resistance in liver disease is due to:**
    (a) Decreased insulin release
    (b) Steatosis
    (c) Hepatocyte dysfunction
    (d) Decreased 'C' peptide level

12. **According to ADA guidelines, the diagnosis of diabetes is made when the fasting blood glucose is more than**
    (a) 126 mg/dl (b) 100 mg/dl
    (c) 140 mg/dl (d) 200 mg/dl

13. **Most common association in MEN I is**
    (a) Gastrinoma (b) Insulinoma
    (c) Lipoma (d) Glucagonoma

14. **True about insulinoma is:**
    (a) Alpha cell tumor
    (b) Most of them are malignant
    (c) C-peptide level is elevated
    (d) It is not associated with MEN 1 syndrome.

15. **Marker for pancreatic non-functional neuro-endocrine tumor (PNET) is:**
(a) Chromogranin-A (b) CD100
(c) CEA (d) PSA

16. **Amyloidosis is seen in which type of diabetes mellitus?**
(a) Maturity onset DM
(b) Type I DM
(c) Type II DM
(d) All of the above

17. **Gene not associated with diabetes mellitus:**
(a) PPAR-gamma (b) KCNJ11
(c) CTLA4 (d) PDGF-R

THYROID, PARATHYROID

18. **Which of the following term describes hyperthyroidism following intake of iodine in patients suffering from endemic goiter?** *(All India 2012)*
(a) Wolff-Chaikoff effect
(b) Jod-Basedow effect
(c) Graves disease
(d) Hashimoto's thyroiditis

19. **A 17 year old girl who was evaluated for short height was found to have an enlarged pituitary gland. Her T_4 was low and TSH was increased. Which of the following is the most likely diagnosis?** *(AIIMS Nov 2011)*
(a) Pituitary adenoma
(b) TSH-secreting pituitary tumor
(c) Thyroid target receptor insensitivity
(d) Primary hypothyroidism

20. **All are true about Hashimoto's thyroiditis except:** *(AIIMS Nov 2011)*
(a) Follicular destruction
(b) Lymphocytic infiltration
(c) Oncocytic metaplasia
(d) Orphan Annie eye nuclei

21. **Hypothyroidism is seen in:** *(AI 2011)*
(a) Hashimoto's Thyroiditis
(b) Graves' disease
(c) Toxic Multinodular Goitre
(d) Struma ovarii

22. **All are true about Hashimoto's thyroiditis except:** *(AIIMS May 2010)*
(a) Follicular destruction
(b) Lymphocytic infiltration
(c) Oncocytic metaplasia
(d) Orphan Annie eye nuclei

23. **MC thyroid cancer is:** *(AI 2008)*
(a) Papillary carcinoma
(b) Follicular carcinoma
(c) Medullary carcinoma
(d) Anaplastic carcinoma

24. **Which of the following gene defect is associated with development of medullary carcinoma of thyroid?** *(AI 2004)*
(a) RET Proto-oncogene
(b) FAP gene
(c) Rb gene
(d) BRCA 1 gene

25. **Medullary carcinoma of the thyroid is associated with which of the following syndrome:** *(AI 2003)*
(a) MEN I
(b) MEN II
(c) Li-Fraumeni syndrome
(d) Hashimoto's thyroiditis

26. **The expression of the following oncogene is associated with a high incidence of medullary carcinoma of thyroid:** *(AIIMS Nov 2005)*
(a) p 53
(b) Her 2 neu
(c) RET proto oncogene
(d) Rb gene

27. **DeQuervain's thyroiditis is also known as:**
(a) Granulomatous thyroiditis *(Delhi PG-2006)*
(b) Struma lymphomatosa
(c) Acute thyroiditis
(d) Hashimoto thyroiditis

28. **Hurthle cells are seen in:** *(Delhi PG-2005)*
(a) Granulomatous thyroid disease
(b) Hashimoto's thyroiditis
(c) Papillary carcinoma of thyroid
(d) Thyroglossal cyst

29. **Which of the following histological type of carcinoma thyroid most commonly metastasizes to lymph nodes?**
(a) Medullary *(Delhi PG-2005)*
(b) Anaplastic
(c) Papillary
(d) Follicular

30. **Struma ovarii is composed entirely of**
(a) Mature thyroid tissue *(Karnataka 2006)*
(b) Immature-thyroid tissue
(c) Primary ovarian carcinoid tissue
(d) None of the above

31. **Oncocytes are found in all of the following except:**
(a) Thyroid *(DNB-2000, 2003, 2006, 2007)*
(b) Pancreas
(c) Pituitary
(d) Pineal body
(e) None of the above

32. **Hurthle cells are seen in:** *(DNB- 2000, 2005)*
(a) Hashimoto's thyroiditis
(b) Granulomatous thyroiditis
(c) Carcinoma of thyroid
(d) Acute thyroiditis

33. **Calcitonin is a marker of thyroid:** *(UP 2001)*
(a) Papillary carcinoma
(b) Medullary carcinoma
(c) Anaplastic carcinoma
(d) Adenocarcinoma

34. **In Hashimoto's thyroiditis, there is infiltration of:**
(a) Macrophages (b) Neutrophils *(UP 2003)*
(c) Leukocytes (d) Eosinophils

35. **Myasthenia gravis is associated with:** *(UP 2006)*
(a) Hypergammaglobulinemia
(b) Thymoma
(c) Squamous cell carcinoma
(d) Hepatic adenoma

36. **In MEN II B syndrome includes all except:**
(a) Hyperparathyroidism *(UP 99, 2007)*
(b) Marfanoid features
(c) Medullary thyroid carcinoma
(d) Pheochromocytoma

37. **Plunging goiter is** *(RJ 2000)*
(a) Solitary nodule
(b) Colloid goiter
(c) Retro-sternal goiter
(d) Medullary ca

38. **All are parts of MEN-I except:** *(RJ 2006)*
(a) Pituitary tumor
(b) Parathyroid tumor
(c) Pancreatic tumor
(d) Medullary carcinoma of thyroid

MOST RECENT QUESTIONS

39. **Psammoma bodies are seen in all except:**
(a) Papillary carcinoma of thyroid
(b) Papillary adenoma of colon
(c) Meningioma
(d) Papillary cancer of the ovary

40. **Papillary carcinoma associated with aggressiveness are all except:**
(a) Follicular variant
(b) Unencapsulated
(c) Tall cell variant
(d) Oxyphilic (Hurthle) cell type

41. **Which thyroid carcinoma is of C-Cell origin:**
(a) Medullary carcinoma
(b) Follicular carcinoma
(c) Papillary carcinoma
(d) Anaplastic carcinoma

42. **All of the following regarding thyroid carcinoma are true except:**
(a) Prognosis of follicular carcinoma is worse than papillary carcinoma
(b) Medullary carcinoma is autosomal recessive
(c) Anaplastic carcinoma causes local invasion early
(d) Medullary and papillary carcinoma both spread by lymphatic route

43. **Hurthle cell tumor is:**
(a) Papillary carcinoma
(b) Follicular carcinoma
(c) Medullary carcinoma
(d) Colloid carcinoma
(e) Ionizing radiation in early decades is a major risk factor

44. **About papillary carcinoma of thyroid, all are true except:**
(a) Prognosis better
(b) Psammoma body present in 50% cases
(c) Early metastasis with poor prognosis
(d) Spreads by the lymphatic route

45. **A 51-year-old man Sonu with a history of recurrent calcium-containing renal stones presents to the emergency room with excruciating flank pain and blood in the urine. This patient is likely to have which of the following underlying disorders?**
(a) Anemia of chronic disease
(b) Chronic Proteus infection
(c) Hyperparathyroidism
(d) Hyperaldosteronism

46. **Fine needle aspiration cytology is not able to detect which of the following?**
(a) Papillary carcinoma
(b) Hashimoto thyroiditis
(c) Follicular cancer
(d) Medullary cancer

47. **High calcium intake can lead to:**
(a) Osteoporosis
(b) Osteopetrosis
(c) Milk alkali syndrome
(d) Renal failure

48. **Most common thyroid cancer after radiation exposure is:**
(a) Papillary cancer (b) Medullary cancer
(c) Follicular cancer (d) Anaplastic cancer

49. **Orphan Annie eye nuclei appearance is characteristic of:**
(a) Papillary carcinoma thyroid
(b) Carcinoma pituitary
(c) Paraganglioma
(d) Meningioma

50. **The laboratory screening test which suggests normal thyroid function is**
(a) TSH (b) Free T4
(c) T3 (d) Free T3

51. **Medullary carcinoma of the thyroid is associated with which of the following syndrome:**
(a) MEN I
(b) MEN II
(c) Fraumeni syndrome
(d) Hashimoto's thyroiditis

52. **Which thyroid carcinoma has amyloid?**
(a) Papillary (b) Follicular
(c) Medullary (d) Anaplastic

53. **Which is not seen in MEN I:**
(a) Parathyroid adenoma
(b) Pancreatic cancer
(c) Prolactinoma
(d) Medullary carcinoma thyroid

54. **Werner syndrome is:**
(a) MEN I (b) MEN IIA
(c) MEN IIB (d) AIP

55. **Psammoma bodies are seen in?**
(a) Papillary carcinoma thyroid
(b) Medullary carcinoma thyroid
(c) Follicular carcinoma thyroid
(d) Anaplastic carcinoma

56. **Lymphatic spread is most commonly seen with which type of thyroid cancer?**
(a) Papillary
(b) Medullary
(c) Follicular
(d) Lymphoma

57. **Fine needle aspiration cytology is not enough to diagnose which of the following?** *(AIIMS Nov 2016)*
(a) Papillary carcinoma of thyroid
(b) Carcinoma breast
(c) Adenocarcinoma lung
(d) Follicular carcinoma of thyroid

58. **Which malignancy develops in long standing goiter?**
(a) Papillary carcinoma
(b) Follicular carcinoma
(c) Medullary carcinoma
(d) Anaplastic carcinoma

59. **All of these are seen in MEN-1 syndrome *except*:** *(AIIMS Nov 2016)*
(a) Foregut carcinoid
(b) Posterior pituitary tumors
(c) Pancreatic neuroendocrine tumors
(d) Parathyroid hyperplasia

60. **All of the following are feature of granulomatous thyroiditis except:**
(a) Hyperthyroidism (b) Hypothyroidism
(c) Painless (d) Giant cell histology

61. **Brown tumour is seen in:**
(a) Hyperthyroidism
(b) Hypothyroidism
(c) Hyperparathyroidism
(d) Hypoparathyroidism

62. **Which of the following is true in parathyroid carcinoma?**
(a) 5–10% incidence
(b) Reduced serum calcium levels
(c) Cytology is diagnostic
(d) Metastasis is essential

63. **In follicular carcinoma, the most commonly detectable chromosomal translocation is:**
(a) PAX8-PPARγ1 (b) RET-PTC
(c) RET (d) JAK –TEL

PITUITARY

64. **Which of the following is true about pituitary tumor?**
(a) It present in 10% of brain tumors *(PGI Dec 2005)*
(b) Erodes the sella and extends into surrounding area
(c) Prolactinoma is least common
(d) It is differentiated by reticulin stain

65. **In Galactorrhea - amenorrhea syndromes, which is the investi-gation you should advise (apart from serum prolactin)?**
(a) TSH
(b) LH
(c) Urinary ketosteroids
(d) HCG

ADRENAL GLAND

66. **Addison's disease was first reported by Thomas Addison. It is still being widely reported from various parts of the world/throughout the world. Which of the following is the most common cause of Addison's disease in India?** *(AIIMS Nov 2011)*
(a) Post-partum pituitary insufficiency
(b) Tuberculous adrenalitis
(c) HIV
(d) Autoimmune adrenal insufficiency

67. **All are true statements about pheochromocytoma except?** *(AI 2011)*
(a) 90% are malignant
(b) 95% occur in the abdomen
(c) They secrete catecholamines
(d) They arise from sympathetic ganglia

68. **All the following familial syndromes are associated with development of pheochromocytomas except:**
(a) Sturge-Weber syndrome *(AIIMS Nov 2002)*
(b) Von Recklinghausen disease
(c) MEN type II
(d) Prader-Willi syndrome

69. **The most common cause of Addison's disease is:**
(a) Autoimmune adrenalitis *(AIIMS May 2002)*
(b) Meningococcal septicemia
(c) Malignancy
(d) Tuberculosis

70. **Most important histopathological indicator of malignancy in Pheochromocytoma is:**
(a) Pleomorphism *(Delhi PG-2005)*
(b) High mitotic activity
(c) Vascular invasion
(d) None

71. **Which of the following is most often involved in multiple endocrine neoplasia I:** *(DNB- 2007)*
(a) Pituitary (b) Pancreas
(c) Parathyroid (d) Thyroid

72. **All are true about pheochromocytoma except:**
(a) 25% are malignant *(UP 2002)*
(b) Variety of APUDOMA
(c) Histological type is chromaffin cells
(d) Most common neuroendocrine hormone secreting tumor

73. **In Cushing syndrome, the tumor is associated with**
(a) Increased level of epinephrine *(UP 2004)*
(b) Decreased level of epinephrine
(c) Elevated levels of cortisol
(d) Increased level of norepinephrine

74. **Vanillylmandelic acid (VMA) is increased in**
(a) Hyperparathyroidism *(UP 2008)*
(b) Pheochromocytoma
(c) MEN-I
(d) Addison's disease

MOST RECENT QUESTIONS

75. **Most common cause of Cushing's syndrome is**
(a) Exogenous corticosteroids
(b) Pituitary tumor
(c) Adrenal adenoma
(d) Adrenal carcinoma

76. **Submucosal neuroma is associated with:**
(a) MEN I (b) MEN II A
(c) MEN II B (d) None of the above

77. **Most common site of pheochromocytoma after adrenal gland is:**
(a) Hilum of kidney
(b) Organs of Zuckerkandl
(c) Neck
(d) Urinary bladder

78. **True about adrenal pheochromocytoma is:**
(a) Chromaffin negative
(b) Mostly malignant
(c) Bilateral in 10% of cases
(d) Unilateral in 10% of cases

79. **Most common cause of Cushing's syndrome is:**
(a) Pituitary adenoma
(b) Adrenal adenoma
(c) Exogenous steroids
(d) Ectopic ACTH

80. **Which of the following is not estrogen dependant carcinoma:**
(a) Lobular carcinoma breast
(b) Follicular thyroid carcinoma
(c) Endometrial leiomyosarcoma
(d) Carcinoma prostate

81. **A 40-year old man with central obesity, "buffalo hump" and vertical purple striae on the abdomen has fasting blood glucose is in the high normal range. Plasma levels of ACTH and cortisol are both increased compared to normal. An overnight high-dose dexamethasone test produces 75% suppression of cortisol levels. This patient most likely has**
(a) Addison's disease
(b) an ectopic ACTH-secreting tumor
(c) Conn's syndrome
(d) Cushing's disease

82. **In Conn's syndrome, all the following are seen, except**
(a) Hypokalemia (b) Hypernatremia
(c) Hypertension (d) Edema

83. **Dilutional hyponatremia is seen in:**
(a) Addison's disease
(b) Diabetes insipidus
(c) Diuretic therapy
(d) None

84. **Tumor that follows rule of 10 is:**
(a) Pheochromocytoma
(b) Oncocytoma
(c) Lymphoma
(d) Renal cell carcinoma

85. **Ectopic pheochromocytoma may originate from which of the following?**
(a) Organ of Zuckerkandl
(b) Bladder
(c) Filum terminale
(d) Meckel diveticulum

86. **Which one of the following is not seen in pheochromocytoma?**
(a) Hypertension (b) Episodic palpitations
(c) Weight loss (d) Diarrhea

87. **Mitotic figures and giant cells are seen in which of the following tumor?**
(a) Benign and malignant thyroid cancers
(b) Benign and malignant pheochromocytoma
(c) Benign and malignant liver tumors
(d) Benign and malignant renal tumors

88. **Homer rosette is seen in:**
(a) Neuroblastoma
(b) Nephroblastoma
(c) Hepatoma
(d) Ependymoma

89. **Which of the following is not part of the "rule of 10" in pheochromocytoma?**
(a) 10% are bilateral
(b) 10% are malignant
(c) 10% are extra adrenal
(d) 10% are symptomatic

90. **Which of the following is not a feature of Sipple Syndrome?**
(a) Pheochromocytoma
(b) Medullary carcinoma
(c) Hyperthyroidism
(d) Hyperparathyroidism

ASSERTION AND REASON QUESTIONS

1–10. Will have two statements, assertion and reason. Read both of them carefully and answer according to these options.
(a) Both assertion and reason are true and reason is correct explanation of assertion.
(b) Both assertion and reason are true and reason is not the correct explanation of assertion.
(c) Assertion is true and reason is false.
(d) Both assertion and reason are false.

1. **Assertion:** C peptide levels are used as a surrogate marker for insulin secretion
Reason: C peptide and insulin are secreted in equal amounts after β cell stimulation
2. **Assertion:** Pheochromocytoma is also referred to as 'rule of 10 tumor'
Reason: Pheochromocytoma is seen in 10% familial cases
3. **Assertion:** FNAC is not useful for diagnosing follicular thyroid cancer
Reason: Capsular invasion is the definitive feature differentiating follicular adenoma from follicular carcinoma
4. **Assertion:** Postpartum thyroiditis presents as a painful enlarged thyroid gland
Reason: Postpartum thyroiditis is preceded by a viral infection (measles, mumps etc)
5. **Assertion:** Graves disease is most common cause of endogenous hyperthyroidism.
Reason: Autoantibodies like TBIG may lead to reduced thyroid function
6. **Assertion:** Myocardial infarction is the commonest cause of death in diabetes
Reason: Uncontrolled blood glucose leads to capillary dysfunction in target organs
7. **Assertion:** Skin hyperpigmentation is a feature of Addison's disease
Reason: ACTH precursor has amino acid sequence similar to melanocyte stimulating hormone.
8. **Assertion:** Non ketotic hyperosmolar is a commoner complication than diabetic ketoacidosis in type 2 diabetes.
Reason: Insulin has a 'fat sparing effect' preventing fatty acid oxidation.
9. **Assertion:** MEN 2A (Sipple syndrome) is characterized by pheochromocytoma, medullary carcinoma of thyroid and parathyroid hyperplasia.
Reason: MEN 2A is associated with a loss of function mutation in RET proto-oncogene
10. **Assertion:** Amyloid deposition is associated with medullary variant of thyroid cancer
Reason–T he altered cacitonin secreted by parafollicular cells gets deposited in the thyroid stroma

Explanations

1. **Ans. (b) Beta cells** *(Ref: Robbins 9/e p446, 8th/442, 1130)*

> - ***Amylin is secreted by*** b ***cells of the pancreas. It reduces food intake and weight gain*** by acting on central neurons in the hypothalamus.

2. **Ans. (b) The level of fasting glucose is > 125 mg/dL and that of post prandial glucose is > 199 mg/dL**
(Ref: Harrison 18th/2970, Robbin 9/e p1106)

3. **Ans. (b) Occurs more commonly in adults than in children**
(Ref: Nelson Pediatrics 18th/660-662; Robbins, 9/e p1121)

> - **Congenital hyperinsulinism** was formerly termed as Nesidioblastosis.
> - It is also known as *diffuse Islet cell hyperplasia.*
> - It can occur in adults also but **more commonly seen in neonates and children.**
> - Hypoglycemic episodes occur due hyperinsulinemia.
> - Medical management includes *Frequent feedings, Diazoxide and Somatostatin.*

4. **Ans. (b) Increasing the number of GLUT4 in muscle and adipose tissue and glucokinase in liver cells**
(Ref: Harrison 17th/2278-9, 2282 Robbins 8th/1134, 9/e p1112)

Insulin acts by binding to its receptor and stimulating intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS). Activation of the phosphatidylinositol-3′-kinase (PI-3-kinase) pathway stimulates translocation of glucose transporters (e.g., **GLUT4**) to the cell surface, an event that is **crucial for glucose uptake by skeletal muscle and fat.** Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

> **Glucokinase** catalyzes the formation of glucose-6-phosphate from glucose, a reaction that is **important for** glucose sensing by the beta cells and for **glucose utilization by the liver.** As a result of glucokinase mutations, higher glucose levels are required to elicit insulin secretory responses, thus altering the set point for insulin secretion, responsible for Maturity Onset Diabetes of Young-1 (MODY-1).

5. **Ans. (c) Follicular adenoma of thyroid**
(Ref: Robbins 9/e p1093, 8th/1118; 7th/1175, Harsh Mohan 6th/810)

6. **Ans. (d) HbA 1C** *(Ref: Robbins 8th/1138, 9/e p1115)*

7. **Ans. (c) Develop ketoacidosis**
(Ref: Robbins 8th/1145, 9/e p1113-1114)

Raju probably has type 1 (juvenile onset) diabetes mellitus, while Antara probably has type 2 (maturity onset) diabetes mellitus. These two types of diabetes differ in many respects. Ketoacidosis is more likely to develop in type 1 diabetes.

Type 1 diabetes has a strong association with HLA-DR3 and HLA-DR4 (option A), while type 2 does not have any strong HLA associations.

Type 1 is usually apparently due to viral or immune destruction of beta cells, while type 2 is apparently usually due to increased resistance to insulin; consequently the 65-year-old, rather than the 16-year-old, is more likely to have relatively high endogenous levels of insulin (option D).

Type 2 diabetes can often be controlled with oral hypoglycemic agents (option B), while type 1 diabetics generally require insulin. Note that some type 2 diabetics also may require insulin as the disease evolves.

8. **Ans. (a) Adrenal gland**
(Ref: Robbins 8th/1156-1157, 9/e p1130-11131)

This is Addison disease, in which severe adrenal disease produces adrenocortical insufficiency. Causes include auto-immune destruction, congenital adrenal hyperplasia, hemorrhagic necrosis, and replacement of the glands by either tumor (usually metastatic) or granulomatous disease (usually tuberculosis). The symptoms can be subtle and nonspecific (such as those illustrated), so a high clinical index of suspicion is warranted. Skin hyperpigmentation is a specific clue that may be present on physical examination, suggesting excess pituitary ACTH secretion. (The ACTH precursor has an amino acid sequence similar to MSH, melanocyte stimulating hormone.) Most patients have symptoms (fatigue, gastrointestinal distress) related principally to glucocorticoid deficiency. In some cases, however, mineralocorticoid replacement may also be needed for symptoms of salt wasting with lower circulating volume.

> - Except in the case of primary pancreatic cancer, complete tumor replacement of the endocrine pancreas (option B) would be uncommon. In any event, pancreatic involvement would be associated with diabetes mellitus.
> - Involvement of the ovaries (option C) by metastatic tumor (classically gastric adenocarcinoma) would produce failure of menstruation.
> - Involvement of the pituitary gland (option D) could produce Addisonian symptoms, but the pigmented skin suggests a primary adrenal problem rather than pituitary involvement.

9. **Ans. (d) Cardiomegaly** *(Ref: internet)*

> **Mauriac syndrome** is a rare complication of type 1 diabetes mellitus in children associated with hepatomegaly, growth impairment and cushingoid features.

10. Ans. (c) Diabetes mellitus

(Ref: Harrison 18th/chapter 53)

Lesions of ***necrobiosis lipoidica*** are found primarily on the shins (90%), and patients can have ***diabetes mellitus*** or develop it subsequently. Characteristic findings include a central yellow color, atrophy (transparency), telangiectasias, and a red to red-brown border. Ulcerations can also develop within the plaques. Biopsy specimens show necrobiosis of collagen and granulomatous inflammation.

11. Ans. (b) Steatosis

(Ref: Robbin 8/e p1136, Joslin's Diabetes Mellitus 14/e p436)

Insulin resistance is defined as the failure of target tissues to respond normally to insulin. It leads to decreased uptake of glucose in muscle, reduced glycolysis and fatty acid oxidation in the liver, and an inability to suppress hepatic gluconeogenesis.

- The *loss of insulin sensitivity in the hepatocytes is likely to be the largest contributor to the pathogenesis of insulin resistance in vivo.*
- *Obesity* is the most important factor in the *development of insulin resistance.*

"In type 2 diabetes patients, the presence of hepatic steatosis is associated with reduced insulin stimulated glucose uptake. Increased hepatic fat accumulation results in impaired peripheral insulin action"....Joslin pg 436

12. Ans. (a) 126 mg/dl *(Ref: Robbins 9th/1106)*

13. Ans. (a) gastrinoma *(Ref: Robbins 9/e p1136)*

Know the following about MEN-1-associated pancreatic endocrine tumors:

- **Pancreatic polypeptide** is the **most commonly** secreted product, however it is **non functional**.
- *In functional tumors,* ***gastrinomas are the commonest.***

14. Ans. (c) C-peptide level is elevated

(Ref: Robbins 9/e p1121)

- **β-cell** tumors (**insulinomas**) are the **most common** of pancreatic endocrine neoplasms.
- **Most** of them are **benign**.
- It is characterized by hypoglycemic episodes when blood glucose is less than 50 mg/dL.
- Plasma levels of **insulin and C peptide** are **elevated**.

15. Ans. (a) Chromogranin-A *(Ref: Robbins 9/e p717)*

16. Ans. (c)) Type II DM *(Ref: Robbins 9/e p259)*

17. Ans. (d)) PDGF-R *(Ref: Robbins 9/e p1116)*

18. Ans. (b) Jod-Basedow effect

(Ref: Harrison 18th/2930, 2932)

- **Jod Basedow effect** is characterized by **excessive thyroid hormone synthesis** caused by increased iodine exposure.
- **Wolff Chaikoff effect** is **iodide dependent suppression** of the thyroid.

19. Ans. (d) Primary hypothyroidism

(Ref: Robbins 8th/1109-1110, 9/e p1083-5)

Analyzing all options,

- In pituitary adenoma/TSH secreting pituitary tumor increased TSH with increased T3/4 would be seen. (excludes 'a' and 'b')
- In thyroid hormone resistance ***increased T_4 as well as T_3*** with ***low TSH*** will be seen. (option 'c' excluded)
- **Primary hypothyroidism** is due to defect in the thyroid gland itself. This is associated with ***high TSH with low T_4*** will be seen.

20. Ans. (d) Orphan Annie eye nuclei

(Ref: Robbins 8th/1111, 9th/1087)

Robbins writes...'The nuclei of **papillary carcinoma** cells contain finely dispersed chromatin, which imparts an optically clear or empty appearance, giving rise to the designation ground-glass or *Orphan Annie eye nuclei'.*

Salient features of Hashimoto Thyroiditis (Chronic Lymphocytic Thyroiditis)

Most common type of thyroiditis[Q] *Most common cause of hypothyroidism in areas having sufficient iodine levels.*
Genetic association
Associated with HLA-DR5, HLA-DR3 and chromosomal defects like Turner and Down syndrome.
Gland morphology
Diffusely enlarged gland with *intact capsule.*
Microscopic finding
Presence of *well developed germinal centers* and extensive lymphocytic infiltration
Atrophied[Q] thyroid follicles lined by epithelial cells having abundant eosinophilic and granular cytoplasm called **Hurthle cells.**[Q] (this is a metaplastic response of epithelium to the ongoing injury)
Chronic inflammation with lymphocytic infiltration[Q] of the thyroid gland (the latter responsible for the term *'struma lymphomatosa'*).
Clinical findings
Painless enlargement of thyroid gland in a middle aged female presenting with hypothyroidism. Associated with type 1 diabetes, SLE, Sjogren syndrome, myasthenia gravis, increased risk of B cell lymphoma

21. Ans. (a) Hashimoto's thyroiditis

(Ref: Harrison 17th/2230, Robbins 9th/1087)

Hashimoto's thyroiditis is a cause of hypothyroidism whereas other diseases mentioned like Graves' disease, toxic Multinodular goiter and struma ovarii result in hyperthyroidism.

Causes of hypothyroidism

- Autoimmune hypothyroidism: **Hashimoto's thyroiditis**, atrophic thyroiditis
- Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
- Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicyclic acid, interferon-alpha and other cytokines, aminoglutethimide
- Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
- Iodine deficiency
- Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis

Causes of hyperthyroidism

- Graves' disease
- Toxic multinodular goiter
- Toxic adenoma
- Functioning thyroid carcinoma metastases
- Activating mutation of the TSH receptor
- Activating mutation of G_{sa} (McCune-Albright syndrome)
- Struma ovarii
- Drugs: iodine excess (Jod-Basedow phenomenon)

22. Ans. (d) Orphan Annie eye nuclei
(Ref: Robbins 8th/1111, 9/e p1096)

Robbins writes…'The nuclei of **papillary carcinoma** cells contain finely dispersed chromatin, which imparts an optically clear or empty appearance, giving rise to the designation ground-glass or *Orphan Annie eye nuclei'*.

23. Ans. (a) Papillary carcinoma
(Ref: Robbins 7th/735-736, 9/e p1095)

24. Ans. (a) RET Proto-oncogene
(Ref: Harrison's 17th/2361, Robbins 7th/1182, 9/e p1095)

- Medullary carcinoma of thyroid (MCT) pheochromocytoma and hyperparathyroidism are present in MEN-2A whereas the association of MCT, pheochromocytoma, mucosal neuroma and Marfanoid habitus is designated MEN-2B.
- Most patients of MEN-2 have mutations of RET-proto-oncogene.
- This gene is located on chromosome 10q11.2.
- Most common germline mutation of RET is at codon 634 and is associated mostly with MEN 2A.
- Most common somatic mutation of RET is at codon 918 and is mostly associated with MEN 2B.
- Other genes given in the question can be remembered from their name only:
  - FAP: Familial adenomatous polyposis
  - Rb: Retinoblastoma
  - BRCA1: Breast cancer

25. Ans. (b) MEN II *(Ref: Robbins 7th/1222, 9/e p1099)*

Multiple endocrine neoplasia (MEN) syndromes are a group of genetically inherited diseases resulting in proliferative lesions (hyperplasia, adenoma and carcinoma) of multiple endocrine glands.

