Pathology

Marrow Edition 6

Volume 1

MARROW

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// ME521-SLC

Contents

General Pathology

Hematology - RBC disorders

Hematology - WBC disorders

Systemic Pathology

CELL ADAPTATIONS

Cell adaptation

00:03:25

Cell organelles affected during cell injury :

- Mitochondria.
- Endoplasmic reticulum.
- Nucleus.
- Plasma membrane.

Causes of cell injury :

- Hypoxia : Decreased Oxygen supply to a tissue.
  Most common cause of cell injury : Hypoxia.
  Most common cause of hypoxia : Ischemia.
  Ischemia refers to decreased blood supply.
  Ischemia is a more severe form of cell injury than hypoxia, as when blood supply decreases, supply of all nutrients including O_2 is diminished.
  Cells most sensitive to hypoxia : Neurons.
  Cells least sensitive to hypoxia : Fibroblasts, skeletal muscle.
- Physical agents e.g. , Radiation.
- Chemical agents e.g. , Carcinogens.
- Infectious agents. e.g. , Bacteria, Viruses.
- Genetic abnormalities e.g. , Mutation.
- Immunologic agents.
- Nutritional imbalances : Deficiency (PEM), excess (obesity).

Manifestation of cell injury

00:11:00

Cell injury may lead to :

- Adaptation : Hypertrophy, hyperplasia, metaplasia, atrophy.
- Reversible cell injury : On removing the injurious stimuli, the cell will revert to normal state.

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- Irreversible cell injury (cell death) : Necrosis, apoptosis, pyroptosis, ferroptosis, necroptosis.
- Intracellular accumulation.
- Pathologic calcification.

Hypertrophy

00:15:32

Hypertrophy : Increased cell size but no increase in number of cells.

Mechanism : Occurs due to increase synthesis of cellular proteins.

- GATA4
- NFAT
- MEF2

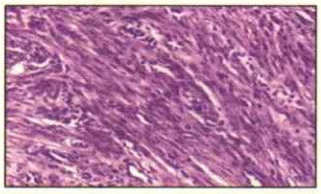
} 3 proteins that are responsible for hypertrophy

Hyperplasia usually occurs in permanent/ non-dividing cells.

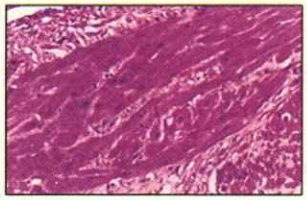
Type of cells based on division ability :

- Permanent/non-dividing cells : Cannot divide at all e.g., cardiac muscle, skeletal muscle.
- Stable cells : Liver or pancreas.
- Labile cells : Rapidly dividing cells e.g., bone marrow, skin epidermis.

Physiological hypertrophy	Pathological hypertrophy
• Uterus during pregnancy. • Breast during lactation. • Skeletal muscle in body builders.	• Left ventricular hypertrophy. • In case of bladder outlet obstruction due to stone, area proximal to stone will undergo hypertrophy.



Normal smooth muscles cells of uterus



Hypertrophied smooth muscle cells

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Hyperplasia 00:24:19

Increase in the number of cells which will lead to increase in size of the organ.
Mechanism : Growth factor induced proliferation of mature cells.
Usually occurs in the dividing cells.
Dividing cells can undergo both hyperplasia and hypertrophy.

Physiological hyperplasia		Pathological hyperplasia
Hormonal : • Breast during pregnancy. • Breast during puberty.	Compensatory : Liver after partial hepatectomy.	Occurs due to hormonal excess : • Increased androgen leads to benign prostatic hyperplasia. • Increased estrogen leads to endometrial hyperplasia

Hyperplastic proliferations are a fertile soil in which cancers can develop.
For e.g., endometrial hyperplasia can lead to endometrial cancer.

Examples of both hypertrophy and hyperplasia :
- Breast during puberty/pregnancy
- Uterus during pregnancy.

Atrophy 00:31:32

Atrophy : Decreased cell size and number leading to decreased organ size.
Mechanism :
- Decreased protein synthesis.
- Increased protein degradation.
- Autophagy.

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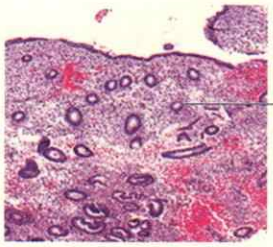
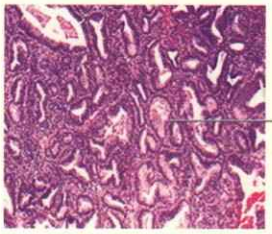
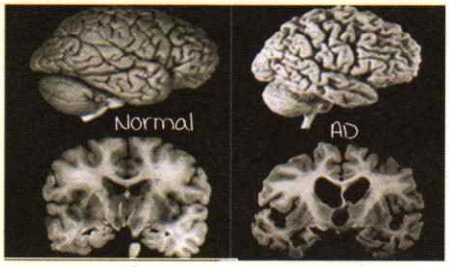
Physiologic atrophy	Pathologic atrophy
• The disappearance of notochord. • Disappearance of thyroglossal duct at puberty. • Involution of uterus after parturition.	• Senile atrophy. • Ischemic atrophy (Decreased blood supply leading to atrophy). • Denervation atrophy (loss of nerve supply). • Pressure atrophy (in case of a tumour, surrounding structures get atrophied due to pressure). • Disuse atrophy. • Nutritional atrophy.



Normal endomaterial gland



Hyperplasia gland



Normal brain Atrophied brain

Metaplasia

00:38:23

It is a reversible change in which one differentiated cell type/ mature cell type is converted to another type.

Epithelial metaplasia : Epithelium gets converted to another type of epithelium.

Mesenchymal metaplasia : Mesenchyme gets converted to another type of mesenchyme.

Mechanism : Reprogramming of stem cells.

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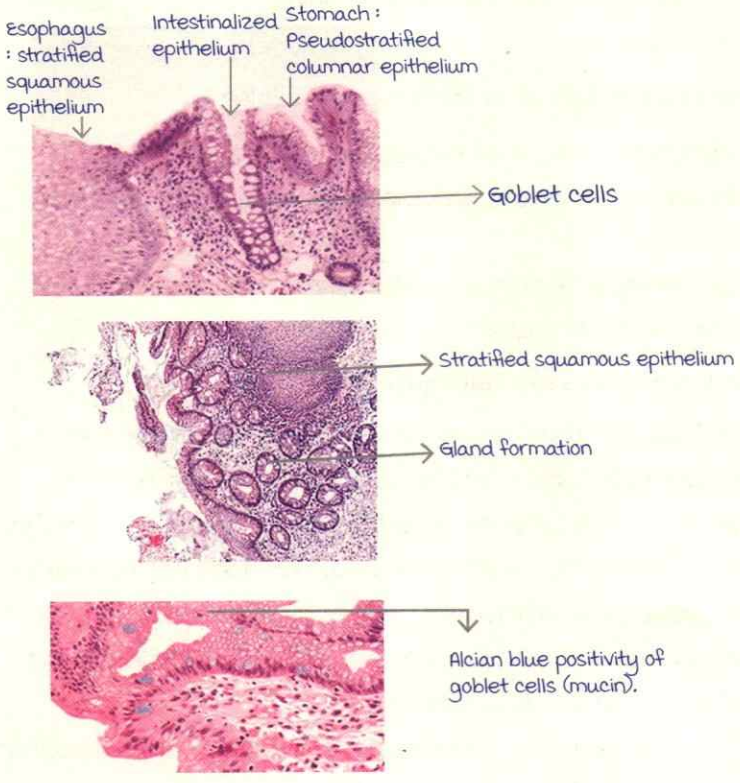
Examples :

- most common metaplasia : In smokers pseudostratified ciliated columnar epithelium of respiratory tract, converts into stratified squamous epithelium (squamous metaplasia). Squamous metaplasia is reversible after cessation of smoking.

- Barrett's esophagus/ Columnar lined oesophagus (CLO) : Stratified squamous epithelium of esophagus is converted to columnar epithelium on exposure to GERD.
- On HPE of Barrett's esophagus : Intestinal metaplasia and goblet cells are seen.
- Special stain for Barrett's esophagus : Alcian blue.
- Goblet cells produce mucin which stains with Alcian blue.
- Barrett's esophagus is a risk factor for



Vitamin A deficiency can lead to metaplasia.

Example of connective tissue metaplasia : Myositis ossificans.

MCQs

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Q. A 57 year old man comes to the physician for a follow up evaluation of chronic, retrosternal chest pain. The pain is worse at night and after heavy meals. He has taken oral pantoprazole for several months without any relief of his symptoms. Upper endoscopy shows ulcerations in the distal esophagus and a proximally dislocated Z-line. A biopsy of the distal esophagus shows mature columnar epithelium with goblet cells. Which of the following microscopic findings underlies the same patho mechanism as the cellular changes seen in this patient?

A. Pseudostratified columnar epithelium in bronchi.
B. Squamous epithelium in bladder.
C. Paneth cells in duodenum.
D. Simple columnar epithelium in endocervix.

The given scenario is that of Barrett's esophagus which shows metaplasia.
Other options are examples of epithelium normally present in those tissues.

Q. Which of the following statements is false :

A. Atrophy is a type of reversible cell injury.
B. Plasma membrane blebbing occurs in reversible cell injury.
C. On removal of stimulus, necrosis can be reversed.
D. Chronic sublethal stimulus can cause cellular aging.

Necrosis is irreversible cell injury.

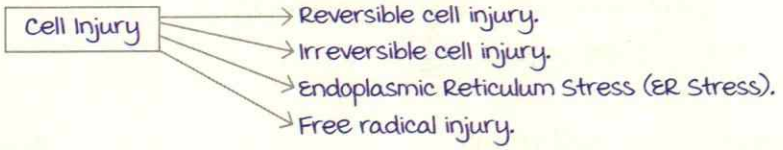
Q. A 20 year old woman had Goodpasture syndrome which progressed to chronic renal failure. She is 165 cm tall and weighs 55 kg. She now has blood pressure measurements in the range of 150/90 to 180/110 mmHg, but does not regularly take medications. Laboratory studies show her blood urea nitrogen is over 100 mg/dL and she requires chronic dialysis. A chest x-ray shows an enlarged heart. The size of her heart is most likely to be the result of which of the following processes involving the myocardial fibres?

A. Hypertrophy.
B. Fatty infiltration.
C. Hyperplasia.
D. Fatty degeneration.
E. Edema.

Active space

CELL INJURY

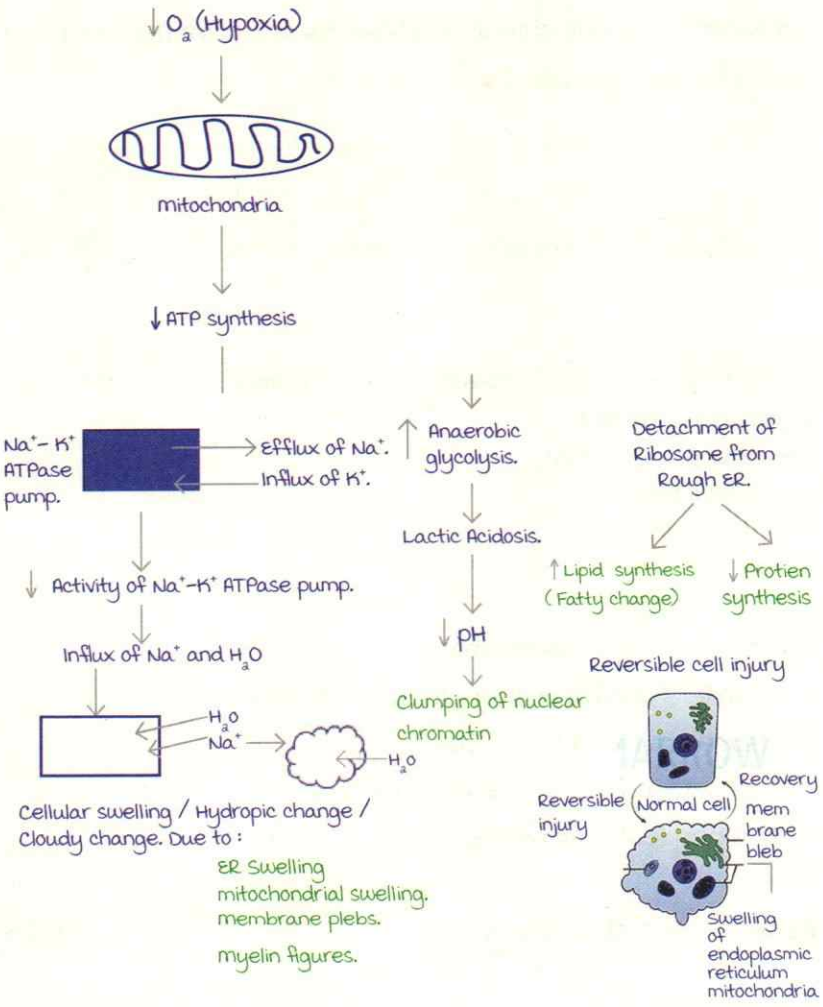
Cell injury (00:00:28)



Reversible Cell Injury :

If injurious stimuli are removed, cell can go back to its normal state.

mechanism :



myelin figures : Due to damage to phospholipid bilayer, Composed of phospholipid Ca^{2+}.

Active space

m/c organelle affected in cell injury : Mitochondria.
Most important morphological feature of reversible cell injury : Cell swelling / Hydropic changes.
Myelin figures :

- Seen in both reversible and irreversible cell injury.
- Composed of Ca^{2+} and phospholipids.
- Looks like myelin.

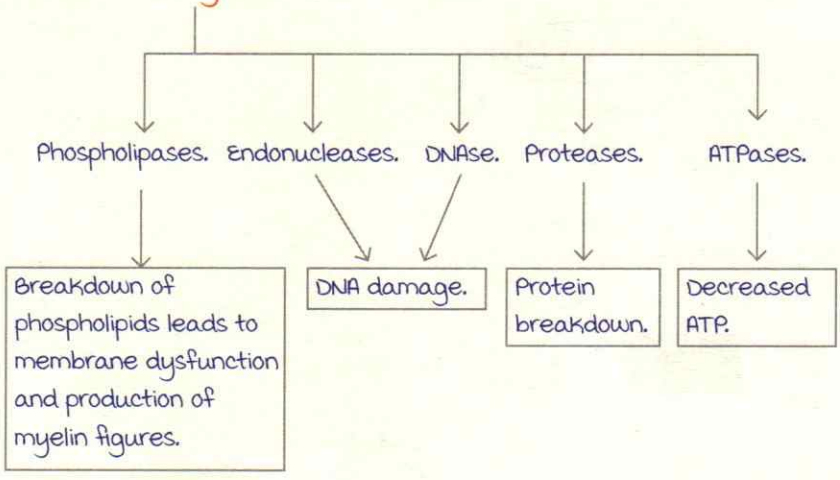
Irreversible cell injury

00:12:28

2 things characterize irreversibility :

- Mitochondrial dysfunction.
- Membrane dysfunction.

Membrane dysfunction :
Persistent injurious stimuli → Loose its selective permeability → Increased cytosolic Ca^{2+}.



Clinicopathological correlation :
In disorders like MI or liver disease : Enzymes can be measured in blood because :

- There is membrane dysfunction.
- They leak out of the cell.

Active space

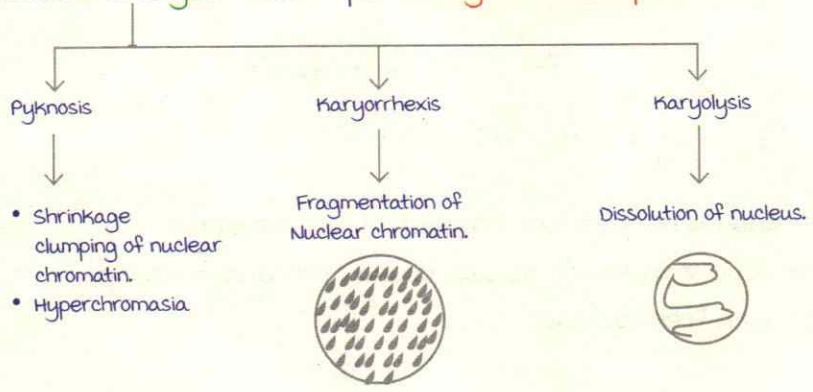
Mitochondrial dysfunction

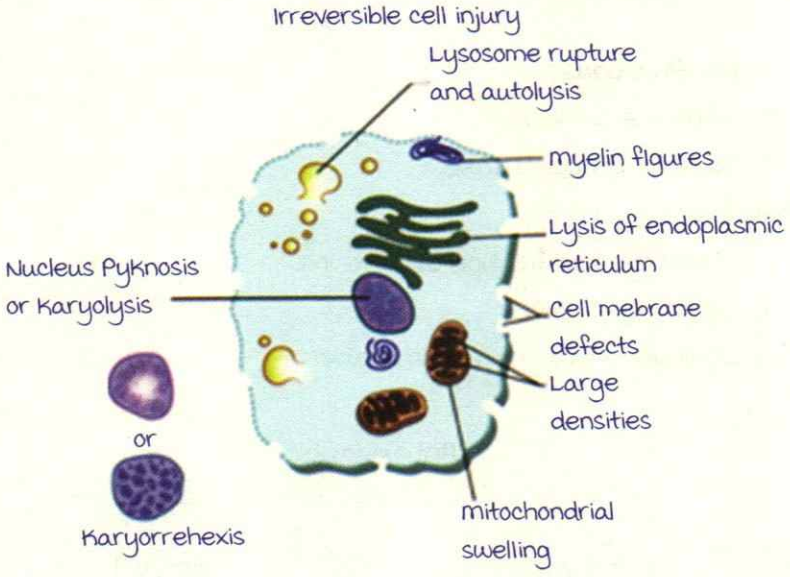
00:19:50

Large, flocculent, amorphous densities : Characteristic feature of irreversible injury.

Only been seen on Electron microscopy.

Nuclear changes : most important light microscopic feature.





Free radical injury

00:27:33

Definition : Molecule with one or more unpaired electrons in their outermost orbit.

Eg : $O_2^{\cdot-}$, $H_2O_2^{\cdot}$, $OH^{\cdot}$, $OONO^{\cdot-}$.

Most potent free radical : $OH^{\cdot}$.

Excess free radicals → Oxidative stress

1. Ageing.
2. Cancers.
3. Neuro degenerative disorders : AD Alzheimer's.
4. Reperfusion Injury.

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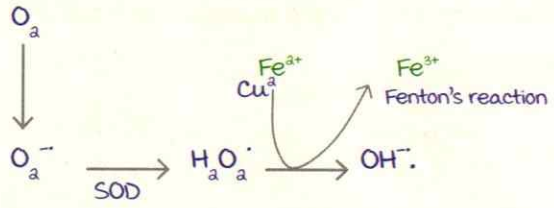
Production of free radicals :



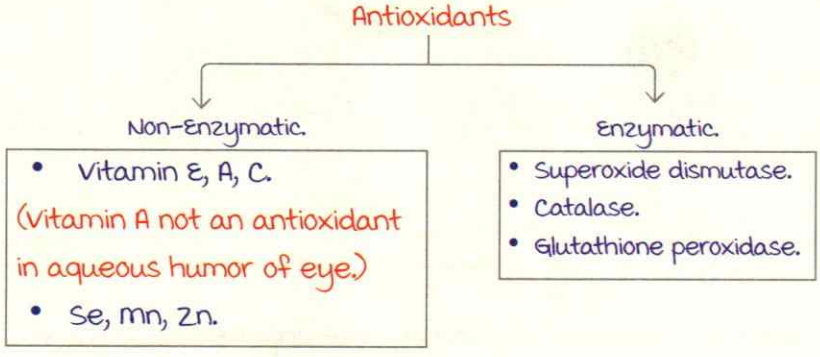
Fe and Cu proteins are transferrin, ferritin and ceruloplasmin. Hence always bound and cannot always produce free radicals.

Enzymes leading to free radicals production 00:34:30

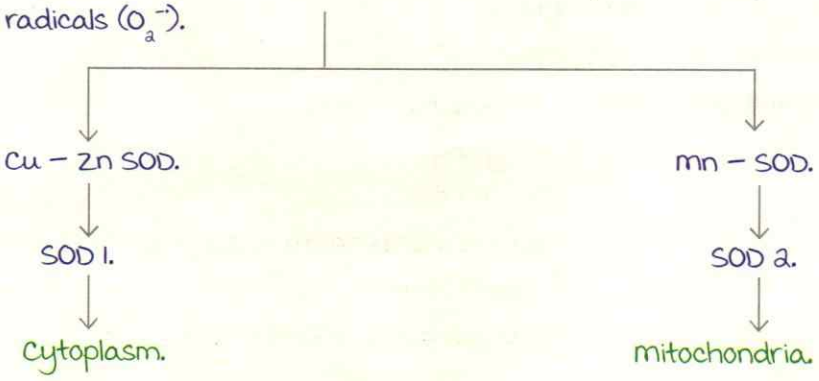
- NADPH oxidase.
- Xanthine oxidase.
- Superoxide Dismutase.

They cause injury by :

1. Oxidative modification of proteins.
2. Damage to DNA.
3. Lipid peroxidation of membranes.



Superoxide dismutase (SOD) : Inactivates superoxide free radicals (O_a^{--}).



Active space

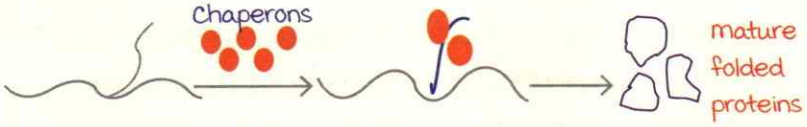
Brain is protected from free radical injury by SOD I.
Clinicopathological correlation :
Mutation of SOD I → Amyotrophic lateral sclerosis.

Catalase → Inactivates H_2O_2 and present in Peroxisomes.

Glutathione Peroxidase : Inactivates both H_2O_2 and OH^- and present in both cytoplasm and mitochondria.
Intracytoplasmic ratio of oxidized glutathione to reduced glutathione : Important indicator of oxidative state of a cell.

Endoplasmic reticulum stress 00:44:50

ER : site of protein synthesis.



Chaperons helps in Proper folding of proteins.
When there is excess protein misfolding → Transported to cytoplasm → Degraded by the ubiquitin proteosome pathway.
Excess protein misfolding leads to misfolded protein disease.

- Familial hypercholesterolemia → LDL receptor.
- Tay sach's Disease → Hexosaminidase α Subunit.
- I AT Deficiency → α I AT.
- CJD → Prion proteins.
- Alzheimer's disease → Aβ amyloid.
- Cystic fibrosis → CFTR.

MCQs
Q. A 65 year old male patient presents to the emergency with substernal chest pain radiating to the left shoulder. The level of troponin I and CK-Mb enzyme was done and it came out to be high. A diagnosis of myocardial infarction was made. Few hours later, the person died. What is the most likely reason for the enzyme leak?
A. Clumping of nuclear chromatin.

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B. Swelling of mitochondria.
C. Defects in cell membrane.
D. Autophagy by lysosomes.

Q. In an experiment, a tissue preparation is subjected to oxidant stress. There are increased numbers of free radicals generated within the cells. Generation of which of the following enzymes within these cells is the most likely protective mechanism to reduce the number of free radicals?
A. Glutathione peroxidase.
B. Catalase.
C. Hydrogen peroxide.
D. NADPH.
E. Myeloperoxidase.

Q. A 53-year-old man suffers a cardiac arrest and his wife calls emergency services. The paramedics arrive a few minutes later and begin life support measures. A regular heart rate is established after 40 minutes of resuscitative efforts as he is being transported to the hospital. A thrombolytic agent (tPA) is administered. Which of the following cellular processes is most likely to occur in his myocardium following administration of the tPA?

A. Apoptosis.
B. Free radical injury.
C. Heterophagocytosis.
D. Squamous metaplasia.
E. Accumultion of cytokeratins.

This is case of ischemia-repurfusion injury.

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CELL DEATH

Irreversible cell Injury : Cell death.

Mechanisms of cell death 00:00:32

1. Necrosis.
2. Apoptosis.
3. Necroptosis.
4. Pyroptosis.
5. Ferroptosis.
6. Autophagy.

Necrosis :

- It is a form of pathological cell death.
- Mechanism :
    I. Denaturation of proteins.
    II. Enzymatic digestion of cells.
- Leads to damaged plasma membrane → Contents leak out of cell → Inflammatory reaction (to clear debris) → Accidental cell death.

Types of necrosis :

1. Coagulative.
2. Liquefactive.
3. Caseous.
4. Fat.
5. Fibrinoid.
6. Gangrenous.

Coagulative necrosis 00:05:38

most common form of necrosis.

morphological features of coagulative necrosis :

- Densely eosinophilic appearance (Loss of cytoplasmic RNA).
- Appear glassy (No glycogen).
- Moth eaten appearance (Organelles digestion by lysosomal enzymes).

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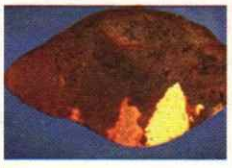
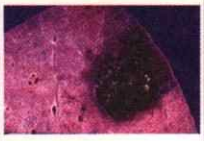
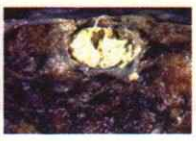
Type of necrosis	Coagulative necrosis	Liquefactive necrosis	Caseous necrosis
Notes.	Infarct is a localised area of coagulative necrosis. Type of dry gangrene.	A.K.A Colliquative necrosis : Due to enzymatic digestion of cells. Type of wet gangrene.	Cheese like appearance. Combination of coagulative + liquefactive necrosis.
Occurrence	Occurs in all solid organs, except brain. • Kidney. • Spleen. • Heart (MC). • Liver etc.	• Brain. • Abscess. • Fungal infections.	
Microscopy	Cell outlines preserved. Densely eosinophilic glassy, moth eaten appearance.	Cell outlines not preferred.	
Examples	1. Burns. 2. Dry gangrene. 3. Zenker's degeneration (Seen in typhoid : Affects rectus abdominis or skeletal muscle).  	Brain. Abscess. Fungal infections. 	Tuberculosis (Caseating granulomas) : Mycolic acid decomposition. Fungal infections : Histoplasmosis. Coccidomycosis 

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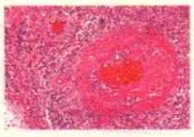
Other necrosis

00:16:38

Type of necrosis	Fat necrosis	Fibrinoid necrosis	Gangrenous necrosis
Notes	Enzymatic or traumatic	Immune complexes → Deposited in vessel wall → Fibrin like appearance → Fibrinoid necrosis.	Gangrene : Dry or wet.
Occurance	• Traumatic : Breast. • Enzymatic : Omentum, pancreas, mesentery.	Seen in type 2 or 3 hypersensitivity reaction.	Seen in lower limbs.
Examples	Pancreatitis → Lipase → Release of free fatty acids → Contact with Calcium → Saponification → Chalky white deposits.	Aschoff nodules (Rheumatic heart disease). Malignant hypertension. Polyarteritis nodosa (vasculitis).	
			

Apoptosis

00:27:25

- Genetically programmed cell death.
- Apoptosis : "Falling off".
- Most studies on apoptosis done on a nematode : Caenorhabditis elegans.
- Single cell death.
- Mechanism of cell to eliminate unwanted cells.
- Both physiological and pathological death.

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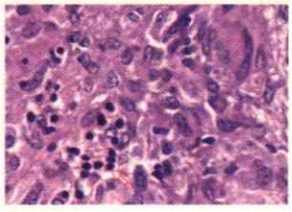
I. Physiological apoptosis :
   1. Organogenesis / embryogenesis.
   2. Involution of hormone dependent tissue up hormone withdrawal.
   3. Endometrial shedding during menstruation.
   4. Death of self-reactive lymphocytes.
   5. Cells which have completed their purpose (neutrophils after inflammation).

II. Pathological apoptosis :
   1. DNA damage.
   2. Misfolded protein diseases (Cystic fibrosis, alpha 1 anti trypsin deficiency).
   3. Diseases with councilman bodies (Hepatitis B).

Morphological features of apoptosis 00:34:42



- Cell size shrinkage : Earliest morphological feature.
- Plasma membrane intact → No inflammation.
- Peripheral chromatin condensation : most characteristic morphological feature.
- Cell membrane blebs, which will disintegrate → Apoptotic bodies : membrane bound with organelles.

Mechanisms of apoptosis 00:40:33

- Three phases :
   1. Initiation phase.
   2. Execution phase.
   3. Removal of apoptotic bodies.
- 2 enzymes : Important in apoptosis :
   1. Caspases :
      - Contains cysteine.
      - Cleaves near the aspartic acid residues.
      - 2 types :
        Initiator caspases (Cas 8, 9, 10).
        Executional caspases (Cas 3, 6, 7).

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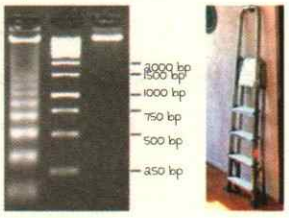
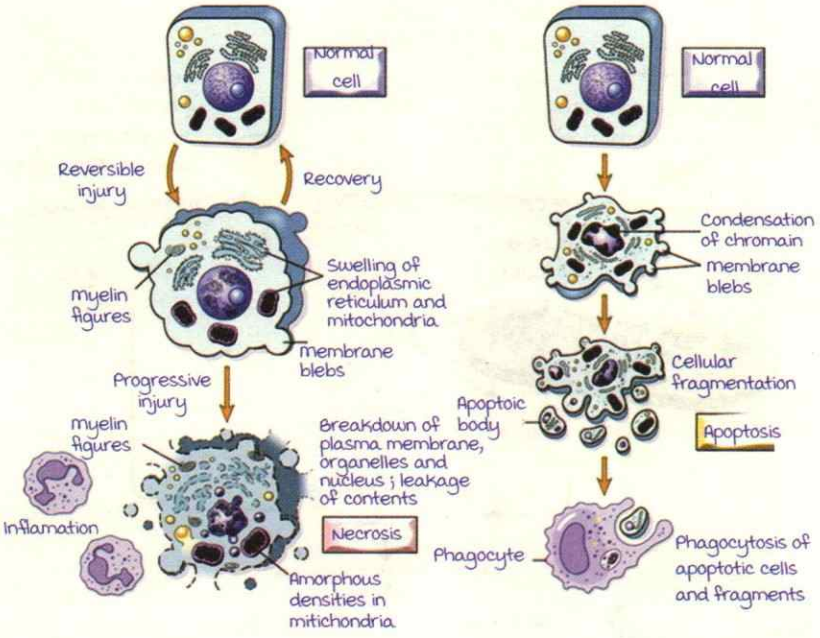
2. Endonucleases :
   - Breakdown of DNA.
   - When apoptotic cells subject to DNA electrophoresis → DNA fragments (which are in various base pairs) → Appear like a ladder → Stepladder pattern.

In a necrotic cell, plain pattern → Smear pattern (as there are no endonucleases





Feature	Necrosis	Apoptosis
Definition	Enzymatic or ischemic process	Genetically programmed cell death
mechanism	Passive	Active
Cell	Group of cells	Single cell
Type of death	Always pathological	Both physiological and pathological
Cell size	Increases	Decreases
Cell membrane	Affected	Intact
Inflammation	Present	Absent
marker	No	_ _ _ _ _ _ _ _ _ _
PAGE	Smear	Step ladder

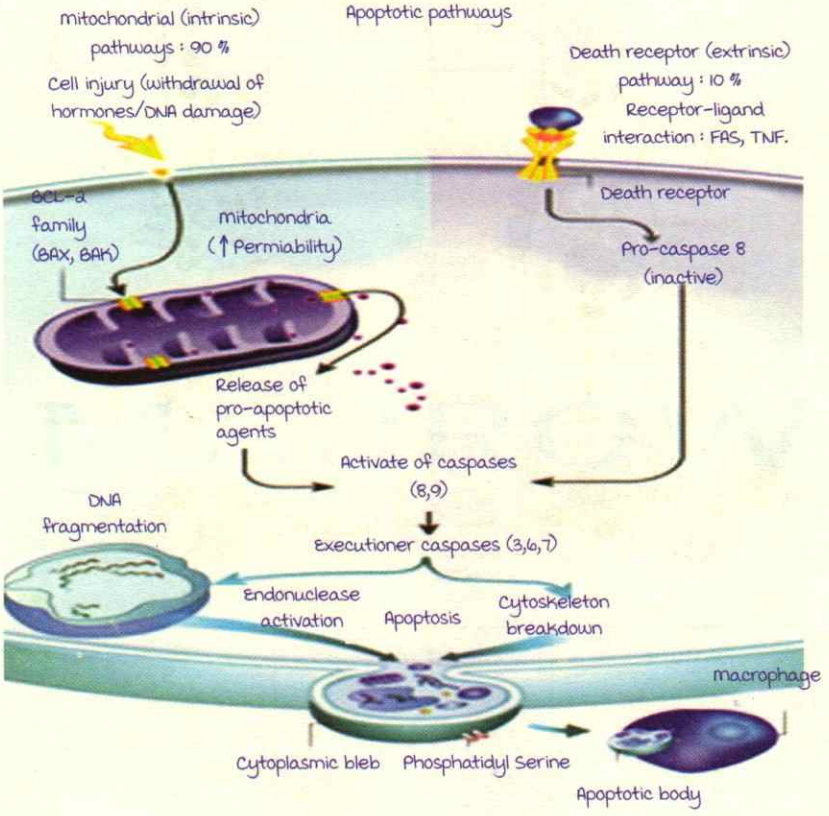
Active space

Regulators of apoptosis

00:47:06

3 basic regulators :

1. Pro-apoptotic factors : Initiate apoptosis.
   - Bax and Bak.
2. Anti-apoptotic : Inhibit apoptosis.
   - BCL-2, BCL-XL, MCL1.
3. Stress sensors : Regulated Initiators of apoptosis.
   - bim, bid, bad, PUMA, NOXA.



Mechanism :

Initiation phase : 2 pathways :

1. Intrinsic.
2. Extrinsic

Intrinsic : Mitochondrial pathway.

- 90% cases.
- MC used.
- MC organelle affected in apoptosis : Mitochondria.

Active space

- Normal cell → Normal mitochondria → Permeabilit maintained by BCL 2 family proteins (Anti-apoptotic) → Cytochrome c inside the mitochondria.
- Signal/any kind of trigger → Activation of stress se sors (Bim, bid, bad, NOXA, PUMA) → Activationn of pro-apoptotic factors (Bax, bak) → Bax, bak channel formed between inner and outer membrane of mitochondria → Release cytochrome c → Leakage out of the cells → Combines with apoptosis activating factor 1 (Apaf 1) → Forms apoptosome → Activates caspase 9 (Initiator caspases) → Activates caspases 3, 6 and 7 (Executor caspases) → Apoptosis.
- Apoptosis :
  - Inhibitors of intrinsic pathway : IAP.
  - SMAC and DIABLO inhibit IAP (Pro-apoptotic).

2. Extrinsic : Death receptor mediated pathway.
   10% cases.
   - FAS Ligand (FAS-L) of T-lymphocyte engage with FAS on another cell → 4 death domains on the cell me brane combines with each other → Forms FADD (FAS Associated Death Domain) → Converts pro-caspase A → Caspase 8 → Activates caspase 3, 6, 7 → Execute apoptosis.
   - Inhibitor of extrinsic pathway : FLIP.

Removal of death cells 01:02:10

- Normal cell → Phosphatidyl serine on innermmembrane → macrophage can't recognise this molecule.
- Apoptotic cells → Phosphatidyl serine moves to outer membrane (phosphatidyl serine flip) → Macrophages recognize apoptotic cells through Annexin 5 → Binds to them → Produces a color to them → Macrophages eat them up.

Marker of apoptotic cell : Annexin 5.

Efferocytosis : Phagocytosis of apoptotic cells.

Active space

Necroptosis 01:08:44

- Necrosis + apoptosis.
- Cell starts as apoptosis (mechanism), end as necrosis (morphological features).
- Mechanism : Caspase independent.
- Programmed necrosis.
- Mechanism :
  TNF + TNF-R1 → Activates RIP K1 and RIP K3 → Phosphorylation of MLKL → MLKL enters plasma membrane → Damage of Plasma membrane + inflammation + free radical Injury (morphologically similar to necrosis).
- Seen in :
  Development of mammalian growth plate (Physiological).
  Pathological conditions:
  1. Acute pancreatitis.
  2. Acute steatohepatitis.
  3. Neurodegenerative disorders.

Pyroptosis 01:13:30

- Cell death associated with fever inducing cytokine (IL1).
- Microbial toxin → Enters cell → Recognized by NOD like receptors → Activates inflammosome → Activates caspase 1 → Activates IL 1 → Fever + inflammation.

Ferroptosis :

- Cell death caused by excess iron.
- Discovered in 2012.
- Excess intracellular iron → Lipid peroxidation of membrane → Free radical Injury → Plasma membrane damage → Cell death.

Active space

Autophagy 01:17:45

- Cell eats its own contents.
- Survival mechanism by cell during nutrient deprivation.
- Mechanism :

Endoplasmic reticulum

↓

Phagosome (Initiation membrane)

↓

Autophagosome (through vesicles)

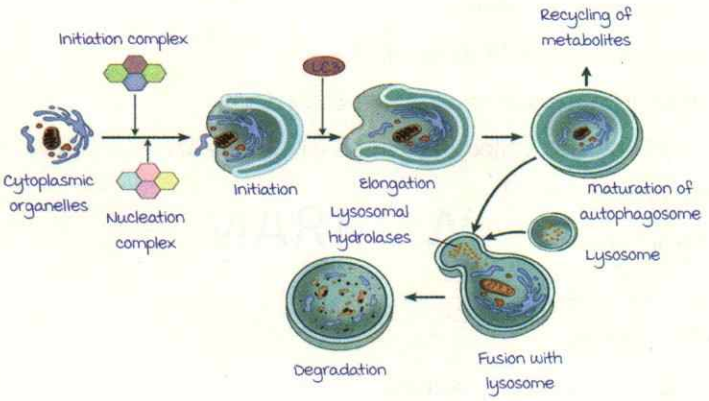
↓

Autophagosome + lysosome

↓

Digestion of cellular contents

- Genes required for formation of autophagosome.
  LC 3 : marker for autophagy.
  ATG 16 L1 : Seen in Crohn's disease.



Cellular stresses like nutrient deprivation active an autophagy pathway.
This proceeds through several phases such as initiation, nucleation, elongation of isolation membrane, and eventually creates a double membrane bound vacuoles known as autophagosomes.
Cytoplasmic materials and cellular organelles are sequestered in autophagosomes, and are degraded after fusion with lysosomes.
In the final stage, digested materials are released for recycling of metabolites.

Q. A 35 year old man who works at a facility processing highly radioactive substances accidentally receives a high, whole-body dose of ionizing radiation estimated to be 1500

Active space

rads (15 gray). He dies 1 week later. At autopsy, histologic examination of the skin shows scattered, individual epidermal cells with shrunken, markedly eosinophilic cytoplasm and pyknotic, fragmented nuclei. These morphologic changes most likely indicate which of the following processes ?

A. Apoptosis.

B. Coagulation necrosis.

C. Liquefaction necrosis.

D. Mutagenesis.

E. Tumor initiation.

Q. Which of the following is not true for necroptosis :

A. Morphological features of necrosis.

B. Programmed cell death.

C. Caspase mediated.

D. Mediated by RIP1 and RIP 3.

E. Seen in neurodegenerative disorders.

Q. Which of the following types of cell death is induced by lipid peroxidation ?

A. Pyroptosis.

B. Necroptosis.

C. Ferroptosis.

D. Programmed cell necrosis.

Q. A 40 year old woman has the sudden onset of severe abdominal pain. On physical examination she has diffuse tenderness in all abdominal quadrants, with marked guarding and muscular rigidity. She has laboratory findings that include serum AST of 43 U/L, ALT of 30 U/L, LDH 630 U/L, and lipase 415 U/L. An abdominal CT scan reveals peritoneal fluid collections and decreased attenuation along with enlargement of the pancreas. Which of the following cellular changes is most likely to accompany these findings ?

A. Coagulative necrosis.

B. Dry gangrene.

C. Fat necrosis.

D. Apoptosis.

E. Liquefactive necrosis.

Active space

INTRACELLULAR ACCUMULATIONS

Intra = Inside Cellular = Cell

These are accumulations that get deposited inside the cell following cell injury.

Depositions :

- Proteins.
- Lipids.
- Glycogen.
- Water.
- Hyaline.
- Calcium.
- Pigments.

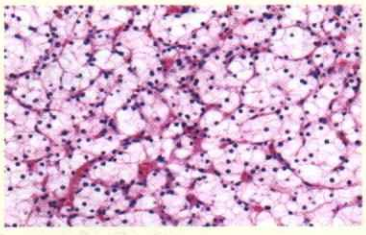
Glycogen 00:02:01

Can be deposited in glycogen storage disorders & in severe diabetic nephropathies (glycogen vacuoles known as Armani Ebstein lesions seen in PCT of kidneys).

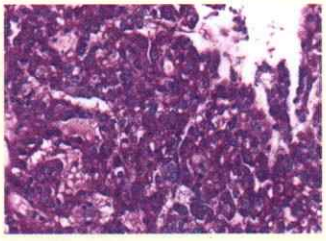
HPE : Clear vacuoles as it dissolves in aqueous fixature.

Special stain : PAS (Periodic Acid Schiff) → Pink/magenta.

Other PAS + : Lymphoblasts, basement membrane and fungi.



HPE of Clear cell RCC

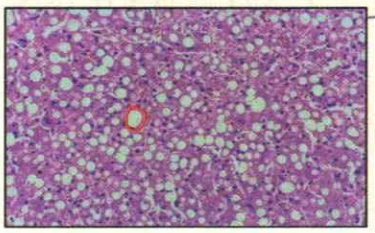


Special stain → PAS

Lipids/Fat :

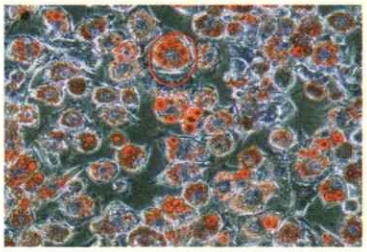
- Triglycerides → Fatty liver/Steatosis.
- Cholesterol and cholesterol esters → Atherosclerosis, xanthomas, cholesterolosis.

Active space



Liver Biopsy : Fat Steatosis.

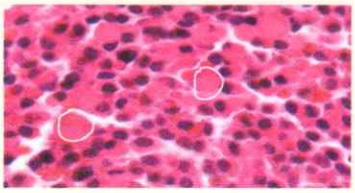
Micronodular. Macronodular.



Special Stain :
Oil red – O.
Sudan black.

Proteins :

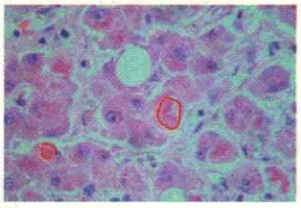
Russel body : Intracytoplasmic inclusion.
Dutcher body : Intranuclear inclusion.
→ Multiple myeloma



Russel bodies in multiple myeloma.

Reabsorption droplets in proteinuria in renal tubules.
HPE : Eosinophilic, granular appearance.

Hyaline :
2 forms → Intracellular & extracellular.
HPE : Pink/eosinophilic, smooth appearance.
Mallory hyaline body : E.g. of intracellular hyaline deposition.
Commonly seen in alcoholic liver disease.
Other conditions where mallory hyaline bodies are seen :
(Mnemonic : New Indian WATCH).



- NASH.
- Indian Childhood cirrhosis.
- Wilson's disease.
- Alcoholic Liver disease.
- Tumors like HCC.
- Cirrhosis like Primary biliary cirrhosis.
- Focal nodular Hyperplasia.

Mallory hyaline bodies are composed of intermediate filaments like CK 8 and CK 18.

Active space

Calcification

00:18:56

Deposition of calcium with small amounts of other minerals.
2 types → Dystrophic and Metastatic.

Dystrophic calcification :

- Dead tissues.
- No abnormality in calcium metabolism.
- Serum Ca^{2+} → Normal.

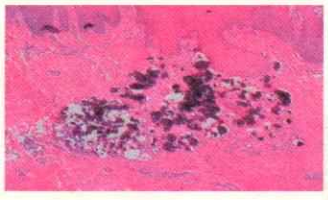
Eg : Mnemonic → RAT.

- Rheumatic vegetations.
- Atheromatic plaques.
- TB lymph nodes.
- Necrosis.
- Dead parasites.
- Monkeberg's medial calcific sclerosis (calcification in tunica media of blood vessels).
- Psammoma bodies → Foci of dystrophic calcification.

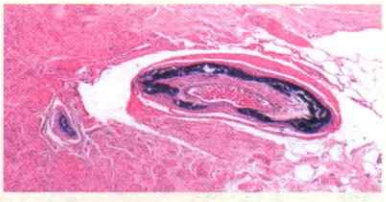
  Seen in

  1. Papillary carcinoma of thyroid.
  2. Papillary renal cell cancer.
  3. Meningioma.
  4. Prolactinoma.
  5. Serous Cystadenocarcinoma of ovary.
  6. Psammoma bodies appear as concentric lamellations.

  HPE : Densely basophilic, gritty.

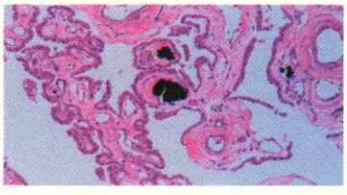


Calcifications
Squamous Epithelium



Monkeberg's Medial
calcific sclerosis

Psammoma bodies with
concentric lamellations.



Active space

Metastatic calcifications :

- In living tissues.
- Abnormality of calcium metabolism.
- Serum Ca^{a+} → High.

Examples :

1. Vitamin D related disorders.
2. Bone diseases like multiple myeloma and Paget's disease.
3. Parathyroid diseases.
4. RCC and breast carcinoma.
5. Sarcoidosis.
6. Milk alkali syndrome.

Calcification begins in mitochondria (except Kidney → Begins in basement membrane of renal tubules).

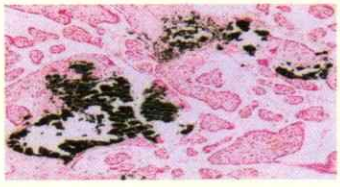
M/C organ affected with calcification →

Lung alveoli > Gastric mucosa.

Special stain for Ca^{a+} :

- Von Kossa : Black Color.
- Alizarin red S : Red color.

(Can even pick up small quantities).



Test for bone mineralization → Tetracycline Labelling Index.

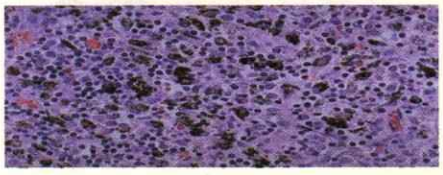
Pigments

00:36:13

Coloured substance deposited in various tissues and organs of the body.

2 types : Exogenous (external substance) and endogenous.

Exogenous : Tattoos, Anthracosis (deposition of carbon or black pigments in lungs).



Endogenous : Lipofuscin, hemosiderin, melanin.

Active space

Lipofuscin :

Pigment is derived from lipid peroxidation of membranes.

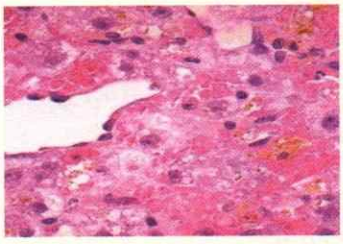
Telltale sign of free radical injury.

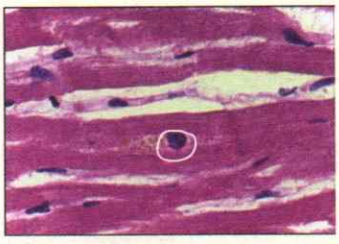
AKA Ageing pigment/Wear and tear pigment.

On ageing, atrophy of organs occur, causing free radical injury. Lipofuschin gets deposited on this, hence it is responsible for brown atrophy of liver and heart.

HPE : Perinuclear brown pigment.

Special stain : Oil red – O.





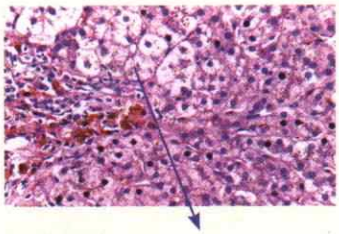
Hemosiderin :

Deposited in conditions of Iron overload (eg., blood transfusion, bruise, hemorrhage).

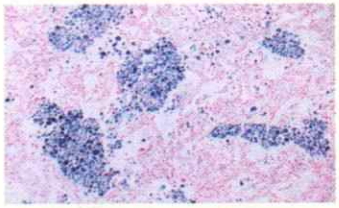
Color of hemosiderin on light microscopy : Golden yellow/ brown and refractile.

Special stain : Prussian blue stain → Perl's reaction.

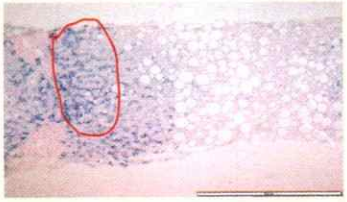
Principle : Potassium ferrocyanide → Ferric ferrocyanide.

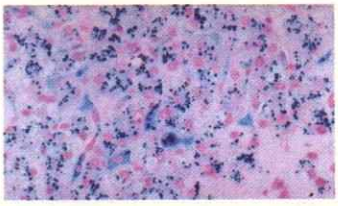


Hemosiderin



Special stain → Prussian blue : Perl's reaction





Active space

Melanin

00:49:18

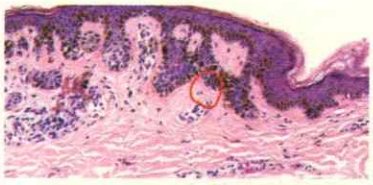
Present everywhere in our body.

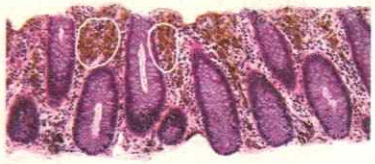
In Brain → Substantia Nigra.

Pale Substantia Nigra → Parkinson's disease.

Black colored pigment.

Derived from tyrosine.





Special stain : Masson Fontana (MF).

2 massons in pathology :

Masson Fontana stain

Masson's trichrome for collagen.

Dopa reaction (most specific), Schmorl's test.

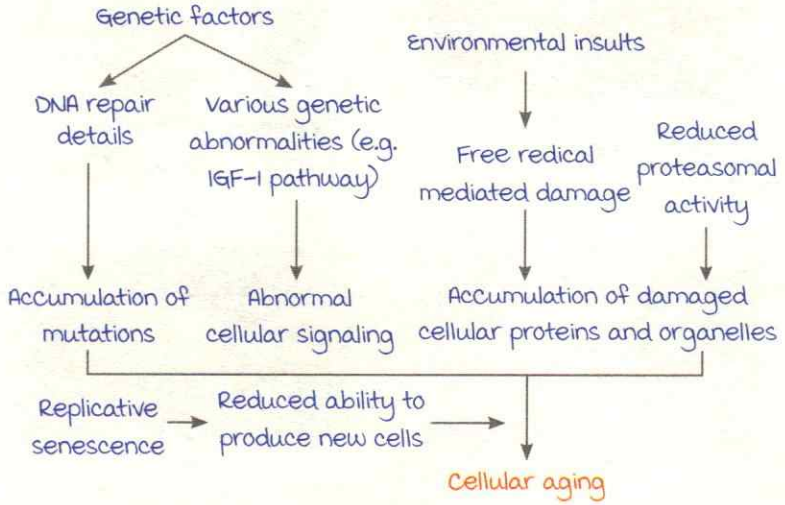
Markers for malignant melanoma :

- HMB – 45
- S – 100
- Melan – A.

Hemochromatosis → Bronze like pigmentation of skin is due to melanin.

Cellular ageing

00:55:38



Active space

Concepts in ageing :

m/c theory of cellular ageing → Free radical mediated damage.

- DNA damage :

Werner syndrome → Syndrome of premature ageing.

Premature ageing due to defect in DNA helicase.

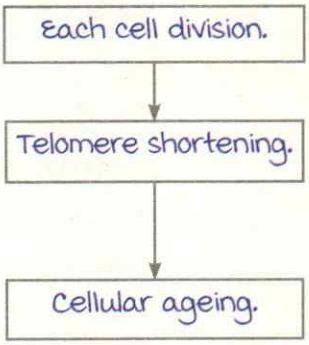
- Cellular senescence :

Hayflick limit → Cells divide only approximately 60 -70 times in their entire lifespan.

Telomeres → Short repeated sequence of nucleotides (TTAGGG) at the ends of chromosomes.

Telomeres are prsent as a protective mechanism that prevents the chromosome from breaking or fusion.

Telomere attrition :



Telomerase :

Enzyme which synthesizes telomeres.

Prevents cellular ageing.

AKA Immortality gene.

Cells with high telomerase activity → Germ cells, Stem cells.

Nil telomerase activity → Somatic cells.

Cancer cells usually have high telomerase activity.

- Dysregulated nutrient sensing :

  It is a mechanism of celllular ageing.

  Calorie restriction has shown to increase lifespan.

Active space

Sirtuins :

They are NAD dependent protein deacetylases.

They inhibit cellular ageing by reducing free radical injury, increasing insulin sensitivity, increasing DNA repair.

Sirtuins levels can be increased by :

- Calorie restriction.
- Wine consumption.

Sirtuins have a role in ageing, DM and cancer.

Cell/Condition	Stain
m/C Stain in Histopathology	Hematoxylin and Eosin.
m/C in Hematology	Romanowsky like Leishman Geimsa.
Reticulocyte	Supravital (Brilliant cresyl blue), New methyl blue.
Lymphoblast	PAS.
myeloblast	NSE, SBB, Oil Red-O.
monoblast	NSE.
Hairy cell	TRAP.
Lipid	Oil red O, sudan Black.
Iron	Prussian Blue.
Calcium	Von Kossa, alizarin red S.
Glycogen	PAS.
Copper	Rhodamine, rubeanic acid.
mast cell	Toluidine blue.
mucin	mucicarmine, Alcian blue.
Reticulin Fibres	Silver.
Elastin fibres	Van geison, VVG.
Collagen	masson trichrome.
melanin	masson Fontana.
H pylori	Warthin starry silver.
Cryptococcus	Indian ink.
Fungi	Silver methenamine, PAS, GMS.
Amyloid.	Congo red.

Active space

MCQs :

Q. A 54 year old man with a chronic cough has a squamous cell carcinoma diagnosed in his right lung. While performing a pneumonectomy, the thoracic surgeon notes that the hilar lymph nodes are small, 0.5 to 1.0 cm in size, and jet black in colour throughout. Which of the following is the most likely cause for this appearance to the hilar nodes?

A. Anthracotic pigment.

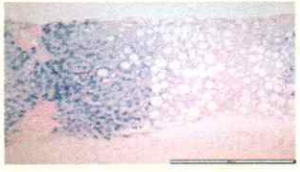
B. Lipochrome deposits.

C. Melanin accumulation.

D. Hemosiderosis.

E. Metastatic carcinoma.

Q. The figure below shows the liver biopsy of a 45 year old patient who presents with raised blood sugar levels, pedal edema, and brownish skin. Investigations show reduced total iron binding capacity. What is the special stain used and the thing stained?



A. Masson's trichrome and collagen.

B. Prussian blue and iron.

C. Reticulin stain and fibrosis.

D. Brilliant cresyl blue and reticulocytes.

Q. While in a home improvement center warehouse buying paint, a 35 year old man hears 'Look out below!' and is then struck on the leg by a falling pallet rack, which strikes him on his left leg in the region of his thigh. The skin is not broken. Within 2 days there is a 5 x 7 cm purple colour to the site of injury. Which of the following substances has most likely accumulated at the site of injury to produce a yellow-brown colour at the site of injury 16 days later?

A. Lipofuscin.

B. Bilirubin.

C. Melanin.

D. Hemosiderin.

E. Glycogen.

Active space

Q. Which of the following is not true about sirtuins?

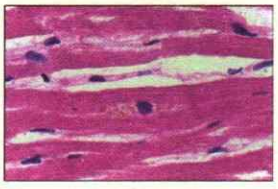
A. NAD dependent protein deacetylases.

B. Levels increased by calorie restriction.

C. Have a role in aging, cancer.

D. Decrease life span.

Q. An 84 year old man dies from complications of Alzheimer disease. At autopsy, his heart is small (250 gm) and dark brown on sectioning. Microscopically, the section is given below. Which of the following substances is most likely increased in the myocardial fibers to produce this appearance of his heart?



A. Hemosiderin from iron overload.

B. Lipochrome from wear and tear.

C. Glycogen from a storage disease.

D. Cholesterol from atherosclerosis.

E. Calcium deposition following necrosis.

6. A 49 year old man with a history of alcohol abuse has increasing abdominal girth. On examination his liver edge is firm. A liver biopsy shows cirrhosis, and individual hepatocytes contain red, globular inclusions positive for cytokeratin with immunohistochemical staining. Which of the following structural elements are these intracellular globules most likely to contain ?

A. Actin and myosin.

B. Cholesterol esters.

C. Fatty acids.

D. Fibronectin.

E. Intermediate filaments.

F. Microtubules

Alcohol liver disease → Mallory hyaline bodies made of intermediate filaments.

Active space

ACUTE INFLAMMATION

Inflammation 00:01:02

Inflammation is the response of vascularized connective tissue to injurious stimuli.

Injurious stimuli / precursors can be :

- Infection.
- Immune reactions.
- Foreign bodies.
- Tissue injury.

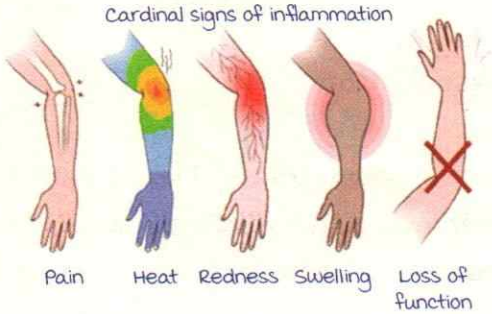
Inflammation

Acute	Chronic
1. Shorter duration	1. Longer duration
2. Sudden onset	2. Insidious onset.
3. Local signs and symptoms are more prominent.	3. Local signs and symptoms are less prominent.
4. Tissue healing and fibrosis are less prominent.	4. Tissue healing and fibrosis are more prominent.
5. Neutrophil mediated	5. monocyte/macrophage mediated.

Signs of inflammation 00:05:52

4 cardinal signs of inflammation as given by Roman scholar Celsus :

- Rubor/redness.
- Tumor/swelling.
- Calor/heat.
- Dolor/pain.



Virchow : Father of modern pathology.

He added the 5th sign of inflammation : Functio laesa/loss of function.

Active space

Mechanism of acute inflammation 00:10:16

All blood vessels are lined by endothelial cells.
CD-34 is the endothelial marker.
In a blood vessel the leukocytes occupy the center, and flow in a laminar fashion, surrounded by RBCs and plasma proteins or fluid which occupy the outer parts.
In acute inflammation, leukocytes in the middle must cross the endothelium and basement membrane to reach site of injury to kill the microbe.

Steps of acute inflammation :

- Vascular events :
    1. Early transient vasoconstriction : Lasts only a few seconds.
    2. Vasodilation.
    3. Increased vascular permeability.
    4. Stasis.
- Cellular events :
    1. Margination.
    2. Rolling.
    3. Adhesion.
    4. Transmigration.
    5. Chemotaxis.
    6. Opsonization.
    7. Phagocytosis.

Vasodilation 00:16:17

Post the early transient vasoconstriction → Arteriolar dilation.
Histamine is the usual mediator.
Increase in blood flow causes redness/rubor and heat/calor.

Increased vascular permeability is seen in the venules.
Histamine is the usual mediator.
This is the hallmark of acute inflammation.
Swelling /tumor due to leakage of protein rich fluid/exudate outside the blood vessel.

Active space

Difference between exudate and transudate :

Exudate	Transudate
Specific gravity > 1.020	Specific gravity < 1.020
Inflammatory edema.	Non-inflammatory edema.
Rich in proteins and cells.	Poor in proteins and cells.
Increased LDH.	Decreased LDH.

Mechanisms of increased vascular permeability :

1. Endothelial cell contraction / retraction / formation of endothelial gaps :
   - Usually affects post capillary venules.
   - Usually mediated by histamine and leukotrienes.
   - Responsible for immediate transient response.

2. Direct endothelial injury :

Mild	Severe
As in burns.	As in sepsis.
Responsible for delayed prolonged response.	Responsible for immediate sustained response.

3. Leucocyte mediated endothelial injury.
4. Increased transcytosis.

Stasis 00:27:42

Stasis is the slowing of blood flow due to leakage of fluid outside causing the RBCs to accumulate inside leading to hyper viscosity of blood.

Margination / pavementing 00:30:00

The process of redistribution of leukocytes from the centre to the margins of the blood vessels.

Active space

Rolling

00:32:23

The leukocytes begin to form loose attachments over the endothelium i.e., roll over the endothelium.

Rolling is mediated by certain molecules called Selectins.

Selectins are of three types, namely :

- E-selectin : Present on the endothelium.
- P-selectin : Present on the platelets and endothelium.
- L-selectin : Present on the leukocytes.

GlyCAM1, CD-34 are receptors present on the endothelium for L-selectin.

Sialyl Lewis X modified glycoproteins are receptors present on leukocyte for E and P selectin.

The expression of selectins is induced by IL-1 and TNF.

Redistribution of P-selectins present in Weibel-Palade bodies is mediated by histamine and thrombin.

Adhesion

00:40:49

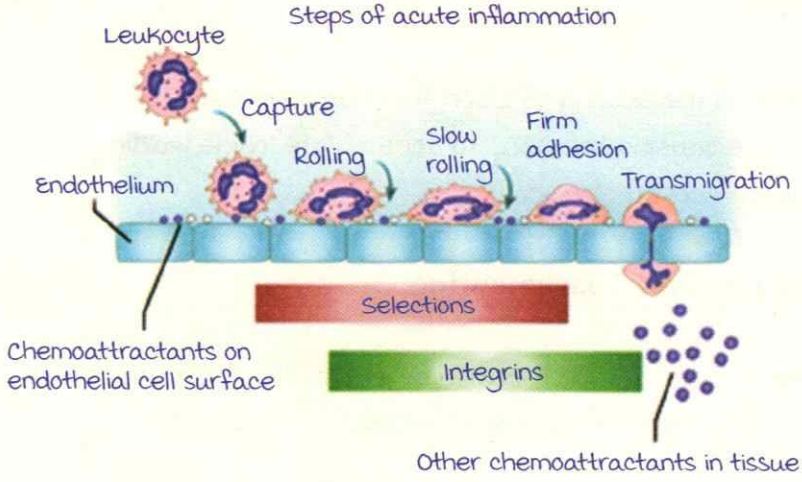
Firm adhesion of the leukocyte to the endothelium is called as adhesion.

Adhesion is mediated by certain molecules called _____

Integrins are of two types, namely :

- β 1 integrin / VLA4.
- β 2 integrin / LFA1 / MAC1.

Both of which are present on the leukocytes.



Active space

VCAM1 receptor present on endothelium for β 1 integrin / VLA4.
ICAM1 receptor present on endothelium for β 2 integrin/LFA1/ MAC1.

Transmigration / Diapedesis :
Movement of leukocyte across the endothelium or basement membrane (BM).
Mediated by PECAM1 / CD31.
The neutrophils synthesize collagenases / matrix metalloproteinases (MMP's) which dissolve the BM and facilitate crossing over the BM.

Chemotaxis 00:47:29

The movement of leukocyte in the direction of a chemical stimuli towards the site of injury.
It is unidirectional and targeted movement.

Chemotactic mediators are broadly :

- Exogenous mediators : Secreted outside the cell, e.g., bacterial cell wall products like N-Formyl methionine.
- Endogenous mediators : Secreted by the leukocyte itself, e.g., LTB4, IL-8, C5a [mnemonic : LIC].

Mechanism of chemotaxis :
Ligand binds to 7-transmembrane G protein coupled receptor → Increase in cytosolic calcium → Polymerization of actin → Chemotaxis.

Opsonization 00:52:53

It is the coating of microbes so that they are easily phagocytosed.
Opsonins used are :

- Fc fragment of IgG (Best opsonin).
- Complement products C3b, C4b, C5b.
- Serum proteins like fibrinogen, C-reactive protein.

Active space

Phagocytosis :

It is the process of killing the microbe.

Discovered by Elie Metchnikoff.

3 steps of phagocytosis :

- Recognition and attachment :
  By various receptors like scavenger receptors, mannose binding receptors and receptors for opsonins.
- Engulfment :
  The neutrophil enters the site of injury, where they form pseudopods which facilitates cup formation around the bacteria. → The cup then detaches to form a vesicle hosting the bacteria, this vesicle is called phagosome. → The phagosome then fuses with the lysosome to form phagolysosome containing lysosomal enzymes.
- Killing :
  It may take place via an oxygen dependent mechanism or an oxygen independent mechanism.

In oxygen dependent mechanism,

$$O_2 \xrightarrow{\text{NADPH oxidase}} O_2^-$$

$$O_2^- \xrightarrow[\text{dismutase}]{\text{Superoxide}} H_2O_2$$

$$H_2O_2 + Cl^- \longrightarrow HOCl.$$

This HOCl kills the bacteria.

H_2O_2 - halide is the most effective bacterial killing system.

Another minor oxygen dependent killing mechanism involves reactive nitrogen species which will lead to the formation of peroxynitrite which can kill the bacteria.

In oxygen independent mechanism, which is a minor killing system is mediated by enzymes like lysozyme, lactoferrin, major basic protein which is present in eosinophils and has got an anti-parasitic effect.

Active space

Frustrated phagocytosis :
It occurs when cell encounters materials that cannot be phagocytosed.
e.g., Immune complexes bound to basement membrane.
This is accompanied by the increased release of lysosomal enzymes.

Leukocyte function defects 01:08:40

Leukocyte function defects :

- Leukocyte adhesion deficiency Type I (LAD I).
- Leukocyte adhesion deficiency Type 2 (LAD 2).

LAD I	LAD 2
Both are autosomal recessive.	
Patients will present with recurrent infection.	
Pathogenesis : Defect in synthesis of β2 integrin CD11 / CD18.	Pathogenesis : Defect in synthesis of sialyl Lewis X modified glycoprotein.
Delayed separation of umbilical stump.	Sometimes associated with Bombay blood group.

Chronic Granulomatous Disease (CGD) :
75% cases are X linked recessive.
25% cases are autosomal recessive.
∴ more common in males.
Pathogenesis : Defect in NADPH oxidase which results in defective oxygen dependent killing.
Clinically, patient may present with increased risk of infections with catalase positive organisms.
Nitro blue tetrazolium test / NBT is the screening test for CGD.
Dihydrorhodamine test / DHR is the confirmatory test done by flow cytometry.

Active space

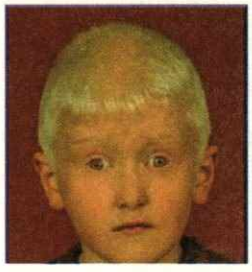
Chediak Higashi syndrome :

Autosomal recessive mode of inheritance.

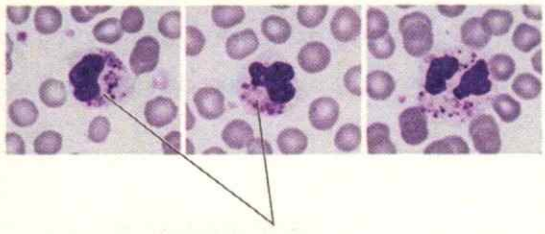
Pathogenesis : Defect in LYST/lysosomal trafficking regulator protein required for phagolysosome fusion.

Clinically, in addition to fever and recurrent infections patient can have oculocutaneous albinism, nerve defects or deafness and thrombocytopenia.

Peripheral smear can show giant granules in neutrophils.



Chediak Higashi syndrome (Albinism).



NET / Neutrophil extracellular traps 01:19:08

NETs are extracellular fibrillar network.