MEN I (Wermer's Syndrome)	MEN II A (Sipple's syndrome)	MEN II B
• Parathyroid hyperplasia/adenoma • Pancreatic islet cell hyperplasia/adenoma/carcinoma • Pituitary hyperplasia/adenoma • *Mutant gene is MEN 1*	• Parathyroid hyperplasia/adenoma • Medullary carcinoma of thyroid • Pheochromocytoma • *Mutant gene is RET*	• Medullary carcinoma of thyroid • Pheochromocytoma • Mucosal and gastrointestinal neuromas • Marfanoid features • *Mutant gene is RET*

26. Ans. (c) RET proto-oncogene *(Ref: Robbins 9/e 1099)*

RET proto-oncogene is mutated in MEN-2A and MEN-2B syndromes. These are associated with medullary carcinoma of thyroid.

27. Ans. (a) Granulomatous thyroiditis
(Ref: Robbins 7th/1170, 9/e p1088)

- DeQuervain's thyroiditis is also referred to as granulomatous thyroiditis or subacute thyroiditis. *(For details, see text)*

28. Ans. (b) Hashimoto's thyroiditis *(Ref: Robbins 9/e p1087)*

- Hurthle cells (Oncocytes) are epithelial cells with abundant eosinophilic, granular cytoplasm.
- Hurthle cells are seen in following conditions:
  - Hashimoto's thyroiditis
  - Hurthle cell adenoma of thyroid
  - Hurthle cell carcinoma of thyroid
- Hurthle cells are eosinophilic due to abundance of mitochondria.
- Hurthle cells are also called *Ashkanazy* cells or *oxyphil cells*.

29. Ans. (c) Papillary *(Ref: Robbins 7th/1180, 9/e p1097)*

- Most papillary carcinoma present as asymptomatic thyroid nodules, but the first manifestation may be a mass in cervical nodes.
- Follicular carcinoma has little propensity for lymphatics but high for vascular invasion and spreads to bones, lungs and CNS.
- In anaplastic Ca direct spread (extensive local invasion) is more common than vascular.

30. Ans. (a) Mature thyroid tissue *(Ref: Robbins 9/e p1030)*

Struma ovarii is a specialized teratoma which is always unilateral and is composed of mature thyroid tissue. It may manifest itself with the features of hyperthyroidism.

31. Ans. (d) Pineal body *(Ref: Internet)*

Oncocytes are large cells with small irregular nuclei and dense acidophilic granules due to the presence of abundant mitochondria. These are found in oncocytomas

of the kidney, salivary glands, and endocrine glands (thyroid, parathyroid, pituitary, adrenal cortex and pancreatic islets).

32. **Ans. (a) Hashimoto's thyroiditis** *(Ref: Robbins 9/e p1087)*

33. **Ans. (b) Medullary carcinoma** *(Ref: Robbins 9/e p1099)*

34. **Ans. (c) Leukocytes** *(Ref: Robbins 9/e p1087)*

35. **Ans. (b) Thymoma** *(Ref: Robbins 9/e p1236)*

36. **Ans. (a) Hyperparathyroidism** *(Ref: Robbins 9/e p1136-1137, 8th/1162; 7th/1222)*

37. **Ans. (c) Retro-sternal goiter** *(Ref: Robbins 9/e p1092)*

38. **Ans. (d) Medullary carcinoma of thyroid** *(Ref: Robbins 8th/1162, 9/e p1136)*

39. **Ans. (b) Papillary adenoma of colon** *(Ref: Robbins 9/e p1096, 1314, 1025, 8th/38,1122; 7th/859)*

40. **Ans. (a) Follicular variant** *(Ref: Robbins 9/e p1096-1097)*

41. **Ans. (a) Medullary carcinoma** *(Ref. Robbins 9/e p1099)*

42. **Ans. (b) Medullary carcinoma is autosomal recessive** *(Ref. Robbins 8th/1124-1126, 9/e p1095)*

43. **Ans. (b) Follicular carcinoma** *(Ref: Robbins 9/e p1098)*

44. **Ans. (c) Early metastasis with poor prognosis** *(Ref: Robbins 8th/1121-1122, 9/e 1097)*

45. **Ans. (c) Hyperparathyroidism** *(Ref: Robbins 9/e p1103)*
The patient's history of recurrent urolithiasis with calcium-containing stones implies a disorder in the regulation of calcium concentration. Hyperparathyroidism is associated with increased parathormone (PTH) levels, which can produce hypercalcemia, hypercalciuria, and, ultimately, renal stones.
Anemia of chronic disease (option A) does not produce calcium stones. The patient presents with a chronic condition and hematuria but the urinary blood loss is not usually significant enough to produce an anemic state.
Hyperaldosteronism (option D) results in potassium depletion, sodium retention, and hypertension. *Primary hyperaldosteronism (Conn's syndrome)* is associated with adrenocortical adenomas in 90% of patients and is characterized by *decreased renin*. **Secondary hyperaldosteronism** results from excessive stimulation by angiotensin II that is caused by **excess renin production** (plasma renin-angiotensin levels are high). Neither condition is associated with renal stones.

46. **Ans. (c) Follicular cancer** *(Ref: Robbins 9th/1094)*
Direct quote... *"Because of the need for evaluating capsular integrity, the definitive diagnosis of adenomas can be made only after careful histologic examination of the resected specimen. Suspected adenomas of the thyroid are therefore removed surgically to exclude malignancy".*

47. **Ans. (c) Milk alkali syndrome** *(Ref: Robbins 9th/65)*
Milk -alkali syndrome is due to excessive ingestion of calcium and absorbable antacids such as milk or calcium carbonate. This is associated with the development of metastatic calcification.

48. **Ans. (a) Papillary cancer** *(Ref: Robbins 9/e p1095)*
- There is a marked increase in the incidence of **papillary carcinomas** among children exposed to **ionizing radiation** (particularly during the first 2 decades of life).
- ***Deficiency of dietary iodine*** (and so, goiter) is linked with a higher frequency of **follicular carcinomas**.

49. **Ans. (a) Papillary carcinoma thyroid** *(Ref: Robbins 8/e p1122, 9/e p1096)*
- The nuclei of papillary carcinoma cells contain finely dispersed chromatin, which imparts an **optically clear** or **empty** appearance, giving rise to the designation **ground-glass** or **Orphan Annie eye nuclei**.

50. **Ans. (a) TSH** *(Ref: Robbins 9th/1083)*

51. **Ans. (b) MEN II** *(Ref: Robbins 8/e p1162, 9/e p1137)*
- ***MEN-2A***, or ***Sipple syndrome***, is characterized by ***pheochromocytoma, medullary carcinoma***, and ***parathyroid hyperplasia***.
- ***MEN-2B*** has significant clinical overlap with MEN-2A. Patients develop medullary thyroid carcinomas, which are usually multifocal and more aggressive than in MEN-2A, and pheochromocytomas. However, unlike in MEN-2A, ***primary hyperparathyroidism is not present***

52. **Ans. (c) Medullary** *(Ref: Robbins 8/e p1125, 9/e p1099)*
Acellular **amyloid deposits**, derived from altered calcitonin polypeptides, are present in the adjacent stroma in many cases of medullary thyroid cancer.

53. **Ans. (d) Medullary carcinoma thyroid** *(Ref: Robbins 8/e p1162, 9/e p1136)*
MEN-1, or *Wermer syndrome*, is characterized by abnormalities involving the *parathyroid, pancreas*, and *pituitary glands*; thus the mnemonic device, the *3Ps*

- *Parathyroid: Primary hyperparathyroidism* is the most common manifestation of MEN-1
- *Pancreas: Endocrine tumors of the pancreas* like gastrinomas associated with Zollinger-Ellison syndrome and insulinomas
- *Pituitary:* The most frequent anterior pituitary tumor encountered in MEN-1 is a *prolactinoma*.

54. **Ans. (a) MEN I....see earlier explanation.....** *(Ref: Robbins 8/e p1162, 9/e p1136)*

55. **Ans. (a) Papillary carcinoma thyroid** *(Ref: Robbins 9th/1096)*

56. **Ans. (a) Papillary** *(Ref: Robbins 9th/1100)*

Direct quote... "Papillary carcinomas are recognized based on nuclear features (ground-glass nuclei, pseudoinclusions) even in the absence of papillae. Psammoma bodies are a characteristic feature of papillary cancers; these neoplasms often metastasize by way of lymphatics, but the prognosis is excellent".

57. **Ans. (d) Follicular carcinoma of thyroid** *(Ref: Robbins 9th/1098)*
There is no reliable cytologic difference between follicular adenomas and minimally invasive follicular carcinomas.

Making this distinction requires extensive histologic sampling of the tumor-capsule-thyroid interface to exclude capsular and/or vascular invasion.

58. Ans. (b) Follicular carcinoma *(Ref: Robbins 9/e p1095)*

Deficiency of dietary iodine (and by extension, an association with goiter) is linked with a higher frequency of **follicular carcinomas.**

59. Ans. (b) Posterior pituitary tumors
(Ref: Robbins 9/e p1136)

MEN-1, or Wermer syndrome is characterized by anterior pituitary tumours and not posterior pituitary tumours.

MEN-1, or Wermer syndrome is characterized by abnormalities involving the parathyroid, pancreas, and pituitary glands; (mnemonic: the 3**P**s)

- **P**arathyroid: Primary hyperparathyroidism is the most common manifestation of MEN-1 (80 – 95% of patients) and is the initial manifestation of the disorder in most patients. This includes both hyperplasia and adenomas.
- **P**ancreas: Endocrine tumors of the pancreas are a leading cause of morbidity and mortality in persons with MEN-1.
- **P**ituitary: The most frequent anterior pituitary tumor encountered in MEN-1 is a prolactinoma; some patients develop acromegaly from somatotrophin-secreting tumors.
- Also know that the spectrum of this disease extends beyond the 3Ps. The duodenum is the most common site of gastrinomas in individuals with MEN-1. In addition, carcinoid tumors, thyroid and adrenocortical adenomas, and lipomas are more frequent than in the general population.

MEN-1 syndrome is caused by germline mutations in the MEN1 tumor suppressor gene, which encodes a protein called menin.

60. Ans. (c) Painless *(Ref: Robbins 9/e p1088)*

- **Granulomatous thyroiditis** is the most common cause of **thyroid pain**

61. Ans. (c) Hyperparathyroidism *(Ref: Robbins 9/e p1102)*

62. Ans. (d) Metastasis is essential for diagnosis
(Ref: Robbins 9/e p1088)

- Diagnosis of parathyroid carcinoma based on ***cytologic detail is unreliable,*** and invasion of surrounding tissues and **metastasis** are the **only reliable criteria**
- Parathyroid carcinoma has an incidence of nearly **1%**

63. Ans. (a) PAX8-PPARγ1
(Ref: Robbins 9/e p1095)

Papillary thyroid cancer	• RET/PTC • **NTRK1** • BRAF
Follicular carcinoma	• **RAS or the PI-3K/AKT arm** • PAX8- PPARG fusion genes
Medullary cancer	• **RET**
Anaplastic cancer	• RAS or PIK3CA mutations, TP53 inactivation, activating mutations of β-catenin

64. Ans. (a) It is present in 10% of brain tumors; (b) Erodes the sella and extends into surrounding area; (d) It is differentiated by reticulin stain;
(Ref: Harrison 16th/208I; Robbins 7th/1159; 9/e p1075, Brains Neurology 11th/558)

- 10% of all intracranial neoplasms are pituitary tumors.
- Benign adenomas are most common.
- The most common pituitary adenoma is microadenoma and about 70% microadenomas are prolactinoma.
- The tumor can erode the sella and extends into surrounding area and gives rise to local mass effect.
- Cellular monomorphism and absence of significant reticulin network distinguishes pituitary adenomas from non-neoplastic anterior pituitary parenchyma.

65. Ans. (a) TSH *(Ref: Robbins 9th/1079)*

Increased serum levels of prolactin, or prolactinemia, cause amenorrhea, galactorrhea, loss of libido, and infertility. This may be caused due to the following reasons:

a. Prolactin-secreting pituitary adenomas.
b. Physiologic hyperprolactinemia: occurs in pregnancy
c. Pathologic hyperprolactinemia: can result from damage of the dopaminergic neurons of the hypothalamus, damage of the pituitary stalk (e.g., due to head trauma), or exposure to drugs that block do-
d. Other causes of hyperprolactinemia include **renal failure** and **hypothyroidism.**

Thus, in the given options, estimation of the serum TSH is the most appropriate answer.

66. Ans. (b) Tuberculous adrenalitis
(Ref: Robbins 9/e p1130, 8th/1155-6, API 7th/1073, Harrison 18th/2955)

The commonest cause of Addison's disease is as follows:

- In **developing** countries – **Tuberculosis**[Q]
- In ***developed countries – Autoimmune (Idiopathic atrophy)***[Q]

67. Ans. (a) 90% are malignant *(Ref: Robbins 9/e p1134)*

Pheochromocytoma is a tumor of the adrenal medulla which produces catecholamines. The patients usually have severe headache, anxiety, increased sweating, tachycardia, palpitations and hypertensive episodes.

Features of 'rule of 10's'in pheochromocytoma

- 10% are *bilateral*[Q]
- 10% are *extra-adrenal*[Q]
- 10% are *malignant* [Q]
- 10% occur in *children* [Q]
- 10% are not associated with hypertension [Q]

Please note

Earlier, it was mentioned that 10% are pheochromocytoma *are familial*[Q] but latest Robbins says "**25% of the individuals with pheochromocytoma and paraganglioma have a germline mutation**"

68. Ans. (d) Prader-Willi syndrome

(Ref: Robbins's illustrated 7th/1219, 9/e p1134)

Pheochromocytoma is associated with the following familial syndromes.

- MEN syndromes type II and type III
- Von Hippel Lindau syndrome
- Von Recklinghausen disease
- Sturge Weber syndrome Famibial paraganglioma 1/3/4

69. Ans. (a) Autoimmune adrenalitis

(Ref: Harrison, 17th/2263, Robbins 9/e p1134)

Addison's disease must involve >90% of the glands before adrenal insufficiency develops.

Idiopathic atrophy due to autoimmune adrenalitis is the most common cause of Addison's disease in the world-whereas tuberculosis is the most common cause of the same in India.

70. Ans. (d) None *(Ref: Robbins 7th/1221, 9th/1135)*

- The histological pattern in pheochromocytoma is quite variable. The tumors are composed of polygonal to spindle-shaped chromaffin cells, clustered with their supporting cells into small nests or alveoli (*Zellballen*), by a rich vascular network.
- Cellular and nuclear pleomorphism is often present, especially in the alveolar group of lesions and giant and bizarre cells are commonly seen.

Mitotic figures are rare and do not imply malignancy. Both capsular and vascular invasion may be encountered in benign lesions. Therefore the diagnosis of malignancy in pheochromocytoma is based exclusively on the presence of metastases. These may involve regional lymph nodes as well as more distant sites, including liver, lung and bone.

71. Ans. (c) Parathyroid *(Ref: Robbins 9/e p1136)*

72. Ans. (a) 25% are malignant *(Ref: Robbins 9/e p1134)*

73. Ans. (c) Elevated levels of cortisol *(Ref: Robbins 9/e p1125)*

74. Ans. (b) Pheochromocytoma *(Ref: Robbins 9/e p1136)*

75. Ans. (a) Exogenous corticosteroids *(Ref: Robbins 8th/1148, 9/e p1125)*

76. Ans. (c) MEN II B *(Ref: Robbins 9/e p1137)*

77. Ans. (b) Organs of Zuckerkandl *(Ref: Robbins 9/e p1134, 8th/1159-1161; 7th/1221)*

78. Ans. (c) Bilateral in 10% of cases *(Ref: Robbins 9/e p1134)*

79. Ans. (c) Exogenous steroids *(Ref: Robbins 9/e p1125)*

80. Ans. (b) Follicular thyroid carcinoma *(Ref: Robbins 8th/1120-1121, 9/e p1095)*

81. Ans. (d) Cushing's disease *(Ref: Robbins 9/e p1125)*

This patient presents with "Cushingoid" signs and symptoms due to hypercortisolism. While the acute effect of cortisol is to produce lipolysis, patients with chronically increased cortisol levels develop a characteristic central obesity and buffalo hump. The mechanism for the redistribution of body fat is an interaction between cortisol and insulin. The weight gain with hypercortisolism usually results from increased appetite. Cortisol excess causes protein catabolism, which leads to poor wound healing, decreased connective tissue, and fragile blood vessels. The combination of thin skin and fragile blood vessels leads to abdominal stretch marks (striae) the are characteristically purple in color. Increased gluconeogenesis and decreased peripheral insulin sensitivity lead to elevated blood glucose. The hypercortisolism due to a functional tumor in the adrenal cortex (primary hypercortisolism) has low plasma ACTH level.

- The patient in the question has increased cortisol and increased ACTH. This could result from either a functional ACTH-secreting tumor in the pituitary (Cushing's disease) or an ectopic tumor (such as a small cell carcinoma of the lung, choice B). To distinguish between these two, we administer high doses of the potent synthetic glucocorticoid, dexamethasone. High-dose dexamethasone should suppress ACTH secretion from the pituitary by at least 50%; secretion from an ectopic tumor typically is not suppressed by dexamethasone.
- Addison's disease (choice A) is primary adrenal insufficiency, with increased plasma ACTH (producing hyperpigmentation) and decreased plasma cortisol and aldosterone compared to normal.
- Conn's syndrome (choice C) results from hypersecretion of aldosterone by the adrenal cortex. In Cushing's disease, it is due in part to the mineralocorticoid-like effects of high plasma cortisol.

82. Ans. (b) Hypernatremia; (d) Edema

(Ref: Sircar pg 532, Harrison 18th/2950)

Harrison mentions that.... "The clinical hallmark of mineralocorticoid excess is hypokalemic hypertension; serum sodium tends to be normal due to the concurrent fluid retention, which in some cases can lead to peripheral edema".

Sircar Physiology writes.... Edema is not seen because of the escape mechanism: escape from the sodium retaining effects of hyperaldosteronism.

83. Ans. (b) Diabetes insipidus

Please don't get confused with the diuretic therapy because it can lead to increased ADH release and thus, may lead to hyponatremia.

84. Ans. (a) Pheochromocytoma...discussed earlier in detail. *(Ref: Robbins 9/e p1134, 8/e p524-5)*

85. Ans. (a) Organ of Zuckerkandl *(Ref: Robbins 9th/1134)*

Ten percent of pheochromocytomas are extra-adrenal, occurring in sites such as the organs of Zuckerkandl and the carotid body.

86. Ans. (d) Diarrhea *(Ref: Robbins 9th/1135)*

The dominant clinical manifestation of pheochromocytoma is hypertension, observed in 90% of patients.

Approximately two thirds of patients with hypertension demonstrate paroxysmal episodes, which are described as an abrupt, precipitous elevation in blood pressure, associated with tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension.

87. **Ans. (b) Benign and malignant pheochromocytoma** *(Ref: Robbins 9/e p1135)*

Pheochromocytomas are difficult to diagnose exclusively from the histological appearance. Cellular and nuclear pleomorphism, including the presence of giant cells, and mitotic figures are often seen in benign pheochromocytomas. So, *the definitive diagnosis of malignancy in pheochromocytomas* is based ***exclusively on the presence of metastases.***

88. **Ans. (a) Neuroblastoma** *(Ref: Robbins 9/e p476)*

89. **Ans. (d) 10% are symptomatic** *(Ref: Robbins 9/e p1134)*

90. **Ans. (c) Hyperthyroidism** *(Ref: Robbins 9/e p1137)*

EXPLANATIONS TO ASSERTION AND REASON QUESTIONS

Explanations(1-10): ***While solving assertion reason type of questions, we can use a particular method.***

1. **First of all, read both assertion (A) and reason (R) carefully and independently analyse whether they are true or false.**
2. **If A is false, the answere will directly be (d) i.e. both A and R are false. You can note that all other options (i.e. a, b or c) consider A to be true.**
3. **If A is true, answer can be (a), (b) or (c), Now look at R. If R is false, answer will be (c)**
4. **If both A and R are ture, then we have to know whether R is correctly explaining A [answer is (a)] or it is not the explanation of assertion [answer is (b)]**

1. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.** *(Ref: Robbins 8th/1133, 9/e p1108)*

Preproinsulin produced in rough endoplasmic reticulum is delivered to the Golgi apparatus where it is cleaed to generate mature insulin and C peptide. Both are stored in secretory granules and equimolar quantities are secreted after β cell simulation.

- Most important stimulus for insulin synthesis and release is glucose itself.

2. **Ans. (c) Assertion is true and reason is false.** *(Ref: Robbins 8th/1159, 9/e p1134)*

Pheochromocytoma is also referred to as 'rule of 10 tumor'. It is associated with the following:

- 10% are *bilateral*Q
- 10% are *extra-adrenal*Q
- 10% are *malignant* Q
- 10% occur in *children* Q
- 10% are not associated with hypertension Q

Most of the earlier texts mention that 10% of these tumors are *familial*Q but Robbins 8th/1159 clearly says that it has been modified.

"As many as 25% of the individuals with pheochromocytoma and paraganglioma have a germline mutation".

3. **Ans. (c) Assertion is true and reason is false.** *(Ref: Robbins 8th/1119, 9/e p1098)*

FNAC is not useful for diagnosing follicular thyroid cancer because it can not distinguish between follicular adenoma from follicular carcinoma. The most reliable feature of follicular cancer is demonstration of capsular invasion or vascular invasion. This is best done with careful histologic examination after specimen resection. Intact capsule encircling the tumor is the hallmark of the benign tumor. ...Robbins 8th/1119

4. **Ans. (d) Both assertion and reason are false.** *(Ref: Robbins 8th/1113, 9/e p1088)*

Postpartum thyroiditis/subacute lymphocytic thyroiditis is a variant of Hashimoto's thyroiditis. It presents as a *painless enlargement of the thyroid* and *transient hyperthyroidism* (lasting about 2-8 weeks). Investigations reveal elevated levels of T_3 and T_4 and reduced TSH.

How to differentiate between Hashimoto and subacute lymphocytic thyroiditis?

- Hurthle cell metaplasia and fibrosis are not prominent as in Hashimoto's thyroiditis.

(Granulomatous Thyroiditis (De Quervain Thyroiditis) is more commonly seen in females *preceded by a viral infection* (caused by coxsackie virus, mumps, measles). The thyroid gland is diffusely enlarged with *intact capsule.*

Clinical features are *pain in neck, sore throat,* fever, fatigue, anorexia, myalgia, enlarged thyroid and the presence of transient hyperthyroidism lasting for 2-6 weeks. It may be followed by asymptomatic hypothyroidism but recovery is seen in most of the patients.

5. **Ans. (b) Both assertion and reason are true and reason is not the correct explanation of assertion.** *(Ref: Robbins 9/e p1089, 8th/1114-5)*

Graves disease is most common cause of endogenous hyperthyroidism. This disease is characterized by breakdown in self tolerance to thyroid auto-antigens (most importantly TSH receptor). The antibodies seen in these patients are as follows:

- **Thyroid stimulating immunoglobulin:** lead to hyperthyroidism
- **Thyroid growth stimulating immunoglobulin:** lead to hyperthyroidism

- **TSH binding inhibitor immunoglobulin (TBIG):** lead to **episodes of hypothyroidism** in some patients.

6. **Ans. (b) Both assertion and reason are true and reason is not the correct explanation of assertion.**

(Ref: Robbins 8th/1138-9, 9/e p1117)

Myocardial infarction is the commonest cause of death in diabetes. It is caused by atherosclerosis of the coronary arteries. Large and medium sized vessel involvement is responsible for macrovascular disease (MI, stroke and lower extremity gangrene).

Capillary dysfunction in target organs leads to microvascular disease (not macrovascular disease) leading to diabetic retinopathy, neuropathy and nephropathy.

7. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.**

(Ref: Robbins 8th/1157, 9/e p1130)

Hyperpigmentation is quite characteristic of primary adrenal disease (Addison's disease) especially at pressure points and sun exposed areas. This is caused by elevated levels of pro-opiomelanocortin (POMC), which is derived from anterior pituitary and is a precursor of ACTH and melanocyte stimulating hormone (MSH).

8. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.** *(Ref: Robbins 9/e p1115)*

Hyperosmolar nonketotic coma is due to the severe dehydration resulting from sustained osmotic diuresis in patients (commoner in elderly) who do not drink enough water to compensate for urinary losses from chronic hyperglycemia. These patients don't develop ketoacidosis and its symptoms (nausea, vomiting, respiratory difficulties) because of elevated portal insulin levels. The 'fat sparing' effect of insulin prevents the formation of ketone bodies by inhibiting the fatty acid oxidation in the liver.

9. **Ans. (c) Assertion is true and reason is false.**

(Ref: Robbins 8th/1162, 9/e p1137)

MEN 2A (**Sipple syndrome**) is characterized by pheochromocytoma, medullary thyroid carcinoma and parathyroid hyperplasia. It is associated with a gain of function (not loss of function mutation) in RET proto-oncogene.

> '**Loss of function**' mutations in RET cause intestinal aganglionosis and Hirschprung disease[Q].

10. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.** *(Ref: Robbins 9/e p1099)*

Amyloid deposition is associated with medullary thyroid cancer. The chemical nature of the amyloid in this condition is ACal. It is because of the deposition of the altered form of calcitonin which gets deposited in the thyroid stroma.

CHAPTER 18

Musculoskeletal System

Golden Points

- Bone specific alkaline phosphatase, osteocalcin and type I collagen extension peptide are markers for bone growth whereas Hydroxyproline, TRAP, Cross linked N and C telopeptides, urine total free deoxypyridinoline are markers of bone destruction/resorption.
- Tetracycline labeling: Best estimation of mineralization of newly synthesized osteoid
- Seronegative spondyloarthropathies are: ankylosing spondylitis, psoriatic arthritis, reactive arthritis (Reiter syndrome), arthritis in IBD (enteropathic arthritis).
- Paget disease involves: Pelvis (most common), tibia, femur, skull, spine (vertebrae), humerus, clavicle.
- Most common malignant tumor of bone: Secondaries (metastasis).
- Ewing's sarcoma arises from **primitive neuroectodermal** cells. It is associated with **t (11 : 22)**. The cells contain **glycogen** in this condition. **MIC-2 (CD 99)** is a marker of: Ewing's sarcoma and peripheral primitive neuroectodermal tumors (PENT).
- ***Metastasis*** is **NOT** seen in bones of: ***small bones of hand and feet.*** It is however observed in the vertebrae (most common), pelvis, proximal half of femur and humerus.
- **Brown tumor** of bone is seen in: **Hyperparathyroidism**.
- **D**ystrophin is lacking in: **D**uchenne's muscular dystrophy.
- **Myasthenia gravis** is associated with **Thymic hyperplasia** (65%) more commonly than with thymoma (15%).
- Perifascicular atrophy is seen in: Dermatomyositis.
- Cytogenetic abnormality of synovial cell sarcoma is **t(X:18)**. It shows a **'Biphasic pattern'** on histology. Its prognosis is dependent on the **grade** of the tumor. Its markers include vimentin, cytokeratin and S-100.
- ***Number of mitoses per high power field*** is the most distinctive feature between leiomyosarcoma and leiomyoma.
- **Rhabdomyosarcoma** is the commonest sarcoma in children and has the presence of **Tadpole cells.**

The **bone** is a type of connective tissue which is **composed of cells** (osteoclasts and osteoblasts) **and the extracellular matrix**. The extracellular components of bone consist of a solid mineral phase (consisting of calcium and phosphate) and an organic matrix consisting of type I collagen (90–95%), serum proteins such as albumin, cell attachment/signaling proteins such as thrombospondin, osteopontin and fibronectin, calcium-binding proteins such as matrix glial protein and osteocalcin and proteoglycans such as biglycan and decorin.

The mineral phase of bone is deposited initially in intimate relation to the collagen fibrils and is found in specific locations in the "holes" between the collagen fibrils. This architectural arrangement of mineral and matrix results in a two-phase material well suited to withstand mechanical stresses.

CELLS OF BONE

Osteoblasts synthesize and secrete the organic matrix. They are derived from cells of mesenchymal origin. As an osteoblast secretes matrix, which is then mineralized, the cell becomes an *osteocyte*. Mineralization is a carefully regulated process dependent on the activity of osteoblast-derived alkaline phosphatase, which probably works by hydrolyzing inhibitors of mineralization. Core-binding factor A1 (*CBFA1*, also called *Runx2*) regulates the expression of several important osteoblast proteins including osterix, osteopontin, bone sialoprotein, type I collagen, osteocalcin, and receptor-activator of NFκB (RANK) ligand. *Runx2* expression is regulated, in part, by bone morphogenic proteins (BMPs).

Key Point

- Cleidocranial dysplasia is caused by heterozygous inactivating mutations in Runx2.
- PTH and 1, 25-dihydroxyvitamin D activate receptors expressed by osteoblasts to assure mineral homeostasis.

Osteoclasts carry out resorption of bone. **Macrophage colony-stimulating factor (M-CSF) plays a critical role** during several steps in the pathway and ultimately leads to fusion of osteoclast progenitor cells to form multinucleated, active osteoclasts. **RANK** ligand, expressed on the surface of osteoblast progenitors and stromal fibroblasts binds to the RANK receptor on osteoclast progenitors and stimulates osteoclast differentiation and activation. Alternatively, a soluble decoy receptor, referred to as osteoprotegerin, can bind RANK ligand and inhibit osteoclast differentiation. Several growth factors and cytokines (including interleukins 1, 6, and 11; TNF; and interferon-gamma modulate osteoclast differentiation and function.