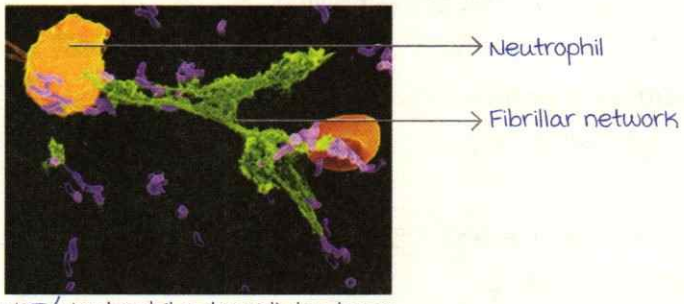
They are produced by neutrophils in response to severe infections.

It helps in limiting the spread of infection.

It produces a lot of antimicrobial substances.

Arginine is the amino acid which help in NET formation.

Some studies show that an increase production of these may cause an increased risk of autoimmune diseases like SLE.



NET/Neutrophil extracellular traps

Active space

Emperipolesis :

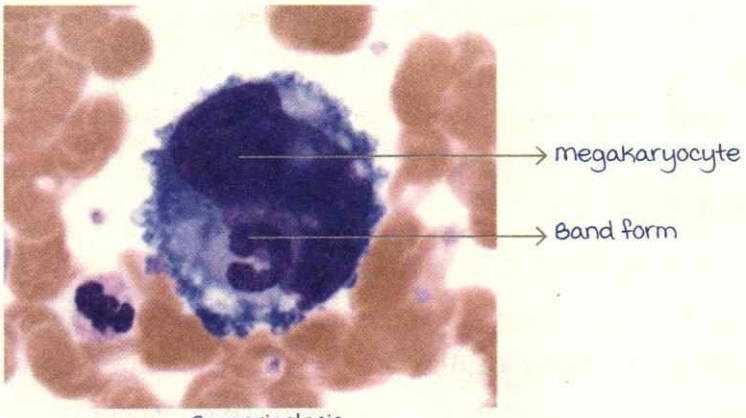
Cell within a cell appearance.

Most important differential diagnosis is phagocytosis.

The cell inside can come out with no abnormality which is not the case in phagocytosis.

Seen in :

1. Rosai Dorfman syndrome.
2. Chronic lymphocytic leukaemia.
3. Haematolymphoid disorders.
4. Myelodysplastic syndrome.



Emperipolesis

MCQs

Q. A 3 year old child has a history of reccurent infections with pyrogenic bacteria, Staph aureus. Neutrophilic leucocytosis is also present. Microscopic examination of biopsy obtained from that area shows microbial organisms but few neutrophils. An analysis of neutrophil function shows a defect in rolling. The child's increased susceptibility to infection is most likely caused by a defect in which if the following molecules :

A. Selectins.

B. NADPH oxidase.

C. LTB 4.

D. Integrins.

Q. A 2 year old boy presents with recurrent infections involving multiple organ systems. Extensive investigation results in diagnosis of chronic granulomatous disease. Which

Active space

of the following most closely characterizes the abnormality in his phagocytic cells?

A. Decreased killing of microrganisms because of enhanced production of hydrogen peroxide.
B. Deficiency of NADPH oxidase.
C. Impaired chemotaxis and migration.
D. Inability to kill streptococci.

Q. Which statement is true regarding NETS?

A. Produced by neutrophils in response to infectious pathogens and inflammatory mediators.
B. Present the spread of microbes by trapping them in their fibrils.
C. Provide a high concentration of antimicrobial substances at the sites of infection.
D. All of the above.

Q. In an experiment, Enterobacter cloacae organisms are added to a solution containing leukocytes and blood plasma. Engulfment and phagocytosis of the microbes is observed to occur. Next a substance is added which enhances engulfment, and more bacteria are destroyed. Which of the following substances in the plasma is most likely to produce this effect?

A. Complement C3b.
B. Glutathione peroxidase.
C. Ig M.
D. P-Selectin.
E. NADPH oxidase.

Q. Sequence of events in acute inflammation :

A. Vasodilation → Stasis → Transient vasoconstriction → Increased permeability.
B. Transient vasoconstriction → Stasis → Vasodilation → Increased permeability.
C. Transient vasoconstriction → Vasodilation → Stasis → Increased permeability.
D. Transient vasoconstriction → Vasodilation → Increased permeability → Stasis.

Active space

CHRONIC INFLAMMATION

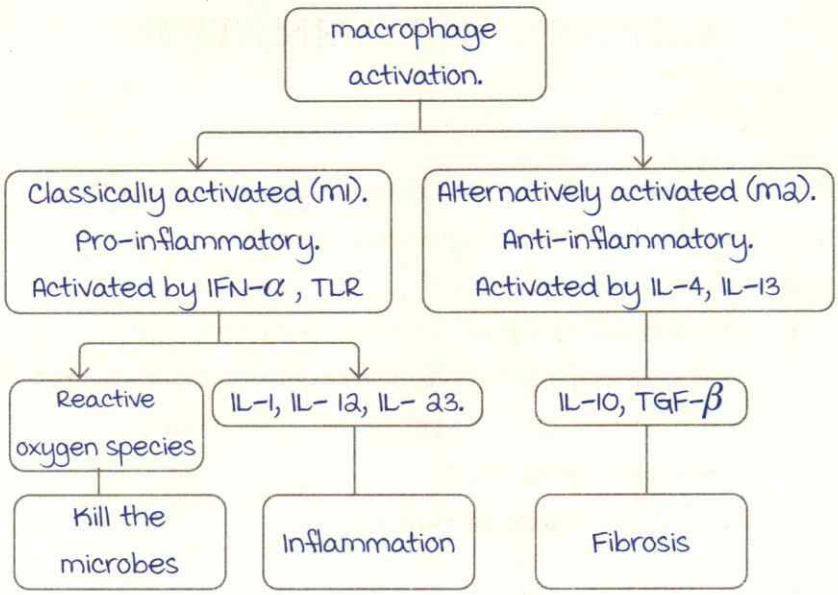
Chronic inflammation : Longer duration and insidious onset.
Most important cell : Monocyte/macrophage.
In chronic inflammmation,

1. Infiltration of tissue with mononuclear cells like lymphocytes, plasma cells or monocytes/macrophages.
2. Tissue destruction and tissue injury (hallmark of chronic inflammation).
3. Attempts at healing or repair.

Cells of chronic inflammation : Monocyte/macrophage.
Monocyte : Cell with horseshoe shaped nucleus which is produced from hematopoietic stem cell. Present in blood.
Tissue specific monocytes are called macrophages.
Monocytes take about 1 day to go to tissue from blood.

Tissue	Name of macrophage
Brain	Microglia
Lymph nodes	Sinus histiocytes
Bone	Osteoclast
Lung	Pulmonary alveolar macrophages (dust cells)
Liver	Kupffer cells
Spleen	Littoral cells
Placenta	Haufbauer cells
Kidney	Mesangial cells

Active space



Other cells of chronic inflammation : CD4+ T lymphocytes, plasma cells.

Granuloma

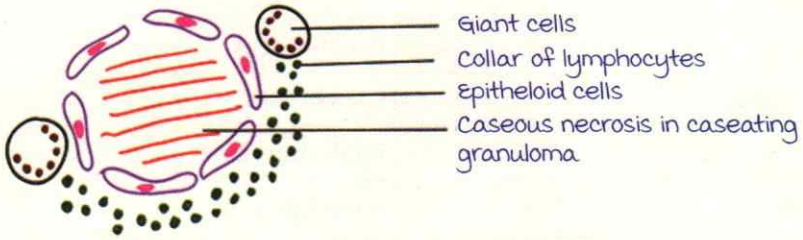
00:10:29

Collection of modified/activated macrophages : Epithelioid cells.

Epithelioid cells are surrounded by a collar of lymphocytes.

Giant cells may be seen.

Caseous necrosis in caseating granuloma.

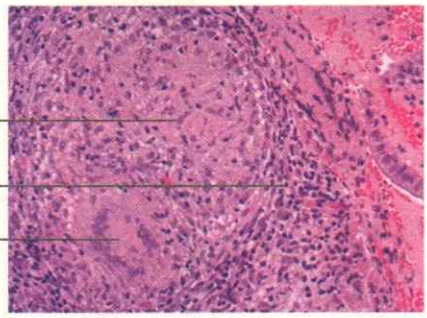


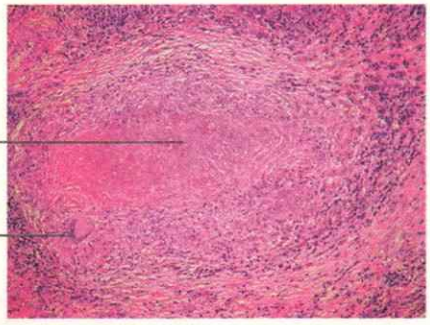
Epithelioid cells : Epithelium like appearance with slipper shaped nucleus.

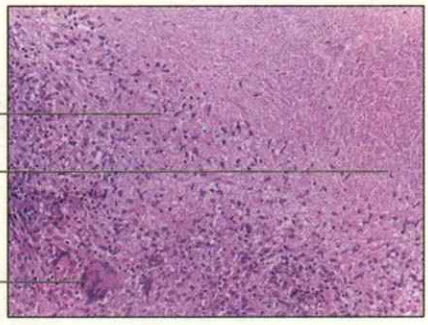
most important cell in a granuloma.

Giant cell is formed by the fusion of a large number of epithelioid cells.

Active space



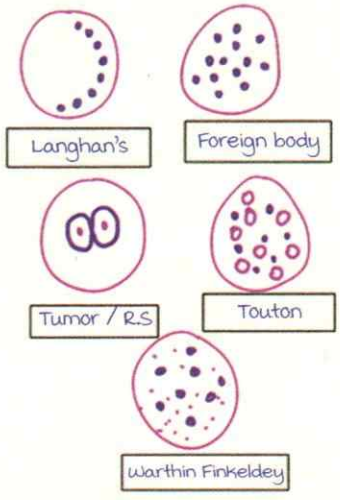




Types of giant cells

00:16:28

- Langhans giant cell : Seen in TB. Horseshoe/necklace arrangement of nuclei.
- Foreign body giant cell : Haphazard arrangement of nuclei. Foreign bodies like talc, sutures.
- Tumor giant cells : Seen in giant cell tumor of bones. Reed-Sternberg cells seen in Hodgkin's lymphoma. Nuclei in RS cell have owl's eye appearance.

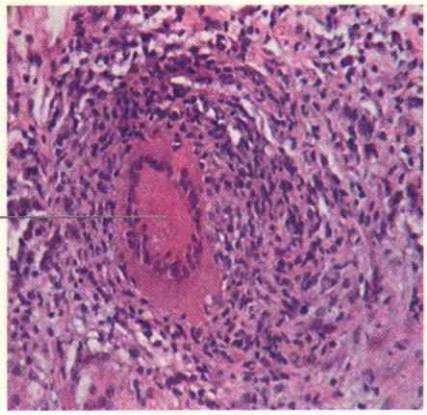


Active space

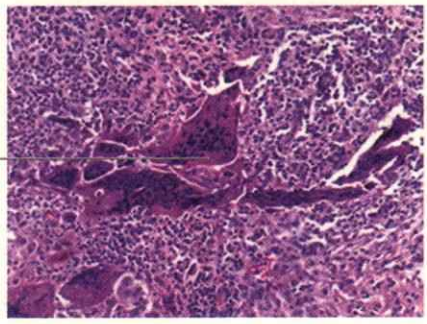
- Touton giant cells :
  Seen in xanthomas (lipid tumor).
  Foamy cytoplasm or vacuolated cytoplasm.
- Aschoff giant cell :
  Seen in rhematic fever, rheumatic heart disease.
  Aschoff body : Aschoff giant cell, lymphocytes, plasma cells, caterpillar cells.
- Warthin Finkeldey cells :
  Seen in measles.
  Intracytoplasmic or intranuclear inclusions seen.

Physiological giant cells : Megakaryocytes, osteoclast.

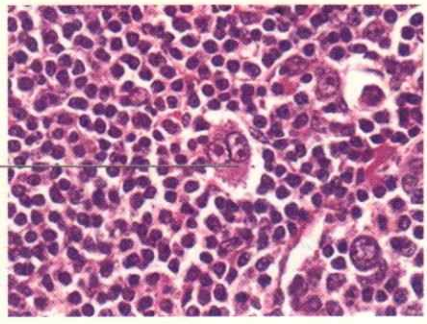
Langhan's giant cell (TB)



Foreign body giant cell.

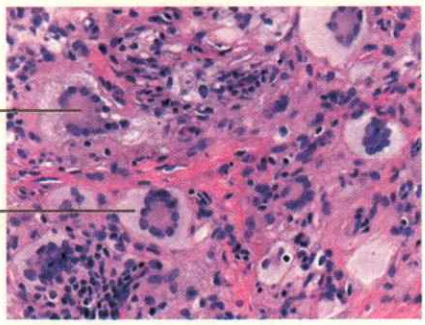


Reed-Sternberg cell.

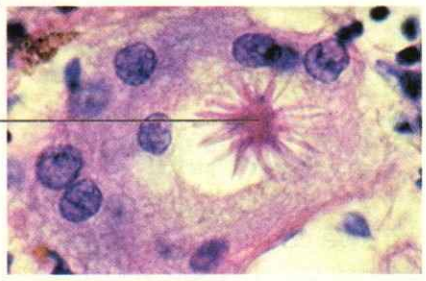


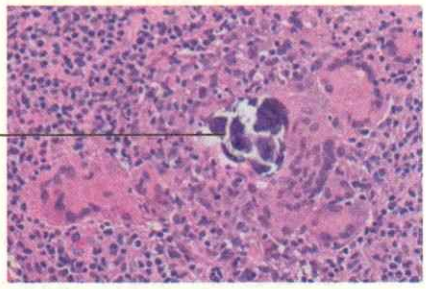
Owl's eye appearance :
Nucleus of Reed-Sternberg cell.
CMV inclusions.

Active space



Inclusions seen in giant cells :



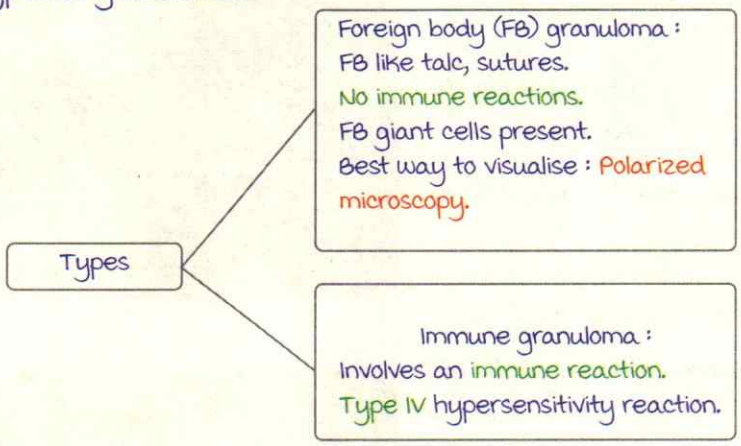


Pathogenesis of granuloma formation 00:23:38

Granuloma formation : Type IV hypersensitivity.
Most important cytokine : _____
Antigen presenting cell combines with CD4+ TH-1 lymphocyte to produce IFN-γ.
IFN-γ → Acts on macrophage → Activated macrophage → Epithelioid cells (hallmark of granuloma formation).
Epithelioid cells are fused to form giant cells and gradually forms a granuloma.

Active space

Types of granulomas :



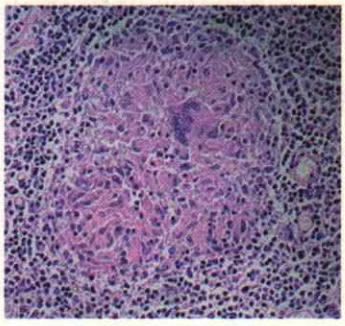
Granulomatous disorders

00:28:16

Infective causes :

- TB : Both caseating granuloma (m/c) and non-caseating granuloma.
  Gross specimen shows yellowish cheesy granuloma : Caseating granuloma.
  Microscopically : Epithelioid cells, Langhan's giant cell with pink caseating necrosis.
  Ziehl-Nielsen stain is done to visualize the acid-fast bacilli.

Caseous necrosis : Gross appearance



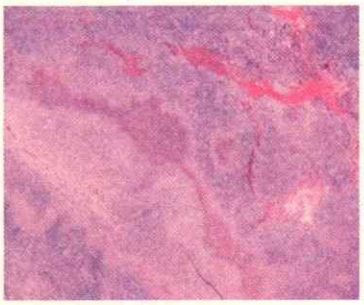
Microscopic appearance

- Leprosy : Tuberculoid leprosy (granuloma formation due to intact immunity as compared to lepromatous).
- Syphilis : Tertiary syphilis/gumma.
  Accompanied by lot of plasma cells.
- Durk's granuloma in malaria.
- Cat-scratch disease.
- Lymphogranuloma venerum.

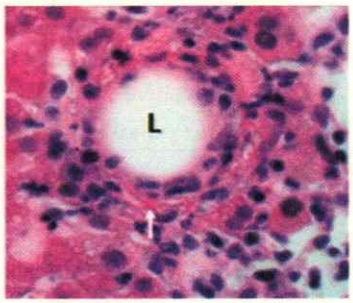
Stellate granuloma.

Active space

- Q fever : Doughnut granuloma/fibrin ring granuloma.
  Drug causing Q fever: Allopurinol.



Stellate granuloma.

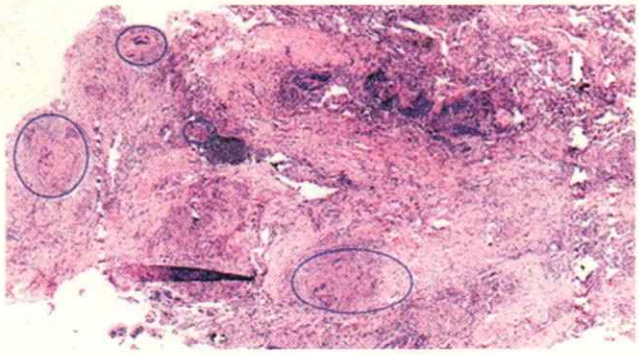


Doughnut ring granuloma.

Non-infective causes of granulomatous diseases

00:35:36

- Sarcoidosis :
  Presence of a non-caseating granuloma (naked granuloma).
  Caseating granuloma can also be seen.
  Asteroid body and Schaumann body seen (giant cell inclusions).
  metastatic calcification.
  Absence of lymphocytic collar : Naked granuloma.
- Crohn's disease.
- Giant cell arteritis (granulomatous arteritis).
- Churg-Strauss syndrome : Eosinophilic granuloma.
- Berylliosis.



Naked granuloma.

Active space

Systemic effects of inflammation :

- Fever : Cytokines involved are IL-1, TNF-α, IL- 6.
- Acute phase reactants :

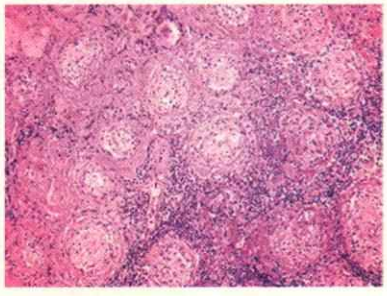
Positive (increased during inflammation)	Negative (decreased during inflammation)
CRP	Transferrin
Fibrinogen	Albumin
IL-6	Transcortin
Hepcidin	
Ferritin	
Haptoglobin	
Ceruloplasmin	
Factor VIII	
VWF	

Q. Which of the following is not a feature of sarcoid granuloma?

A. Non caseating.
B. Giant cells have cytoplasmic inclusions.
C. Fibroblastic proliferation at the periphery of granuloma.
D. Peripheral mantle of lymphocytes.

Ans : Naked granuloma is seen.

Q. The figure below is from a hilar lymph node from a 54 year old man who sought medical care for low grade fever, anorexia, fatigue, night sweats and persistent cough with hemoptysis. A chest X ray revealed a right apical infiltrate with cavitation while sputum examination revealed acid fast bacilli. This condition is typified by a form of inflammation that invariably includes which of the following?



A. Caseous necrosis.
B. Multinucleated giant cells.
C. Clusters of epithelioid cells.
D. Prominent granulation tissue.

Ans : A granuloma is not formed without a cluster of epithelioid cells.

Active space

Q. A 40-year-old woman had laparoscopic surgery 3 months ago. Now she has a small 0.5 cm nodule beneath the skin at the incision site that was sutured. Which of the following cell types is most likely to be most characteristic of the inflammatory response in this situation?

A. Mast cell.
B. Eosinophil.
C. Giant cell.
D. Neutrophil.
E. Plasma cell.

Ans : Likely to be a foreign body granuloma.

Q. Macrophages play an important role in phagocytosis and chronic inflammation. Which of the following cells perform the same function in liver?

A. Merkel cell.
B. Sinusoidal cell.
C. Kupffer cell.
D. Hepatocytes.

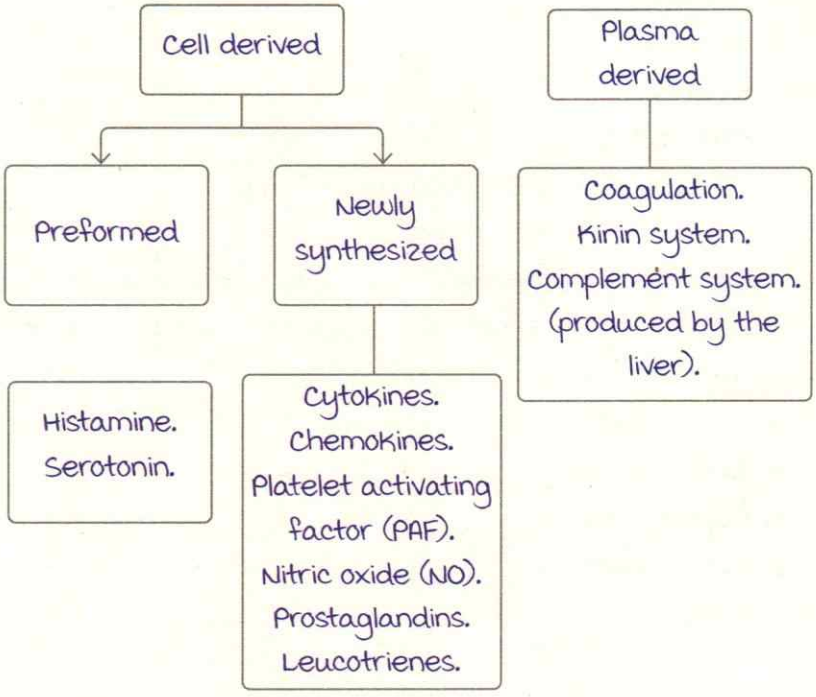
Active space

MEDIATORS OF INFLAMMATION

Mediators of inflammation

00:00:59

Mediators :



Role of mediators :

	Histamine	Serotonin
Sources	• Mast cell (richest source of histamine). • Basophil. • Platelets. Stain for mast cell → Toluidine Blue.	• Enterochromaffin cells of gastrointestinal tract (richest source). • Platelets.
Precursor	Histidine.	Tryptophan.
Functions common to both	1. Vasodilation. 2. Increased vascular permeability. 3. Bronchoconstriction.	1. Vasodilation. 2. Increased vascular permeability. 3. Bronchoconstriction.

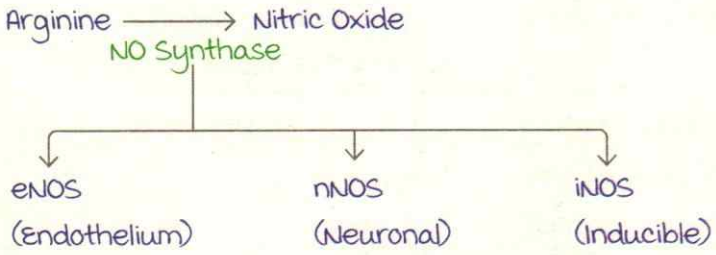
Active space

Platelet activating factor (PAF) 00:08:48

- Produced by :
  1. Platelets.
  2. Endothelial cells.
  3. Neutrophils.
- 1000 times more potent than histamine.
- Functions :
  1. Activates platelets (platelet aggregation).
  2. Vasoconstriction.
  3. Bronchoconstriction.

Nitric oxide (NO) :

- Colorless and odorless gas.
- Also called EDRF (Endothelium Derived Relaxation Factor).
- Produced from Arginine (amino acid).

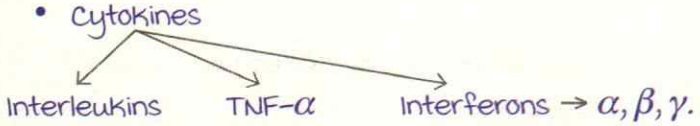


Functions :

1. Anti-microbial.
2. Smooth muscle relaxation.
3. Vasodilation.
4. Reduces platelet aggregation.

Cytokines 00:15:04

- Soluble polypeptides.
- Cytokines



Interleukins :

1. Acute infection : IL-1, IL-6.

Active space

2. Chronic infection : IL-12, IL-17.
3. Most common cytokine in fever : IL-1.
4. Most common cytokine in acute phase reactant : IL-6.

TNF alpha :

- MC cytokine in cancer cachexia.
- Reduces appetite by mobilizing lipid and protein.
- Cachexia : Lean and thin (emaciation).

Interferon alpha :

- Antimicrobial action.

Interferon gamma :

- Granuloma formation (MC cytokine : chronic inflammation).

Function	Cytokine
Pro inflammatory	IL 1, IL2, IL 4, IL6, IL8, IFN gamma, TNF alpha
Anti inflammatory	IL 4, IL 6, IL 10, TGF beta
Both pro and anti	IL 4, IL 6
Cancer cachexia	TNF alpha
Granuloma formation	IFN gamma
Fibrosis	TGF beta, PDGF
Angiogenesis	VEGF
Fever	IL 1
Eosinophil activation	IL 5

Chemokines

00:23:48

- Small molecules which act as chemo attractants (chemotaxis) for specific cell types.
- 3 types :
  1. CXC (α) : Cysteine-X-Cysteine (X : Any amino acid other than cysteine).
     Chemoattracted to neutrophils, Ex : (IL 8).
  2. C-C (β) : Cysteine-Cysteine together.
     Specific for : Eosinophils (Eotaxin), Macrophages

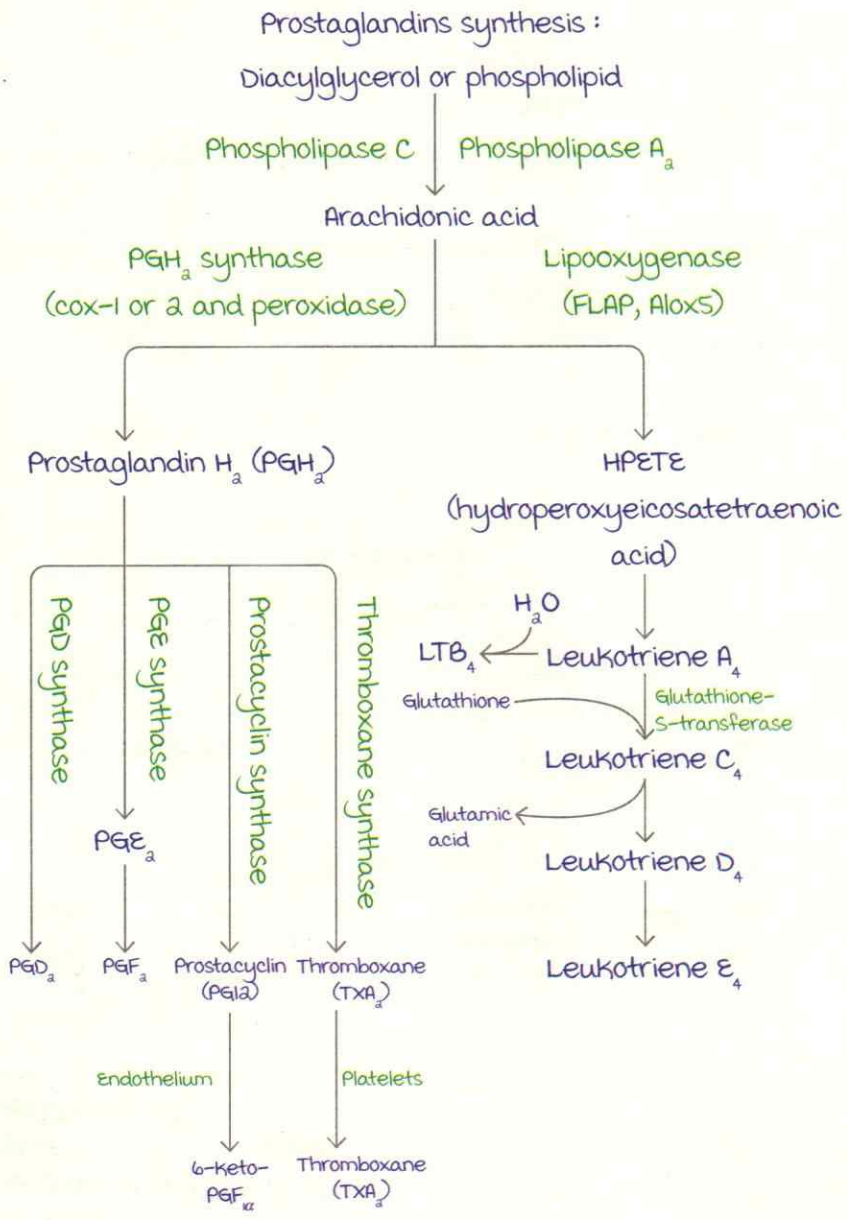
Active space

(MIP-1α), Monocytes (MCP-1).

3. Chemokine (γ) : Cysteine.
   Specific for : Lymphocytes (Lymphotaxin).
4. CX3C chemokine (δ) :
   Specific for : Monocytes (Fractalkine), T-cells.

Arachidonic acid metabolites 00:28:38

- Prostaglandins and Leukotrienes :
- 20 carbon poly unsaturated fatty acid (PUFA).



Active space

Functions of prostaglandins

00:33:08

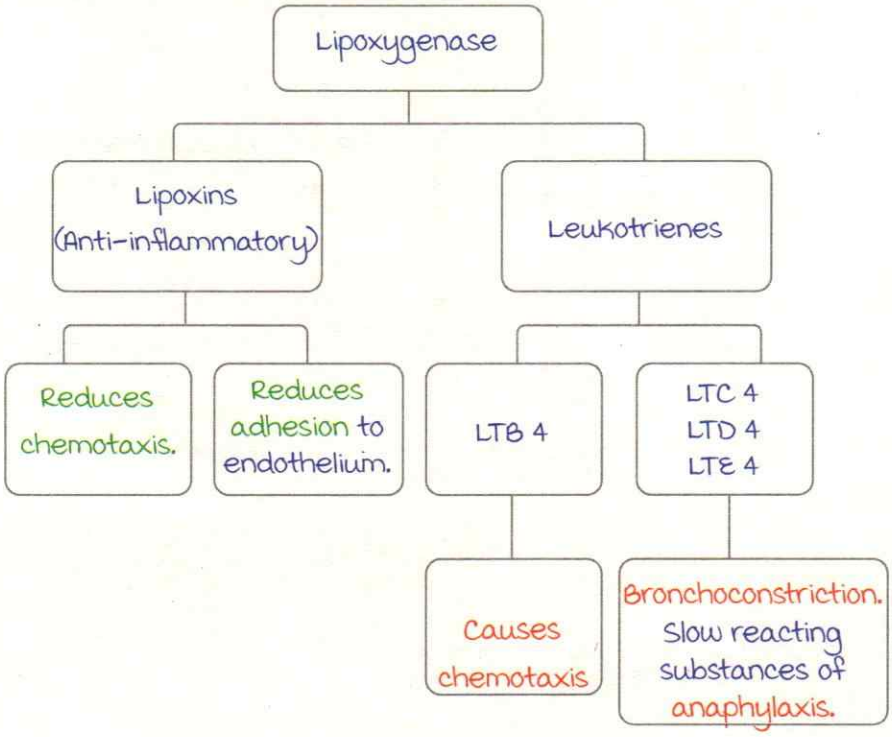
1. Prostacyclins (PGI 2) :
   - Vasodilation.
   - Decreases platelet aggregation.
   - Present on endothelial cells.

2. Thromboxanes (TXA-2) :
   - Vasoconstriction.
   - Increases platelet aggregation.

3. PGD2 : Neutrophil chemotaxis.
   PGE2 : Fever, Pain.
   PGF2α : Uterine and bronchial smooth muscle contractions.

Cyclooxygenase pathway is caused by 2 enzymes :
- COX 1 → most tissues.
- COX2 → Inducible in inflammation.

Lipoxenase pathway :

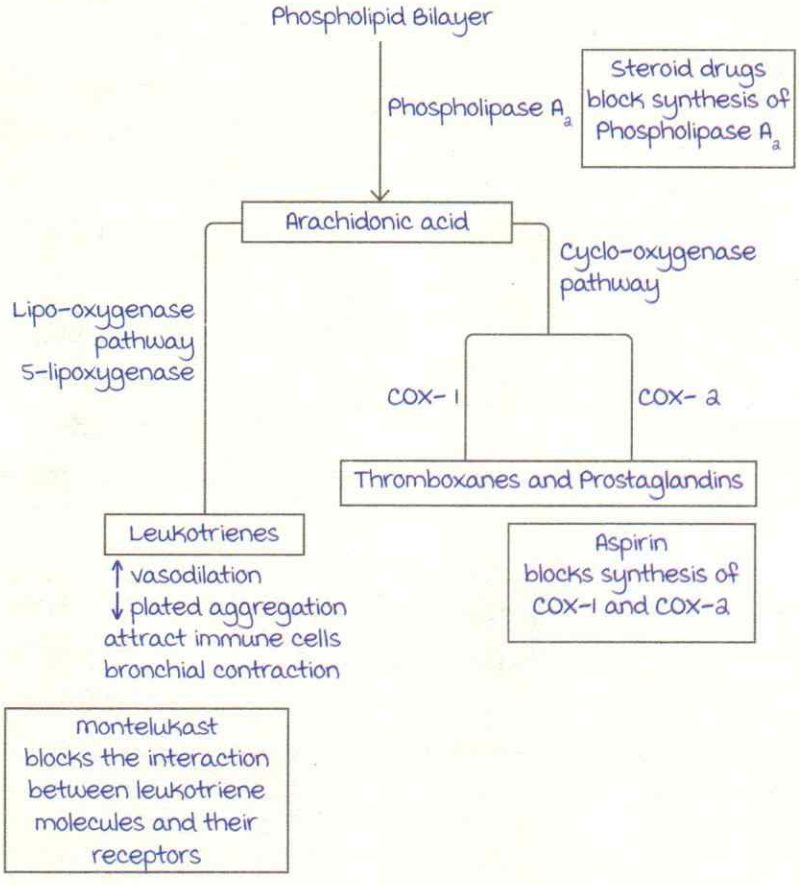


Active space

Pharmacological applications of AA pathway 00:40:05

1. Steroids :
   - Broad spectrum anti-inflammatory drugs.
   - It inhibits Phospholipase A2 → AA not formed → No inflammation.
2. Aspirin, Ibuprofen :
   - Cyclooxygenase inhibitors (COX-1 & COX-2 inhibitors) → No prostaglandins → No inflammation → No pain.
   - Aspirin causes gastric ulcers (COX-1 : Gastro protective).
3. Selective COX-2 inhibitors → more potent and less side effects.
4. Leukotriene receptor antagonists :
   - Leukotrienes → Bronchoconstriction → Inhibition can lead to Bronchodilation → Used for treatment of bronchial asthma.
   - Drugs : Montelukast, Zafirlukast.

Drugs inhibiting COX and LOX pathway
Eicosanoids Derived from Arachidonic Acid : Two Pathways



Active space

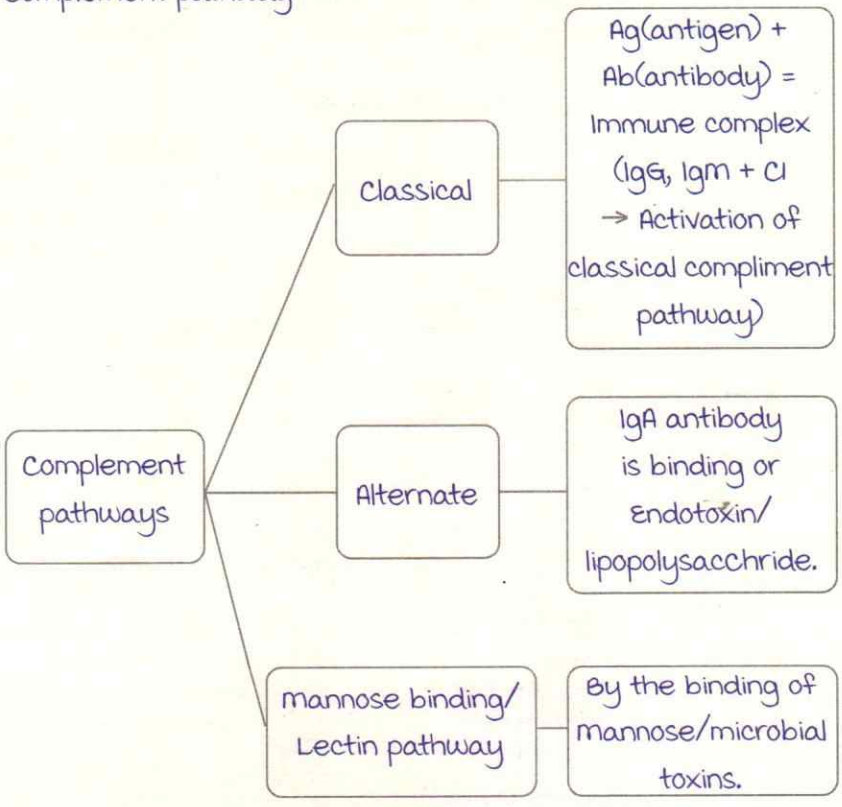
Action	mediator
Vasodilation	PGI2, PGD2, PGE2
Vasoconstriction	TXA2, LTC4, D4, E4
Increased vascular permeability	Leukotrienes C4, D4, E4
Chemotaxis	LTB4
Bronchoconstriction	LTB4

Plasma derived mediators

00:47:13

1. Complement system :
   - It is a series of 20 compliment proteins in plasma, secreted by liver.
   - Inactive precursors $\xrightarrow{\text{Proteolysis}}$ Active precursors.

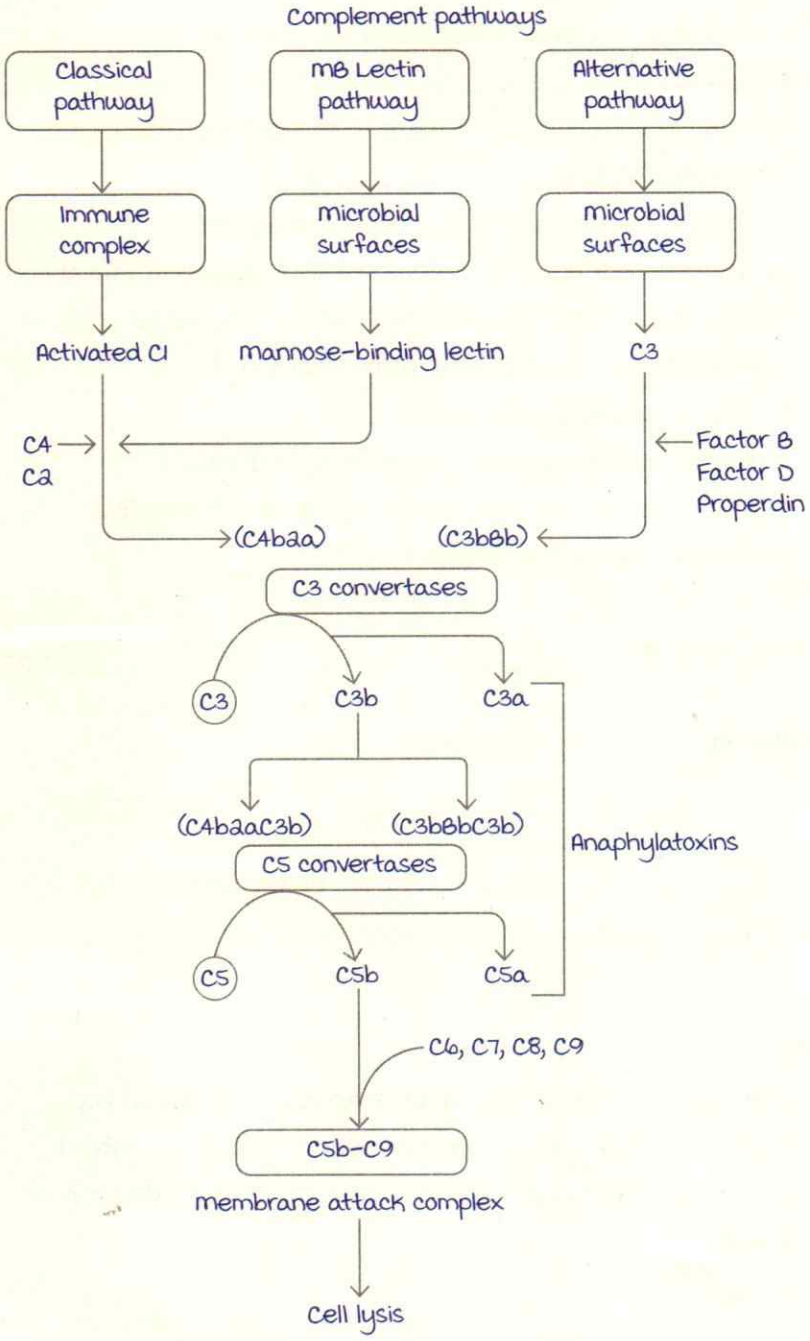
Complement pathway :



- most critical/important step in compliment cascade :

Active space

- Final step in Compliment activation : Formation of MAC pool (membrane attack complex) or C5b-9.



Functions of compliment pathways 00:52:46

1. Anaphylatoxins → C3a & C5a.
2. Chemotactic → C5a.
3. Opsonin → C3b.
4. MAC → C5b-9.

Active space

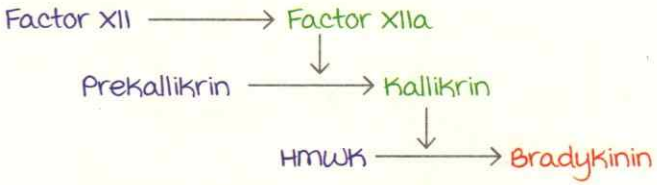
Clinical application :

Compliment factor deficiencies :

1. C 1 inhibitor → Hereditary angioneurotic edema.
   - Swelling of lips, eyes, larynx in patients.
2. C 2 (early component) → Increased risk of autoimmune disorders like SLE.
   - Most common compliment factor deficiency.
3. Deficiency of MAC → Increased risk of Neisseria infections.
4. Deficiency of CD55 (DAF)/CD59(MIRL) → Increased risk of PNH (Paroxysmal Nocturnal Hemoglobinuria).
   - Decay-accelerating factor (DAF).
   - Membrane inhibitor of reactive lysis (MIRL)
5. Deficiency of factor H, I, CD 46, Properdin → Atypical Hemolytic Uremic Syndrome (HUS).

Kinin system

00:58:25



Bradykinin causes pain & vasodilatation.

MCQ

Q1. Which one of the following substances is produced by the action of lipoxygenase on arachidonic acid, is a potent chemotactic agent and causes aggregation and adhesion of leucocytes?

A. C5a.
B. TXA2.
C. LTB4.
D. IL 8.

Q2. A 22 year old man develops marked right lower quadrant abdominal pain over the past day. On physical examination there is rebound tenderness on palpation over the right lower quadrant. Laparoscopic surgery is performed, and

Active space

the appendix is swollen, erythematous, and partly covered by a yellowish exudate. It is removed, and a microscopic section shows infiltration with numerous neutrophils. The pain experienced by this patient is predominantly the result of which of the following two chemical mediators ?

A. Complement C3b and IgG.
B. Interleukin-1 and tumor necrosis factor.
C. Histamine and serotonin.
D. Prostaglandin and bradykinin.
E. Leukotriene and HPETE.

Q3. A 45 year old woman has had a chronic, non-productive cough for 3 months, along with intermittent fever. She has a chest radiograph that reveals multiple small parenchymal nodules along with hilar and cervical lymphadenopathy. A cervical lymph node biopsy is performed. Microscopic examination of the biopsy shows noncaseating granulomatous inflammation. Cultures for bacterial, fungal, and mycobacterial organisms are negative. Which of the following chemical mediators is most important in the development of her inflammatory response ?

A. Interferon gamma.
B. Bradykinin.
C. Complement C5a.
D. Histamine.
E. Prostaglandin E2.

Q4. In a lab exercise for medical students, an unknown compound is studied. The students are informed that the compound has been isolated from endothelial cells and its synthesis can be inhibited by aspirin. In the lab, the students demonstrate that the compound is a potent vasodilator and platelet anti aggregant. The substance is most likely which of the following mediators?

A. LTC4.
B. LXA4.
C. TXA2.
D. PGI 2.

Active space

Q5. An episode of marked chest pain lasting 4 hours brings a 51 year old man to the emergency room. He is found to have an elevated serum creatine kinase. An angiogram reveals a complete blockage of the left circumflex artery 2 cm from its origin. Which of the following substances would you most expect to be elaborated around the region of tissue damage in the next 3 days as an initial response to promote healing?

A. Histamine.
B. Immunoglobulin G.
C. Complement component C3b.
D. Leukotriene B4.
E. Vascular endothelial growth factor.

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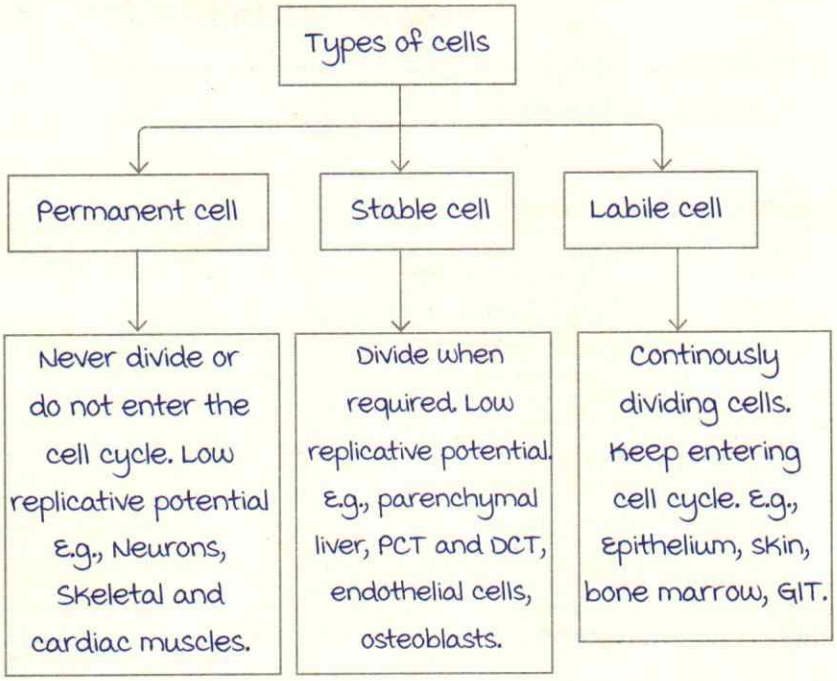
WOUND HEALING AND TISSUE REPAIR

Regeneration : Dead cells are replaced by same parenchymal cells.

E.g., Following resection of a lobe of liver for tumour, rest of the liver regenerates via hyperplasia.

Repair : Dead cells are replaced by fibrous connective tissue.

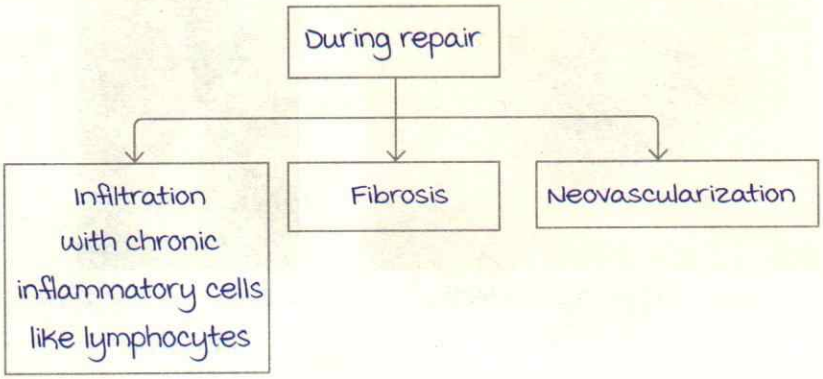


Following a brain injury, repair can happen only by neuroglia, not neurons.

Skeletal and cardiac muscle can adapt only by hypertrophy.

Repair

00:06:18



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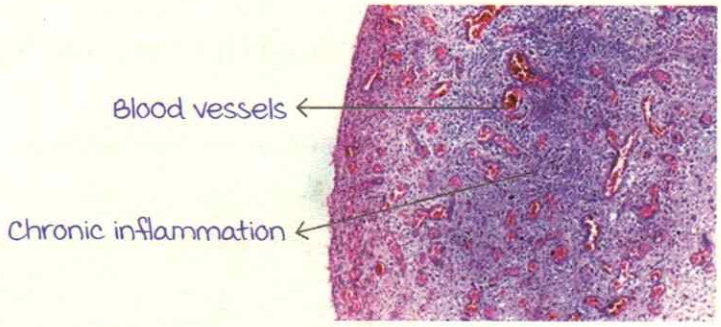
Hallmark of repair : Granulation tissue formation.

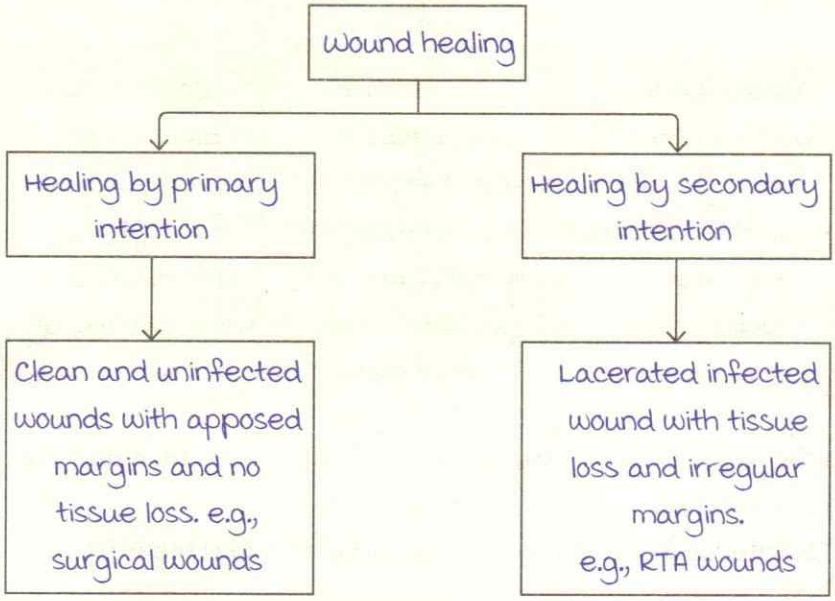
Hallmark of granulation tissue : New blood vessel formation.

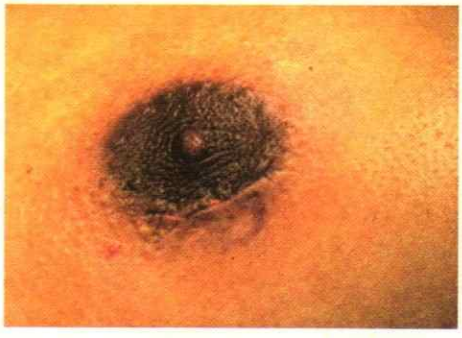
Cytokine helping in neovascularization : VEGF.



Granulation tissue apppears red because of new blood vessels formed, and edematous as these vessels are leaky.

Types of wound healing :





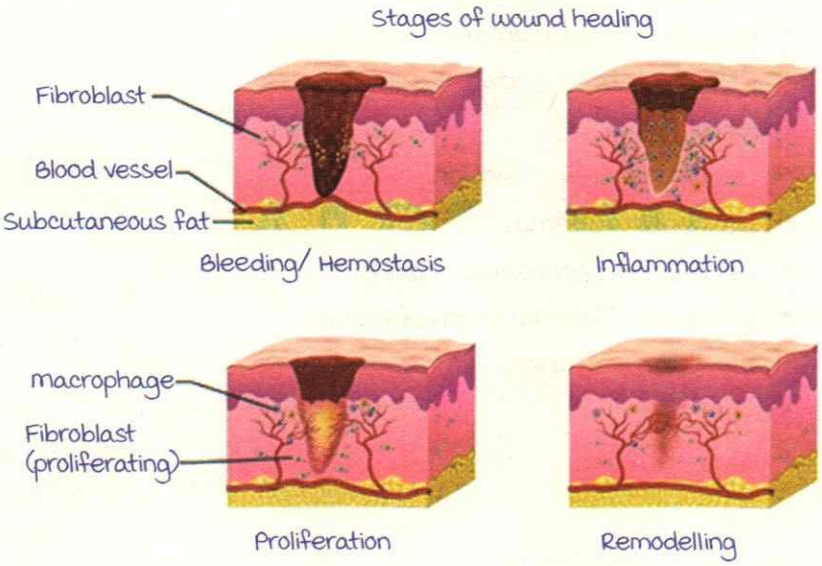
Healing by primary intention

Healing by secondary intention

Active space

Steps in wound healing

00:13:32



Stages :

1) Hemostasis : Stoppage of bleeding.
2) Inflammation : Acute inflammatory cells (neutrophils) arrive at the site of injury. This is followed by proliferation of monocytes, lymphocytes.
3) Proliferative phase : Repair occurs via prolifertaion of macrophages and fibroblasts.
4) Remodelling : Scar formation.

At 0 hours (immediate) :

- Hemostasis.
- With the help of fibrin.

Within 24 hours :

- Neutrophils from margins start coming towards the clot.
- Mitosis begins in the basal layer of epidermis.

After 24–48 hours :

- Dense neutrophilic infiltrate.
- Thin continuous epithelial layer is formed.

On Day 3 :

- Neutrophils are replaced by macropghages.
- Early granulation tissue.
- Collagen fibres are evident at the margins of wound.

Active space

On Day 5 :

- Maximum granulation tissue.
- Maximum neovascularization.
- Collagen fibres bridge the incision.

3rd week :

- Decreased inflammation.
- Decreased edema.
- Decreased neovascularization.
- Increased fibroblastic proliferation.
- Maximum collagen.

On Day 28 :

- Scar formation.

In secondary intention :

- More inflammatory cells.
- Bigger clot.
- More granulation tissues.
- Bigger scar.
- Wound contraction mediated by myofibroblasts occurs here, not seen in primary intention.

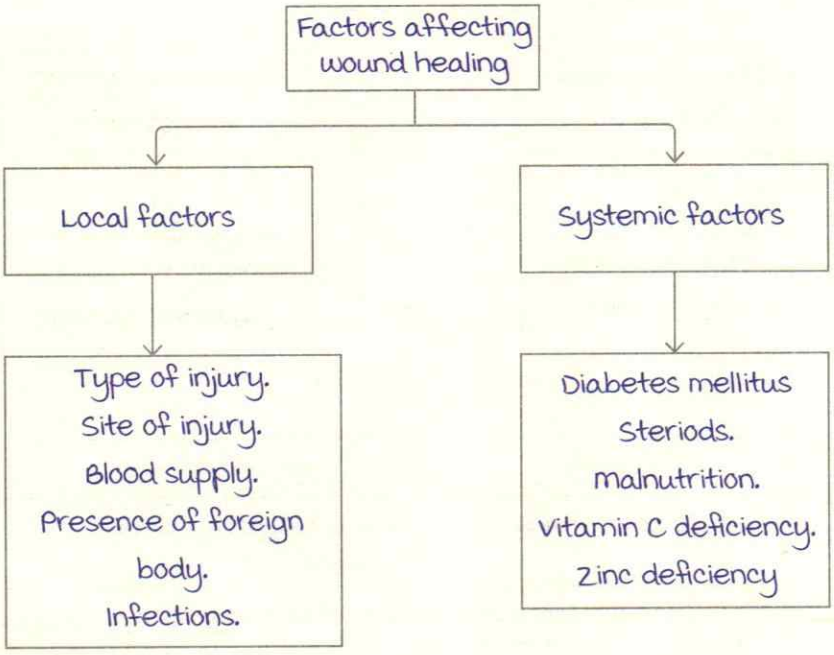
After 1 week : wound regains 10% of its normal strength.
After 3 months (approx. 12 weeks) : 70–80% of its strength.
Wound never regains its original strength.

Initial collagen formed is type III collagen.
Type III is replaced by Type I collagen.

Type I collagen :
more abundant,
Strong and has the highest tensile strength.
At the end the ratio of Type I collagen : Type III collagen : 4:1.

Active space

Factors affecting wound healing 00:26:42



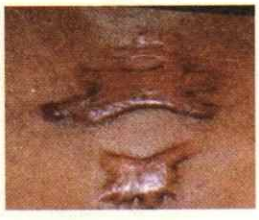
most common cause of delayed wound healing : Infections.

Collagens :
Triple helical structure.
Vitamin C is required for hydroxylation and crosslinking of collagen.

4 types :
Type I : most abundant, maximum tensile strength. Seen in skin, bones and tendons.
Type II : Present in vitreous humour and cartilage.
Type III : Present in Keloid, uterus and granulation tissue.
Type IV : Basement membrane.

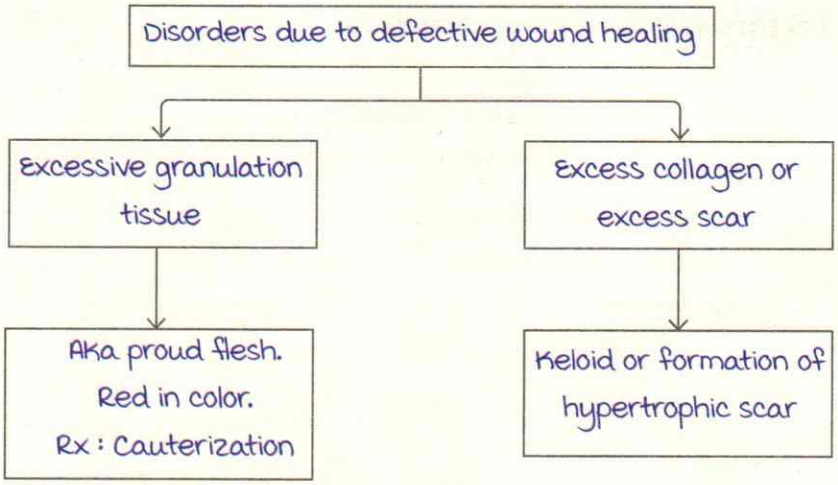
Disorders due to defective wound healing 00:31:58

Keloid



Hypertrophic scar

Active space



Keloid	Hypertrophic scar
Scar crosses wound margins	Scar raised just above the surface
Donot regresses spontaneously	Spontaneous regression
Thick, haphazard collagen bundles	Thin orderly arrangement of collagen bundles
Masson's trichrome stain is used for demonstation	-

Keloid induction for cosmetic purposes :

Desmoid : Excessive proliferation of fibroblasts.

Q. A 19 year old truck driver is involved in a collision. He incurs blunt force abdominal trauma. In response to this injury, cells in tissues of the abdomen are stimulated to enter the G1 phase of the cell cycle from the G0 phase. Which of the following cell types is most likely to remain in G0 following this injury?

a. Smooth muscle.
b. Endothelium.
c. Skeletal muscle.
d. Fibroblast.
e. Hepatocyte.

Active space

Q. A 36 year old woman has a laparotomy performed for removal of an ovarian cyst. She recovers uneventfully, with no complications. At the time of surgery, a 10 cm long midline abdominal incision was made. The tensile strength in the surgical scar will increase so her normal activities can be resumed. most of the tensile strength will likely be achieved in which of the following time periods ?

a. One week.
b. One month.
c. Three months.
d. Six months.
e. One year.

Q. A 22 year-old man incurs a stab wound to the chest. The wound is treated in the emergency room. Two months later there is a firm, 3x2 cm nodular mass with intact overlying epithelium in the region of the wound. On examination the scar is firm, but not tender, with no erythema. This mass is excised and microscopically shows fibroblasts with abundant collagen. Which of the following mechanisms has most likely produced this series of events ?

a. Keloid formation.
b. Development of a fibrosarcoma.
c. Poor wound healing from diabetes mellitus.
d. Foreign body response from suturing.
e. Staphyloccocal wound infection.

most common site of Keloid formation : Chest or sternal region.

Treatment of Keloid :

Intralesional injections like Triamcilone.

Hypertrophic scar regresses spontaneously.

No treatment required.

Exuberant granulation tissue treated by cautery.

Active space

HEMODYNAMIC DISORDERS

Hyperaemia & congestion 00:02:00

Increased blood volume in the dilated vessels.

Hyperaemia	Congestion
Active	Passive
Red in colour (due to increased Oxygenated blood)	Blue, red in color (due to deoxygenated blood)
Arteriolar dilatation	Impaired venous outflow
Example : Inflammation	Example : Right heart failure

Examples of congestion :

Acute pulmonary congestion :

Characterized by focal hemorrhages, alveolar and septal edema.

Chronic pulmonary congestion :

Heart failure cells.

In CHF : Hemosiderin laden microphages in lungs are seen.

Stain : Prussian blue stain/pearl's stain.

Acute hepatic congestion : Centrilobular necrosis, fatty change.

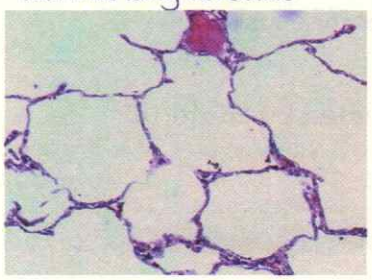
Chronic hepatic congestion : Nutmeg liver.

Chronic venous congestion in spleen : Gamma gandy body.

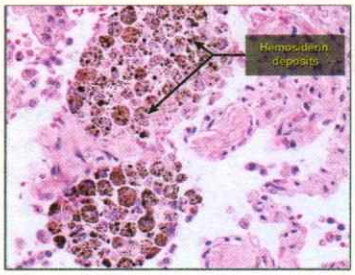
↓

Fibrosis, calcification, hemorrhage and hemosiderin.

Normal lung alveolae

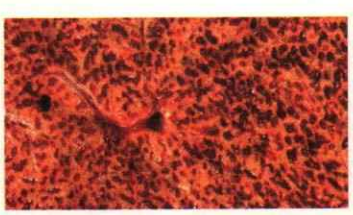


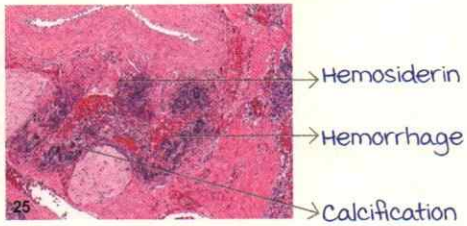
Heart failure cells



Active space

Nutmeg liver





Thrombosis

00:10:35

Thrombi is an aggregate or a mass of platelets.

Causes of thrombosis : Virchow triad :

1. Endothelial injury.
2. Alterations in normal blood flow (stasis or turbulence).
3. Hypercoagulability of blood.

Causes of Hypercoagulability of blood :

Primary cause/genetic

- Factor 5 Leiden mutation (mc)
- Prothrombin gene mutation
- Protein C & S deficiency
- Antithrombin deficiency
- Hyperhomocysteinemia

→ venous thrombosis

(Arterial thrombosis)

Dysfibrinogenemia

Secondary/acquired

Pregnancy, OCP,
Obesity
Nephrotic syndrome
Prolonged immobilization
surgery
microangiopathic
hemolytic anemia
TTP, HUS, DIC.
APLA
Hyperhomocysteinemia
(due to Vitamin B12
deficiency).

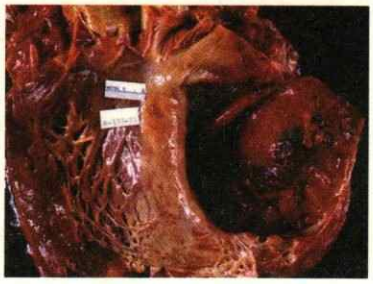
Active space

Types of thrombus

00:15:58

Mural thrombi	Arterial thrombi	Venous thrombus
Originates in heart / aorta & attached to the wall	Occurs in rapidly flowing arterial blood	Occurs in slow moving blood of veins
	Turbulence	Stasis
	Propagates retrograde to the point of attachment	Develops along the direction of blood flow
	Grossly white in color as more platelets present.	Red in color, more RBCs present.

Mural thrombi



Lines of Zahn :

Alternate light (due to platelets) and dark (due to RBC) areas.

Seen in arterial & venous thrombosis.

To differentiate,

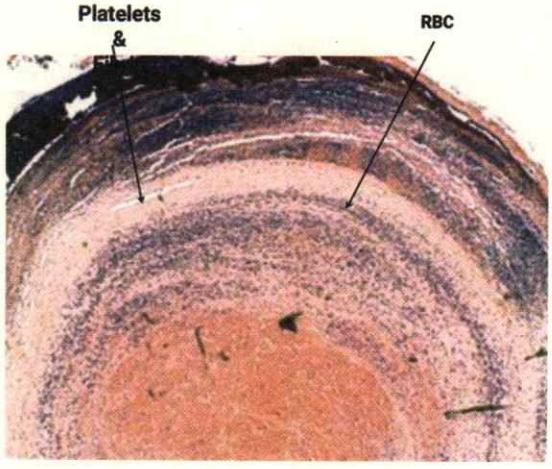
Antemortem clot : Lines of Zahn present.

Post-mortem clot : Lines of Zahn absent.

It is gelatinous.

Lower portion is red as RBC settle down by gravity.

Upper portion is yellowish because of plasma accumulation.



Active space

Fate of thrombus : (mnemonic : DOPE)

- Dissolution
- Organisation
- Propagation
- Embolism

Emboli

00:22:54

Embolus is a detached intravascular solid, liquid/gaseous mass carried by the blood stream to a site distant from its original site.

Pulmonary emboli [PE]

MCC : DVT [deep vein thrombosis].

Usually, asymptomatic due to the dual blood supply.

Two types PE :

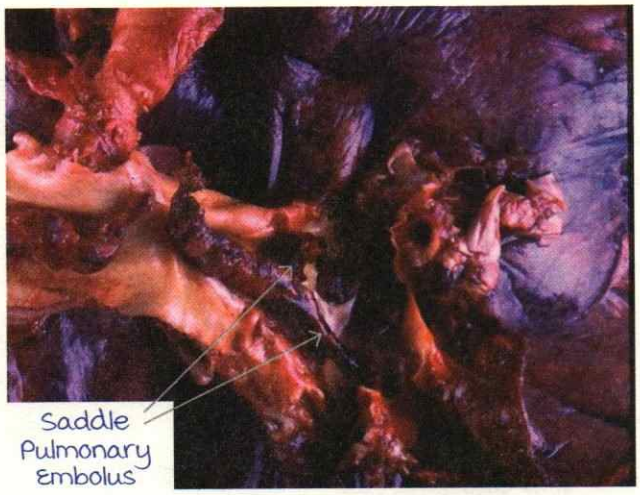
Saddle embolus :

Present at the bifurcation of the pulmonary vasculature.

It can lead to sudden cardiac death.

Paradoxical emboli :

It can pass through inter arteriolar/interventricular defect and reach the systemic circulation.



Saddle Pulmonary Embolus

Active space

Fat embolism :

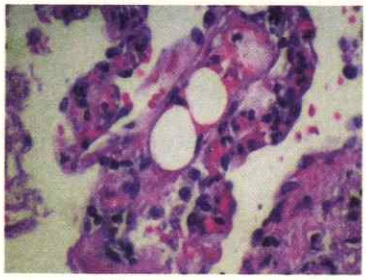
MCC : Fracture of a long bone.

Develops 1 to 3 days after a fracture

C/F ; Dyspnoea, delirium, decreased platelet count.

Microscopically : Fat globules in urine.

On chest x ray : Bat wing appearance.



Air embolism and Amniotic fluid embolism 00:28:56

Air embolism :

A/K/A Caisson's disease, Decompression sickness.

Seen in deep sea divers :

Rapid change in atmospheric pressure

↓

Increased production of nitrogen bubbles

>100 ml air is required to produce air embolism.

C/F : Bends (gas bubbles in the joint produce pain).

Chokes (gas bubbles in lung).

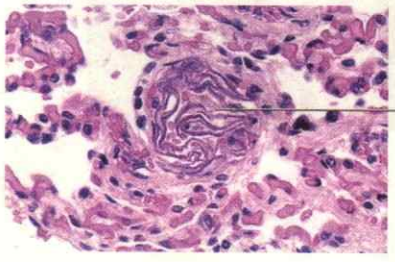
Amniotic fluid embolism :

It is seen as a pregnancy / labour complication.

It is seen in post-partum period / during labour.

Tear in placental membrane : The fetal tissue enters maternal circulation.

Microscopically : Squamous epithelial cells, lanugo hair, fat from vernix casiosa.



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Infarct

00:33:28

An infarct is a localised area of coagulative necrosis.

It is wedge shaped.

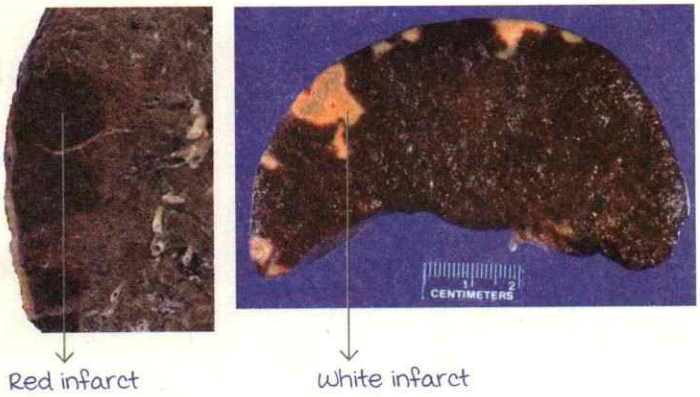
Two types :

Haemorrhagic/red infarct	Pale/white infarct
Seen in organs with dual blood supply. e.g., GIT, lungs.	Seen in organs with end arterial circulation. e.g., heart, kidney, spleen.
Seen in loose tissues – ovaries.	Seen in solid organs.
Ill-defined margins	Well defined margins

Liver shows both white & red infarcts.

Lung : Red infarct

Wedge shaped spleen : White infarct



Red infarct White infarct

MCQs :

Q. A 23 year old man undergoes surgery for fracture of pelvis and left femur resulting from a motor vehicle accident. The next day he develops dyspnea, speech difficulty and a petechial skin rash. Which of the following types of embolism is the likely cause of these findings?

A. Air

B. Amniotic fluid

C. Fat

D. Paradoxical

Active space

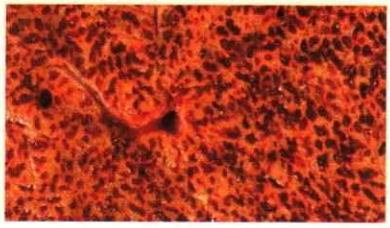
Q. What does the image below indicate :

A. Sago spleen – Amyloidosis.

B. Nutmeg liver – red areas are viable pericentral, white areas are periportal necrotic.

C. Red areas are necrotic near central vein while white areas are viable,fibrotic periportal areas.

D. Lardaceous spleen.



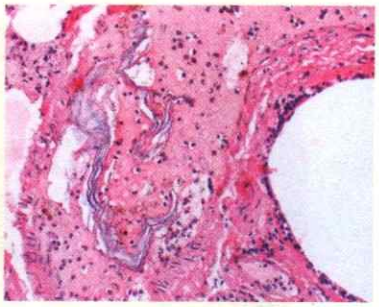
Q. An autopsy from the lung revealed presence of laminated swirls of squamous cells in pulmonary arteriole as shown below. What is the most likely pathogenesis?

A. Pulmonary embolism.

B. Air embolism.

C. Marrow embolism.

D. Amniotic fluid embolism.



Active space

NEOPLASIA BASICS

Basics of neoplasia :

- Neo means New.
- Plasia means Growth.

Neoplasm : Any new growth independent of growth factors.

Divided into two types:

- Benign tumours.
- Malignant tumours.

Desmoplasia :

- Extreme fibrosis leading to hard tumours.
- more likely to be malignant.

Terminologies 00:05:12

1. Benign tumours :

- Usually ends in suffix : oma.
- Epithelial origin : Papilloma.
- mesenchymal origin :
  - Lipoma.
  - Osteoma.
  - Chondroma.
  - Fibroma.
  - Adenoma (Tumour constituting of glands).

2. Malignant tumours :

- Epithelial origin :
  - Called as carcinoma.
  - Eg : Squamous cell carcinoma.
    - Transitional cell carcinoma.
    - Adenocarcinoma.
- mesenchymal origin :
  - Called as sarcoma.
  - Eg : Osteosarcoma.
    - Chondrosarcoma.

Active space

Fibrosarcoma.

Leiomyosarcoma.

Exceptions :

Malignant tumours ending with suffix oma :

- Melanoma.
- Chloroma :

  Soft tissue involvement of AML.

  Most common AML resulting in chloroma : AML M2.

  Most common site of chloroma : Orbit.

  Most common presentation : Proptosis.

  Also known as granulocytic sarcoma.
- Seminoma.
- Lymphoma.
- Teratoma.

3. Mixed tumours :

Different germ layer derivative.

Teratoma :

Derivative of ≥2 germ layers.

- Benign : Mature teratoma.
- Malignant : Immature teratoma.
- Monodermal teratoma :

  Single germ layer.

  Struma ovarii.

Pleomorphic adenoma :

- Usually affects salivary gland.
- Most commonly affected : Parotid gland.
- Biphasic tumour
- Shows two components :

  Epithelial component : Glands.

  Mesenchymal component : Chondromixoid tissue.

Wilm's tumour :

- Triphasic tumour.
- Three components :

  Epithelial component.

  Mesenchymal component.

Active space

Blastemal component.

4. Choriostoma :

- Ectopic rest of normal tissue.
- Normal tissue in abnormal location.
- Eg : Pancreatic tissue in the stomach.

5. Hamartoma :

- Haphazard/abnormal/disorganized proliferation of tissues indigenous to the site of origin.
- Eg : Pulmonary hamartoma :

  Now considered as a benign tumour.

  Some rearrangement in chromosome 12 have been identified.

Properties of a tumour 00:17:04

1. Anaplasia :

Lack of differentiation.

Differentiation : Defined as the structural and functional similarity to original cell.

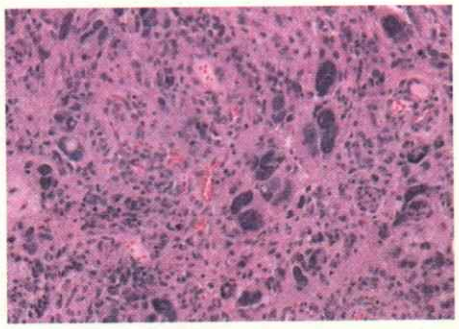
- Pleomorphism : Variation in size and shape of cell.
- High Nucleus : Cytoplasmic (N/C) ratio :

  Normal N/C ratio : 1:4 to 1:6.

  Malignant cells N/C ratio : 1:1.
- Hyperchromatic nuclei.
- Prominent nucleoli.
- Loss of polarity.
- Abnormal mitosis :

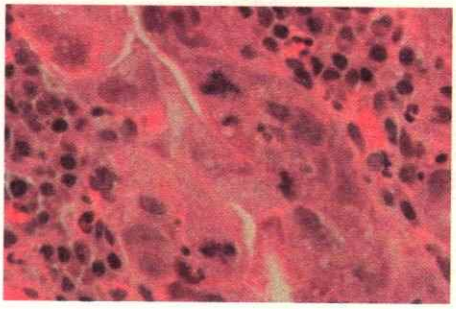
  Bipolar mitosis.

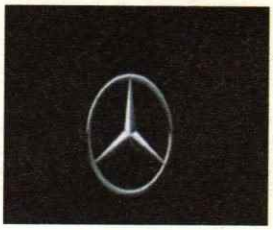
Anaplasia



Active space

Tripolar atypical mitosis : mercedes Benz sign.





2. Rate of growth :

- Benign tumor : Slowly growing.
- Malignant tumor : Rapidly growing.
- Minimum tumour weight which can be clinically detected : 1 $g/10^9$ cells.
- Maximum tumour weight usually compatible with life : 1 $Kg/10^{12}$ cells.

3. Local invasion

Benign tumours :

- Usually encapsulated.
- No local invasion.

Malignant tumours :

- Non encapsulated.
- Local invasion present.
- Eg : Carcinoma lung invading trachea, oesophagus.

4. Metastasis :

- Distant spread of tumour.
- Most important point to differentiate benign from malignant tumour : metastasis > local invasion.
- Hallmark of malignancy : Anaplasia.

	Benign	malignant
Anaplasia	Absent	Present
Growth	Slow	Rapid
Local invasion	Absent	Present
metastasis	Absent	present

Active space

Two malignancies which do not metastasize :

- Basal cell carcinoma (Rodent ulcer).
- Glioma.

Routes of metastasis 00:32:25

1. Lymphatic route :

Most carcinomas metastasize by this route

Exceptions :

- Follicular carcinoma thyroid.
- Choriocarcinoma.
- Hepato cellular carcinoma.
- Renal cell carcinoma.

2. Haematogenous :

Most sarcomas metastasize by this route.

Exceptions :

- Synovial sarcoma.
- Rhabdomyosarcoma.

Invade vein more than artery (Due to thinner walls of vein).

3. Direct seeding of body cavities :

- Mucinous carcinoma ovary/appendix spread through peritoneum : Pseudomyxoma peritonei.

4. Transcoelomic spread :

- Krukenberg tumour :

  Spread of carcinoma stomach to other organs via peritoneum, like ovary.

Terms 00:37:33

1. Metaplasia :

- Reversible change.
- One differentiated cell type to another differentiated cell type.
- Examples :

  Ciliated epithelium to squamous epithelium in smokers.

Active space

Barrett's oesophagus.

Vitamin A deficiency.

Myositis ossificans.

1. Desmoplasia :

- Abundant fibrosis/collagen laid down by a tissue.
- This makes the tissues hard.

2. Anaplasia :

- Lack of differentiation.
- Irreversible.
- Breach of basement membrane.

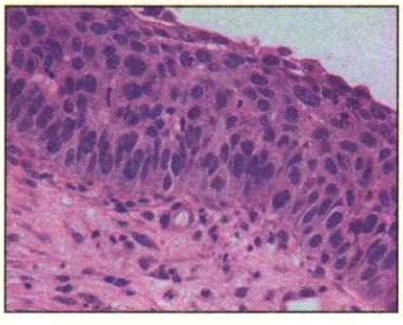
3. Dysplasia :

- Disordered growth/proliferation.
- Show anaplasia.
- Partially reversible.
- Example : Carcinoma in situ.

  Basement membrane is intact.

  Malignant cells are limited by basement membrane.

  PAS stain used for identification of carcinoma in situ (stains basement membrane: Magenta colored).



Cell cycle

00:44:42

Active space

Phases of cycle :

1. G0 Phase :

- Resting phase.

2. G1 Phase :

- Gap 1 phase.

- Prepares itself for DNA replication.

3. S Phase :

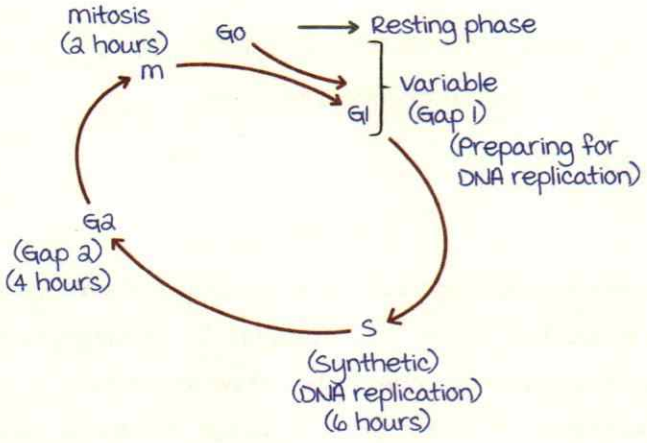
- Phase of DNA replication.
- Approximately 2 hours duration.
- Phase of no return.

4. G2 Phase :

- Gap 2 phase.
- Prepares itself for mitosis.
- Approximately 4 hours duration.

5. M Phase :

- Mitosis.



Longest phase : G0 or G1 phase (variable).

Most radiosensitive phase of cell cycle : G2M phase (M > G2).

Most radio resistant phase of cell cycle : S phase.

Most radio sensitive cell in the body : Lymphocyte.

Most radio resistant cell in the body : Platelet.

Most radio sensitive tumour in the body : Ewing's sarcoma.

Cell cycle regulation :

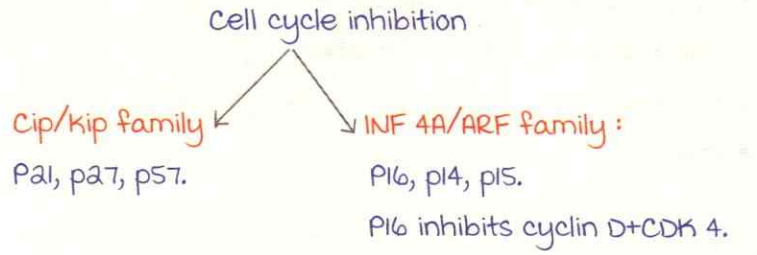
1. Cyclins and CDK (cyclin dependent Kinases) :
Cyclins combine with CDK and phosphorylates it, thus moving to next phase of cell cycle.

Active space

Cyclins		CDK
D	+	4, 6
E	+	2
A	+	2
B	+	1

Cell cycle inhibition

00:52:08



Cyclin D associated with mantle cell lymphoma.
Cyclin E associated with breast cancer.

Questions :

1. An experiment is conducted in which proliferating cells are subjected to ionizing radiation. The ionizing radiation leads to arrest in a checkpoint that monitors completion of DNA replication. It is observed that there are increased numbers of chromosomal abnormalities in these cells. Which of the following is the checkpoint affected by the ionizing radiation ?
   A. G0/G1.
   B. G1/S.
   C. S/G2.
   D. G2/M (most radiosensitive phase).
   E. M/G0.

2. A study is performed to analyse characteristics of malignant neoplasms in biopsy specimens. The biopsies were performed on patients who had palpable mass lesions on digital rectal examination. Of the following microscopic findings which is most likely to indicate that

Active space

the neoplasm is malignant?

A. Pleomorphism.
B. Atypia.
C. Invasion.
D. Increased N: C ratio.
E. Necrosis.

3. A 60 year old man who has a 90 pack year history of cigarette smoking has had a chronic cough for the past ten years. He has begun to lose weight (3Kg) during the past year. No abnormal findings are noted on physical examination. He has a chest radiograph that reveals a right hilar mass. A sputum cytology shows atypical, hyperchromatic squamous cells. What is the most common initial pathway for metastases from this lesion?

A. Bloodstream.
B. Pleural cavity.
C. Contiguous spread to chest wall.S
D. Lymphatics (since epithelial malignancy).
E. Bronchi.

4. A 62 year old man has complained of pain on urination for the past week. He is afebrile. On cystoscopy, a slightly erythematous 1cm diameter area is seen on the bladder mucosa. This area is biopsied and on microscopic examination shows cells with marked hyperchromatism and increased nuclear/cytoplasmic ratio involving the full thickness of the epithelium. However, these changes are confined to the epithelium above the basement membrane. Which of the following terms best describe these biopsy findings ?

A. metaplasia.
B. Minimal dysplasia.
C. Microinvasion.
D. Hyperplasia.
E. Carcinoma in situ.

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5. A 53 year old woman feels a lump in her right breast. Her nurse practitioner palpates an irregular 3cm mass that is not movable because it appears fixed to the overlying skin, which is retracted. A mastectomy is performed and the pathologist on sectioning the breast finds a 3 X 3.5cm ovoid mass that does not have discrete borders, but appears to infiltrate into the surrounding fibrofatty breast stroma. The mass is firm. white, and has a fibrous consistency. Which of the following features is most likely demonstrated by the gross appearance of this mass ?

   A. Anaplasia.
   B. Aplasia.
   C. Desmoplasia.
   D. Dysplasia.
   E. metaplasia.

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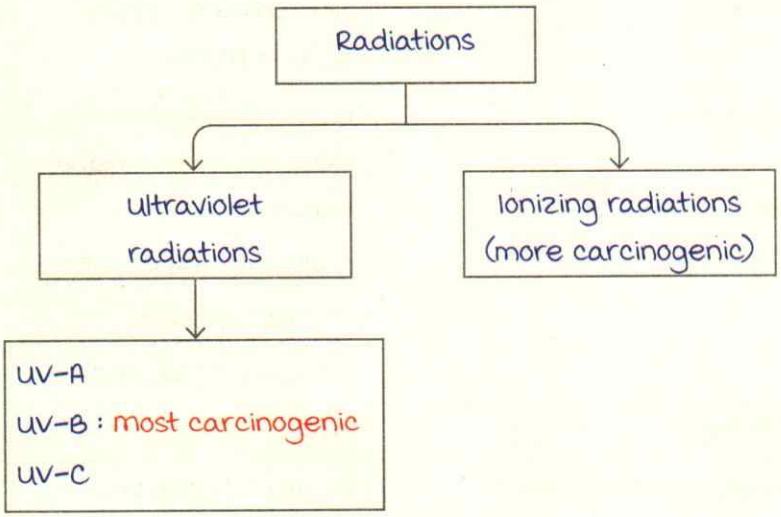
TYPES OF CARCINOGENESIS

Radiation carcinogenesis 00:00:57



UV-B radiation causes skin cancers like basal cell carcinoma and malignant melanoma.

Theoretically, UV-C is most carcinogenic but does not reach down due to ozone layer.

Most common cancer caused by ionizing radiation → acute myeloid leukemia.

Leukemia which is never caused by radiation → CLL.

Other cancers associated with radiation :

Papillary carcinoma of thyroid.

- Risk factor for follicular carcinoma thyroid is long standing goiter/iodine deficiency.

Carcinoma breast.

Carcinoma lung.

Organs most resist to radiation : Bone, gut.

Active space

Chemical carcinogenesis

00:05:19

Chemical	Cancer
Polycyclic aromatic hydrocarbons (PAH)	Lung cancer
Arsenic	Skin cancer, hepatic angiosarcoma
Asbestos	Lung adenocarcinoma → most common malignancy caused. Malignant mesothelioma → most specific malignancy caused
Aflatoxin	HCC
Beta naphthylamine/ azo dyes. People working in dry cleaning industry. Those who store wool in naphthalene balls.	Bladder carcinoma
Benzene	Leukemia, AML
Diethylstilbesterol (DES)	Clear cell carcinoma vagina
Polyvinylchloride (PVC)	Hepatic angiosarcoma
Cadmium	Prostate cancer

Most common lesion caused by asbestos → pleural plaque.
HPE of asbestosis : Ferruginous bodies/asbestos bodies → asbestos fibers coated with iron.

- Stained with prussian blue.
- Dumb-bell shaped/beaded/fusiform rod like structures.

Marker for mesothelioma : _____

Active space

Amphibole asbestos fibers are more carcinogenic.

Mothers exposed to DES → Clear cell carcinoma of vagina or cervix in daughter.

Chemical carcinogens are of two types :

Directly acting carcinogens	Indirectly acting carcinogens
Do not require any conversion	Requires conversion to active metabolites by cytochrome p450 enzymes
Less potent	more potent
e.g. : Chemotherapeutic agents, alkylating agents	e.g. : PAH

Chemical carcinogenesis takes place in 2 phases :
Initiation phase → Irreversible.
Promotion phase.

Microbial carcinogenesis

00:13:31

Parasites	Viruses	Bacteria	Fungi
Schistosoma haematobium → bladder cancer (SCC). Clonorchis, Opisthorchis → cholangio carcinoma.	Hepatitis B, C → HCC. HTLV-I → adult T-cell leukemia. HHV-8. EBV. HPV.	H. pylori	Aspergillus ↓ Aflatoxin ↓ HCC.

Schistosoma converts transitional epithelium to squamous epithelium by metaplasia → SCC.

Helicobacter pylori :
Causes the following cancers :

- Gastric adenocarcinoma → most common malignancy caused.

Active space

- MALToma → most specific malignancy caused.

Gram negative bacilli.

Pathogenesis :

Two toxins produced are → cag A and vac A → causes cancer.

Mostly affects the pyloric antrum of the stomach → antral biopsy.

Does not penetrate the stomach mucosa.

- Seen floating over the mucosa.

Special stains used are :

Warthin's starry silver stain → small black coloured bacilli seen floating over the mucosa.

Modified Giemsa stain.

Steiner stain.

Viral carcinogenesis

00:19:43

Adult T-cell leukemia :

Caused by HTLV- I (human T-cell lymphoma virus).

HPE : Clover leaf cells.

Pathogenic factor : Tax gene.

Diseases caused by HHV- 8 :

Primary effusion lymphoma.

Kaposi's sarcoma.

- Borderline blood vessel tumor (vascular tumor).
- Usually seen in HIV positive patients or those with immunodeficiency.
- On microscopy : Spindle shaped cells with slit like spaces.

Multicentric Castleman's disease.

Ebstein Barr virus (EBV) :

Binds to CD21 receptor on B-cell.

Diseases caused by EBV :

- Infectious mononucleosis/kissing disease.

Active space

Downey cells → ballerina skirt appearance.

- Hodgkin's lymphoma.
  Nodular lymphocyte predominant > nodular sclerosis variant : Not associated with EBV.
- B- cell lymphomas.
- Burkitt's lymphoma.
  Translocation t(8: 14) → amplification of c-myc.
  Marker : bcl- 6.
  Microscopic appearance : Starry sky appearance.
- Leiomyosarcoma.
- Post-transplant lymphoproliferative disorder.
- Nasopharyngeal carcinoma.

Pathogenesis of EBV :

LMP-1 : Latent membrane Protein- 1.

Increased activation of NF- κβ pathway → increased growth signaling → increased cell proliferation.

EBNA-2.

IL-10.

Human papilloma virus (HPV) :

Strains of HPV are :

Low risk	High risk
HPV 6, 11	HPV 16, 18
Genital warts. CIN I.	CIN II, III. Cervical cancer. Penile cancer. Laryngeal cancer.

Pathogenesis of HPV :

Produces two proteins E6 and E7.

E6 combines with p53 (tumor suppressor gene) and degrades it.

E7 combines with Rb and causes its degradation.

Both causes increased cell proliferation.

Active space

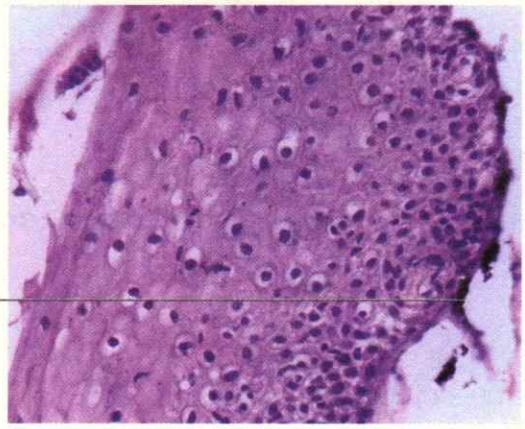
HPE :

Koilocytes → large cell with thick membrane and raisinoid nucleus, with perinuclear halo.

Produced by E4 protein.

Thick membrane
Raisinoid nucleus
Peri- nuclear halo

Koilocyte



Microbe	Cancer
H. Pylori	Gastric adenocarcinoma. MALTOMA.
HPV	Cervical cancer. Anogenital cancer. Laryngeal cancer.
HTLV I	Adult T cell leukemia
HBV	Hepatocellular carcinoma
HHV 8	Kaposi's sarcoma. Primary effusion lymphoma multicentric Castleman disease..
EBV	HL. NHL. Burkitt's lymphoma. Nasopharyngeal carcinoma. PTLD.

Active space

Q. A 51 year old man has worked for 10 years in a factory producing plastic pipe but not following safety standards. He has noted weight loss, nausea, and vomiting worsening over the past 5 months. On examination he is afebrile. There is generalized muscle wasting. Laboratory studies show the serum alkaline phosphatase is 405 U/L with AST 47 U/L, ALT 35 U/L, and total bilirubin 1.2 mg/dL. An abdominal CT scan reveals a 12 cm right liver lobe mass. Liver biopsy reveals a neoplasm composed of spindle cells forming irregular vascular channels. With immunohistochemical staining the cells demonstrate vimentin positivity and cytokeratin negativity. Exposure to which of the following substances most likely led to development of this neoplasm ?

A. Benzene.

B. Radon.

C. Cyclophosphamide.

D. Asbestos.

E. Vinyl chloride.

Q. Pathogenic mechanism of HPV in cervical cancer is :

A. Degradation of cyclin D1.

B. Upregulation of BCL2.

C. Instability of E6 and E7.

D. Down regulation of p16INK4a.

Q. A clinical study is performed of oncogenesis in human neoplasms. It is observed that some neoplasms appear to develop from viral oncogenesis, with serologic confirmation of past viral infection. Which of the following neoplasms is most likely to arise in this manner ?

A. Retinoblastoma.

B. Small cell anaplastic carcinoma.

C. T-cell leukemia.

D. Prostatic adenocarcinoma.

E. Hepatic angiosarcoma.

Active space

Q. HHV 8 is related to all except :

A. Kaposi's sarcoma.

B. Primary effusion lymphoma.

C. Adult T cell lymphoma.

D. Castleman's disease.

Q. A 56 year old man has had a chronic cough for the past year. He is a non-smoker. He had an episode of hemoptysis 3 days ago. No abnormal findings are noted on physical examination. A chest X-ray demonstrates a 6 cm perihilar mass. A sputum sample is collected, and the sputum cytology report reads, Atypical cells present suggestive of squamous cell carcinoma.Which of the following environmental exposures is most likely to be associated with these findings ?

A. Asbestos.

B. Radon.

C. Silica.

D. Benzene.

E. Formaldehyde.

Q. A previously healthy 42 year old man has a skin nodule on his right hand that has become larger and darker with more irregular outlines over the past 3 months. On physical examination this lesion is 1.2 cm diameter, darkly pigmented, and a slightly raised nodule on the dorsum of his right hand. No other skin lesions are noted. Three non tender enlarged lymph nodes are palpable in the right axilla. The lesion is excised and microscopic examination shows a neoplasm composed of darkly pigmented polygonal and spindle cells. Which of the following risk factors is most important for development of this neoplasm ?

A. Cigarette smoking.

B. Allergy to latex gloves.

C. Inheritance of a faulty RB gene.

D. Prior job-related handling of asbestos.

E. Chronic exposure to ultraviolet radiation.

Active space

HALLMARKS OF NEOPLASIA

Hallmarks of carcinogenesis 00:01:51

1. Self sufficiency in growth signals.
2. Insensitivity to growth inhibitory signals.
3. Limitless replicative potential.
4. Evasion of apoptosis.
5. Sustained angiogenesis.
6. Altered cellular metabolism.
7. Invasion and metastasis.
8. Escape of immune recognition.

Self sufficiency in growth signals 00:03:08

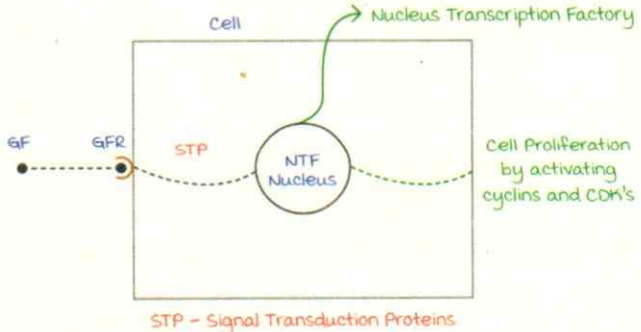
Proliferation without growth factors.

Proto-oncogenes : Normal genes which are required for cell proliferations.

mutation in these genes converts proto oncogenes into oncogenes leading to production of cancer.

This mutation is called gain of function mutation.

- Every cell requires growth factor for proliferation.
- Growth factor combines with cell through growth factor receptor on the surface of the cell.
- Growth factor after combining with growth factor receptor enters the cell through signal transduction protein (STP).
- STP transmits signals to nucleus.
- Nuclear transcription factors are present inside the cell which leads to cell proliferation by activating cyclins and cyclin dependent kinases.



Active space

Any defect in growth factor/ growth factor receptor/ STP/ NTF/ cyclins ⟶ Cancer.

Growth factors	Cancer
Hepatocyte growth factor	Hepatocellular carcinoma
HST - 1	Osteosarcoma
PDGF - β / sis	Increased risk of astrocytoma
Growth factor receptors	Cancer
EGFR - 1 (ERB 1)	Lung adenocarcinoma
EGFR - 2 (ERB 2 /Her 2 nu)	Breast and ovarian cancer.
ALK gene on chromosome 2	Anaplastic large cell lymphoma. Inflammatory myofibroblastic tumor. Adenocarcinoma of lung.
C-Kit	Gastrointestinal stromal tumor and seminoma.
RET on chromosome 10. (Gain of function mutation).	Increased risk of medullary carcinoma of thyroid and MEN II syndrome.

Loss of function mutation in RET : _____

Signal transduction proteins :

1) RAS : m/c oncogene affected in human malignancy.

(m/c gene affected in human malignancy : p53).

RAS is divided into 3 types : K-RAS, H-RAS and N-RAS.

K-RAS : Increased risk of KPL tumors.

K : Colon cancer.

P : Pancreatic cancers.

L : Lung cancer.

H-RAS : Bladder cancer.

N-RAS : Melanoma.

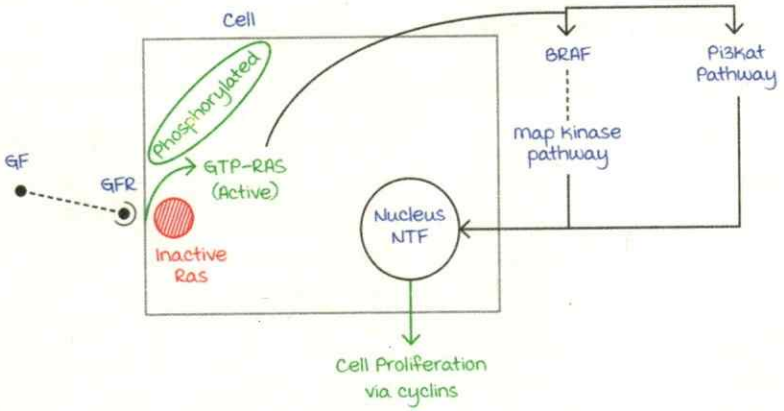
- RAS inside the cell is inactive due to combination of GDP.
- GF (signal) binds with GFR enters the cell & phosporylates RAS.
- Phosphorylated RAS is a GTP RAS (active), it is a proto oncogene.

Active space

- GTP RAS activates 2 pathways :

1. BRAF Kinase MAP pathway.
2. Pi3KAT pathway.

- Through these pathway signals are sent to nucleus containing NTF.
- NTF are activated leading to cyclin activation resulting in cell proliferation.



Any defect in RAS/BRAF/Pi3KAT ⟶ Cancer.

BRAF is affected in :

- Hairy cell leukemia (HCL)
- Langerhans cell histiocytosis (LCH).
- melanoma.
- Pilocytic astrocytoma.
- Papillary carcinoma of thyroid.
- Colon cancer.

NOTCH gene mutation implicated in T-ALL.

ABL gene mutation : t(9 : 22) : CML.

1. If products are 210 Kda (Kilo dalton) : CML.
2. If products are less than 190 Kda : ALL.

Nuclear transcription factors :

myc is a oncogene.

3 types :

N-myc : Amplification leads to neuroblastoma.

L-myc : Lung cancer (small cell).

C-myc : Amplified in Burkitt's lymphoma.

Active space

Cyclins and CDK's :

t(11 : 14) : mantle cell lymphoma.
On chromosome 11 : Cyclin D 1.
On chromosome 14 : Ig H locus.
Translocation causes over expressiion of cyclin D 1 leading to increased cell proliferation resulting in mantle cell lymphoma.

Oncogenes in human malignancy :

Gene	Cancer
C Kit	GIST
RET	medullary carcinoma of thyroid and MEN II.
ALK	ALCL, Adenocarcinoma of lung and inflammatory myelofibroblastic tumor.
ABL	CML
K RAS	Colon and pancreatic cancer
H RAS	Bladder cancer
N RAS	Melanoma
C myc	Burkitts lymphoma.
L myc	Small cell lung cancer
N myc	Neuroblastoma
NOTCH	ALL-T

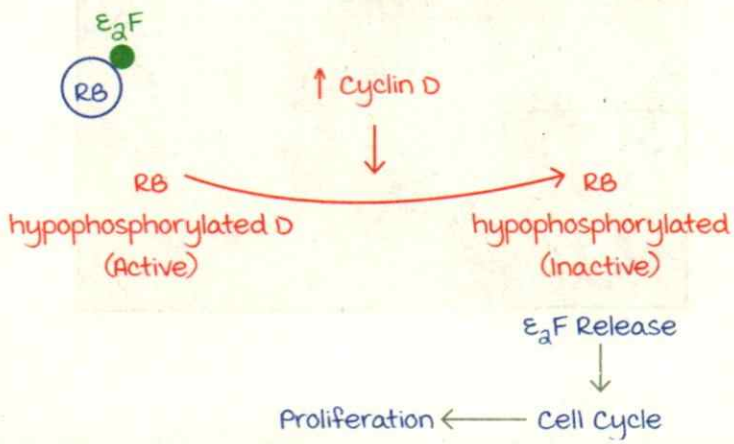
Insensitivity to growth inhibitory signals 00:28:46

Tumor supressor genes :
Normal genes which decreases cell proliferation.
Loss of function mutation leads to increased cell proliferation and cancer.

1) RB gene :
Located on chromosome 13q 14.
Mutation of RB leads to increased risk of retinoblastoma and osteosarcoma.
Governor of genome.
RB hypophosphorylated : Active RB.
RB hyperphosphorylated : Inactive RB.

Active space

Role of RB in cell cycle :



RB is active in hypophosphorylated state.
RB has E2F transcription factor in its pocket.
Increase in cyclin D/CDK 4 inactivates the activated RB.
Due to release of E2F transcription factor (required by the cell for cell cycle), cell cycle is progressed leading to proliferation.

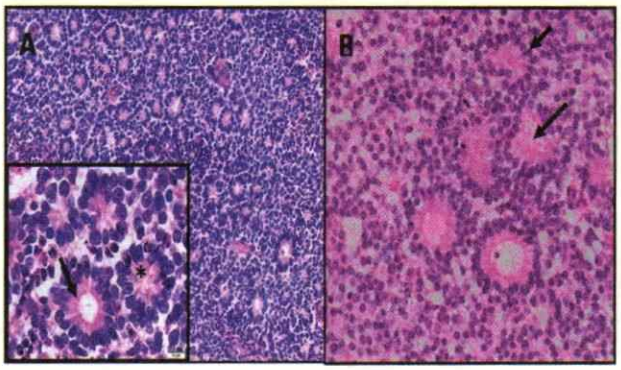
Role of RB is that it regulates G1 S checkpoint of cell cycle.
Hence called as governor of cell cycle.

Knudson's two hit hypothesis :
First described for retinoblastoma.
Both alleles are defective.
For retinoblastoma to develop, both the alleles have to be mutated.

Loss of heterozygosity :
To develop retinoblastoma, 1st mutation has to occur by birth.
But the disease does not present by birth.
2nd mutation acquire later on and and develop retinoblastoma.
This is known as loss of heterozygosity.

HPE of retinoblastoma : Small round blue cells with scanty cytoplasm.
Flexner Wintersteiner rosettes (it is a true rosette : Central space is empty).
Fleu reite is also seen.

Active space



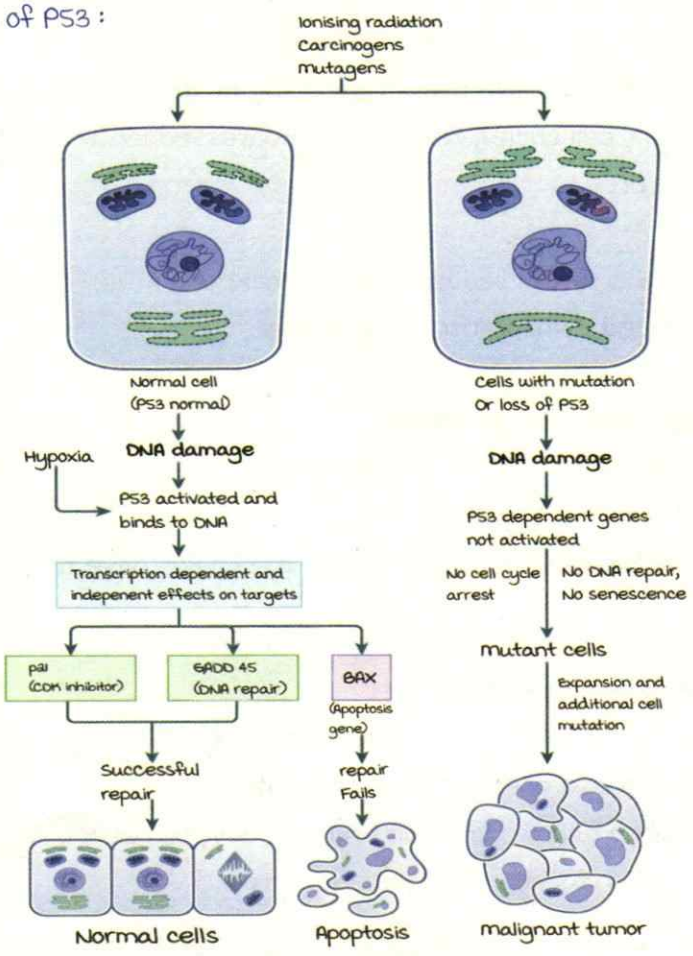
P53 gene :

Chromosome 17p.

m/c affected gene in human malignancy (> 50% of cancers).

Guadian of genome or molecular policeman of cells.

Role of P53 :



In case of DNA damage :

P53 is activated, which inturn activates p21 causing stoppage of cell cycle.

P53 will try to repair DNA by activating GADD 45.

Active space

In stubborn cells where those two mechnism dont work, p53 activates BAX causing apoptosis.
Loss of p53 : mutant cells are produced due to lack of repair, cell cycle arrest or senescence.

In congenital mutation of p53 : Li fraumani syndrome.
many cancers can develop in this syndrome such as :
4 B's :
Bone cancer.
Breast cancer.
Blood cancer.
Brain cancer.

p63 : Helps in squamous cell differentiation.

TSG's :

Gene	Chromosome	Tumors
RB	13q	Retinoblastoma and osteosarcoma.
p53	17p	Li fraumani syndrome
NF 1	17	Neurofibroma and meningiomas
NF 2	22	Schwanomma
BRCA 1	17	Breast cancer and ovarian cancer
BRCA 2	13	male breast cancer, female breast cancer and prostate cancer.
WT 1	11	Wilms tumor
WT 2	11	Wilms tumor
PTEN	10	Endometrial cancer and prostate cancer, Cowden syndrome.
VHL	3	Clear cell RCC, Cerebellar hemangioblastoma.
APC	5	FAP

Limtless replicative potential 00:50:20

Telomerase :
maximum telomerase activity present in cancer cells.
Elaboration of telomerase : No telomere shortening and cells won't die.

Active space

Evasion of apoptosis 00:51:26

Increased synthesis of antiapoptotic factor :
t(14 : 18) : Follicular lymphoma.
Chromosome 18 : Ig H locus.
Chromosome 14 : bcl 2.
Due to translocation : Increased activity of bcl2 (anti apoptotic gene) leading to decrease apoptosis resulting in increased cell proliferation → Follicular lymphoma.

Sustained angiogenesis 00:53:04

Increase secretion of :
Proangiogenic factors and Anti angiogenic factors.
Cancer cells increase pro angiogenic factors (increase blood supply) like :

- Vascular endothelial growth factor (VEGF).
- Platelet derived growth factor (PDGF).
- Fibroblast growth factor (FGF).

Anti angiogenic factors (decrease blood supply) like :

- Vasculostatin.
- Endostatin.
- Angiostatin.
- Thrombospondin.

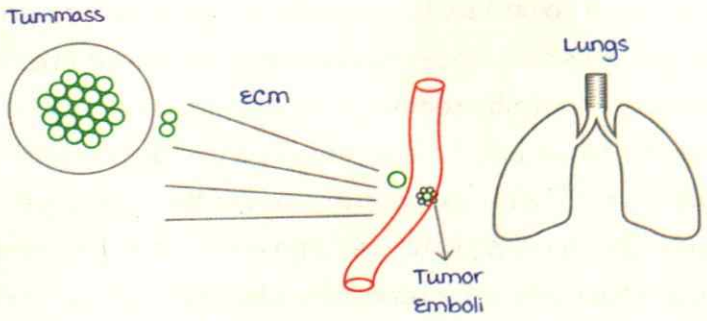
Altered cellular metabolism 00:54:55

Warburg effect :
Sir Otto warburg : Nobel prize for discovering this effect.
Cancer cells undergoes aerobic glycolysis.
PET scan is based on this Warburg effect.

Invasion and metastasis 00:56:06

Tumor has to cross extra cellular matrix to reach the lung :

Active space



All tumor cells are joined by E-cadherin.

1. Detachment of cells by loss of E-cadherin.

2. These detached cells attaches to extracellular matrix by integrin.

3. Degrades extracellular matrix by : Matrix metallo proteinases (2,9).

Can express type IV collagen, cathepsins, urokinase.

Elaborate collagenase and enters blood vessels.

4. Epithelial to mesenchymal transition (EMT).

mediated by Snail & Twist.

5. Tumor cells attaches with platelets is called as tumor emboli → either reach lymphatics or organs.

(Hematogenous route common for sarcomas.

Lymphatic route common for carcinomas.

Except HCC & RCC : Hematogenous route.)

Escape of immune recognition 01:04:10

Decreased expression of MHC antigens.

Selective outgrowth of antigen negative variants.

Repair pathway defects 01:05:29

3 pathways :

1. Defect in nucleotide excision repair : Xeroderma pigmentosa.

2. Defect in mismatch repair : HNPCC.

3. Homologous recombination :

   a. Fanconi anemia.

   b. Ataxia telangectasia.

   c. Bloom syndrome.

Active space

Q. A change in bowel habits prompts a 53 year old woman to see her physician. On physical examination there are no lesions noted on digital rectal examination, but her stool is positive for occult blood. A colonoscopy is performed and reveals a 6 cm friable exophytyic mass in the caecum. A biopsy of this mass is performed and microscopic examination shows a moderately differentiated adenocarcinoma. Which of the following laboratory findings is most likely to be present in this patient?

A. K-RAS mutation in the neoplastic cells.

B. Neoplastic cells positive for vimentin.

C. Stool culture with Shigella flexneri.

D. Presence of HIV-1 RNA.

E. DNA topoisomerase I autoantibody.

Q. A 52 year old man has had increasing fatigue for the past 6 months. On physical examination he has a palpable spleen tip. Laboratory studies show a WBC count of 189,000/microliter. The peripheral blood smear shows many mature and immature myeloid cells present. Cytogenetic analysis of cells obtained via bone marrow aspiration reveals a t(9:22) translocation. This translocation leads to formation of a hybrid gene that greatly increases tyrosine kinase activity. Which of the following genes is most likely translocated to cause these findings?

A. p53.

B. RB.

C. ABL.

D. NF-1.

E. RAS.

Q. Mother of a 4 year old boy notices that his abdomen is enlarged. Physical examination shows an ill defined abdominal mass. An abdominal CT shows a 9 cms mass in the region of right adrenal gland. The mass is removed and microscopic appearance shows small blue cells wtih Homer wright rosettes. Which of the following genes is most likely to have undergone alterations to produce these findings?

A. K RAS.

Active space

B. BCL2.

C. N myc.

D. P53.

Q. A 64 year old man has noted a 5 Kg weight loss along with increasing fatigue over the past year. He has experienced dull abdominal pain for the past week. He has developed abdominal distention with lack of stools in the past two days. On physical examination, bowel sounds are reduced. An abdominal CT scan reveals a mass involving the descending colon. At laparotomy, a partial resection of the left colon is performed, with removal of an encircling mass. Microscopically, the mass is found to be a moderately differentiated adenocarcinoma. Which of the following laboratory test findings is most likely to be present in this man?

A. Microcytic hypochromic anemia.

B. Positive antinuclear antibody test.

C. Hyperglycemia.

D. Elevated alpha-fetoprotein.

E. Lactate dehydrogenase.

Q. In an experiment, it is observed that chronic, increased exposure to ionizing radiation results in damage to cellular DNA. As a consequence, a protein is now absent that would arrest the cell in the G1 phase of the cell cycle. Subsequent to this, the cell is transformed to acquire the property of unregulated growth. The absent protein is most likely the product of which of the following genes?

A. RAS.

B. TP53.

C. MYC.

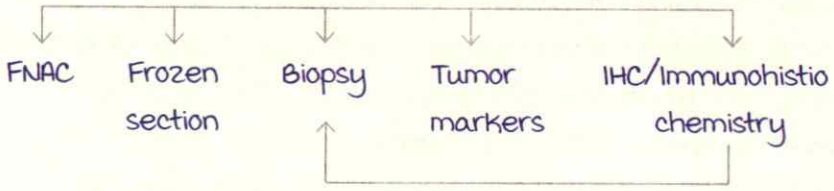
D. ABL.

E. BCL-2.

Active space

LAB DIAGNOSIS OF CANCERS

Investigations 00:00:45



Fine Needle Aspiration Cytology (FNAC) 00:02:45

23–30 G small bore needle.
Technique : The needle is pierced into the swelling and aspirated. The sample is placed on a slide, stained and visualized under a microscope.
Used for easily accessible organs : Lymph node, breast, thyroid.

FNAC of lymph nodes is usually done if TB is suspected.
If the material taken in the syringe can indicate the condition of the patient.
If the material is cheesy, caseous or yellow in colour : AFB stain must be done.
Advantage of the procedure : Less invasive.
Disadvantage of the procedure : Target is missed in the procedure resulting in false negative reports.
Sample of thyroid is contaminated with blood with only few cells left for FNAC, as it vascular organ.

Fine needle non aspiration cytology (FNNAC) :
As we do not aspirate, this technique can be used for highly vascular organs like thyroid.

PAP smears / Exfoliative cytology :
Lung cancers : Broncho alveolar lavage specimen.
CIN / cervical intraepithelial neoplasia : PAP smear.

Active space

Image guided FNAC :
On ultrasound guided FNAC : lesion is localized hence target is not missed. ↑ Sensitivity of FNAC.
For very small or deeper lesions.

Follicular carcinoma of thyroid cannot be diagnosed by FNAC.
Because on FNAC, Follicular Adenoma and follicular carcinoma cannot be differentiated because capsular and vascular invasion is not visualized.

Biopsy 00:09:20

To be done to confirm the diagnosis based on FNAC.

Biopsy

Incisional biopsy	Excisional biopsy
Some part of tissue is left behind.	The entire tissue is taken out.
E.g. : True cut biopsy.	

True cut biopsy :
An incision is made (in breast : Around the areola) and true cut biopsy gun is inserted through the incision.
An ultrasound probe can be used for better localization.
Once localized the biopsy gun is triggered to cut and remove the tissue.
Useful for breast cancer and soft tissue lesions

Fixatives :
Biopsy specimen tissue is fixed most commonly 10% neutral buff formalin for histopathology.

For electron microscope, fixative used is 2.5% glutaraldehyde.

For testicular biopsy : Bouin's fluid (sperms are destroyed by formalin).

Active space

Stains used in Pathology :

Cell/ condition	Stain
most common stain in histopathology	Hematoxylin and eosin
most common in hematology	Romanowsk like Leishman/ Geimsa
Reticulocyte	Supravital
Lymphoblast	PAS
myeloblast	NSE,SBB,OIL RED O
monoblast	Non specific esterase /NSE
Hairy cell	TRAP
Lipid	Oil red O, sudan black
Iron	Prussian blue
calcium	Von Kossa, Alzarine red S
Glycogen	PAS
Copper	Rhoamine, rubeanic acid
mast cell	Toluidine blue
mucin	mucicarmine Alcian blue
Reticulin fibres	Silver
Elastin fibres	Van geison
Collagen	masson trichrome
melanin	masson fontanna
H. pylori	Warthin starry silver
Cryptococcus	India ink
Fungi	Silver methanamine PAS
Amyloid	Congo red

Immunohistochemistry / IHC 00:15:40

On biopsy specimen, antigen antibody reaction is done and visualised.

Active space

Uses of IHC :

- Origin of the tumor.

E.g. : In a poorly differentiated tumor to differentiate epithelial, mesenchymal and vascular origin, all 3 markers are added. The positive marker gives the origin of the tumor.

- In diagnosis of unknown primary.

- Prognostic and therapeutic significance.

E.g. : Especially in breast cancer cases, 3 markers (ER,PR & HER 2 neu are added :

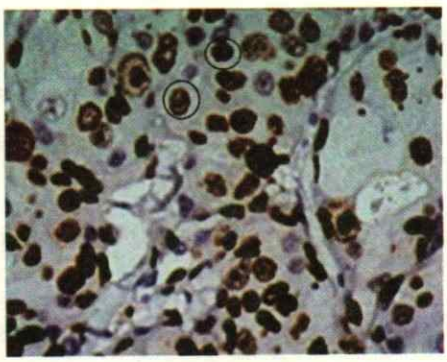
Estrogen receptor/ER, Progesterone receptor/PR] + : Good prognosis. Treated by Tamoxifen.

Her2 neu + : Poor prognosis. Treated by Traztuzumab, Herceptin.

Technique :

Certain cancers have particular cell types, with specific antigens.

E.g. : If epithelial malignancy is suspected, they have Cytokeratin antigen. Cytokeratin antibodies are added, if they react with the antigen, a positive reaction gives a color. No colour is produced in the absence of epithelial malignancy. If IHC is positive, usually gives a brown color.



Brown color indicates + IHC.

Active space

Important IHC markers applied on Biopsy :

Cell of origin/tumor	marker
Epithelial origin	Cytokeratin
Mesenchymal origin (Sarcomas)	Vimentin
Glial	GFAP / Glial fibrillary acid protein
Smooth muscle (E.g. : Leiomyosarcoma)	SMA / Smooth muscle actin
Skeletal muscle / Rhabdomyosarcoma	Desmin, myogenin, myo D1
Vascular e.g : Angiosarcoma.	Vwf, CD31, VEGF, Factor VIII.
Neuroendocrine e.g. : Pheochromocytoma, Neuroblastoma, Medullary carcinoma of thyroid, Paraganglioma.	NSE Chromogranin Synaptophysin
Hepatic e.g : Hepatocellular carcinoma	Hep par1, arginase 3 Alpha feto protein / AFP
GIST / Gastro Intestinal Stromal Tumor	DOG1, CD 34, CD117
Malignant melanoma	Hmb 45, S 100, Melan A
Malignant mesothelioma	Calretinin, CK 5/6
Ewings sarcoma	CD 99, MIC 2
Osteosarcoma	Osteopontin, osteonectin, osteocalcin

Tumor markers are released in the blood :

marker	Condition
PSA / Prostate Specific antigen	Prostate ca
PAP	Prostate ca
Calcitonin	Medullary ca thyroid
PSA & PAP are organ specific but not cancer specific.	
CEA	Colon ca, pancreatic ca
HCG	Chorio ca

Active space

marker	Condition
AFP/ Alpha feto protein	Hepatocellular ca, NSGCT Non seminomatous germ cell tumor like yolk sac tumor, Hepatoblastoma
Immunoglobulins	multiple myeloma
Carbohydrate Antigen/CA 19-9	Colon ca, pancreatic ca
CA 125	Ovarian ca
CA 15-3	Breast ca
Catecholamines	Pheochromocytoma

Clinical scenario :
A 3 year old child presents with a testicular mass, microscopy showed presence of Schiller Duval bodies. What is the diagnosis and which Tumor marker used is ?
Schiller Duval bodies are seen in Yolk sac tumor (testicular tumor). Tumor marker : Alpha feto protein.

markers for unknown primary : CK7/CK20 profile

CK 7 +/CK20 + : Bladder Ca, Stomach, pancreas.
CK 7 -/CK 20- : Hepatocellular carcinoma.
Renal cell carcinoma.
CK 7 +/CK20 - : Cancers of female genital tract, breast, cervix, endometrium, lung and thyroid.
CK 7 -/CK20 + : Colorectal Cancer.

Frozen section

00:29:28

It is a intra-surgical procedure.
Done during lumpectomy, to check if the margins are involved or not.
The sample is taken and margins are labelled & sent for histopathology lab.
Quick procedure compared to normal processing of the tissue.
Stain used : Oil red O.

Active space

Paraneoplastic syndromes

00:31:25

Are symptom complexes in cancer patients which cannot be explained by the local or indigenous spread of tumor or by the elaboration of the hormones.

Syndrome	Tumor	Substance
SIADH / Syndrome of inappropriate secretion of ADH	Small cell ca lung	ADH
Cushing's syndrome	Small cell ca lung	ACTH
Hypercalcemia	SCC lung Breast Ca	PTHrP/ Parathyroid hormone related peptide.
Polycythemia	RCC	Erythropoeitin
Migratory thrombophlebitis	Ca pancreas Ca colon	
Hypertrophic pulmonary osteoarthropathy	Small cell ca lung	
Acanthosis nigricans (velvety thickening)	Ca stomach Ca colon	Epidermal growth factor
Myasthenia garvis	Thymoma Ca lung	

Most common paraneoplastic syndrome : _ _ _ _ _ _ _ _ _ _ _

Most common endocrinopathy : Cushing syndrome.

Tumor producing maximum paraneoplastic syndromes :

Small cell carcinoma of lung.

Clinical scenario :

60 year old male smoker presents with a centrally located mass in the lung. He has moon like face and striae on the body. The histopathology image is given. What is the marker to be used ?

Active space

microscopy showed Small cell carcinoma of the lung.
marker used due to its neuroendocrine origin :
NSE, chromogranin & synaptophysin.

Cancer cachexia :
Loss of body fat, muscle mass, anorexia.
TNF- α is the responsible cytokine.

Tumor lysis syndrome :
Seen in rapidly proliferating tumors (Burkitt lymphoma).
Results in : Hyperuricemia, hyperkalemia, hypocalcemia.

Recent updates :
Role of microRNAs in cancer :
- Oncogenic micro RNA 155, 200 : Seen in B cell lymphomas.
- Tumor suppressor micro RNA 15, 16 : Detected in CLL.

DICER mutation : Seen in cancers of female genital tract.

Q. A 62 year old man with an 80 pack year history of smoking experiences an episode of hemoptysis. On physical examination, he has puffiness as well as plethora of the face, pedal edema, bruises of the skin, & a blood pressure of 165/100 mm Hg. A chest radiograph reveals a 5 cm right upper lobe lung mass. A fine needle aspirate of this mass yields cells consistent with small cell anaplastic lung carcinoma. A bone scan shows no metastases. Immunohistochemical staining of the tumor cells is likely to be positive for which of the following hormones?
A. Parathormone related peptide.
B. Erythropoietin.
C. ACTH.
D. Insulin.
E. Gastrin.
Patient has small cell carcinoma with Cushing's syndrome as a paraneoplastic syndrome, it shows raised ACTH.

Q. Which of the following markers is used for the diagnosis of Rhabdomyosarcoma?

Active space

A. Desmin.
B. Cytokeratin.
C. Myeloperoxidase.
D. Synaptophysin.

Q. Which of the following IHC markers is positive in a neuroendocrine tumor?
A. Cytokeratin.
B. Calretinin.
C. GFAP.
D. Synaptophysin.

Q. A 5 year old child who presented with proptosis of one of the eyes was found to have a desmin positive tumor. What is the probable diagnosis?
A. Ewings sarcoma.
B. Embryonal rhabdomyosarcoma.
C. Leukemia.
D. Retinoblastoma.

Ewings sarcoma : CD99, mic 2. Retinoblastoma : RB.

Q. A 49 year old man complains of pain in his left thigh for 3 months. On physical examination his thigh is increased in size, compared to the right. A plain film radiograph reveals the presence of a 15 cm solid mass that does not appear to arise from bone, but it does have infiltrative margins. A biopsy of this mass is taken, and on microscopic examination the mass is composed of highly pleomorphic spindle cells. Which of the following immunohistochemical markers is most likely to be demonstrated in the cells of this mass?
A. Cytokeratin.
B. Factor VIII.
C. Alpha fetoprotein.
D. Lambda light chain.
E. Vimentin.
Suspected : Leiomyosarccoma (non bony origin in thigh).

Active space

TRICKS TO DIAGNOSE TUMORS

Squamous cell carcinoma :

Identified by :

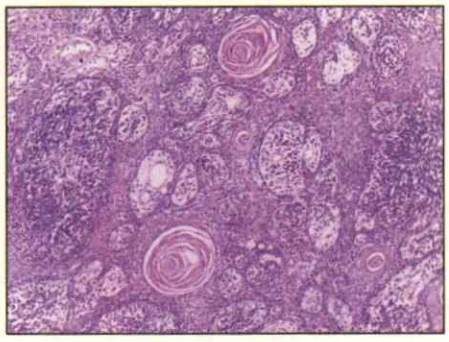
Desmosomes (in HPF).

Keratin pearls.

Marker : Being an epithelial malignancy.

- Cytokeratin.
- p63.

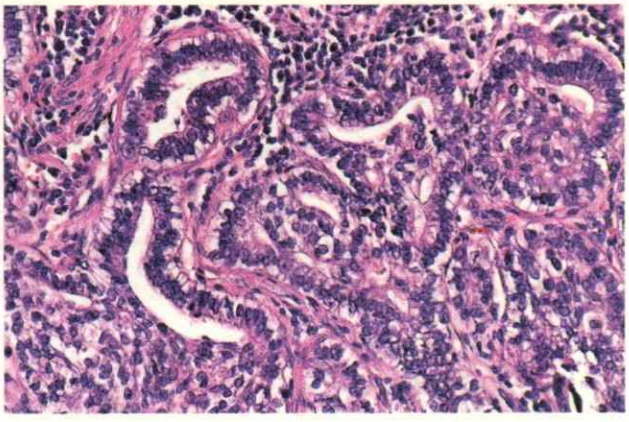
Stratified squamous epithelium



Keratin pearls

Adenocarcinoma :

Glands with the lumen inside lined by pleomorphic cells.



Papillary tumor :

Identified by :

- Papillae : Finger like projections with fibrovascular core.

Exception :

In papillary RCC, no fibrovascular core (foamy histiocytes +nt).

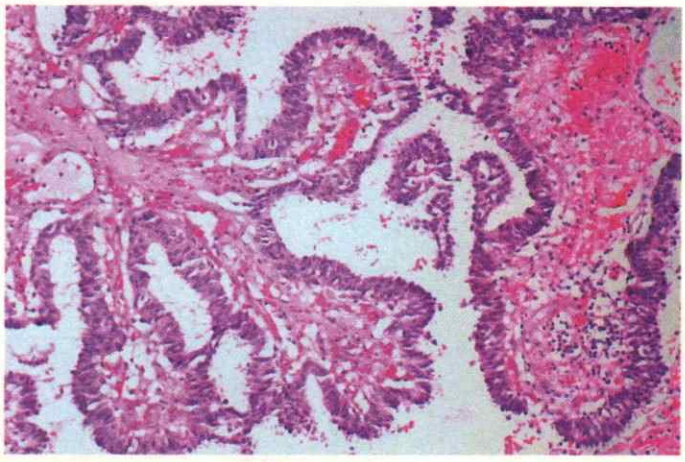
Active space

In papillary carcinoma, thyroid papillae are lined by Orphan Annie eye nuclei that are optically clear nuclei.

- Psammoma bodies :

  Foci of dystrophic calcification.

  Basophilic : Dense blue colour.



Neuroendocrine tumour :

History of diarrhea, flushing.

Identified by : Cells with salt and pepper chromatin.

Cells are usually arranged in nests.

Commonly seen in :

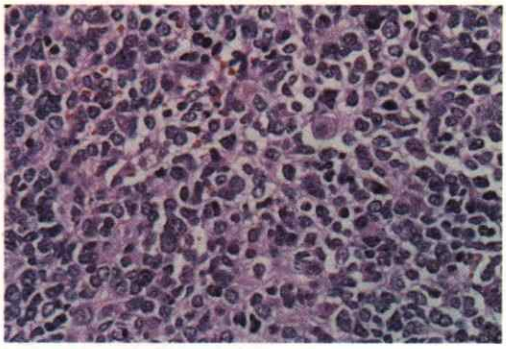
Small cell carcinoma of lung.

Pheochromocytoma.

Carotid body tumor.

Paraganglioma.

Neuroblastoma.



Positive IHC marker :

- NSE.
- Synaptophysin.
- Chromogranin.

In electron microscopy, shows :

Dense, core Neurosecretory granules.

Rosette :

Purple coloured tumor cells arranged like flower.

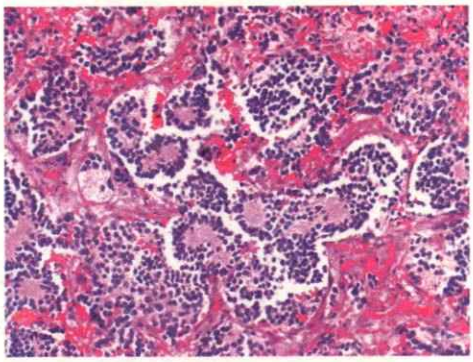
Sheets of cells with scanty cytoplasm.

Seen in round small blue cell tumours of childhood.

Active space

E.g. :

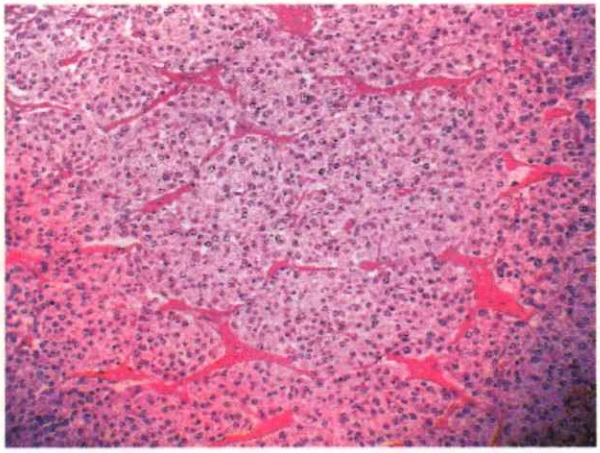
- Neuroblastoma.
- Retinoblastoma.
- Hepatoblastoma.
- Lymphoma.
- Medulloblastoma.
- Rhabdomyosarcoma.
- Ewing Sarcoma/PNET.
- Nephroblastoma/ Wilm's Tumor.



Pheochromocytoma :

A 30 year old male with episodic hypertension, palpitations, headache. CT scan shows a mass in adrenal. What is the most likely diagnosis ?

A. Pheochromocytoma



On microscopy shows Zell Ballen pattern (pink colour cells and nests in between are seen).

Identify by history /the salt and pepper chromatin .

Electron microscopy and the markers are same as that of neuroendocrine tumors.

Cribriform pattern :

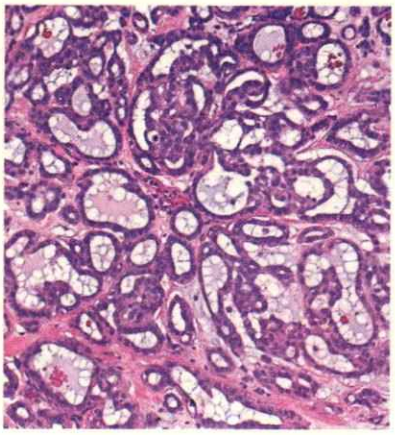
Cookie cutter pattern / Swiss cheese pattern.

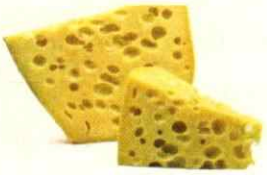
Seen in :

Cribriform DCIS (ductal carcinoma in situ).

Adenoid cystic carcinoma of salivary gland.

Active space



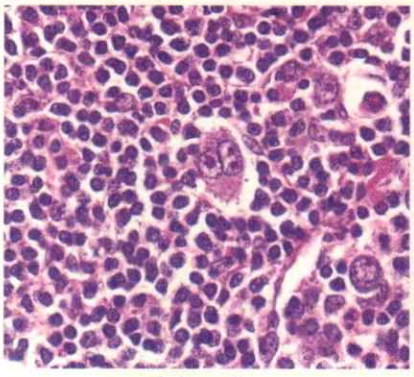


Owl's eye :

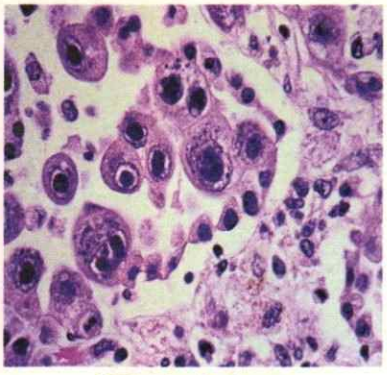
Seen in :

Reed-Sternberg cells in Hodgkin lymphoma.

Cytomegalovirus inclusions.



RS cells



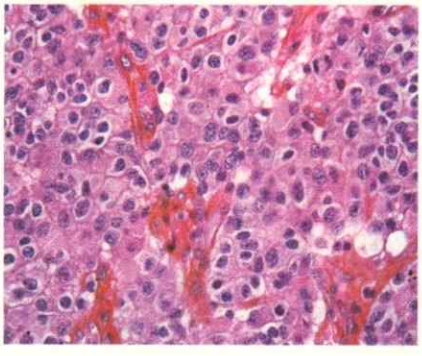
CMV inclusions.

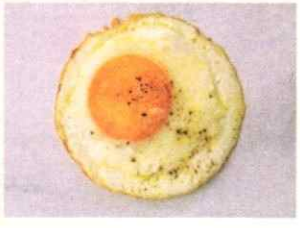
Fried eggs appearance :

Seen in :

Oligodendroglioma (grade 2 astrocytoma).

Bone marrow biopsy of hairy cell leukemia.





Active space

Coffee bean nuclei :

Longitudinal groove present.

Seen in :

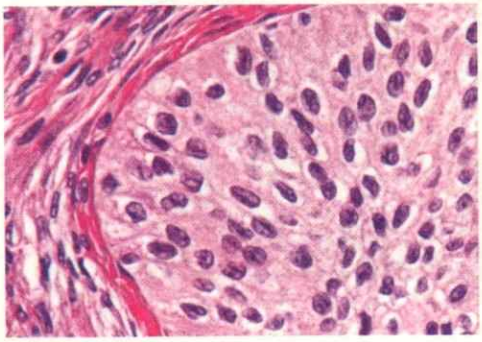
Papillary carcinoma thyroid.

Langerhans cell histiocytosis.

Brenner's tumor.

Chondroblastoma.

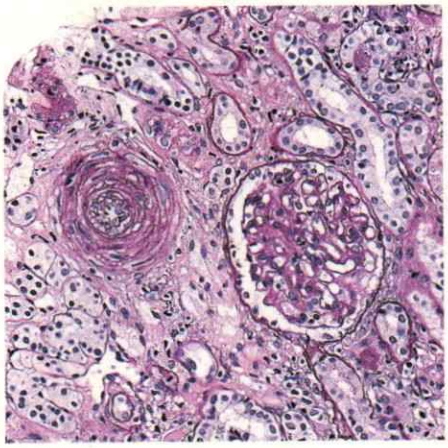
Granulosa cell tumor.



Onion skin appearance :

Seen in :

- Biopsy of malignant hypertension.
- Biopsy of Chronic inflammatory demyelinating polyneuropathy(CIDP) .
- Biopsy of Primary sclerosing cholangitis.
- In gross appearance of spleen in SLE.
- X ray of Ewing's sarcoma.
- In Electron Microscopy of Tay sach's disease.