Concept

- *Most hormones that influence osteoclast function do not directly target this cell but instead influence M-CSF and RANK ligand signaling by osteoblasts.*
- Both PTH and 1,25$(OH)_2$D increase osteoclast number and activity, whereas estrogen decreases osteoclast number and activity by this indirect mechanism.
- **Calcitonin**, in contrast, binds to its receptor on the basal surface of osteoclasts and **directly inhibits osteoclast function.**

Remodeling of bone

The cycle of bone remodeling is carried out by the basic multicellular unit (BMU), comprising a group of osteoclasts and osteoblasts. In cortical bone, the BMUs tunnel through the tissue, whereas in cancellous bone, they move across the trabecular surface. The process of bone remodeling is initiated by contraction of the lining cells and the recruitment of osteoclast precursors. These precursors fuse to form multinucleated, active osteoclasts that mediate bone resorption. Osteoclasts adhere to bone and subsequently remove it by acidification (protons secreted by type II carbonic anhydrase) and proteolytic digestion (by cathepsin K). As the BMU advances, osteoclasts leave the resorption site and osteoblasts move in to cover the excavated area and begin the process of new bone formation by secreting osteoid, which is eventually mineralized into new bone. After osteoid mineralization, osteoblasts flatten and form a layer of lining cells over new bone.

Remodeling of bone occurs along lines of force generated by mechanical stress.

Biochemical markers of bone resorption

a. Amino and carboxy terminal crosslinking telopeptide of bone collagen
b. Pyridinoline
c. Free lysyl-pyridinoline
d. Tartarate-resistant acid phosphatase (TRAP)
e. Hydroxyproline (not very specific)

Biochemical markers of bone formation

a. Bone specific alkaline phosphatase
b. Procollagen type IC and IN propeptide
c. Osteocalcin
d. Alkaline phosphatase (not very specific)

Concept

- **Tetracycline** is absorbed into bone and so, it is used as a **marker of bone growth for biopsies in humans.** Tetracycline binds to newly formed bone at the bone/osteoid (unmineralized bone) interface where it shows as a linear fluorescence. **Tetracycline labeling** is used to **determine the amount of bone growth within** a certain period of time, usually a period of approximately **21 days.** Tetracycline is incorporated into mineralizing bone and can be detected by its fluorescence.
- **In double tetracycline labeling**, a *second dose is given 11–14 days after the first dose*, and the amount of bone formed during that interval can be calculated by measuring the distance between the two fluorescent labels.

PAGET'S DISEASE (OSTEITIS DEFORMANS)

Paget's disease (osteitis deformans) can be characterized as a *collage of matrix madness*. It is marked by regions of *furious osteoclastic bone resorption*, which is *followed by a period of hectic bone formation*. The net effect is a gain in bone mass. It has the following three stages:

i. Initial osteolytic stage
ii. Mixed osteoclastic-osteoblastic stage
iii. Burnt-out quiescent osteosclerotic stage.

Paget's disease usually begins after the age of 40 years and is more common in whites. It has been **linked to slow virus infection by paramyxovirus**. It can be involving one bone or monostotic (tibia, ilium, femur, skull, vertebra, humerus) in about 15% of cases and affecting multiple bones or polyostotic (pelvis, spine, skull) in the remainder. The *axial skeleton or proximal femur is involved in upto 80% of cases.*

On radiography, the Pagetic bone is typically enlarged with thick, coarsened cortices and cancellous bone. There is **increased serum alkaline phosphatase and increased urinary excretion of hydroxyproline**. The most common symptom is pain. Bone overgrowth in the craniofacial skeleton may produce *leontiasis ossea* and the weakened Pagetic bone may lead to invagination of base of skull (*platybasia*).

The **histologic hallmark** is the **mosaic pattern** of **lamellar bone** which is produced by prominent cement lines that anneal haphazardly oriented units of lamellar bone. The involved bones are weak and fracture easily.

The **complications** of the disease include arteriovenous shunts within the marrow resulting in *high output cardiac failure* and *increased risk of development of sarcomas* like osteosarcoma, chondrosarcoma, etc. ***Secondary osteoarthritis*** and ***chalk-stick type fractures*** are the other complications in Paget's disease.

Key Point

- **Paget's disease:** Weak but thick, vascular bone
- **Mosaic pattern** of lamellar bone seen microscopical

BENIGN TUMORS OF THE BONE

Osteoma

Subperiosteal osteomas are benign tumors affecting most often the skull and facial bones. They are usually solitary and are detected in middle-aged adults. Multiple osteomas are seen in the setting of *Gardner's syndrome.*

Osteoid osteoma and osteoblastoma

Osteoid osteoma and *osteoblastoma* are terms used to describe benign bone tumors that have identical histologic features but that differ in size, sites of origin, and symptoms. **Osteoid osteoma** is *less than 2 cm* in size and usually affects patients in their teens and twenties. They *usually involve the femur or tibia,* where they commonly *arise in the cortex* and less frequently within the medullary cavity. Osteoid osteomas are painful lesions. The pain is characteristically *nocturnal,* and is dramatically relieved by aspirin.

Microscopically, there is a central nidus of osteoid surrounded by dense sclerotic rim of reactive cortical bone. X-ray shows the presence of central radiolucency surrounded by a sclerotic rim.

Concept

Osteoblastoma differs from osteoid osteoma in that it more frequently **involves the spine**; the ***pain is dull, achy, and not responsive to salicylates;*** and it does **NOT** induce a marked bony reaction.

Osteochondroma (Exostosis)

It is a benign bony *metaphyseal* growth capped with cartilage originating from the epiphyseal growth plate. It is seen in adolescent males as a firm, solitary growth at the end of long bones. It may be asymptomatic or may cause pain and deformity. Rarely, it may undergo malignant transformation.

Multiple osteochondromas occur in *multiple hereditary exostosis,* which is an autosomal dominant hereditary disease.

There is inactivation of both copies of the *EXT* gene in growth plate chondrocytes in the pathogenesis of osteochondromas. Multiple osteochondromas become apparent during childhood.

Chondroma

Chondromas are benign tumors of hyaline cartilage that usually occurs in bones of endochondral origin. These can be

- *Enchondroma:* When origin is intramedullary
- *Subperiosteal or juxtacortical:* Originate from the surface of bone

Enchondromas are most common intraosseous cartilage tumors. Their *favored sites are short tubular bones of hand and feet.*

Enchondromas are composed of well-circumscribed nodules of cytologically benign hyaline cartilage. The center of the nodule can calcify whereas peripheral portion may undergo enchondral ossification. The unmineralized nodules of cartilage produce well-circumscribed oval lucencies that are surrounded by a thin rim of radiodense bone (**O ring sign**).

Patients with **Ollier's disease** may undergo malignant transformation to *chondrosarcoma* whereas those with **Maffuci's syndrome** have *increased risk of ovarian cancer and brain gliomas.*

Key Point

Ollier's disease is a syndrome of multiple enchondromas (or enchondromatosis)

Key Point

Maffuci's syndrome is association of soft tissue hemangiomas with enchondromatosis.

MALIGNANT TUMORS OF THE BONE

Osteosarcoma

It is the **most common primary malignant tumor of the bone**. It has a *bimodal age distribution* with almost 75% occurring in patients younger than age 20. The second peak occurs in the elderly with conditions like Paget disease, bone infarcts, and prior irradiation. It is more commonly seen in the males with *increased risk of the development in patients with familial retinoblastoma.*

The patients usually have localized pain and swelling. It arises from the *metaphysis* of the long bones with the **knee** being the *most commonly affected site*. The tumor is a large, firm white-tan mass with necrosis and hemorrhage. Microscopically, there is presence of anaplastic cells producing osteoid and bone.

The tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation. The triangular shadow between the cortex and raised ends of periosteum is known radiographically as *Codman's triangle.*

Key Point

The formation of bone by the tumor cells is characteristic of osteosarcoma.

Key Point

The classic **X-ray** findings include bone destruction, **sunray pattern** due to radiating opacities in the tumor like sunrays and **Codman's triangle**.

Chondrosarcoma

These are group of tumors that produce neoplastic cartilage.

- Similar to chondroma, chondrosarcoma can be:
  - Intramedullary
  - Juxtacortical
- **Chondrosarcomas** are *second most common malignant matrix-producing tumor of bone (Most common is osteosarcoma)*
- **Histologically**, Chondrosarcomas are composed of malignant hyaline and myxoid cartilage. Spotty calcifications may be present and central necrosis may create cystic spaces. Tumors vary in cellularity and cytological atypia. ***Malignant cartilage infiltrates the marrow space and surrounds pre-existing bony trabeculae.***
- Chondrosarcomas commonly *arise in central portions of skeleton* (including pelvis, shoulder and ribs). In contrast to chondroma, chondrosarcoma rarely involve the distal extremities. The *clear cell variant* of chondrosarcoma characteristically *originates from Epiphysis of tubular long bones.*

Osteoclastoma or Giant cell tumor of bone

It is a malignant tumor containing multinucleated giant cells mixed with stromal cells. It is more commonly seen in the females and the most commonly affected age group is 20-40 years. The tumor involves the *epiphysis* of the long bones usually *around the knee* (distal femur and proximal tibia). Microscopically, there is presence of *osteoclast like giant* cells (having 100 or more nuclei) distributed in a background of mononuclear stromal cells. Most of the tumors are solitary.

Radiographically, giant cell tumors are large, *purely lytic, and eccentric*, and erode into the subchondral bone plate. The overlying cortex is frequently destroyed, producing a bulging soft tissue mass delineated by a thin shell of reactive bone. This gives rise to the **soap bubble appearance**. The tumor has high rate of recurrence after excision.

Key Point

Other giant cell lesions include:

- Brown tumor seen in hyper-parathyroidism
- Giant cell reparative granuloma
- Chondroblastoma
- Pigmented villonodular synovitis

Ewing's sarcoma and primitive neuroectodermal tumor (PNET)

Ewing sarcoma and PNET are primary malignant *small round cell tumors* of bone and soft tissue. Both Ewing's sarcoma and PNET are the same tumor, differing only in their degree of neural differentiation. *Tumors that demonstrate neural differentiation by any analysis are called PNETs, and those that are undifferentiated are known as Ewing's sarcoma.*

Of all bone sarcomas, Ewing's sarcoma has the youngest average age at presentation and approximately 80% patients are younger than age 20 years. Boys are affected slightly more frequently than girls. The classic translocation is t(11;22)(q24;q12) and the most common fusion gene (EWS-FLI1) generated acts as a dominant oncogenes to stimulate cell proliferation. The presence of p30/32, a product of mic-2 gene, is a cell surface marker form Ewing's sarcoma.

Ewing's sarcoma and PNET usually **arise in the diaphysis** of long tubular bones, especially the femur and the flat bones of the pelvis.

The tumor is composed of sheets of *uniform small, round cells that are slightly larger than lymphocytes having scant cytoplasm, which may appear clear because it is rich in glycogen.* There is presence of **Homer-Wright rosettes** (where the tumor cells are arranged in a circle about a central fibrillary space) which are *indicative of neural differentiation.*

They present as painful enlarging masses, and the affected site is frequently tender, warm, and swollen with the patients having systemic findings like fever, increased ESR, anemia and leukocytosis (all of which results in the tumor resembling infection). **X-ray** shows the characteristic periosteal reaction producing layers of reactive bone deposited in an '**onion-skin**' pattern.

Note: *Metastatic tumors are the most common form of skeletal malignancy.*

Key Point

The presence of p30/32, the product of the ***mic-2 gene*** (which maps to the pseudoautosomal region of the X and Y chromosomes) is a cell-surface marker for **Ewing's sarcoma** (and other members of a family of tumors called PNETs).

SOFT TISSUE TUMORS

SYNOVIAL SARCOMA

These tumors forms about 10% of all soft tissue sarcomas. Less than 10% of them are intra-articular. 60-70% involve the lower extremities especially around knee and thigh. The **histologic hallmark** of biphasic synovial sarcoma is the **dual lining of differentiation of the tumor cells** (e.g. **epithelial-like and spindle cells**). The calcified concretions can be present which help in the diagnosis radiologically.

Immunohistochemically, these tumor cells yield **positive reactions for keratin and epithelial membrane antigen** (differentiating from most other sarcomas). Most synovial sarcomas show a characteristic chromosomal translocation **t(X ; 18)** producing SYT-SSX1 or - SSX2 fusion genes. This specific translocation is associated with poor prognosis.

Architectural Patterns in Soft Tissue Tumors

Pattern	Tumor Type
Fascicles of eosinophilic spindle cells **intersecting at right angles**	Smooth muscle
Short fascicles of spindle cells radiating from a central point (like **spokes on a wheel**)—storiform	Fibrohistiocytic
Nuclei arranged in columns—palisading	Schwann cell
Herringbone	Fibrosarcoma
Mixture of fascicles of spindle cells and groups of epithelioid cells—biphasic	Synovial sarcoma

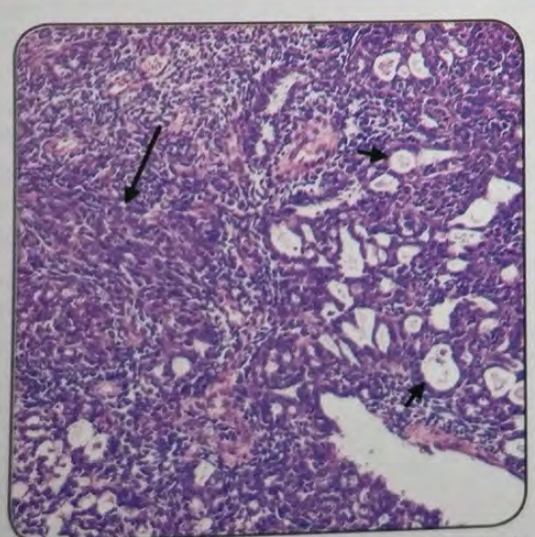


Fig. 1: Biphasic Appearance in Synovial Sarcoma: Spindle cells (long arrow) and epithelioid cells (short arrows)

MUSCULAR DYSTROPHIES

The muscular dystrophies are a heterogeneous group of inherited disorders, often beginning in childhood, that are characterized clinically by *progressive muscle weakness and wasting*. The two most common forms of muscular dystrophy are **X-linked**: Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). **BMD is less common and much less severe than DMD.**

DMD and BMD are caused by abnormalities in a gene encoding a protein termed dystrophin.

Dystrophin and the dystrophin-associated protein complex form an interface between the intracellular contractile apparatus and the extracellular connective tissue matrix. The role of this complex of proteins is transferring the force of contraction to connective tissue, so, myocyte degeneration occurs in the absence of dystrophin.

Muscle biopsy specimens from patients with **DMD** show minimal evidence of dystrophin by both staining and Western blot analysis. **BMD** patients have a mutation causing a *reduced amount of altered dystrophin.*

Histopathologic abnormalities common to DMD and BMD include

- Variation in fiber size due to the presence of both small and enlarged fibers
- Increased numbers of internalized nuclei
- Degeneration, necrosis, and phagocytosis of muscle fibers
- Regeneration of muscle fibers
- Proliferation of endomysial connective tissue
  - **DMD** cases also often show *enlarged, rounded, hyaline fibers that have lost their normal cross-striations,* believed to be hypercontracted fibers, this finding is rare in BMD. In later stages, **the muscles eventually become almost totally replaced by fat and connective tissue.** Cardiac involvement consists of interstitial fibrosis, more prominent in the subendocardial layers.

Mnemonic

Duchenne **M**uscular **D**ystrophy (DMD)
Doesn't **M**ake **D**ystrophin (no formation)

Recent Exam Question

Panfascicular atrophy: characterized by the muscle fiber atrophy often involves an entire fascicle and is seen with **spinal muscular atrophy.**

- Boys with DMD are normal at birth, and early motor milestones are met on time. Walking is often delayed and weakness begins in the pelvic girdle muscles and then extends to the shoulder girdle giving rise to **Gower's sign** (child uses his hands to climb upon himself on getting up from the floor). Enlargement of the calf muscles associated with weakness, a phenomenon termed *pseudohypertrophy* caused initially by an increase in the size of the muscle

fibers later by an increase in fat and connective tissue. **Cognitive impairment** is a component of the disease. Serum creatine kinase is elevated during the first decade of life but returns to normal in the later stages of the disease, as muscle mass decreases. *Death results from respiratory insufficiency, pulmonary infection, and cardiac decompensation.*

Recent Exam Question

Perifascicular atrophy: seen with **dermatomyositis**.

Mnemonic

Becker **M**uscular **D**ystrophy (BMD)
Badly **M**ade **D**ystrophin (reduced formation of an altered protein)

- Boys with **BMD** develop symptoms at a **later age** than those with DMD. The onset occurs in later childhood or in adolescence, and it is accompanied by a **slower and variable rate of progression**. Cardiac disease is frequently seen in these patients.

Multiple Choice Questions

1. **A 10 year old girl presents with a tibial mass. Histopathological examination reveals a small round cell tumor. Which of the following molecular findings is most likely to be present?** *(AII India 2012)*
   (a) 22q translocation
   (b) 11q deletion
   (c) 7p translocation
   (d) n-myc amplification

2. **Which of the following is the most specific test for rheumatoid arthritis?** *(AII India 2012)*
   (a) Anti Ig M antibody
   (b) Anti CCP antibody
   (c) Anti Ig A antibody
   (d) Anti IgG antibody

3. **Onion bulb appearance of nerve ending on biopsy is seen in:** *(AIIMS Nov. 2010)*
   (a) Diabetic neuropathy
   (b) Amyloid neuropathy
   (c) Leprous neuritis
   (d) Chronic inflammatory demyelinating polyneuropathy (CIDP)

4. **The rate of newly synthesized osteoid mineralization is best estimated by:** *(AIIMS Nov. 2010)*
   (a) Tetracycline labeling
   (b) Alizarine red staining
   (c) Calceine stain
   (d) Von Kossa stain

5. **Which of the following is false in relation to Osteosarcoma?** *(DPG 2011)*
   (a) Paget's disease and prior irradiation are pre-disposing factors
   (b) Rb gene mutation is associated with hereditary variant
   (c) C-myc gene implicated in the genesis
   (d) Codman's triangle is the characteristic X-ray finding

6. **Cytogenetics for synovial cell sarcoma is:** *(AI 2008)*
   (a) t (X: 18)
   (b) t (17, 9)
   (c) t (9, 22)
   (d) t (11, 14)

7. **MIC-2 mutation associated with:** *(AIIMS Nov 2009)*
   (a) Osteosarcoma
   (b) Ewing's sarcoma
   (c) Alveolar soft tissue sarcoma
   (d) Dermatofibrosarcoma protuberance

8. **A 9-year-old girl has difficulty in combing hairs and climbing upstairs since 6 months. She has Gower's sign positive and maculopapular rash over metacarpophalangeal joints. What should be the next appropriate investigation to be done?** *(AIIMS Nov 2008)*
   (a) ESR
   (b) RA factor
   (c) Creatine kinase
   (d) Electromyography

9. **Antibody found in myositis is:** *(AIIMS Nov 2008)*
   (a) Anti-Jo 1
   (b) Anti scl 70
   (c) Anti Sm
   (d) Anti Ku

10. **CD-99 is for:** *(AIIMS May 2008)*
    (a) Ewing's sarcoma
    (b) SLL
    (c) Dermatofibroma protruberans
    (d) Malignant histiocytic fibroma

11. **Bone resorption markers are all except:** *(AIIMS May 2008)*
    (a) Tartarate resistant alkaline phosphatase (TRAP)
    (b) Osteocalcin
    (c) Crosslinked-N-telopeptides
    (d) Urine total free deoxypyridinoline

12. **A 50-year-old lady presented with a 3-month history of pain in the lower third of the right thigh. There was no local swelling; tenderness was present on deep pressure. Plain X-rays showed an ill-defined intramedullary lesion with blotchy calcification at the lower end of the right femoral diaphysis, possibly enchondroma or chondrosarcoma. Sections showed a cartilaginous tumor. Which of the following histological features (if seen) would be most helpful to differentiate the two tumors?** *(AIIMS May 2006)*
    (a) Focal necrosis and lobulation
    (b) Tumor permeation between bone trabeculae at periphery
    (c) Extensive myxoid change
    (d) High cellularity

13. **Dystrophic gene mutation leads to:** *(AIIMS May 2003)*
    (a) Myasthenia gravis
    (b) Motor neuron disease
    (c) Poliomyelitis
    (d) Duchenne's muscular dystrophy

14. **Giant cells are seen in:** *(PGI Dec 2006)*
(a) Osteoclastoma
(b) Chondroblastoma
(c) Chordoma
(d) Osteitis fibrosa cystica

15. **"Biphasic pattern" on histology is seen in which tumor?** *(Delhi 2010)*
(a) Rhabdomyosarcoma
(b) Synovial cell sarcoma
(c) Osteosarcoma
(d) Neurofibroma

16. **An epiphyseal bone lesion is:** *(Delhi 2009 RP)*
(a) Osteogenic sarcoma
(b) Chondroblastoma
(c) Ewing's sarcoma
(d) Chondromyxoid fibroma

17. **Mosaic pattern of lamellar bone histology is found in:**
(a) Osteopetrosis *(Delhi PG-2006)*
(b) Osteoid osteoma
(c) Osteitis deformans
(d) Osteomalacia

18. **Which one of the following inflammatory markers of muscle biopsy is diagnostic of polymyositis?**
(a) CD8/MHC-I complex *(Karnataka 2006)*
(b) Vascular cell adhesion molecules
(c) Intracellular adhesion molecules
(d) Membrane attack complex

19. **Bone tumor arising from epiphysis is:** *(DNB 2001)*
(a) Osteogenic sarcoma
(b) Ewing's sarcoma
(c) Chondromyxoid fibroma
(d) Giant cell tumor

20. **The commonest malignant bone tumor is:** *(DNB 2001)*
(a) Multiple myeloma (b) Osteosarcoma
(c) Ewing's sarcoma (d) Giant cell tumor

21. **Characteristics microscopic features of osteogenic sarcoma is:** *(UP 2000)*
(a) Osteoid formation
(b) Osteoid formation by mesenchymal cells with pleomorphism
(c) Codman's triangle
(d) Predominant osteoclast

22. **Ground glass appearance is found in:** *(UP 2001)*
(a) Inverted papilloma
(b) Fibro calcification
(c) Fibrous dysplasia of bones
(d) Chronic osteomyelitis

MOST RECENT QUESTIONS

23. **Paget's disease increases the risk of:**
(a) Osteoma (b) Osteosarcoma
(c) Fibrosarcoma (d) All

24. **Osteoclast are stimulated by:**
(a) Thyroxine (b) PTH
(c) Calcitonin (d) Estrogen

25. **Large intracytoplasmic glycogen storage is seen in which malignancy?**
(a) osteosarcoma
(b) Mesenchymal chondrosarcoma
(c) Ewing's sarcoma
(d) Leiomyosarcoma

26. **Osteoblastoma resembles histologically:**
(a) Osteosarcoma
(b) Osteoid osteoma
(c) Chondroblastoma
(d) Chondrosarcoma

27. **Syncytial osteoclastic giant cells are seen in All Except:**
(a) Osteosarcoma
(b) Ewing's sarcoma
(c) Chondroblastoma
(d) Aneurysmal bone cyst

28. **Hyaline cartilage contains which type of collagen:**
(a) Type I (b) Type II
(c) Type III (d) Type IV

29. **Tophi in gout are found in all regions, except:**
(a) Bone
(b) Skin
(c) Muscle
(d) Synovial membrane

30. **Which of the following is true about psoriatic arthritis?**
(a) Involves distal joints of hand and foot
(b) Pencil in cup deformity
(c) Sacroiliitis
(d) All of the above

31. **Ewings sarcoma arises from:**
(a) G cells
(b) Totipotent cells
(c) Neuroectodermal cells
(d) Neurons

32. **Dystrophin is lacking in:**
(a) Polio
(b) Duchenne's muscular dystrophy
(c) Peroneal muscular atrophy
(d) Spinal muscular atrophy

33. **A 42 year-old woman Paro presents with slowly progressive syndrome comprising of features like pain and tenderness in multiple joints, with joint stuffiness on rising in the morning. Joint involvement is symmetric, with the proximal interphalangeal and metacarpophalangeal joints especially involved. The physician finds presence of tenderness in all the inflamed joints. Which of the following laboratory abnormalities is most likely associated in this patient?**

(a) Antibodies to double-stranded DNA
(b) IgM anti-IgG antibodies
(c) HLA-B27 antigen
(d) Urate crystals and neutrophils in synovial fluid

34. Most common malignant bone tumor:
(a) Osteogenic sarcoma
(b) Secondaries
(c) Osteoma
(d) Enchondroma

35. Paget disease of the bone is also called:
(a) Osteitis fibrosa (b) Brittle bone disease
(c) Fibrous dysplasia (d) Osteomalacia

36. In the giant cell tumor of the bone, the cell of origin is:
(a) Fibroblast cells
(b) Osteoclast and precursors
(c) Osteoblast and precursors
(d) Sinusoidal cells

37. Which of these is characteristic of Gout?
(a) Podagra (b) Anasarca
(c) Cheiroarthropathy (d) Calcinosis cutis

38. A 27-year old male presents with low backache, that occurs early in the morning, associated with stiffness, and persists for more than 30 minutes. On examination, his chest expansion is also restricted. The most probable diagnosis is:
(a) Rheumatoid arthritis
(b) Oteoarthritis
(c) Gouty arthritis
(d) Ankylosing spondylitis

39. Polyarticular rheumatoid arthritis is diagnosed when more than _ joints are involved?
(a) Two (b) Three
(c) Four (d) Five

40. All of the following are true about Paget's disease of the bone except:
(a) Association with virus
(b) Progress to chondrosarcoma
(c) May turn onto a malignant lesion
(e) Osteosclerotic phase seen

41. Which is rheumatoid arthritis autoantibody?
(a) Anti DLE (b) Anti CCP
(c) Anti ds DNA (d) Anti histone

42. Potts puffy tumor is:
(a) Osteomyelitis of frontal bone
(b) Osteomyelitis of ethmoid
(c) Osteomyelitis of maxilla
(d) Osteomyelitis of mandible

43. Fibrinoid necrosis is seen in:
(a) Diabetes (b) Rheumatoid arthritis
(c) Pancreatitis (d) Alzheimer's disease

44 All is true about fibrous dysplasia except:
(a) Benign
(b) Trabeculae mimic Chinese characters
(c) Can be polyostotic
(d) Extramedulllary

45. Spindle cell tumour is:
(a) Leiomyoma
(b) Schwannoma
(c) Fibrous histiocytoma
(d) Alveolar soft tissue sarcoma

46. Colloid bodies are seen in:
(a) Psoriasis (b) Lichen planus
(c) Leprosy (d) Tuberculosis

47. Koenon tumor is seen in:
(a) NF
(b) Tuberous sclerosis
(c) Turners syndrome
(e) Sturge Weber syndrome

48. Secondary allograft rejection is mediated by:
(a) Memory cells (b) Antibodies
(c) Immune complexes (d) None of the above

49. Dystrophin is absent:
(a) Duchenne muscular dystrophy
(b) Becker's muscular dystrophy
(c) Myotonic dystrophy
(d) Limb-girdle dystrophy

ASSERTION AND REASON QUESTIONS

1–4. Will have two statements, assertion and reason. Read both of them carefully and answer according to these options.
(a) Both assertion and reason are true and reason is correct explanation of assertion.
(b) Both assertion and reason are true and reason is not the correct explanation of assertion.
(c) Assertion is true and reason is false.
(d) Both assertion and reason are false.

1. **Assertion:** Patients with Duchene's muscular dystrophy have difficulty in walking.
   Reason: Altered dystrophin is responsible for muscular weakness in muscular dystrophy.
2. **Assertion:** Osteosarcoma is associated with the radiological appearance of Codman's triangle.
   Reason: The tumor results in reactive periosteal bone formation.
3. **Assertion:** Great toe is the most commonly affected joint in gout.
   Reason: Uric acid is deposited in less temperature
4. **Assertion:** Reiter syndrome is a n example of seronegative spondyloarthropathy
   Reason: Reiter syndrome is associated with HLA B-27

Explanations

1. Ans. (a) 22q translocation *(Ref: Robbins 8th/1232)*

Ewing sarcoma and primitive neuroectodermal tumor are primary malignant small round-cell tumors of bone and soft tissue. Both differ in their degree of differentiation. PNETs demonstrate neural differentiation whereas Ewing sarcomas are undifferentiated. Analyzing some features of Ewing sarcoma with the data in stem of the question:

- Arises in ***diaphysis and metaphysis*** (mass in the tibia in question)
- Most patients are ***10 to 15 years old*** (10 year old girl)
- Approximately 95% of patients with Ewing tumor have **t(11;22)**^{Q} (q24;q12) or **t(21;22)**^{Q} (q22;q12)
- Microscopically there are ***sheets of small round cells*** that contain ***glycogen***.

Please note that the option 'b' (11q deletion) given in the question should not be confused with the answer because in Ewing sarcoma we find 11q translocation and not deletion ☺

2. Ans. (b) Anti CCP antibody

(Ref: Robbins 8th/1237-1240, Harrison 17th/2088)

- Rheumatoid factor is an IgM antibody reactive with the Fc portions of the patients' own IgG. However, it is not specific for rheumatoid arthritis as it can also be seen in a wide range of autoimmune disorders, inflammatory disease and chronic infection.
- **Anti cyclic citrullinated peptide antibody** (anti CCP antibody) test is more specific than rheumatoid factor for diagnosis of rheumatoid arthritis. It is more commonly seen in the aggressive disease.

3. Ans. (d) Chronic inflammatory demyelinating polyneuropathy (CIDP) *(Ref: Robbins 8th/1259)*

- CIDP can result from altered triggering of T cells by antigen-presenting cells.
- Most cases occur in **adults**, and **males** are affected slightly more often than females.
- **Onset is usually gradual,** sometimes subacute; in a few, the initial attack is indistinguishable from that of GBS. An acute-onset form of CIDP should be considered when GBS deteriorates >9 weeks after onset or relapses at least three times.
- Symptoms are both motor and sensory in most cases. **Weakness of the limbs** is usually symmetric but can be strikingly asymmetric.
- **Death** from CIDP is **uncommon.**

Contd...

Contd...