Active space

Schiller duval body/ Glomeruloid body :

Seen in :

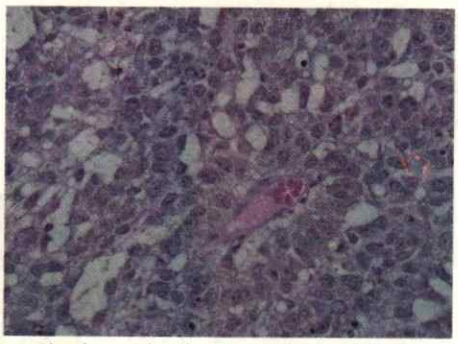
- Yolk sac tumor.

  markers :

  Alpha fetoprotein.

  Alpha 1 antitrypsin .

- Glioblastoma multiforme (grade 4 brain tumor)



Blood vessel with RBCs in the center and another layer of cells outside :Schiller Duvel body .

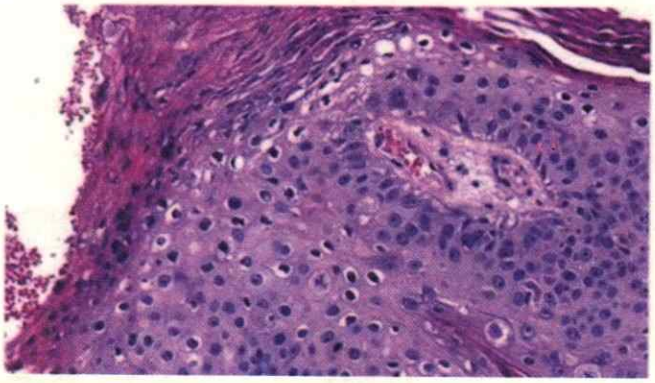
Koilocyte :

History of a genital wart or cervical cancer → Human Papilloma Virus infection.

Identified by : Koilocyte

Characteristic feature :

- Thick membrane.
- Resinoid nucleus.
- Perinuclear halo.

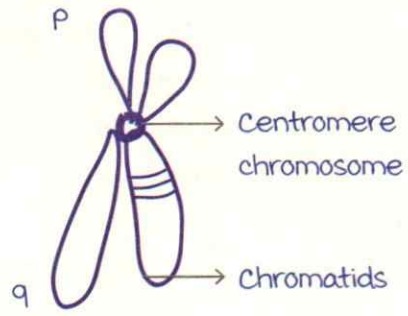


Active space

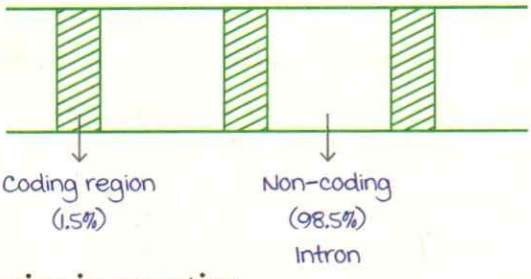
GENETICS - BASIC CONCEPTS AND DIAGNOSIS

Introduction 00:02:00

Genetics is the study of genome.
There are approx. 20,000-30,000 genes in our body.
These genes are located on the chromosome.
The short arm of very chromosome is called as P (petite).
The long arm is called as Q.
Every gene has got 2 alleles, Out of which one is received from the father and the other from the mother.



Structure of a gene :
Coding region, called the extron, consist of 1.5 % of the gene.
Non-coding region called the intron, comprises 98.5% approx of the gene.



Terminologies in genetics 00:04:14

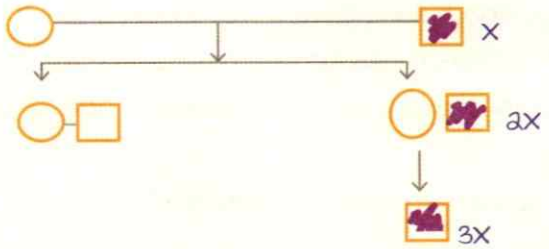
1. Homozygous :
When both the alleles are same AA or aa.
2. Heterozygous :
When both alleles are different : Aa.
3. Dominant disorder:
It can manifest in a heterozygous state.

Active space

4. Recessive :
   It can only manifest in the homozygous state.
   The heterozygous state in a recessive disease is known as a carrier.
5. Co-dominant : Both the alleles will act dominant & will simultaneously express.
   Example : ABO blood group, HLA typing.
6. Incomplete penetrance :
   This is a property of autosomal disorder.
   For example : Suppose 100 induviduals are affected with marfans, in which only 80 people will show symptoms and the rest will escape symptoms.
   Here the penetrance is 80%.
7. Variable expressivity : Different expression of clinical features. Despite having the same defective gene is seen in autosomal dominant disorders.
   For example: If there are 4 individuals with the defective gene of neurofibromatosis - 1.
   Individual 1 : Manifests skin lesion.
   Individual 2 : Manifests neurofibromas.
   Individual 3 : Manifests with eye lesions.
   Individual 4 : Manifests with skin and eye lesion.
   Here there is variable expression of the clinical features.
8. Pleiotropy :
   A single mutant gene can produce multiple end effects.
   For example : In sickle cell anaemia, glutamic acid is replace by valine at the 6th position of the beta globin chain.
   All the defect is at a single site, it can lead to multiple organ defects like splenomegaly, auto-splenectomy, microvascular occlusions.
9. Anticipation : In some cases the severity of the diseases increased with each successive generation.
   For example: If severity of a disease is "X", severity become 2X in next generation & so on.

Seen in trinucleotide repeat mutations like Fragile X syndrome (CGG repeats).

Active space



10. Polymorphism : Here people differ in genome only by 0.5%. (99% of the genome is almost same).
    It is of 2 types : Single nucleotide polymorphism and copy number variations.
11. Mutation : It is a permenant heritable gene in DNA.
    Can be divided into 2 types ;
    Point mutation : If a sinlge loci/nucleotide is affected, it is called point mutatuion.
    It can be classified into :
    - Silent mutation : Single nucleotide change but it does not produce a different amino acid or protein.
    - Missense mutation : A single nucleotide change but produces a different amino acid and protein. (Example : Sickle cell anemia)
    - Nonsense mutation : There is a single nucleotide change but it will produce a stop codon (UAA,UAG, UGA). Example : Beta-thalessemia.
    - Frame shift mutation : Insertion or deletion of 1 or 2 nucleotides results in a shift in the reading frame of DNA.
      Example : Beta-thalessemia.

Micro RNA

00:19:21

It is a non-coding RNA.
(DNA leads to RNA and RNA becomes a protein, if it does not become a protein, it is called a non-coding RNA.)
It is only 22 nucleiotides in length.
It has some role in post transcriptional silencing.
It is of 2 types :

- Tumor suppressing miRNA (Good) : miR 15, 16.
  In cases of CLL, there is a deletion of miRNA 15,16.

Active space

- Oncogenic miRNA (Bad) : miRNA 155, 200.
- The various B cell lymphomas can be associated with increased expression of miRNA 150, 200.

Epigenetics :

They are hereditory chemical modifications in the DNA/ Histones/ chromatin.

They are reversible.

No change in the nucleotide sequence.

Occur by 2 processes :

1. DNA methylation (more common).
2. Histone deacetylation.

The role of epigenetics :

- Regulation of gene expression.
- X chromosome inactivation.
- Involved in cellular aging .
- Involved in various cancers.

It can be diagnosed in lab by 2 techniques :

Bisulphate sequencing.

Immunoprecipitation assays.

Gentic diagnostic techniques

00:25:53

Cytogenetic analysis :

- Karyotyping.
- FISH.

The cytogenetic techniques are used for known defects.

They can easy pick the chromosomal disorders.

They are usually for bigger defects.

molecular genetic assays :

- MLPA (multiplex ligation probe analysis).
- PCR (polymerase chain reaction).
- Sequencing.
- Array.

molecular techniques are used for unknown mutations or unknown loci.

Also used in molecular defects.

Active space

PCR :

Types :

1. Sanger sequencing :
   It is the gold standard for sequence determination.
2. Pyrosequencing : When the specimen is contaminated or the sample is very small.
3. Single base primer extention :
   When there is a known genetic defect.
4. Restriction fragement menth analysis :
   Unknown genetic defects.
5. Real time PCR : Quantitative estimation like in CML, to determine the load of cells with t (9:22).
6. Genome wide association studies :
   To see the trend of disease in a population.
7. Amplicon length analysis : Done for repetition of genome like trinucleotide repeat mutation.

Questions :

1. A 63 year old female presented with a breast lump measuring 6 X 5 cm. Truecut biopsy reveals IDC. Tumor cells are send for genetic testing. The number of tumor cells are very less and the sample had lost fat. Which technique is best suited?
   a. Sanger sequencing.
   b. RFLP.
   c. RT PCR.
   d. Pyrosequencing.

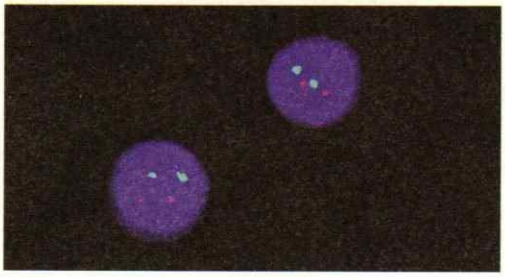
2. A patient has been diagnosed with CML and is started on Imatinib mesylate. The patient shows good response with it and is taken up for evaluation of Bcr: abl fusion remaining copies. Which of the following is the most suitable technique ?
   a. Sanger sequencing
   b. RFLP.
   c. RT PCR.
   d. GWAS.

Active space

FISH/ Fluorescent in situ hybridisation. 00:33:56

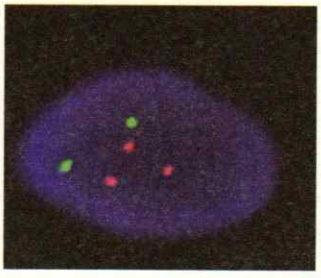
Applications :

- Chromosomal disorders (aneuploidy, deletion, trisomy)
- Translocations.
- Amplifications.

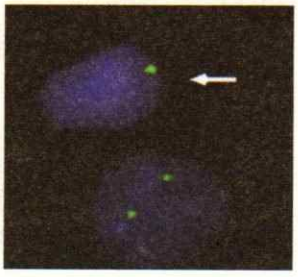


Normal : 2 green and 2 red dots (signals) → double chromosomes of each type.

Q. 1) 1 year old child with simian crease. Red is for chromosome 21. Image of FISH shows trisomy 21 (Down's syndrome).



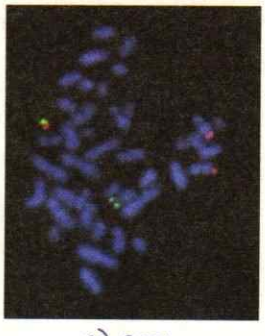
1) Downs syndrome



2) Turners syndrom

Q. 2) 16 year old girl with primary amenorrhoea and webbed neck. Green signifies X chromosome. 3 green signal. Loss of 1 X, which means patient has XO : Turners syndrome.

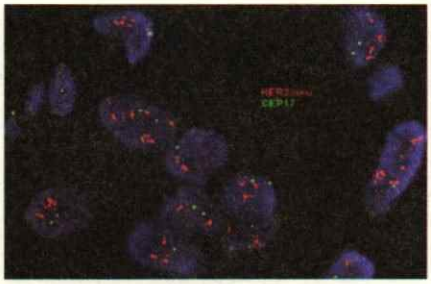
Q. 3) 14 year old male patient from Bihar with massive splenomegaly.
In image, red is chromosome 9 & green is chromosome 22
Here 1 red and green signal has fused with each other.
Diagnosis is CML.



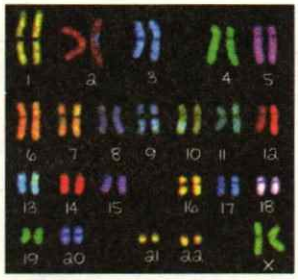
3) CML

Active space

Her2 neu amplification : Here multiple red and green signals can be appreciated, which is feature of amplification. Useful in a patient for breast cancer, if IHC for HER 2 nue come equivocal, FISH is often done.



Her2neu

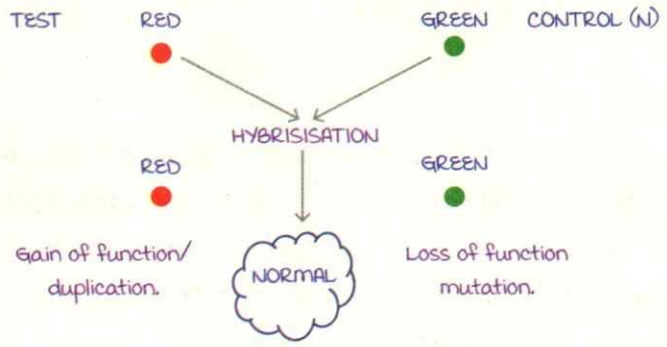


Spectral Karyotyping

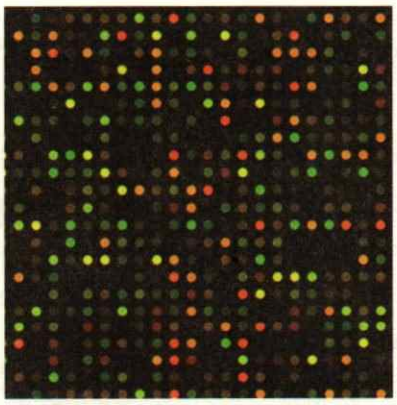
FISH is usually done in interphase of cell cycle.

Spectral Karyotyping :
It is a modification of FISH, which is actually a 5 colour FISH.

Comparative genomic hybridisation 00:42:41



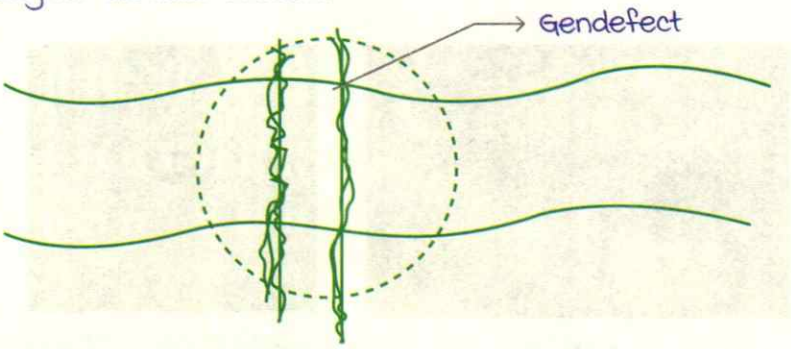
This is called as a microarray. Multiple people can be tested together.



Microarray

Active space

GEEN (Genome editing with engineered nucleases) :
Here the genome is being edited by engineered nucleases. Here DNA can be deleted, or it can be inserted in to genome using a molecular scissors.



The molecular scissors will create site specific breaks and join the ends by non-homologous end joining.

Nucleases available :

- TALEN.
- Zn-finger endonuclease.
- CRISPR-CAS9.

Drawbacks : Can be misused.

Question :

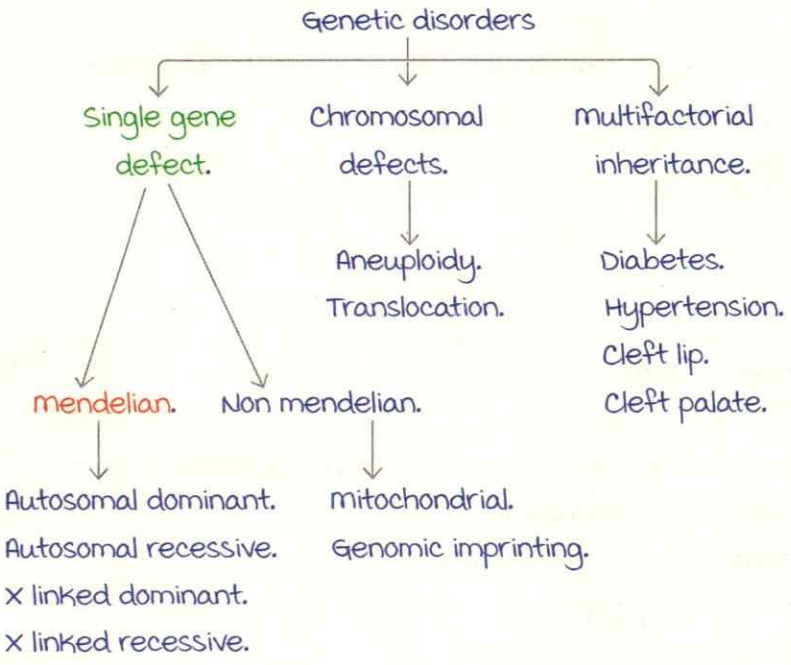
1. Biopsy from a 8 year old child with leg swelling was showing small round blue tumour cells consistent with a diagnosis of Ewing's sarcoma. What is the best method to detect translocation in this malignancy?
    a. Next generation sequencing.
    b. FISH.
    c. PCR.
    d. Conventional Karyotyping.

2. A patient who has autosomal dominant gene for type I osteogenesis imperfecta has blue sclera and slightly reduced height while,his brother has multiple fractures and deformities. This is an example of :
    a. Polymorphism.
    b. Mutation.
    c. Variable expressivity.
    d. Reduced penetrance

Active space

GENETICS - MENDELIAN MODES

Classification of genetic disorders 00:00:43



Autosomal dominant disorders 00:01:33

Males = females.

Can be expressed in a heterozygal state.

At least one parent of index case is affected.

Manifests in adulthood.

Due to defects in structural proteins.

Better prognosis.

Skip generations are absent.

Two properties :

- Incomplete penetrance →

  Eg: 100 people have defective gene for achondroplasia.

  80 people show disease.

  Penetrance = 80%.

Active space

- Variable expressivity →
  Clinical features vary in individuals with same genotype.

Genotypes in autosomal dominant disorder :

- Only genotypes possible: Aa & aa.
- A → Affected ; a → Normal.

Homozygous (AA) dominant is incompatible with life.

Q. Father is affected (Aa) & mother is normal (aa). What percentage of children will be affected?

Answer :

	a	a
A	Aa	Aa
a	aa	aa

50% will be affected and 50% will be normal.

Examples : Mnemonic → He Has A Very DOMINANT Father.

- Huntington's disease.
- Hereditary spherocytosis.
- Achondroplasia.
- VWD, VHL.
- Dystrophia myotonica.
- Osteogenesis imperfecta.
- Marfan's syndrome.
- Intermittent porphyria.
- NF-1.
- Adult onset polycystic kidney disease.
- NF-2.
- Tuberous sclerosis.
- Familial adenomatous polyposis, Familial hypercholestrolemia.

Marfan syndrome 00:13:33

Defect in Fibrillin 1 (FBN 1) gene on chromosome 15.
Defect in Fibrillin 2 (FBN 2) gene : Congenital contractural arachnodactyly.

Active space

Pathogenesis :

Fibrillin I gene is a helical protein with TGF-beta inside.

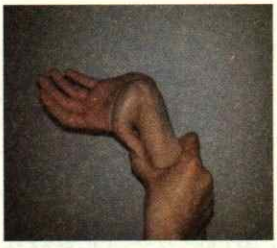
Mutation of fibrillin → Excess of TGF-Beta → Destroys elastin fibers.

Clinical presentation :

Skeletal defects →

Most striking feature.

- Tall stature :
  Long bones(span exceeds height).
- Long Spidery fingers & toes.
- Hyperextensible joints :
  Most common involved → Thumb.
- Dolicocephalic head.
- High arched palate.
- Pectus excavatum & scoliosis can occur.



Ocular defects :

- Ectopia lentis (Supero temporal dislocation of lens).
- Myopia.

CVS defects :

- Mitral valve prolapse →
  Most common cardiovascular defect.
- Aortic dissection →
  Most common cause of death.

Life expectany is halved due to cardiovascular complications.

Diagnosis of marfan's syndrome (Revised Ghent's criteria):

- Family history.
- Clinical signs & symptoms.
- Fibrillin I gene mutation.

Biopsy of vessels → Cystic medial degeneration.

Stain for elastin → Verhoeff's Van Gieson (VVG) stain.

Treatment :

TGF-Beta blocker (Losartan).

It is thought that President Abraham Lincoln & Julius Caeser may have had marfan's syndrome.

Active space

Neurofibromatosis Type 1 & Type 2 :

Neurofibromatosis Type 1 (NF-1) :

Gene on chromosome 17 encodes for neurofibromin.

Presentation :

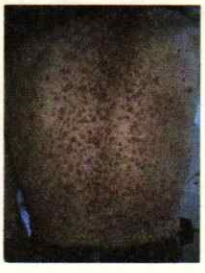
- Cafe-au-lait spots (> 6 spots).
- Neurofibromas.
- Lisch nodules (Pigmented iris hamartomas).

Patient can develop tumors :

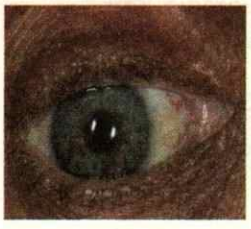
- Optic nerve gliomas.
- Meningiomas.
- Pheochromocytoma.

Can be associated with Juvenile myelo monocytic leukemia.

Multiple neurofibromas



Lisch nodules



Neurofibromatosis type 2:

Gene on chromosome 22.

Increased risk of bilateral acoustic neuroma or schwannommas.

Autosomal recessive disorders 00:26:46

Males = Females.

Only expressed in homozygous states.

When heterozygous → Carrier/ trait.

Show complete penetrance.

Usually due to enzyme deficiency.

Skip generations present.

Manifests in childhood/ infancy.

Active space

Examples :

Mnemonic → ABCDEFGHI.

- Alpha antitrypsin deficiency, Ataxia telengiectasia, Alkaptonuria.
- Beta thalessemia.
- Cystic fibrosis, Congenital adrenal hypoplasia.
- Deafness.
- Emphysema.
- Fredrich's ataxia.
- Gaucher's disease, Glycogen storage disorders, Galactosemia.
- Hemochromatosis, Homocystinuria.
- Inborn errors of metabolism.

2 lysosomal storage disorders that are not autosomal recessive :

- Fabry's disease.
- Hunter's disease.

Hematological enzyme deficiency that is not autosomal recessive:

- G-6PD deficiency.

Lysosomal storage disorders 00:31:03

Disorders	Enzyme deficiency
Sphingolipidoses	
Gaucher's disease.	Glucocerbrosidase.
Tay sach's disease.	Hexosamimindase A.
Fabry's disease.	Alpha galactosidase A.
Krabbe disease.	Galactocerbrosidase.
Niemann pick disease.	Sphingomyelinase.
Mucoplysaccharidoses	
Hurler syndrome.	Alpha L iduronidase.
Hunter syndrome.	Iduronate 2 sulfatase.

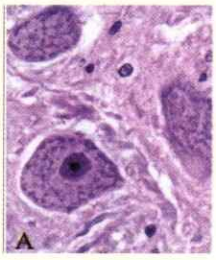
Active space

Tay Sachs disease :

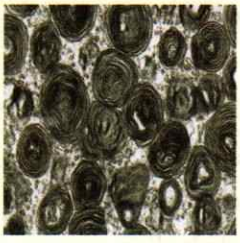
Mnemonic → TAYSACHS

- Autosomal recessive.
- Young adults.
- Cherry red Spot.
- Common in Askenazi jews.
- CNS defects.
- Hexosaminidase alpha subunit deficiency leads to accumulation of GM 2 Ganglioside.
- Onion Skinning appearance in electron microscopy.

Brain biopsy : Ballooned neurons.



Electron microscopy : Onion skin appearance.



Onion skin appearance in medicine :

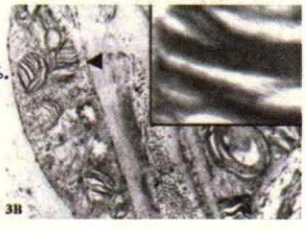
- Biopsy of malignant hypertension.
- Nerve biopsy of CIPD.
- Biopsy of primary sclerosing cholangitis.
- Gross specimen of spleen in SLE.
- X-ray of ewing's sarcoma.
- Electron microscopy of Tay sach's disease.

Neimann pick disease :

Defect of sphingomyelinase.

Sphingomyelin accumulate in lysosomes.

Electron microscopy : Zebra bodies.



Gaucher's disease :

Most common lysosomal storage disorder.

Deficiency of _____

Accumulation of glucocerebroside.

Active space

Clinically manifests in three forms :

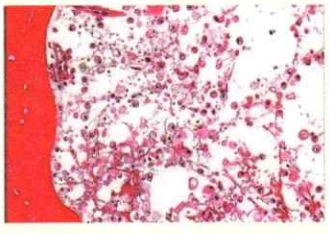
1. Non neuronopathic →
   - Most common form.
   - Affects adults.
   - Some glucocerebrosidase activity present.
   - No CNS symptoms.
   - Hepatosplenomegaly, fractures, bone pain.
2. Neuronopathic →
   - Less common.
   - Absent glucocerebrosidase activity.
   - Infants.
   - CNS symptoms present.
3. Intermediate.

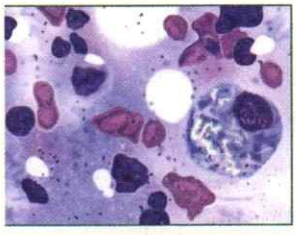
Biopsy → Gaucher's cells.

Wrinkled/crumbled tissue paper appearance.

Stains :

- PAS+
- Oil red O +
- Pearl's stain +





Pseudo gaucher's cell → Chronic myeloid leukemia (PAS–).

X linked recessive disorders 00:41:45

Males >>> Females.

Females are usually carriers.

Females can be affected when there is random X inactivation during Lyon's hypothesis.

Examples :

Mnemonic → Lady Hardinge College Girls Don't Care About Foolish Words.

- Lesch Nyhan syndrome.
- Hemophilia A & B, Hunter's disease.
- Colour blindness.

Active space

- G6PD deficiency.
- Duchenne muscular dystrophy.
- Chronic granulomatous disease.
- Agammaglobunemia.
- Fabry's disease,Fragile X syndrome.
- Wiskott aldrich syndrome.

Father is affected, mother is normal. :

	X	X
X^0	XX^0	XX^0
Y	XY	XY

All daughters are carriers.

All sons are normal.

Father doesn't inherit the disease to sons, all daughters are carriers.

X linked dominant disorders

00::46:15

Rare disorders.

Examples :

Mnemonic→: RAVI.

- Rett's syndrome.
- Alport syndrome.
- Vitamin D resistant rickets.
- Incontinentia pigmenti.

Alport syndrome :

- Inherited by any mode.
- Most common mode : X linked dominant inheritance.

Clincal scenarios

00::47:04

Q. Father has achondroplasia,mother is normal. What percentage of children will have achondroplasia?

Answer :

Mode of inheritance → Autosomal dominant (Heterozygous state)

	a	a
A	Aa	Aa
a	aa	aa

Active space

50% will be affected and 50% will be normal.

Q. Husband has sickle cell anemia, wife is a carrier of sickle cell anemia. what is the percentage of children affected with sickle cell anemia?

Answer :

mode of inheritance → Autosomal recessive.

	A	a
A	AA	Aa
A	AA	Aa

50% will be affected, 50 % carriers.

Q. Husband has HbA2 : 4.8%, wife has HbA2 : 2%. what is the percentage of children affected with thalssemia major?

ANS:

Normal HbA2 level: 2-3.5%.

Beta Thalssemia trait HbA2 level: 4-9%.

mode of inheritance: Autosomal recessive.

	A	a
A	AA	Aa
A	AA	Aa

50% Kids will be carriers, while 50% will be normal.

Hence no children with thalssemia major.

Q. A 22 year old man is evaluated for mitral regurgitation due to mitral valve prolapse. Examination reveals a tall, slender, young man with long extremities and long tapering fingers. Pupillary dilation reveals bilateral dislocation of lens. This patient is potentially at increased risk for development of which of the following?

A. Aortic dissection (marfan's syndrome).

B. Lisch nodules.

C. Non caseating granuloma.

D. Rapidly progressive renal failure.

Active space

Q. Which of the following dyads are correct?

A. Marfan syndrome : AR.

B. PKU : AD.

C. Vit. D resistant rickets : AD.

D. Alkaptonuria : AR.

E. DMD : XLR.

Q. A patient has an autosomally inherited condition. The patient and his grandfather show evidence of disease, but the patient's father is asymptomatic. This is an example of?

A. Mutation.

B. Polymorphism.

C. Variable expressivity.

D. Reduced penetrance.

Active space

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GENETICS : NON-MENDELIAN MODES AND PEDIGREE

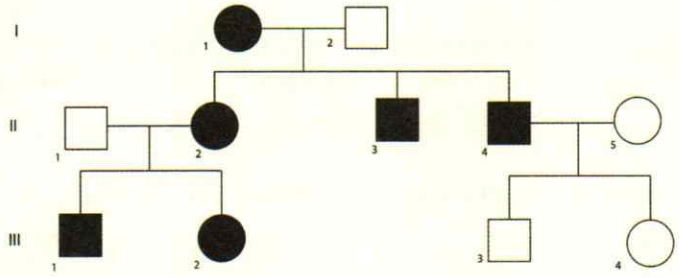
Mitochondrial inheritance 00:02:44

Exclusively maternally inherited.

Pathogenesis :
During fusion of ova and sperm, the ova eliminates all sperm mitochondrial DNA by ubiquitin protease pathway.

↓

Zygote DNA contains only maternal mitochondrial DNA
Mother transmits disease to all children, whereas father to none.



Mitochondrial genome 00:07:26

Mitochondrial genome : 37 genes, 12 t-RNA, 2 r-RNA.
Heteroplasmy : Presence of normal + Mutant mitochondrial DNA in same person.
Organs affected are : CNS, eye, skeletal muscles.
Disorders :

- MELAS : Mitochondrial Encephalopathy, Lactic acidosis and Stroke like episodes : MC.
- Leigh syndrome.
- Leber's hereditary optic neuropathy.
- Pearson syndrome.
- CPEO : Chronic Progressive External Ophthalmoplegia.
- Kayrnesare syndrome.
- NARP syndrome.

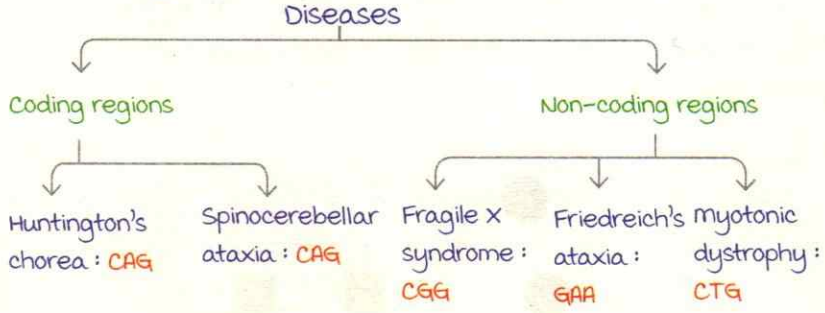
Active space

Trinucleotide repeat mutation 00:12:48

Mutations which causes increased number of codons that causes disease.

1st generation : CAG 40 : Normal.
↓ ↑ Mutation
2nd generation : CAG 100 : Premutation.
↓
3rd generation : CAG 1000 : Full mutation.

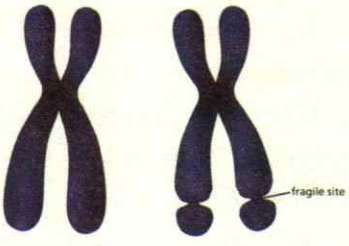
Anticipation : The severity of the disease increases with each successive generation.



These diseases mostly involve cytosine and guanine nucleotides.

Fragile X syndrome 00:22:53

X linked recessive disorder
When cells are cultured in folate deficient media, constriction is seen in X chromosome.



Fragile X chromosome

Due to loss of function mutation in FMR 1 gene leading to increased CGG repeats.
Normal : 6 to 55 CGG repeats.
Premutation : 55 to 200 CGG repeats.
Full mutation : 200 to 4000 CGG repeats.
Fragile X syndrome, Huntingtons chorea follow non mendelian mode of inheritance despite being X linked and Autosomal dominant diseases respectively

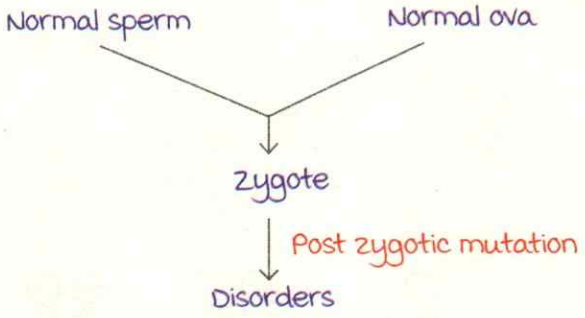
Active space

Clinical features :

- 2nd MC genetic cause of mental retardation.
- MC inherited cause of mental retardation.
- Macroorchidism (large testis) : most distinctive feature.
- Large head.
- Large everted ears.
- Large jaws/mandible.

Fragile X tremor / ataxia : Gain of function mutation in FMR 1 gene (Premutation).
Fragile X associated ovarian failure : Gain of function mutation in FMR 1 gene (premutation).

Gonadal Mosaicism :
Type of autosomal dominant inheritance.



No risk to the sibling.
Examples :

- Tuberous sclerosis.
- Osteogenesis imperfecta.

Genomic imprinting 00:40:16

Gene silencing / inactivation.
Physiologically either paternal / maternal allele is inactivated : Only one allele is functional.
Happens by the process of Epigenetics : Lowers expression of genes.

- DNA methylation.

Active space

- Histone deacetylation.

Chromosome 15q11

- Prader willi syndrome
- Angelman syndrome

Prader willi syndrome

00:46:11

Pathogenesis :

Deletion (70%) | Uniparental disomy (15-20%) | Abnormal genome imprinting (4%)

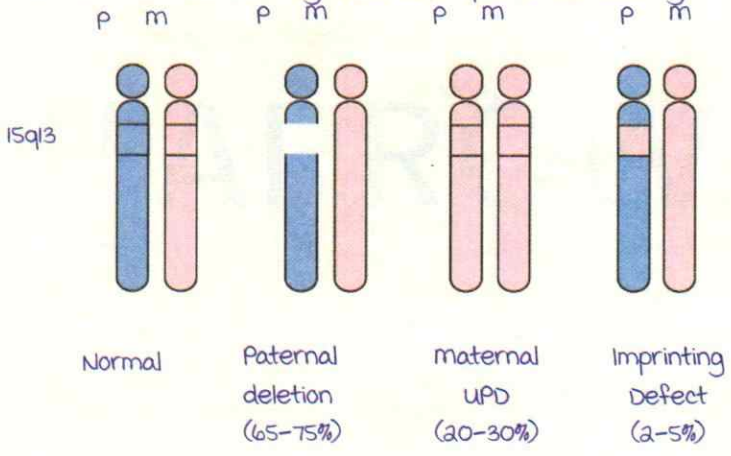
Deletion :

Maternal allele is silenced and only paternal allele is functioning normally.

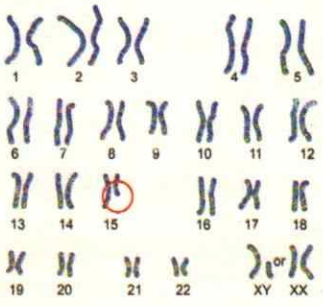
If paternal allele is deleted and maternal allele is silenced : Prader willi syndrome.

Uniparental disomy :

If both the alleles are maternal (maternal disomy) which are non-functional they lead to uniparental disomy.



SNORP gene mutation have been observed lately.

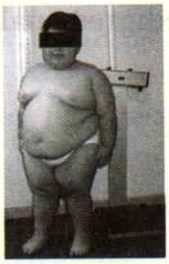


Clinical features

- Small bird like head.
- Mentally retarded.

Active space

- Respiratory problems.
- Obesity.
- Short lifespan.
- Hyperphagia.
- Hypogonadism.
- Hypotonia.

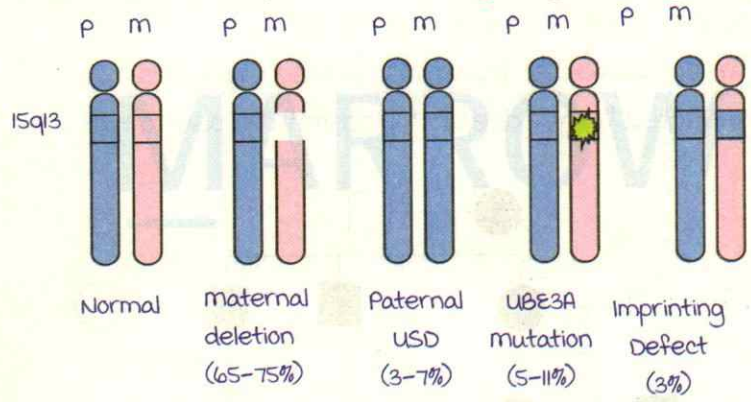


Angelman syndrome

00:53:16

Paternal gene is silenced, maternal gene is functional.

Maternal deletion + paternal silencing : Angelman syndrome.



UBE3A gene mutation have been implicated lately.

Clinical features

- Inappropriate laughter : Happy puppet syndrome.
- Stiff / ataxic movements : Hand flapping.
- Microcephaly.
- Seizures.
- Mental retardation.

Prader willi syndrome	Angelman syndrome
Chromosome 15	Chromosome 15
maternal imprinting	Paternal imprinting
Paternal deletion	maternal deletion
Maternal disomy	Paternal disomy
SNORP gene	UBE3A gene
Hyperphagia, obesity, mental retardation	Happy puppet syndrome

Active space

Pedigree analysis

01:00:24

Types :

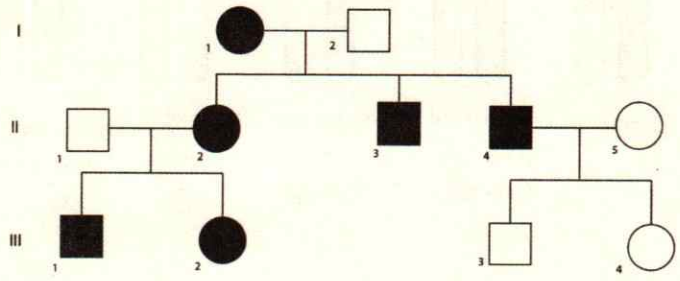
- Mitochondrial inheritance
- Autosomal dominant
- Autosomal recessive
- X linked recessive
- X linked dominant
- Gonadal mosaicism

Steps for pedigree analysis :

1. Rule out mitochondrial inheritance

   Affected mother transmits disease to all kids

   Affected father does not transmit disease to kids



2. Rule out whether dominant/recessive disorders.

   Dominant : skip generation absent

   Recessive : skip generation present

   If recessive,

   Male = female : Autosomal

   Male >>> female : X linked

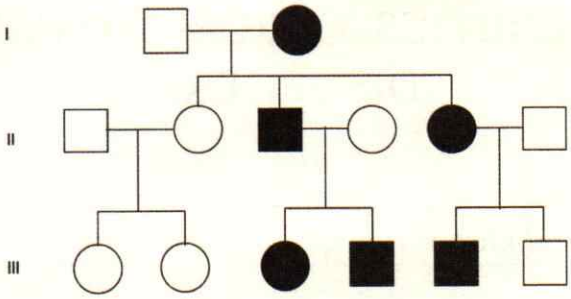
   If dominant,

   Autosomal : Father to son transmission present.

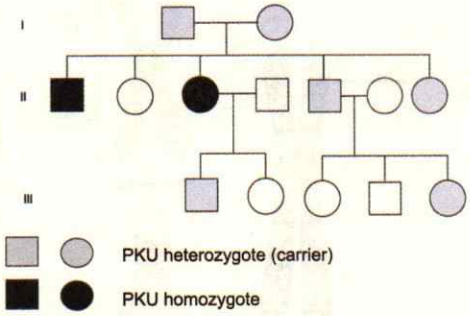
   X linked : Father to son transmission absent and 100% daughters are affected.

   Gonadal mosaicism : One child affected, but none of the parents affected.

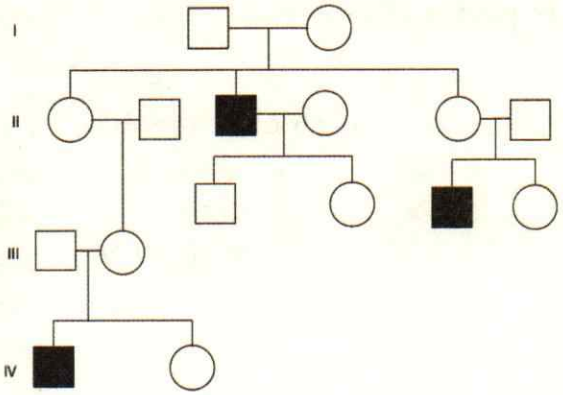
Active space



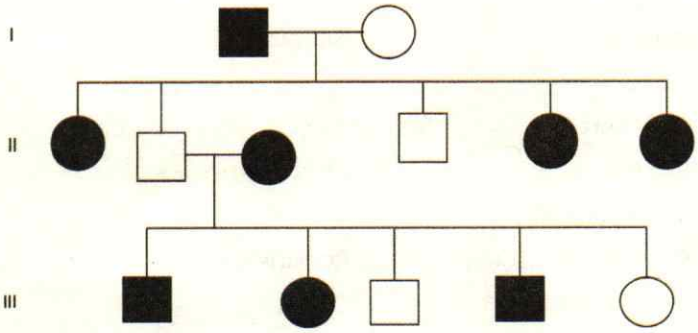
1. Autosomal Dominant



2. Autosomal Recessive



3. X -linked recessive



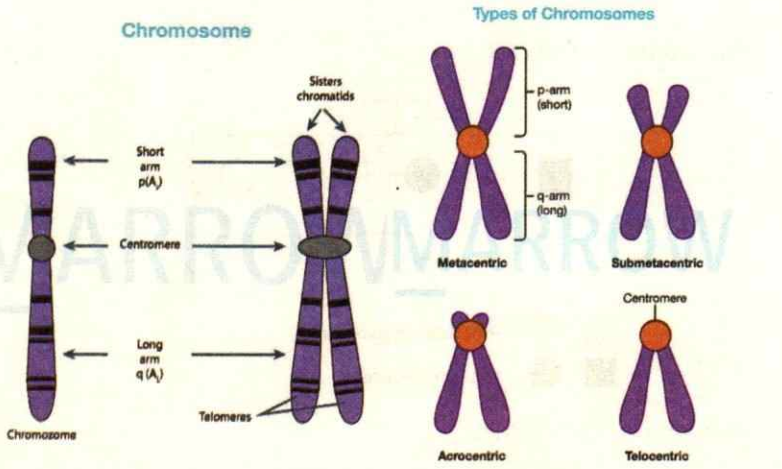
4. X-linked Dominant

Active space

GENETICS- CHROMOSOMAL DISORDERS

Structure of chromosome

00:01:12



Depending on position of centromere, types of chromosomes :

- **Metacentric** — p = q — Chr. 1
- **Submetacentric** — p < q — Chr. X
- **Acrocentric** — p <<< q — Chr. 13, 14, 15, 21, 22, Y
- **Telocentric** — only one arm. Doesn't exist in humans

Chromosomal abnormalities

00:07:54

Chromosomal abnormalities

Structural

- Deletion
- Insertion
- Translocation
- Ring chromosome
- Iso chromosome
- Inversion

Numerical

Any variation from haploid no. of 23 is Aneuploidy.

Aneuploidy

- Monosomy
- Trisomy

Only monosomy compatible with life : Turner's syndrome.

Active space

Structural abnormalities 00:11:22

1. Insertion : Portion of a chromosome inserted.
2. Deletion : Portion of a chromosome deleted.
3. Ring chromosome : Break at both ends, fusion of damaged sticky ends. Functionally inactive.
   Ring chromosome seen in Turner's syndrome.
4. Isochromosome : If division happens horizontally leads to Two short/ two long arms.
   MC Isochromosome : i X q
   MC Isochromosome in cancer : i 17 q
   MC Isochromosome in testicular tumor : i 12 p
5. Inversion : Two breaks with attachment of inverted segment.

   - Para – centric: If same side of centromere
   - Peri – centric: On opposite side

6. Translocation : Exchange of material between two chromosomes.

   - Balanced
   - Robertsonian: Translocation between 2 acrocentric chromosomes. Chr. 13, 14, 15, 21, 22, Y. Produces one very short arm and one very long arm.

t (14:21) Robertsonian translocation seen in 4% cases of Down's syndrome.

Down's syndrome 00:22:26

Trisomy 21.
MC chromosomal disorder.
MC genetic cause of mental retardation.
MC inherited cause of mental retardation : _____
_____

Pathogenesis :

- Meiotic non-dysjunction (95%) : Occurs in oogenesis.

47 chromosomes are present. Maternal age is a risk factor.

Active space

- Robertsonian translocation (4%).

46 chromosomes are present.

Maternal age is not a risk factor.

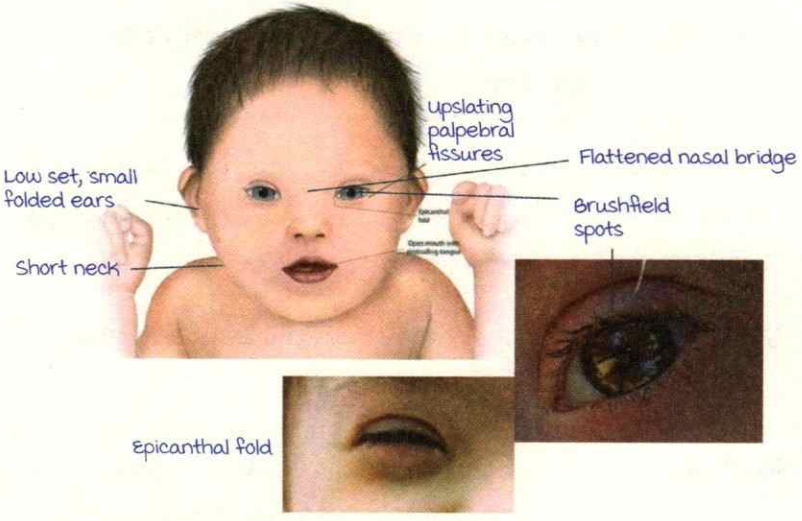
- Mosaics (1%).

Triple test : AFP, β – HCG, unconjugated estradiol.

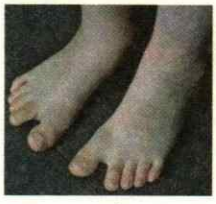
Quadruple test : Triple test + Inhibin.

Clinical features and complications of Down's syndrome

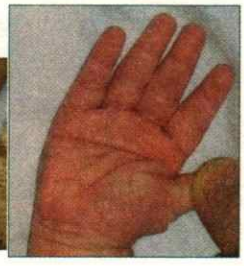
00:30:25



All these facial characteristic features give rise to an appearance called as Mongloid Idiocy.

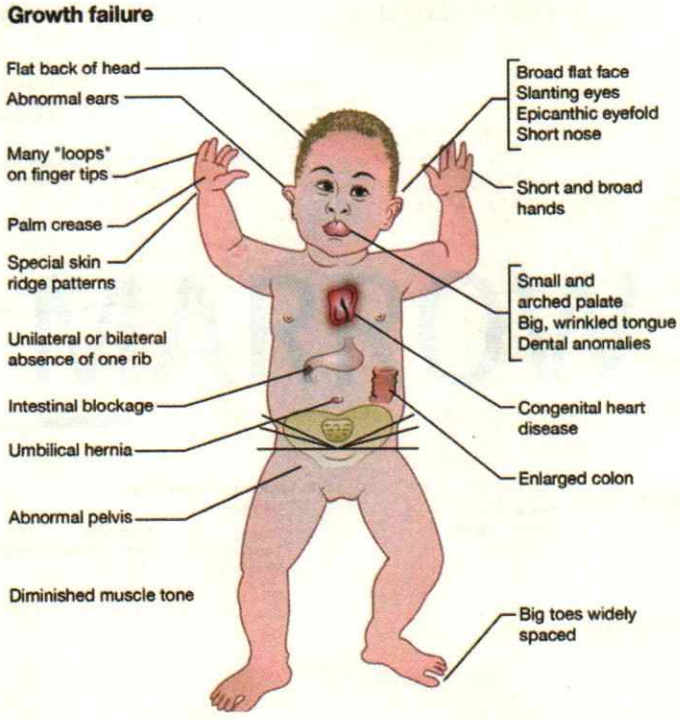

Sandle Gap/Saddle toe


Normal Palm crease


Simian crease

- Simian crease : Single palmer crease.
- Clinodactyly.
- Overlapping fingers.
- Sandle Gap/ Saddle toe : Increased gap between 1st & 2nd toe.

Active space



Complications of Down's syndrome :

1. Cardiovascular defect :
   MC Cardiovascular defect : Endocardial cushion defect, VSD.
2. GIT : Annular pancreas, Duodenal atresia, Hirschsprung disease.
3. Acute leukemia :
   MC leukemia : ALL
   MC leukemia in children < 3 yrs : AML
   MC subtype of AML : AML M7
4. Endocrine : Hypothyroidism.
5. CNS : Premature Alzheimer's disease.

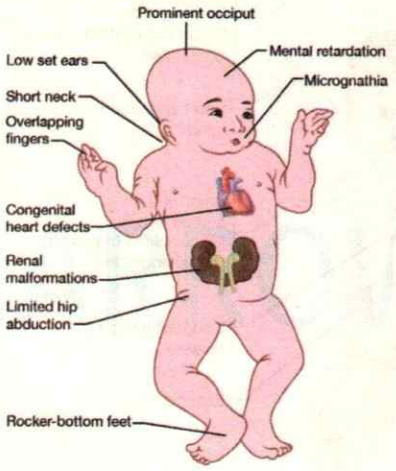
Edward and Patau syndrome 00:39:55

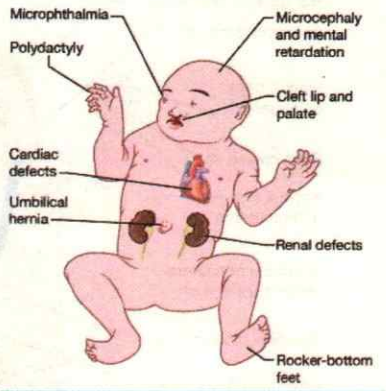
Common features of both syndromes :

- Mental retardation.
- CVS defects.
- Rocker bottom feet.
- Prominent occiput.

Active space

Edward syndrome : Trisomy 18 Patau syndrome : Trisomy 13





Incidence: 1 in 15,000 births
Karyotypes:

Trisomy 13 type : 47,XX, +13
Translocation type : 46,XX ,+13,(der13:14)(q10:q10)
Mosaic type : 46,XX/47, XX,+13

del 22 9q 11.2

A/K/A DiGeorge syndrome or Velo cardio facial defects.
(mnemonic : CATCH 22)

Cleft lip/ palate

Abnormal facies

Thymic hypoplasia

Cardiacdefect

Hypocalcemia

del 22q11. 2

Defect in development of 3rd & 4th pharyngeal pouch.
Causes thymic & parathyroid hypoplasia

Trisomy 22 (Cat eye syndrome)
Multiple colobomas in the eye.

Cat cry syndrome (del 5p)

- Cat like cry.
- Behavioural abnormalities.
- Developmental delay.

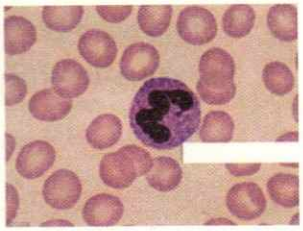
CRI-DU-CHAT Syndrome

Sex chromosomal disorders 00:47:10

Lyon's hypothesis :
Only one of the X chromosomes is genetically active.
Other X, of either paternal or maternal origin becomes

Active space

inactive (occurs randomly).
Inactivated X chromosome : Barr body.
Shape : Drumstick appearance.
Sample : Buccal mucosa.


Barr body

Clinical applications :

Normal male	XY	No barr body
Normal Female	XX	1 barr body

No. of barr body = No. of X chromosome : 1

Clinical applications of barr body :
Turner's syndrome (XO) : No barr body.
Klinefelter syndrome (XXY) : Extra barr body.

Klinefelter's syndrome 00:53:43

MC cause of male hypogonadism.
More the no. of X chromosome, more is the mental retardation.

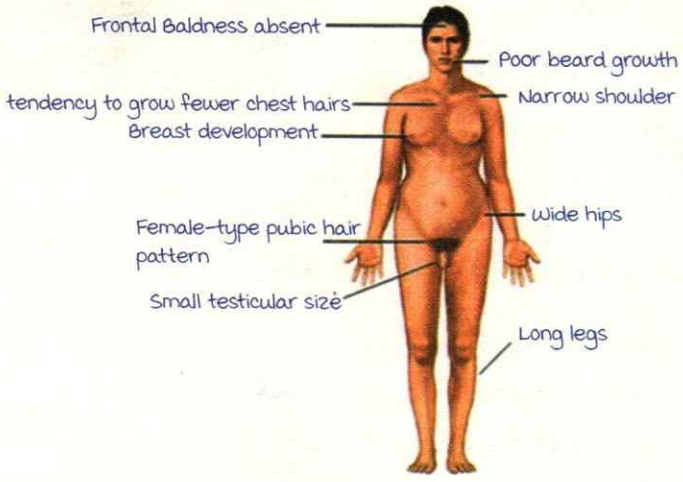
Pathogenesis :
Meiotic non dysjunction (occurs in both oogenesis & spermatogenesis)

1. Syndromes associated with advanced maternal age :
   Down's syndrome, XXX syndrome.
2. Syndromes associated with advanced paternal age :
   - Marfan syndrome.
   - Osteogenesis imperfecta.
   - Achondroplasia.
3. Syndrome associated with both advanced maternal and paternal : Klinefelter.

Clinical features :
- Tall stature.
- Poor muscle tone.
- Reduced secondary sexual characteristics.
- Gynecomastia.
- Eunuchoid body habitus.
- Long extremities.

Active space

- Frontal baldness absent.
- Testicular atrophy : Infertility.



Testicular Biopsy : Atrophy of seminiferous lobules.
Hyalinisation of seminiferous lobules.
Leydig cell hyperplasia.

Hormonal changes :

Increased FSH, LH and decreased testosterone.

CVS changes : MVP.

Increased risk of developing extragonadal germ cell tumour and Breast CA.

Turner's syndrome

01:02:40

MC cause of female hypogonadism.

Pathogenesis :

1. Meiotic non -dysjunction.
2. Anaphase lag.
3. Ring chromosome.
4. Isochromosome.
5. Mosaics.

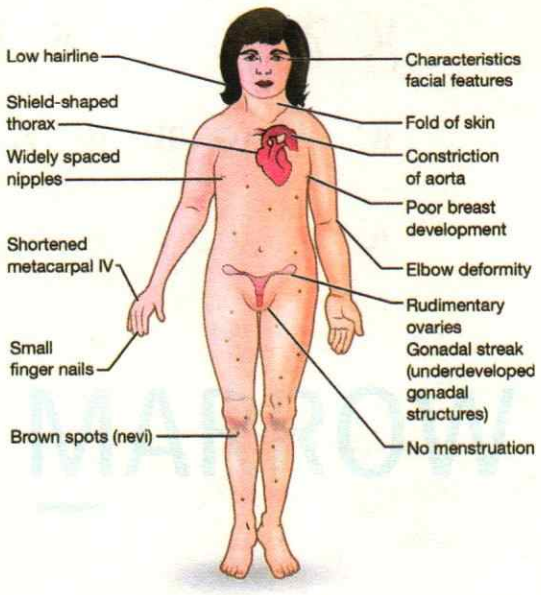
Webbed neck due to lymphedema.

Elbow deformity : Cubitus valgus.

Ovaries : Streaked ovaries.

Clinical features :

Active space



MCC primary amenorrhea : Turner's syndrome.
MC CVS defect : Bicuspid aortic valve
MC cause of death : Co-arctation of aorta

Mnemonic : CLOWNS
Cardiac abnormalities, Cubitus valgus, Cystic hygroma.
Lymphedema
Streaked Ovaries
Webbed neck
Normal intelligence, Nipples widely spaced
Short stature, Short 4th metacarpal

Increased risk of developing Gonadoblastoma.

Noonan's syndrome :
Same Clinical features of Turner's syndrome.
Normal Karyotype.
Mutation in chromosome 12.

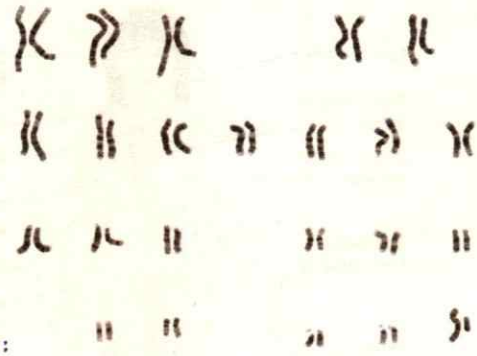
Karyotyping 01:10:59

Karyogram : Arrangement of chromosomes in descending order of length followed by sex chromosomes.

Uses : To diagnose structural & numerical abnormalities of chromosome.

Active space

Normal Karyogram



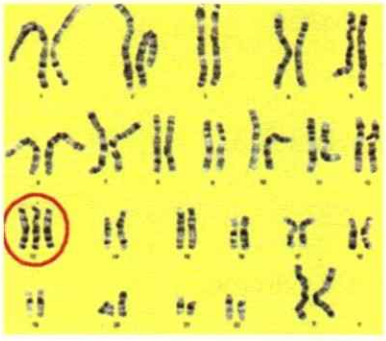
Sample taken from :

- Amniocentesis.
- Chorionic villi sampling.
- Peripheral blood lymphocytes.
- Skin fibroblasts.

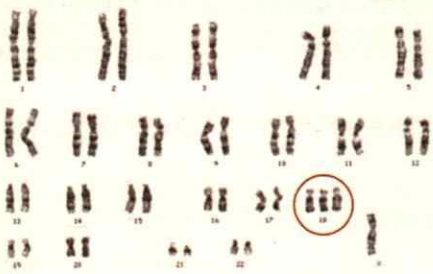
Arrest the cells in metaphase (using colchicine).

Staining : MC G-banding (Giemsa banding).
Q - banding (quinacrine).
Using light microscope,
resolution required for Karyotyping : 5 mb.

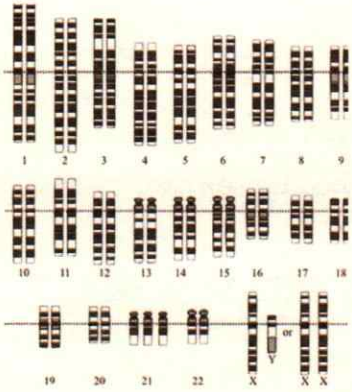
Patau syndrome



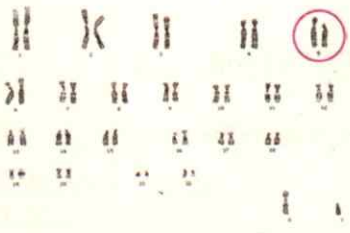
Edward syndrome



Down's syndrome

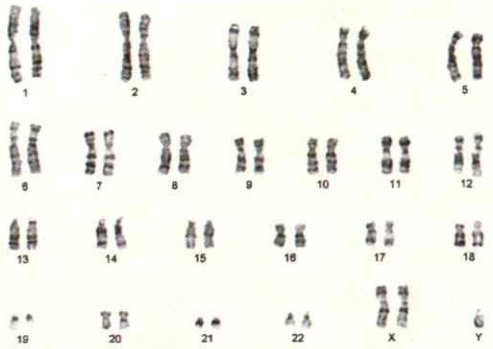


Cri-Du-Chat syndrome



Active space

Klinefelter's syndrome



MCQs :

Q. All of the following are characteristic of Turner's syndrome except:

A. Webbed neck

B. Coarctation of aorta

C. Cubitus valgus

D. Umbilical hernia

Q. Which chromosome contains the most known genetic disease of any human chromosome?

A. I

B. II

C. 9

D. 6

Q. A tall man with gynecomastia and testicular atrophy has a testicular biopsy that shows sparse, completely hyalinized seminiferous tubules. Leydig cells are present in large clumps. Which of the following genetic disorders should be suspected?

A. Trisomy 18

B. Trisomy 21

C. 45, XO

D. 47, XXY

Q. A tall man presents with complaints of infertility. Examination shows gynecomastia and reduced secondary sexual characteristics. Karyotyping analysis revealed an XXY karyotype. Which of the following is not true about the condition?

Active space

A. Levels of FSH are reduced.

B. Testosterone levels are reduced.

C. Plasma estradiol levels are elevated.

D. Increased risk for breast cancer.

Q. A 21 year old girl with short stature says that her breasts have not developed properly and periods have not started as yet. She also has low posterior hair line. The Karyogram from the patient is given below. Which of the following is true for the disease patient is suffering from?

A. Endocardial cushion defect is the CVS complication.

B. Short fourth metacarpal.

C. Abnormal facies.

D. Micrognathia.

Active space

IMMUNITY-TYPES OF IMMUNE CELLS

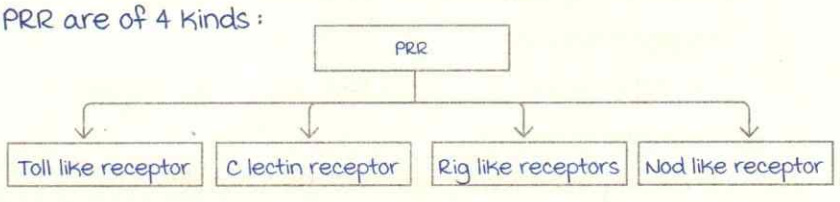
Types of immunity 00:01:19

Innate and adaptive immunity.

Innate	Adaptive
Present by birth.	Acquired later on exposure to antigen.
Non specific	Specific
No memory.	memory present.
Examples include : 1. Epithelial barriers like skin, GIT. 2. Plasma proteins like C-reactive protein. 3. Neutrophils, macrophages, dendritic cells, complement.	Cells are of 2 types : 1. B lymphocytes : Provides humoral immunity and produces antigens. 2. T lymphocytes : Involved in cell mediated immunity and help with immunity against intracellular microbes.

Pattern recognition receptors (PRR) :
This is a component of innate immunity. The receptors are present on the plasma membrane or cytoplasm or endosome.
The purpose of these receptors : To recognize specific patterns on microbes.
The receptors on :
The plasma membranes : Detect extracellular organism.
In the cytoplasm : Detect intracellular organism.
On the endosome : Detect ingested microbe.

PRR are of 4 kinds :



Toll like receptor (TLR) :
There are around 10 TLR's discovered, and are located on the plasma membrane.

Active space

Function :

To detect gram positive and gram negative bacteria.

C lectin receptor :

Located on the plasma membrane.

Detect the fungal glycans.

Rig like receptors :

Present on the cytoplasm and detect viruses.

Nod like receptor :

Present on the cytoplasm and detects :

N : Necrotic debris.

O : Ion transport.

D : Diabetes mellitus.

After detection of these, the NOD like receptor activates caspase 1 which then causes production of IL-1 and leads to result in inflammation and fever.

Inflammasome can be involved with NOD like receptor.

Different types of immune system cells 00:10:31

Natural Killer cell (NK) :

- Usually produced by a large granular lymphocyte.
- Constitutes 5 to 10% of circulating blood lymphocytes.
- It is not a B cell and a non T cell. It does not have both T cell and B cell receptors and is referred to as null cell.
- Not MCH restricted (unlike T cell).
- Function :

  It can be part of both innate and adaptive immunity.

  1. Innate immunity :

     Directly Kill the virus infected cells or tumor cells.
  2. Adaptive immunity :

     Antibody dependant cell mediated cytotoxicity.
- Popular markers for NK cell : CD 15 and CD 56.

  CD 56 : Role is still not fully understood.

  CD 16 : Detect and binds to Fc fragment of IgG on target cells and Kill the cell by perforins and releasing toxins and granzymes.

Active space

- NK cells have 2 different kinds of receptors.
  1. Activating receptors : NKG2D.
  2. Inhibitory receptors : CD94, CD 96.
  These prevent self cells from being attacked by NK cells.
- Cytokines produced by NK cells :
  IFN-γ : (Cytokine majorly responsible for granuloma formation). This cytokine leads to the activation of macrophages (to epithelioid cell).
- Cytokines responsible for the proliferation of NK cells :
  IL-2 and IL-15.

B lymphocyte

00:17:57

- Constitute around 15-20% of circulating blood lymphocyte.
- They are responsible for humoral immunity, i.e. produce antigens against extracellular microbes.
- These cells mature in the bone marrow.
- Common sites of B lymphocytes :
  1. Cortex of the lymph node.
  2. Peyer's patches in GIT.
  3. White pulp of spleen.
- In cases of B lymphocytic defect like Bruton agammaglobulinemia, the above mentioned sites would be atrophic.
- Markers for B lymphocytes :
  CD 10 or CALLA, CD 19, CD 20, CD 21, CD 22, CD 23, Ig α (CD 79a), Ig β (CD 79b).
  CD 79a and CD 79b are also signal transduction molecules present on the surface of B lymphocyte.
- Pan B cell marker : CD 19.
- Receptor for EBV on B cell : CD 21.

Infections caused by EBV :

- Infectious mononucleosis.
- Hodgkins lymphoma.
- Burkitts lymphoma.
- Non hodgkins lymphoma.

Active space

- Nasopharyngeal carcinoma.
- Post transplant lymphoproliferative disorders.

B cell receptors :
These are IgM or IgD antibody along with signal transduction molecules.

Mechanism of activation of B lymphocytes :
This activation can occur by 2 pathways :

- T cell independent pathway :
  This is activated when the antigen is a lipopolysaccharide.
  This antigen activates B cell which forms a plasma cell, which produces IgM.

- T-cell dependant pathway :
  This pathway is activated when a proteinaceous antigen is present.
  The B cell has CD 40 receptor & helper T-cell has CD 40L.
  The antigen first interacts with the CD 40L and forms IgM and IgD antibodies, which then undergo class switching mechanism to form IgG, IgA and IgE.
  IgG : Crosses placenta.
  IgA : Present in all body secretions.
  IgE : most critical antibody in type I hypersensitivity reaction.
  IgM : It has the highest molecular weight, pentameric structure and is called as millionaire's antibody.

- The helper T cell also forms IL-4 and IFN-γ.

Increased IgM secretion disorder is seen in : Waldenstrom macroglobulinemia/hyperviscosity syndrome.

Plasma cell disorder which produces abnormal immunoglobins which are monoclonal : multiple myeloma.

Active space

T lymphocytes 00:27:22

They are responsible for cell mediated immunity and constitute 60 to 70% circulating lymphocyte.
There are 2 types of T-cells :
CD 4 & CD 8 T cells (ratio 2 : 1).
This ratio is decreased in HIV patients and increased in sarcoidosis patients.

These cells mature in the thymus and are found at :

- Paracortex of the lymph node.
- Periarteriolar lymphoid sheath.
- Intraepithelial lymphocytes.

In a patient with T cell disorder, these sites undergo hyperplasia.

Markers of T cell :

- CD 1, 2, 3, 4, 5, 7, 8.
- Pan T cell marker : CD 3.

T cell receptors are of 2 types :

- αβ : Present on 95% of cells and is a polypeptide which is MHC restricted.
- γδ : Present on 5% of cells and provides protection against the microbes which try to enter through the epithelial barriers.

Helper T cell	Cytotoxic T cell
CD 4+ T cell.	CD 8+ T cell.
MHC II restricted.	MHC I restricted.
1st line of defence in the body.	2nd line of defence in the body.
It helps the B cell in producing the antibodies.	It directly kills the infected cell by perforin granzyme mechanism.
It helps in the activation of macrophages.	

Active space

The 3 types of helper T cells :

- TH 1 : Cytokines produced are IFN-γ (signature cytokine produced by TH 1) and IL-12.
  IFN-γ helps in the activation of macrophages and helps in the production of IgG antibody.
  It also helps in the fight against intracellular microbes.

- TH 2 : It produces 3 other antibodies, IL-4, IL-5 and IL-13.
  IL-4 : Causes increased production of IgE antibody and plays a role in activation of macrophages.
  IL-5 : Helps in the production of eosinophils and helps in the activation of mast cells.
  IL-13 : Activation of macrophages.
  TH 2 lymphocyte helps in fighting helminthic infections.

- TH 17 : Leads to the production of 2 cytokines, IL-17 and IL 22.
  They play a role in recruitment of neutrophils and macrophages.
  TH 17 helps in fighting against extracellular microbes.

Active space

HYPERSENSITIVITY REACTIONS

Types of hypersensitivity reactions 00:00:52

Type I
Type II — Antibody mediated hypersensitivity reaction.
Type III

Type IV → Cell mediated hypersensitivity reaction

Type V → Modification of Type 2 hypersensitivity reaction.

Type I hypersensitivity reaction 00:01:28

AKA Anaphylactic hypersensitivity (HS) reaction.

Examples :

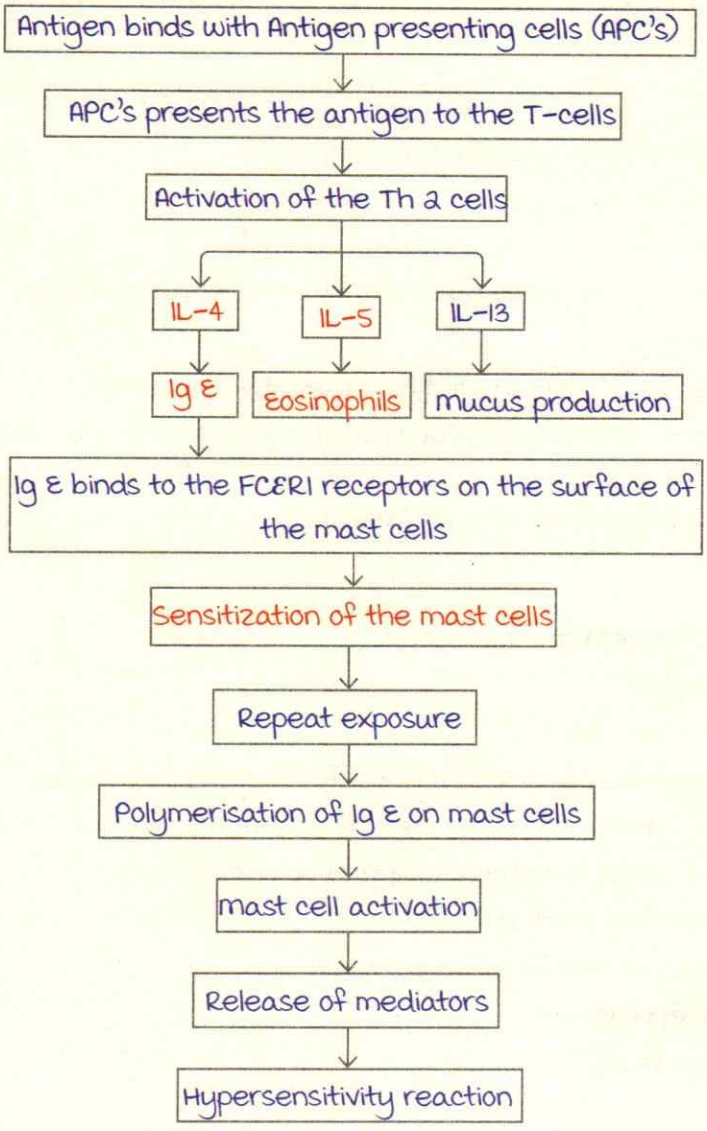
mnemonic : ABCD

- Atopy/Allergies/Anaphylaxis (food/pollen allergies).
  - Atopy → Genetic determination of allergy.
  - Gene for atopy is located on chromosome 5.
- Bronchial asthma.
- Casoni's test (Hydatid disease).
- Drug reactions.
- Hay fever.
- PK reactions.
- Theobald Smith phenomena.

mechanism :

1st exposure of the antigen → mast cells get sensitised → Repeated exposure of the antigen → Hypersensitivity reaction occurs.

Active space



Types of mediators released :

- Preformed mediators (from the stored granules of the mast cells) :
  1. Histamine (earliest mediator to be released).
  2. Proteases/enzymes.
  3. Chemotactic factors : Like C3a and C5a.
- Activation of Phospholipase A2 : Production of arachidonic acid metabolites like prostaglandins, leukotriens and platelet activating factor.

Active space

Phases :

- Immediate phase → Occurs within minutes.
  1. Vasodilation.
  2. Increased vascular permeability.
  3. Increased mucus production.
- Late reaction → Occurs within 2-24 hours.
  1. Fibrosis.
  2. Increased production of inflammatory cells.
  3. Epithelial damage.

Most important cell in type I HS reaction → Mast cell.
Stain for mast cell → Toluidine blue.
Important cell in the late phase of type I HS reaction : Eosinophils.
Most important antibody in type I HS reaction : IgE.
Most important cytokine in type I HS reaction : IL-4 & IL-5.
Earliest mediator released in type I HS reaction : Histamine.

Type II hypersensitivity reactions 00:13:48

Antibody mediated HS reaction.
Examples :
Mnemonic : My Blood Group Is RH Positive.

- Myasthenia gravis.
- Blood transfusion reaction.
- Grave's disease, Good pasteur syndrome.
- Idiopathic thrombocytopenic purpura (ITP), Immune hemolytic anemia.
- Rheumatic fever.
- Hyperacute graft rejection.
- Pernicious anemia, Post-Streptococcal Glomerulo Nephritis (PSGN).

Mechanism :

- Opsonisation and phagocytosis.
- Inflammation and Complement activation.
- Antibody-dependent cell-mediated cytotoxicity (ADCC).

Active space

Opsonisation and phagocytosis :
It is mediated by IgG antibody (F_c portion of IgG is the most potent opsonin), in which IgG antibody coats the antigenic cell due to which macrophages can phagocytose these cells easily.

Examples :
- Hemolytic disease of the newborn.
- Blood transfusion reaction.
- Drug reaction.

Inflammation and complement activation :
- Occurs when the antibody is bound to the surface of the basement membrane or the extracellular matrix.
- The antibody will lead to activation of the complement factors causing neutrophil chemotoxis and then tissue injury.

Examples :
- Good pasteur syndrome.
- Glomerulonephritis.
- Graft rejection.

ADCC/Antibody dependent cell mediated cytotoxicity :
i. There is no complement activation or tissue injury.
ii. Antibodies are produced against the cell-surface receptors.

Examples :
- Grave's disease → Anti-TSH receptor antibody.
- myasthenia gravis → Antibody against the ACh receptors. (Recently classified under type V HS reaction) (Type V> II)

Type III hypersensitivity reactions 00:22:30

AKA Immune complex mediated HS reaction.
Examples → Mnemonic : SHARP
- Serum sickness, Shick test, SLE (Visceral lesion is type 3 HS reaction and hematological lesion is type 2 HS reaction)
- Henoch Schonlein purpura.
- Arthus reaction.

Active space

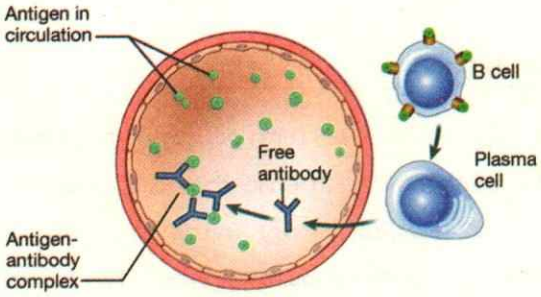
- Reactive arthritis.
- PSGN, Poly arteritis nodosa (PAN).

Formation of immune complex takes approximately 5-7 days.

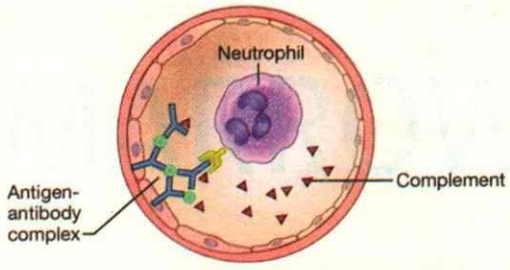
Immune complex deposition :

- most pathogenic immune complexes are small to medium-sized which usually have excess of antigens.
- Immune complexes are usually deposited in organs which have a high filteration rate like kidneys or the joints.
- Immune complex-mediated inflammation and tissue injury takes approximately 10-14 days.

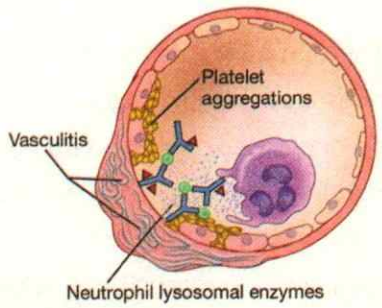
Immune complex disease-
Type III Hypersensitivity Reactions



Immune complex formation



Immune complex deposition



Immune complex-mediated inflammation and tissue injury

Active space

Type IV hypersensitivity reactions 00:28:08

AKA cell mediated HS reaction/delayed type HS reaction.

Examples :

- Granuloma formation.
- Tuberculin test.
- Lepromin test.
- Contact dermatitis.
- Sarcoidosis.
- Multiple sclerosis.
- Rheumatoid arthritis : Type 4 > type 3.
- Hypersensitivity pneumonitis : Both type 3 and type 4 HS reaction.
- Acute and chronic graft rejection.

Hyperacute graft rejection is due to type 2 HS reaction.

Clinical scenarios 00:35:08

Q. A 15-year-old healthy girl with no major medical problems notes blotchy areas of erythema that are pruritic over the skin of her arms, legs, and trunk within an hour every time she eats seafood, followed by diarrhea. These problems abate within 3 hours, and then physical examination reveals no abnormal findings. Which of the following immunologic abnormalities is she most likely to have?

A. Localized anaphylaxis.
B. Cell-mediated hypersensitivity.
C. Complement activation.
D. Hypergammaglobulinemia.
E. Immune complex deposition.

Q. Twelve hours after going on a hike through dense foliage, a 40-year-old man notices a slightly raised and tender irregular reddish rash on one forearm that was not covered by clothing. This rash gradually increases in intensity for 2 days and then fades away after two weeks. Which of the following forms of immunologic hypersensitivity is most likely demonstrated in this patient?

Active space

A. Type I hypersensitivity.
B. Type II hypersensitivity.
C. Type III hypersensitivity.
D. Type IV hypersensitivity.

Explanation : Hypersensitivity pneumonitis occurs on exposure to foliage/ moldy hay/bird poop etc.

Q. A 30-year-old woman has experienced myalgias for the past 3 months. On physical examination she has 5/5 motor strength in all extremities. She has dullness to percussion at lung bases. A chest x-ray shows bilateral pleural effusions. Laboratory studies show a positive antinuclear antibody test at a titer of 1:1024. Her serum urea nitrogen is 30 mg/dL. A renal biopsy is performed and microscopic examination shows a granular pattern of immunofluorescence staining with antibody to complement component C1q. This pattern is most typically produced as a consequence of which of the following immunologic mechanisms?

A. IgE coating mast cells.
B. Antiglomerular basement membrane antibody.
C. Antigen-antibody complexes.
D. Macrophage release of lymphokines.
E. Release of prostaglandins.

Explanation : SLE (visceral component). Type III reaction

Q. A 48-year-old man has had a chronic cough with fever for 2 months. On physical examination his temperature is 37.9°C. A chest radiograph reveals a diffuse bilateral reticulonodular pattern. A transbronchial biopsy is performed and microscopic examination shows focal areas of inflammation containing epithelioid macrophages, Langhans giant cells, and lymphocytes. These findings are most typical for which of the following immunologic responses?

A. Type I hypersensitivity.
B. Type II hypersensitivity.
C. Graft versus host disease.
D. Polyclonal B-cell activation.
E. Type IV hypersensitivity. TB granuloma

Active space

Q. A 9-year-old boy has a sore throat. A throat culture grows group A hemolytic Streptococcus. He receives antibiotic therapy. However, 17 days later he develops dark-coloured urine. Laboratory studies show 3+ blood on urinalysis. A renal biopsy is performed. On immunofluorescence staining the biopsy shows granular deposition of IgG and complement around glomerular capillary loops. Which of the following immune hypersensitivity mechanisms is most likely responsible for this pattern of findings?

A. Type I.
B. Type II.
C. Type III. PSGN
D. Type IV.

Active space

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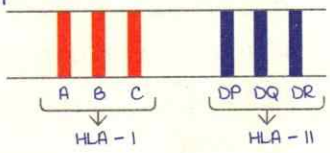
HLA AND GRAFT REJECTION

Major histocompatibility complex (MHC) 00:01:26

It is A/K/A Human leucocyte antigen (HLA).

The gene is located on Chromosome 6p.

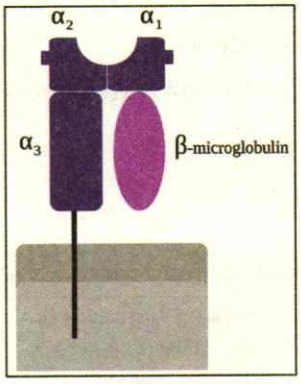
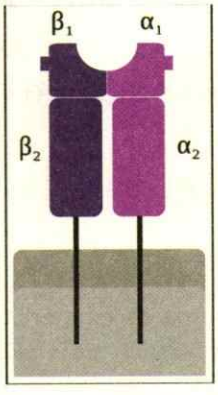
MHC is of 3 types :



MHC I.

MHC II.

MHC III : Encoded by Heat shock protein (HSP), Complement proteins, properdin. It may have a role in autoimmune diseases.

HLA I	HLA II
• Present on all nucleated cells & platelets. • Encoded by A, B, C. • Presents the antigen to CD8+ T lymphocytes. • Role in graft rejection. • Structure : β2 microglobulin is present. Peptide binding cleft between α1 and α2.	• Present only on antigen presenting cells (APCs – B cells, fibroblasts, dendritic cells). • Encoded by DP, DQ, DR. • Presents the antigen to CD4+ T lymphocytes. • Role in GVHD. • Structure : Peptide binding cleft is between α1 and β1.
	

Role of MHC 00:10:20

Paternity testing.

Prediction of incidence of autoimmune disorders.

Active space

HLA B27 : Ankylosing spondylitis.

HLA DR3, DR4 : Diabetes mellitus.

HLA DQ2, DQ8 : Celiac disease.

HLA B5, B51 : Behcet's disease.

Anthropology testing.

HLA matching in Organ transplantation and Bone marrow/ stem cell transplantation.

Most important HLA which needs to be typed : HLA-DR.

All 6 loci match only in case of identical twins.

HLA A, B, DR : Should definitely match with each other (DR>B>A).

All the loci have 2 alleles each.

Matching is expressed as 12/12 for all loci or 6/6 for HLA A, B, DR.

HLA matching is not done for : Cornea, Liver, Heart, Lung transplant.

Grafts and Graft reactions 00:17:28

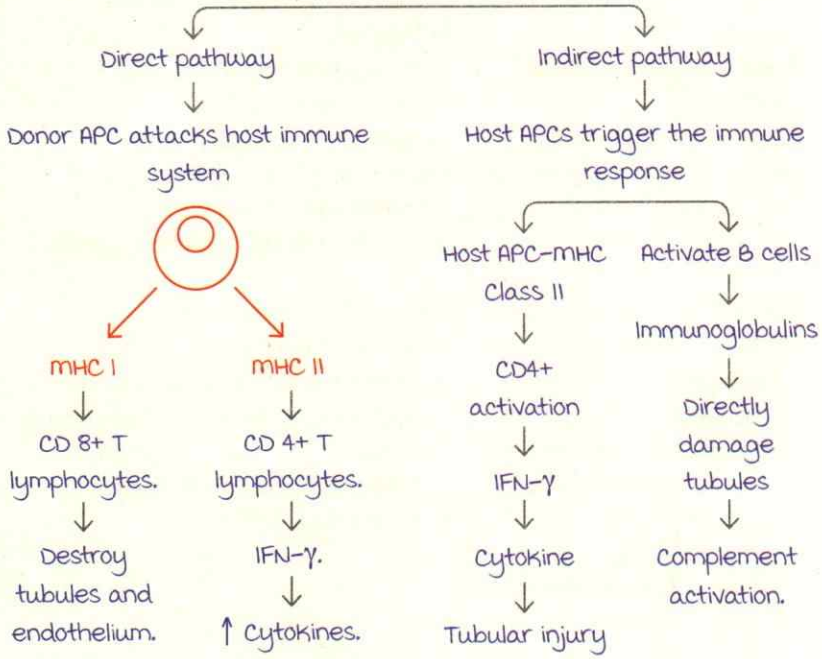
- Isograft : Between identical twins.
- Autograft : From one part of one's own body to another.
- Allograft : Between genetically different individuals but same species.
- Xenograft : Between different species.
- Orthoptic graft : Graft is placed in the same anatomic location as the donor.
- Heterotopic graft : Different anatomic location from the donor.

Graft reactions :

Graft rejection	Graft vs Host disease (GVHD)
Host is immunocompetent. Host cells attack graft cells.	Host is immunosuppressed. Graft cells attack host cells. Seen in bone marrow transplantation.

Mechanism of graft rejection 00:23:50

Example : Kidney transplantation.



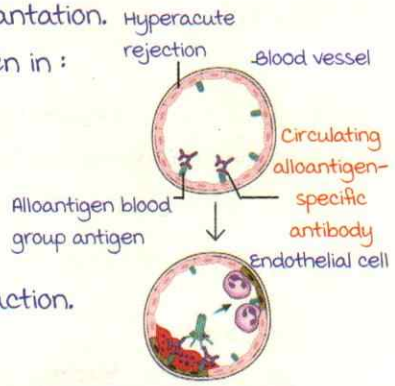
Hyperacute graft rejection 00:29:00

Occurs within minutes of transplantation.

Due to preformed antibodies seen in :

- Previous pregnancy.
- ABO & Rh incompatibility.
- Previous blood transfusion.
- Previous transplantation.

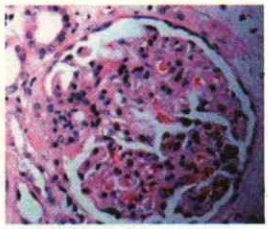
It is a type II hypersensitivity reaction.



Gross appearance of Kidney :
Cyanosed, mottled, flaccid.

Microscopically :

- Fibrinoid necrosis.
- Microthrombi.
- Neutrophilic infiltrate.



Prevention : Donor specific antibody test should be done.

Active space

Acute graft rejection

00:36:35

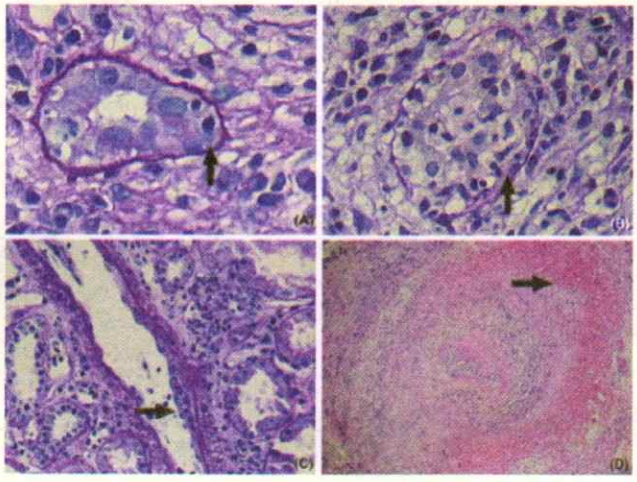
Acute cellular rejection	Acute humoral rejection
Mediated by CD4+ or CD8+ T cells. Type IV hypersensitivity reaction. Responsive to increasing dose of immunosuppressive drugs. Microscopic appearance : • Tubulointerstitial pattern : Tubulitis : Destruction of tubules + inflammatory cells in tubules. Mononuclear inflammatory infiltrate. • Vascular pattern : Endothelitis	Mediated by newly synthesized antibodies. It causes endothelial damage & complement activation. Type II or III hypersensitivity. No response to increasing dose of immunosuppressive drugs. Treatment : B cell depleting agents. Microscopic appearance : • Fibrinoid necrosis in vessels. • Deposition of C4d in peritubular capillaries. (Complement breakdown product). C4d is the marker for acute humoral rejection.

Chronic rejection

00:44:20

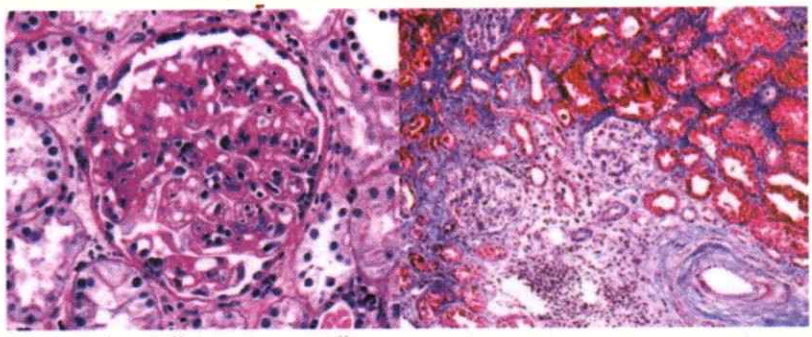
It is the m/c type of graft rejection.
It occurs within months to years of transplantation.
It may be cell mediated (Type IV hypersensitivity) or antibody mediated (Type II).

Microscopically :



Active space

- Transplant glomerulopathy.
- Duplication of glomerular basement membrane.
- Interstitial fibrosis.
- Glomerular sclerosis.
- Tubular atrophy.



Glomerulus-inflammatory cells within the capillary loops (glomerulitis), accumulation of mesangial matrix, & duplication of capillary basement membrane.

Interstitial fibrosis and tubular atrophy. (trichrome stain), contrasted with the normal kidney. Artery-prominent arteriosclerosis

Graft vs host disease (GVHD) 00:49:33

GVHD is a complication of hematopoietic stem cell transplantation.

It is A/K/A Runt's disease in animals.

Type IV hypersensitivity reaction.

Acute GVHD	Chronic GVHD
< 100 days duration. Organs affected : Skin : Excoriation. GIT : mucosal ulceration → Diarrhoea. Liver : Jaundice.	> 100 days duration. Organs affected : Skin : Scleroderma. GIT : Strictures. Liver : Cirrhosis.

Y linked graft rejection :

A/K/A sex linked graft rejection (Eichwald silmser effect).

It occurs when male gives graft to a female.

(Y chromosome contains UTY gene → Encodes for enzyme histone demthylase : minor histocompatibility antigen).

Active space

Complications of transplants 00:55:24

1. Infections :
   CMV is the m/C following transplantation : Owl's eye inclusions.
   BK polyoma virus infection : _____
2. Graft rejection.
3. GVHD.
4. Increased risk of malignancy :
   Squamous cell carcinoma (m/C) : HPV associated.
   Kaposi's sarcoma : HHV-8 associated.
   Non-Hodgkin's lymphoma : EBV associated.
   Post-transplant lymphoproliferative disorder :
   EBV associated (Poor prognosis).

MCQs :

Q. A patient has to receive liver transplant from his brother, who is not his twins. On HLA typing, HLA matched are the A, B and DRB1 locus. These siblings are considered as :

A. Matched, unrelated donors
B. Mismatched, related donors
C. Matched, related donors
D. Mismatched, unrelated donors

Q. Which of the following statements about graft vs host disease is least correct?

A. Occurs when host is immunocompromised.
B. Occurs when donor cells are immunocompromised.
C. Is also called RUNT disease.
D. A common cause is stem cell transplantation.

Q. Acute humoral renal transplant rejection is characterized by the following except:

A. Presence of anti donor antibodies.
B. Necrotizing vasculitis.
C. Interstitial and tubular mononuclear cell infiltrate.
D. Acute cortical necrosis.

Active space

Q. Most commonly involved organs in graft versus host disease are all except:

A. Gut

B. Liver

C. Skin

D. Kidney

Q. A 25 year old female with CRF receives a cadaveric renal transplant. One month later, she experienced increasing creatinine and urea levels and a renal biopsy was performed. She was treated with steroids and her renal function improved. Which of the following changes was most likely seen in the biopsy specimen before steroid therapy was initiated?

A. Interstitial infiltration by CD3+ lymphocytes and tubular epithelial damage.

B. Extensive fibrosis of interstitium and glomeruli with marked thickening blood vessels.

C. Fibrinoid necrosis of renal arterioles and thrombi.

D. Glomerular deposition of serum amyloid associated protein.

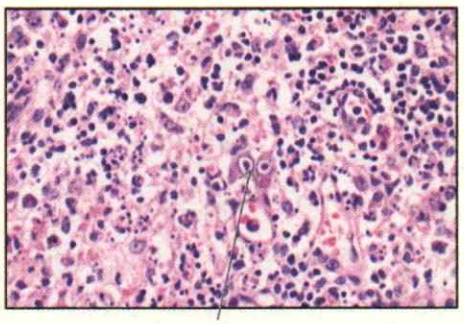
Q. A 30 year old patient who had undergone a renal transplant presented with fever and dyspnea. The histopathological examination from a lung lesion is given below. What is the most likely diagnosis?

A. Mycobacterium

B. BK polyoma virus

C. Herpes infection

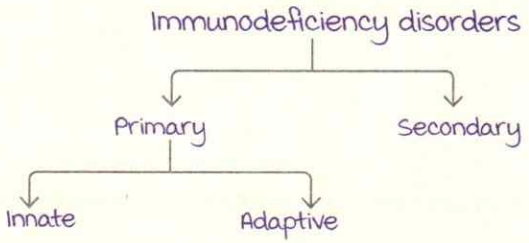
D. CMV



Owl's eye inclusions

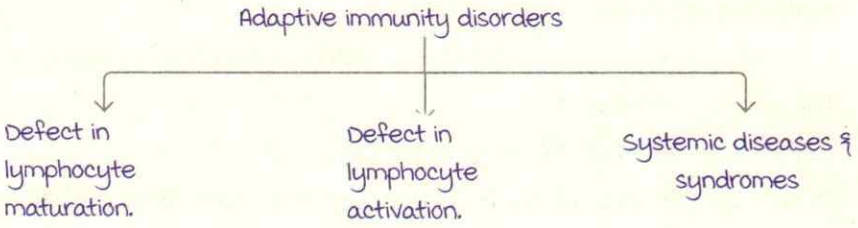
Active space

IMMUNODEFICIENCY DISORDERS



Secondary immunodeficiency causes :

- HIV.
- Cancer.
- Chemotherapy.
- Malnutrition (most common secondary cause).



Defect in lymphocyte maturation 00:03:30

Bruton's agammaglobulinemia :
X linked recessive.
Seen in boys >> girls.

Pathogenesis :
Due to BTK gene (Bruton tyrosine kinase) defect → Defective maturation of B cell lymphocytes → Decreased mature B cells and plasma cells → Defective humoral immunity.
T cells are normal → Cell mediated immunity is intact.

Histology :
Hypoplastic / absent germinal centers.

Active space

Clinical presentation :
Usually manifests after 6 months of age.
Recurrent sino-pulmonary infections / infections with enterovirus or Giardia.

Diagnosis :
Flow cytometry :
Presence/absence of surface Ig can be seen.
In bruton's agammaglobulinemia → Absence of surface Ig.

DiGeorge syndrome :
Also known as 22q 11 deletion syndrome / Velocardiofacial defects.
Defect : Deletion of 22q 11 → defect in TBX 1 gene →
defective development of 3rd & 4th pharyngeal pouches →
Defective development of thymus & parathyroid gland →
Defective T cell development and Hypocalcemia.
Mnemonic : CATCH 22
Cleft lip and palate.
Abnormal facies.
T cell defect, thymic hypoplasia.
Cardiac abnormality (MC defect : TOF).
Hypocalcemia.
22q 11 deletion.

SCID (Severe Combined Immuno Deficiency) :
Defect in B cell, T cell and NK cell.

Pathogenesis :
2 modes of inheritance :
- X -linked recessive : (MC).

Males >>> females.
Mutation in common γ chain of cytokine receptors →
Reduced synthesis of IL 2, 4, 7, 11 and 15.
Decreased production of :
1. IL4 → Since responsible for isotype switching :
   Decreased production of immunoglobulins.
2. IL7 → Decreased levels of T cell lymphocytes.

Active space

3. ILIS → Defect in NK cells.

- Autosomal recessive : Deficiency of Adenosine deaminase (ADA) → Accumulation of toxic metabolites → Destruction of B cells , T cells and NK cells.

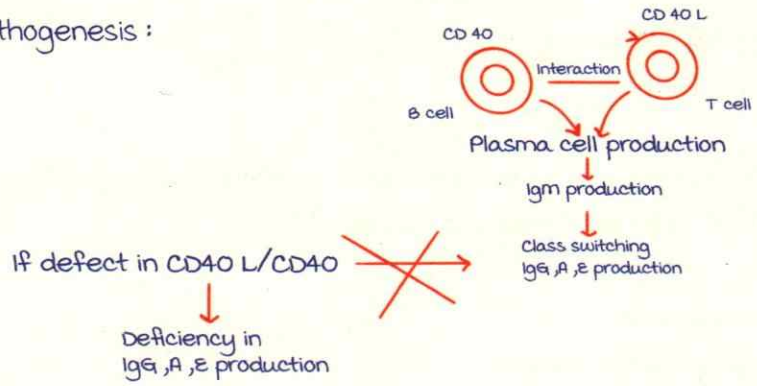
Clinical presentation :
Can present with any kind of infection. (viral /protozoal / fungal /bacterial).
Candidial infection / diaper rashes can be seen.

Treatment :
First disease to be treated with gene therapy .
Hematopoeitic stem cell transplantation.

Defect in lymphocyte activation 00:17:08

Hyper IgM syndrome :
Increased production of IgM.
Decreased level of Ig G, A, E.
X Linked Recessive disorder.
Males>>> females (more common).

Pathogenesis :



Most common defect in hyper IgM : CD40 L defect.
2nd most common defect in hyper IgM : CD40 defect.
Therefore, defect in class switching.

Clinical Features :

- Increased production of IgM :
  Autoimmune thrombocytopenia.

Active space

Autoimmune hemolytic anemia.

Autoimmune neutropenia.

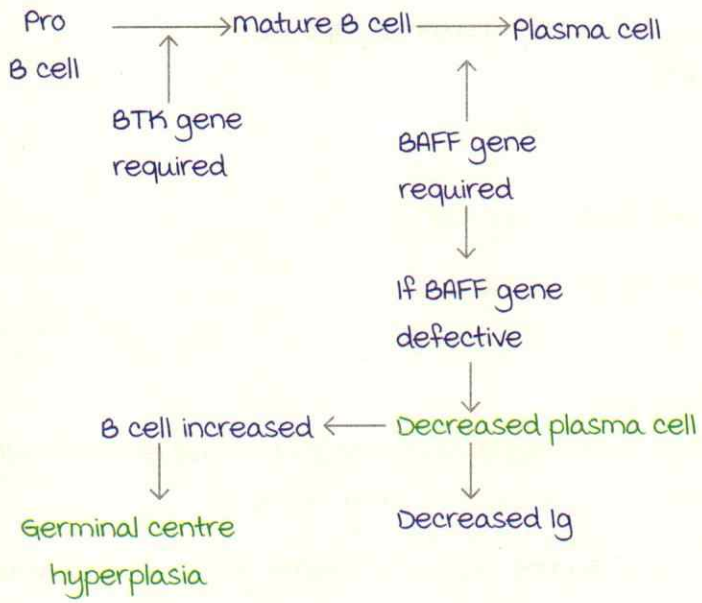
- Decreased the level of Ig G, A, E :

  Increased risk of sinopulmonary infections.

Common variable immunodeficiency :

It is a diagnosis of exclusion.

Pathogenesis : Mutation in the BAFF gene.



Isolated Ig A deficiency :

most common primary immuno deficiency disorder.

Decreased production of Ig A, G_2, G_4.

Clinical presentation :

Increased risk of sinopulmonary infection.

Increase the risk of anaphylactic reaction (can present in a person undergoing blood transfusion for the first time).

Wiscott Aldrich syndrome 00:24:58

X linked Recessive disorder.

more common in males >>> females.

Pathogenesis : WASP gene defect on chromosome XP 11.2.

Active space

Clinical Triad :

- Eczema.
- Thrombocytopenia (Decreased platelets, small sized platelets).
- Immuno deficiency due to defective T cell development.

Decreased IgM, increased IgA and normal IgG.

Mnemonic : WAITER

Wiscott, WASP gene defect.

Aldrich.

Immunodeficiency.

T cell deficiency, Thrombocytopenia

Eczema.

Recurrent infections.

Ataxia telangiectasia

00:28:19

Autosomal recessive disorder.

Incidence : male = female .

Pathogenesis :

Defect in ATM gene on chromosome 11 (WT gene for Wilm's tumor is also present on chromosome 11).

Normal ATM gene acts a DNA repair sensor and activates P53 if any DNA damage occurs.

Defective ATM gene does not activate P53 and may cause :

- Ataxia telangiectasia.
- Malignancy.
- Premature aging.
- Neurodegenerative disorders.

Clinical scenarios :

Q. A male infant is born at term. No congenital anomalies are noted on examination. A year later he has failure to thrive and has been getting one bacterial pneumonia after another with both Hemophilus influenzae and Streptococcus pneumoniae cultured from his sputum. Which of the following diseases is he most likely to have?

A. DiGeorge syndrome.

B. Selective IgA deficiency.

Active space

C. Epstein-Barr virus (EBV) infection.
D. Acute leukemia.
E. X- linked agammaglobulinemia.

Digeorge syndrome is a birth defect with abnormal facies & cleft lip and palate.
Selective IgA deficiency will not manifest after a year & doesn't produce the symptoms mentioned here.

Q. A 5 year old boy and his 4 year old brother have had recurrent pneumonia, meningoencephalitis, sinusitis, otitis, & diarrhea since infancy. Bacterial & viral agents have been implicated, as well as Pneumocystis, Cryptosporidium & Giardia. Laboratory studies show serum IgG 47 mg/dL, IgA 5 mg/dL, and IgM 671 mg/dL. Normal numbers of B and T cells are present. These children are most likely to have a mutation involving a gene encoding for which of the following?
A. NADPH oxidase.
B. Wiskott-Aldrich syndrome protein.
C. Cytokine receptor common gamma chain.
D. CD40 L.
E. Complement C 1 inhibitor.

Explanation :
IgM 671 mg/dl could suggest hyper IgM syndrome.
CD40 L is the MC defect here.
NADPH oxidase deficiency causes granulomatous disease.
Wiskott-Aldrich syndrome protein will have a history of Eczema, small sized platelets etc.
Cytokine receptor common gamma chain is X linked recessive.
Complement C 1 inhibitor seen in hereditary angioneurotic edemas.

Q. An 11 month old infant has had upper and lower respiratory tract infections almost continuously since the time of birth, with organisms including Pneumocystis jiroveci & Pseudomonas aeruginosa identified. The baby also has oropharyngeal candidiasis. The baby succumbs to a cytomegalovirus pneumonitis. At autopsy, the thymus is

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markedly hypoplastic and lymph nodes throughout the body are small, with absent germinal centers on microscopic examination. Which of the following mechanisms is most likely to explain these findings?

A. Adenosine deaminase deficiency.

B. Failure of B cell maturation to plasma cells.

C. Human immunodeficiency virus infection.

D. Autoantibodies to both T and B lymphocytes.

E. Failure of development of 3rd and 4th pharyngeal pouches.

Explanation :

Adenosine deaminase deficiency is seen in AR , SCID.

Failure of development of 3rd and 4th pharyngeal pouches seen in Digeorge syndrome .

Q. A neonate born at term developed tetany soon after birth. On physical examination the infant has a heart murmur. Laboratory studies show a serum calcium of 6.3 mg/dL. Echocardiography reveals a membranous intraventricular septal defect. Within the next year, this infant has bouts of Pneumocystis jiroveci pneumonia, Aspergillus fumigatus pneumonia, and parainfluenza virus and herpes simplex virus upper respiratory infections. Which of the following abnormalities most likely explains the development of this infant's findings?

A. Abnormal Wiskott-Aldrich syndrome protein.

B. 22q-chromosome deletion.

C. Reduction in CD4 lymphocytes.

D. Defect in NADPH oxidase.

E. Failure of B cell maturation into plasma cells..

The symptoms are suggestive of Digeorge syndrome.

Active space

AMYLOIDOSIS

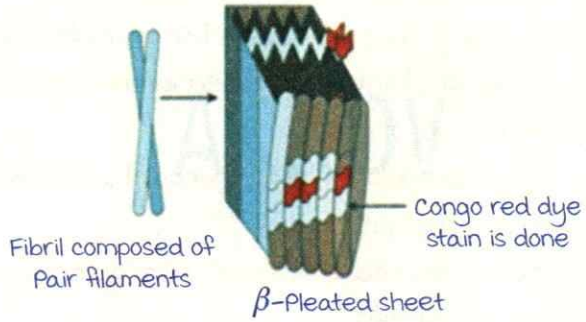
Introduction 00:01:10

Pathologic proteinaceous extracellular hyaline eosinophilic substance deposited in various tissue and organs.
misfolded protein.
Hyaline : Pink substances.

Physical nature :
In electron microscopy, appear as non branching fibrils of indefinite length with 7.5–10 nm diameter.

In X-ray crystallography (or infrared spectroscopy) :
Cross beta pleated sheet structure (this is responsible for apple-green birefringence under polarized lens).

Structure of Amyloid Material



Amyloid in electron microscopy with 7.5–10 nm diameter

Best stain : Congo red.
Chemical nature :
Consists of

- Amyloid protein : 95%
- P protein : 5% (depends on the disease condition.)

Active space

Classification of Amyloidosis 00:07:00

Classification → Localised.
→ Generalised.
→ Familial.

1. Localised amyloid and its protein :
   - Medullary carcinoma of thyroid :
     Amyloid seen is Acal (95% amyloid protein & 5% calcitonin protein).
   - Prion disease :
     Apr (95% amyloid protein & 5% prion protein).
   - Type 2 Diabetes mellitus :
     Amyloid islet associated pancreatic polypeptide (AIAPP).
   - Alzheimer's disease :
     ABeta (part of neuritic plaque).

2. Generalised : Multiple organ involved.
   - Primary amyloidosis :
     Most common type of amyloidosis.
     Seen in light chain disorders like multiple myeloma.
     AL (amyloid & light chain called lambda light chains commonly deposited).
     In MM, accumulation of immunoglobulins hence light chain are precipitated.
     Most common cause of death : Cardiac failure.
   - Secondary amyloidosis :
     Also called reactive systemic amyloidosis.

Deposited in

Chronic inflammatory conditions :
Rheumatoid arthritis(MCC).
IBD.
TB.
Bronchiectasis.

Chronic neoplasms :
Hodgkin's lymphoma.
Renal cell carcinoma.

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Chronic inflammation.
↓
Cytokines : IL-1, IL-6 released.
↓
Act on liver.
↓
Produce serum amyloid associated protein (SAA).
↓
AA produced.

Most common cause of death : Renal failure.

3. Amyloid seen in chronic renal failure (CRF)/ long term hemodialysis :
   Uncommon
   Dialysis membranes (DM) filters out the unwanted substances out.
   Earlier the DM did not filter out $\beta 2$ microglobulin , hence it accumulated leading to $A\beta_2m$ amyloid formation.
   Deposited in joints, tendons, median nerve leading to Carpal tunnel syndrome.

4. Senile/ Cardiac amyloidosis :
   ATTR (transthyretin) .
   In aged/ cardiac patients normal transthyretin is deposited.

Familial amyloidosis

00:18:08

Familial amyloidosis

- Familial mediterranean fever. AA/Apyrin
- Familial amyloidoic polyneuropathy. ATTR with mutant transthyretin

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Disease / condition	Type of amyloid
Primary amyloidosis	AL
Secondary amyloidosis	AA
Familial mediterranean fever	AA/Apyrin
Familial amyloidotic polyneuropathy	ATTR (mutant transthyretin)
Senile/ cardiac amyloidosis	ATTR
CRF/ long term dialysis	Abeta2m
Prion disease	Apr
Diabetes mellitus	AIAPP
medullary ca thyroid	Acal
Alzheimer's disease	Abeta

Diagnosis :

Biopsy(Bx) site :

If localised : Bx taken form that localised tissue.

If generalised : Bx →
- Abdomen fat pad aspirate (best).
- Rectal (not best as painful & invasive).
- Gingival (usually macroglossia seen)

Abdomen fat pad > rectal > gingival.

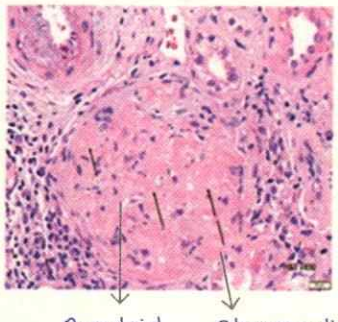
Bx is H & E stained :

In Kidney Bx

Extracellular : pink.

Glomeruli with pinkish material that is amyloid.

Eosinophilic hyaline pink : Can be sclerosis/fibrin/ hyaline : So to differentiate



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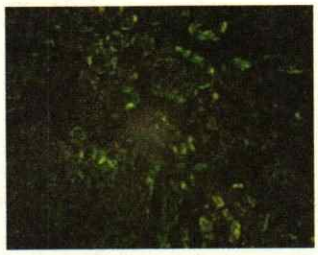
Amyloid Congo red is used.

Stains used :

- Congo red (Best).
  Congo red gives Salmon pink colour but under polarised lens apple-green birefringence seen.



- PAS :
  Appear magenta colour.
- Methyl violet/ crystal violet : metachromatic satin.
- Thioflavin S
- Thioflavin T

  — shows Immunofluorescence.

Gross stain :

Paint the cut surface of the organ with Lugol's iodine.

↓

Giving a mahogany brown color .

↓

Add Sulphuric acid (H_2SO_4).

Turns blue	Remains brown
↓	↓
Amyloid present.	No Amyloid.

Organ involvement of amyloid 00:28:46

Gross :

Any organ with amyloidosis. → Organomegaly with waxy appearance.

Organs :

- Kidney (most common organ affected).

Affects : Glomeruli,
Tubules,
mesangium (earliest to involve).

Clinically manifested with nephrotic syndrome.

- Liver :
  Earliest part affected is space of Disse.
  Produces pressure atrophy of hepatocytes cirrhosis.

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- Heart :

  Earliest part affected is subendocardium.

  Can lead to :

  Arrhythmia.

  Heart Failure.

  Restrictive Cardiomyopathy.

  Normal ATTR deposited.

- Skin :

  Pinch Purpura.

- Spleen :

  Spleen contains follicles and in between follicles sinuses are there.

2 appearances

Sago spleen :
If follicles/white pulp are affected → produce whitish nodules looking like sago grains.

Lardaceous spleen :
If sinuses /red pulp affected → Large geographical map like areas

Sago spleen

Important MCQ's

00:35:12

- Most common biopsy site : Abdomen Fat Pad .
- Best stain for amyloid : Congo Red.
- Gross stain for amyloid : Lugol's Iodine & Sulphuric Acid.
- M.C. organ affected : Kidney.
- M.C. cause of death in Primary amyloidosis : Cardiac failure.
- M.C. cause of death in secondary amyloidosis : Renal failure.

Active space

- Liver : part affected earliest → Space of disse.
- Spleen : appearance → Sago spleen & Lardaceous spleen.

Q. Elderly diabetic on hemodialysis. Which amyloid is likely to be deposited?

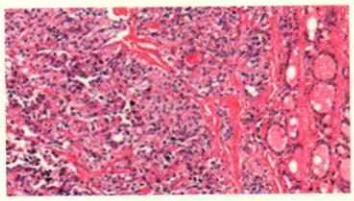
A. AA.
B. Abeta.
C. Transthyretin.
D. Beta 2 microglobulin.

Q. A 55 year old man has developed progressive renal failure for the past 5 years. Microscopic examination of a renal biopsy shows extensive glomerular and vascular deposition of pink amorphous material on H&E staining. This material demonstrates apple-green birefringence under polarized light after Congo red staining. Immunohistochemical staining of these deposits is positive for lambda light chains. Which of the following conditions is most likely to be present in this man?

A. Rheumatoid arthritis .
B. Tuberculosis.
C. Systemic lupus erythematosus.
D. Multiple myeloma.
E. Alzheimer disease.

Q. A 45 year old women developed a thyroid swelling. The microscopic image from the swelling is shown. What type of amyloid deposits are seen in this condition?

A. AL.
B. ATTR.
C. Acal.
D. Apyrin.



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Q. A 60 year old woman has developed crippling arthritis over the past 20 years. On physical examination the arthritis primarily involves her hands and feet, with marked joint deformities characterized by ulnar deviation and swan-neck deformities of her fingers. She has an irregular heart rate. Laboratory studies show that her rheumatoid factor titer is markedly elevated, but her antinuclear antibody test is negative. A rectal biopsy shows submucosal deposition of pink amorphous material that stains positively with Congo red. Which of the following precursor proteins most likely gave rise to these deposits?

A. Serum amyloid-associated protein.
B. Lambda immunoglobulin light chains (AL).
C. Transthyretin (ATTR).
D. Amyloid precursor protein (Aβ).
E. Beta-2-microglobulin (Aβ2m in CRF).

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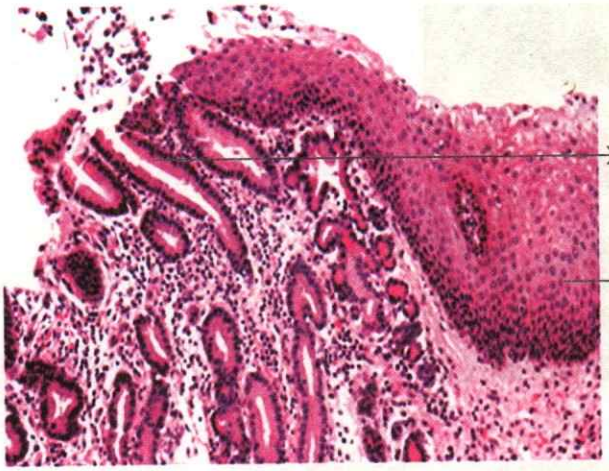
GENERAL PATHOLOGY IMAGES

General pathology images 00:00:44

Barret's esophagus :

- HPE shows metaplasia & goblet cells.
- Stain used : Alcian blue or mucicarmine.
- It is a risk factor for Ca-esophagus.



metaplasia :

- One cell type gets converted into another cell type.
- Vitamin A deficiency can lead to metaplastic transformation.
- Example of connective tissue metaplasia : myositis ossificans.

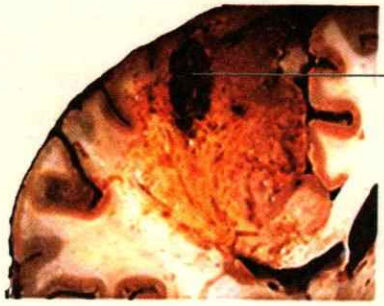
Coagulative necrosis of liver :

White/pale infarct
Wedge shaped

Brain is not affected by coagulative necrosis.

Active space

Liquefactive necrosis of brain :



→ Liquefactive necrosis

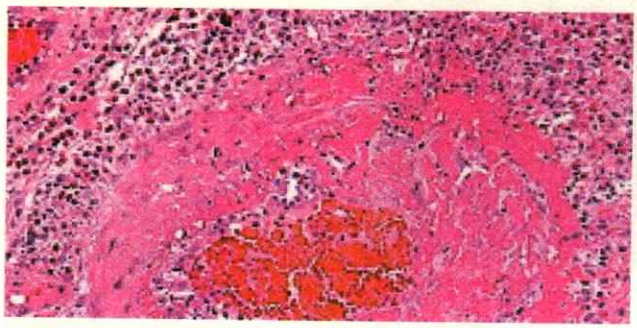
Caseous necrosis of lung :

→ Cheesy appearance

Fat necrosis :

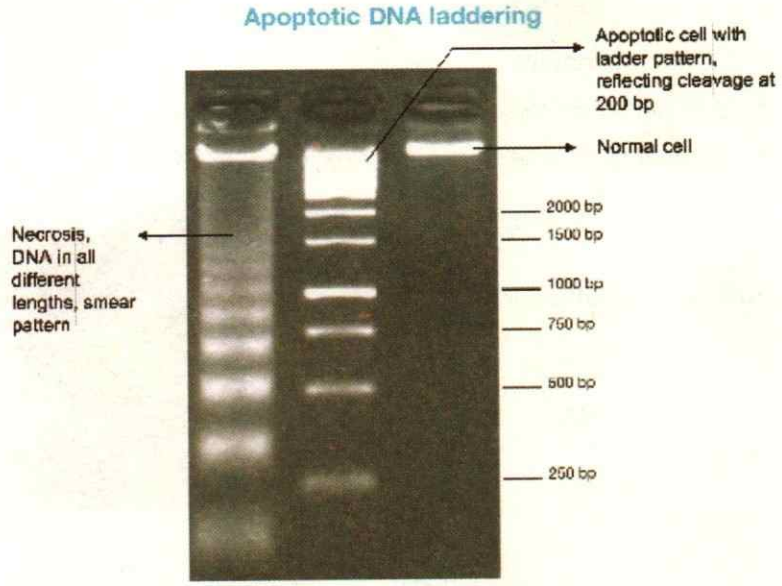
→ Chalky white deposits. Seen in pancreas, breast, omentum, mesentery.

Fibrinoid necrosis :



Fibrinoid necrosis in an artery. The wall of the artery is bright pink with dark neutrophils

Active space

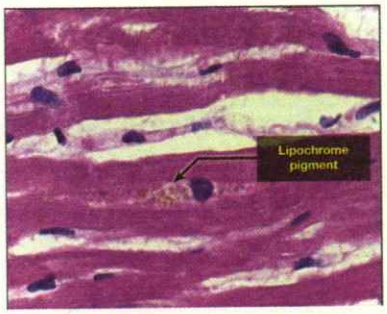


Lipofuscin :

Also known as aging pigment or, wear & tear pigment.

Its a perinuclear, brown coloured pigment.

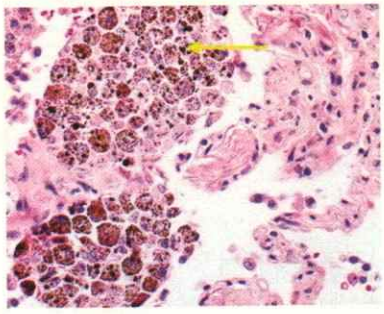
Lipofuscin is responsible for brown atrophy of liver & heart.



Hemosiderin :

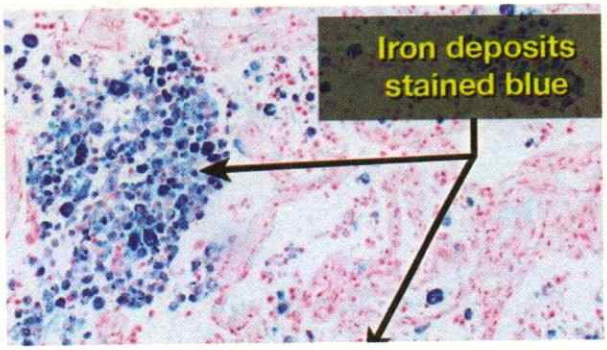
Its not a perinucluclear pigment.

It shows Prussian blue/ Perl's stain positivity.



Haemachromatosis :

On Perl's stain lots of iron deposits can be seen.



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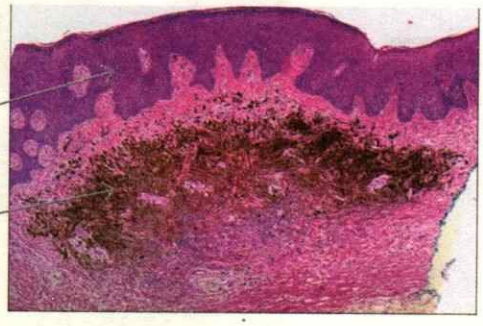
Melanin :

- Colour of melanin : Black.
- It is derived from tyrosine (amino acid).
- Special stain used : Masson Fontana, DOPA Rx.

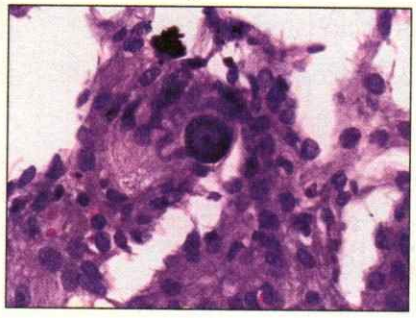


Slide of meningioma patient :

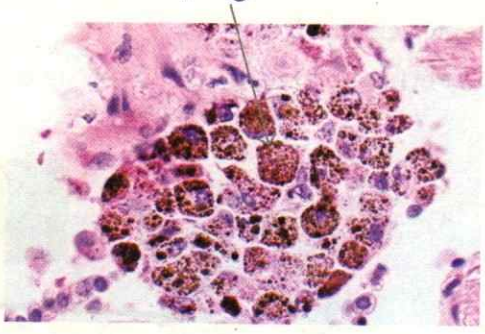
Psammoma bodies : Foci of dystrophic calcification.

Psammoma bodies can be seen in :

- Papillary carcinoma of thyroid.
- Papillary renal cell carcinoma.
- Serous cystadenocarcinoma of ovary.
- Meningioma.
- Prolactinoma.

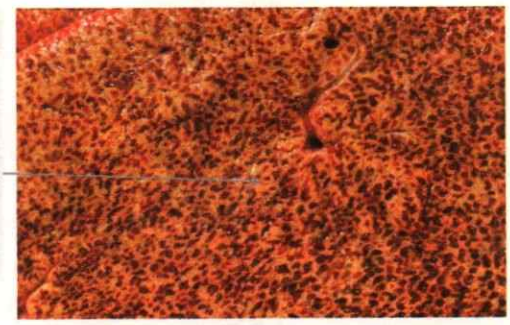


Lung biopsy of a patient with heart failure showing heart failure cells (hemosiderin laden macrophages)



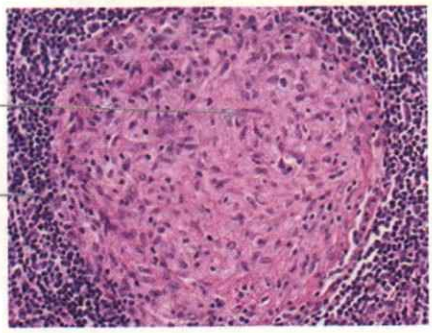
Active space

Nutmeg liver :
Characteristic feature of CVC liver.
Brownish spots

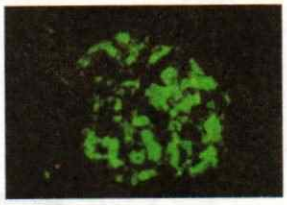


Red infarct of lung

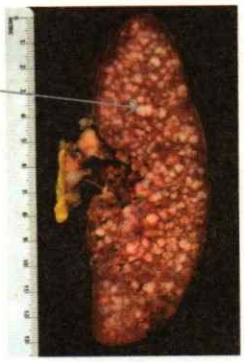
Granuloma :
Epithelioid cells (modified macrophage)
Collar of lymphocytes



Kidney biopsy showing :
Apple green birefringence of glomerulus



Sago-spleen showing tapioca appearance : Seen when spleen follicles are affected with amyloid.
When sinuses are affected with amyloid, it is called as lardaceous spleen.



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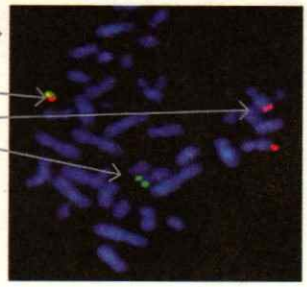
Fluorescent in-situ hybridization →

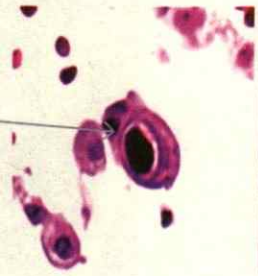
Indicates translocation.

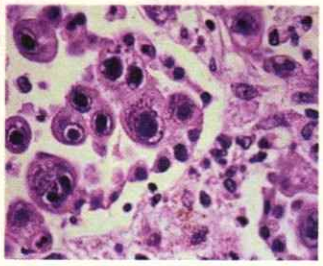
A set of chromosomes.



Owl's eye in pathology :

CMV inclusions





R-S cell

Small round blue cell tumor of childhood :

Small round cells with scanty cytoplasm

Rosettes

E.g. :

Neuroblastoma,

Nephroblastoma,

Retinoblastoma,

Hepatoblastoma,

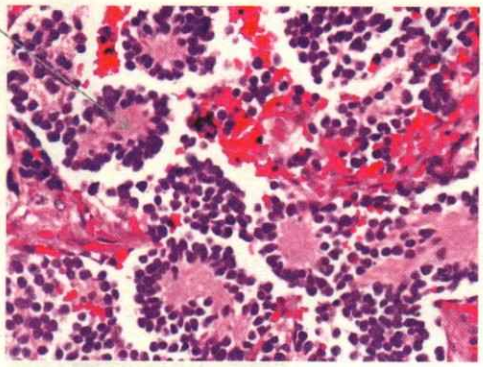
medulloblastoma,

PNET,

Ewing Sarcoma,

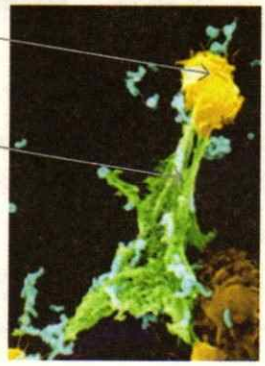
Rhabdomyosarcoma,

Lymphomas.



NET's (Neutrophil extracellular trap)

Extracellular fibrillar meshwork



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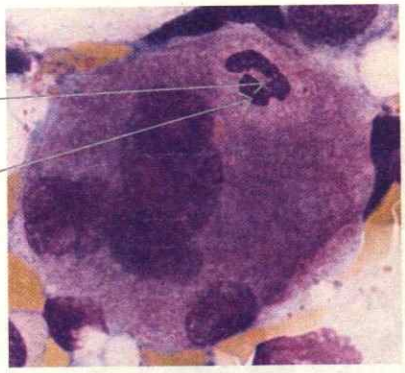
Emperipolesis : Cell within a cell appearance

Functionally viable cell

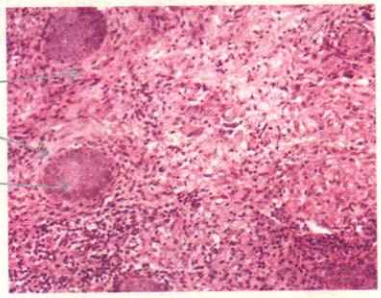


TB granuloma :

Epithelioid cells

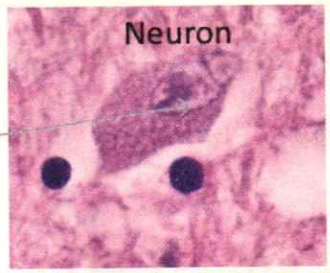
Collar of lymphocytes

Langhan's Giant cells

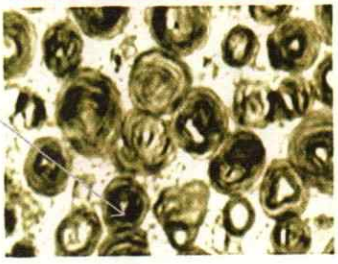


Tay Sach's disease :

Ballooned neurons



Onion skin appearance on electron microscopy



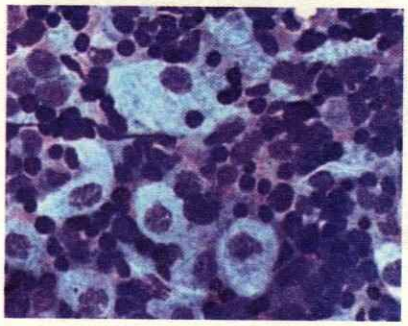
Niemann Picks disease :

Zebra bodies seen on electron microscopy

Active space

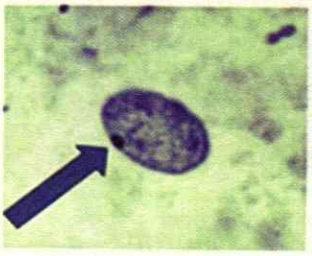
Gaucher's cells : PAS positive.

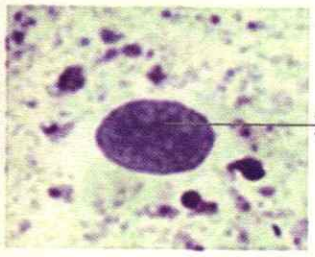
Crumpled tissue paper appearance of cytoplasm



Pseudo gaucher's cells are seen in CML.

Female Male

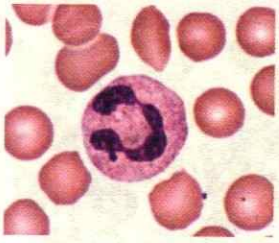




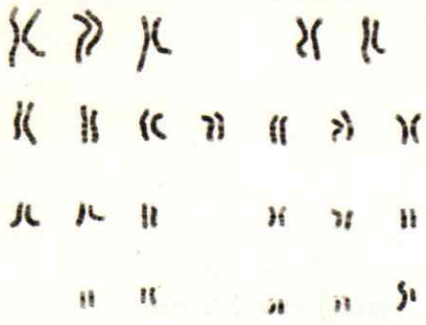
No Barr body (in male)

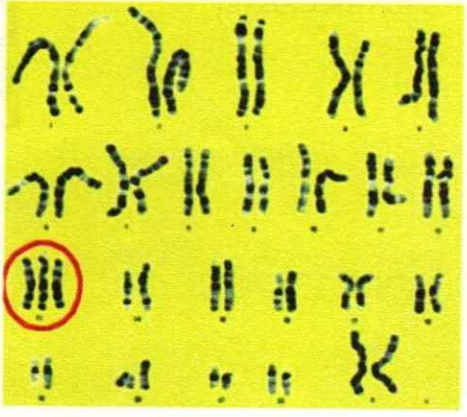
Barr body, an inactivated X chromosome

Shape of Barr body : It has a drumstick appearance



Normal Karyogram

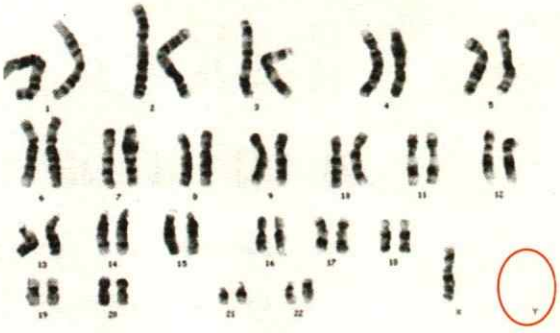




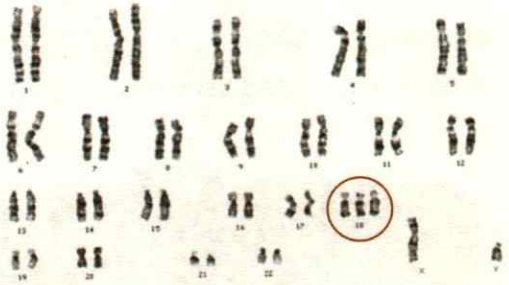
Karyogram showing trisomy of Patau syndrome

Active space

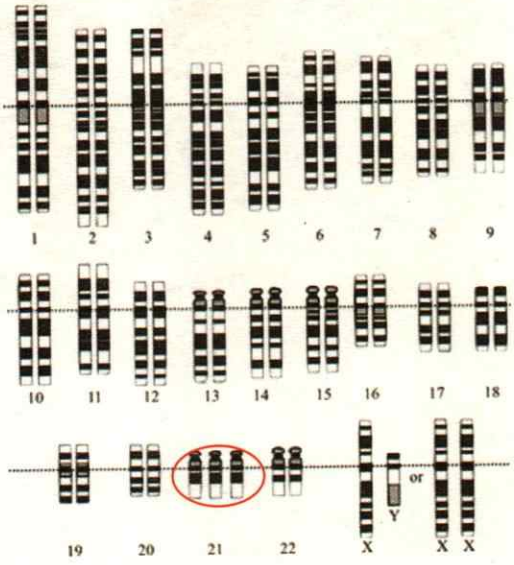
Karyogram of Turner's syndrome



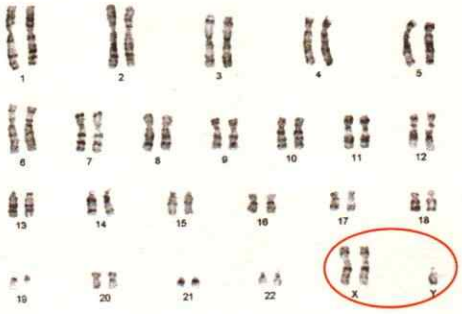
Karyogram of Edward's syndrome



Karyogram showing trisomy 21 – Down's syndrome



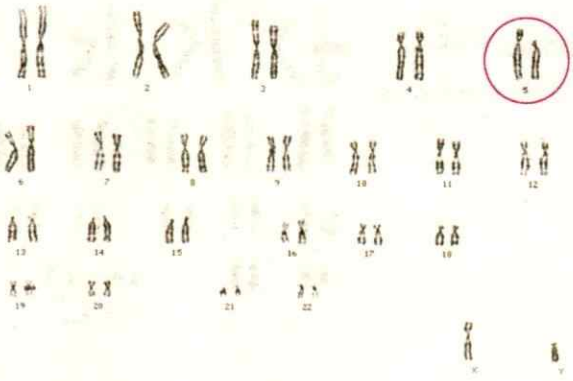
Karyogram of Klinefelter's syndrome



Active space

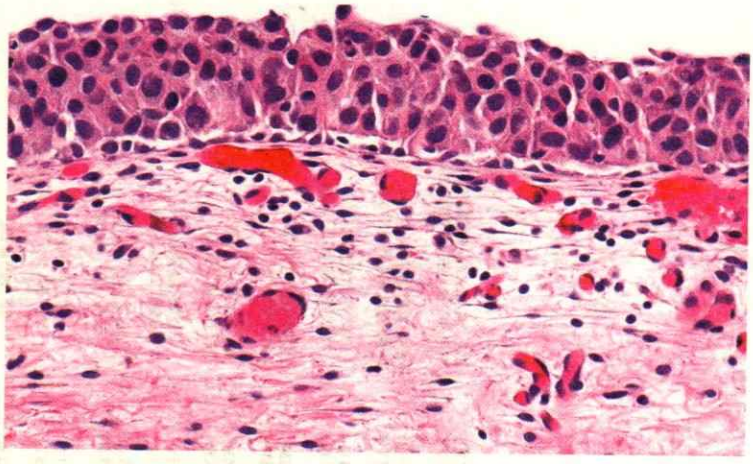
Karyogram of CRI-DU CHAT syndrome

a) Karyotype (G banding)



Carcinoma in-situ :

The cancer is limited by the_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

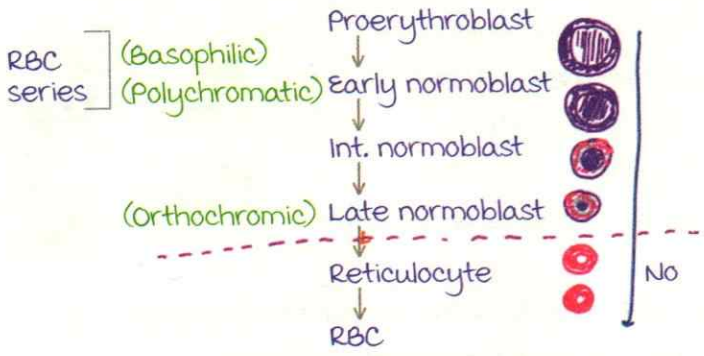


Active space

RBC : INTRODUCTION AND HYPOPROLIFERATIVE ANEMIA

RBC introduction :

- Normal size of an RBC : 7-8 µm.
- To identify if the RBCs are macrocytic, microcytic or normal, the size of an RBC is compared with the nucleus of lymphocyte.
- Life span of RBC : 120 days.
- RBCs do not have nucleus and has a central 1/3rd pallor.
- Biconcave shape of RBS is maintained by the protein spectrin.
- RBCs originate from Haemopoietic Stem Cells (HSC) which develop into the Common Myeloid Progenitor (CMP) cells.
- HSC → CMP → Proerythroblast → Early normoblast (basophilic normoblast) → Intermediate normoblast (polychromatic normoblast) → Late normoblast (orthochromic normoblast) → Reticulocyte → RBC formed.