- Biopsy typically reveals little inflammation and **onion-bulb changes** (imbricated layers of attenuated Schwann cell processes surrounding an axon) that result from recurrent demyelination and remyelination
- The diagnosis rests on characteristic clinical, CSF, and electrophysiologic findings. The CSF is usually acellular **with an elevated protein level.** Electrodiagnostically, variable degrees of conduction slowing, prolonged distal latencies, temporal dispersion of compound action potentials, and conduction block are the principal features.
- Treatment: If the disorder is mild, management can be awaiting spontaneous remission otherwise high-dose **IVIg, PE, and glucocorticoids** are all effective.

4. Ans. (a) Tetracycline labeling *(Ref: Bancroft 6th/358)*

Tetracycline is absorbed into bone and so, it is used as a marker of bone growth for biopsies in humans. Tetracycline binds to newly formed bone at the bone/osteoid (unmineralized bone) interface where it shows as a linear fluorescence. Tetracycline labeling is used to determine the amount of bone growth within a certain period of time, usually a period of approximately 21 days. Tetracycline is incorporated into mineralizing bone and can be detected by its fluorescence. In double tetracycline labeling, a second dose is given 11–14 days after the first dose, and the amount of bone formed during that interval can be calculated by measuring the distance between the two fluorescent labels.

5. Ans. (c) C-myc gene implicated in the genesis

(Ref: Robbins 8th/1225)

- Osteosarcoma is defined as a malignant mesenchymal tumor in which the cancerous cells produce bone matrix. It is the most common primary malignant tumor of bone, exclusive of myeloma and lymphoma.
- It has a bimodal age distribution; 75% occur in patients younger than age 20. The smaller second peak occurs in the elderly, who frequently suffer from conditions like Paget disease, bone infarcts, and prior irradiation.
- The tumors usually arise in the metaphyseal region of the long bones of the extremities, and almost 60% occur about the knee
- Genetic mutations seen with osteosarcoma are that of RB gene, p53, CDK4, p16, INK4A, CYCLIN D1, and MDM2.
- **The formation of bone by the tumor cells is characteristic of Osteosarcoma**

Contd...

Contd...

- Osteosarcoma typically present as painful and progressively enlarging masses.
- Radiographs of the primary tumor usually show a large, destructive, mixed lytic and blastic mass that has permeative margins. The tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation.
- The triangular shadow between the cortex and raised ends of periosteum is known radiographically as **Codman triangle**

6. **Ans. (a) t (X: 18)** *(Ref: Robbins 7th/1323)*

7. **Ans. (b) Ewing's sarcoma** *(Ref: Harrison 17th/613)*

8. **Ans. (c) Creatine kinase** *(Ref: Harrison 17th/2699)*
   - The diagnosis of the patient is most likely to be dermatomyositis (DM) as suggested by proximal muscle weakness (Gower's sign positive) and skin rash.
   - The clinical picture of the typical skin rash and proximal or diffuse muscle weakness has few causes other than DM. However, proximal muscle weakness without skin involvement can be due to many conditions other than PM or IBM.

   DM usually occurs alone but may overlap with scleroderma and mixed connective tissue disease. Fasciitis and thickening of the skin, similar to that seen in chronic cases of DM, have occurred in patients with the eosinophilia-myalgia syndrome associated with the ingestion of contaminated L-tryptophan.

   The CK level usually parallels disease activity, it can be normal in some patients with active IBM or DM, especially when associated with a connective tissue disease. The CK is always elevated in patients with active PM. Along with the CK, the serum glutamic-oxaloacetic and glutamate pyruvate transaminases, lactate dehydrogenase, and aldolase may be elevated.

   Muscle biopsy is the definitive test for establishing the diagnosis of inflammatory myopathy and for excluding other neuromuscular diseases. Inflammation is the histologic hallmark for these diseases; however, additional features are characteristic of each subtype.
   As biopsy is not given in the options, we will mark CK as the answer.

9. **Ans. (a) Anti-Jo 1** *(Ref: Harrison 17th/2038)*

10. **Ans. (a) Ewing's sarcoma** *(Ref: Harrison 17th/614, 615)*
    - ***CD 99 is a marker associated with the diagnosis of Ewing's sarcoma.***
    - ***Granulosa cell tumour*** is also often found to be associated with CD 99.

11. **Ans. (b) Osteocalcin** *(Ref: Harrison 17th/2368)*
    Osteocalcin is a protein secreted by **osteoblasts.** It is made virtually only by osteoblasts. Thus, it is a **bone formation marker,** i.e. *osteoblastic marker.*

Biochemical markers of bone resorption	Biochemical markers of bone resorption
a. Amino and carboxy terminal crosslinking telopeptide of bone collagen	a. Amino and carboxy terminal crosslinking telopeptide of bone collagen
b. Pyridinoline	b. Pyridinoline
c. Free Lysyl-pyridinoline	c. Free Lysyl-pyridinoline
d. Tartarate-resistant acid phosphatase (TRAP)	d. Tartarate-resistant acid phosphatase (TRAP)
e. Hydroxyproline (not very specific)	e. Hydroxyproline (not very specific)

12. **Ans. (b) Tumor permeation between bony trabeculae at periphery**
    (Ref: Robbins 8th/1227-1230; Sternberg's pathology 4th/276, 281)
    - Chondromas are benign tumors of hyaline cartilage that usually occurs in bones of endochondral origin. These can be:
    - *Enchondroma:* when origin is intramedullary
    - *Subperiosteal or juxtacortical:* Origin from the surface of bone
    - **Ollier disease** is a syndrome of multiple enchondromas (or enchondromatosis)
    - **Maffucis syndrome** is associated of soft-tissue hemangiomas with enchondromatosis.
    - Enchondromas are composed of well-circumscribed nodules of cytologically benign hyaline cartilage. Centre of the nodule can calcify whereas peripheral portion may undergo enchondral ossification.
    - **Chondrosarcoma** – These are group of tumors that produce neoplastic cartilage
    - Similar to chondroma, chondrosarcoma can be:
      - Intramedullary
      - Juxtacortical
    - Chondrosarcomas are second most common malignant matrix-producing tumor of bone. (Most common is osteosarcoma).
    - Histologically, chondrosarcomas are composed of malignant hyaline and myxoid cartilage. Spotty calcifications may be present and central necrosis may create cystic spaces. Tumors vary in cellularity and cytological atypia.
    - Malignant cartilage infiltrates the marrow space and surrounds pre-existing bony trabeculae.
    - Chondrosarcomas commonly arise in central portions of skeleton (including pelvis, shoulder and ribs). In contrast to chondroma, chondrosarcoma rarely involve the distal extremities.
    - Clear cell variant of chondrosarcoma characteristically originate from epiphysis of tubular long bones.

13. **Ans. (d) Duchenne's muscular Dystrophy**
    (Ref: Robbins 8th/1268-1269)

14. Ans. (a) Osteoclastoma. *(Ref: Robbins 7th/1302)*

Osteoclastoma (giant cell tumor) is so named because it contains a profusion of multinucleated osteoclast-type giant cells. This tumor is supposed to have a monocyte lineage and the giant cells are believed to form via fusion of the mononuclear cells.

Other giant cell lesions include:

- Brown tumor seen in hyperparathyroidism
- Giant cell reparative granuloma
- Chondroblastoma
- Pigmented villonodular synovitis.

15. Ans. (b) Synovial cell sarcoma

(Ref: Harrison 17th/2184; Robbins 7th/1317)

Synovial cell sarcoma arise from primitive mesenchymal tissue that differentiate into epithelial and spindle cells.

16. Ans. (b) Chondroblastoma *(Ref: Robbins 8th/1228)*

- Chondroblastoma is a rare benign tumor occurring in young patients in their teens with a *male-to-female ratio of 2:1.*
- Most arise near the *knee.*
- Chondroblastoma has a striking predilection for *epiphyses and apophyses* (epiphyseal equivalents, i.e., iliac crest). Chondroblastomas are usually *painful.*
- Radiographically, they produce a *well-defined geographic lucency* that commonly has *spotty calcifications.*
- The tumor cells are surrounded by *scant amounts of hyaline matrix* that is deposited in a lacelike configuration; nodules of well-formed hyaline cartilage are distinctly uncommon.
- When the matrix calcifies, it produces a characteristic *chicken-wire pattern of mineralization.*

Osteogenic sarcoma and chondromyxoid fibroma arises from metaphysis whereas Ewing sarcoma arises from medullary cavity.

17. Ans. (c) Osteitis deformans *(Ref: Robbins 7th/1285)*

- The histologic hallmark in *osteitis deformans (Paget's disease) is mosaic pattern of lamellar bone.*
- This pattern which is likened to a jig saw puzzle, is produced by prominent cement lines that anneal haphazardly oriented units of lamellar bone.

18. Ans. (a) CD8/MHC-I complex *(Ref: Robbins 7th/1343)*

Polymyositis is an example of inflammatory myopathy which is characterized by the presence of symmetrical proximal muscle weakness and elevated muscle enzymes. It is diagnosed with the help of T cell infiltrates within the muscle fascicles (endomysial involvement). The presence of CD8/MHC I complex is required for the diagnosis of this condition.

Note: It differs from dermatomyositis by the absence of rash (no cutaneous involvement) and its occurrence mainly in the elderly. In DM, there is presence of perifascicular atrophy (defined by the presence of groups of atrophic fibers at the periphery of the fascicles).

In another inflammatory myopathy called inclusion body myositis, there is presence of endomysial inflammation, basophilic granular deposits around the edge of slit-like vacuoles (rimmed vacuoles) and loss of fibers (being replaced with fat cells and connective tissue). There is characteristically presence of β amyloid deposits and cytochrome oxygenase negative fibers are seen.

19. Ans. (d) Giant cell tumor *(Ref: Robbins 8th/1233)*

20. Ans. (a) Multiple myeloma *(Ref: Robbins 8th/609-611)*

21. Ans. (b) Osteoid formation by mesenchymal cells with pleomorphism *(Ref: Robbins 8th/1226; 7th/1294-1296)*

22. Ans. (c) Fibrous dysplasia of bones

(Ref: Robbins 8th/1231; 7th/1300-1301)

23. Ans. (b) Osteosarcoma *(Ref: Robbins 8th/1216)*

24. Ans. (b) PTH *(Ref: Robbins 8th/1207-1208)*

25. Ans. (c) Ewing's sarcoma

(Ref: Robbins 8th/1232 ; 7th/1295,1298,1301)

26. Ans. (b) Osteoid osteoma *(Ref: Robbins 8th/1224)*

27. Ans. (a) Osteosarcoma *(Ref: Robbins 8th/1226,1228,1234)*

28. Ans. (b) Type II *(Ref: Robbins 8th/1235)*

29. Ans. (a) Bone *(Ref: Robbins 8th/1243-1244 ; 7th/1312)*

30. Ans. (d) All of the above

(Ref: Robbins 8th/1241; 7th/1310)

31. Ans. (c) Neuroectodermal cells....see text for details ....

(Ref: Robbins 8/e p1232)

32. Ans. (b) Duchenne's muscular dystrophy

(Ref: Robbins 8/e p1268)

Mnemonic: **DMD**

- **D**uchenne's **m**uscular **d**ystrophy: Does not **M**ake **D**ystrophin

Mnemonic: **BMD**

- **B**ecker's **m**uscular **d**ystrophy: **B**adly **M**ade **D**ystrophin

33. Ans. (b) IgM anti-IgG antibodies

(Ref: Robbins 8th/1238-9)

Symmetric polyarthritis with involvement of the proximal interphalangeal and metacarpophalangeal joints in a female patient are characteristics of rheumatoid arthritis. Rheumatoid factor, an IgM antibody directed against the Fc portion of IgG, is found in about 80% of affected individuals.

The most specific antibody for rheumatoid arthritis is anti-CCP (cyclic citrullinated peptide) antibody.

34. Ans. (b) Secondaries... *(Ref: Robbins 8/e p1235)*

Metastatic tumours are the most common form of skeletal malignancy..(Ref: Robbins)

35. Ans. (a) Osteitis fibrosa *(Ref: Robbins 9/e p1189)*

Paget disease is a disorder of increased, but disordered and structurally unsound, bone mass.

36. Ans. (c) Osteoblast and precursors

(Ref: Robbins 9/e p1203)

The neoplastic cells of giant cell tumor are ***primitive osteoblast precursors*** but they represent only a minority of the tumor cells. The bulk of the tumor consists of non-neoplastic osteoclasts and their precursors.

37. **Ans. (a) Podagra** *(Ref: Robbins 9/e p1216)*
Podagra is the involvement of the great toe in a patient with gout. As the book mentions; most first attacks are monoarticular; 50% occur in the **first metatarsophalangeal joint.**

38. **Ans. (d) Ankylosing spondylitis** *(Robbins 9th/1213)*
Ankylosing spondylitis causes destruction of **articular cartilage and bony ankylosis, especially of the sacroiliac and apophyseal joints** (between tuberosities and processes). It is also known as *rheumatoid spondylitis* and *Marie- Strümpell disease*. Disease involving the sacroiliac joints and vertebrae becomes symptomatic in the **second and third decades of life** as **lower back pain and spinal immobility**. Involvement of peripheral joints, such as the hips, knees, and shoulders, occurs in at least one third of affected individuals. Approximately 90% of patients are *HLA-B27 positive*; associations have also been found with the IL-23 receptor gene.

39. **Ans. (d) Five** *(Ref: Robbins 9/e p1209; Harrison 18/e p)*
- Rheumatoid arthritis is characterized by is a chronic inflammatory disorder of autoimmune origin that may affect many tissues and organs but principally attacks the joints, producing a non suppurative proliferative and inflammatory synovitis. The earliest involved joints are typically the small joints of the hands and feet.
- The initial pattern of joint involvement may be monoarticular, *oligoarticular (less than 4 joints)*, or **poly-articular (>5 joints)**, usually in a symmetric distribution.

40. **Ans. (b) Progress to chondrosarcoma**
(Ref: Robbins 9/e p1189-91)

Paget's disease

- Paget disease is a disorder of locally increased but disordered bone.
- Typically **asymptomatic**, it is usually **discovered incidentally**.
- A **mosaic pattern** of mineralization is the histologic hallmark at the late stage of the disease.
- Genetic and possibly **viral infectious** etiologies have been proposed.
- The most dreaded complication is **sarcoma** (osteosarcoma or fibrosarcoma), which occurs in less than 1% of all individuals with Paget disease, and in 5% to 10% of those with severe polyostotic disease.

41. **Ans. (b) Anti CCP** *(Ref: Robbins 9/e p1210)*

42. **Ans. (a) Osteomyelitis of frontal bone**
Pots puffy tumor is the osteomyelitis of frontal bone usually associated with subperiosteal abscess.

43. **Ans. (c) Rheumatoid arthritis** *(Ref: Robbins 9/e p1211)*

44. **Ans. (d) Extramedulllary** *(Ref: Robbins 9/e p1206)*

45. **Ans. (c) Fibrous histiocytoma** *(Ref: Robbins 9/e p1158)*

46. **Ans. (b) Lichen planus** *(Ref: Robbins 9/e p1167)*
Lichen planus is characterized by the presence of colloid or Civatte bodies.

47. **Ans. (b) Tuberous sclerosis** *(Ref: Robbins 9/e p1316)*

48. **Ans. (a) Memory cells** *(Ref: Immunology/134)*

49. **Ans. (a) Duchenne muscular dystrophy**
(Ref: Robbins 9/e p1242)

EXPLANATIONS TO ASSERTION AND REASON QUESTIONS

Explanations (1-4): While solving assertion reason type of questions, we can use a particular method.

1. First of all, read both assertion (A) and reason (R) carefully and independently analyse whether they are true or false.
2. If A is false, the answere will directly be (d) i.e. both A and R are false. You can note that all other options (i.e. a, b or c) consider A to be true.
3. If A is true, answer can be (a), (b) or (c), Now look at R. If R is false, answer will be (c)
4. If both A and R are ture, then we have to know whether R is correctly explaining A [answer is (a)] or it is not the explanation of assertion [answer is (b)]

1. **Ans. (b) Both assertion and reason are true and reason is not the correct explanation of assertion.**
(Ref: Robbins 8th/1268-9)
Patients with Duchene's muscular dystrophy have difficulty in walking. This is attributed to the absence of the skeletal muscle contractile protein dystrophin in these patients.

Altered dystrophin is responsible for muscular weakness in patients of Becker's muscular dystrophy.

Mnemonic:
Duchenne **M**uscular **D**ystrophy (DMD) **D**oesn't **M**ake **D**ystrophin (no formation)
Becker **M**uscular **D**ystrophy (BMD) **B**adly **M**ade **D**ystrophin (reduced formation of an altered protein)

2. **Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.**
(Ref: Robbins 8th/1226)

Osteosarcoma is associated with the radiological appearance of Codman's triangle because the tumor frequently breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation.

> The formation of bone by the tumor cells is characteristic of osteosarcoma.

3. Ans. (a) Both assertion and reason are true and reason is correct explanation of assertion.

(Ref: Robbins 8th/1243)

- Great toe is the most commonly affected joint in gout because uric acid gets supersaturated in the peripheral joints (ankle and toes) especially so in the lower temperatures.

4. Ans. (b) Both assertion and reason are true and reason is not the correct explanation of assertion.

(Ref: Robbins 8th/1241)

The seronegative spondyloarthropathies include the following: Mnemonic: PAIR

> **P** : **P**soriatic arthritis
> **A** : **A**nkylosing spondylitis
> **I** : **I**nflammatory bowel disease (Crohn' disease and ulcerative colitis) associated arthritis
> **R** : **R**eiter syndrome

These are called seronegative because they are not associated with specific autoantibodies although they are associated with HLA B-27 as well as a triggering infection.

ANNEXURE

Some medically important autoantibodies:

Anti-actin antibodies	coeliac disease, autoimmune hepatitis, gastric cancer
Anti-ganglioside antibodies	
Anti-GD3	Guillain-Barré syndrome
Anti-GM1	Traveler's diarrhea
Anti-GQ1b	Miller-Fisher syndrome
Anti-glomerular basement membrane antibody (Anti-GBM antibody)	Good pasture syndrome
Anti-Hu antibody	Small cell lung carcinoma
Anti-Jo 1 antibody (anti-histidyl-tRNA synthetase)	Polymyositis
Anti-liver/kidney microsomal 1 antibody (anti-LKM 1 antibodies)	Autoimmune hepatitis
Anti-mitochondrial antibody	Primary biliary cirrhosis
Anti-neutrophil cytoplasmic antibody (ANCA)	Ulcerative colitis
Antinuclear antibody (ANA)	
Anti-p62 antibodies in Anti-sp100 antibodies in Anti-glycoprotein210 antibodies in Anti-ds DNA antibody	Primary biliary cirrhosis Primary biliary cirrhosis Primary biliary cirrhosis SLE
Anti-extractable nuclear antigen antibodies (Anti-ENA antibodies)-	
Anti-Ro antibody	Sjögren syndrome
Anti-La antibody	Sjögren syndrome

Contd...

Contd...

Anti-PM/Scl (anti-exosome) antibody	scleroderma + polymyositis/ dermatomyositis.
Anti-Scl 70 antibody	Sclerosis and scleroderma
Anti-topoisomerase antibodies	
Anti-transglutaminase antibodies	
Anti-centromere antibodies	
Anti-tTG	Coeliac disease
Anti-eTG	Dermatitis herpetiformis

IMMUNOHISTOLOGICAL MARKERS FOR SOME CANCERS

CD-99	Ewing's/PNET, ovarian granulose cell tumors
LCA [CD-45]	Lymphoma
CD15	Hodgkin's lymphoma
	Adenocarcinoma
Desmin	Sarcoma
Vimentin	Sarcoma
CD-31	Kaposi's sarcoma
	Angiosarcoma
Thyroid transcription factor-1	Thyroid carcinoma, lung adenocarcinoma
CD-68 and HAM 56	Malignant fibrous histiocytoma
CD117 or DOG-1	Gastrointestinal stromal tumors (GIST)
HMB-45	Melanoma
CD-103	Hairy cell leukemia

CHAPTER 19

Miscellaneous

1. SALIVARY GLAND TUMORS

About 65 to 80% of the salivary gland tumors arise within the parotid, 10% in the submandibular gland, and the remainder in the minor salivary glands, including the sublingual glands. *The likelihood of a salivary gland tumor being malignant is inversely proportional to the size of the gland* which means the tumors in minor salivary glands are more likely to be malignant and those in parotid are mostly benign.

These tumors usually occur in adults, with a slight female predominance except Warthin tumor which occur more often in males than in females.

Pleomorphic Adenoma or Mixed Tumors

- They are the *most common benign tumors* that are derived from a mixture of ductal (epithelial) and myoepithelial cells, and therefore they show both epithelial and mesenchymal differentiation. About 60% of tumors in the parotid are mixed tumors.
- *Radiation exposure* increases the risk. Most pleomorphic adenomas present as rounded, well-demarcated masses rarely exceeding 6 cm.
- The epithelial elements resemble ductal cells or myoepithelial cells and are typically dispersed within a mesenchyme-like background of loose myxoid tissue containing islands of chondroid and, rarely, foci of bone.
- Tumors present as painless, slow-growing, mobile discrete masses.
- A carcinoma arising in a pleomorphic adenoma is referred to as a *carcinoma ex pleomorphic adenoma* or a *malignant mixed tumor*. The incidence of malignant transformation increases with the duration of the tumor.

Warthin's Tumor (Papillary Cystadenoma Lymphomatosum)

- It is the second most common benign salivary gland neoplasm. It arises almost always in the parotid gland and occurs more commonly in males than in females, usually in the fifth to seventh decades of life. About 10% are multifocal and 10% bilateral. It is more common in smokers.
- Most Warthin's tumors are round to oval, encapsulated masses, 2 to 5 cm in diameter.
- On microscopic examination, the cystic spaces are lined by a double layer of neoplastic epithelial cells resting on a dense lymphoid stroma. The **double layer of lining cells is distinctive**, with a surface palisade of columnar cells having an abundant, finely granular, eosinophilic cytoplasm, imparting an oncocytic appearance, resting on a layer of cuboidal to polygonal cells.

Mucoepidermoid Carcinoma

They occur mainly (60 to 70%) in the parotids. They are the **most common form of primary *malignant* tumor of the salivary glands**. Mucoepidermoid carcinomas can grow up to 8 cm in diameter, lack well-defined capsules and are often infiltrative at the margins. It is associated with a balanced translocation, **t(11;19)** producing a fusion gene made-up of MECT1 and MAML2.

The basic histologic pattern is that of cords, sheets, or cystic configurations of squamous, mucous, or intermediate cells. The hybrid cell types often have squamous features, with small to large mucus-filled vacuoles, best seen with mucin stains.

Two other salivary gland tumors include: Adenoid cystic carcinoma and acinic cell tumor.

Adenoid cystic carcinoma is a relatively uncommon tumor. In 50% of cases, it is found in the minor salivary glands (in particular; the palate). These tumors have a **tendency to invade perineural spaces.** They have high chances of recurrence and eventually, 50% or more disseminate widely to distant sites such as bone, liver, and brain.

The acinic cell tumor is composed of cells resembling the normal serous acinar cells of salivary glands. **Most arise in the parotids** and the small remainder arises in the submandibular glands. They *rarely involve the minor glands.* Most characteristically, the cells have apparently *clear cytoplasm*, but the cells are sometimes solid or at other times vacuolated. The cells are disposed in sheets or microcystic, glandular, follicular, or papillary patterns. There is usually little anaplasia and few mitoses. On histologic evaluation, they are composed of small cells having dark, compact nuclei and scant cytoplasm. These cells tend to be disposed in tubular, solid, or cribriform patterns. The spaces between the tumor cells are often *filled with a hyaline material* thought to represent **excess basement membrane.**

2. OTHER IMPORTANT TUMORS

a. Neuroblastoma

It is the **most common extracranial solid tumor of childhood** and the most frequently diagnosed tumor of infancy.

- Most cases are sporadic. *Familial* cases (1-2%) result *from germline mutation in anaplastic lymphoma kinase (ALK) gene.*

- *Most common site of origin is adrenal medulla (40%) followed by para-vertebral sympathetic chain in abdomen (25%) and posterior mediastinum (15%).*
- Adrenal neuroblastomas are malignant neoplasms arising from the sympathetic neuroblasts in the medulla of the adrenal gland. There are two clinical types, based on the differences in distribution of metastasis. First (**Pepper type**) occurs in the stillborn and in young infants and metastasizes to the liver and regional lymph nodes, then the lungs, and late in the course, the calvarium and other flat bones. The second (**Hutchinson**) type is characterized clinically by secondary growth in the orbit, meninges, skull and long bones and occurs in children up to 15 years of age.
- Histologically, it is one of the **small round blue cell tumor**. It shows central space filled with eosinophilic fibrillary material called *neuropil* surrounded by concentrically arranged tumor cells **(Homer-Wright pseudorosettes).**

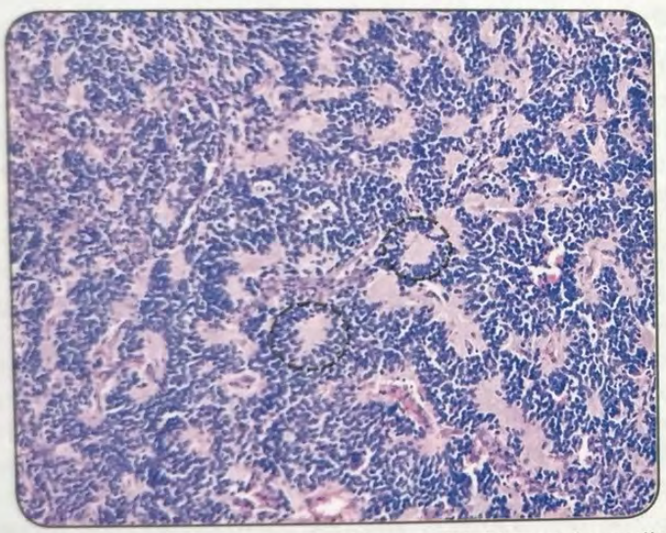


Fig. 1: Neuroblastoma showing Homer-Wright pseudorosettes

Note: Other small round cell tumors can be remembered as (Sofia LOREN)

Sophia	**S**mall round cell tumors
L	**L**ymphoma
O	**O**at cell carcinoma
R	**R**habdomyosarcoma
E	**E**wing's sarcoma
N	**N**euroblastoma

- Tumor cells are *positive for neuron specific enolase and contain dense core granules.*
- Maturation of some of the cells (to form ganglion cells) along with presence of primitive neuroblasts is called **ganglioneuroblastoma.** Even better differentiation with few neuroblasts is designated **ganglioneuroma**.
- Only presence of ganglion cells is not enough for designation of maturation. **Presence of Schwannian stroma, mature Schwann cells and fibroblasts is a histologic pre-requisite for the designation of ganglioneuroblastoma and ganglioneuroma.**
- Metastasis develops early and widely. Hematogenous spread may occur to liver, lungs, bone marrow and bones.
- About 60-80% children present with stage 3 or 4 tumors.
- Apart from stage 1, 2, 3 and 4, stage 4S (special stage) is present in neuroblastoma. It signifies localized primary tumor with dissemination limited to skin, liver and/or bone marrow. **Stage 4S is limited to infants < 1 year.**

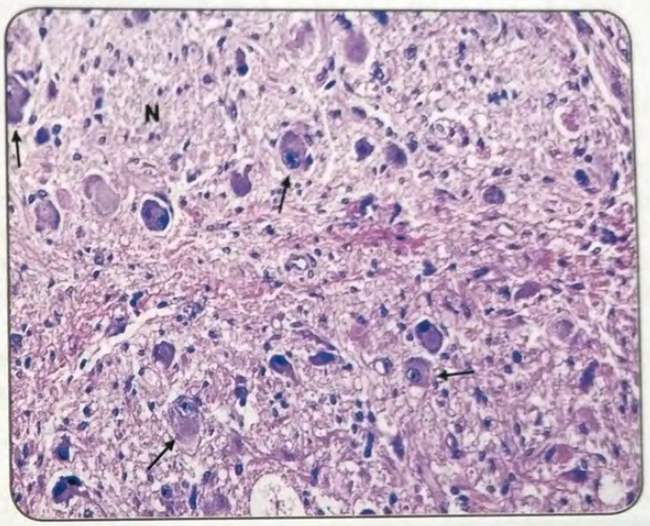


Fig. 2: Ganglioneuroma

Prognostic Factors

Factor	Favorable	Unfavorable
1. Stage	1, 2A, 2B, 4S	3, 4
2. Age	<18 months	>18 months
3. Histology		
Schwannian stroma	Present	Absent
Gangliocytic differentiation	Present	Absent
Mitotic rate	Low	High
Mitotic karyorrhexis index	<200/5000 cells (≤ 4%)	>200/5000 (> 4%)
Intramural calcification	Present	Absent
4. DNA Ploidy	Hyperdiploid or near triploid	Near diploid
5. N-Myc	Not amplified	Amplified
6. Genetics		
17q gain	Absent	Present
1p loss	Absent	Present
11q loss	Absent	Present
TRKA expression	Present	Absent
TRKB expression	Absent	Present
MRP expression	Absent	Present
CD44 expression	Present	Absent
Telomerase expression	Absent	Highly expressed

Note:
- Age for prognosis in 7th edition of Robbins was 1 year, in 8th edition, this has been changed to 18 months.
- Chromosome 11q loss, TRKB expression are included in prognostic factors in 8th edition of Robbins.

b. Retinoblastoma

- Retinoblastoma is the *most common malignant eye tumor of childhood.*
- 90% cases are diagnosed before 7 years. Hereditary retinoblastoma when affecting both eyes is called bilateral retinoblastoma.
- Bilateral retinoblastoma + pineal gland tumor in suprasellar or parasellar region is called **Trilateral retinoblastoma**
- These tumors *arise from neuroepithelium of the retina*
  - A characteristic feature is **Flexner Wintersteiner rosettes** consisting of clusters of cuboidal or short columnar cells arranged around a central lumen. The nuclei are displaced away from the lumen and photoreceptor like elements are produced from it. Retinoblastoma also shows **Homer Wright rosettes** which are radial arrangement of cells around a central tangle of fibrils.
- **Fleurettes** representing photoreceptor differentiation of tumor cells is also seen.