- Basophillic appears blue, polychromic normoblast will be both pinkish and bluish, and late normoblast is pinkish color (orthochromic).
- As we move along from proerythroblast (largest cell), the cell size decreases and nuclear size also decreases. At the stage of reticulocyte, the RBC has no nucleus.
- Reticulocyte is the first cell which is non-nucleated and takes 1-2 days to mature into an RBC.
- Hemoglobin production starts at the stage of

Active space

proerythroblast and can only be seen on electron microscopy.

- In intermediate normoblast, the hemoglobin is visible through a light microscope.

Reticulocyte

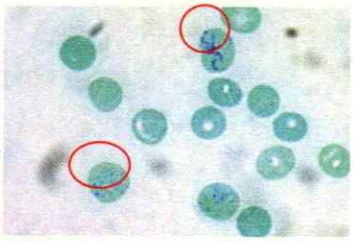
00:11:09

It is the immediate precursor of RBC and the 1st precursor with no nucleus.
Normal retic count is : 0.5–1.5%.

Special stain used to view a reticulocyte : Supravital stain.

Brilliant cresyl blue. New methylene blue (best stain for retic).

- Supravital stain stains the living state or living structure of a cell (in this case RNA).
- Basic steps : Sample on glass slide → Add stain → Incubate for 30 mins → Count the reticulocytes on smear.
- Because it stains living structures, the slide has to be analyzed on time and never delayed.
- The blue filaments in the reticulocytes are the RNA, i.e., there is a reticulum (meshwork) of RNA and hence named as reticulocyte.



Another blue stain to be remembered is Prussian Blue or Pearl Stain done for hemosiderin or iron.

↑ Retic count : Reticulocytosis.
↓ Retic count : Reticulocytopenia.

Causes of Reticulocytosis	Causes of Reticulocytopenia
Acute & chronic blood loss	Bone marrow suppression
Hemolytic anemia	Aplastic anemia
Response to treatment in Iron or Vit.B_{12} anemia	Megaloblastic anemia

Active space

Corrected reticulocyte count :

Retic count with degree of anemia taken into consideration.

$$\text{Corrected Retic Count} = \frac{\text{Retic \%} \times \text{Patient Hb}}{\text{Normal Hb for that age}}$$

Also note that, Hct → Hb % x 3.

Reticulocyte Production Index (RPI) :

$$\text{RPI} : \frac{\text{Corrected Reticulocyte Count}}{\text{Maturation time.}}$$

Normal maturation time is 1-2 days.

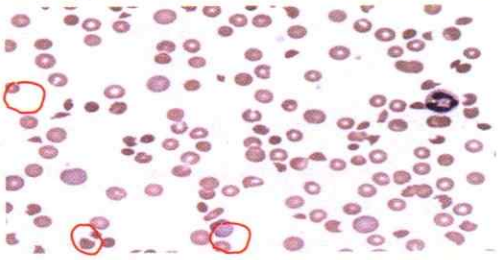
Packed cell volume and maturation time are related as such :

PCV	Maturation Time
45	1 day
35	1.5 days
25	2 days
15	2.5 days

These numbers are important to find the RPI for a given PCV.

Reticulocyte on a peripheral smear :

Polychromasia (pinkish bluish hue) on a peripheral smear is usually a reticulocyte.



RBC Indices

00:27:45

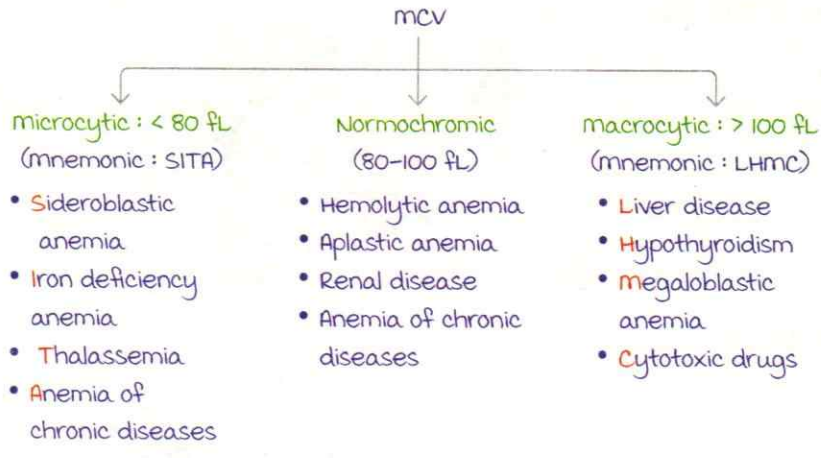
- MCV :
  Mean Corpuscular Volume, signifies the size/volume of the RBC. Normal value : 82-96 fl (80-100 fl)
  MCV = PCV/RBC count.
- MCH :
  Mean Corpuscular Hemoglobin. It is the average volume of Hb in a single RBC.
  MCH = Hb/RBC count.
  Normal MCH = 27-32 pg.

Active space

- MCHC : Mean Corpuscular Hemoglobin Concentration.
  i.e. Average volume of Hb in a given volume of packed red cells.
  MCHC = MCH/MCV.
  Normal MCHC : 33–37gm/dL.
  Raised MCHC is seen in Hereditary spherocytosis, because of water loss, and concentration of more Hb in smaller spherical RBC.
  Normal MCHC is seen in megaloblastic anemia due to B_{12} deficiency.
- RDW :
  Red Cell Distribution width. Normal RDW : 11.5 – 14.5%.
  Indicates the co-efficient of variation of red cell size or degree of anisocytosis.

RDW helps to differentiate iron deficiency anemia from thalassemia. Microcytic anemia is seen in both of them.
Iron deficiency anemia : RDW raised.
Thalassemia : RDW normal.

Anemia Based on MCV :



Anemia based on MCH :

- Hypochromic anemia : < 27 pg.
- Normochromic anemia : 27–32 pg.

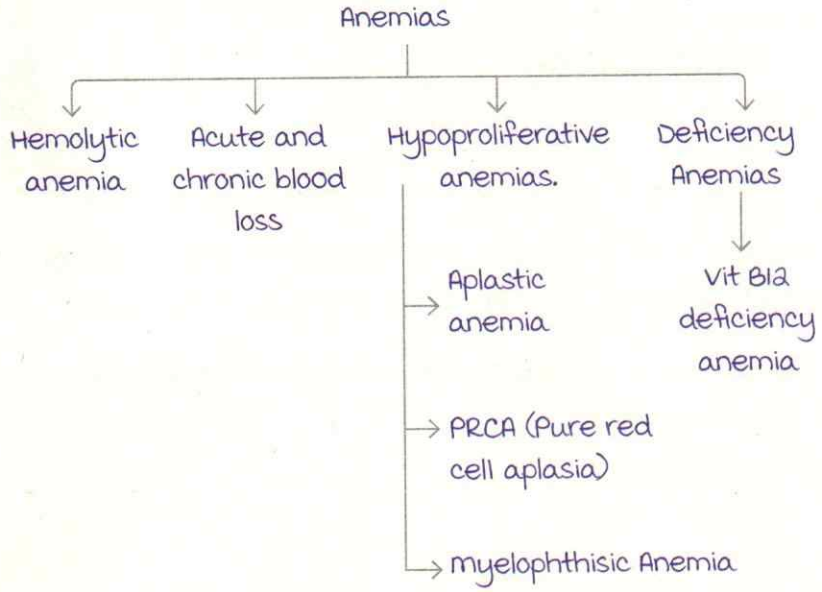
Variation in red cell size : Anisocytosis.
Variation in red cell shape : Poikilocytosis.

Active space

Anemias

00:51:07

Decreased Hb/red cell mass/hematocrit.



Hypoproliferative anemias :

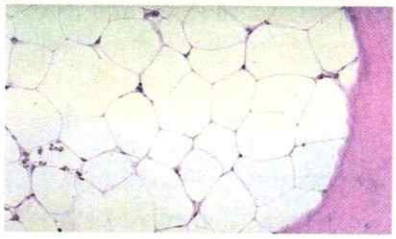
Aplastic anemia :

- Generalized bone marrow suppression seen. Decreased Hb, TLC, platelet counts & reticulocytes.
- Causes : Inherited or acquired.
  a. Acquired causes are more common like drugs, chemicals, viruses (Parvo Virus B19, HIV, Hep B,C).
  b. Inherited causes : Fanconi's anemia – DNA repair defect, Diamond Schachman Syndrome, dyskeratosis congenita (short telomeres).
- Clinical presentation : Pallor, fatigue, increased infections, bleeding tendencies.
- Spleen is never involved in aplastic anemia, therefore splenomegaly is never seen.
- Lab tests : Pancytopenia and reticulocytopenia seen.
  On peripheral smear : Normocytic normochromic anemia with pancytopenia.
  Next step :
  BMA (Bone marrow aspiration) : Dry tap is seen because there are few cells in the bone.
- Therefore, IOC : Bone marrow biopsy.

Active space

Increased fat and decreased cellularity is seen (space that cells used to occupy is now replaced by fat).

Bone marrow biopsy showing increased fat and reduced cells.



Also note that fat naturally increases with increase in age.
Normal cellularity in bone marrow = 100-age of patient.

Causes of dry tap on bone marrow aspiration (IOC is biopsy) :

1. Aplastic anemia.
2. Myelofibrosis.
3. Hairy cell leukemia.
4. AML-M7.
5. Myelophthisic Anemia.

Treatment :
Stem cell transplantation.
GM-CSF.

Severe aplastic anemia :
Criteria for severe aplastic anemia :

- BM cellularity < 25%.
- Any 2 of the following :
    a. Platelet count is < 20,000/μL.
    b. Corrected reticulocyte count < 1%.
    c. Absolute Neutrophil Count (ANC) < 500/μL.

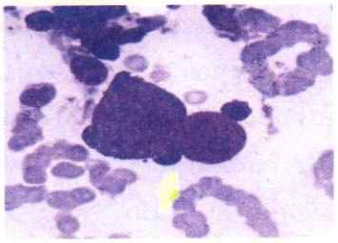
Very Severe aplastic anemia :
All above criteria but ANC < 200/μL.

Pure Red Cell Aplasia 01:06:39

Reduced erythroid precursors, Hb & retic count.
W
Causes :
Inherited : Diamond Blackfan syndrome.
Acquired : Parvovirus B19, thymoma, large granular lymphocytic leukemia, certain B cell disorders.

Active space

In Parvovirus B19, the erythroid precursors show dog ear erythroid precursors seen.



Myelophthisic Anemia :

Anemia caused by a space occupying lesion of the bone marrow like metastatic cancer, any granulomatous lesion of the bone.

RBC profile in these patients are tear drop shaped also called as dacryocytes.

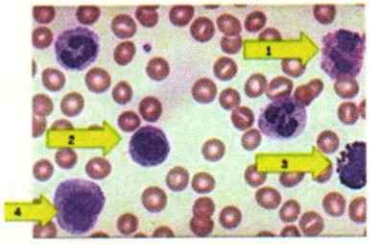
The smear will show a _____ blood picture (immature cells appear in blood because of no space in the bone).

Q. A 65-year-old female is diagnosed with pure red cell aplasia and a mediastinal mass. Which of the following can be the likely cause?

A. Thymoma.
B. Non Hodgkin lymphoma.
C. Bronchogenic Ca.
D. Germ cell tumour.

Q. Identify the cells marked in the given image

A. Lymphocytes.
B. Monocytes.
C. Eosinophils.
D. Basophils.



- A-3,B-4,C-1,D-2
- A-2,B-4,C-1, D-3
- A-2,B-4,C-3,D-1
- A-2,B-1,C-4,D-3

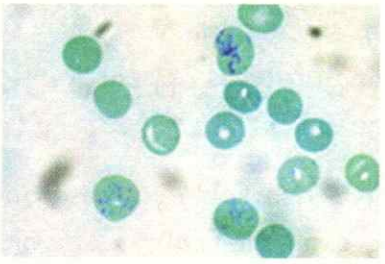
Q. Which of the following conditions will have the least chances of a dry tap on bone marrow aspiration?

A. Hairy cell leukemia.
B. Follicular lymphoma.
C. AML-M7.
D. Myelodysplastic syndrome.

Active space

Q. A 59-year-old woman with a history of chronic kidney disease comes to the physician for a 3-month history of easy fatiguability. Physical examination shows subconjunctival pallor. Her haemoglobin concentration is 8.9 g/dL, mean corpuscular volume is 86 μm^3, and serum ferritin is 110 ng/mL. Treatment with erythropoietin is begun. A peripheral blood smear is obtained one week after treatment. A photomicrograph of the smear after specialized staining is shown. The prominent colour of the intracellular structure in some of the cells is most likely the result of staining which of the following?

A. Ribosomal RNA.
B. Golgi apparatus
C. Mitochondria.
D. Nuclear remnant.
E. Lysosomes.



Q. An 18-year-old male presented to the OPD with gum bleeding, fever for the past 2 months. General examination showed pallor and the systemic examination was unremarkable. Laboratory examination revealed Hb level : 3 gm/dl, TLC : 1500, Platelets 15000. Further examination shows a low reticulocyte count, and bone marrow examination revealed fatty streaks and absent megakaryocytes but no immature cells. What is the likely diagnosis?

A. Acquired aplastic anemia.
B. PNH
C. Myelodysplastic syndrome.
D. Tuberculosis.

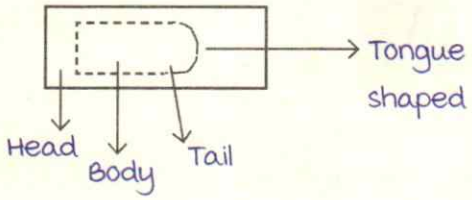
Active space

PERIPHERAL SMEAR EXAMINATION

Peripheral smear 00:02:48

A drop of blood is put on a glass slide. Another glass slide (spreader) is put at 30–45 degrees on the first slide and blood is spread to produce a tongue shaped smear. Smear has 3 parts : Head, body and tail.

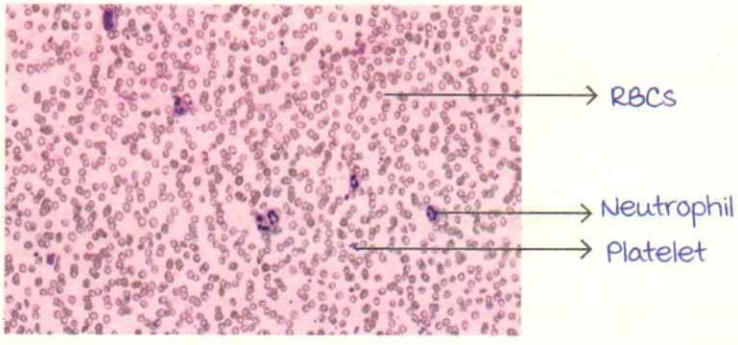
Parts of a peripheral smear :



Staining peripheral smear :
Romanowsky stain is most commonly used.
Common Romanowsky stains : Leishman, Giemsa, Wright and Jenner.
Components : methylene blue (basic dye), Eosin Y (acidic component).

Supravital stains : Brilliant cresyl blue and new methylene blue (best) are used to stain reticulocytes.

Normal peripheral smear :

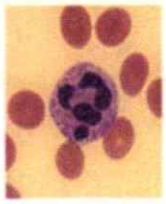


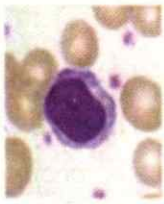
RBCs : Small cells with pallor in central 1/3rd . Size of RBCs

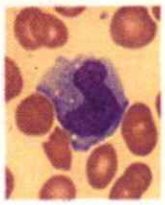
Active space

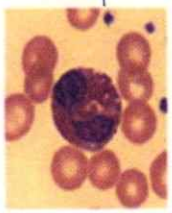
are compared with nucleus of a lymphocyte (7-8 microns). If smaller → microcytic and larger → macrocytic.

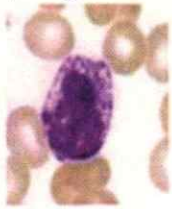
Types of WBCs :


Neutrophil


Lymphocyte & Platelets


Monocyte


Eosinophil


Basophil

Neutrophils : 3-5 lobes. Few small granules in cytoplasm.
2 lobes : Pseudo pelger huet cells seen in myelodysplastic syndrome.
>5 lobes : Hyper segmented neutrophil seen in megaloblastic anemia (Vit B12, folic acid deficiency).

Lymphocytes : No granules in cytoplasm.

Monocytes : Big cell with Kidney shaped nucleus. No granules in cytoplasm.

Eosinophils : Brick red granules in cytoplasm, Bilobed nucleus. Increases in allergic reaction

Basophils : Purplish granules obscure the entire nucleus.

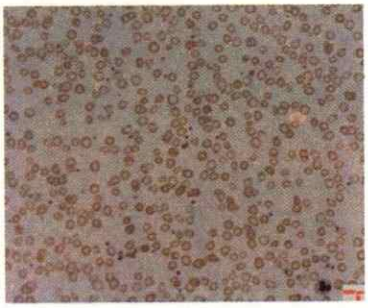
RBC abnormalities on peripheral smear 00:09:52

Microcytic hypochromic (MCV <80 fl) :
Small RBCs with >1/3rd central pallor.
S : Sideroblastic anemia; lead poisoning.
I : Iron deficiency anemia.

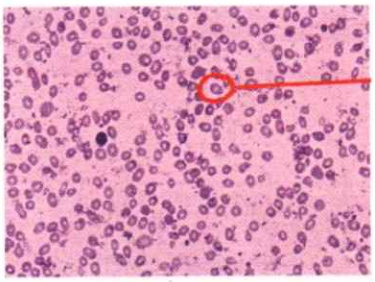
Active space

T: Thalassemia.
A : Anemia of chronic disease.

The image shows anisocytosis (variation in size) and pencil cell. High RDW, low MCV and low MCH.



Macrocytic (MCV >100 fl) :
Bigger, oval cell with no central pallor.
L : Liver disease.
H : Hypothyroidism.
M : Megaloblastic anemia (Vit B_{12}/folate deficiency).
C : Cytotoxic drugs.

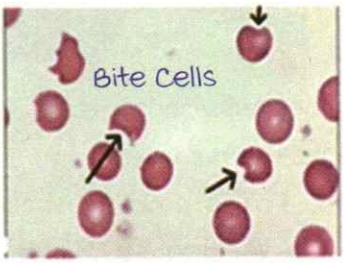


Pencil cells :

- Iron deficiency anemia.

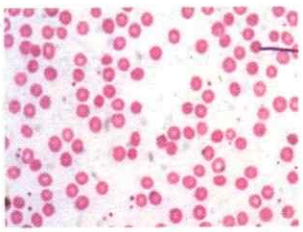
Bite cells :

- G6PD deficiency.



Spherocytes :
Small cells (spherical) with no central pallor.

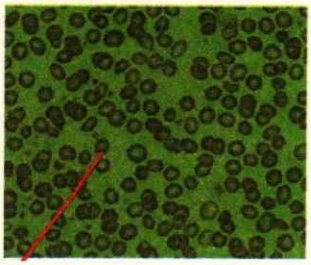
- Hereditary spherocytosis.
- Autoimmune hemolytic anemia (most common cause).
- Blood transfusion reactions.
- Burns.



Active space

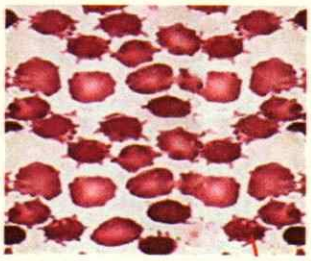
Burr cells/Echinocytes :
RBCs with blunt projections.

- Chronic renal failure.
- Uremia.
- Liver disease



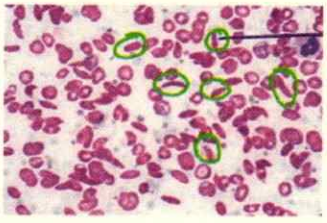
Spur cell/acanthocytes :
RBCs with sharp projections.

- Abetalipoproteinemia.



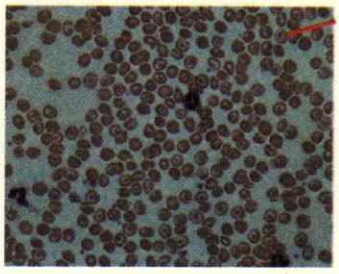
Sickle cells :

- Sickle cell anemia.



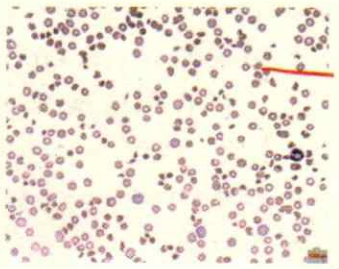
Target cells/codocytes :
Looks like a target.

- Thalassemia (most common).
- Liver disease.
- Iron deficiency anemia.



Schistiocytes (helmet) cells :
Fragmented red cells.

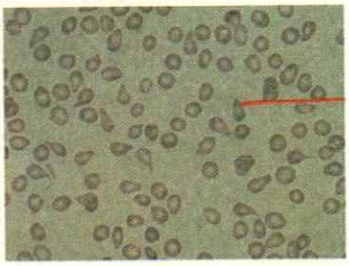
- Microangiopathic hemolytic
- Anemia : HUS, TTP and DIC.
- Prosthetic cardiac valves.
- Mechanical disruption of RBCs.



Active space

Tear drop cells/dacrocytes :

- myelofibrosis.
- myelodysplastic syndrome.
- myelophthisic anemia.
- Leucoerythroblastic blood picture.

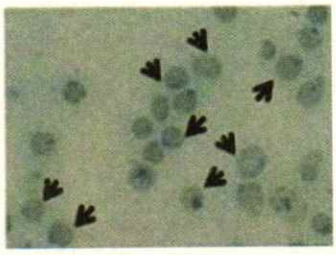


Heinz bodies :

Seen on new methylene blue stain.

Denatured hemoglobin.

- G6PD deficiency.

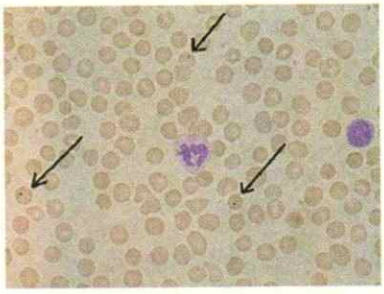


Heniz Bodies
New methylene Blue stain

Howell Jolly bodies :

Remnant of nucleus.

- Asplenia.
- Megaloblastic anemia.
- Thalassemia.



Pappenheimer bodies :

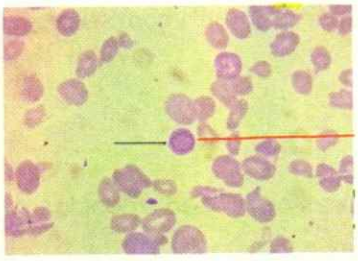
multiple, composed of iron.

- Sideroblastic anemia.

Cabot ring :

Figure of 8/ring configuration. Formed by_____

- Megaloblastic anemia (Vit B12/folate deficiency).
- Thalassemia.



Active space

Rouleaux formation :

Stack of coin appearance.

- Multiple myeloma (conditions with high ESR/ blood viscosity).

Polychromasia :

Neither pink nor purple.

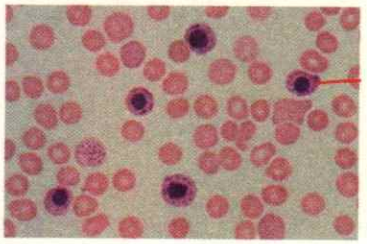
- Hemolytic anemia (Reticulocytes).

Basophilic stippling :

Bluish colored dots.

2 types :

- Fine : Seen in megaloblastic anemia, thalassemia.
- Coarse : Seen in sideroblastic anemia.



Stomatocytes :

Slit like space in RBCs.

- Hereditary stomatocytosis.

WBC changes

00:19:44

Hypersegmented neutrophils : >5 lobes.

- Megaloblastic anemia due B12/folate deficiency.

Bilobed neutrophils.

Myelodysplastic syndrome.

Toxic granules : Neutrophil with coarse granules, separate nuclei.

- Sepsis.

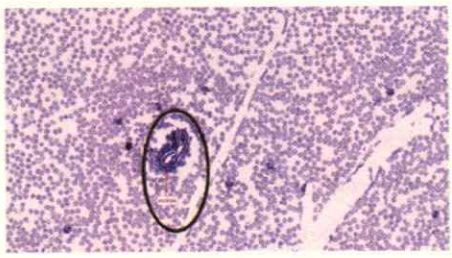
Dohle bodies : Patches of dilated endoplasmic reticulum.

- Sepsis.

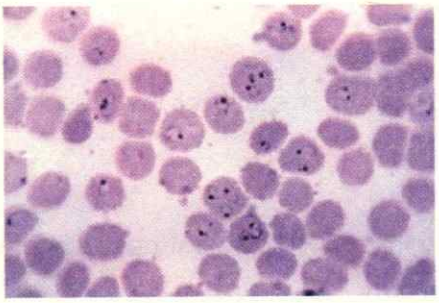
Active space

Infections :

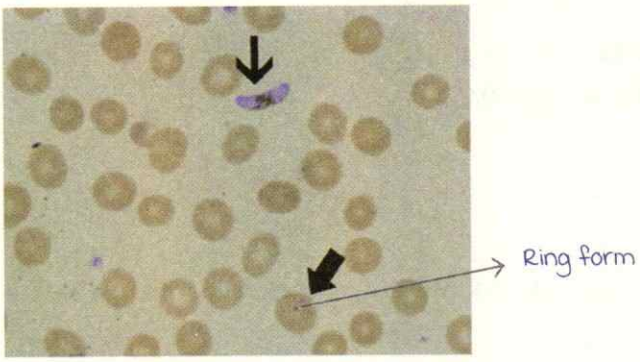
Microfilaria :



Malaria : Ring form of Plasmodium vivax.



Malaria : Gametocyte of Plasmodium falciparum.



Clinical case discussions 00:30:38

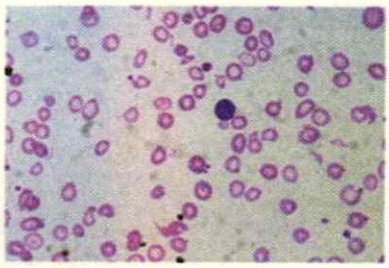
Q. A 17 year old male presented with fatigue

Lab tests : Hb – 9gm%

- MCV – 67 fl
- MCH – 20pg
- MCHC – 16 gm/dl
- RBC count – 3.9 x 106/ul
- WBC – 6000/L

Active space

- PLC – 3.5 lakhs



Impression ???

Hb, MCV, MCH, MCHC, RBC counts are low.
WBC and platelet counts are normal.
Peripheral smear shows microcytosis, hypochromia and anisocytosis.
Impression : Iron deficiency anemia.
Confirm by iron profile : Serum iron, serum ferritin, total iron binding capacity.
Start on iron therapy. Monitor treatment by reticulocyte count.

Q. A 15 year old male, with history of weakness since few months

- Hb – 6gm/dl
- MCV – 105 fl
- Reticulocyte count < 1%
- WBC – 1000/ul
- Plc – 90,000/ul

Impression ??

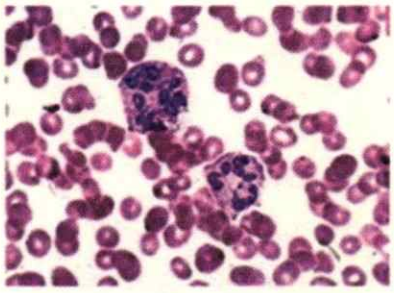
Hb, reticulocyte count, WBC, platelet counts are low.
MCV is high.
Impression : Pancytopenia
Evaluate the cause.

- Aplastic anemia.
- Leukemia.
- Paroxysmal nocturnal hemoglobinuria (reticulocyte count is high).
- Megaloblastic anemia due to B12 deficiency.

Active space

Q. A 32 year old female, vegtarian present with fatigue

- Hb – 7 gm%
- TLC – 1300/UL
- PLC – 1 lakh
- MCV – 132fl
- MCH – 28 pg
- MCHC – 39 gm/dl



Impression ??

Hb, TLC, platelet count are low.
MCV is high.
MCH and MCHC are normal.
Peripheral smear shows macro ovalocytes with hypersegmented neutrophils.
Impression : megaloblastic anemia due to B12 deficiency.

Active space

MICROCYTIC HYPOCHROMIC ANAEMIA

Mnemonic : SITA.

Sideraoblastic anaemia.

Iron deficiency anaemia.

Thalassemia.

Anaemia of chronic disorders.

Iron deficiency anaemia (IDA) 00:01:42

Most common of the nutritional deficiencies.

Daily requirement : 10-20milligrams/day.

Rich source :

Iron → Haem form. (mostly)
Iron → Non Haem form.

In the Haem form : 80% is in haemoglobin.
20% is in enzymes or others.

Iron is seen in Fe^{2+} (ferrous) & Fe^{3+} (ferric) form.

Iron absorbed from duodenum as Fe2+ form only.

Most common site of iron absorption : Duodenum.

Storage form of Iron :

1. Ferritin.
2. Haemosiderin.

Transportation form of iron : Transferrin.

Causes of IDA 00:06:41

- Decreased intake :
  - Poverty.
  - Low socioeconomic status.

Active space

- Increased demand :
  Puberty.
  Pregnancy.
  Lactation.
- Impaired absorption :
  In certain malabsorption syndromes.
  Vit B12 deficiency causing worm : Fish tape worm (Diphyllobothriasis).
- Chronic blood loss :
  GI/colon malignancy.
- Worm infestation : Ancylostoma duodenale (hookworm).

Factors :

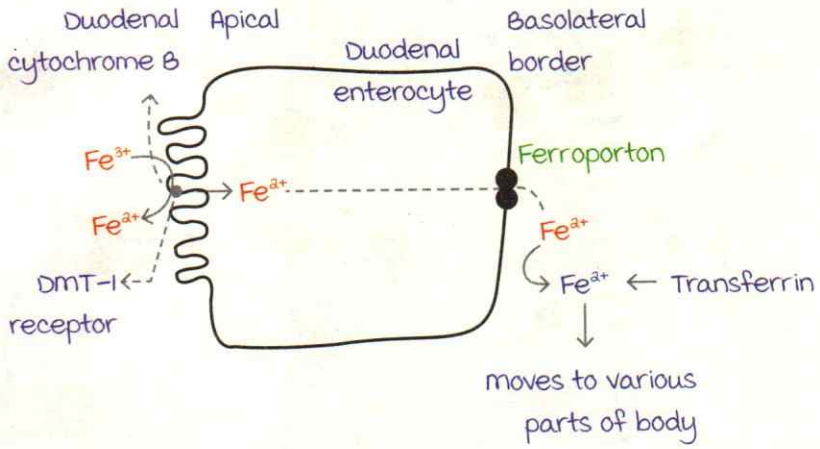
Increasing iron absorption : Acidic pH , Vit. C /Ascorbic acid, amino acids, citric acid.

Decreasing iron absorption : Alkaline pH, tannates , phytates, tea (only have iron after 30 mins).

Mechanism of iron absorption 00:12:34

Haem iron directly enters as Fe^{2+}.

Non-Haem mostly in form of Fe^{3+} and is converted to Fe^{2+}.



Active space

At the villi of duodenum,

Duodenal cytochrome B

Fe^{3+} ⟶ Fe^{2+}

↓

Fe^{2+}

↓

via Divalent metal Transporter1 (DMT1) receptor

↓

Fe^{2+} enters the enterocyte

↓

Some are stored as mucosal ferritin and some move onto basolateral border

↓

Fe^{2+} moves out of basolateral border

↓

Hephasetin or ceruloplasmin

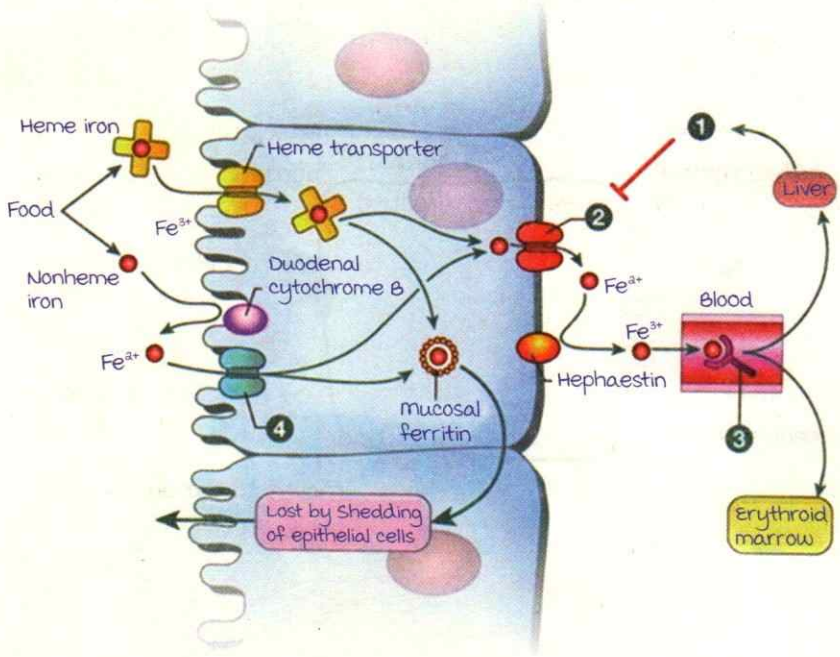
Fe^{2+} ⟶ Fe^{3+}

↓

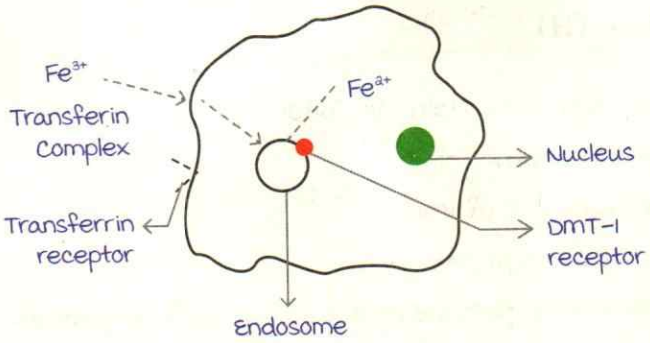
combines with Transferrin

↓

moved to Liver, Bone marrow



Active space



At the bone marrow,

In Erythroid precursors, iron & porphyrin combines forming hemoglobin.

Erythroid precursors have transferr in receptors to which Fe^{3+}- Transferrin complex binds and enters the enterocyte & into the endosomes.

In the enterocyte, Iron is stored in endosome having DMT-1 receptor which will again convert to Fe^{3+} and comes out.

DMT 1 is present in :

- Placenta.
- macrophages.
- Erythroid precursors.

Transferrin (TF)

00:21:37

Transporting molecule for iron.

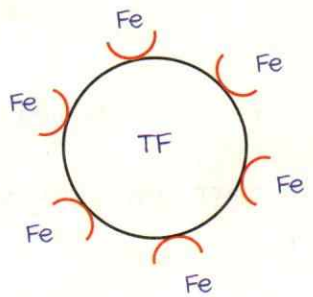
1 TF can combine with 6 molecules of iron ideally.

But clinically 1 TF combines with only 2 Fe molecules implying Transferrin saturation (TS) = 2/6 x 100 = 33%.

Early erythroid precursors (EP) have more TF receptors (TFR) but in late EP, TFR sheds off.

Soluble TFR ratio (STFRc) : measure of_____

_____



Active space

Hepcidin (H)

00:25:39

Hep : Hepatocytes. Cidin : Inhibitor.

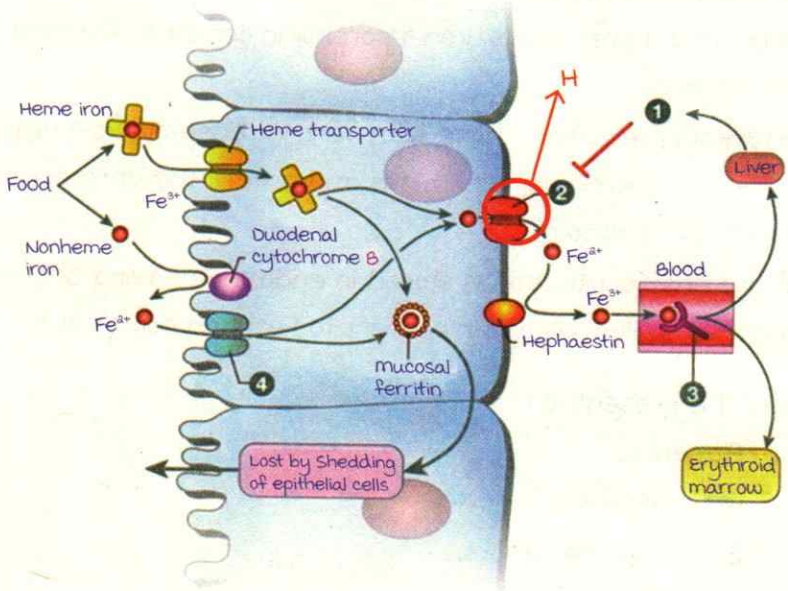
Produced by liver.

master regulator of iron.

Inhibits Fe absorption.

Increase in H, implies decrease in iron and vice versa.

Mechanism :



H binds to Ferroportin and degrades it.

↓

Fe not released

↓

Decrease in serum iron

↓

Microcytic hypochromic anaemia.

H is an acute phase reactant, hence increased during inflammation.

Genes Regulating H :

HFE
HJV
} Mutation causes hemochromatosis by iron overload.

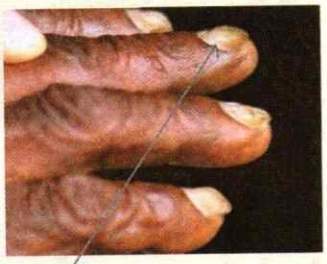
TMPRSS 6 : Seen in Iron Refractory Iron Deficiency Anaemia (IRIDA).

Active space

Clinical features

00:31:52

Usually seen in middle aged women.



- Pallor.
- Fatigue.
- Dyspnoea.
- Palpitation.
- Angular stomatitis , cheilitis.
- Koilonychia (spoon shaped nails).
- PICA : H/o child eating mud, clay.
- Plummer Vinson Syndrome or Peterson Brown Kelly Syndrome.
- Triad :
  - Fe deficiency anemia.
  - Esophageal webs.
  - Atrophic glossitis.

Investigations :

1. CBC :

Hb low

RBC mass low

TLC normal

Platelet count ideally normal but clinically seen as thrombocytosis/increased called as reactive thrombocytosis.

MCV, MCH, MCHC all are decreased.

RDW : Indicator of anisocytosis.

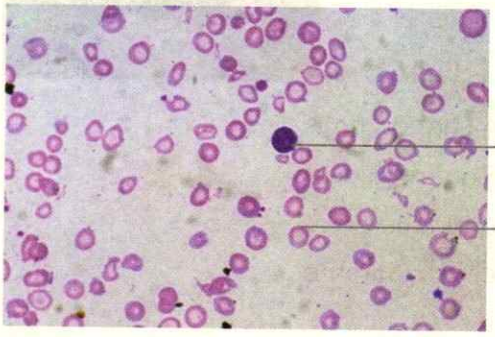
Variation in RBC size seen so increased.

2. Peripheral smear :

- microcytic hypochromic RBC : Smaller cell and have more than one third central pallor.
- Pencil cells.
- Anisopoikilocytosis.

RBC size is 7-8 microns and is comparable to the size of nucleus of small lymphocyte.

Active space



Iron studies

00:41:22

Expensive so can be skipped for patients in lower social economic strata and can start on Fe therapy.

- Serum Fe decreased.
- Serum ferritin decreased :

  Ferritin is the storage form. It is the sensitive test and one of the earliest parameters to decrease.
- S. TIBC : Binding capacity of iron to receptor.

  Here, No Fe implying increased S.TIBC.
- Transferrin Saturation (TS) : Decreases
- Free erythrocyte Protoporphyrin level : Increases.
- Bone marrow Fe : Golden Standard Test.

  Stain for iron hemosiderin in bone marrow is Prussian blue or Pearl stain. Decrease in stainable iron.

  It is not done as is painful and invasive.
- STFRc assay to Log Ferritin ratio :

  > 1.5 : indicator of FDA.

  STFRc increases and ferritin decreases in FDA.
- STFRC Assay : Sensitive test.

Active space

Order of sensitivity test : STFRc assay to Log Ferritin ratio > STFRc assay > S. Ferritin.

Stages of anaemia :

Stage 1 : Decrease in storage.
Decrease in Ferritin.

Stage 2 : Iron Deficient Erythropoiesis.

Stage 3 : Iron Deficiency Anaemia.

Peripherals Smear finding is seen stage 3.

Treatment : Iron therapy

Monitoring is done with Retic count :

First indicator to increase.

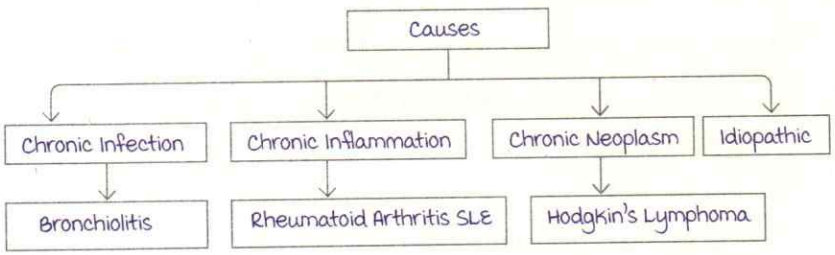
Starts increasing in 5 to 7 days of iron therapy.

CBC peripherals smear done and started on iron therapy → Then after a week → Investigation for iron studies done and also retic count → If count increases continue Fe therapy.

Mentzer Index : $\frac{\text{MCV}}{\text{RBC Count.}}$

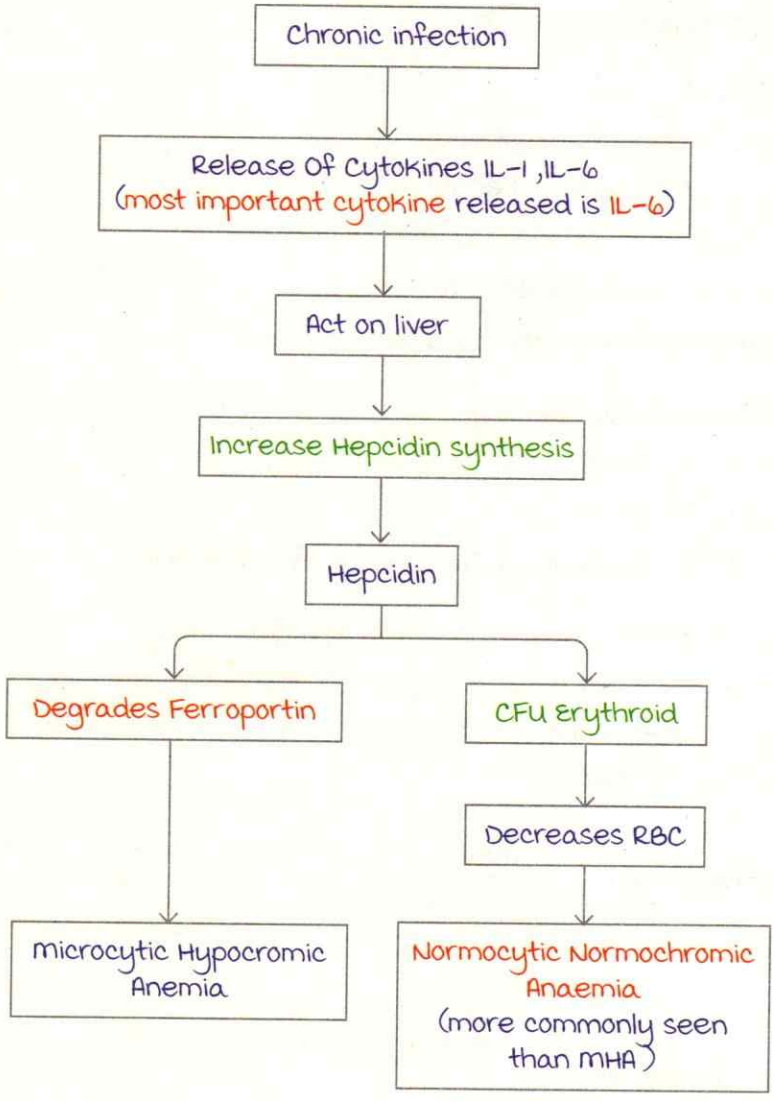
> 13 : FDA
< 13 : Thalessemia
} Aids in differentiating both.

Anaemia Of Chronic Disease (AOCD) 00:51:22



Active space

Pathogenesis :



Investigation :

- Hb, TLC, Platelet count decreases.
- MCV MCH MCHC normal or decreased.
- Peripherals smear shows normocytic normochromic anemia sometimes as normocytic hypocromic anemia.
- Iron profile :
  Serum iron : Decreases.
  Serum Ferritin : Increases as stores of Fe increased and would not get released.
  S.TIBC : Decreased as it is a measured with Serum Ferritin and is overloaded with Fe.

Active space

- STFRc assay to Log Ferritin ratio :

  <1.5 implies AOCD.

  S. Ferritin is high.

Treatment : Treat the cause.

Sideroblastic anaemia(SA) 00:58:18

Opposite to iron profile study in FDA.

Sider is iron & Blastic is immature precursors.

Excessive iron in immature precursors but cannot be utilised by EP for Hb synthesis.

Causes:

- Genetic
  - Enzyme Deficiency
  - X linked SA
- Acquired
  - Alcohol
  - Anti TB Drugs (Isoniazid)
  - Vitamin B6 Deficiency

Pathogenesis :

Hb Synthesis Pathway :

Succinyl Co A

↓ ALA Synthase(rate limiting)

ALA Production

↓ ALA Dehydrogenase

Porphobilinogen production

↓ By many reactions

Protoporphyrin ← Iron
(Occurs in mitochondria)

↓ Fe chelatase

Heme

Active space

If defect in ALA Synthase/ ALA Dehydrogenase/ Ferrochelatase :

No protoporphyrin formed but Fe accumulation increases.

No Hb is formed.

Vit B6 is needed in Hb synthesis.

Alcohol is mitochondrial poison.

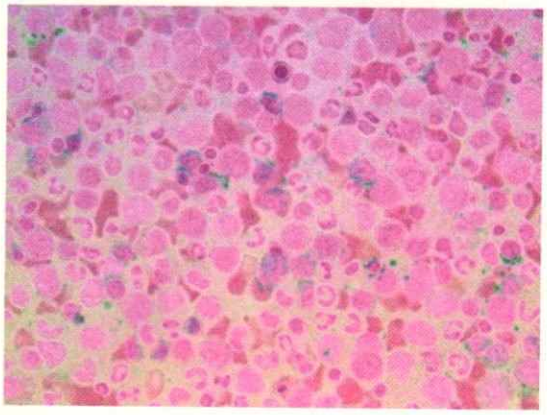
- Bone marrow aspiration :

  Ringed Sideroblast :

  Mitochondria is located in perinuclear area and Fe keeps accumulating in the mitochondria.

  more than 5 iron granules in perinuclear location and covering one third of nucleus is called as Ringed Sideroblast.

  Seen using Prussian blue stain.



- CBC :

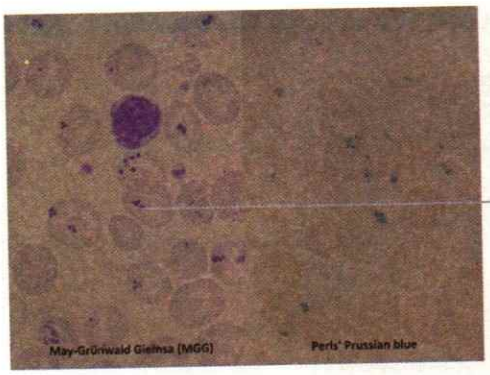
  Hb decreased.

  TLC , platelet count normal.

  MCV MCH MCHC decreased in MHA.

- Peripheral smear :
  1. Pappenheimer bodies : Iron in mature RBCs.
  2. Microcytic hypochromic red cells.
  3. Coarse basophilic stippling.

Active space



- Iron profile :

  Serum Iron increases.

  Serum Ferritin increases.

  S. TIBC decreases.

  TS increases.

Treatment :

Phlebotomy.

Iron chelaters.

	S. Iron	S. F erritin	S.TIBC	P/S	Extra
Iron deficiency anaemia	Dec	Dec	Inc	Pencil cells	RDW inc mentzer Index >13
Sideroblastic anaemia	Inc	Inc	Dec	Ringed sidero-blasts Coarse Ba-sophilic Stippling	
Anaemia of chronic disease	Dec	Inc or normal	Dec		ESR inc
Thalassemia	N	N	N	N	HbA2 inc mentzer index <13

HbA2 Inc ⟶ >3.5 ⟶ Thalassemia trait.

Scenario 1 :

Q. A 17 year old male presented with fatigue. Lab tests w:

Hb : 9 gm%.

MCV : 67 fl.

MCH : 20pg.

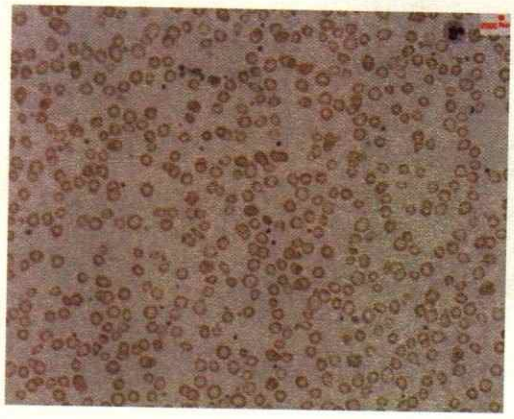
MCHC : 16 gm/dl.

RBC count : 3.9 x 106/μL.

WBC : 6000/L.

Active space

Answer : MH cells present s/o FDA. Advise Fe studies.



Q. Which of the following is used in the treatment of sideroblastic anemia?

A. Vitamin B12.

B. Vitamin B6.

C. Vitamin B1.

D. Iron.

Q. Which of the following is not involved in iron metabolism:

A. Hepcidin.

B. Transthyretin.

C. Transferrin.

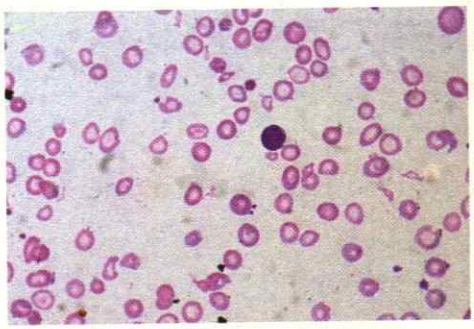
D. Ceruloplasmin.

Scenario 2 :

Q. A 33 year old woman presents with dysphagia and atrophic glossitis. The peripheral smear from this patient is given below. Which of the following lab findings is consistent with her likely diagnosis?

Options	S.Ferritin	TIBC	Transferrin saturation
1	High	Normal	High
2	Normal	Normal	High
3	Low	High	Low
4	High	Low	Low

Active space



Answer :

Pencil cells present.

MH are red cells present thrombocytosis present in femal.e

Dysphagia and atrophic glossitis present. Suggestive FDA classical presentation of Plummer Vinson disease.

Q. In iron deficiency anaemia, all of the following are increased except

A. Transferrin saturation.

B. RBC protoporphyrin.

C. TIBC.

D. Ferritin soluble receptors.

Active space

MEGALOBLASTIC ANAEMIA

- Megaloblastic anemia (MA) is a type of macrocytic anemia.
- Megalo =Large, blastic = Immature.

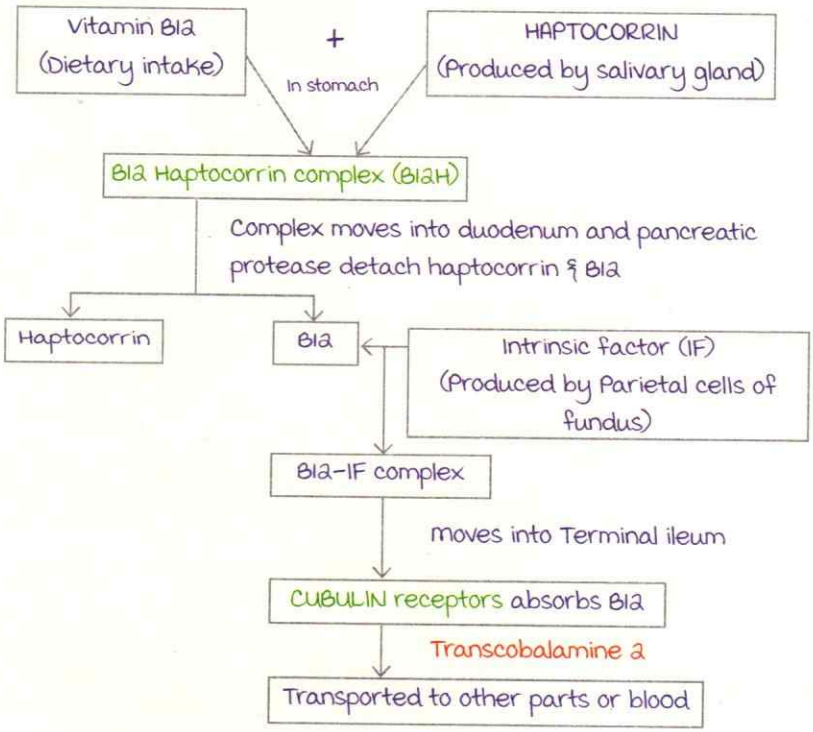
INDEX

MA Due To Vitamin B12 Deficiency 00:00:48

Vitamin B12 (B12) :

- Also called as Cyanocobalamine.
- Water soluble (non toxic).
- Daily requirement is 2-3mcg.
- Source : Dairy products (milk), egg, fish, meat (usually deficient in vegetarian people).

Mechanism of action :



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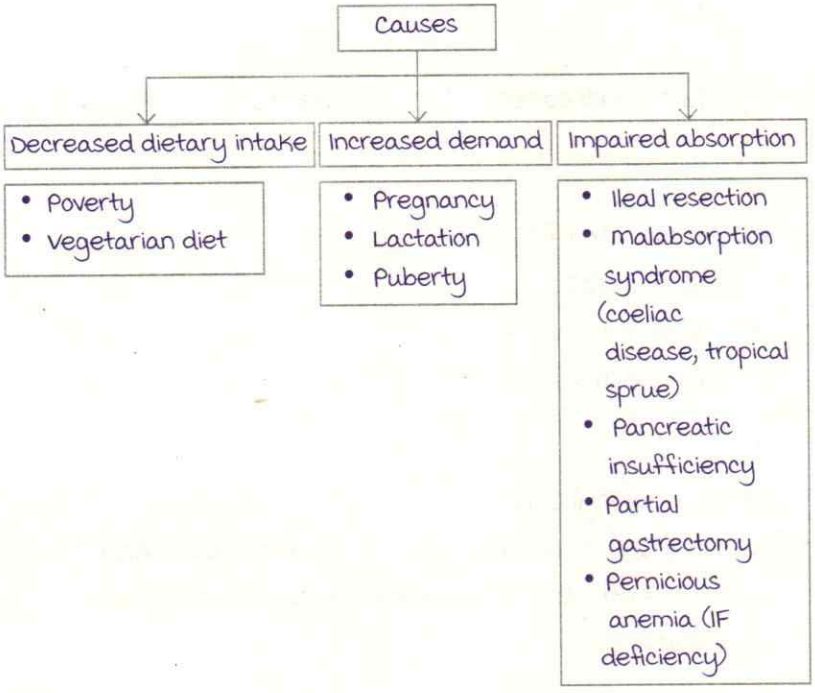
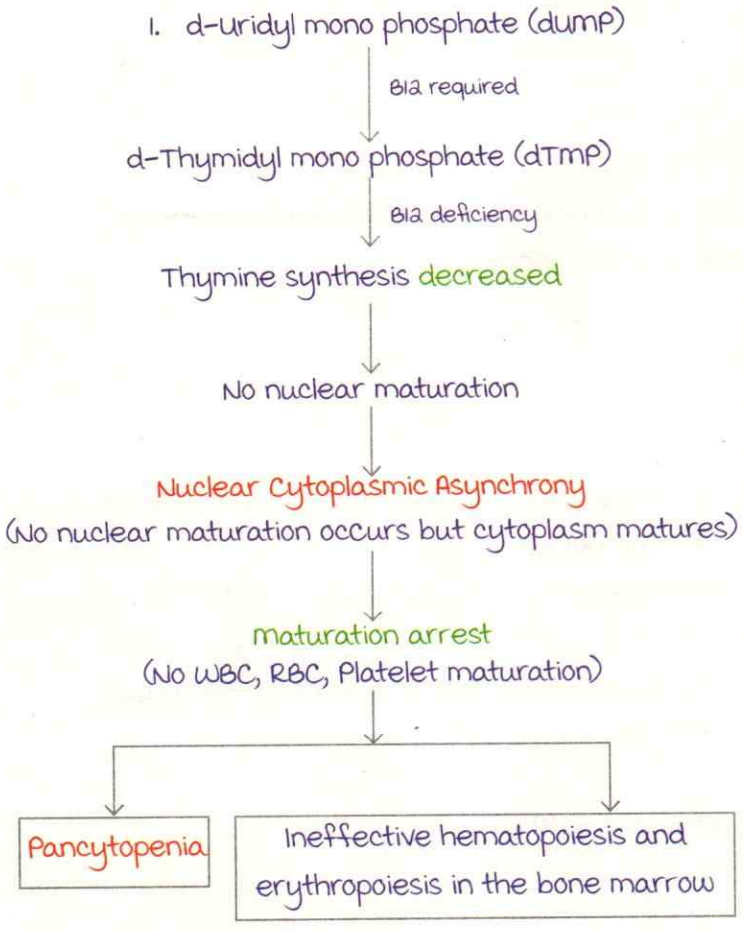
- The site of maximum B12 absorption is Terminal ileum.
- Transportation molecule is _____



Biochemical reaction catalyzed by B12 :



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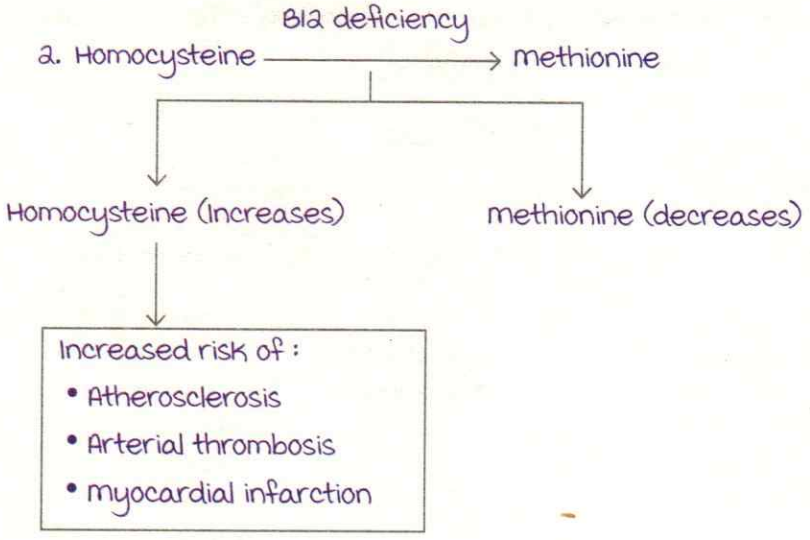


3. Methyl Malonyl CoA $\xrightarrow{B12}$ Succinyl CoA.

- Succinyl CoA is a component of neuronal lipids and myelin sheath, so it's decrease causes neurological complications.

Clinical features :

- Pallor.
- Fatigue.
- Jaundice.
- Splenomegaly.
- Neurological complications like Sub Acute Combined Degeneration of Spinal Cord.

Investigation :

- CBC :
  1. Decrease in hemoglobin, total count, platelet count. (Pancytopenia)
  2. Increase in MCV (as large RBC) : >100 femtolitres.
  3. Increase in MCH as they appear hyperchromic.
  4. Normal MCHC (as size of RBC and hemoglobulin also increase).

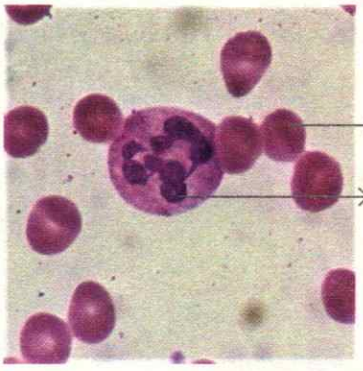
- Peripheral smear (PS) :
  In RBCs -

Active space

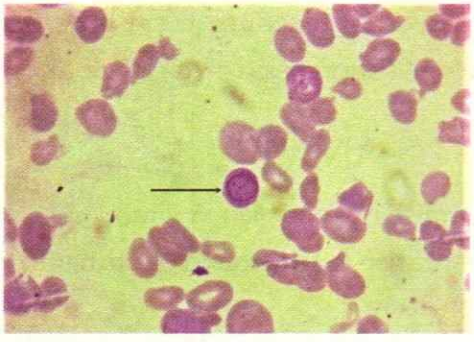
1. Macro ovalocytes :
   - Large ovular RBC and macrocytic, (sometimes no central pallor).
   - Earliest finding.
2. CABOT rings :
   - Appear like either figure of 8 or round ring shaped formed by microtubules .
3. HOWELL JOLLY BODY : Remnant of nucleus formed due to ineffective hematopoiesis / erythropoiesis.
4. Fine Basophilic stippling : RBC appear to have fine bluish dots .

In WBCs : Hyper segmented neutrophils (>5 lobes) is seen

- Criteria for diagnosis : >5% neutrophils with 5 or more lobes.
  Single neutrophil with 6 or more lobes.

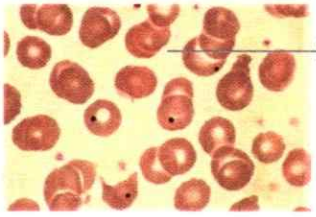


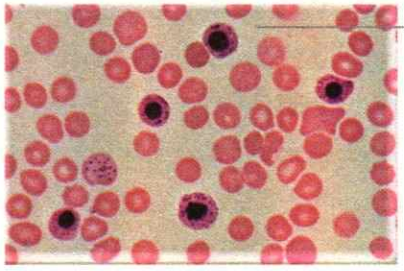
Hyper segmented neutrophil (8 lobes)



Cabot ring

Active space





- Bone marrow aspirate :
  1. Erythroid hyperplasia.
  2. Reversal of M : E ratio.
  3. Shows large immature precursors of RBCs, WBCs, megakaryocyte.
  4. Large Erythroid precursor with sieve like chromatin (thin chromatin that have not matured) called megaloblast.
  5. Giant metamyelocytes and band forms.
  6. Giant megakaryocytes.

- Biochemical investigations :
  1. Vitamin B12 assay.
  2. Serum Homocysteine levels.
  3. Serum Methyl malonyl CoA.
  4. Serum LDH (as ineffective erythropoiesis).
  5. Reticulocyte count (because there is general bone marrow suppression of all lineages).

- Treatment :
  a. Dietary intake of food rich in Vitamin B12.
  b. Supplementation with Vitamin B12 tablets (Neurobion forte).
  c. Intramuscular Vitamin B12 injections.

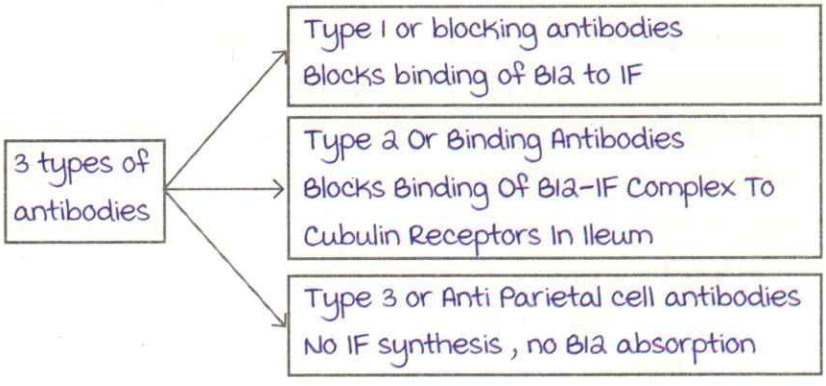
Active space

MA Due To Folate Deficiency Anemia 00:34:01

- Derived from word Folia meaning green leafy vegetables(spinach, broccoli).
- Overcooking destroys folate.
- In pregnancy folate deficiency causes Neural Tube Defect.
- Site of folate absorption : Jejunum.
- Deficiency is seen in alcoholics.
- Neurological complications seen in B12 deficiency are absent here as folate doesnt help in mylination. If B12 deficiency is treated with folate anemia improves as Folate helps in Thymine synthesis but neurological symptoms worsen.

Pernicious Anemia 00:37:09

- Type 2 Hypersensitivity Reaction (Antibody mediated).
- Autoimmune reaction.
- Pathogenesis :



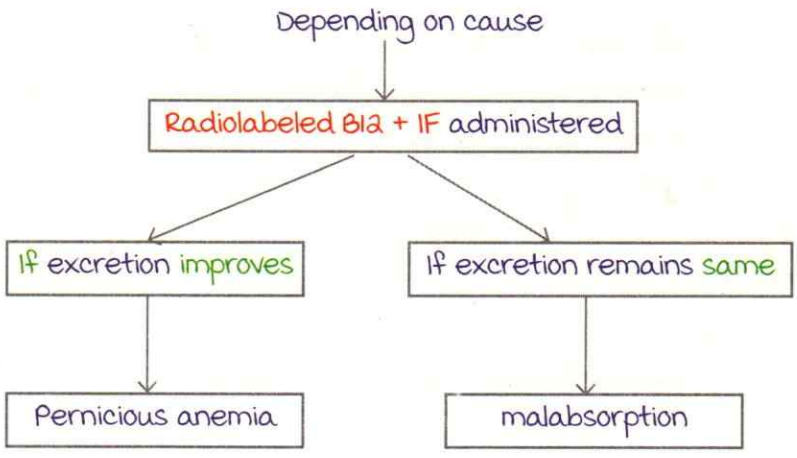
- Clinical features :
  1. Pallor.
  2. Fatigue.
  3. Beefy tongue.
  4. Atrophic Glossitis.
  5. Increased risk of autoimmune disorders.
  6. Increased risk of Gastric Adenocarcinoma.
  7. Fundic gland atrophy.

Active space

Schilling's Test

00:41:16

- Not used nowadays.
- Not for diagnosis but to identify cause of B12 deficiency anemia.
- Radio-labelled vitamin B12 administered and depending on its excretion in 24 hours.
  - > 8% ⟶ Normal
  - < 8% ⟶ Vitamin B12 deficiency



EXTRA POINTS :

- Site of maximum absorption of iron : Duodenum.
- Coarse basophilic stippling seen in Sideroblastic anemia.
- In myelodysplastic syndrome- Hyposegmented neutrophil (Pseudo Pelger-Huet) is seen .
- Pancytopenia is seen in
  1. Aplastic anemia .
  2. MA due to B12 deficiency.
  3. Leukemia.

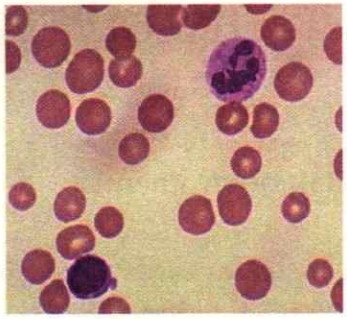
Clinical scenario :

Q. A 55-year-old man comes to the physician because of the Balance problems. He follows a vegan diet And does not eat meat, eggs or dairy. Physical examination shows pale oral mucosa and conjunctivae. Neurological examination shows normal strength in all extremities and decreased sense to vibration in his lower extremities bilaterally. A Peripheral blood smear is shown. Which of the following enzymes is most likely impaired ?
A. Succinate dehydrogenase.

Active space

B. Pyruvate carboxylase.
C. Methylmalonyl coA.
D. Dopamine beta hydroxylase.

Answer : Methylmalonyl coA.