THYMOMA

- The **thymus** is *derived from the third and fourth pharyngeal pouches* and is located in the anterior mediastinum. The thymus is composed of epithelial and stromal cells and lymphoid precursors.
- **If a lymphoid cell within the thymus becomes neoplastic, the disease that develops is a lymphoma** which is a **T cell lymphoblastic lymphomas** in most of the cases. **If the epithelial cells of the thymus become neoplastic, the tumor that develops is a thymoma.**
- **Thymoma is the most common cause of an anterior mediastinal mass in adults.** Thymomas are most common in the fifth and sixth decade. Majority (90%) of thymomas are in the anterior mediastinum. *Thymomas are epithelial tumors and all of them have malignant potential.* They may have a *variable percentage of lymphocytes within the tumor.* The epithelial component of the tumor may consist primarily of round or oval cells derived mainly from the cortex or spindle-shaped cells derived mainly from the medulla or combinations thereof.
- These tumors present clinically in 40% patients as causing symptoms due to compression on the mediastinal structures or due to their association with myasthenia gravis. In addition to myasthenia gravis, other paraneoplastic syndromes, such as acquired hypogammaglobulinemia, pure red cell aplasia, Graves disease, pernicious anemia, dermatomyositis-polymyositis, and Cushing syndrome, can be seen.
- *Epstein-Barr virus may be associated with thymomas.*

WHO Histologic Classification of Thymus Tumors

Type	Histologic Description
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma
C	Thymic carcinoma

The genetic lesions in thymomas are not well characterized. Some data suggest that *Epstein-Barr virus may be associated with thymomas.*

3. SCLERODERMA

There are three major forms of scleroderma: diffuse, limited (CREST syndrome) and morphea/linear. Diffuse and limited scleroderma are both a systemic disease, whereas the linear/morphea form is localized to the skin.

Diffuse Scleroderma

Diffuse scleroderma (progressive systemic sclerosis) is the **most severe form**. It has a rapid onset, involves more widespread skin hardening, will generally cause much internal organ damage (especifically the lungs and gastrointestinal tract), and is generally more life-threatening.

Limited Scleroderma/CREST Syndrome

The limited form is much milder. It has a slow onset and progression. Skin hardening is usually confined to the hands and face, internal organ involvement is less severe, and a much better prognosis is expected. In typical cases of limited scleroderma, *Raynaud's phenomenon may precede scleroderma by several years.* The scleroderma may be limited to the fingers—known as **sclerodactyly.**

The limited form is often referred to as **CREST syndrome** characterized by:

- Calcinosis
- Raynaud's syndrome
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia

CREST is a limited form associated with **antibodies against centromeres** and usually spares the lungs and kidneys.

Morphea/Linear Scleroderma

Morphea/linear scleroderma involves isolated patches of hardened skin. There generally is no internal organ involvement.

Diagnosis is by clinical suspicion, presence of autoantibodies (especifically anti-centromere and anti-scl70/anti-topoisomerase antibodies) and occasionally by biopsy. Of the antibodies, 90% have a detectable anti-nuclear antibody. *Anti-centromere antibody is more common in the limited form (80-90%) than in the systemic form (10%), and anti-scl70 is more common in the diffuse form (30-40%).*

Multiple Choice Questions

1. **The immune-cytochemical feature of Langerhans cell histiocytosis is positivity for which of the following?** *(AI 2012)*
   (a) CD1a
   (b) CD99 (mic-2)
   (c) HMB-45
   (d) CD117

2. **In the congenital dystrophic variety of epidermolysis bullosa, mutation is seen in the gene coding for** *(AI 2012)*
   (a) Laminin 4
   (b) Collagen type 7
   (c) Alpha 6 integerin
   (d) Keratin 14

3. **The marker for Langerhans cell histiocytosis is:** *(AI 2010)*
   (a) CD 1a
   (b) CD 20
   (c) CD 3
   (d) CD 30

4. **For examination of fungus from a sample, uniformly stain by:** *(AI 2010)*
   (a) Alizarin
   (b) PAS
   (c) MassonTrichome
   (d) Giemsa

5. **All are components of photoreceptor matrix, except:** *(AI 2008)*
   (a) MMP
   (b) TIMP
   (c) SPARC
   (d) MIMECAN

6. **Acinic cell carcinomas of the salivary gland arise most often in the:** *(AI 2006)*
   (a) Parotid salivary gland
   (b) Minor salivary glands
   (c) Submandibular salivary gland
   (d) Sublingual salivary gland

7. **In familial Mediterranean fever, the gene encoding the following protein undergoes mutation** *(AI 2005)*
   (a) Pyrin
   (b) Perforin
   (c) Atrial natriuretic factor
   (d) Immunoglobulin light chain

8. **To which of the following events is 'good' outcome in Neuroblastoma associated** *(AI 2004)*
   (a) Diploidy
   (b) N-myc amplification
   (c) Chromosome/p depletion
   (d) Trk A expression

9. **Splenic macrophages in Gaucher's disease differ from those in ceroid histiocytosis by staining positive for:** *(AI 2004)*
   (a) Lipids
   (b) Phospholipids
   (c) Acid-fast stain
   (d) Iron

10. **A 70 years old male who has been chewing tobacco for the past 50 years presents with a six months history of a large, fungating, soft papillary lesions in the oral cavity. The lesion has penetrated into the mandible. Lymph nodes are not palpable. Two biopsies take from the lesion proper show benign appearing papillomatosis with hyperkeratosis and acanthosis infiltrating the subjacent tissues. The most likely diagnosis is:** *(AI 2004)*
    (a) Squamous cell papilloma
    (b) Squamous cell carcinoma
    (c) Verrucous carcinoma
    (d) Malignant mixed tumour

11. **Hereditary retinoblastoma develop the following chromosomal deletion:** *(AI 2003)*
    (a) 13q14
    (b) 11p13
    (c) 14q13
    (d) 22q11

12. **All the statement about lactoferin are true, except:**
    (a) It is present in secondary granules of neutrophil
    (b) It is present in exocrine secretions of body *(AI 2003)*
    (c) It has great affinity for iron
    (d) It transports iron for erythropoiesis

13. **Protein involved in intercellular connections is:** *(AI 2001)*
    (a) Connexins
    (b) Integrins
    (c) Adhesins
    (d) None of the above

14. **Which of the following stains is used to detect lipid in frozen section biopsy in histopathology laboratory?** *(AIIMS Nov 2009)*
    (a) PAS
    (b) Oil Red O
    (c) NSE
    (d) Silver Methanamine

15. **Young boy presented with multiple flaccid bullae and oral lesions. Diagnostic finding in skin biopsy immunofluorescence test would be:** *(AIIMS Nov 2009)*
    (a) Fish net IgG in dermoepidermal junction
    (b) Linear IgG in dermoepidermal junction
    (c) Linear IgG in dermal papillae
    (d) Granular IgA in reticular dermis

16. **A 14 years old girl on exposure to cold develop pallor of extremities followed by pain and cyanosis. In later ages of life she is prone to develop?** *(AIIMS Nov 2008)*
(a) Systemic lupus erythematosus
(b) Scleroderma
(c) Rheumatoid arthritis
(d) Histiocytosis

17. **Which is false about acrodermatitis? enteropathica?** *(AIIMS Nov 2008)*
(a) Triad of diarrhea, dementia and dermatitis
(b) Low serum zinc levels
(c) Symptoms improve with zinc supplementation
(d) Autosomal recessive

18. **Which of the following statement is incorrect?** *(AIIMS Nov 2008)*
(a) Selenium deficiency causes cardiomyopathy
(b) Zinc deficiency causes pulmonary fibrosis
(c) Increased calcium intake cause iron deficiency
(d) Vitamin A deficiency occurs after 6 months to 1year of low vitamin A diet

19. **A patient presents with mediastinal mass with sheets of epithelial cells giving arborizing pattern of keratin reactivity along with interspersed lymphoid cells. The apt diagnosis would be:** *(AIIMS May 2008)*
(a) Thymoma
(b) Thymic carcinoid
(c) Primary mediastinal lymphoma
(d) Non-Hodgkin lymphoma

20. **Ultrastructural finding in case of Paraganglioma:**
(a) Deposition of glycogen *(AIIMS May 2008)*
(b) Enlarged mitochondria
(c) Shrunken mitochondria
(d) Dense core granules

21. **Brain natriuretic peptide is degraded by:**
(a) Neutral endopeptidase *(AIIMS May 2007)*
(b) Elastase
(c) Collagenase
(d) Ompatrilat

22. **Why fetal cells continue to divide but terminally differentiated adult cells do not divide:** *(AIIMS Nov 2006)*
(a) There are many cyclin inhibitors which prevent cell to enter into S phase in adult
(b) Phosphatase absent in fetal cells
(c) Proteinase is absent in fetus
(d) Absence of CD kinase

23. **All of the following are examples of a round cell tumor, except:** *(AIIMS Nov 2005)*
(a) Neuroblastoma
(b) Ewing's sarcoma
(c) Non-Hodgkin's lymphoma
(d) Osteosarcoma

24. **The tissue of origin of the Kaposi's sarcoma is:**
(a) Lymphoid (c) Neural *(AIIMS May 2005)*
(b) Vascular (d) Muscular

25. **"Tophus" is the pathognomic lesion of which of the following condition:** *(AIIMS May 2003)*
(a) Multiple myeloma
(b) Cystinosis
(c) Gout
(d) Eale's disease

26. **Which of the following diseases have an underlying mitochondrial abnormality?** *(PGI Dec 01)*
(a) Krabbe's disease
(b) Fabry's disease
(c) Mitochondrial myopathy
(d) Oncocytoma
(e) Fanconi's syndrome

27. **Foam cells seen in:** *(PGI Dec 2005)*
(a) Alport's syndrome
(b) Niemann-Pick disease
(c) Atherosclerosis
(d) Pneumonia

28. **Which among the following is the best tissue fixative?**
(a) Formalin *(Delhi PG-2007)*
(b) Alcohol
(c) Normal saline
(d) Methylene blue

29. **All of the following are forms of panniculitis except:** *(Delhi PG-2006)*
(a) Weber-Christian disease
(b) Erythema induratum
(c) Erythema nodosum
(d) All of the above

30. **Warthin-Finkeldey cells are seen in:**
(a) Measles (b) Rubella
(c) Influenza (d) Rickettsial pox

31. **Pathogenesis is sequence of events in response to:** *(Delhi PG-2004)*
(a) Expression of disease upto clinical manifestation
(b) Expression of disease upto non-clinical manifestation
(c) The etiological agent for the initial stimulus to the ultimate expression of disease
(d) None

32. **All of the following characteristics are true of liposarcoma except that it:** *(Karnataka 2009)*
(a) Is commonly found in the retroperitoneum
(b) Frequently gives rise to embolization in lymphatics
(c) Is the most common soft tissue sarcoma
(d) Arises very rarely in subcutaneous tissue

33. **All of the following are correctly matched except:**
(a) Russell bodies – Multiple myeloma *(Karnataka 2008)*
(b) Russell bodies – Alcoholic liver disease
(c) Michaelis Gutmann bodies – Langerhans histiocytosis
(d) Civatte bodies – Lichen planus

34. Most common second malignancy in patients with familial retinoblastoma is: *(Karnataka 2004)*
(a) Teratoma
(b) Medullary carcinoma
(c) Osteosarcoma
(d) Malignant melanoma

35. Hutchison's secondaries in skull are due to tumors in:
(a) Lung *(DNB-2000, 2003)*
(b) Breast
(c) Liver
(d) Adrenals
(e) Testes

36. Rosette shaped arrangement of cells are seen in:
(a) Thecoma of ovary *(DNB- 2000, 2006, 2007)*
(b) Ependymoma
(c) Neurofibroma
(d) Lymphoma

37. Spontaneous regression though rare is seen in:
(a) Burkitt's lymphoma *(DNB- 2000)*
(b) Wilms' tumor
(c) Neuroblastoma
(d) Melanoma

38. Perioral pallor and Dennie's lines are seen in:
(a) Atopic dermatitis *(DNB- 2008)*
(b) Chronic actinic dermatitis
(c) Blood dyscrasias
(d) Perioral contact dermatitis

39. Most common tumor of parotid gland is:
(a) Pleomorphic adenoma *(UP 2001)*
(b) Warthin's adenoma
(c) Mucoepidermoid carcinoma
(d) Mixed tumor

40. MC malignant tumor of parotid glands is:
(a) Pleomorphic adenoma *(UP 2001)*
(b) Mucoepidermoid carcinoma
(c) Warthin's tumor
(d) Mixed tumor of salivary gland

41. Punctate basophilia is found in: *(UP 2001)*
(a) DDT poisoning
(b) Mercury vapors inhalation
(c) Cyanide poisoning
(d) Lead poisoning

42. Epulis is *(UP-98, 2004)*
(a) Tumor of gingiva
(b) Tumor of enamel of tooth
(c) Disarrangement of tooth
(d) Dysplastic leukoplakia

43. Most common tumor of infancy is *(UP 2005)*
(a) Lymphangioma
(b) Rhabdomyoma
(c) Hemangioma
(d) Lipoma

44. Triad of biotin deficiency is *(UP 2005)*
(a) Dermatitis, glossitis, steatorrhea
(b) Dermatitis, glossitis, alopecia
(c) Mental changes, diarrhea, alopecia
(d) Dermatitis, dementia, diarrhea

45. Basophilic stippling is seen in: *(UP 2006)*
(a) Cadmium poisoning
(b) Lead poisoning
(c) Chromium poisoning
(d) Iron poisoning

46. Most common tumor of infancy is *(UP 2005, 2007)*
(a) Lymphangioma
(b) Rhabdomyoma
(c) Hemangioma
(d) Lipoma

47. Pleomorphic adenoma usually arises from
(a) Parotid gland *(UP 2007)*
(b) Submandibular gland
(c) Minor salivary gland
(d) Superficial lobe

48. Direct Coomb's test detects: *(UP 2008)*
(a) Antigen in serum
(b) Antibodies on RBC surface
(c) Antigen on RBC surface
(d) Antibodies in serum

49. In vitamin deficiencies, patient is vulnerable to infection with: *(RJ 2000)*
(a) Measles
(b) Mumps
(c) Rubella
(d) Whooping cough

50. Paralytic food poisoning is caused by: *(RJ 2000)*
(a) *Staphylococci*
(b) *E. coli*
(c) *B. cereus*
(d) *Clostridia*

51. Which is not present in anterior mediastinum?
(a) Lymphoma *(RJ 2000)*
(b) Thymoma
(c) Teratoma
(d) Neurofibroma

52. Nonbacterial verrucous endocarditis is associated with
(a) Rheumatic carditis *(RJ 2001)*
(b) Rheumatoid arthritis
(c) SLE
(d) Infective endocarditis

53. Frozen section biopsy in not used for: *(Bihar 2005)*
(a) Enzyme (b) Amyloid
(c) Fat (d) Proteins

54. Rodent ulcer is due to: *(RJ 2002)*
(a) Syphilis
(b) Burns
(c) Basal cell carcinoma
(d) TB

MOST RECENT QUESTIONS

55. Most common salivary gland tumor in adult is:
(a) Mucoepidermoid carcinoma
(b) Lymphoma
(c) Pleomorphic adenoma
(d) None

56. Soft chancre is caused by:
(a) Syphilis
(b) TB
(c) Chancroid
(d) *L. donovani*

57. Kobner's phenomena is seen in:
(a) Psoriasis
(b) Lichen planus
(c) Toxic epidermal necrolysis
(d) All

58. Pellagra is characterized by all except:
(a) Diarrhea (b) Dementia
(c) Dermatitis (d) Diplopia

59. Smoking causes all cancers except:
(a) Liver (b) Pancreas
(c) Bladder (d) Lung

60. Endothelial cells have:
(a) Weibel-Palade bodies
(b) Gamma-Gandy bodies
(c) Both
(d) None

61. Which one of the following conditions is NOT associated with occurrence of pellagra?
(a) People eating mainly corn-based diet
(b) Carcinoid syndrome
(c) Phototherapy
(d) Hartnup disease

Explanations

1. **Ans. (a) CD1a** *(Ref: Robbins 8th/631-2)*

Entities in Langerhans cell histiocytosis

- Letterer-Siwe syndrome (multifocal multisystem LCH)
- Pulmonary Langerhans' cell histiocytosis: seen in adult smokers and can regress on cessation of smoking.
- Eosinophilic granuloma.

The tumor cells in Langerhans cell histiocytosis express HLA-DR, S-100^{Q}, and CD1a^{Q}.

2. **Ans. (b) Collagen type 7** *(Ref: Robbins 8th/1196)*

Epidermolysis bullosa are a group of non inflammatory disorders caused by defects in structural proteins which lend stability to the skin. It can be of the following types:

- **Simplex type**: defect in **basal layer of epidermis** due to mutation in gene for keratin 14 or 5
- **Junctional type**: blisters occur at the level of **lamina lucida**
- **Dystrophic type**: blisters beneath the **lamina densa** due to defect in COL7A1 gene for **collagen type VII**^{Q}

Clinical importance

Squamous cell cancers^{Q} can arise in these chronic blisters. **Non-Herlitz junctional epidermolysis bullosa** is caused by defect in LAMB3 gene encoding ***laminin Vβ3.***

3. **Ans. (a) CD 1a** *(Ref: Robbins 8th/631-632)*

Langerhans cell histiocytosis (LCH) has the following entities:

- The tumor cells express **HLA-DR, S-100, and CD1a**.
- *The presence of* ***Birbeck's granules*** *in the cytoplasm is characteristic* which have a **tennis-racket appearance** under the electron microscope.

4. **Ans. (b) PAS**

(Ref: Robbins 8th/336, Harsh Mohan 6th/12-13)

- PAS (Periodic Acid Schiff) stain is used for Carbohydrates particularly glycogen and all mucins, amoebae and fungi

Other frequently asked stains:

Stains	Substance
Congo red with polarizing light	Amyloid
Ziehl Neilson stain	Tubercle bacilli
Masson's Trichrome	Extracellular collagen
Perl's stain	Hemosiderin, iron
Masson-Fontana	Melanin, argentaffin cells
Alizarin	calcium
Feulgen reaction	DNA
Giemsa	Campylobacter, leishmaniae, malaria parasites

- Silver methanamine is a better stain for fungi and stains *Pneumocystis* and the fungi black in color.
- Mucicarmine is for staining cryptococci

5. **Ans. (d) MIMECAN**

(Ref: Robbins 7th/105, 109-111; Retina; Stephen J.Ryan 4th/140)

- Ryan says the retinal pigment epithelial (RPE) cells actively synthesize and degrade extracellular matrix (ECM) components. Deposition of ECM molecules is polarized with different components secreted apically and basally. The apical domain of the RPE cells is embedded in the interphotoreceptor matrix which is produced by RPE and inner segments of the photoreceptors. Degradation of ECM is regulated by the equilibrium between matrix metalloproteinases [(MMP) and their tissue inhibitors (TIMPs)].
- The normal RPE expresses membrane bound type I (MT_1-MMP) and type 2 (MT_2 MMP) metalloproteinase as well as the metalloproteinase inhibitors TIMP-1 and TIMP-3. TIMP-3 accumulates in Brusch membrane and is seen in age related macular degeneration (ARMD).
- Patients with SPARC (ostionectin) (Secreted Protein Acidic and Rich in Cysteine) contributes to tissue remodeling in response to injury and functions as an angiogenesis inhibitor. SPACR (sialyprotein associated with cones and rodes) is a glycoprotein identified in human interphotoreceptor matrix.
- MIMECAN is a member of small leucine rich proteoglycans (SLRP) gene family. They are essential for normal collagen fibrillogenesis in various connective tissues like cornea. It is not present in photorceptor matrix. It is also known as osteoglycin.

6. **Ans. (a) Parotid salivary gland** *(Ref: Robbins 7th/794)*

- Acinic cell tumors of salivary glands are uncommon tumors representing 2 to 3% of salivary gland tumors.
- These are composed of cells resembling the normal serous acinar cells of salivary glands.
- Most of these arise in the parotids. The remainder arises in submandibular glands.
- Most parotid tumors are benign but half of submandibular and sublingual and most minor salivary gland tumors are malignant.

7. **Ans. (a) Pyrin** *(Ref: Robbins 7th/261, Harrison 17th/2144)*

8. Ans. (d) Trk A expression *(Ref: Robbins 7th/503)*

- Neuroblastoma has good prognosis in infants (< 1 year old) regardless of the stage. These tumors are hyperdiploid or near triploid.

Prognostic factors in Neuroblastoma

- **Age and stage:** Good prognosis in infants regardless of stage. In children > 1 year, stage III and IV poor prognosis as compared to stage I or II.
- **Genetics:** Hyperdiploid or near triploid and high expression of Trk-A have good prognosis whereas near-diploidly, deletion of chromosome 1p or 14, gain of chromosome 17q and N-myc amplification is associated with unfavorable outcome.
- 3.
  Tumor markers: Telomerase and MRP expression has poor prognosis whereas CD 44 expression associated with good prognosis.
- **Histology:** Differentiation (into Schwann cells and gangliocytes), low mitotic rate and intramural calcification has good prognosis.

Note: Most characteristic cytogenetic abnormality in neuroblastoma is 1p deletion.

9. Ans. (a) Lipids *(Ref: Harrison 17th/2548, 2455)*

- Ceroid histiocytosis also known as neuronal cerebrolipofuschinosis is a group of diseases where lipofuschin, a yellow brown cytoplasmic pigment is deposited in the neurons. Lipofuschin is a lipid.
- In Gaucher's disease, all patients have a nonuniform infiltration of bone marrow by lipid laden macrophages termed Gaucher cells's.

Thus both these disorders have 'lipids' in the macrophages.

GAUCHER'S DISEASE

- It is autosomal recessive lysosomal storage disorder due to deficiency of enzyme α-glucosidase resulting in accumulation of glucosylceramide.
- Decreased activity (0-20%) of α-glucosidase in nucleated cells is required for diagnosis.
- Type 1 disease do not involve CNS and present as hepatosplenomegaly with skeletal dysplasia whereas Type 2 Gaucher's disease is a severe CNS disease leading to death by 2 year of age. Type 3 disease has highly variable manifestations in CNS and viscera.

10. Ans. (c) Verrucous carcinoma
(Ref: Robbins 7th/1037; Ackerman's surgical pathology 8th/235)

Verrucous carcinomas also referred to as giant condyloma accuminatum or **Buschke-Lowenstein tumour** is considered an intermediate lesion between condyloma acuminata and invasive squamous cell carcinoma. It is important to distinguish verrucuous carcinomas from squamous cell carcinoma as these tend to remain localized and are cured by wide excision, however they may undergo malignant transformation to invasive squamous cell carcinomas.

Features of verrucuous carcinomas

- Predilection for **males** > 50 years
- Predisposed in **tobacco** users, poor oral hygiene
- **Grossly**, it is a soft, large, wart like (papillomatous) lesion which may show fungation
- **Microscopically:**
  - Cytological features of malignancy are absent or minimal and rare
  - Epithelium is thickened and thrown into papillary folds
  - The folds project both above and below the level of surrounding mucosa and crypt like surface grooves exhibit marked, pre-keratin plugging.
  - The deep border of epithelial projections is 'pushing' and not infiltrative.

11. Ans. (a) 13q14 *(Ref: Harrison's 17th/413)*

The term contiguous gene syndrome refers to genetic disorders that mimic single gene disorders. They result from deletion of a small number of tightly clustered genes. Because some are too small to be detected cytogenetically, they are termed as **microdeletion syndromes**
The important **microdeletion syndromes are:**

1. Wilms' tumor – Aniridia complex (WAGR syndrome)	11p 13
2. Retinoblastoma	13q 14.11
3. Prader-Willi syndrome	15q11-13
4. Angelman's syndrome	15q11-13
5. DiGeorge's syndrome/Velocardiofacial syndrome	22q 11
6. Miller-Dieker syndrome	17p 13

Deletions involving the long arm of chromosome 22 (22q 11) are the most common microdeletions identified to date.

Note: Important microduplication syndromes include Beckwith-Wiedemann syndrome (11p 15) and Charcot- Marie-Tooth syndrome type IA (17 p 11.2)

12. Ans. (d) It transports iron for erythropoiesis
(Ref: Harper 25th/775, Harrison 17th/378,815,847)

- Transport of iron for erythropoiesis is done by transferin and not by lactoferin.
- Lactoferin is found in specific/secondary granules in neutrophils and in many exocrine secretions and exudates (milk, tears, mucus, saliva, bile, etc.)

13. Ans. (a) Connexins *(Ref: Harrison 17th/2479)*

- **Connexins** are complex protein assemblies that traverse the lipid bilayer of the plasma membrane and form a continuous channel. A pair of connexins from adjacent cells joins to form a gap junction that bridges the 2-4 mm gap between the cells. These are important for communications in neurons and glial cells.
- **Adhesions** are microbial surface antigens that frequently exist in the form of filamentous projection (pili or fimbria) and bind to specific receptors on epithelial cell membranes.

- **Integrins** are a family of cell membrane glycoproteins. These are involved in cell adhesion.

14. Ans. (b) Oil Red O *(Ref: Harsh Mohan 6th/12-13)*

Lipids are detected in histopathology by the use of the following stains:

- *Oil red O*: Mineral oils stain red and unsaturated fats stain pink
- *Sudan Black B*: Unsaturated fats stain blue black
- *Osmium tetroxide*: Unsaturated fats stain brown-black whereas saturated fats are unstained.

Regarding other options:

- PAS (Periodic Acid Schiff) stain is for carbohydrates particularly glycogen and all mucins
- Silver Methanamine is for fungi
- Non-specific esterase (NSE) is for staining myeloblast in patients of Acute myeloid leukemia (AML)

15. Ans. (a) Fish net IgG in dermoepidermal junction *(Ref: Robbins 8th/1192-1193, Harrison 17th/336-339)*

- The inflammatory bullous lesions may be Pemphigus vulgaris, Bullous pemphigoid and dermatitis herpetiformis. The presentation of multiple flaccid bullae and oral lesions in a young boy is suggestive of *Pemphigus vulgaris*. An important histological finding in pemphigus is **acantholysis** which is dissolution, or lysis, of the intercellular adhesion sites within a squamous epithelial surface. The **suprabasal acantholytic blister** that forms is *characteristic of pemphigus vulgaris*. The antibody in pemphigus vulgaris reacts with *desmoglein 1 and 3*, a component of the desmosomes that appear to bind keratinocytes together. By direct immunofluorescence, lesional sites show a characteristic **netlike pattern** of intercellular IgG deposits.

About other options:

- Bullous pemphigoid generally affects *elderly* individuals. The *bullae are tense* and oral lesions are present in 10-15% of affected individuals. The **subepithelial acantholytic blister** is *characteristic of bullous pemphigoid*. The antibody in bullous pemphigoid reacts with bullous pemphigoid antigens 1 and 2 (BPAG 1 and 2) present in *dermoepidermal junction*. Linear IgG in dermoepidermal junction are seen by direct immunofluorescence. (option 'B').
- Dermatitis herpetiformis is characterized by *urticaria and grouped vesicles*. The disease results from formation of antibodies against gliadin and is associated with *celiac disease*. By direct immunofluorescence, dermatitis herpetiformis shows granular deposits of **IgA** selectively localized in the *tips of dermal papillae*. (option 'D').
- Pemphigus foliaceous is having the antibody reacting with *desmoglein 1 alone*. There is selective involvement of superficial epidermis at the level of the stratum granulosum. It usually affects the scalp, face, chest, and back, and the mucous membranes are only rarely affected. Linear IgG in dermal papillae is a feature of Pemphigus foliaceous. (option 'C').

16. Ans. (b) Scleroderma *(Ref: Harrison 17th/2096)*

- The girl in this case is showing Raynaud's phenomenon and is likely to suffer later from systemic sclerosis.
- **Raynaud's phenomenon** is characterized by episodic digital ischemia, manifested clinically by the sequential development of digital blanching, cyanosis, and rubor of the fingers or toes following cold exposure and subsequent rewarming.
- Raynaud's phenomenon is broadly separated into two categories: The **idiopathic** variety, termed *Raynaud's disease*, and the **secondary** variety, which is associated with other disease like scleroderma.

17. Ans. (a) Triad of diarrhea, dementia and dermatitis *(Ref: Harrison 17th/449)*

- **Acrodermatitis enteropathica** also known as **Brandt Syndrome or Danbolt-Cross syndrome** is an autosomal recessive metabolic disorder affecting the uptake of zinc, characterized by periorificial and acral *dermatitis, alopecia and diarrhea.*

18. Ans. (b) Zinc deficiency causes pulmonary fibrosis *(Ref: Harrison 17th/449)*

Element	Deficiency	Toxicity
Calcium	Reduced bone mass, osteoporosis	Renal insufficiency (milk-alkali syndrome), nephrolithiasis, impaired iron absorption
Selenium	Cardiomyopathy, heart failure, striated muscle degeneration	*General:* Alopecia, nausea, vomiting, abnormal nails, emotional lability, peripheral neuropathy, lassitude, garlic odor to breath, dermatitis *Occupational:* Lung and nasal carcinomas, liver necrosis, pulmonary inflammation
Zinc	Growth retardation, altered taste and smell, alopecia, dermatitis, diarrhea, immune dysfunction, failure to thrive, gonadal atrophy, congenital malformations	*General:* Reduced copper absorption, gastritis, sweating, fever, nausea, vomiting *Occupational:* Respiratory distress, pulmonary fibrosis

19. Ans. (a) Thymoma *(Ref: Harrison 17th/89, Devita 6th/1023)*

- Tumors made up of **two different lineage of cells,** i.e. lymphocytes and epithelial cells suggests the diagnosis of thymoma.
- Thymoma is the *most common cause of an anterior mediastinal mass in adults*, accounting for ~40% of all

mediastinal masses. Thymomas are most common in the fifth and sixth decade. Some 90% of thymomas are in the anterior mediastinum. Thymomas are epithelial tumors and all of them have malignant potential. They may have a variable percentage of lymphocytes within the tumor, but genetic studies suggest that the lymphocytes are benign polyclonal cells. The epithelial component of the tumor may consist primarily of round or oval cells derived mainly from the cortex or spindle-shaped cells derived mainly from the medulla or combinations thereof.