Q. A 51-year-old man has become increasingly fatigued for the past 10 months. On physical examination there are no abnormal findings. Laboratory studies show his Hgb – 9.2, Hct – 27.9% , MCV –132 fl, Platelet count – 242,000/microliter, & WBC count 7590/ microliter. Which of the following morphological findings is most likely to be present on examination of his Peripheral blood smear?

A. Hypersegmented neutrophils.
B. Nucleated red blood cells.
C. Blasts with Auer bodies.
D. Hypochromic, microcytic RBCs.
E. Schistocytes.

Answer : Hypersegmented neutrophils > Nucleated red blood cells.

Active space

HEMOLYTIC ANEMIA : PART 1

Hemolytic anemia

00:01:16

Caused by excessive destruction of RBCs.

Hemolytic anemia can produce two types of defects :

- Intracorpuscular defects : Defect inside RBCs.
- Extracorpuscular defects : Defect outside RBCs.

Intracorpuscular defects : Either hereditary or acquired.

Hereditary :

- Red cell membrane defects : Hereditary spherocytosis, hereditary elliptocytosis.
- Enzyme deficiencies : G6PD deficiency, pyruvate kinase deficiency, hexokinase deficiency.
- Hemoglobinopathies : Sickle cell anemia, thalassemia.

Acquired :

Paroxysmal nocturnal hemoglobinuria (only acquired intracorpuscular defect).

Extracorpuscular defects : Either immune mediated or non - immune mediated.

Immune mediated : Autoimmune hemolytic anemia.

Non immune mediated : Infections like malaria.

Hemolysis can be intravascular or extravascular.

Intravascular hemolysis	Extravascular hemolysis
Hemolysis occurs inside a vessel	Hemolysis occurs outside a vessel. Example : Liver, spleen
Hepatomegaly or splenomegaly are usually absent	Hepatomegaly or splenomegaly are usually present
Serum haptoglobin is reduced	Serum haptoglobin is usually not decreased
Hemoglobinuria and hemosiderinuria are seen	Hemoglobinuria and hemosiderinuria are absent

Active space

General clinical features 00:12:10

Triad :

Pallor.

Jaundice.

Splenomegaly.

Usually, unconjugated bilirubin is increased.

Chronic hemolysis : Increased risk of gallstones (pigment gallstones).

Splenomegaly and gallstones are seen in extravascular hemolysis.

General lab investigations :

- Hemoglobin : Decreased.
- MCV, MCH and MCHC : Usually normal.
- Peripheral smear : Specific for anemia.
- Liver function tests : Deranged, increased bilirubin.
- Reticulocyte count : Increased.
- Serum haptoglobin : Decreased (intravascular hemolysis).
- Hemoglobinuria (intravascular hemolysis).
- Hemosiderinuria (intravascular hemolysis).
- Serum LDH : Increased.

Hereditary spherocytosis 00:17:02

75% of cases : Autosomal dominant.

M = F.

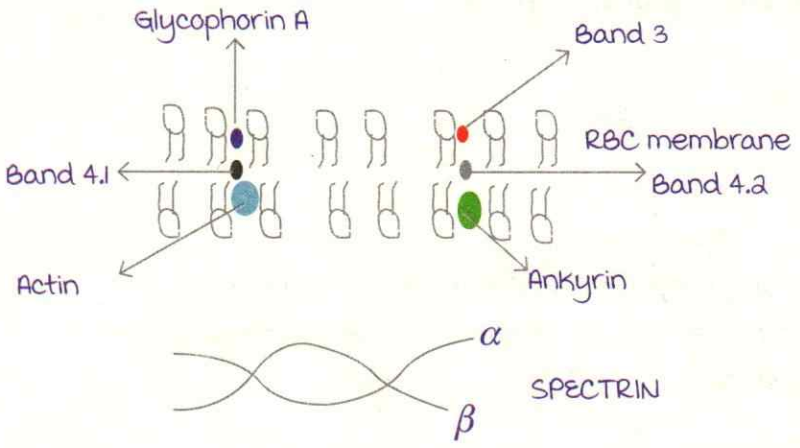
Pathogenesis :

Spectrin (contains alpha and beta chains) is responsible for biconcave shape/stability of RBCs.

Membrane bound proteins :

- Ankyrin, band 4.2, band 3.
- Actin, band 4.1 and glycophorin A.

Active space



Mutation of any of these proteins

↓

Unstable RBC membrane (loss)

↓

RBC tries to have minimum surface : volume ratio 2O

↓

Sphere (no central pallor)

↓ SPLEEN

Spherical RBCs when pass through spleen trapped in splenic sinusoids

↓

Extravascular hemolysis

Life span of normal RBCs : 120 days.
Life span of RBCs in hereditary spherocytosis : 10 to 20 days.

- Increase in MCHC is seen in hereditary spherocytosis. It is due to loss of K+ and water due to dehydration.
- Most important/common protein defective in hereditary spherocytosis is ankyrin.
- Protein defect not seen in hereditary spherocytosis : Glycophorin A.
- Most abundant protein in RBC membrane : Glycophorin A.

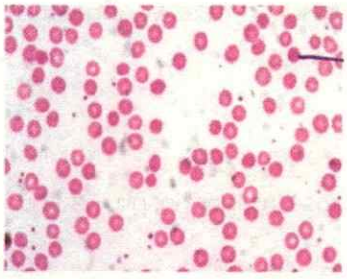
Active space

- Spectrin mutations :
  Common in hereditary elliptocytosis.
  Produces most severe defects.

Clinical features :
Pallor, jaundice, splenomegaly, increased risk of gallstones.
Aplastic crisis : Seen with parvovirus B19 infection.
Hemolytic crisis : Caused by EBV virus.

Lab tests :

- Hemoglobin : Decreased.
- TLC, platelet count : Normal.
- MCV, MCH : Usually normal (MCV can be low).
- MCHC : Increased.
- RDW : Increased.
- Reticulocyte count : Usually increased (It decreases in aplastic crisis).
- Peripheral smear :
  Presence of spherocytes.
  (small RBCs with no central pallor).

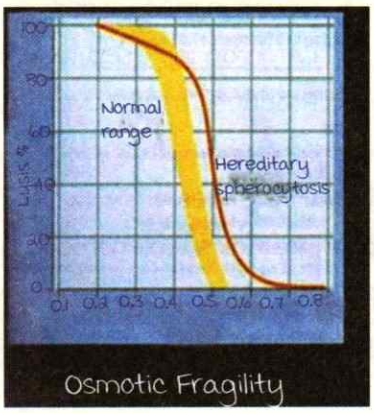


Other causes of spherocytes : Autoimmune hemolytic anemia (most common cause), burns, blood transfusion reactions.

Screening test :
RBCs of patient are suspended in increasing concentrations of normal saline.
Principle : Normal RBCs (biconcave) are isotonic with 0.9% NaCl : RBCS swell and rupture if suspended in increasing concentrations of normal saline (Normally, starts at 0.5% NaCl and completes by 0.3% NaCl)
Spherocytic RBCs are fragile. They burst quickly at must lower concentration. The osmotic fragility curve shifts to the right.

Active space

Osmotic fragility curve shifts to the left in thalassemia.
Nestroft test is based on this principle.



Confirmatory test for hereditary spherocytosis : EMA binding test done by flow cytometry.

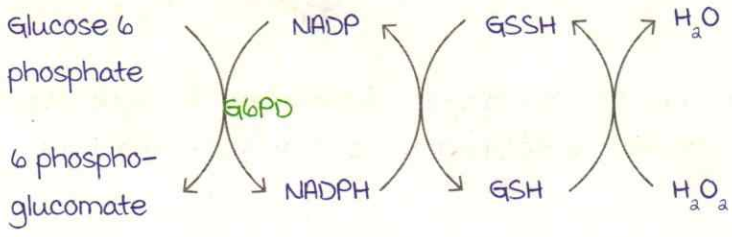
Treatment :
Splenectomy (spherocytic RBCs stay but anemia is corrected)
Peripheral smear of splenectomy patients show Howell jolly bodies.

G6PD deficiency

00:40:44

X-linked recessive inheritance.
M >>> F.

Pathogenesis :
Hexose monophosphate shunt (HMP shunt) :



Deficiency of G6PD causes increase in hydrogen peroxide (H_2O_2) in a cell.
H_2O_2 is a free radical → Oxidative stress in a cell → RBC lysis.

Conditions causing hemolysis in G6PD deficiency :

- Chronic infections : Pneumonia.
- Drugs : Antimalarials (primaquine).
- Fava beans (favism).

G6PD deficiency is more common in people of African and

Active space

mediterranean descent.
G6PD deficiency provides protection against plasmodium falciparum.

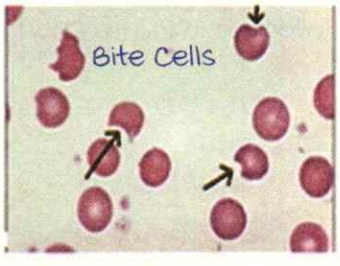
Oxidative stress can lead to intravascular hemolysis, or it can lead to cross linking of sulfhydryl groups in hemoglobin → Denaturation of hemoglobin → Heinz bodies.
When RBCs with Heinz bodies pass through spleen → Splenic macrophages try to pluck these Heinz bodies → membrane loss → Bite cells → Extravascular hemolysis.

Clinical features :
Episodic pallor, jaundice, hemoglobinuria (only when there is oxidative stress).
Splenomegaly are gallstones are features of chronic anemia are usually absent as hemolysis is episodic.

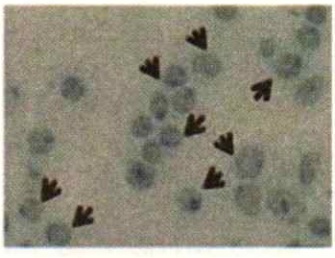
Lab investigations :

- Hemoglobin : Decreased.
- TLC, platelet count : Normal.
- MCV, MCH, MCHC : Usually normal.
- Reticulocyte count : Increased.
- Increase in urinary bilirubin.
- Peripheral smear : Bite cells or degmacytes and Heinz bodies.

Bite Cells



Heniz Bodies
New methylene Blue stain



Heinz bodies are not seen on Romanowsky stain. They are seen on supravital stains like crystal violet or new methylene blue.

Active space

Other tests for G6PD deficiency :
1. Methemoglobin reduction test.
2. G6PD enzyme assay.

Hemolysis occurs more in older RBCs.

Treatment : Avoid oxidative stress.

Paroxysmal nocturnal hemoglobinuria (PNH) 00:57:26

Only acquired intracorpuscular defect.
Defect is at the level of stem cells.

Pathogenesis :
Normally, PIG A (phosphatidyl inositol glycan A) gene that synthesizes GPI anchored proteins :

- CD55 (DAF : Decay accelerating factor).
- CD 59 (MIRL : membrane inhibitor of reactive lysis).
- C 8 binding protein.

These GPI anchored proteins decrease the activity of complement (complement regulatory proteins).

In PNH, there is a mutation in PIG A gene → Decreased synthesis of GPI anchored proteins (CD 55, CD 59, C8 binding protein) → Increased complement activity → Complement mediated hemolysis → Intravascular hemolysis.
Complement also damages endothelium and leads to thrombosis.

Most common/important protein defective in PNH is CD59 (MIRL).

Clinical features :

- Pancytopenia.
- Nocturnal hemoglobinuria (seen in 25% of cases) : Blood pH decreases in sleep and increases complement activity.
- Thrombosis : Most common cause of disease related death in PNH.
  Most commonly it presents as hepatic vein thrombosis.

Active space

Complications :

- Acute myeloid leukemia.
- Myelodysplastic syndrome.
- Aplastic anemia.

Diagnosis :

- Hemoglobin, TLC, platelet count decreased.
- Peripheral smear :
  Normocytic normochromic anemia + pancytopenia.
- Reticulocyte count : Increased.
- Increased unconjugated bilirubin.

Other tests :

1. Ham's test / acidified serum lysis test.
2. Sucrose lysis test.
3. Flow cytometric evaluation of CD55 and CD59 : Best test.

Treatment :

Stem cell transplantation : Best treatment.

Eculizumab : Complement inhibitor.

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HEMOLYTIC ANAEMIA : PART 2

Normal Hb in adults :

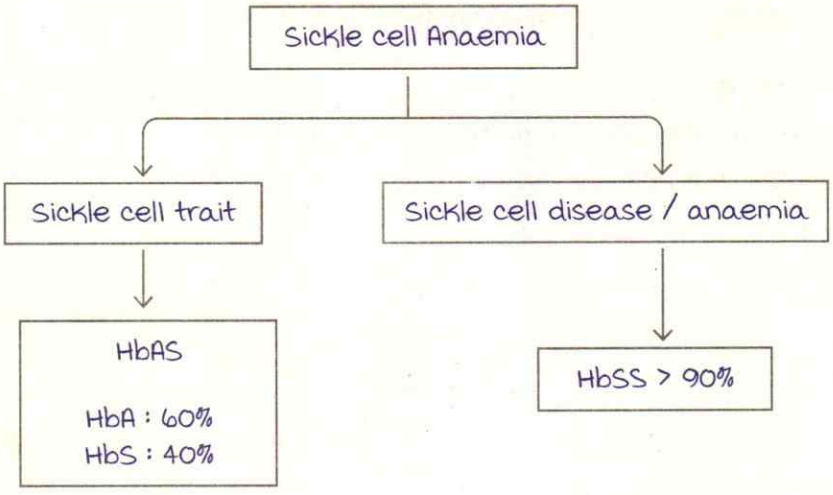
- HbA $\alpha_2\beta_2$ 95 – 97%.
- HbF $\alpha_2\gamma_2$ < 1%.
- HbA2 $\alpha_2\delta_2$ 2 – 3.5%.

Defective production of any of these Hb : Hemoglobinopathies.

Sickle cell anaemia (SCA) 00:03:08

Autosomal recessive.

Males = Females.



Pathogenesis:

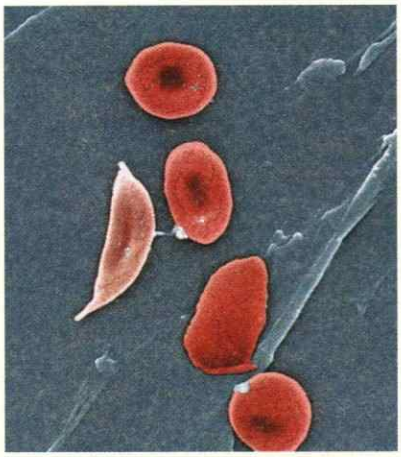
missense point mutation : Glutamic acid (negative charge) replaced by valine (neutral charge) at the 6th position of β-chain of hemoglobin.

Here HbA is replaced by HbS.

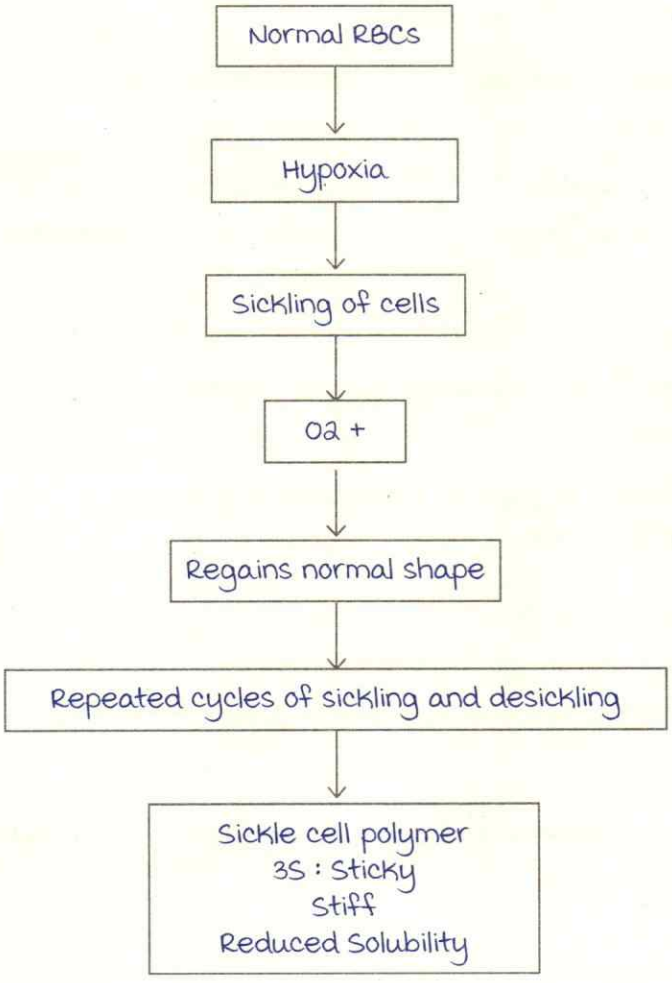
SCA provides protection against Plasmodium falciparum.

more common in Mediterranean and African race.

Active space



Sickle cell RBC



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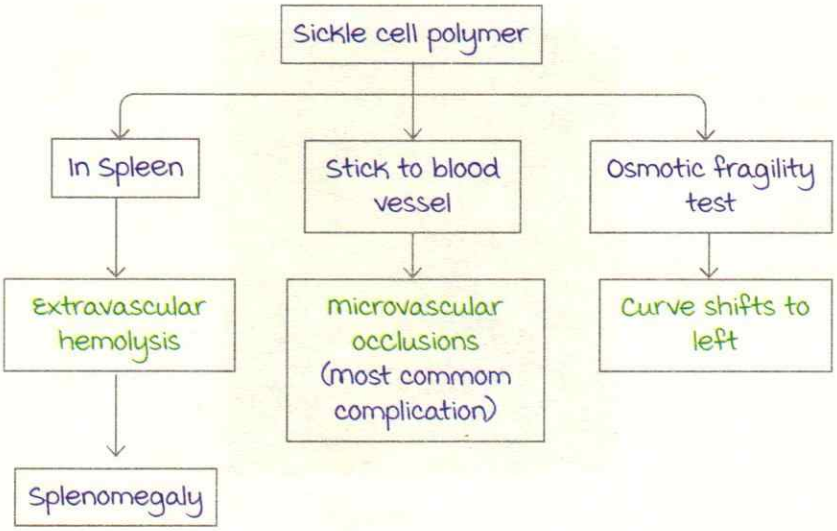


Factors affecting sickling :

Increase in sickling :	Decrease in sickling :
1. Hypoxia.	1. HbF
2. Dehydration.	2. Clinical features of SCA don't
3. Increased MCHC.	3. manifest until 6 months of age.
4. Acidosis (low pH)	

Treatment of SCA : Hydroxyurea (increases HbF).

Sickle cell anaemia : Clinical features and complications

00:17:00

Clinical features:

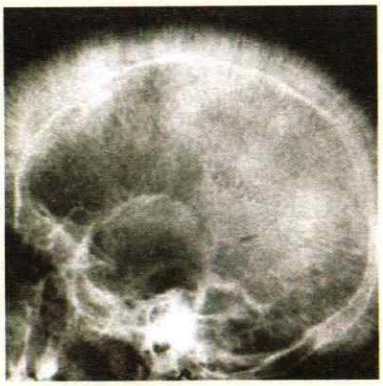
Initially : Pallor, jaundice Splenomegaly.

Later : Auto splenectomy (due to splenic infarcts).

X-ray skull :

Crew-cut/Hair on end appearance (due to extramedullary hematopoiesis).

Active space



Complications :

Microvascular occlusions cause Vaso-occlusive crisis.

- Brain : Stroke.
- Bone : Dactylitis, fish mouth vertebrae.
- Lungs : Acute chest syndrome.
- Priapism.

Aplastic crisis : Parvovirus B19 infection.

Sequestration crisis : Entire spleen sequestered with blood.

Haemolytic crisis : Epstein Barr Virus infection.

Laboratory investigations 00:24:08

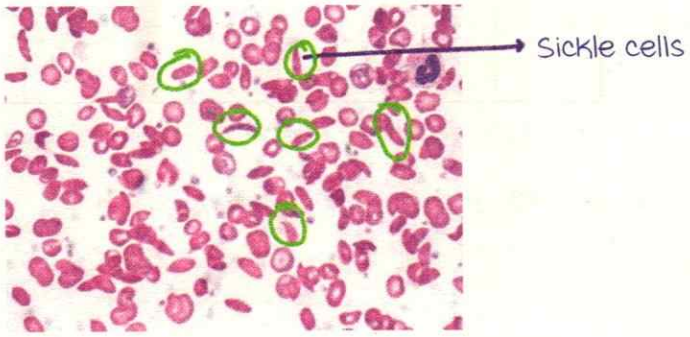
Hb : Low.

Reticulocyte count : High.

Bilirubin : High.

Low ESR : sickle cells are sticky and less soluble, hence they do not settle down.

Peripheral smear : Sickle cells.



Active space

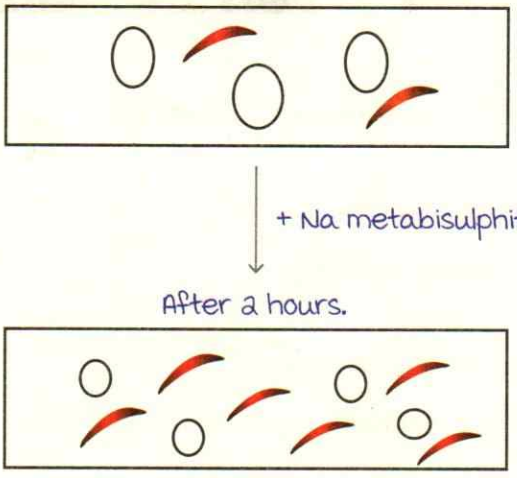
Tests for sickle cell anaemia :

1. Sickling test.

Add 2% sodium metabisulphite or sodium dithionate (O_2 consuming agents) to one drop of patient's blood sample.

Artificial hypoxia is induced. The number of sickle cells increase after 2 hours.

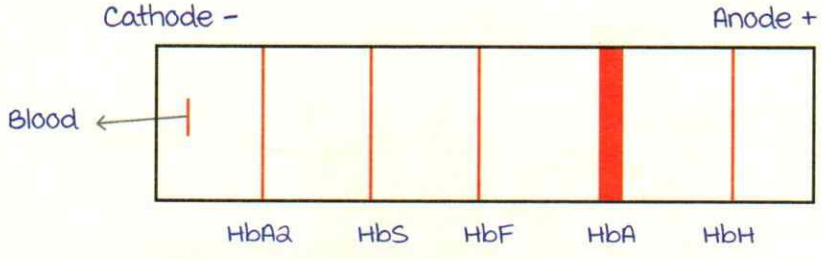
High false-positive rate.



2. Solubility test.

3. Haemoglobin electrophoresis :

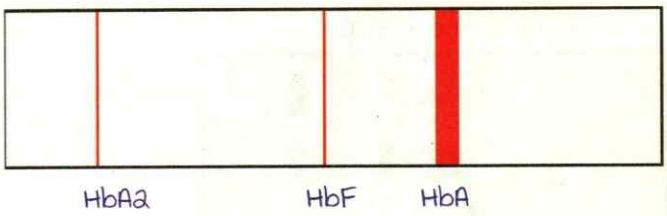
Principle : Movement of different Hb varies according to electric charge or solubility in a medium.



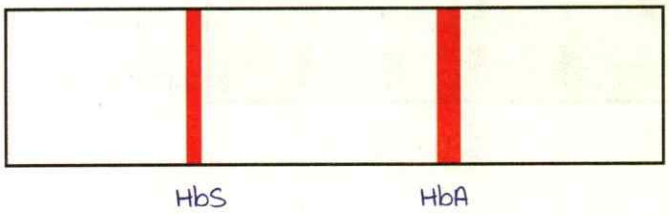
Mnemonic : HAFSA2 : From anode to cathode.

Active space

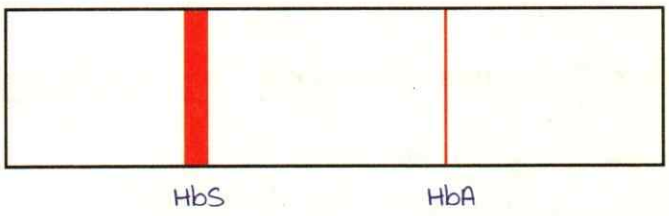
Normal Individuals :



Sickle cell trait :



Sickle cell disease :



Haemoglobin cellulose acetate electrophoresis.

Done at pH 8.4.

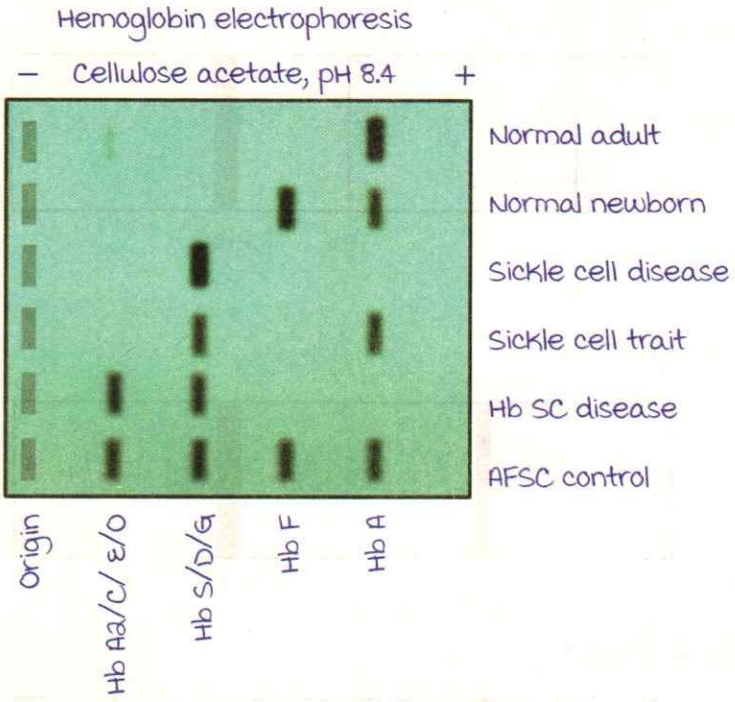
In HbC, Glutamic acid is replaced by Lysine at the 6th position of the β-chain of Haemoglobin.

Not a quantitative test.
more than one type of Haemoglobin can come at the same position.

High-performance liquid chromatography (HPLC) :

Principle : Differential adsorption of various Hb.
Gold standard for diagnosis hemoglobinopathies.

Active space



Sickle cell anaemia : Treatment

00:36:44

Stem cell transplant (ideal)

Hydroxyurea (increases HbF)

Feature	Hereditary Spherocytosis	G6PD deficiency	Sickle cell anemia
Inheritance	AD M = F	X linked recessive M ≫ F	AR M = F
Pathogenesis	MC protein defect : Ankyrin	Defect in G6PD	missense point mutation Glu is replaced by Val at the 6th position of beta chain
Clinically	Pallor, jaundice, Splenomeglay	Episodic haemolysis, Haemoglobin-uria	Pallor, jaundice, autosplenectomy, crisis like bone pain, fracture, chest pain
Relevant in history		H/O chronic infection, drugs, fava beans	Crisis like bone pain, fracture, chest pain

Active space

Feature	Hereditary Spherocytosis	G6PD deficiency	Sickle cell anemia
Haemolysis	E/V	Both	E/V
P/S	Spherocytes	Bite cells, Heinz bodies	Sickle cells
Special test	Osmotic fragility	methaemoglobin reduction test	Sickling test, Hb electrophoresis. HPLC
Best test	Flow cytometric analysis	Same	HPLC
Treatment	Splenectomy	Avoid oxidative stress	Hydroxyurea, stem cell transplant

Thalassemia

00:42:08

more common in the region around the mediterranean sea.

In India : Common in Punjabis / Sindhis.

Autosomal recessive (AR).

β Thalassemia	α Thalassemia
Reduced synthesis of β chains	Reduced synthesis of α chains
Gene for β chain is on chromosome 11.	Gene for α chain is on chromosome 16.
most commonly due to mutations	most commonly due to gene deletions
more common	Less common.

β Thalassemia :

Types of mutations :

1. Splicing mutations : most common cause of β^+ Thalassemia.
2. Chain termination mutations :most common cause of β^0 thalassemia.
3. Frameshift mutations.
4. Transcription mutations.
5. Base pair deletions.

Active space

Types of β Thalassemia :

β Thalassemia major : $\beta^{\circ}/\beta^{\circ}$.

β Thalassemia minor/ trait : β^{+}/β.

β Thalassemia intermedia : β^{+}/β^{+}.

Terminologies :

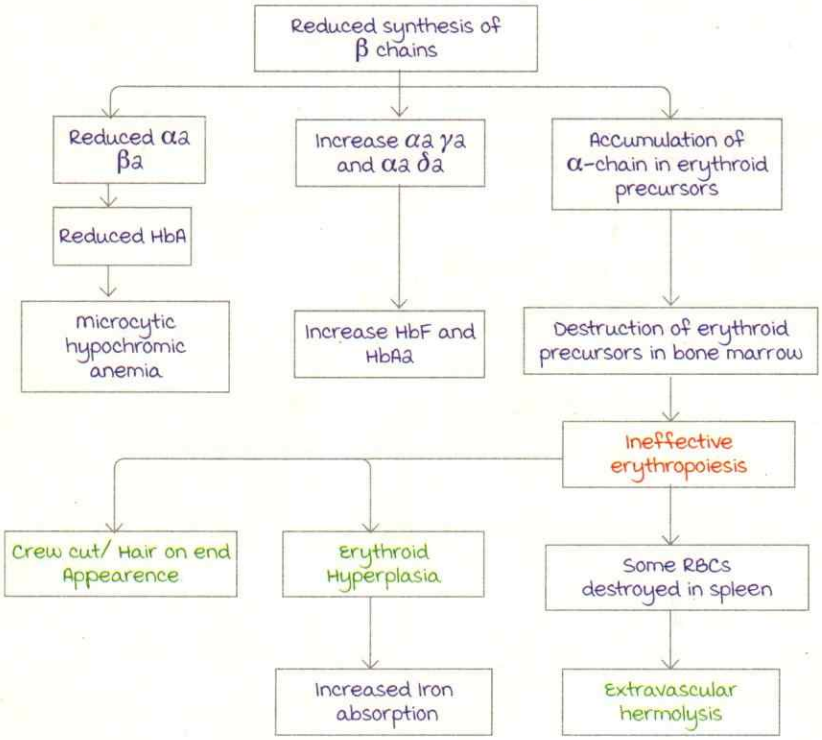
β : Normal.

β^{+} : Partial deficiency of β-chain.

β° : Complete deficiency of β-chain.

Pathogenesis :

Reduced synthesis of β chains.



Clinical presentation :

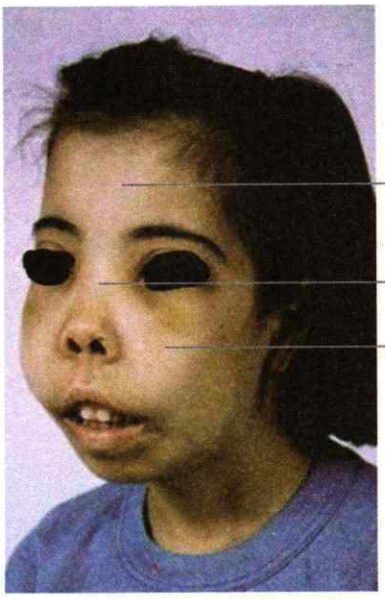
Feature	Beta thal major	Beta thal intermedia	Beta thal minor
	markedly reduced synthesis of beta chain	moderately reduced synthesis	minor reduced synthesis
Clinically	Severe pallor, jaundice, hepatospleno, h/o repeated blood transfusion, chipmunk facies	Pallor, jaundice, hepatospleno-megaly	Mild pallor, asymptomatic, no response to iron therapy

Active space

Hb	3 – 5gm%	5 – 8gm%	> 8gm%
P/S	many target cells, basophilic stippling, cabot ring	Few target cells	No target cells
RBC indices	MCV, MCH, MCHC reduced. RDW- N	MCV,MCH,MCHC reduced, RDW-N	Not much
Iron profile	Iron increased	Normal	Normal
Hb electro-phoresis	more increased HbF	Both increased	HbA2 3.5-9%
HPLC	Raised HbF	Both	Raised HbA2

Beta thalassemia major

Chipmunk Facies :



Lab diagnosis :

Hb : very low (3 – 5gm%).

MCV
MCH
MCHC
} Reduced.

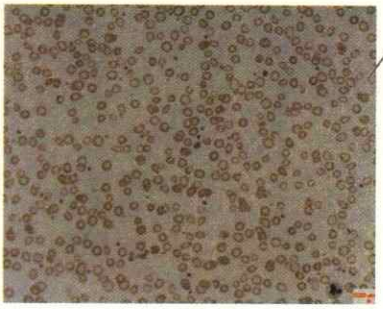
RDW : Normal (used to differentiate from iron deficiency anaemia).

Peripheral smear :

- Microcytic hypochromic red cells.
- Target cells.

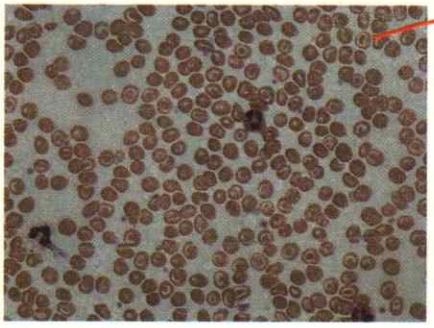
Active space

- Basophilic stippling.
- Howell Jolly bodies.



→ Microcytic hypochromic RBis

S – Sideroblastic anemia
I – Iron Def.
T – Thalassemia
A – Anemia of chronic disease



→ Target cells

1 Thalassemia
2 Liver disease
3 megaloblastic anemia

Hb electrophoresis : Increase in HbF, HbA2 : variable.

Most common cause of death : Iron overload due to repeated transfusions and erythroid hyperplasia.

Thalassemia minor/trait :

Lab diagnosis:
Hb : Reduced (8–10 gm%).

MCV
MCH
MCHC
} Normal or reduced.

RDW : Normal.
Peripheral smear : Microcytic hypochromic RBCs / Normocytic normochromic RBCs. Few target cells.

Iron profile : Normal.

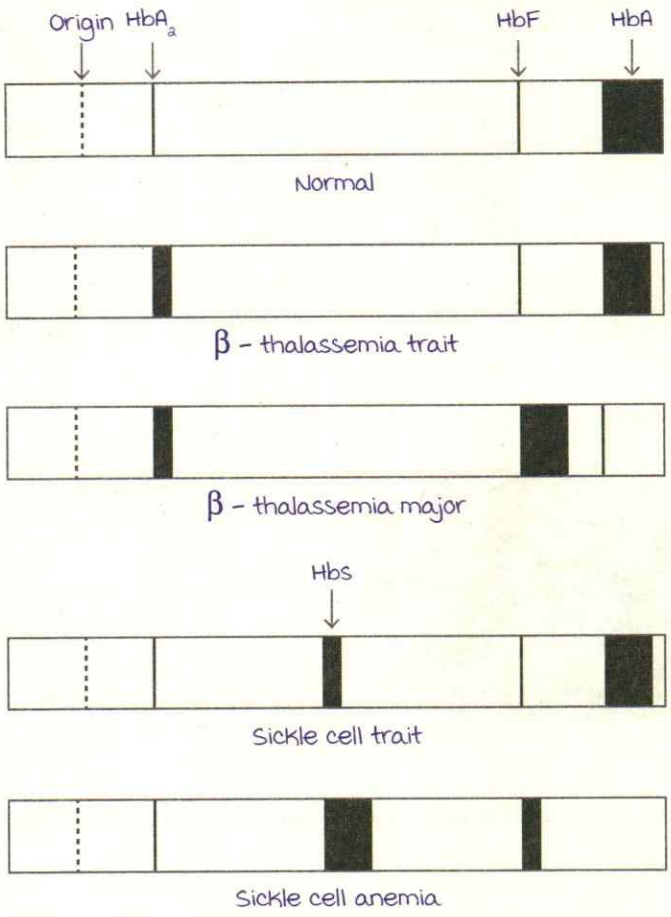
Hb electrophoresis : Increased HbA2

HPLC : Increased HbA2 : 4 to 9 % is diagnostic of beta – thalassemia trait.

HbA2 : > 9 % is diagnostic of Hb E disease.

Active space

Patterns of hemoglobin electrophoresis



Screening test :

NESTROF / Naked Eye Single Tube Red Cell Osmotic Fragility Test

Iron deficiency Anaemia	β Thalassemia minor
RDW : Increases	RDW : Normal
mentzer index > 13 (mcv/ RBC count)	mentzer index < 13
HbA : Normal	HbA2 : 4 – 9 %
Iron profile : Abnormal	Iron profile : Normal

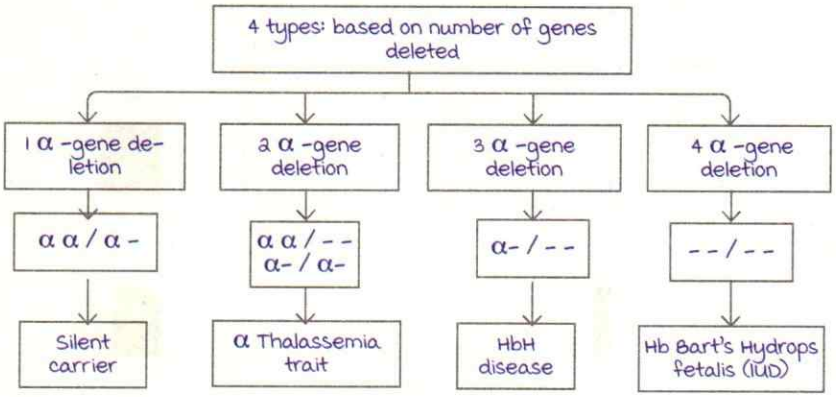
In all pregnant women, electrophoresis is done to screen for β Thalassemia minor/ trait.

If diagnosed, the husband's blood is also screened.

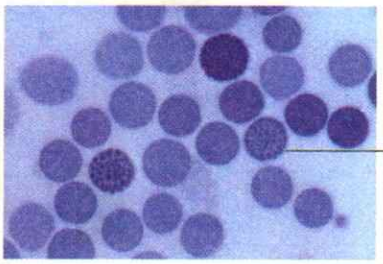
If both have the trait, the child can get β Thalassemia major.

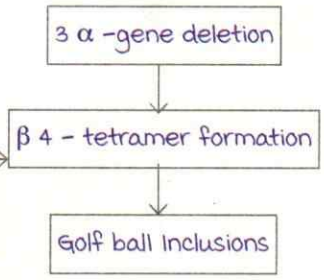
α – Thalassemia :

Active space



HbH disease :



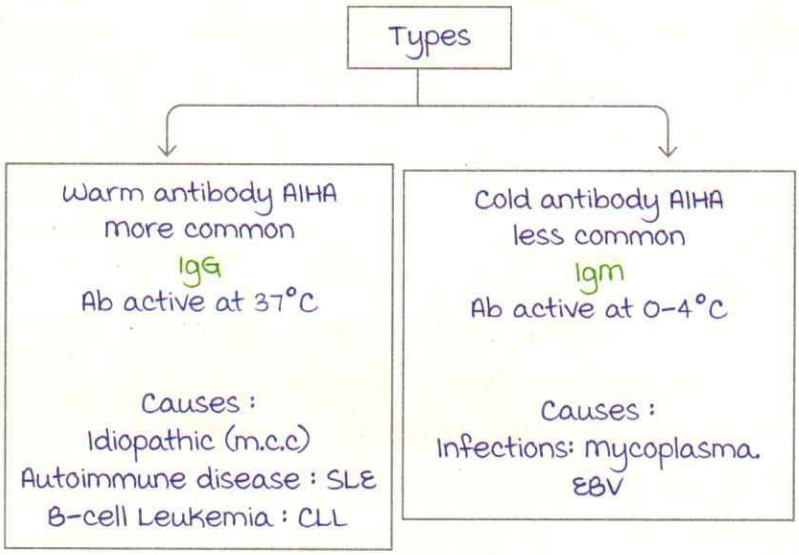


Hb Bart's hydrops fetalis : γ4 tetramers : Results in death of the child.

Autoimmune haemolytic anaemia (AIHA) 01:18:04

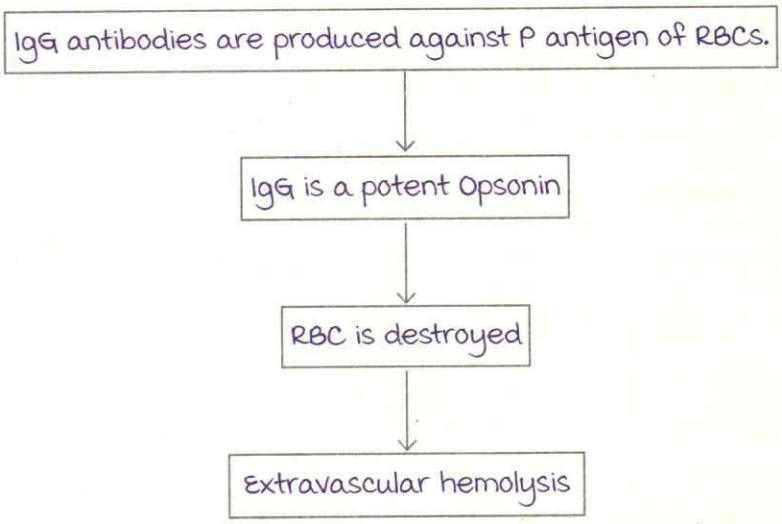
Type II hypersensitivity reaction.

Due to antibodies against RBC membrane proteins.

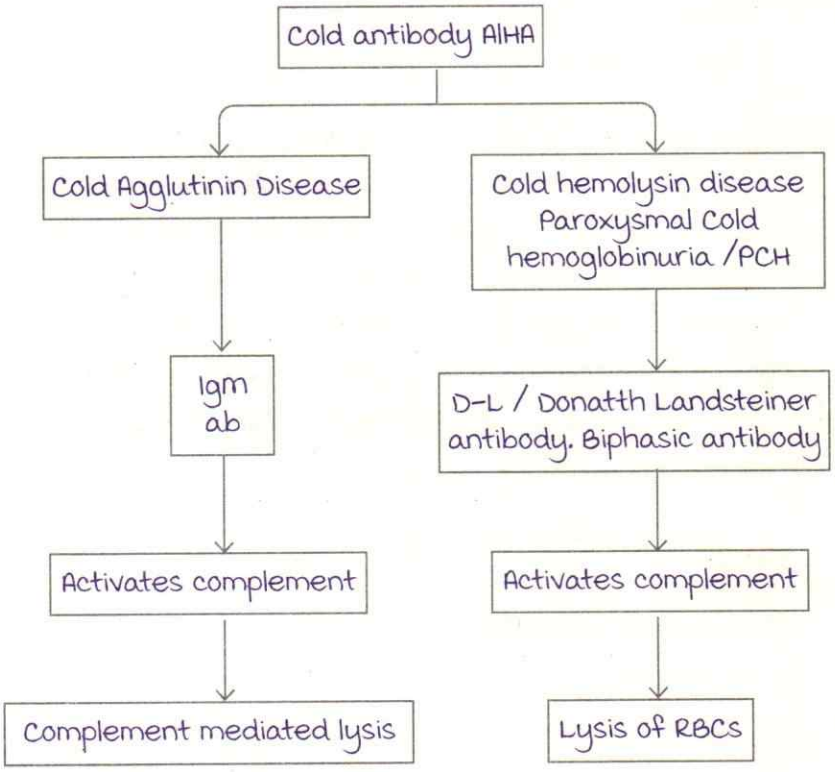


Active space

Warm antibody AIHA :



Cold antibody AIHA :



Lab tests :

Peripheral smear : Spherocytes.

Coomb's test positive.

RBC clumps (agglutination) in cold antibody.

Active space

Intravascular haemolysis	Extravascular haemolysis
G6PD Deficiency	G6PD Deficiency
Microangiopathic haemolytic anaemias (MAHA)	Hereditary Spherocytosis
Prosthetic cardiac valves	Sickle cell Anaemia.
mechanical disruption of RBCs	Thalassemia
Plasmodium falciparum Malaria	AIHA
AIHA (PCH)	

Microangiopathic haemolytic anaemia (MAHA) :

- Haemolytic uremic Syndrome (Hus).
- Thrombotic Thrombocytopenic Purpura (TTP).
- Disseminated intravascular coagulation (DIC).

Q. A 28-year-old African American male is given prophylactic medicines and vaccines before travelling for a business trip. Four days later, he comes back to the physician with jaundice and dark urine. Labs show anaemia, reticulocytosis and hyperbilirubinemia. The peripheral blood smear and special stain are shown below. His condition has most likely which of the following inheritance patterns?

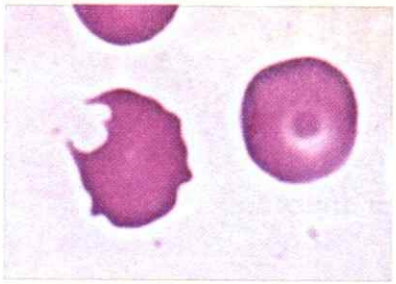
A. Autosomal dominant.

B. AR.

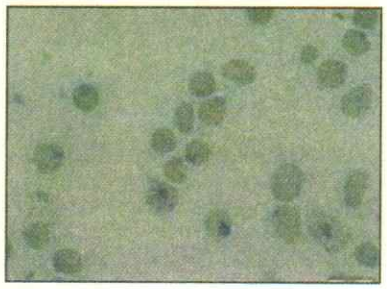
C. X Linked recessive.

D. Mitochondrial.

E. X linked dominant.



Bite cells



Heinz bodies

Active space

Ans :Haemolytic anaemia :

Because the patient has : Reticulocytosis + anaemia + hyperbilirubinemia.

Intravascular Haemolytic anaemia : Because the patient has : Episodic haemolysis + haemoglobinuria

RBCs : Bite cells + Heinz bodies : G6PD deficiency.

Mode of inheritance : X linked recessive.

Q. A 42-year-old male presents to his primary care physician with complaints of fatigue and occasionally darkened urine over the past 3 months. Upon further questioning, the patient reveals that he has regularly had dark, 'cola-coloured' urine when he has urinated at night or early in the morning. However, when he urinates during the day, it appears a much lighter yellow colour. Laboratory workup is initiated and is significant for a haemoglobin of 10.1 g/dL, elevated LDH, platelet count of 101,000/uL, and leukopenia. Urinalysis, taken from an early morning void, reveals brown, tea-coloured urine with haemoglobinuria and elevated levels of hemosiderin. Which of the following is responsible for this patient's presentation?

A. Deficiency of C-1 esterase-inhibitor.
B. Autosomal dominant deficiency of spectrin protein in the RBC membrane.
C. Presence of a temperature-dependent IgG autoantibody.
D. Deficiency of CD-55 and CD-59 cell membrane proteins.
E. Autosomal recessive deficiency of platelet Glycoprotein IIb/IIIa receptor.

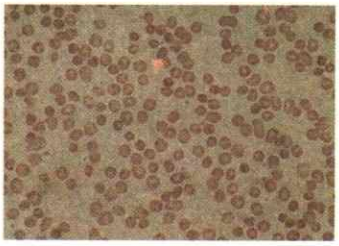
Ans : Hemoglobinuria at night/ early morning : Paroxysmal Nocturnal Hemoglobinuria.

Features of Pancytopenia : Haemoglobin of 10.1 g/dL, elevated LDH, platelet count of 101,000/uL, and leukopenia.

In PNH : Deficiency of CD-55 and CD-59 cell membrane proteins.

Active space

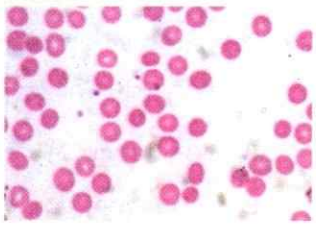
Q. A 34-year-old man presented with pallor and gall stones. His father and paternal aunt had a similar illness that was treated successfully by splenectomy. His peripheral blood smear is shown below. What is the next investigation which you will do for diagnosis?



A. Hb electrophoresis.
B. Sickling test.
C. Osmotic fragility test.
D. NESTROF test.

Ans. Hemolytic anaemia : Pallor and gall stones.
Splenectomy : TOC in Hereditary spherocytosis.
Is autosomal dominant : Present in all generations.
Peripheral smear: Small spherical cells without central pallor.
HS is Diagnosed by the Osmotic fragility test.

Q. The peripheral smear of a patient is given below. Which of the following is not likely to be associated with this PS?



A. Hereditary spherocytosis.
B. Blood transfusion reaction.
C. Autoimmune hemolytic anaemia.
D. Megaloblastic anaemia.

A. Peripheral smear: Small spherical cells without central pallor.

Spherocytes are not seen in Megaloblastic anaemia.

Q. A 10-year-old boy complained of fatigue and abdominal pain after playing football. He also complained of painful swelling of digits in the past. USG abdomen shows a small spleen. Which of the following is the most likely diagnosis?

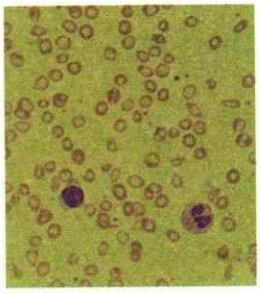
A. Thalassemia.
B. Iron deficiency anaemia.
C. Sickle cell anaemia.
D. Acute pancreatitis.

Active space

Ans. Dactylitis + small spleen due to Auto splenectomy seen in Sickle cell anaemia.

Case 1.

- 23-year-old male presented with fatigue and anaemia.
- Apparently normal 8 years ago, after which he had low Hb and was transfused blood.
- Examination : Pallor, hepatosplenomegaly.
- Lab reports : Hb- 8 gm%.
- MCV : 65.
- MCH : 25.
- MCHC : 28.
- RDW : 15.
- Iron studies : Raised serum iron and ferritin.



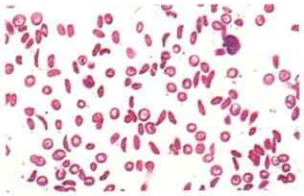
What is the next investigation in this case?
Probable diagnosis?

Microcytic hypochromic anaemia : SITA.

Next Investigation : Hb electrophoresis and HPLC.
Probable diagnosis : β Thalassemia Intermedia.

Case 2.

- A 3-year-old male child from Rajasthan.
- Presented with pallor, icterus and history of on and off abdominal and joint pains.
- Past history : pneumonia at 1 year of age, was admitted for fever, anemia and jaundice earlier.
- Examination : Mild splenomegaly.
- Lab studies :
- Hb : 7gm/dl
- RDW : 26.
- P/S shown.



Next Investigation : Hb electrophoresis and HPLC.
Probable diagnosis : Sickle cell Anaemia.

Active space

WBC INTRODUCTION

Introduction to hematology

00:03:38

Hematopoiesis : Formation of blood cells.

Starts in the yolk sac.

Age	Organ of hematopoiesis
3rd week of gestation	Yolk sac
3rd month of gestation	Liver
4th month of gestation	
Just before birth	Bone marrow

Bones involved in hematopoiesis : Long bones, axial skeleton.

Site of bone marrow aspiration / biopsy :

Adults : Iliac crest in the posterior superior iliac spine.

Child : Shin of tibia.

Origin of blood cells

Hemopoietic stem cell (CD 34).

Common Lymphoid Progenitor (CLP).

- T cells.
- B cells.
- Natural Killer cells.

Common Myeloid Progenitor (CMP).

- Erythroblasts → RBCs.
- Megakaryoblasts → Platelets.
- Myeloblasts → Neutrophils.
- Eosinophils.
- Basophils.
- Monoblasts → Monocytes.

White blood disorders

00:09:32

Normal Total leukocyte count (TLC) : 4,000 – 11,000 cells/cu.mm.

WBC series :

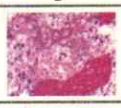
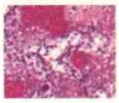
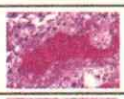
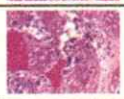
Size decreases.

- Myeloblast.
- Promyelocyte → Largest cell.
- Myelocyte → Differentiates into neutrophils, eosinophils basophils
- Metamyelocyte.
- Band form.
- Mature WBC

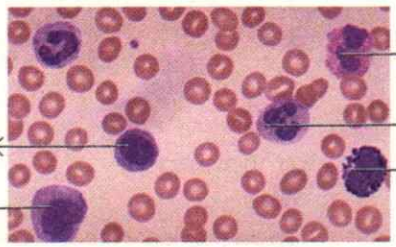
Active space

In myeloproliferative disorders, there will be an increase in RBCs, WBCs and platelets since all 3 cell lines have a common precursor.
Lymphoproliferative disorders will have raised lymphocytes.

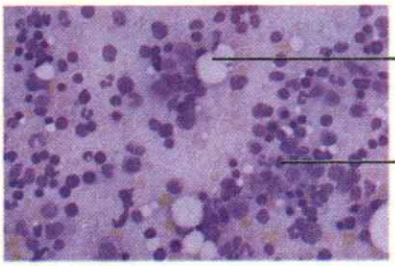
Types of WBCs :
Granulocytes : Granules present in the cell – Neutrophils, eosinophils, basophils.
Agranulocytes : No granules present in th cell – Lymphocytes, monocytes.

WBC	Description	Diagram
Neutrophils	3–5 lobed nucleus, small bluish granules in the cytoplasm.	
Eosinophil	Bilobed/spectacle shaped (2 lobes) nucleus, brick red granules.	
Basophil	Bluish granules obscuring the nucleus.	
Lymphocyte	Smallest cell, big nucleus, minimal cytoplasm, no granules.	
Monocyte	Largest cell, kidney shaped nucleus.	

Interpretation of a peripheral smear : Contains only mature cells.



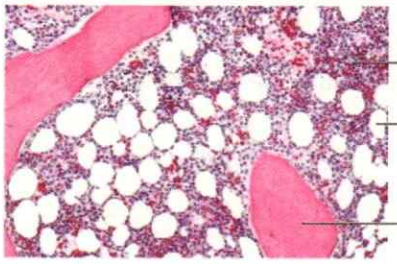
Interpretation of a bone marrow aspirate : Contains mature and immature cells.



Active space

Normal myeloid : erythroid ratio : 3 : 1 to 15 : 1.

Interpretation of a bone marrow biopsy :



% cellularity of the bone marrow : 100 − age of the patient.

Cellularity decreases as age increases.

Non-neoplastic lesions of WBCs

00:22:21

Increased WBC count : Leucocytosis.

Decreased WBC count : Leucopenia.

WBC Cell	Normal Count	Causes of increase in WBC cells
Neutrophil	40–70 %	Neutrophilia : Acute infections. Bacterial infections except TB : Lymphocytosis Tissue injury : Burns, MI Leukemoid reactions.
Lymphocyte	15–40%	Lymphocytosis : Chronic infections. Viral infections Tuberculosis Rickettsiosis Chronic lymphoproliferative disorders e.g CLL.
Eosinophil	1–6 %	Eosinophilia : Allergic reactions. Type I Hypersensitivity. Bronchial asthma. Hay fever. Tropical pulmonary eosinophilia. Parasitic infections. Hodgkin's lymphoma.
Basophil	< 1%	Basophilia : myeloproliferative disorders like CML (part of diagnostic criteria), polycythaemia vera, myelofibrosis.
Monocytes	2–8 %	Monocytosis : Chronic infections. Malaria. Rickettsiosis. Endocarditis.

Active space

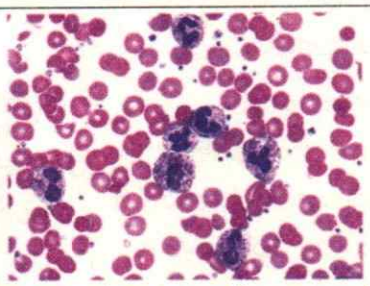
Agranulocytosis : Marked reduction in the WBC count.

M/C cause : Drug toxicity.

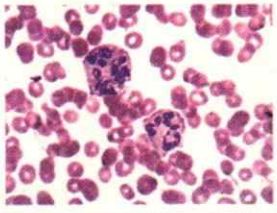
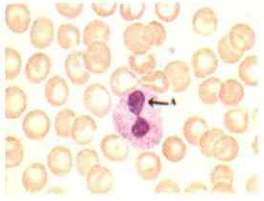
Severe infections occur when WBC count < 500 cells/cu.mm.

Morphological abnormalities of WBCs 00:34:02

Neutrophils in infection in smear shows 2 abnormalities :

Abnormality	Features
Toxic Granules	 Coarse granules slightly larger than normal granules.
Döhle bodies	Patches of dilated Endoplasmic Reticulum (ER)

Neutrophils based on number of lobes :

Description	Image
Hypersegmented neutrophils : > 5 lobes. Seen in megaloblastic anaemia due to deficiency of Vit B12 / folate.	
Hyposegmented neutrophils : 2 lobes. Seen in pseudo-pelget Huet cell in myelodysplastic syndrome (MDS).	

1. May Hegglin Anomaly :

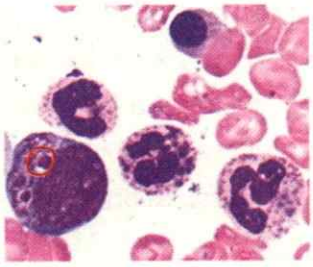
Occurs due to MYH9 mutation.

HEG

Giant platelets.

Low platelet count.

I
N — Inclusions in the neutrophils.



Active space

Chediak Higashi Syndrome :

Due to abnormal LYST protein, required for phagolysosomal fusion.

Giant granules in the neutrophil.

Infectious mononucleosis/ 'kissing disease' 00:41:14

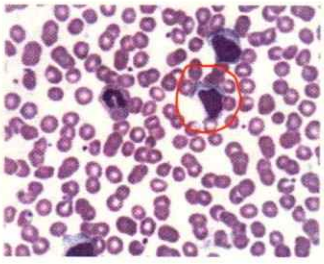
Usually caused by EBV and affects B lymphocytes.

Usually affects young adults via close contact (exchange of saliva by kissing).

Clinical presentation :

Fever, sore throat, splenomegaly.

P/S : Downey cells : Reactive T lymphocytes that have a ballerina skirt appearance.



Diagnosis : monospot test : To look for heterophile antibodies.

Hemophagocytic LymphoHistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS) :

Pathogenesis : Reactive condition (can be EBV associated) that involves

Activation of macrophages and CD8+ T lymphocytes

↓

Cytopenia → Systemic Inflammation.

Clinical presentation : Hepatosplenomegaly.

Lab Tests :

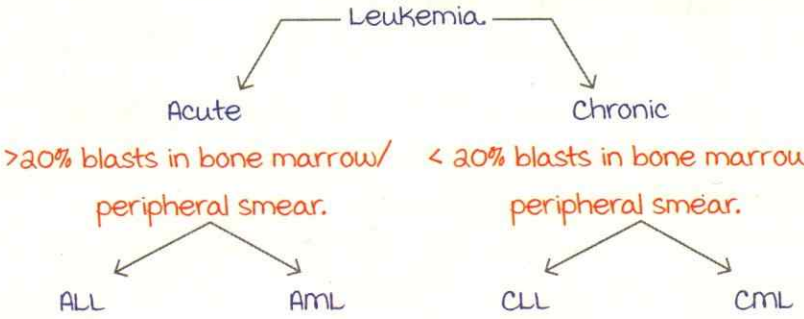
- Anaemia.
- Thrombocytopenia.
- Abnormal LFTs.
- Increased triglyceride levels.
- Increased ferritin.
- Increased soluble IL-2 receptors.
- Coagulation abnormalities → DIC.

Active space

Neoplasms of WBCs

00:49:07

Leukemia	Lymphoma
Involvement of peripheral blood and/or bone marrow.	Systemic/tissue involvement like lymph nodes and spleen.
Investigation : Flow cytometry.	Biopsy and histopathological examination.

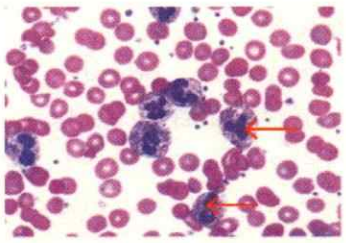


WBC Neoplasms :

Type	Examples
Myeloid	AML Myeloproliferative Neoplasm (MPN) - CML Myelodysplastic Syndromes (MDS) MDS/MPN
Lymphoid	ALL Chronic lymphoproliferative disorders
Dendritic	Langerhans Cell Histiocytosis (LCH)

MCQs

A 45 year old man admitted to ICU develops sepsis 3 days after insertion of a central venous catheter. A peripheral blood smear obtained is shown below. What does the structure marked by the arrow indicate?



A. Toxic granules.
B. Creola bodies.
C. Dohle bodies.
D. Howell jolly bodies.

Creola Bodies : Asthma.
Howell Jolly bodies : Post splenectomy.

Q. A 16yrs/F presents with a 5 day history of low grade fever and sore throat. On physical examination, bilateral enlarged,

Active space

tender cervical lymph nodes and splenomegaly +. CBC normal. P/S : Presence of atypical mononuclear cells with lots of cytoplasm. The cells showed a "ballerina skirt" appearance. Which one of the listed findings is most likely to be present in this person?

A. Group A streptococci on culture of exudate.
B. Fried egg appearance on bone marrow biopsy.
C. Heterophile antibodies in serum.
D. Toxic granules in WBCs.

Atypical mononuclear cells with lots of cytoplasm showing a ballerina skirt appearance : Downey cells.
Diagnosis : Infectious mononucleosis.
B) Fried egg : Oligodendroglioma and Hairy cell Leukemia.
D) Toxic granules : In sepsis/ infection.

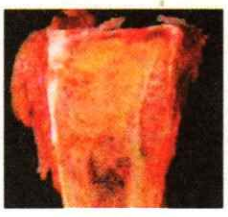
Clinical case scenarios :

1. A 32 year old man with fever and sore throat 5 days.
Examination : Tender cervical lymphadenopathy.
Lab tests : Hb –14 gm/dl,
PLC : 2,77,000/microl,
WBC count : 13,200/microl.
DLC :78 segsmented, 10 band forms, 10 lymphocytes and 2 eosinophils. Diagnosis?

Answer : Indicates acute/ bacterial infection.
As there is neutrophila (DLC of neutrophils : 88)
Band forms : Immature WBCs (shows shift to left).

2. A 4 year old male child presents with fever, recurrent infections and sensorineural deafness.
Labs : Normal.

Answer :
The child has features of albinism along with with reccurent infections and sensorineural deafness.
These features could indicate that the child has Chediak Higashi syndrome.



Peripheral smear : Giant granules in neutrophils.

Active space

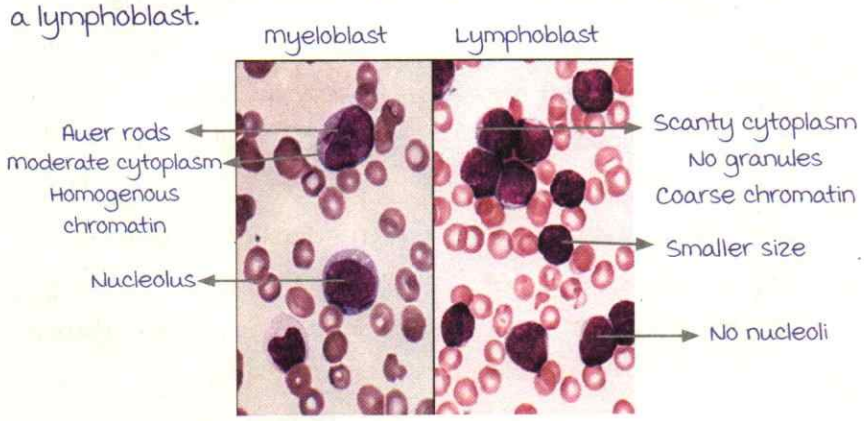
ACUTE LYMPHOBLASTIC LEUKEMIA

Acute leukemia : Introduction 00:00:46

WHO Criteria : >20% blasts in the bone marrow and/or peripheral blood.
FAB (French-American-British) criteria : >30% blasts in the bone marrow and/or peripheral blood.

morphological features	Lymphoblast	myeloblast
Size	Smaller	Larger
Amount of cytoplasm	Scanty	moderate
Granules in cytoplasm	Absent	Present
Auer rods	Absent	Present (hallmark)
Faggot cells (bunch of Auer rods)	Absent	Present
Chromatin	Coarse/clumped	Opened up/ Homogenous
Nucleoli	Pinkish, 1 in number	2-5, prominent
Stains	Dot positivity with PAS	MPO+, NSE+, SBB+
Flowcytometry markers	B-ALL : CD19-23, CD79a, CD10 T-ALL : CD1,2,3,5,7, CD10	CD13, CD33, CD117, MPO

The nuclear features are the most important morphological feature that helps in distinguishng between a myeloblast and a lymphoblast.



Active space

Acute lymphoblastic leukemia (ALL) 00:15:30

MC cancer in children. Age : 2-9 yrs.

Presentation :

- Pallor, fatigue due to decreased Hb.
- Increased risk of infections due to reduced WBC.
- Bleeding tendencies due to reduced platelet counts.
- Hepatosplenomegaly (HSM).
- Bone pains, sternal tenderness due to periosteal expansion.
- Can involve CNS, testis, spleen, lymph node. (Differentiating feature from AML).

FAB classification of ALL : Based on morphology of blasts.

ALL-L1	ALL-L2	ALL-L3
Most common	Moderate	Least common
Best prognosis	Moderate	Worst prognosis
Small, homogenous blasts having scanty cytoplasm with no nucleoli.	Large, heterogenous blasts, moderate cytoplasm with prominent nucleoli.	Blue cytoplasm with vacuoles (fat : Oil red O+) aka Burkitt lymphoma-like.

Homogenous blasts are blasts that have the same size and shape.

WHO classification of ALL :

B-ALL

- Most common (85%)
- Usually occurs in children.
- Tissue involvement absent
- Mediastinal involvement absent.
- Loss of function mutation in genes PAX5, E2A, EBF.
- Better prognosis.

T-ALL

- Less common (10-15%)
- Usually occurs in teenage/adults.
- Tissue involvement present.
- Mediastinal involvement present.
- Gain of function mutation in NOTCH 1 gene.
- Poor prognosis.

Active space

Lab diagnosis :

Investigation of Choice : _____

CBC :

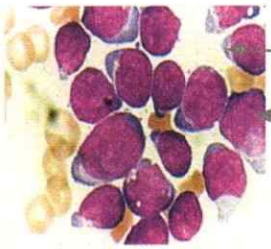
- Hb : Decreased.
- TLC : Decreased/increased.
- Platelet count : Reduced

Peripheral smear : > 20% lymphoblasts.

Aleukemic leukemia : No blasts on peripheral smear.

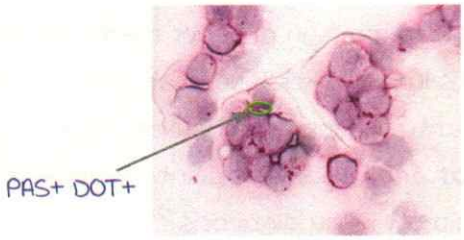
Bone marrow aspirate (BMA) : > 20% lymphoblasts.

Lymphoblasts look like hand mirror cells.



Stains : DOT positivity in PAS+.

Differentiate from diffuse PAS+ in AML-M6.



Markers :

Both Pre-B & Pre-T lymphoblasts are TdT+

B-ALL : CD 19, CD20, CD21

T-ALL : CD 1,2,3,5,7, CD10

Both are CD10 + which is referred as CALLA (Common ALL Antigen)

Treatment :

Stem cell transplantation/chemotherapy (VAPD regimen).

Drugs : Vincristine.
L-Asparaginase.
Prednisolone.
Doxorubicin.

Active space

Prognostic factors for ALL :

Good prognosis	Bad prognosis
2-9 years	<1, >10yrs
Females	male
Whites	Blacks
ALL-L1	ALL-L3
B-ALL	T-ALL
CNS, testis, spleen, lymph nodes not involved.	If involved
Hyperdiploidy (>50 chromosomes) m/C genetic abnormality in ALL.	Hypodiploidy
Trisomy 4, 7, 10; t(12:21)	t (9:22) (190 KD)
Blast count <1 lakh	>1 lakh

MCQ

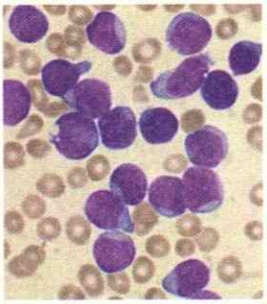
Q. A 11 year old boy complaints of feeling of discomfort in his chest. Physical examination showed generalized lymphadenopathy. Chest X ray shows mediastinal widening while CT shows a 6cm mass in anterior mediastinum. A biopsy of the mass shows lymphoid cells with stippled nuclear chromatin and scanty cytoplasm. The cells express TdT, CD2 and CD7. Molecular analysis shows point mutation in NOTCH 1 gene. What is the most likely diagnosis ?