20. Ans. (d) Dense core granules

(Ref: Robbin's 7th/769; Devita 6th/900)

- Paraganglioma is a neuroendocrine tumor and **like other neuroendocrine tumors, the ultrastructure shows dense core granules** *(neurosecretory granules)*
- The tumor cells are separated by ***fibrovascular stroma*** and surrounded by ***sustentacular cells.***
- ***Chief cells are neuroendocrine cells and are positive for regular neuroendocrine markers, e.g.***
  - Chromogranin
  - Synaptophysin
  - euron specific enolase
  - Serotonin
  - Neurofilament
- The chief cells are **S-100 protein negative** but the **sustentacular cells are S-100 positive and are focally positive** for **glial fibrillary acid protein.**
- ***Paraganglioma cells are never positive for cytokeratin like other neuroendocrine tumors.***

21. Ans. (a) Neutral endopeptidase

(Ref: Ganong 22nd/462, , Harrison's 17th/233,2146,2103)

- **Brain natriuretic peptide (BND) or B type natriuretic peptide** is a hormone produced by the ventricles of the heart. It has been shown to increase in response to ventricular volume expansion and pressure overload.
- BNP is a marker of ***ventricular systolic*** and ***diastolic function.***
  - BNP also has a prognostic significance in systemic sclerosis (with pulmonary artery hypertension) and in amyloidosis involving the heart.
- **Atrial natriuretic peptide** (ANP) is a hormone released by atrial walls of the heart when they become stretched. Because in heart failure, there is almost always excessive increase in both the right and left atrial pressures that stretch the atrial walls the circulating levels of ANP in the blood increase fivefold to tenfold in severe heart failure. The ANF in turn has a direct effect on the kidneys to increase greatly their excretion of salt and water. Therefore ANP plays a natural role to prevent the extreme congestive symptoms of cardiac failure.
- Both ANP as well as BNP are metabolized by neutral endopeptidases and the inhibitors of this enzyme (omapatrilat and sampatrilat) are used for the management of CHF.

22. Ans. (a) *There are many cyclin inhibitors which prevent cell to enter into S phase in adult*

(Ref: Robbins, 7th/42, 43, 308, 309)

- After a fixed number of divisions, normal cells become arrested in a ***terminally non dividing state*** known as replicative senescence. It occurs due to shortening of telomeres.
- **Telomeres** are ***short repeated sequences of DNA*** present at the linear ends of chromosomes that are important for ***ensuring the complete replication*** of chromosomal ends and ***protecting*** chromosomal terminals from fusion and degradation. When somatic cells replicate a *small section* of the telomere is ***not duplicated*** and telomeres become ***progressively shortened.*** The loss of telomere function leads to ***activation of p53 dependent cell cycle checkpoints causing proliferative arrest or apoptosis.***
- ***Germ cells, some stem cells and cancer cells continue to divide*** because in these cells telomere *shortening is prevented by sustained function of the enzyme* ***telomerase that maintains the length of the telomere*** by nucleotide addition.

23. Ans. (d) Osteosarcoma *(Ref: Robbin's 7th/500, 8th/475)*

- Most of the malignant pediatric neoplasms are unique in many respects:
  - They tend to have a more primitive *(embryonal)* rather than pleomorphic-anaplastic microscopic appearance, are often characterized by sheets of cells with small, round nuclei, and frequently exhibit features of organogenesis specific to the site of tumor origin. Because of this latter characteristic, these tumors are frequently designated by the suffix *-blastoma*, for example, nephroblastoma (Wilms' tumor), hepatoblastoma, and neuroblastoma.
  - Owing to their primitive histologic appearance, many childhood tumors have been collectively referred to as **small round blue cell tumors**.
  - The differential diagnosis of such tumors includes
    - Neuroblastoma
    - Wilms' tumor
    - Lymphoma
    - Rhabdomyosarcoma
    - Ewing sarcoma/Primitive neuroectodermal tumor.

24. Ans. (b) Vascular

(Ref: Harrison 17th/1186-1187, Robbins 7th/548, 550)

25. Ans. (c) Gout *(Ref: Robbins 8th/1243-1246)*

Tophi are formed by large aggregations of urate crystals. They are surrounded by macrophages, lymphocytes and foreign body giant cells. They are characteristic of gout. They are seen in the

- Articular cartilage of joints*

- Periarticular ligaments*
- Tendons and soft tissues*
- Achilles tendon*
- Ear lobes*

Other important points

- Most common joint involved in Gout is Big Toe (First metatarsophalangeal joint)
- The diagnosis is made by presence of monosodium urate crystal in polarized light which are needle shaped and strongly negative birefringent crystal.

26. Ans. (c) Mitochondrial myopathy
(Ref: Robbins 7th/33, 1342, Harrison' 16th/2534, 374)

27. Ans. (a) Alport's syndrome; (b) Niemann-Pick disease; (c) Atherosclerosis
(Ref: Robbin's 7th/523, 988 ,163)

- Foam cells are lipid laden phagocytes. In Niemann-Pick disease, they are widely distributed in spleen, liver, lymph nodes, bone marrow, and tonsils.
- During atherosclerosis, oxidized LDL is ingested by macrophages forming foam cells.
- In Alport's syndrome, interstitial cells of kidney may acquire a foamy appearance owing to accumulation of neutral fats and mucopolysaccharides forming foam cells.

28. Ans. (a) Formalin *(Ref: Harsh Mohan 6th/276)*
Formalin is the best tissue fixative.

29. Ans. (d) All of the above
(Ref: Robbins 7th/1265, 8th/1199)

- Panniculitis is an inflammatory reaction in the subcutaneous fat that may affect principally the connective tissue septa separating lobules of fat or predominantly the lobules of fat themselves.
- The various forms of panniculitis are:
  - **Erythema nodosum: Most common form of panniculitis** and usually has an acute presentation. Its occurrence is often associated with infections (β-hemolytic streptococci, TB and less commonly, coccidiodomycosis, histoplasmosis and leprosy), drug administration (sulfonamides, oral contraceptives), sarcoidosis, inflammatory bowel disease, and certain malignant neoplasms.
  - **Erythema induratum:** Uncommon type of panniculitis that affects primarily adolescents and menopausal women. It is a primary vasculitis affecting deep vessels with subsequent necrosis and inflammation within the fat. There is no associated underlying disease.
  - **Weber-Christian disease** (*relapsing febrile nodular panniculitis*): It is a rare form of lobular, nonvascular panniculitis seen in children and adults.
  - Factitial panniculitis: It is a result of self-inflicted trauma or injection of foreign or toxic substances, is a form of secondary panniculitis.
  - Lupus erythematosus may occasionally have deep inflammatory components with associated panniculitis.

30. Ans. (a) Measles *(Ref: Robbins 7th/364)*

31. Ans. (c) The etiological agent for the initial stimulus to the ultimate expression of disease *(Ref: Robbins 7th/4)*
Pathogenesis refers to the sequence of events in the response of cells or tissues to the etiological agent, from the initial stimulus to the ultimate expression of the disease".

32. Ans. (b) Frequently gives rise to embolization in the lymphatics *(Ref: Robbins 7th/1318)*
Liposarcomas are *one of the most common sarcomas* of adulthood and are uncommon in children. They usually *arise in the deep soft tissues* of the *proximal extremities and retroperitoneum* and are notorious for developing into large tumors. Histologically, liposarcomas can be divided into well-differentiated, myxoid, round cell, and pleomorphic variants. The cells in well-differentiated liposarcomas are readily recognized as lipocytes. In the other variants, some cells indicative of fatty differentiation called **lipoblasts** are almost always present. The myxoid and round cell variant of liposarcoma has a **t(12;16)** chromosomal abnormality.

33. Ans. (c) Michaelis Gutmann bodies—Langerhans histiocytosis
(Ref: Robbins 7th/1258, 680-681, 905, 1027-1028, 701-702)

Russell bodies
Inclusions containing immunoglobulins present in the cytoplasm of patients of multiple myeloma; similar inclusions in the nucleus are called Dutcher bodies.
Mallory bodies
Eosinophilic cytokeratin inclusions seen in alcoholic liver disease (can also be seen in Wilson's disease, Indian childhood cirrhosis, chronic cholestatic conditions, hepatocellular cancer and primary biliary cirrhosis)
Civatte bodies
Lichen planus is a disease characterized by "purple, pruritic, polygonal papules" and characterized histologically by dense lymphocytic infiltrates along dermoepidermal junction. The lymphocytes are intimately associated with basal keratinocytes which show degeneration and necrosis contributing to *saw-toothing* of dermo-epidermal junction. Anucleate, necrotic basal cells may get incorporated into the inflamed papillary epidermis where they are called colloid or Civatte bodies.
Michaelis Gutmann bodies
Seen in Malacoplakia (vesicle inflammatory reaction associated with *E. coli* infection characterized by raised mucosal plaques and histologically by infiltration with large, foamy macrophages having laminated mineralized concretions of calcium inside lysosomes called Michaelis Gutmann bodies).

Contd...

Contd...

Langerhan's histiocytosis

It is a term used for proliferative disorders of dendritic cells which has three disorders namely Letterer-Siwe syndrome, Hand-Schuller-Christian disease and eosinophilic granuloma. The presence of *Birbeck's granules* in the cytoplasm is a characteristic feature. These granules have a rod-like structure and terminal dilated ends (**Tennis racket appearance**)

34. **Ans. (c) Osteosarcoma** *(Ref: Robbins 7th/299)*
    - Patients with familial retinoblastoma are also at greatly increased risk of developing osteosarcoma and some other soft tissue sarcomas (*Robbins pg 299*)
    - Alterations in 'RB pathway' involving INK 4a proteins, cyclin D-dependent kinases and RB family proteins which are present in normal cells lead on to inactivation of tumor suppressor gene (CRB gene) and associated somatic/inherited mutations cause the increased risk of other tumors.

35. **Ans. (d) Adrenals**
    (Ref: Arch Ophthal. 1939; 22(4):575-580)
    Adrenal neuroblastomas are malignant neoplasms arising from the sympathetic neuroblasts in the medulla of the adrenal gland. There are two clinical types, based on the differences in distribution of metastasis. First (**Pepper type**) occurs in the stillborn and in young infants and metastasizes to the liver and regional lymph nodes, then the lungs, and late in the course, the calvarium and other flat bones. The second (**Hutchinson**) type is characterized clinically by secondary growth in the orbit, meninges, skull and long bones and occurs in children up to 15 years of age.

36. **Ans. (b) Ependymoma** *(Ref: Robbins 8th/1334)*

37. **Ans. (c) Neuroblastoma** *(Ref: Robbins 8th/477)*

38. **Ans. (a) Atopic dermatitis** *(Ref: Robbins 8th/1187-1189)*

39. **Ans. (a) Pleomorphic adenoma** *(Ref: Robbins 8th/757)*

40. **Ans. (b) Mucoepidermoid carcinoma**
    (Ref: Robbins 8th/759; 7th/791)

41. **Ans. (d) Lead poisoning** *(Ref: Robbins 8th/407)*

42. **Ans. (a) Tumor of gingiva** *(Ref: Robbins 8th/748)*

43. **Ans. (b) Rhabdomyoma** *(Ref: Robbins 8th/584)*

44. **Ans. (b) Dermatitis, glossitis, alopecia**
    (Ref: Harsh Mohan 6th/254)

45. **Ans. (b) Lead poisoning** *(Ref: Robbins 8th/406-407)*

46. **Ans. (b) Rhabdomyoma** *(Ref: Robbins 8th/584)*

47. **Ans. (a) Parotid gland** *(Ref: Robbins 8th/757)*

48. **Ans. (d) Antibodies in serum** *(Ref: Robbins 8th/653)*

49. **Ans. (a) Measles** *(Ref: Robbins 8th/432-433)*

50. **Ans. (d) *Clostridia*** *(Ref: Robbins 8th/378-379)*

51. **Ans. (d) Neurofibroma** *(Ref: Robbins 8th/730)*

52. **Ans. (c) SLE** *(Ref: Robbins 8th/220)*

53. **Ans. (b) Amyloid** *(Ref: Robbins 8th/253)*

54. **Ans. (c) Basal cell carcinoma** *(Ref: Robbins 8th/1180)*

55. **Ans. (c) Pleomorphic adenoma** *(Ref: Robbins 8th/261)*

56. **Ans. (c) Chancroid** *(Ref: Robbins 8th/366)*

57. **Ans. (d) All** *(Ref: Robbins 8th/1191-1192)*

58. **Ans. (d) Diplopia** *(Ref: Robbins 8th/438)*

59. **Ans. (a) Liver** *(Ref: Robbins 8th/273; 7th/923)*

60. **Ans. (a) Weibel-Palade bodies** *(Ref: Robbins 8th/990)*

61. **Ans. (c) Phototherapy**
    (Ref: Harrison, Chapter 74. Vitamin and Trace Mineral Deficiency and Excess)
    Niacin deficiency causes pellagra which can be due to the following reasons:
    - People eating corn-based diets
    - In alcoholics
    - In congenital defects of intestinal and kidney absorption of tryptophan like Hartnup disease
    - In patients with carcinoid syndrome

CHAPTER 20

Recent Papers

PATHOLOGY

1. **Stellate granuloma is seen in:** *(AI 2018 Pattern)*
   (a) Crohn disease
   (b) Berryliosis
   (c) Cat scratch disease
   (d) Syphilis

2. **Warthin Finkeldey cells are seen in:** *(AI 2018 Pattern)*
   (a) Mumps (b) Measles
   (c) Rubella (d) Chicken pox

3. **Which of the following has pyrogenic activity?** *(AI 2018 Pattern)*
   (a) TGF-beta (b) IL-6
   (c) IL-5 (d) IL-2

4. **Which of the following is an opsonin?** *(AI 2018 Pattern)*
   (a) C5a (b) C3b
   (c) C3a (d) C5b

5. **Which of the following is true about keloid?** *(AI 2018 Pattern)*
   (a) It is associated with elevated levels of growth factors
   (b) It has greater amount of collagen and vascularity
   (c) It does not spread beyond wound site
   (d) Wide excision is the treatment of choice

6. **Factor V mutation is commonly associated with:** *(AI 2018 Pattern)*
   (a) Hemarthrosis (b) Hematemesis
   (c) Thrombosis (d) Epistaxis

7. **RET proto-oncogene is associated with:** *(AI 2018 Pattern)*
   (a) Medullary thyroid cancer
   (b) Paraganglioma
   (c) Papillary thyroid cancer
   (d) CNS tumors

8. **Which of the following mutation is seen in Cowden syndrome?** *(AI 2018 Pattern)*
   (a) STK11 mutation (b) SMAD4 mutation
   (c) PTEN mutation (d) PTCH mutation

9. **Absence of differentiation is known as:** *(AI 2018 Pattern)*
   (a) Metaplasia (b) Anaplasia
   (c) Dysplasia (d) Any of the above

10. **Neuroendocrine tumor is having which of the following as an immunohistochemical marker?** *(AI 2018 Pattern)*
    (a) Cytokeratin (b) Calretin
    (c) Synaptophysin (d) Carcinoembryonic antigen

11. **Which of the following is not false about ataxia telangiectasia?** *(AI 2018 Pattern)*
    (a) It is associated with normal immune function
    (b) Serum levels of IgM are increased
    (c) It is X linked recessive disease
    (d) There is presence of amphicytes in different organs.

12. **Which of the following is X linked disease?** *(AI 2018 Pattern)*
    (a) Thalassemia
    (b) Galactosemia
    (c) Color blindness
    (d) Sickle cell disease

13. **Hyperacute rejection occurs within:** *(AI 2018 Pattern)*
    (a) 12 hours
    (b) 2 weeks
    (c) 1 month
    (d) 3 month

14. **Nude mice is able to accept xenograft because they do not have:** *(AI 2018 Pattern)*
    (a) B cells
    (b) T cells
    (c) Natural killer cells
    (d) Macrophages

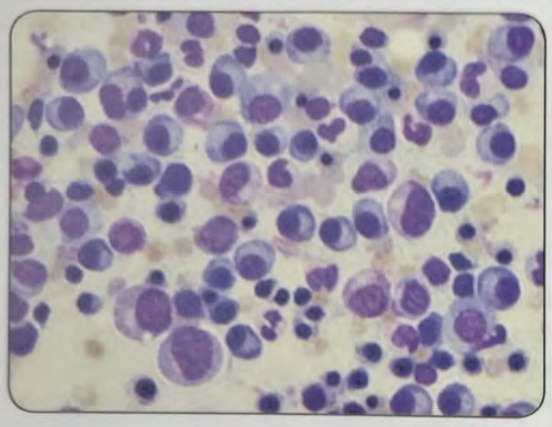
15. **Mean transformation time for HIV to AIDS is:** *(AI 2018 Pattern)*
    (a) 5 years
    (b) 9 years
    (c) 10 years
    (d) 12 years

16. **Which of the following is the best test for diagnosis of paroxysmal nocturnal hemoglobinuria?** *(AI 2018 Pattern)*
    (a) Sucrose lysis test
    (b) Ham test
    (c) Flow cytometry
    (d) Bone marrow aspiration

17. **Lymphohistiocytic variant of Reed Sternberg cell is seen in which of the following?** *(AI 2018 Pattern)*
    (a) Lymphocyte rich HL
    (b) Lymphocyte predominant HL
    (c) Nodular sclerosis HL
    (d) Mixed cellularity HL

18. **CD59 deficiency leads to:** *(AI 2018 Pattern)*
    (a) Chediak Higashi disease
    (b) TTP
    (c) Paroxysmal nocturnal hemoglobinuria (PNH)
    (d) Burkitt's lymphoma

19. **Biopsy of the bone marrow of a patient is shown below. What is the likely hematological disease associated with it?** *(AI 2018 Pattern)*
(a) Myelofibrosis (b) Metastatic cancer
(c) Multiple myeloma (d) Myelodysplastic syndrome

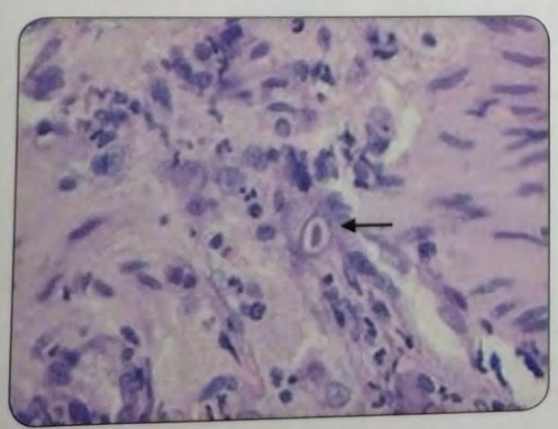


20. **Which of the following is not true regarding von Willebrand disease?** *(AI 2018 Pattern)*
(a) Normal platelet count
(b) Quantitative defects are seen in subtypes 1 and 3 von Willebrand disease
(c) Hemarthrosis is the usual presentation
(d) Produced by endothelial cells

21. **Which of the following hematological problems can be precipitated by parvovirus?** *(AI 2018 Pattern)*
(a) Haemolytic crisis
(b) Aplastic crisis
(c) Pure red cell aplasia
(d) Pancytopenia

22. **The earliest manifestation in the intestine of Crohn's disease is:** *(AI 2018 Pattern)*
(a) Stricture
(b) Aphthous ulcer
(c) Cobblestone mucosa
(d) Perforation

23. **A 42-years-old patient has immunodeficiency and complaints of dysphagia. His upper GI endoscopy reveals multiple ulcers in the distal esophagus. The biopsy picture is shown for the patient as under. What is the likely diagnosis?** *(AI 2018 Pattern)*



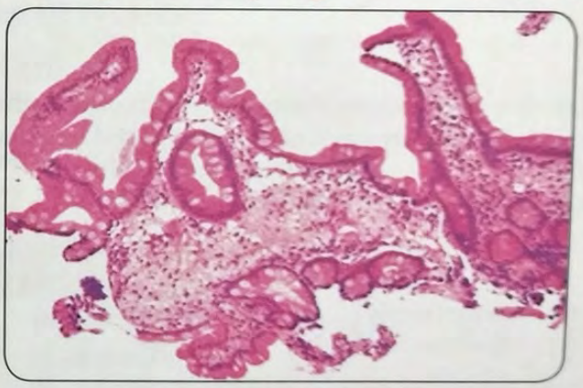
(a) CMV infection
(b) Herpes infection
(c) Candida
(d) Drug induced esophagitis

24. **Which of the following is a histological feature of Crohn disease?** *(AI 2018 Pattern)*
(a) Non caseating granulomas are seen
(b) Pseudopolyps are seen
(c) Non involvement of serosa
(d) Backwash ileitis may be seen in some patients

25. **Most common cause of pancreatitis is:** *(AI 2018 Pattern)*
(a) Alcohol
(b) Gallstones
(c) Trauma
(d) Smoking

26. **Most common location of the chronic gastric ulcer is:** *(AI 2018 Pattern)*
(a) Greater curvature
(b) Lesser curvature near proximal stomach
(c) Lesser curvature near incisura
(d) Pylorus

27. **Small intestinal biopsy reveals PAS+ macrophages in the lamina propria as shown below. Which of the following is the likely diagnosis?** *(AI 2018 Pattern)*

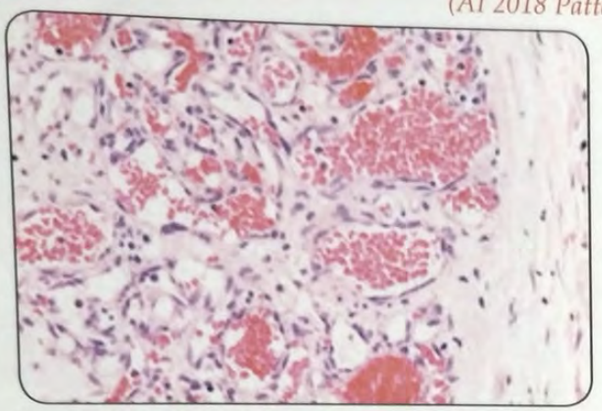


(a) Gluten sensitive enteropathy
(b) Whipple's disease
(c) Abetalipoproteinemia
(d) Giardiasis

28. **A 50-year male presented with cutaneous vasculitis, glomerulonephritis and peripheral neuropathy. Which of the following investigations will help in establishing the diagnosis?** *(AI 2018 Pattern)*
(a) P ANCA
(b) C ANCA
(c) Anti HCV antibody
(d) Anti HAV antibody

29. **Stunning of myocardium without any acute coronary syndrome is:** *(AI 2018 Pattern)*
(a) Subendocardial infarction
(b) Restrictive cardiomyopathy
(c) Takotsubo cardiomyopathy
(d) Transmural infarction

30. A teenager has a progressively increasing soft reddish swelling on his chest. Its histological appearance is given below. Which of the following is the likely diagnosis? *(AI 2018 Pattern)*

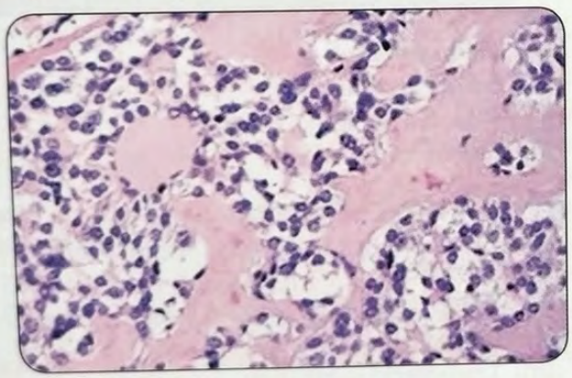


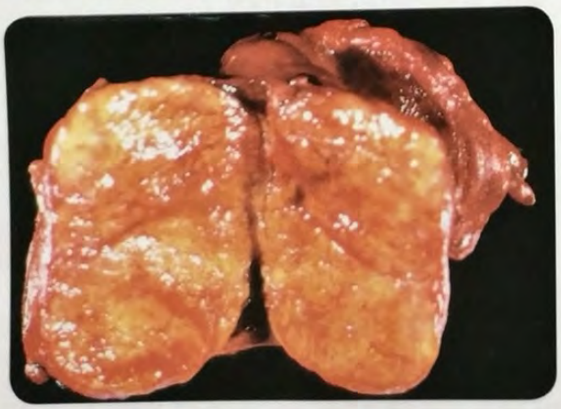
(a) Lipoma (b) Hemangioma
(c) Fibroadenoma (d) Fibroma

31. Which of the following indicates 'flipping effect'? *(AI 2018 Pattern)*

(a) LDH2>LDH1 (b) LDH1>LDH2
(c) LDH2>LDH3 (d) LDH2>LDH4

32. A middle-aged female undergoes a surgery for a neck swelling. The gross and the microscopic images are shown as under. What is the most probable diagnosis of this patient? *(AI 2018 Pattern)*





(a) Hashimoto thyroiditis
(b) Follicular cancer thyroid
(c) Medullary cancer of the thyroid
(d) Anaplastic cancer of the thyroid

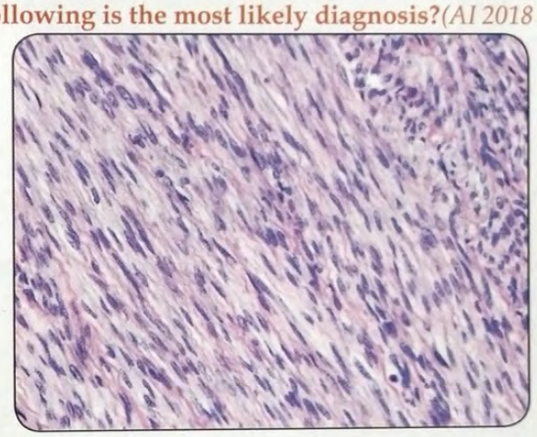
33. All of the following are true about Graves disease except: *(AI 2018 Pattern)*

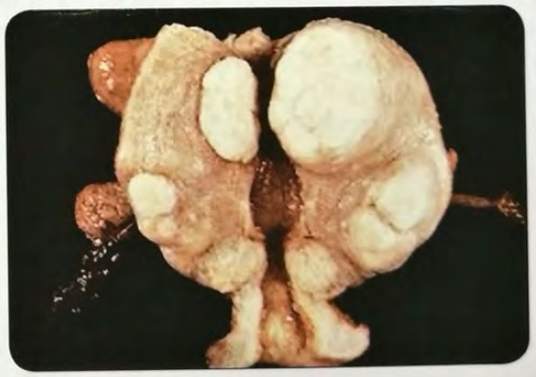
(a) More common in males
(b) Autoimmune in aetiology
(c) May result in hyperthyroidism
(d) Non thyroid manifestations can also be seen

34. VMA is elevated in which of the following condition? *(AI 2018 Pattern)*

(a) Conn syndrome
(b) Pheochromocytoma
(c) Tuberous sclerosis
(d) Addison disease

35. A female has undergone hysterectomy with the following gross and histological features. Which of the following is the most likely diagnosis? *(AI 2018 Pattern)*





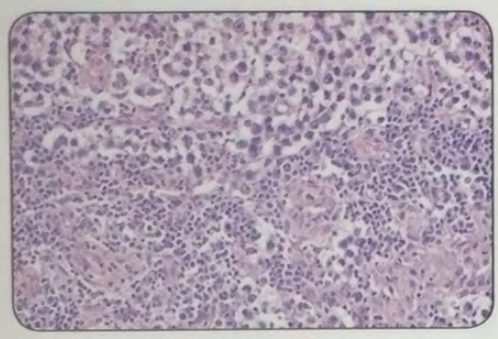
(a) Leiomyosarcoma
(b) Leiomyoma
(c) Mixed Mullerian tumor
(d) Vaginal carcinoma

36. Extramammary Paget's disease is seen in: *(AI 2018 Pattern)*

(a) Ovary (b) Uterus
(c) Vagina (d) Vulva

37. A middle-aged adult undergoes orchiectomy. Looking at the gross and the histological findings, which of the following is the likely diagnosis? *(AI 2018 Pattern)*

(a) Lymphoma (b) Seminoma
(c) Yolk sac tumor (d) Teratoma

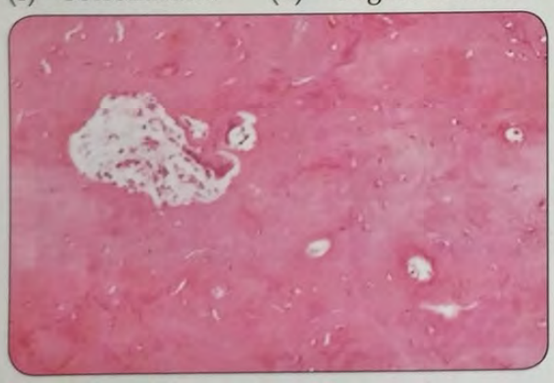


38. Which of the following is a most important infiltrate in rheumatoid arthritis? *(AI 2018 Pattern)*

(a) Dendritic cells (b) Macrophages
(c) Neutrophils (d) CD4+ Helper cells

39. Biopsy of a long bone was taken and the histology is shown below. Which of the following is the likely diagnosis? *(AI 2018 Pattern)*

(a) Osteoporosis (b) Osteosclerosis
(c) Osteomalacia (d) Paget's disease



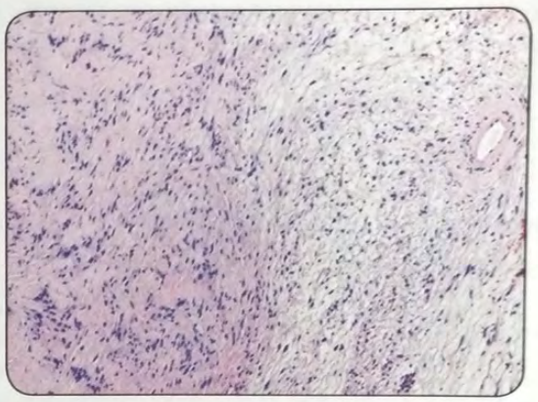
40. Pathogenesis of myasthenia gravis is which of the following? *(AI 2018 Pattern)*

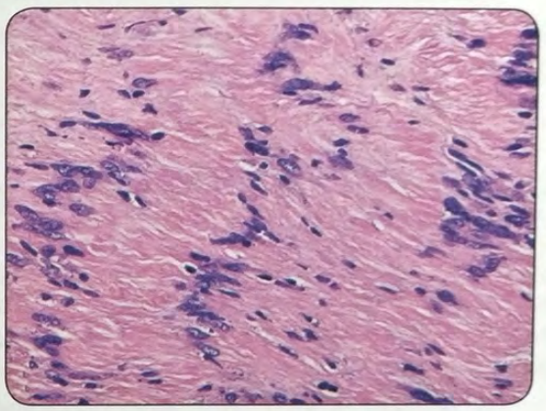
(a) Mutations in ryanodine receptors
(b) Auto antibodies against acetylcholine receptors
(c) Auto antibodies against synaptobrevin
(d) Auto antibodies against presynaptic calcium channels

41. Which of the pathognomic feature of Alzheimer's disease? *(AI 2018 Pattern)*

(a) Lewy body (b) Plaques and tangles
(c) Pick bodies (d) Red neuronal degeneration

42. Patient presented with painless proptosis. Biopsy from the orbital mass showed the following image. *(AIIMS Nov 2017 Pattern)*



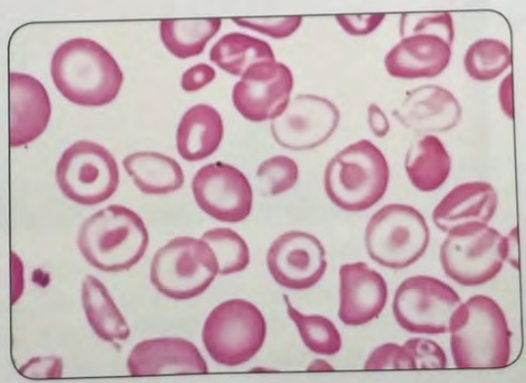


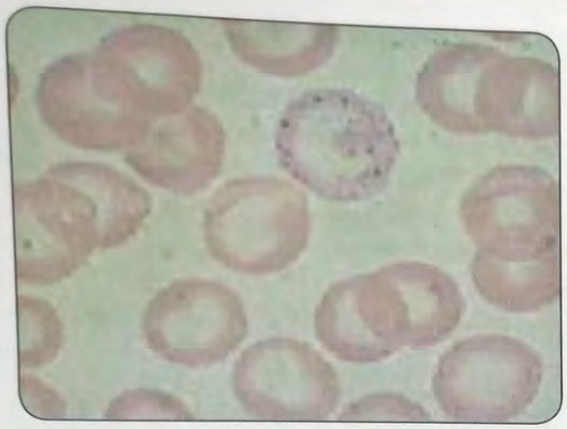
(a) Neurofibroma
(b) Schwannoma
(c) Rhabdomyoma
(d) Leiomyoma

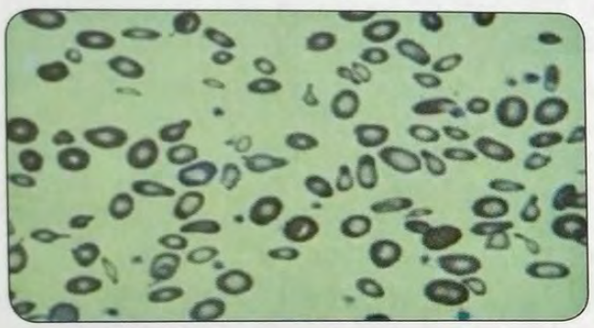
43. All of the following decrease in iron deficiency anemia except: *(AIIMS Nov 2017 Pattern)*

(a) Ferritin
(b) TIBC
(c) Serum iron
(d) Transferrin saturation

44. A 6 year old patient with anemia, on electrophoresis shows HbFof 90% and HbA2 of 3%. Which of the following will be seen on peripheral smear: *(AIIMS Nov 2017 Pattern)*







(a) A,B (b) A,C
(c) B,C (d) ABC

45. Which of there is not involved in iron metabolism? *(AIIMS Nov 2017 Pattern)*

(a) Hepcidin (b) Ferroportin
(c) Transthyretin (d) Ceruloplasmin

46. A voluntary donorunderwent apheresis for platelet donation for the first time after which he developed perioral tingling and numbness. This is seen because *(AIIMS Nov 2017 Pattern)*

(a) His platelet count was low for donation
(b) He underwent apheresis for the first time
(c) Due to fluid depletion
(d) Due to citrate based anticoagulant

47. Which of the following anticoagulant preservative can be used to store blood, so that it can be kept for 35 days? *(AIIMS Nov 2017 Pattern)*

(a) Acid citrate dextrose (ACD)
(b) CPD Citrate phosphate dextrose
(c) Citrate phosphate dextrose-adenine (CPD-A)
(d) CP2D – citrate phosphate double dextrose

48. Which is the best anticoagulant to send sample for serum electrolyte measurement? *(AIIMS Nov 2017 Pattern)*

(a) EDTA (b) Lithium heparin
(c) Sodium fluoride (d) Citrate

49. In a platelet poor plasma sample calcium and tissue thromboplastin is added. This is used to assess which of the following pathway? *(AIIMS Nov 2017 Pattern)*

(a) Extrinsic (b) Intrinsic
(c) Fibrinolytic (d) Common

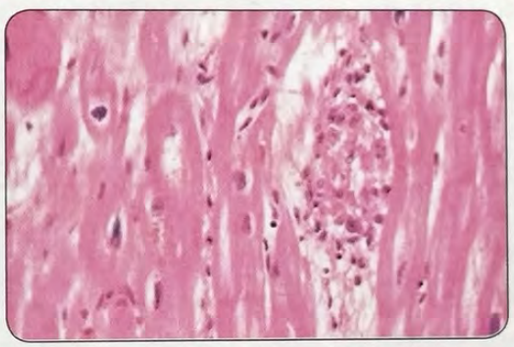
50. Tumor cells in chronic lymphocytic leukemia or small lymphoblastic lymphoma (CLL/SLL)arisefrom which of the following? *(AIIMS Nov 2017 Pattern)*

(a) Mature B cell
(b) Naive B cell
(c) Centrocytes of germinal center
(d) Progenitor B-cell

51. Fixative agent for PAP smear is which of the following? *(AIIMS Nov 2017 Pattern)*

(a) Normal saline (b) 95% ethanol
(c) Formalin (d) Air drying

52. A 30 year old male presented with severe dyspnea. His investigations showed mitral stenosis with left atrial enlargement. The histopathology report from his mitral valve is shown below. What is the likely diagnosis of these patients? *(AIIMS Nov 2017 Pattern)*

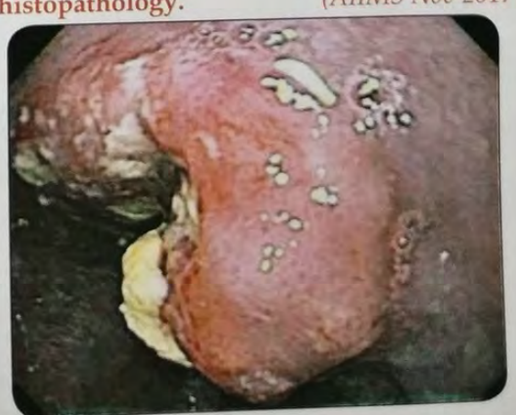


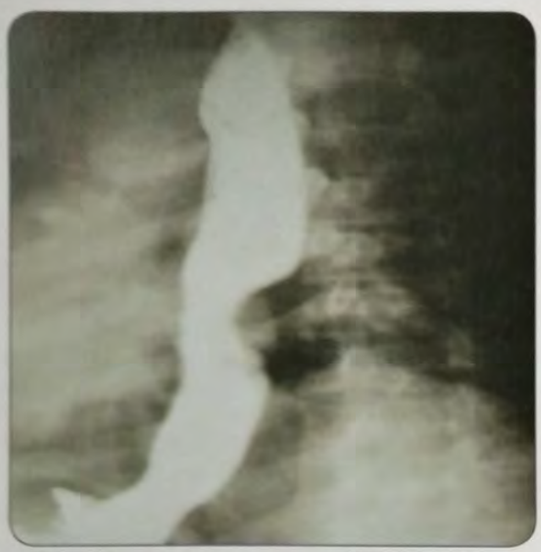
(a) Sarcoidosis (b) Fungal granuloma
(c) Tuberculosis (d) Rheumatic heart disease

53. A patient presented with headache and fever. His investigations revealed hemoglobin of 16g/dl, TLC of 21,000/ uL, platelet count of 3,75,000. His DLC showed Neutrophils (25%), Lymphocytes (20%), Metamyelocytes and myelocytes 40%and eosinophils5%. Which of the following is the next best investigation in this patient? *(AIIMS Nov 2017 Pattern)*

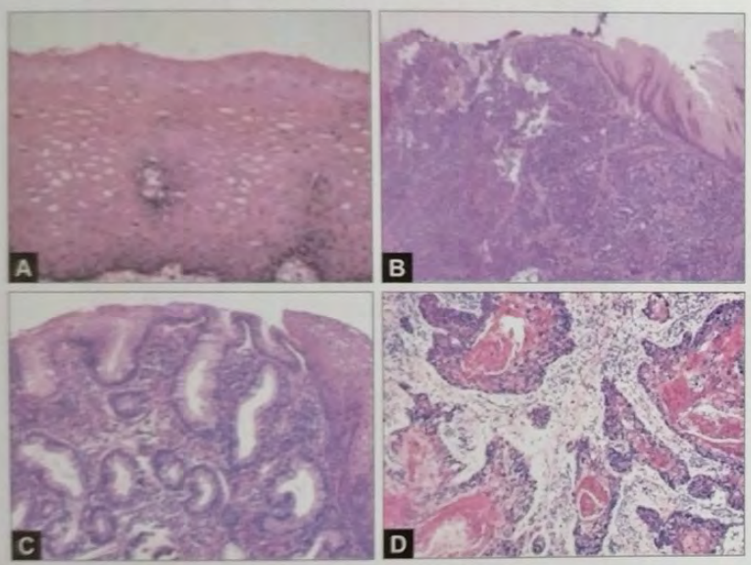
(a) JAK 2 mutation
(b) EPO level
(c) Philadelphia chromosome
(d) Bone marrow biopsy

54. On endoscopy and barium swallow the following findings are seen which of the following will be seen on histopathology. *(AIIMS Nov 2017 Pattern)*



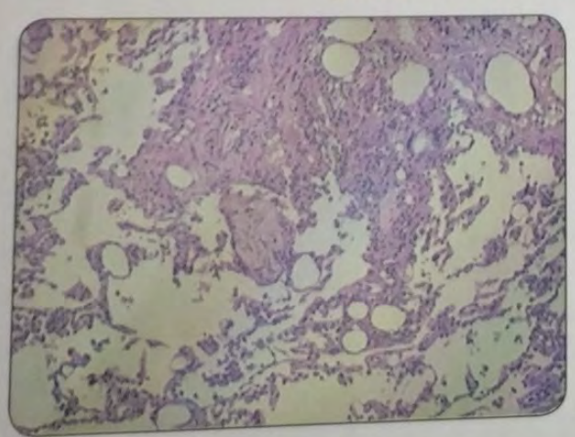


Which of the following is an expected finding in this patient?



55. Patient with history of long standing depressive illness comes to the emergency with acute breathlessness. The X-ray shows diffuse infiltrates with predominance in right middle lobe and right lower lobe. The patient did not survive and the following picture in the lungs was seen on autopsy. It is suggestive of?

(AIIMS Nov 2017 Pattern)



(a) Severe necrosis with fungal hyphae, severe fungal pneumonia
(b) Coagulation necrosis, Tuberculosis
(c) Vegetable matter; Aspiration pneumonia
(d) Severe necrosis; severe necrotizing pneumonia

56. Hepatitis B infection persists in 3% asymptomatic individuals. Why is there an increased risk of developing liver cancer in these patients?

(AIIMS Nov 2017 Pattern)

(a) Inability to induce inflammation to remove organism
(b) Increased liver transaminases
(c) High rate of hepatocyte proliferation
(d) Integration of viral DNA to host DNA

57. In a known case of breast cancer, Fluorescent In situ hybridization (FISH) for gene amplification will be done based on which of the following immunohistochemistry (IHC) staining for HER2/neu?

(AIIMS Nov 2017 Pattern)

(a) 1 (b) 2
(c) 3 (d) Any of the above

58. Inhibition of phosphorylation of the Rb gene will have which of the following effect on cell cycle?

(AIIMS May 2017 Pattern)

(a) Inhibition of cell cycle at G1 phase
(b) Inhibition of cell cycle at G2 phase
(c) The cell cycle will progress as it is and the cell will divide
(d) There will be no effect on cell cycle as for Rb gene phosphorylation is not needed

59. Which of the following is a tool used in gene editing?

(AIIMS May 2017 Pattern)

(a) CRISPR (b) Big Data
(c) Gene Xpert (d) HealthCare App

60. MHC Class II proteins are expressed by:

(AIIMS May 2017 Pattern)

(a) B-cells, dendritic cells and macrophages
(b) Platelets
(c) T-cells
(d) All nucleated cells

61. In thymus, which gene is responsible for recognition of self-antigens? *(AIIMS May 2017 Pattern)*

(a) NOTCH 1 (b) AIRE
(c) Rb (d) PTEN

62. In a 30-year-old female patient with polyarthritis, testing reveals nucleolar pattern of ANA staining. What is the likely course of this patient?

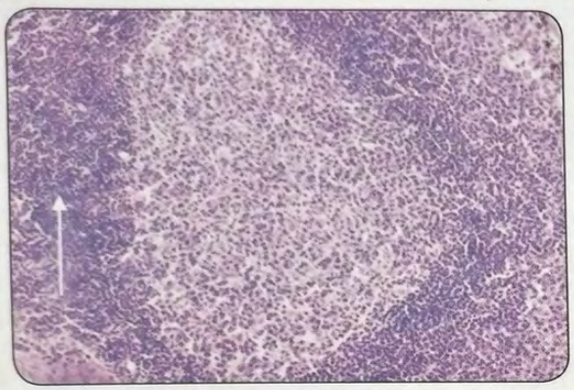
(AIIMS May 2017 Pattern)

(a) Malar rash, alopecia and renal failure
(b) Sclerodactyly, esophageal dysmotility and Raynaud's phenomenon
(c) Sjogren syndrome
(d) Painful genital and oral blisters and ulcers

63. A new marker for mantle cell lymphoma especially useful in Cyclin D1 negative cases is:
(AIIMS May 2017 Pattern)

(a) SOX11 (b) MYD88
(c) Annexin V (d) ITRA 1

64. On histopathological examination of lymph node as shown below, what zone is represented by the marked area? *(AIIMS May 2017 Pattern)*



(a) Germinal center
(b) Mantle zone
(c) Marginal zone
(d) Paracortical area

65. Which of these is true about intracellular iron homeostasis in iron deficiency anemia?
(AIIMS May 2017 Pattern)

(a) Ferritin mRNA concentration decreases and ferritin synthesis increases
(b) Transferrin receptor 1mRNA upregulation and increased receptor expression
(c) Ferritin mRNA concentration increases and ferritin synthesis decreases
(d) Transferrin receptor 1mRNAdownregulation and decreased receptor expression

66. What does the red cell distribution width represents?
(AIIMS May 2017 Pattern)

(a) Anisocytosis
(b) Level of hypochromia
(c) Poikilocytosis
(d) Anisochromia

67. What will be the corrected reticulocyte count in a patient with a hemoglobin of 5 and absolute reticulocyte count of 9%? *(AIIMS May 2017 Pattern)*

(a) 4.5%
(b) 6%
(c) 1%
(d) 3%

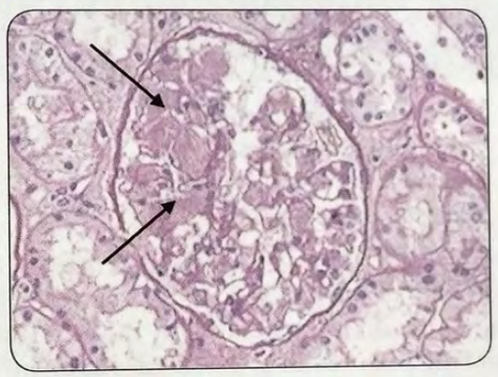
68. All the following markers are expressed on the surface of T-cells at some stage of development except:
(AIIMS May 2017 Pattern)

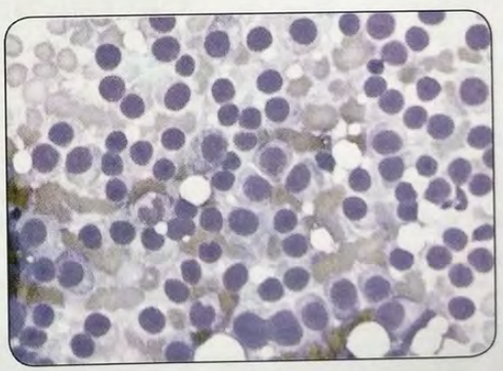
(a) CD1a (b) CD34
(c) PAXS (d) Tdt

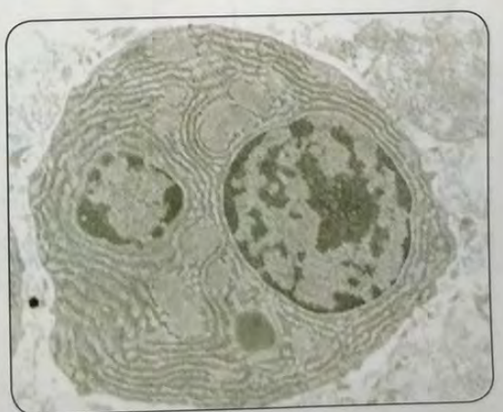
69. A patient presented with complaints of fever and right sided neck swelling. A biopsy from the swelling revealed normal lympho-mononuclear cells with interspersed Reed Sternberg cells. On immune-histochemistry, these cells were found to be CD2O positive, while they were negative for CD3O, CDI5 and EBV latent membrane protein. What is the diagnosis?
(AIIMS May 2017 Pattern)

(a) Lymphocyte rich Hodgkin's lymphoma
(b) Diffuse large B-cell lymphoma
(c) Nodular lymphocyte predominant Hodgkin's lymphoma
(d) Small cell lymphoma

70. A 70-year-old male presented with severe intractable diarrhea. His bone marrow and renal biopsy was done which is as shown below. What is the most appropriate diagnosis? *(AIIMS May 2017 Pattern)*

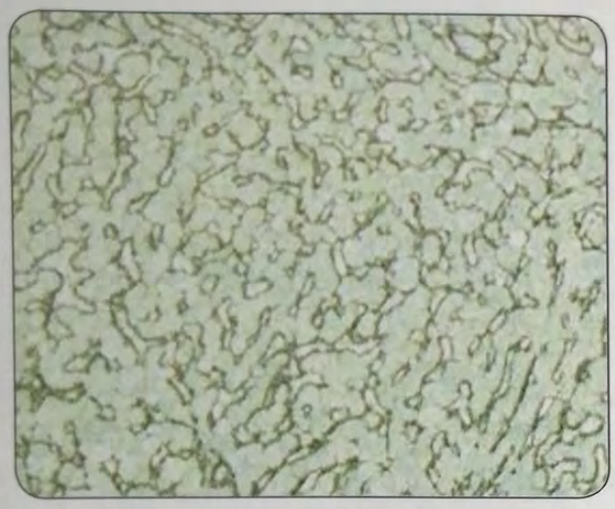






(a) Multiple myeloma
(b) Urate nephropathy
(c) Amyloidosis
(d) Hodgkin lymphoma

71. **In the following liver biopsy, which special stain has been used?** *(AIIMS May 2017 Pattern)*

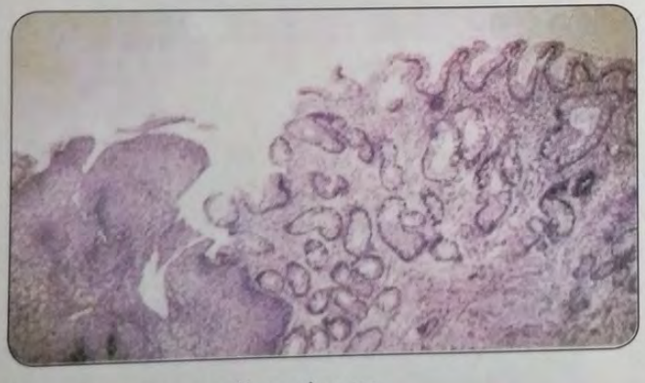


(a) Masson's trichrome stain
(b) Grimelius silver stain
(c) Steiner silver stain
(d) Sweet's reticulin stain

72. **An old man had severe chest pain. The patient died on the way to the hospital. In the hospital, at autopsy tetrazolium chloride staining of the heart was done. What will be the color of viable myocardium?** *(AIIMS May 2017 Pattern)*

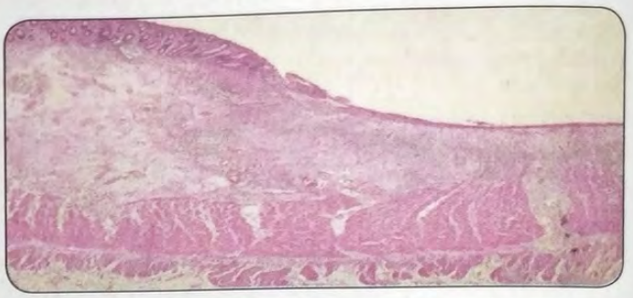
(a) Blue
(b) Dark brown
(c) Red
(d) Pink

73. **A 55-year-old patient presented with dysphagia. Identify the diagnosis from upper GI biopsy of esophagus showed in the following picture:** *(AIIMS May 2017 Pattern)*



(a) Squamous cell carcinoma
(b) Barrett's esophagus
(c) Eosinophilic esophagitis
(d) Adenocarcinorna

74. **A middle-aged female presented with recurrent bloody diarrhea. Colonoscopy reveals multiple geographic ulcers and histopathological examination is shown below. What is the likely diagnosis?** *(AIIMS May 2017 Pattern)*



(a) Adenocarcinoma colon
(b) Crohn's disease
(c) Pseudomembranous colitis
(d) Amoebic colitis

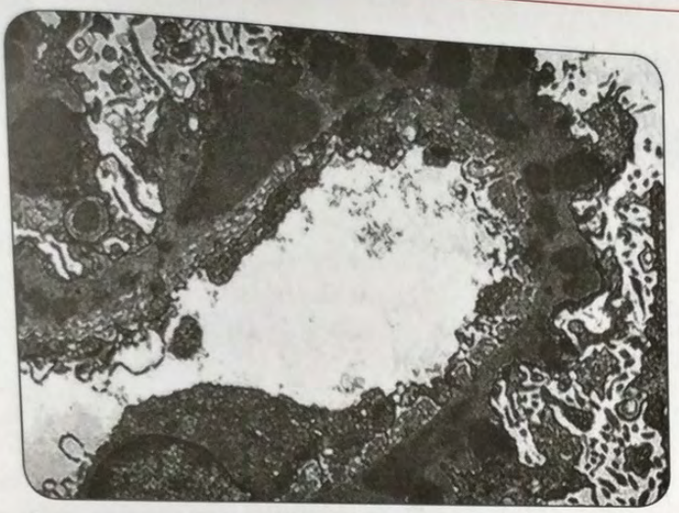
75. **Maximum risk of carcinoma pancreas is seen in which of these?** *(AIIMS May 2017 Pattern)*

(a) Peutz Jegher syndrome
(b) Hereditary atypical mole syndrome
(c) Hereditary pancreatitis
(d) Familial adenomatosis polyposis

76. **Anaplastic Lymphoma Kinase (ALK) gene expression is seen in which of the following tumor?** *(AIIMS May 2017 Pattern)*

(a) Inflammatory myofibroblastic tumor
(b) Synovial sarcoma
(c) Fibromatosis
(d) Ewing sarcoma

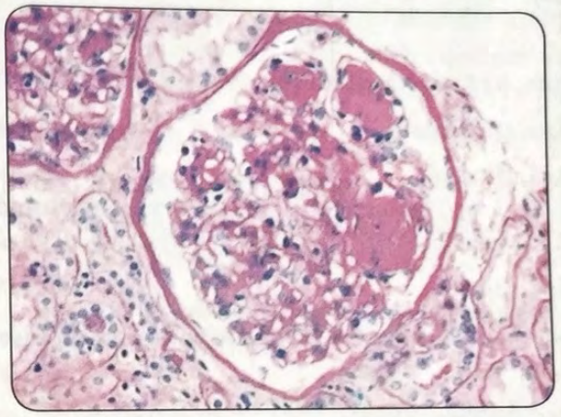
77. **A 43-year-old male presented with facial puffiness and a history of frothy urine for 4 days. Acute kidney injury is suspected. A renal biopsy was done and Direct immunofluorescence and electron microscopic image is as shown below. What is the likely diagnosis?** *(AIIMS May 2017 Pattern)*



(a) Membranous glomerulopathy
(b) Membranoproliferative glomerulopathy
(c) Minimal change disease
(d) Focal segmental glomerulosclerosis

78. An elderly male patient presented with blurring of vision. Fundus examination revealed cotton wool spots on retina and systemic examination showed decreased peripheral sensations and increased urine output. What finding is the following renal biopsy showing?

(AIIMS May 2017 Pattern)



(a) Kimmelstien Wilson lesion
(b) Amyloid deposits
(c) Crescents
(d) Hyaline atherosclerosis

Explanations

1. **Ans. (c) Cat scratch disease** *(Ref: Robbins 9/e p27)*
2. **Ans. (b) Measles** *(Ref: Robbins 9/e p355)*
3. **Ans. (b) IL-6** *(Ref: Robbins 9/e p86, Harrison 19/e p124)*
   IL-1, IL-6, TNF-α, IFN-α and ciliary neurotropic factor (a member of the IL-6 family) are pyrogenic cytokines.
4. **Ans. (b) C3b** *(Ref: Robbins 9/e p78)*
5. **Ans. (b) It has greater amount of collagen and vascularity** *(Ref: Robbins 9/e p109)*
6. **Ans. (c) Thrombosis** *(Ref: Robbins 9/e p123-124)*
7. **Ans. (a) Medullary thyroid cancer** *(Ref: Robbins 9/e p1099)*
8. **Ans. (c) PTEN mutation** *(Ref: Robbins 9/e p291)*
   - PTEN (phosphatase and tensin homologue) is a membrane-associated phosphatase coded by a gene on chromosome 10q23.
   - It is mutated in Cowden syndrome, an autosomal dominant disorder marked by frequent benign growths, such as skin appendage tumors, and an increased incidence of epithelial cancers, particularly of the breast, endometrium, and thyroid.
9. **Ans. (b) Anaplasia** *(Ref: Robbins 9/e p270)*
10. **Ans. (c) Synaptophysin** *(Ref: Robbins 9/e p717)*
    Neuroendocrine markers include chromogranin, synaptophysin and neuron specific enolase.
11. **Ans (c) It is X linked recessive disease** *(Ref: Robbins 9/e p1299)*

- Ataxia-telangiectasia is an autosomal recessive disorder characterized disorder characterized by an ataxic-dyskinetic syndrome beginning in early childhood, with the subsequent development of telangiectasias in the conjunctiva and skin, along with immunodeficiency.
- The abnormalities are predominantly in the cerebellum, with loss of Purkinje and granule cells.
- Cells in many organs (e.g., Schwann cells in dorsal root ganglia and peripheral nerves, endothelial cells, pituicytes) show a bizarre enlargement of the nucleus to two to five times normal size and are referred to as ***amphicytes***.
- The lymph nodes, thymus, and gonads are hypoplastic.
- Many affected individuals develop lymphoid neoplasms, which are most often T-cell leukemias.

12. **Ans. (c) Color blindness** *(Ref: Robbins 9/e p142)*
13. **Ans. (a) 12 hours** *(Ref: Robbins 9/e p233)*
14. **Ans. (b) T cells** *(Ref: The Nude Mouse in Oncology Research/ch 2)*
    Nude mouse is a laboratory mouse strain which has a nonfunctioning or absent thymus due to a mutation in the FOXN1 gene. So, it has no T cells and therefore, has no graft rejection.
15. **Ans. (c) 10 years** *(Ref: Robbins 9/e p252, Harrison 19/e p1229)*
    A chronic infection develops and persists with varying degrees of continual virus replication in the untreated patient for a **median of ~10 years** before the patient becomes clinically ill.
16. **Ans. (c) Flow cytometry** *(Ref: Robbins 9/e p642, CMDT 2018/518)*
    FLAER Flow cytometry is the gold standard investigation for the diagnosis of PNH.
17. **Ans. (b)Lymphocyte predominant HL** *(Ref: Robbins 9/e p608)*
18. **Ans. (c) PNH** *(Ref: Robbins 9/e p642)*
19. **Ans. (c) Multiple myeloma** *(Ref: Robbins 9/e p600)*
    The histology shows a plasma cell with a **cart wheel appearance** and so, is suggestive of multiple myeloma.
20. **Ans. (c) Hemarthrosis is the usual presentation** *(Ref: Robbins 9/e p662)*
21. **Ans. (b) Aplastic crisis** *(Ref: Robbins 9/e p633-635)*
22. **Ans. (b) Aphthous ulcer** *(Ref: Robbins 9/e p798)*
23. **Ans. (a) CMV infection** *(Ref: Robbins 9/e p755)*
    The presence of an owl eye appearance of a nucleus (as shown in the figure) is suggestive of cytomegalovirus infection
24. **Ans. (a) Non caseating granulomas are seen** *(Ref: Robbins 9/e p798)*
25. **Ans. (a) Alcohol** *(Ref: Robbins 9/e p888)*
26. **Ans. (c) Lesser curvature near incisura** *(Ref: Robbins 9/e p766)*

- **Gastric peptic ulcers** are predominantly located along the **lesser curvature** near the interface of the body and antrum
- **Most common site** for peptic ulcer is **duodenum**.

27. **Ans. (b) Whipple's disease** *(Ref: Robbins 9/e p791)*
    Presence of blunting of villi with foamy macrophages is suggestive of Whipple's disease in the given patient.
28. **Ans. (c) Anti HCV antibody** *(Ref: Robbins 9/e p927)*
    Essential mixed cryoglobulinemia is a systemic condition in which deposits of cryoglobulins composed principally of IgG-IgM complexes induce cutaneous vasculitis, syn-

ovitis, and a proliferative glomerulonephritis, typically MPGN.

Most cases of essential mixed cryoglobulinemia have been **associated** with infection with **hepatitis C virus**, and with **MPGN type I glomerulonephritis**.

29. Ans. (c) Takotsubo cardiomyopathy *(Ref: Robbins 9/e p543)*

When there is pathology involving only smaller intramural vessels, the elevated levels of catechols exacerbate ischemia caused by the vasospasm. This may lead to sudden cardiac death or an ischemic dilated cardiomyopathy, so-called *takotsubo cardiomyopathy*.

30. Ans. (b) Hemangioma *(Ref: Robbins 9/e p517)*

Microscopic examination is showing increased number of blood vessels which are filled with blood. This is seen with hemangioma.

31. Ans. (b) LDH1>LDH2 *(Ref: Robbins 9/e p544)*

LDH1>LDH2 is seen with myocardial infarction as more amount of LDH1 is released due to damage to myocardial cells.

32. Ans. (c) Medullary cancer of the thyroid *(Ref: Robbins 9/e p1099)*

The histology shows the presence of amyloid deposition in the histology section. Acellular ***amyloid deposits*** derived from calcitonin polypeptides are present in the stroma in patients of medullary thyroid cancer.

33. Ans. (a) More common in males *(Ref: Robbins 9/e p1089)*

34. Ans. (b) Pheochromocytoma *(Ref: Robbins 9/e p1135)*

35. Ans. (b)Leiomyoma *(Ref: Robbins 9/e p1019)*

The uterus is reveals multiple tumors in submucosal (bulging into the endometrial cavity), intramural, and subserosal locations that display a firm white appearance on sectioning. Histologically, leiomyomas show well-differentiated, regular, spindle-shaped smooth muscle cells associated with hyalinization.

36. Ans. (d) Vulva *(Ref: Robbins 9/e p999)*

- Extra mammary Paget's disease is seen in the skin of the vulva is *similar in its manifestations to Paget disease of the breast.*
- In the vulva, it presents as a pruritic, red, crusted, map like area, usually on the labia majora.
- In contrast to Paget disease of the nipple, in which 100% of patients have an underlying ductal breast carcinoma, **vulvar Paget is typically not associated with underlying cancer.**
- Histologically, **Paget cells** are larger than surrounding keratinocytes. The cells have pale cytoplasm containing mucopolysaccharide that stains with periodic acid–Schiff (**PAS**), Alcian blue, or mucicarmine stains. In addition, the cells express cytokeratin.
- The treatment consists of **wide local excision.**

37. Ans. (b) Seminoma *(Ref: Robbins 9/e p976)*

- Seminoma is the commonest germ cell tumor.
- It produces a bulky mass with a homogenous grey white appearance without hemorrhage and necrosis.
- Microscopically, is characterised by round to polyhedral cells with distinct cell membrane, central nucleus and clear cytoplasm.

38. Ans. (d) CD4+ Helper cells *(Ref: Robbins 9/e p1209)*

39. Ans. (d) Paget's disease *(Ref: Robbins 9/e p1189)*

The histology is classical picture of the mosaic pattern which is seen in patients with Paget's disease of the bone.

40. Ans. (b) Auto antibodies against acetylcholine receptors *(Ref: Robbins 9/e p1235-6)*

41. Ans. (b) Plaques and tangles *(Ref: Robbins 9/e p1290)*

The major microscopic abnormalities of AD are **neuritic (senile) plaques** and **neurofibrillary tangles**.

42. Ans. (b) Schwannoma *(Ref: Robbins 9/e p1247)*

The presence of Antoni A and Antoni B areas in this often asked question confirms the diagnosis of schwannoma of this patient.

Microscopically, schwannomasare comprised of an admixtureof dense and loose areas referred to as **Antoni A** and **Antoni B** areas, respectively. The dense eosinophilicAntoni A areas often contain spindle cells arranged intocellular intersecting fascicles. Palisading of nuclei is commonand "nuclear-free zones" that lie between the regions of nuclearpalisading are termed **Verocay bodies**.

43. Ans. (b) TIBC *(Ref: Robbins 9/e p652, Harrison 19/e p627)*

Iron deficiency anemia is characterized by reduced serum iron, % transferrin saturation and serum ferritin. The only parameter increased in these patients is total iron binding capacity.

44. Ans. (d) ABC *(Ref: Robbins 9/e p655)*

The presence of HbFof 90% and HbA2 of 3% is suggestive of thalassemia major. Now, looking at the images, they represent A (target cells), B (Howell Jolly bodies) and C (microcytic cells with tear drop cells suggestive of poikilocytosis). Since, all the three can be seen I a patient with thalassemia major, so, the answer for the question is A,B,C.

45. Ans. (c) Transthyretin *(Ref: Robbins 9/e p642)*

- **Hepcidin** is an **inhibitor of iron absorption** in the body
- **Ferroportin** increases **intake** of iron from the duodenal cells
- **Ceruloplasmin** is involved in the **oxidation** of ferrous iron into ferric iron.
- Transthyretin is involved in the **trans**port of **thy**roid hormones and **ret**inol

46. Ans. (d) Due to citrate based anticoagulant

(Ref: Wintrobe's hematology 13/e p674-5)

Apheresismeans to separate or to take away. There are now continuous-flow devices in which incoming blood is continuously subjected to a centrifugal force. A standing cell gradient is established. The fraction(s) to be removed are pumped into a bag, and the rest is reinfused continuously. An increasing proportion of blood components is being collected using automated cell separation.

Apheresis donors face the additional potential complication of **transient hypocalcemia**from the **citrate infused when anticoagulated blood components are returned** to them from the apheresis device. Symptoms consist of tingling or muscle cramps. Citrate symptoms are **treated** by **slowing the flow** of the device or giving the donor **oral calcium supplements.**

47. Ans. (d) Citrate phosphate dextrose-adenine (CPD-A)

(Ref: Wintrobe's hematology 13/e p674-5)

Preservative	Shelf life
Acid citrate dextrose	21 days
Citrate phosphate dextrose	21 days
Citratephosphate double dextrose	21 days
Citrate phosphate dextrose-adenine	35 days

48. Ans. (b) Lithium heparin *(Ref: WHO Guidelines)*

WHO Guidelines for Use of anticoagulants in diagnostic laboratory investigations

Lithium heparin can be used for the assessment of serum electrolytes.

49. Ans. (a) Extrinsic *(Ref: Robbins 9/e p656)*

For clotting pathway studies, a platelet poor plasma sample is taken.

- **Prothrombin time (PT):** This test assesses the **extrinsic and common** coagulation pathways. The clotting of plasma after addition of an **exogenous source of tissue thromboplastin** (e.g., brain extract) **and Ca2+ ions** is measured in seconds.
- Partial thromboplastin time (PTT). This test assesses the **intrinsic and common** clotting pathways. The clotting of plasma after addition of **kaolin, cephalin, and Ca2+ ions** is measured in seconds.

50. Ans. (b) Naive B cell *(Ref: Robbins 9/e p593)*

Direct lines.... "DNA sequencing has revealed that theIg genes of some CLL/SLL are *somatically hypermutated* whereas others are not, suggesting that the cell of origin-may be either a **postgerminal center** memory B cell or a **naive B cell.**"

51. Ans. (b) 95% ethanol *(Ref: Robbins 9/e p340)*

The rule about fixing the smear immediately applies here as well. A **solution of ether 50 % and alcohol (95%) 50 %** in a small widemouthed jar can be used, keeping the lid on. Two slides at a time can be placed back to back in the jar for 15 minutes after which they are removed and allowed to dry and examined under microscope.

Important fixatives for future questions

Tissue	Fixatives fluid
Light microscopy	10% formaldehyde
Electron microscopy	2% glutaraldehyde
Bone marrow biopsy	Zenker fluid
Bone marrow aspirate	Helly fluid

52. Ans. (d) Rheumatic heart disease *(Ref: Robbins 9/e p558)*

- The image given in the question is suggestive of Aschoff body. **Aschoff bodies**, consisting of foci of T lymphocytes,occasional plasma cells, and plump activated macrophages called **Anitschkow cells** (pathognomonic for RF).
- In patient with mitral stenosis we would suspect rheumatic heart disease as a suspected etiology.
- So, the diagnosis with both the history presented and the histological finding is rheumatic heart disease.

53. Ans. (c) Philadelphia chromosome

Presence of the clinical picture given is suggestive of a left shift (TLC with myeloid bulge) which could be due to a myeloproliferative disorder like CML or leukemoid reaction. So, to confirm the diagnosis, a Ph chromosome study should be done.

54. Ans. (d) *(Ref: Robbins 9/e p759)*

- Image A....Normal esophagus with stratified squamous epithelium
- Image B....esophagus with glandular differentiation (adenocarcinoma)
- Image C....presence of intestinal epithelium with goblet cells (Barret's esophagus)
- Image D....presence of keratin pearls suggestive of squamous cell cancer

Looking at the lesion given in the question, it is present in the middle part of esophagus with an exophytic lesion on endoscopy. That's the commonest location of the esophageal cancer in India. The commonest histological subtype of esophageal cancer is squamous cell cancer an so, the answer is option D.

55. Ans. (c) Vegetable matter; Aspiration pneumonia

Presence of long standing depression is a risk factor for depressive illness. The presence of refractive mate-

rial with a granuloma is seen with a foreign body (like vegetable matter). Infiltrates within the right middle and right lower lobe also suggests a foreign body. The presence of vegetable matter in the lungs is possible only due to aspiration. Hence, the answer (c).

56. Ans. (c) High rate of hepatocyte proliferation

(Ref: Robbins 9/e p328)

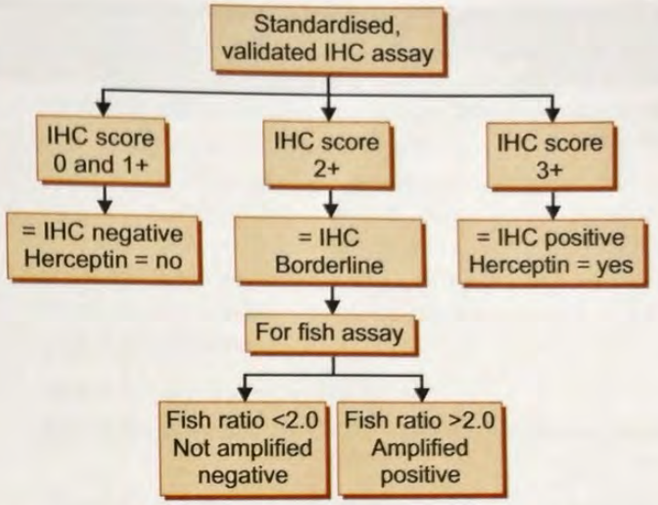
The HBV and HCV genomes do not encode anyviral oncoproteins, and although the HBV DNA is integratedwithin the human genome, **there is no consistent pattern of integration in liver cells.** Indeed, while the oncogeniceffects of HBV and HCV are multifactorial, the***dominant effect seems to be immunologically mediated chronic inflammation and hepatocyte death leading to regeneration and, over time, genomic damage.***

Chronicviralinfection leads to the **compensatory proliferation of hepatocytes**.Onekey mutagenic step is the **activation of the NF-κBpathway in hepatocytes** in response to mediators derivedfrom the activated immune cells. This activation blocks apoptosis, allowing thedividing hepatocytes to incur genotoxic stress and to accumulatemutations. Although ***this seems to be the dominantmechanism in the pathogenesis of virus-induced hepatocellularcarcinoma***, the HBV genome also contains genesthat may directly promote the development of cancer

57. Ans. (b) 2

Try to understand the following: when we do immunohistochemistry, it is given a score as follows:

- **Positive:**
  - IHC 3+ (strong positive): tumor displays complete, intense circumferential membranous staining
- **Equivocal:**
  - IHC 2+: incomplete circumferential membrane staining or weak/moderate and within > 10% of invasive tumor cells; or complete and circumferential membrane staining that is intense and within ≤ 10% of invasive tumor cells
- **Negative:**
  - IHC 1+: incomplete faint membrane staining and within > 10% of invasive tumor cells
  - IHC 0: no staining observed or incomplete faint membrane staining within ≤ 10% of invasive tumor cells



58. Ans. (a) Inhibition of cell cycle at G1 phase

(Ref: Robbins 9/e p292)

RB is a key negative regulator of the G1 /S cell cycle transition. For details, see the diagram in the theory of the chapter on Neoplasia.

59. Ans. (a) CRISPR *(Ref: Robbins 9/e p28-29)*

Genomic editing is a process using a nuclease called Cas9 that was originally identified in prokaryotes that can be used together with guide RNAs called **CRISPRs** (Clustered Regularly Interspaced Short Palindromic Repeats) to selectively alter or correct DNA sequences, such as disease- causing mutations.

60. Ans. (a) B-cells, dendritic cells and macrophages

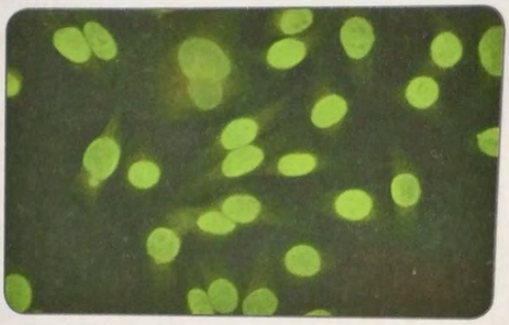
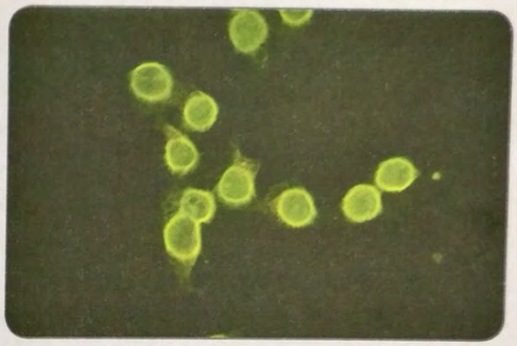
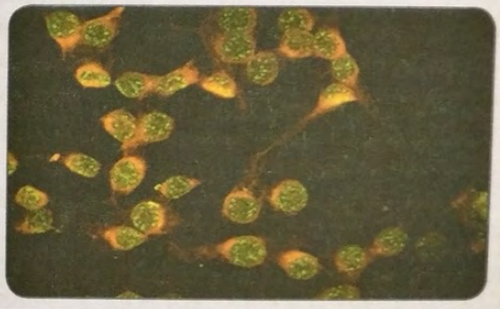
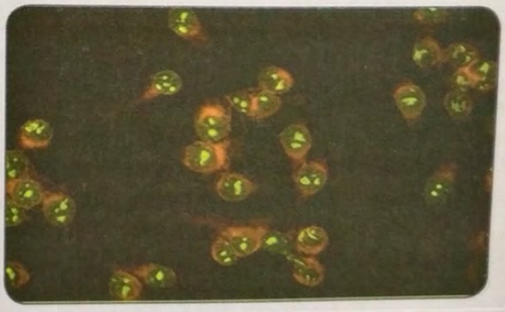
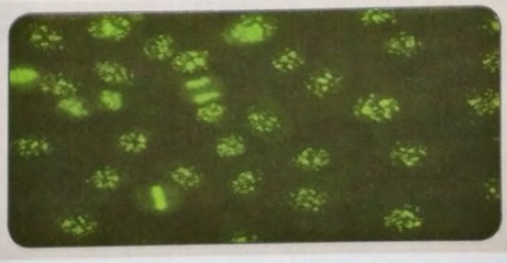
(Ref: Robbins 9/e p195)

B-cells, dendritic cells and macrophages are all antigen presenting cells. MHC II proteins are expressed on the surface of antigen presenting cells.

61. Ans. (b) AIRE *(Ref: Robbins 9/e p213)*

- A protein called **AIRE** (autoimmune regulator) stimulates expression of some ***"peripheral tissue-restricted"*** self antigens in the ***thymus*** and is thus critical for deletion of immature T cells specific for these antigens.
- Mutations in the AIRE gene are the cause of an a***utoimmune polyendocrinopathy*** called ***Autoimmune polyendocrine syndrome type 1 (APS1)***.

62. Ans. (b) Sclerodactyly, esophageal dysmotility and Raynaud's phenomenon *(Ref: Robbins 9/e p218)*

Recent exam topic: Antinuclear antibody staining patterns		
Pattern	**Antigen**	**Image**
Homogeneous or diffuse nuclear staining	Chromatin, histones	
Rim or peripheral staining	Double stranded DNA	
Speckled pattern (MC and least specific pattern)	Antibody against extractable (Non-DNA) nuclear antigens like ribonucleoprotein, Sm antigen, SS-A and SS-B reactive antigens	
Nucleolar pattern (seen in systemic sclerosis)	RNA (Bright fluorescence is seen within the nucleoli)	
Centromeric pattern (seen in CREST syndrome)	Centromeres	

Crithidia organisms are very important as they serve as a substrate for the double stranded DNA test.

63. Ans. (a) SOX11

(Ref: WHO update on Lymphoid Malignancies)

SOX11 expression is detected in most cyclin D1 negative mantle cell lymphoma.

> ***SOX11 expression*** **is detected in most cyclin D1 negative mantle cell lymphoma.**

64. Ans. (b) Mantle zone

In lymph nodes the B cells are concentrated in discrete structures, called follicles, located around the periphery, or cortex, of each node. If the B cells in a follicle have recently responded to an antigen, this follicle may contain a central region called a germinal center. The T lymphocytes are concentrated in the paracortex, adjacent to the follicles.

65. Ans(b) Transferrin receptor 1 mRNA upregulation and increased receptor expression

Iron deficiency anemia is characterized by decreased ferritin, increased transferrin and increased transferrin receptors. So, option "b" is the best answer here.

66. Ans. (a) Anisocytosis *(Ref: Robbins 9/e p630)*

Red cell distribution width is the coefficient of variation of red cell size and volume. This is indicated by anisocytosis.

67. Ans. (d) 3%

Corrected reticulocyte count = reticulocyte% $\times \frac{Hb}{15}$

Applying the same in our question, $\frac{9 \times 5}{15} = 3\%$

68. Ans. c. PAX5 *(Ref: Robbins 9/e p590)*

This is a modified version of previous question.

This question should be attempted by ruling out the options.

- CD1a: though a specific marker of Langerhans cell but CD1 to CD8 are present on T cell surface.
- CD34: hematopoetic stem cell marker, so would be expressed in early stage of T cell development.
- Tdt: known T cell marker useful for diagnosis of T cell ALL.

> PAX5 (and genes like E2A, and EBF) are required for B-cell development…Robbins 9th/590

69. Ans (c) Nodular lymphocyte predominant Hodgkin's lymphoma *(Ref: Robbins 9/e p609)*

- ***Nodular lymphocyte predominant Hodgkin's lymphoma*** is characterized by the presence of L-H subtype of Reed Sternberg cells.
- In contrast to the Reed-Sternberg cells found in classical forms of HL, L&H variants express B-cell markers typical of germinal-center B cells, such as CD20 and BCL6, and are ***usually negative for CD15 and CD30***. EBV is not associated with this subtype.

70. Ans (a) Multiple myeloma *(Ref: Robbins 9/e p595)*

The interpretation of the images is as follows:

- Image A: amyloid deposition in the glomeruli
- Image B: presence of large number of plasma cells in the bone marrow
- Image C: electron microscopic appearance of a plasma cell showing inclusions

The combination of the three images suggests the presence of multiple myeloma in these patients which is characterised by increased number of plasma cells in the bone marrow, high chances of renal amyloidosis and presence of intracellular inclusions in the electron microscopic examination.

71. Ans. (d) Sweet's reticulin stain

The Science of Laboratory Diagnosis pg 19,

(Ref: Robbins Basic Pathology 10/e p163)

> - Reticulin fibres are demonstrated by silver impregnation technique one of which is Sweet's reticulin stain.
> - Reticulin fibres can also be demonstrated by the PAS technique.

72. Ans. (c) Red *(Ref: Robbins 9/e p544-5)*

Triphenyltetrazolium chloride (TTC) is a gross histochemical stain which imparts a **brick-red color to intact, noninfarcted myocardium** where lactate dehydrogenase activity is preserved. Since dehydrogenases leak out through the damaged membranes of dead cells, an ***infarct appears as an unstained pale zone.***

73. Ans. (b) Barrett's esophagus *(Ref: Robbins 9/e p757)*

Barret's esophagus is signified by the presence of columnar cells with goblet cells as is seen in the given image.

74. Ans. (b) Crohn's disease *(Ref: Robbins 9/e p799)*

The presence of transmural inflammation in the given image without the presence of any overlying membrane is suggestive of the presence of Crohn disease. The question mentions geographical ulcers which are produced by the fusion of aphthous ulcers in Crohn's disease.

Absence of a flask shaped ulcer and pseudomembrane rules out the presenc of amoebic colitis and pseudomembranous colitis respectively.

75. Ans. (a) Peutz Jegher syndrome *(Ref: Robbins 9/e p894)*

Disorder	Gene	Increased risk of cancer (fold)
Peutz-Jeghers syndrome	*STK11*	*130*
Hereditary pancreatitis	PRSS1, SPINK1	50-80
Hereditary non-polyposis colorectal cancer	Multiple, including MLH1, MSH2	8-10
Familial atypical multiple-mole melanoma syndrome	CDKN2A	20-35
Strong family history	Unknown	14-32
Hereditary breast and ovarian cancer	Multiple genes	4-10

76. Ans. (a) Inflammatory myofibroblastic tumor

(Ref: Robbins 9/e p894)

Inflammatory myofibroblastic tumor

- More common in children
- Equal male-to-female ratio
- Presenting symptoms include fever, cough, chest pain, and hemoptysis.
- Grossly, the lesion is firm, 3 to 10 cm in diameter, and grayish white.
- Microscopically, there is proliferation of spindle-shaped fibroblasts and myofibroblasts, lymphocytes, plasma cells, and peripheral fibrosis.
- Some of these tumors have **activating rearrangements of the anaplastic lymphoma kinase (*ALK*) gene** located on 2p23.

77. Ans (a) Membranous glomerulopathy

(Ref: Robbins 9/e p915-6)

Clinical picture is suggestive of nephrotic syndrome. Biopsy is suggestive of the presence of **subepithelial electron dense deposits** with effacement of foot processes overlying deposits on the electron microscopy. The direct immunofluorescence shows **diffuse granular deposits** along the glomerular basement membrane. Both the above findings are associated with the diagnosis of **membranous glomerulopathy**.

78. Ans (a) Kimmeistien Wilson lesion

(Ref: Robbins 9/e p1118)

The clinical picture (cotton wool spots on fundus, decreased peripheral sensations and increased urine output) is suggestive of ***diabetes mellitus***. The image depicted in the question is suggestive of the most characteristic feature of diabetes which is ***nodular glomerulosclerosis*** also known as **Kimmelstien Wilson lesion**.

CHAPTER 21

Important Stains and Bodies

HEMATOXYLIN AND EOSIN (H & E)

This is the **most commonly used stain in routine pathology**. Hematoxylin, a basic dye stains acidic structures a purplish blue. Nuclei (DNA), ribosomes and rough endoplasmic reticulum (with their RNA) are therefore stained blue with H&E. Eosin, in contrast is an acidic dye which stains basic structures red or pink. Most cytoplasmic proteins are basic and therefore stained pink or pinkish red. In summary, H&E stains nuclei blue and cytoplasm pink or red.

PERIODIC ACID-SCHIFF (PAS)

This stain is versatile and has been used to stain many structures including glycogen, mucin, mucoprotein, glycoprotein, as well as fungi. PAS is useful for outlining tissue structures—basement membranes, glomeruli, blood vessels and glycogen—in the liver.

ROMANOWSKY STAINS

These histology stains are used for blood and bone marrow. Examples of Romanowsky histology stains include Wright's stain, Giemsa stain and Jenner's stain. These histology stains are based on a combination of eosin and methylene blue.

SILVER STAINS

These histology stains use silver. Argyrphilic tissue has an affinity for silver salts. The silver salts will be seen in argyrphilic tissues. Silver histology stains are used *to show melanin and reticular fibers.*

SUDAN STAINS

Sudan histology stains are used for staining of lipids and phospholipids. Examples of such histology stains are Sudan black, Sudan IV, and oil red O.

TYPE OF STAIN	Used for staining
Acid Fast Stain	Mycobacterial Organisms and other Acid Fast Organisms
Aldehyde Fuchsin	Pancreatic Islet Beta Cell Granules
Alician Blue	Mucins and Muco-substances
Alizarin Red S	Calcium

Contd...

Contd...

Bielschowsky Stain (Uses Silver)	Reticular Fibers, Neurofibrillary Tangles and Senile Plaques
Cajal Stain	Nervous Tissue
Congo Red	Amyloid
Cresyl Violet (Nissl Stain)	Neurons and Glia
Fontana Masson's	Melanin and Argentaffin Cells
Giemsa	Bone Marrow
Golgi Stain	Neurons
Gomori Methenamine Silver (GMS)	Fungi
Gram Stain (Taylor's)	Bacteria
Hematoxylin & Eosin (H&E)	General Stain Used in Routine Pathology
Luna Stain	Elastin and Mast Cells
Luxol Fast Blue (LFB)	Myelin
Masson's Trichrome	Connective Tissue, Collagen
Mucicarmine	Epithelial Mucin
Oil-Red-O (On Frozen Sections)	Lipid
Orcien Stain	Elastin fibers
Osmium Tetroxide	Lipids
Periodic Acid-Schiff (PAS)	Glycogen, Fungi
Phosphotungstic Acid-Haematoxylin	Fibrin, Cross Striations of Skeletal Muscle Fibres
Picrosirius Red (polarized)	Collagen
Reticulum Silver	Reticulum Fibres
Safranin O	Mucin, Cartilage and Mast cells
Toluidine Blue	Mast Cell Granules
Verhoeff Vangieson (VVG)	Elastic Fibres
Von Kossa	Calcium Salts

Inclusion Bodies

A. INTRA-CYTOPLASMIC

Rabies	Negri bodies
Small pox	Guarnieri bodies
Molluscum Contagiosum	Henderson Peterson bodies
Fowl pox	Bollinger bodies
Trachoma	Halberstaedter- Prowazeki bodies

B. INTRA-NUCLEAR

Cowdrey Type A	
Herpes Virus	Lipschutz Inclusions
Yellow fever	Torres Bodies
Cowdrey Type B	
Adenovirus (Basophilic)	
Poliovirus (acidophilic)	

C. BOTH INTRANUCLEAR AND INTRACYTOPLASMIC

Measles Virus

Other Important Bodies

Asteroid body	Sarcoidosis and Sporotrichosis
Ferruginous body	Asbestosis
Torres body	Yellow fever
Lafora body	Myoclonic epilepsy
Michaelis Gutmann body	Malacoplakia
Mallory bodies	Primary biliary cirrhosis
	Alcoholic hepatitis
	Wilson's disease
	Chronic cholestasis
	Hepatocellular carcinoma
Miyagawa's Corpuscles	Buboes from LGV
Leishman Donovan Bodies	Kala –Azar
Babes- Ernst Granules	Corynebacterium diphtheriae
Donovan Bodies	Granuloma Inguinale
Lewis Bodies	Parkinsonism
Russell Bodies	Multiple Myeloma
Warthin- Finkedely Giant Cells	Measles
Owl-Eye Inclusions	CMV and Herpes
Keratin Pearls	Squamous Cell Carcinoma
Pick Body	Pick's Disease

Contd...

Contd...

Aschoff Bodies	Rheumatic Fever
Bodies of Arantius	Aortic Valve Nodules
Body of Highmore	Mediastinum Testis
Bollinger Bodies	Fowlpox
Brassy Body	Dark Shrunken Blood Corpuscle in Malaria
Call Exner Bodies	Granulosa Theca Cell Tumor
Chromatid Bodies	Entamoeba histolytica Pre-cyst
Citron Bodies	Clostridium septicum
Civatte Bodies	Lichen Planus
Councilman Bodies	Hepatitis
Coccoid X Bodies	Psittacosis
Creola Bodies	Asthma
Gamma Gandy Bodies	Congestive Splenomegaly
Guarnieri Bodies	Vaccinia
Henderson Peterson Bodies	Molluscum contagiosum
Heinz Bodies	G 6 PD Deficiency
Hirano Bodies	Alzheimer's Disease
Levinthal Coles Lille Bodies	Psittacosis
Mooser Bodies	Endemic Typhus
Moot Bodies	Multiple Myeloma
Psammoma Bodies	Papillary Carcinoma of Thyroid, Ovary and Salivary Glands,
	Meningioma, Mesothelioma
Reilly Bodies	Hurler's Syndrome
Rokitansky Bodies	Teratoma
Ross's Bodies	Syphilis
Rushton Bodies	Odontogenic Cyst
Sclerotic Bodies	Chromoblastomycosis
Sandstorm Bodies	Parathyroid Glands
Schiller Duval Bodies	Yolk Sac Tumor
Schaumann Bodies	Sarcoidosis
Verocay Bodies	Schwannoma
Winkler Bodies	Syphilis
Zebra Bodies	Metachromatic Leukodystrophy