A. Burkitt's lymphoma.
B. Hodgkin's lymphoma : Nodular sclerosis.
C. CMantle cell lymphoma.
D. Lymphoblastic lymphoma.

Q. A 7 year old girl is brought to the physician by her mother because of a 2 week history of generalized fatigue, intermittent fever, and progressively worsening shortness of breath. Physical examination shows pallor, jugular venous distention, and non tender cervical and axillary lymphadenopathy. Inspiratory stridor is heard on auscultation of the chest. The liver is palpated 3 cm below the right costal margin. Her hemoglobin concentration is 9.5 g/dL, leukocyte

Active space

count is 66,000 mm3, and platelet count is 102,000 mm3. An X-ray of the chest shows a mediastinal mass. A bone marrow aspirate taken shows the image below. Which of the following additional findings is most likely in this patient ?



A. t(8:14)
B. Positive MPO staining.
C. t(9:22)
D. Reed Sternberg cells.
E. Positive CD3/CD7 staining.

Explanation :
Bone marrow aspirate shows cells that are hand mirror shaped with coarse chromatin, no nucleoli. These are lymphoblasts (seen in ALL) and since the child has a mediastinal mass, the diagnosis could be T-ALL.
T-ALL shows positive CD3/ CD7 staining.

Positive MPO staining : myeloblasts.
t(8:14) : Burkitt's lymphoma.
t(9:22) : CML.
Reed Stenberg cells : Hodgkin's lymphoma.

Active space

ACUTE MYELOID LEUKEMIA

Age : 15-40 years.

Clinical presentation :

- Pallor, fatigue : Due to decreased haemoglobin.
- Increased risk of infection : Due to decreased TLC.
- Petechiae, purpura : Due to decreased platelets.
- Hepatosplenomegaly.
- CNS, testis and lymph node are not commonly involved.
- Gum bleeding/gum hyperplasia (more common with M4 & M5).
- Chloroma : more common with AML M2.
- Disseminated intravascular coagulation (DIC) : more common with AML M3.

Risk factors :

- Radiation.
- Downs syndrome (AML M7).
- Blooms syndrome.
- Fanconi's anaemia .

FAB classification of AML

00:06:46

Based on the morphology of the blast :

AML-M0 : AML undifferentiated.

AML-M1 : AML without maturation.

AML-M2 : AML with maturation.

AML-M3 : Acute promyelocytic leukaemia.

AML-M4 : Acute myelomonocytic leukaemia.

AML-M5 : Acute monocytic leukaemia.

AML-M6 : Acute erythroleukemia .

AML-M7 : Acute megakaryocytic leukaemia.

AML-M0 → MPO negative.

AML-M1 → < 10 % mature cells.

Active space

AML-M2 :

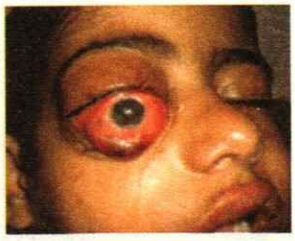
> 10 % mature cells.

Associated with t (8 : 21) translocation RUNX1 : RUNXT1.

Most common AML associated with a chloroma.

Chloroma :

- Also known as granulocytic sarcoma/myeloblastoma.
- Soft tissue involvement of AML.
- It is MPO positive, has greenish colour.
- Most common site is orbit. Patient presents with proptosis.
- Arbiskov cells : monocytes which are present in a chloroma.



AML : chloroma

AML-M3 (Acute promyelocytic leukaemia) 00:15:45

Associated with t (15 : 17) translocation,

PML gene — RARA gene (retinoic acid receptor alpha)

PML-RARA fusion protein

↓

Reduction in the vitamin A levels

↓

Reduced conversion of promyelocytes to myelocytes

↓

Increase in number of promyelocytes

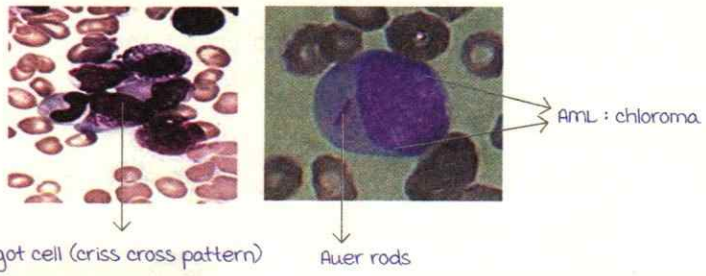
↓

Acute promyelocytic leukaemia

Some promyelocytes have more granules : Granules will fuse with each other to form Auer rods (morphological hall mark of myeloblast).

Active space

Auer rods form criss cross pattern structure called Faggot cell.



Some granules contain procoagulant material → Breakage of granules causes its release → DIC.

Treatment of AML M3 :
All trans retinoic acid (ATRA) & Arsenic trioxide.
Best prognosis of all the AML.

AML M4 & M5

00:23:42

Tissue involvement leads to gum bleeding and gum hyperplasia. Skin involvement is called leukaemia cutis.
Non Specific Esterase (NSE) positivity.
AML M4 is associated with inversion of chromosome 16.

AML M6 :
Also known as Di Guglielmo disease.
It shows diffuse positivity with PAS (Periodic Acid Schiff).

AML M7 :

- It is the least common type of AML.
- Usually associated with Down's syndrome.
- Megakaryocytes secrete PDGF (Platelet Derived Growth factor), which is responsible for myelofibrosis, hence this is associated with myelofibrosis.
- Can be associated with dry tap on bone marrow aspiration.
- CD 41 & CD 61 are markers (of megakaryoblasts) which can be used.

Active space

WHO classification of AML

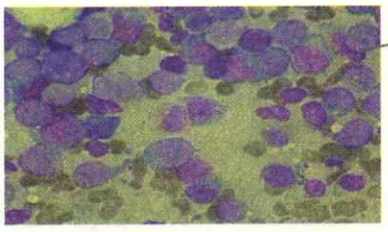
00:28:29

i) AML with recurrent genetic abnormality : Good prognosis.
   a. AML with t (8:21) RUNX1 : RUNXT1 → AML M2.
   b. AML with t (15:17) PML : RARA fusion gene → AML M3.
   c. AML with inversion 16 or t (16:16), CBFB MYH 11 fusion gene → AML M4 (associated with eosinophilia).
ii) AML with MDS like features : Poor prognosis.
iii) AML with therapy related : Poor prognosis.
iv) AML NOS (not otherwise specified) : Waste basket category. It includes all AML except for promyelocytic leukaemia from FAB classification.
   - AML undifferentiated.
   - AML without maturation.
   - AML with maturation.
   - AML with myelomonocytic maturation.
   - AML with monocytic maturation.
   - AML with erythroid maturation.
   - AML with megakaryocytic maturation.

Lab diagnosis of AML

00:33:58

Hb ↓, TLC ↑ or ↓, Platelets ↓.
Peripheral smear > 20% myeloblasts.
Bone marrow aspiration > 20% myeloblasts.



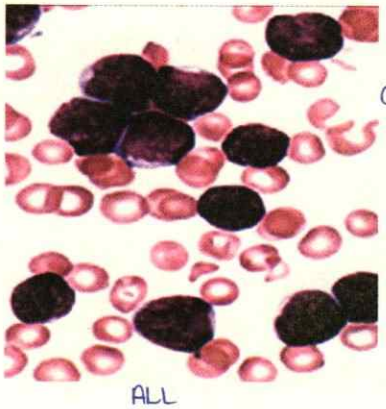
AML

→ Cells with
- Moderate cytoplasm.
- Granules +.
- Smooth/homogenous chromatin.
- Prominent nucleoli.

Stain : MPO+ (myeloperoxidase), NSE+, SBB + (Sudan Black B).
Markers : CD 13, CD 33, CD 117 and myeloperoxidase.

Active space

Diagnosis of AML can also be made even if the blasts are <20%, when patient has t (8:21), t (15:17) or inversion 16.



ALL

Cells with
a. Scanty cytoplasm.
b. No granules.
c. Coarse chromatin.
d. Inconspicuous nucleoli.

Treatment

00:38:32

Definitive treatment is stem cell transplantation.
For AML M3 : ATRA & arsenic trioxide.

Investigation of choice is flow cytometric assessment of markers except for AML M3 (FISH analysis).

Bi phenotypic leukemia :
Blasts shows dual marker positivity, for both myeloid and lymphoid markers.

Q. A 4 year old male presents with fever, bleeding gums and fatigue for 4 days. CBC shows Hb of 8 gm%, TLC 86,000/μL, plc 25,000/μL. DLC shows neutrophils 20%, lymphocyte 40%, eosinophil 10% basophils 0%, monocytes 5%, abnormal cells 25%. Bone marrow aspiration shows cells below as 60%. What is your diagnosis ?

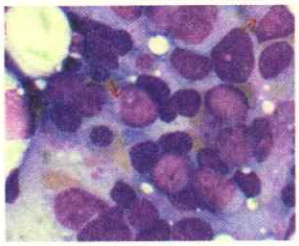
A. CML.
B. CLL..
C. Acute leukemia.
D. myelofibrosis.

Q. A patient presented with painless bilateral proptosis. What is the next investigation to diagnose it as chloroma ?

A. Blood hemoglobin.
B. Peripheral smear.
C. Platelets.
D. Bone marrow (reticulin).

Active space

A 50 year old female presented with the following findings Hb 9.8%, TLC 15,700/cumm, plc 3 lac/cumm. PS showed increased neutrophils with 14% blasts, 15% myelocytes and metamyelocytes. Cytogenetic study revelaed t(8:21). What is your diagnosis ?



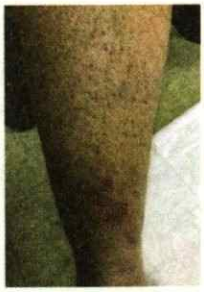
A. AML.
B. MDS.
C. CML.
D. ALL.

Clinical case :

A 32 year old male smoker with a week history of easy fatiguability, petechiae on the right leg and fever. The patient says he was absolutely fine a weeks back.

On examination :

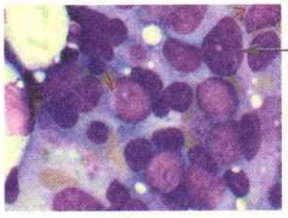
- Pallor.
- Petechiae.
- Splenomegaly.



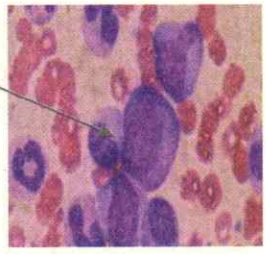
CBC :

- Hb : 7gm%.
- TLC : 15,000/cumm.
- Plc : 60,000/cumm.

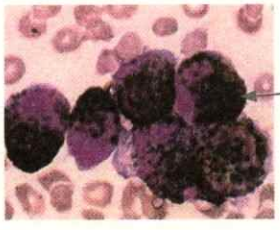
Peripheral smear :



Bone marrow aspirate :



MPO special stain :



Diagnosis : AML.

Active space

MYELOID DISORDERS

Myeloid disorders comprise of :

1. AML.
2. Myeloproliferative neoplasms.
3. Myelodysplastic syndrome (MDS).
4. MDS / MPN.

MPN :

- CML (Chronic Myeloid Leukaemia).
- PCV (Polycythaemia Vera).
- Essential Thrombocytosis (ET).
- Myelofibrosis.

Common features of MPN :

1. Pan-myelosis (increased RBC, WBC, platelet count) : This happens because all these cells arise from the myeloid series.
2. Associated with mutations in the growth signalling pathways (usually tyrosine-kinase pathway) → Cells become independent of growth factor signalling.
3. Increased risk of transformation to AML.
4. Extramedullary haematopoiesis (as bone marrow is full of myeloid cells, haematopoiesis may shift to other areas, like liver or spleen, causing hepatosplenomegaly.
5. Can develop fibrosis in the spent phase → Leading to myelofibrosis → Pancytopenia.

Chronic myeloid leukemia 00:05:04

- Usually in middle aged to elderly.
- C/O dragging sensation in the abdomen (clinical feature of massive splenomegaly).
- Hepatomegaly.

Active space

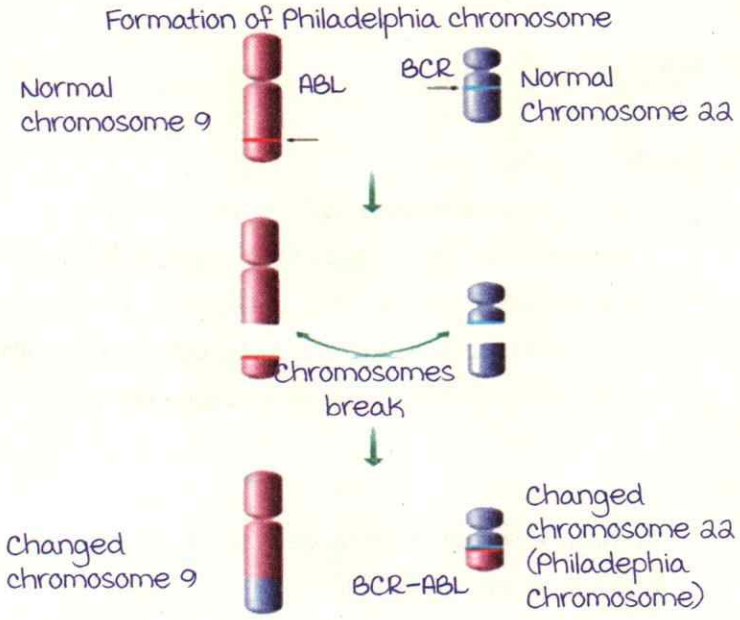
Other causes of massive splenomegaly in India :

- Malaria.
- Kala-azar (especially if patient is from Bihar).
- Myeloproliferative disorders, like CML, PCV, myelofibrosis.
- Storage disorders like Gaucher's disease.
- Hairy cell leukaemia.

Pathogenesis :

According to WHO, 95% patients have t(9 : 22) type of translocation → ABL gene on chromosome 9 translocates to BCR gene on chromosome 22 and fusion occurs → Changed chromosome 22 → Philadelphia chromosome.

t(9 : 22) → BCR : ABL fusion transcript (210 KDa) → Constitutive activation of Tyrosine Kinase → Tyrosine Kinase/ growth signalling pathway becomes independent of growth factors → Auto-activatation → myeloproliferation → CML.



Treatment :

- Tyrosine Kinase inhibitors : Imatinib mesylate (only symptomatic relief).
- Stem cell transplant is definitive treatment.

Imatinib is also used to treat Gastrointestinal Stromal Tumor (GIST).

Active space

ALL also can present with t(9 : 22) translocation with fusion transcript of 180 KDn with a very strong tyrosine kinase activity, therefore has a very bad prognosis.

Phases of CML :

Diagnostic criteria by WHO:

Chronic phase	Accelerated phase	Blast crisis
• Blast count : < 10%	• Blast count : 10–19 % • Basophilia > 20% • Increasing/massive splenomegaly. • Increasing TLC. • Persistent thrombocytopenia. • Persistent thrombocytosis, unresponsive to therapy.	• Blast count : > 20% • Extramedullary blast proliferation

Lab diagnosis of CML

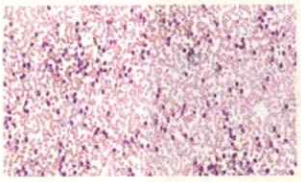
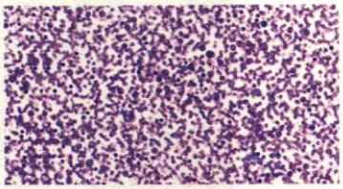
00:14:10

1. Complete blood count :
    - RBC normal + Elevated TLC (> 40,000/cu.mm) + Elevated PLC (thrombocytosis – 6 lakh/cu.mm).
    - For unknown reasons, t(9 : 22) usually affects only the myeloid and megakaryocytic cells and not the erythroid cells, therefore Hb remains normal.

2. Peripheral smear :
    - Immature rapidly dividing cells start moving from bone marrow to peripheral blood.
    - Therefore, immature cells like promyelocytes, myelocytes, band forms, neutrophils and basophils (bluish granules obscuring the nucleus) can be seen in the peripheral smear, giving the appearance of bone marrow.

"College girl/garden party appearance" as every cell looks different (non uniform appearance).

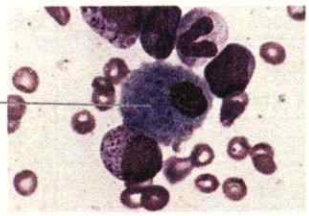
Active space

Convent girl appearance : Seen in CLL which has mature lymphocytes (smudge cells) where every cell looks the same (uniform appearance).

3. Bone marrow aspirate :

- Increased myeloid : erythroid ratio.
- Dwarf megakaryocytes (due to lack of space since the bone marrow is flooded with cells).
- Sea blue histiocytes (cytoplasm with blue colour)
- Pseudo-Gaucher Cell (crumpled tissue paper appearance of cytoplasm, but not seen in Gaucher's disease).



4. NAP/LAP score :

measurement of activity in granules by staining.

NAP : Neutrophil Alkaline Phosphatase (Normal : 40-100)

Decreased in patients with CML, except in some cases of blast crisis.

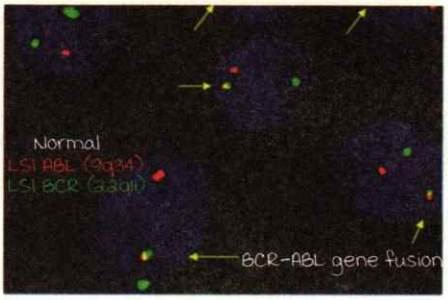
LAP : Leukocyte Alkaline Phosphatase.

Increased NAP Score	Decreased NAP Score
myeloproliferative neoplasms (MPN) except CML	CML
Infections	Paroxysmal Nocturnal Hemoglobinuria (PNH)
Stress	myelodysplastic syndrome (MDS)
Pregnancy	
Leukemoid reactions.	

FISH (Fluorescent In-Situ Hybridization) : IOC.

To confirm t(9 : 22) translocation.

Active space



Differential diagnosis of CML :

	Leukemoid reactions	CML
Aetiology	Infections	myeloproliferative neoplasm
t(9 : 22) translocation	Absent	Present
Massive splenomegaly	Absent	Present
Basophilia on P/S	Not seen	Can be seen
Pseudo-gaucher cells on BMA	Not seen	Can be seen
NAP score	Increased	Decreased
Treatment	Antibiotics	Imatinib mesylate.
TLC count	< 50,000/cu.mm	> 50,000/cu.mm

Polycythaemia vera

00:28:28

Diagnostic criteria :

2008	2014
Major criteria : 1. Hb : > 18.5 g/dL (men). > 16.5 g/dL (women). or other evidence of increased red cell volume. 2. Presence of JAK2, V617F or JAK2 exon 12 mutation.	Major criteria : 1. Hb : > 16.5 g/dL (men). > 16 g/dL (women). or Hct : > 49% (men). > 48% (women). 2. BM trilineage myeloproliferation with pleomorphic megakaryocytes. 3. Presence of JAK2 mutation.
Minor criteria (2008) : 1. BM trilineage myeloproliferation. 2. Subnormal serum erythropoietin level. 3. Endogenous erythroid colony growth.	Minor criteria (2014) : 1. Subnormal serum erythropoietin level.

Active space

JAK STAT pathway is the most common to be mutated in PCV.

Clinical features :

1. Increased Hb causes :
   - Stasis.
   - Neurological abnormalities.
2. Increased TLC :
   - Intense itching (pruritis) after a hot water bath (myeloproliferation → Increased basophils + mast cells → Increased histamine release → Intense itching).
   - Flushing.
3. High platelet count :
   - Bleeding tendencies
4. Hepatosplenomegaly
5. Erythropoietin is low.
6. JAK STAT analysis can be done.

Secondary polycythaemia :

Seen in :

- Smokers.
- People living in high altitude (they have a reddish appearance as they have higher amounts of Hb).
- People with COPD.

Polycythaemia Vera	Secondary polycythaemia
Low or subnormal erythropoietin levels, as the RBCs are not dependent on erythropoeitin levels anymore.	They have high serum erythropoietin levels.

Treatment : Phlebotomy.

Essential Thrombocytosis (ET) :

WHO diagnostic criteria (all 4 should be present) :

1. Sustained increase in TLC ≥ 4.5 Lakh/cu.mm.
2. Exclusion of WHO diagnostic criteria for CML/PCV or other MPN.
3. Megakaryocytic hyperplasia/proliferation on bone marrow biopsy.

Active space

Megakaryocytes → Staghorn appearance on bone marrow biopsy.

4. Presence of JAK2 V617F, MPL or Calreticulin mutation (Any one of these mutations should be seen).

Clinical features :

- Increased platelets can clog small arteries of hand and feet causing throbbing pain.
- Parasthesias (raised PLC).
- Transient ischemic attack.

myelofibrosis :

Diagnostic criteria :

Presence of 3 major OR 2 major and atleast 1 minor.

Major	Minor
1. Atypical megakaryocytic hyperplasia with reticulin/ collagen fibrosis. 2. Exclusion of WHO criteria for PV, CML, MDS, other MPDS. 3. JAK2V617F or other clonal marker, if not rule out secondary fibrosis.	1. Leukoerythroblastosis. 2. Elevated serum LDH. 3. Anemia. 4. Palpable splenomegaly.

Clinical features :

- Usually seen in elderly patients.
- Massive splenomegaly.
- Can occur as spent phase in CML/MPN.

Pathogenesis :

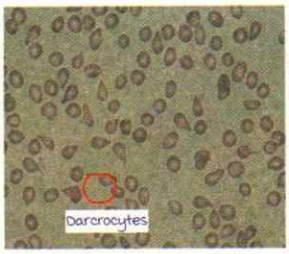
Megakaryocytic hyperplasia → Increased Platelet Derived Growth Factor (PDGF) which is fibrogenic → Causes fibrosis → myelofibrosis.

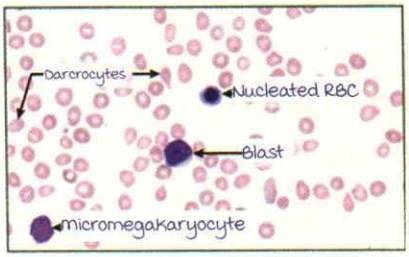
Lab diagnosis :

1. CBC : Pancytopenia.
2. Peripheral smear :
   - Pancytopenia.

Active space

- Erythroid cells appear as tear drop cells/dacrocytes.
- Leucoerythroblastic blood picture (WBC precursors + Immature RBCs seen in the peripheral blood).





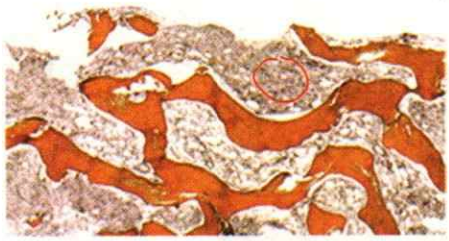
Leucoerythroblastic picture is also seen in space occupying lesions of bone marrow like metastatic cancers, granulomas.

3. Bone marrow aspirate : Dry tap (no material comes on aspiration).

Other conditions that show dry tap :

- Hairy cell leukemia.
- myelofibrosis.
- metastatic cancers.
- AML-M7.

4. Bone marrow biopsy → using reticulin stain → Black coloured fibres (reticulin fibrosis).



Myelodysplastic syndrome (MDS) 00:48:35

Characteristics :

- Dysplasia in RBC, WBC and megakaryocytic lineage.
- Increased risk of transformation to AML.
- Cytopenias seen.

Active space

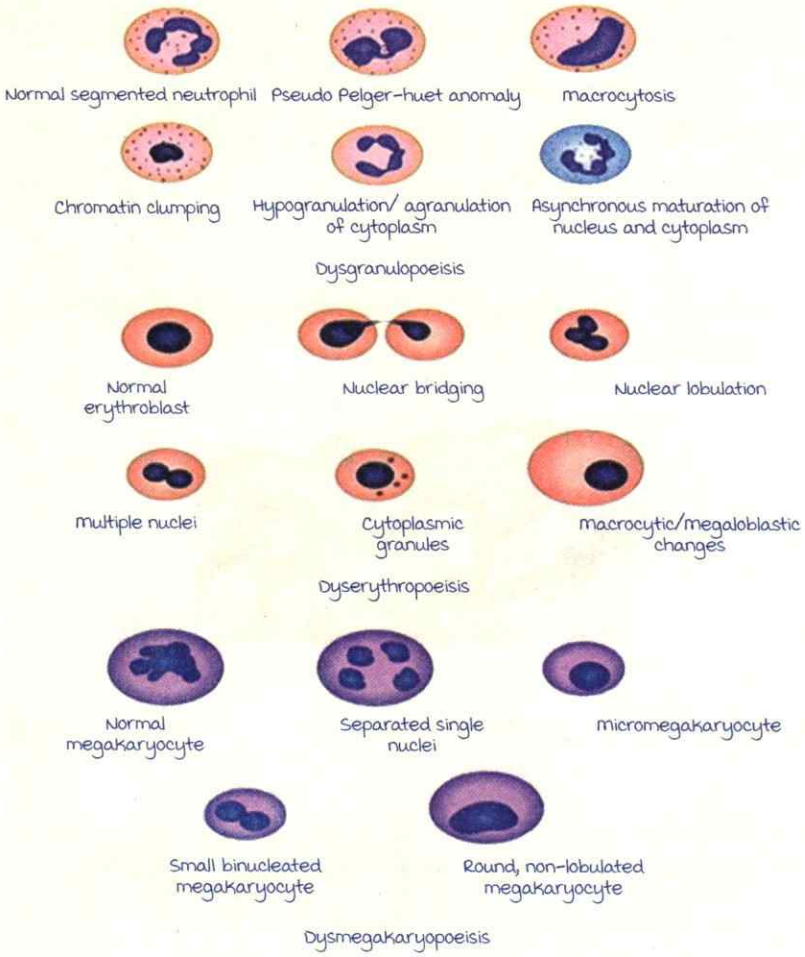
Types of MDS :

1. Primary.
2. Secondary or therapy related.

m/c cytogenic anomaly associated with adult MDS :
del 5q (Deletion of 5q).
m/c cytogenic anomaly associated in childhood MDS :

Features of dysplasia :

- Dysgranulopoeisis – dysplastic granulopoiesis.
- Dyserythropoeisis.
- Dysmegakaryopoeisis.



Active space

Langerhans cell Histiocytosis (LCH) 00:53:00

Proliferation of immature dendritic cells.

Associated with BRAFV600E mutations (> 50% cases).

Disease could be :

1. Unisystem : Unifocal or Multifocal.
2. Multisystem.

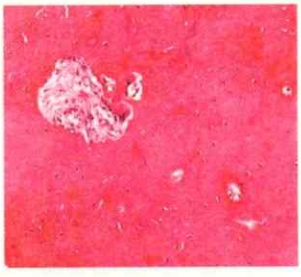
Unifocal	Multifocal	Multisystem
Example : Eosinophilic granuloma. Seen usually in children.	Example : Hand Schuller Christian disease. Triad : Exophthalmos + calvarian bone defects + Diabetes Insipidus.	Example : Leiterer Siewe disease.

Diagnosis :

- Biopsy/histopathology : Coffee bean nuclei (nuclei have a groove like coffee beans).
- Electron microscopy : Pentalaminar tubules with dilated terminal ends, appearing as tennis racquet, (Tennis racquet appearance with Birbeck granules)
- Markers : CD-1a, langerin, S-100, CD-207.

Tennis racquet is also seen in :

- Langerhans cell histiocytosis.
- Sarcoma Botryoides.



Coffee bean nuclei seen in :

- Papillary cancer of thyroid.
- Langerhans cell histiocytosis.
- Brenner's tumour.
- Chondroblastoma.
- Granulosa cell tumour of ovary.

Active space

MCQs

1. A 63 year old female living in a hilly area has Hb of 16 gm%, TLC 21000/cu.mm. DLC showed metamyelocytes and myelocytes 40%, N 25%, L40%, E5%. Platelet count is 3.2 lakh/u. He presented with hypertension and on examination spleen was just palpable below costal margin. What is the next step?

A. Philadelphia chromosome.

B. JAK STAT mutation assessment.

C. Bone marrow with reticulin stain.

D. Erythropoeitin levels.

Case of secondary polycythemia as she is living in a hilly area + raised Hb. Confirmation by serum erythropoeitin levels.

2. A 5 year old girl is brought to you by her father, who states that the girl is drinking a lot of water lately. Physical examination reveals exophthalmos. Further workup shows the (presence of multiple lytic bone lesions involving her calvarium and base of skull. What is the most likely diagnosis?

A. Letterer siwe disease.

B. Hand schuller Christian disease.

C. Eosinophilic granuloma.

D. Unifocal Langerhans cell histiocytosis.

3. A 48-year-old man has experienced increasing malaise and difficulty concentrating at work for the past 6 months. On physical examination he has splenomegaly but no lymphadenopathy. He is afebrile.

Laboratory studies show Hgb 12.0 g/dL, Hct 35.8%, MCV 92 fL, platelet count 390,000/uL, and WBC count 190,000/uL with differential count 73 segs, 12 bands, 6 metamyelocytes, 2 myelocytes, 2 myeloblasts, and 5 lymphs. The leukocyte alkaline phosphatase (LAP) score is very low. A bone marrow biopsy is performed. Which of the following microscopic findings is most likely to be found in this biopsy?

A. Sheets of plasma cells.

B. Atypical cytokeratin positive glands.

C. Numerous mature and immature myeloid cells.

D. Predominance of adipocytes.

E. Granulomas that have many acid fast bacilli.

Active space

Clinical case :

A 65 year old male with dragging sensation in abdomen

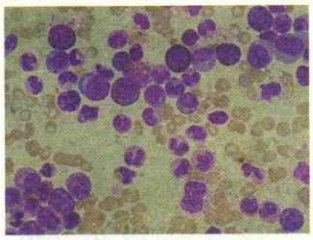
Examination : massive splenomegaly

Lab studies show :

Hb : 9 gm%.

TLC : 80,000/cu.mm.

PC : 6.5 lakhs.



Answer : CML.

Active space

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HODGKIN'S LYMPHOMA

Clinical differences between Hodgkins & non Hodgkin's lymphoma

00:02:59

Clinical differences between Hodgkin and Non Hodgkin lymphomas	
Hodgkin lymphoma	Non Hodgkin 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.	mesenteric nodes and Waldeyer ring commonly involved.
Extranodal involvement uncomon.	Extranodal involvement common.
Bimodal age distribution (seen at 15 to 20 yrs and in elderly).	Elderly.

- Most common lymph node affected in Hodgkin's lymphoma : Cervical.
- Reed Sternberg cells (RS cells) in an inflammatory background are present in Hodgkin's lymphoma, but absent in non Hodgkin's lymphoma.

Active space

WHO classification of Hodgkin's lymphoma 00:06:10

Hodgkin's lymphoma

Classical	Non classical
1. Nodular sclerosis.	Lymphocyte predominant (NLPHL).
2. Mixed cellularity.	
3. Lymphocyte rich.	
4. Lymphocyte depleted.	
RS cells are CD15+, CD30+	RS cells are CD15−, CD30−, CD20+, CD45+, BCL6+

CD20+, CD45+, BCL6+ are also referred as EMA + (Epithelial marker Antigen).

most sensitive marker : CD30+

Pathogenesis :

EBV

↓

↑ expression of LMP 1 (virulence factor for EBV)

↓

↑ activation of NF Kβ growth signaling pathway

↓

↑ B cell proliferation

↓

Hodgkin's lymphoma (HL)

HL is a disorder of B cells arising from post germinal center B cell.

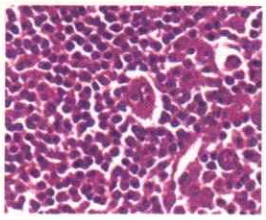
Clinical presentation :

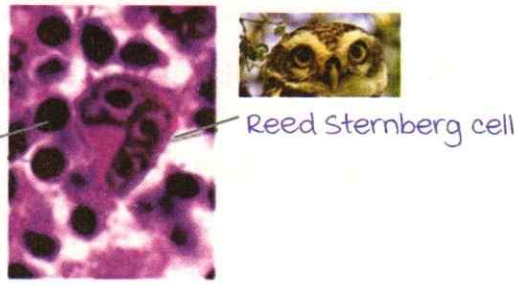
- Fever, night sweats, weight loss (B symptoms) are present. Intermittent cyclical trend (waxing & waning) in fever is characteristically known as Pel Ebstein fever.
- Painless cervical lymphadenopathy (rubbery lymph nodes on palpation).
- Paraneoplastic syndrome :
  Production of amyloid (AA type).
  Pain on alcohol ingestion.

Active space

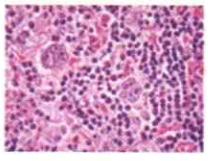
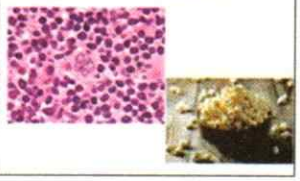
Reed sternberg cells 00:14:49

Large cells (15 – 45μ).
Binucleate.
Prominent eosinophilic macronucleoli (5 – 7μ).
Mirror image of each other.
Called as Owl's eye appearance.



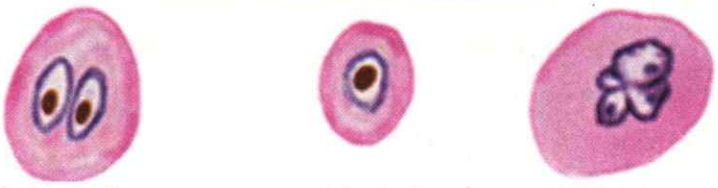


Variants of RS cells :

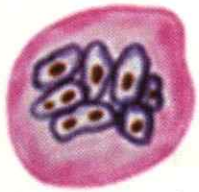
Lacunar	Mononuclear	Lymphohistiocytic (LH)
Empty space around the nuclei. Seen in Nodular sclerosis HL.	Single nucleus. Seen in lymphocyte rich HL.	Also called as popcorn cell. Seen in NLPHL.
		

Pleomorphic and mummified variants of RS cells are seen in Lymphocyte depleted HL.

Reed Sternberg cell variants



Active space


Pleomorphic RS cell


Lacunar cell


Mummified cell

1. Nodular sclerosis Hodgkin's lymphoma :
   - Most common Hodgkin's Lymphoma worldwide/western world.
   - Equal predisposition in males and females.
   - Uncommonly associated with EBV.
   - Mediastinal involvement can be seen.
   - Lacunar RS Cells present.
   - CD15+, CD30+
   - On H & E : Nodules surrounded by pinkish sclerotic areas with lacunar cells within.
   - Excellent prognosis.

2. Mixed cellularity Hodgkin's lymphoma :
   - Males are commonly affected than females.
   - Most common Hodgkin's Lymphoma in India.
   - No mediastinal involvement.
   - 70% cases associated with EBV. Most Common HL associated with EBV.
   - Maximum association with B Symptoms.
   - Maximum association with HIV.
   - LN biopsy : Polymorphous cells including lymphocytes, eosinophils, macrophages, RS cells.

3. Lymphocyte rich HL :
   - Large number of lymphocytes, few RS cells.
   - Mononuclear RS cells.

4. Lymphocyte depleted HL :
   - Least common HL.
   - Worst prognosis.
   - Mummified/reticular RS cells.
   - Occurs in immunocompromised hosts.

Active space

Non classical HL

00:31:26

Nodular lymphocyte predominant HL :

- Lymphohistiocytic variant of RS cells (popcorn cells) present.
- CD15−, CD30−, CD20+, CD45+, BCL6+.
- Best prognosis amongst all Hodgkin's Lymphoma.

	Nodular sclerosis	Mixed cellularity	Lymphocyte rich	Lymphcyte depleted	Predominant (non classical HL)
	most common type of HL	most common type in India		HIV associated	
m : F	m = F	m > F	m > F	m > F	m > F
Age	Adolescent and young adult	Biphasic (young adults as well as >55 years)	Old age	Old age	Young males
RS cell	Lacunar variant having a clear space surrounding the cell.	Has eosinophils & plasma cells. Has maximum number of RS cells.	Mononuclear variant of RS. Lowest number of RS cells.	Pleomorphic necrobiotic or mummified variant of RS cells. Maximum are of necrosis.	LH cells (popcorn cells) in the background. Other cells are scanty. B cells are absent.
Markers	CD 15+ CD30+	CD 15+ CD30+	CD 15+ CD30+	CD 15+ CD30+	CD 15− CD 30− CD20+ BCL6+ EMA+
EBV	Uncommon (usually not associated)	Associated	Associated	Associated	Not associated
Prognosis	Excellent	Very good	Good to excellent	Poor	Excellent

Ann Arbor staging :

- Stage I : Single lymph node region (I) or single extralymphatic organ or site (I_E).
- Stage II : ≥ 2 lymph node regions on same side of diaphragm (II) or with limited, contiguous extra lymphatic tissue involvement (II_E).

Active space

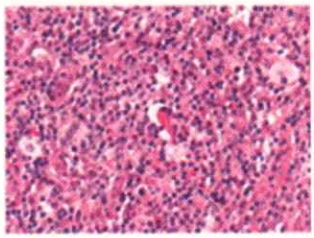
- Stage III : Both sides of diaphragm involved, may include spleen (IIIs) or local tissue involvement (III_E).
- Stage IV : multiple/disseminated foci involved with ≥ 1 extralymphatic organs (i.e. bone marrow).

(A) or (B) designates absence/presence of B symptoms.
(E) Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow.

Important prognostic marker : Stage > type.

Treatment :
(ABVD Regimen)
Adriamycin.
Bleomycin.
Vincristine/Vinblastine.
Dacarbazine.

Q. A 19 year old college student presents for evaluation of persistently enlarged nontender supraclavicular lymph nodes. She says she is otherwise healthy and provides no significant medical history. She is experiencing night sweats and has had a 4.5 Kg (10 lb) weight loss over the past 3 months. Three supraclavicular lymph nodes are palpable above her right shoulder. No other lymphadenopathy is noted. On Xray chest, mediastinal lymphadenopathy is noted. Results of the lymph node biopsy are shown in the image. Which of the following is the most likely diagnosis ?



A. Burkitt lymphoma.
B. Follicular lymphoma.
C. Hodgkin lymphoma, lymphocyte depleted type.
D. Hodgkin lymphoma, nodular sclerosing type.
E. T lymphocyte lymphoblastic lymphoma.

Active space

Q. Who among the following patients is likely to have the best prognosis ?

A. A patient with mononuclear variant of Reed Sternberg cells on lymph node biopsy.

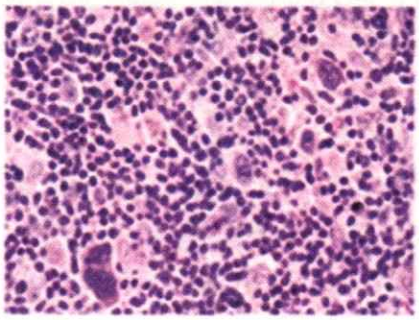
B. A patient whose lymph node biopsy shows lacunar Reed Sternberg cells.

C. A patient with RS cells amidst mixed variety of back ground cells.

D. A patient with mummified RS cell.

Clinical case 1 :

- A 38 year old female.
- Clinically itching all over the body more at night for the past one year. All dermatologists ordered allergic tests but they were normal.
  For the past 10 days she had fever, night sweats and weight loss.
- CT scan showed cervical lymphadenopathy.
- Biopsy from the lymph node is shown below.



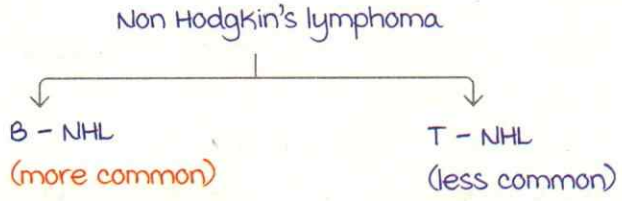
Answer : Hodgkin's lymphoma (can also present as itching).

Active space

NON HODGKIN'S LYMPHOMA

The WHO classification of the lymphoid neoplasms :

1. Precursor B cell neoplasms (immature B cells) (B-ALL).
2. Peripheral B cell neoplasms (mature B cells).
3. Precursor T cell neoplasms (immature T cells) (T-ALL).
4. Peripheral T cell and NK cell neoplasms (mature T cells and natural killer cells).
5. Hodgkin lymphoma (Reed Sternberg cells and variants).



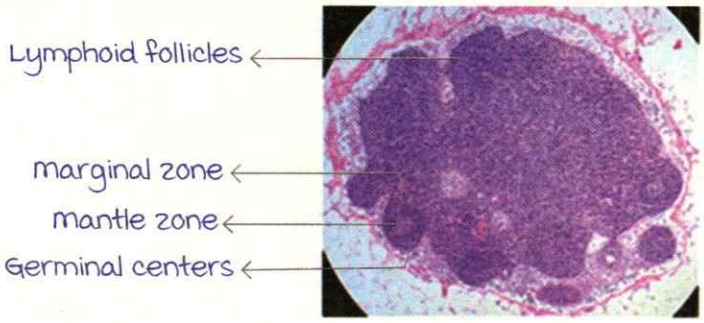
Peripheral B cell neoplasms :

1. Chronic lymphocytic leukemia/small lymphocytic leukemia.
2. B cell prolymphocytic leukemia.
3. Lymphoplasmocytic leukemia (develops from walden strom macroglobulinemia).
4. Splenic & nodal marginal zone lymphoma.
5. Extranodal marginal zone lymphoma.
6. Follicular lymphoma.
7. Marginal zone lymphoma.
8. Hairy cell leukemia.
9. Plasmacytoma/plasma cell myeloma.
10. Diffuse large B cell lymphoma.
11. Burkitt lymphoma.13 &

T lymph nodes : Histology 00:03:59

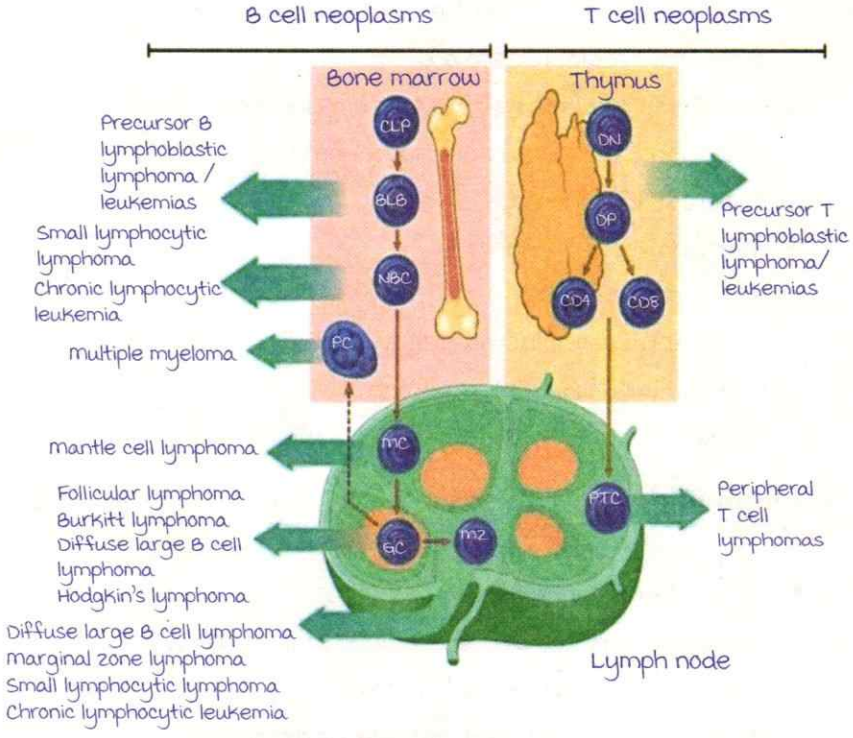
- Shows lymphoid follicles.
- Germinal centers are the pale staining areas in the center of lymphoid follicles.
- Mantle zone is present outside germinal centers.
- Marginal zone is present outside mantle zone.

Active space



- Lymphoma arising from mantle zone cells is known as mantle cell lymphoma.
- Lymphoma arising from marginal zone is known as marginal cell lymphoma.
- Precursor lymphoblastic leukemia : B-ALL arise from precursor/immature cells.
- CLL/SLL arise from naive B Cell.
- Follicular lymphoma, Burkitt lymphoma, diffuse large B cell lymphoma, Hodgkin's lymphoma arises from Germinal center.

  DLBCL, CLL/SLL, Marginal zone lymphoma arise from marginal zone.



Active space

Chronic lymphocytic leukemia(CLL)/ small lymphocytic leukemia(SLL)

00:07:58

Age : 60 to 70 years.
Most common leukemia in elderly.
Pathogenesis : Deletion of 13q, 11q, 17p causes deletion of microRNA 15 - 16.

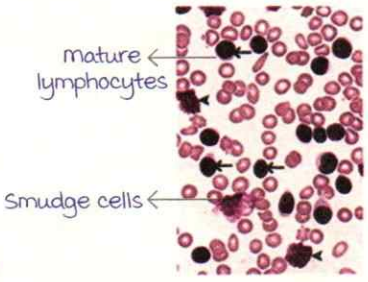
BTK (Bruton Tyrosine Kinase) gene mutation
↓
↑ BTK
↓
↑ B cells
↓
↑ IgGs (antibodies) which can attack RBCs or platelets leading to Auto Immune Hemolytic Anemia (AIHA) or thrombocytopenia.

Evan's syndrome : CLL + AIHA + thrombocytopenia.

Clinical presentation :
Fatigue (earliest symptom).
Painless lymphadenopathy.
Hepatosplenomegaly.
Features of AIHA/thrombocytopenia.

Lab tests :
CBC :

- Hb : Reduced
- TLC : Might be raised
- Platelet counts : may be normal
- DLC : Absolute lymphocytosis > 5000/mm^3.



Peripheral smear :
Smudge cells/basket/parachute cells :
As lymphocytes loose vimentin (cytoskeletal protein), the cytoplasm become fragile and cell boundaries get smudged on making peripheral smear.

Active space

All lymphocytes look similar, are referred as convent girls appearance.

Bone marrow aspirate : > 30 % lymphocytosis.

Lymph node biopsy :

Small lymphoid cells + Activated lymphoid cells → Proliferation centers. (Pathognomonic of CLL).

Investigation of choice :

Flow cytometry : Cells are CD5+, CD23+ (dual positivity).

New marker : CD200.

Prognostic markers :

Good prognosis : Del of 13q, deletion of micro RNA 13 & 15 (Also seen in multiple myeloma).

Bad prognosis :

- Increased expression of CD23, CD38, $\beta 2$ microglobulin, LDH.
- Increased expression of Notch 1.
- Increased expression of ZAP 70.
- Presence of 11q and 17p deletion.

Rai and Binet scoring system is used.

CLL can transform into DLBCL (Diffuse Large B cell Lymphoma) known as _____

CLL can also transform into prolymphocytic leukemia.

Follicular lymphoma (FL)

00:25:10

Most common type of indolent NHL in the world.

Pathogenesis :

t (14 : 18)

- IgH locus
- bcl2

Due to increase in bcl2 expression, it can be used as flow cytometric marker.

↑ expression of bcl2 (anti-apoptotic gene)

↓

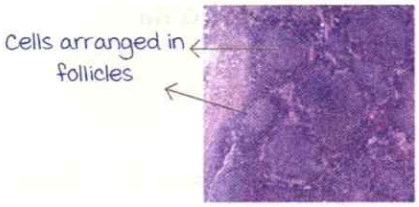
↑ cell proliferation

↓

Follicular lymphoma.

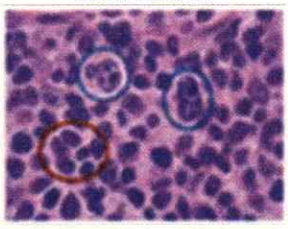
Active space

Lymph node biopsy :
Cells are arranged in follicles.
In follicular hyperplasia, non uniform sizes of follicles & Bcl2 expression is negative
Two types of cells visible :

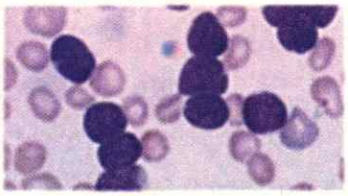


1. Centrocytes : Small cells with cleaved nuclear contours (called buttock cells due to their appearance).

Centrocytes & centroblasts



Cleaved lymphocyte



2. Centroblasts : Large cells with prominent nucleoli.
Bone marrow examination : Para-trabecular lymphoid aggregates.

Markers : CD19, CD20+, bcl2+
90% cases have MLL gene mutations.
30-50% cases of FL can transform into DLBCL.

Mantle cell lymphoma

00:33:10

Pathogenesis :

t(11 : 14)
↙ ↘
Cyclin D1 IgH locus
↓
↑ Expression of cyclin D1 (moves the cell cycle from G1 to S phase)
↓
↑ Cell proliferation
↓
Mantle cell lymphoma.

Polypoid lesions in intestine : Lymphomatoid polyposis.
LN biopsy shows small, cleaved lymphocytes.
Markers : CD5+, CD23-, Cyclin D1.
Marker for cyclin D1 negative mantle cell lymphoma : SOX 11.

Active space

Burkitt's lymphoma

00:37:58

It is a B cell disorder.

Pathogenesis :

Most common translocation : t(8 : 14)

t(8 : 14)

↓ ↓

c-myc IgH locus

↓

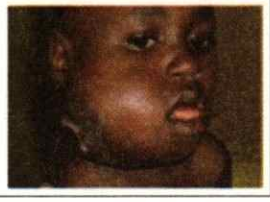
↑ expression of c-myc oncogene

↓

Burkitt's lymphoma.

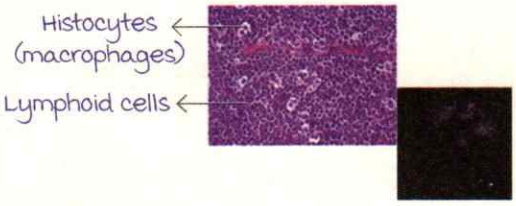
Other translocations : t(2 : 8), t(8 : 22)] ↑ c-myc

n-myc : Increased risk of neuroblastoma, L-myc : increase risk of small cell lung cancer.

African/endemic	Sporadic	HIV associated
Most cases EBV associated. Most common site : Jaw, mandible 	15 - 20% cases are EBV associated. Most common site : GIT, ileocaecum, peritoneal mass.	Can occur anywhere.

Lymph node biopsy : Starry sky appearance.

Lymphoid cells : Sky.
Macrophages : Stars.



Marker for rapid proliferation :

Mib - 1 index, Ki 67 score (almost 100 %).

Aggressive tumor.

Chemo sensitive.

Most common cause of tumor lysis syndrome.

Active space

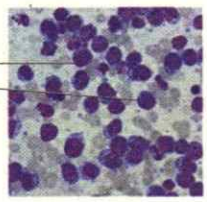
Bone marrow aspirate :

Lymphoid cells with vacuolated cytoplasm (filled with fat).

Oil red O+.

(seen in ALL – L3/ Burkitt lymphoma like).

Marker : bcl6+.



Diffuse large B cell lymphoma (DLBCL) 00:50:02

Most common type of NHL worldwide.

Aggressive tumour.

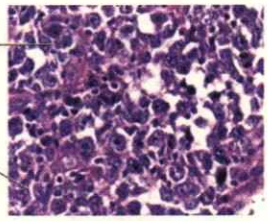
Poor prognosis.

Pathogenesis : t(14 : 18) or dysregulation of bcl 6.

Diagnosis of exclusion.

LN Biopsy shows :

- Sheets of pleomorphic lymphoid cells
- Complete effacement of LN architecture.
- 4 – 5 times the size of a small lymphocyte.



Markers : bcl 6+, surface Ig+

Variants :

Primary effusion lymphoma	Immunodeficiency associated DLBCL
HHV 8 association. Can present with pleural effusion.	Associated with HIV+ or transplant association.

HHV 8 associated disorders :

- Primary effusion lymphoma
- Castleman's disease.
- Kaposi's sarcoma.

Active space

Marginal zone lymphoma :

Also known as MALToma.

Most common site of MALToma : Stomach.

Usually arises at sites of chronic inflammation : Hashimoto's thyroiditis, H. pylori, Sjogren's syndrome.

Pathogenesis : t(11 : 18) translocation.

Marker : CD43+, CD5−, CD23−.

CLL : CD 5+, CD23+.
Mantle cell lymphoma : CD5+,CD23−.

Hairy cell leukemia (HCL)

00:57:48

Arises from B cell.

Clinically present as massive splenomegaly.

In HCL, red pulp of spleen is involved commonly.

Causes of massive splenomegaly :

- Myleoproliferative disorder
- CML
- myelofibrosis
- Malaria
- Kala azar
- Glycogen storage disorder or lysosmal storage disorder

Pathogenesis :

Associated with BRAF V600E mutation (90% cases).

BRAF V600E mutation is seen in :

- Papillary carcinoma of thyroid.
- Langerhans cell histiocytoma.
- Pilocytic astrocytoma.
- Hairy cell leukemia.
- Melanoma.

Increased risk for atypical mycobacterium infections.

Lab diagnosis :

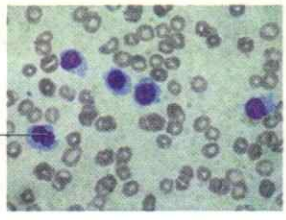
CBC : Pancytopenia (reduced Hb, TLC, platelet counts).
Due to myelofibrosis.

Peripheral smear :

Cells with hairy projections seen (can be artifact).

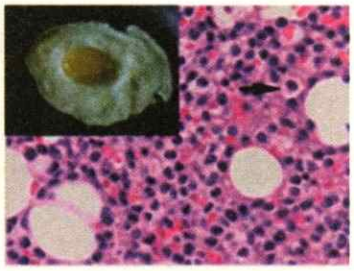
Best visualised : Phase contrast microscopy.

Bone marrow aspirate : Dry tap seen.



Active space

Bone marrow biopsy :
Fried egg/honey comb appearance.
Fried egg appearance is seen in :
Hairy cell leukemia
Oligodendroglioma.



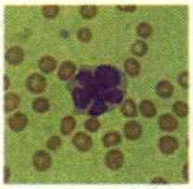
Special stain : TRAP+ (Tartrate resistance acid phosphatase).
Markers : CD25, CD11c, CD103, Annexin A1.
Annexin is marker for hairy cell leukemia & apoptosis.

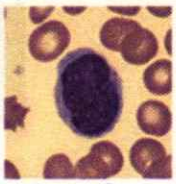
Feature	Follicular L	mantle cell L	Burkitt's L	DLBCL	marginal zone L
Incidence	mc type indolent NHL world wide			MC NHL in India/ worldwide	
Pathology	t(14 : 18), MLL gene	t(11 : 14)	t(8 : 14), t(2 : 8)	Dys bcl 6, t(14 : 18)	t(11 : 14)
Histology	Follicles, centrocytes, centroblasts	Small, cleaved lymphocytes	Starry sky appearance	Large, pleomorphic cell	Lymphoepithelial lesion
markers	Bcl2 +	Cyclin D 1+, CD 5+, CD23- SOX 11	CD19, 20, BCL 6 +	CD19, 20, bcl 6 +	CD 43+
Extra	Para trabecular lymphoid aggregates	Lymphomatoid polyposis	EBV associated, jaw, GIT		Site of chronic inflammation

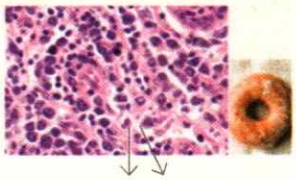
T cell NHL

Feature	Adult T cell leukemia	mycosis fungoides / Sezary syndrome	Anaplastic large cell Lymphoma (ALCL)
Pathology	HTLV I	Cutaneous Tcell lymphoma (usually affects skin)	ALK gene on chromosome 2p
Histology	Flower cells/ clover leaf cells	Sezary cells : Cerebriform nuclei. Pautrier's microabscesses. Epidermotropism : T lymphocytes invading epidermis	Hallmark cells/ Doughnut cell (voluminous cytoplasm, resembes doughnut).

Active space


Flower cells


Cerebriform nuclei


Doughnut cells

ALK gene mutation on Chromosome 2p is associated with :

- ALCL.
- Adenocarcinoma of lung.
- Inflammatory myofibrolytic tumor.

Doughnut granuloma : Seen in Q Fever.

Q. A 65 year old male patient with chronic fatigue and lymphadenopathy presents to the OPD. His peripheral smear shows the presence of smudge cells. Which of the following additional investigations will you do to arrive at a diagnosis?

A. Flow cytometry.
B. Cytogenetics.
C. FISH.
D. Bone marrow examination.

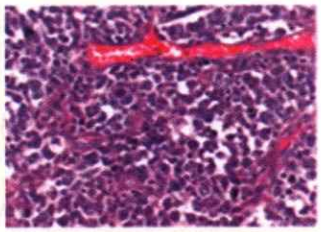
Q. A boy presents with fever, night sweats, weight loss for 2 months. Ultrasound of the abdomen showed the enlargement of para aortic lymph nodes. Biopsy of the mass showed a starry sky appearance. The most likely genetic abnormality seen is ?

A. Translocation (8 : 14) c-myc.
B. Translocation (9:22) BCR-ABL.
C. Mutation of Rb.
D. D. Mutation of p53.

Q. A 35 year old man presented with fever. On examination, he had enlarged and ulcerated tonsils. His peripheral blood smear showed lymphocytosis. Mono spot test was negative. Tonsillectomy was done. The biopsy of the same showed large cells mixed with lymphocytes.
The cells were positive for CD20,

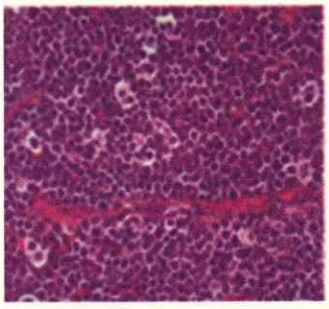
Active space

EBVLMP1, MUM1 and CD 79a.
The cells are negative for CD15.
Your most probable diagnosis ?



A. Infectious mononucleosis.
B. Hodgkin's lymphoma.
C. EBV positive DLBCL.
D. EBV positive mucocutaneous ulcer.

Q. A 6 year old boy is brought to the physician because of abdominal distention, fatigue and night sweats over the past4 months. He also has a 2 month history of postprandial fullness and recurrent non bilious vomiting. He appears pale. Abdominal examination shows hepatosplenomegaly and shifting dullness. There is mild tenderness on palpation. Examination of the skin shows multiple non blanching maculae. A CT scan of the abdomen shows mesenteric and retroperitoneal lymph node enlargement and nodular thickening of omentum. A photomicrograph of a biopsy specimen from an enlarged mesenteric lymph node is shown. Immunohistochemical staining of the Ki-67 nuclear antigen shows that the proliferation index of the specimen is > 99%. The structure indicated by the arrows is most likely which of the following?



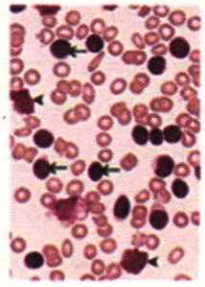
A. Neutrophil.
B. B lymphocyte.
C. T lymphocyte.
D. Macrophage.

Q. A 54 year old woman, on treatment for CLL, notices rapidly growing swellings in her neck and axilla. She also complaints of fever and weight loss. The Physician suspects a transformation to diffuse large B cell lymphoma. What is this called?

A. Sezary syndrome.
B. Kostmann's syndrome.
C. Chediak Higashi syndrome.
D. Richter syndrome.

Active space

Clinical case 1



- A 65 year old man.
- Easy fatigueability, weight loss and anorexia.
- Examination : Splenomegaly, lymphadenopathy.
- Lab studies :

  TLC : 90,000 permicrol

  DLC : 76% lymphocytes

  P/S is shown here.

What will be the next investigation?

Answer : Flow cytometry which will show dual positivity CD5+, CD23+.

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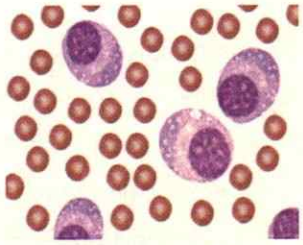
PLASMA CELL DISORDERS

Plasma cell disorders 00:00:55

Plasma cell disorder encompasses 5 disorders :

- Multiple myeloma.
- Monoclonal gammopathy of Undetermined Significance/ MGUS : most common plasma cell disorder.
- Smoldering myeloma (asymptomatic myeloma).
- Plasma cell leukemia.
- Waldenstrom's macroglobulinemia.

All these disorders arise from post germinal centre B cells as plasma cells arise from B cells.
Plasma cells secrete immunoglobulins.
Normal immunoglobulins are polyclonal.
There is excessive production of abnormal immunoglobulins (monoclonal) in plasma cell disorders.



Plasma cell

Plasma cells are not seen in peripheral smear and are seen only in bone marrow aspirate.

- Oval shaped cell with eccentric nucleus.
- Perinuclear hoff/halo is seen due to the presence of Golgi zone.
- Cartwheel or clock face chromatin.

Multiple myeloma 00:07:13

Average age of presentation is 60 – 70 years.

Pathogenesis :
del 13q and t (11 : 14) are two cytogenetic abnormalities seen in multiple myeloma (mm). These abnormalities lead to excess production of plasma cells.
This will lead to excessive production of abnormal immunoglobulins. IgG > IgA > IgM > IgD > IgE.
most common immunoglobulin increased in MM is IgG followed by Ig A.

Active space

There is increased risk of infections due to abnormal immunoglobulins. Most common cause of death in a patient with MM is infection.

The excessive immunoglobulin production leads to increased number of light chains which can lead to :

- AL type of amyloidosis.
- Bence Jones proteinuria.
- Casts in Kidney due to its deposition leading to renal failure causing a decreased erythropoietin production. It in turn causes anemia.
  Increased levels of Ig D usually leads to renal failure.

del 13q is also seen in chronic lymphocytic leukemia.
t (11 : 14) is also seen in mantle cell lymphoma.

The excessive production of plasma cells leads to increased activation of MIP 1_{α} causing :

- Increased osteoclastic activity : Increased bone resorption leading to hypercalcemia. It causes lytic or punched out bone lesions.
- Decreased osteoblastic activity : Normal or decreased alkaline phosphatase levels.

Interleukin 6 is responsible for the proliferation of plasma cell.

Clinical features of multiple myeloma 00:17:40

The clinical features in patients with MM include :

- Pallor.
- Fatigue.
- Bone pain and pathological fractures : The most common bone affected is vertebra (lumbar).
  It usually affects the bones of axial skeleton (ribs, sternum, vertebrae etc.)
- Renal failure: Due to excess level of IgD.

Diagnostic criteria for multiple myeloma :

Active space

New IMWG Criteria for MM diagnosis :

Clonal bone marrow plasma cells ≥ 10% or biopsy proven bony or extramedullary plasmacytoma plus a myeloma defining event :

One or more biomarkers of malignancy :	or	Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder :
• Clonal bone marrow plasma cells ≥ 60% • Involved : Uninvolved sFLC ratio ≥ 100* • > 1 focal lesion on MRI studies. * Involved freelite concentration must be > 100 mg/l		• Hypercalcaemia • Renal insufficiency • Anaemia • Bone lesions] CRAB features

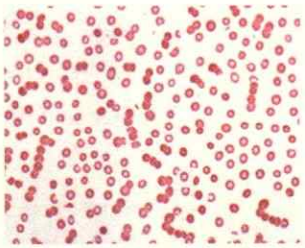
Hypercalcemia : Serum calcium > 11 mg/dl.
Renal insufficiency : Serum creatinine > 2mg/dl.
Anemia : Hemoglobin < 10 gm/dl.
Bone lesions : Lytic or punched out lesions.
Biomarkers of malignancy mnemonic : SLIM criteria.

- S : ≥ sixty percent.
- LI : Free Light chain (FLC) ratio ≥ 100.
- M : MRI studies showing > 1 focal lesion.

Lab diagnosis of MM :
Complete blood count :

- Hemoglobin : Low (Anemia of chronic disease : Normocytic normochromic)
- Total leukocyte count : Normal.
- Differential leukocyte count : Normal.
- Platelet count : Normal.

Peripheral smear : Rouleaux formation.
Normal RBCs are negatively charged and repel each other.
In MM, the RBCs are coated with immunoglobulins and sticks to each other forming rouleaux.



Rouleaux formation

Active space

Rouleaux formation is also seen in :

- Autoimmune disorders.
- Early HIV.
- Diseases with raised ESR.

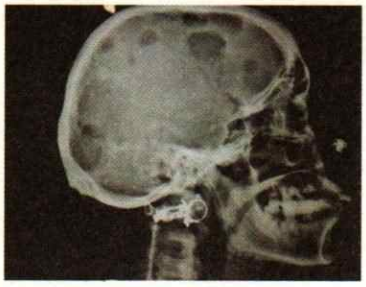
Biochemical tests

00:26:26

The tests include :

- Serum Ca^{2+} → Hypercalcemia with metastatic calcification.
  Dystrophic calcification is seen with normal serum calcium levels.
- Kidney function test : Abnormal.
- Serum Albumin/globulin ratio : Reversed.
- ESR : Raised.
- Serum β2 microglobulin : Raised. Most important prognostic factor in multiple myeloma.
- Bence Jones proteinuria : These are light chains of immunoglobulins. Normal proteins in the urine precipitate when heated at 100° C. Bence Jones protein precipitate at 40 – 60° C and disappears on boiling. It reappears on cooling.
  The test is not specific to multiple myeloma.

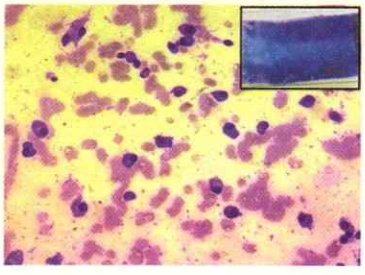
X-ray will show lytic or punched out lesions :



Lytic Lesions

Bone marrow aspirate :

- ≥ 10% plasma cells.
- 4 different types of cells according to WHO :
  1. Flame cells : Ig appears like a flame.
  2. Mott/morular/ mulberry cell : Ig appears like a grape like cluster

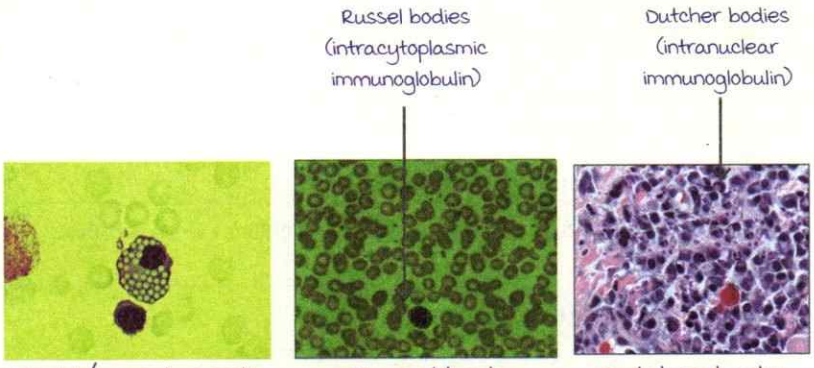


Bone marrow aspirate

Active space

3. Russel body : Ig appears as an intracytoplasmic inclusion.
4. Dutcher body : Intranuclear inclusion.

All these cells are produced due to excess production of immunoglobulin (Ig) by the plasma cell.



Serum/urine protein electrophoresis 00:35:42

It shows an M band (myeloma or monoclonal Ig band).
There is increased γ globulin levels on electrophoresis.
In multiple myeloma there is an increased serum IgG > 3 g/dl.

On bone marrow biopsy sheets of plasma cells are seen.

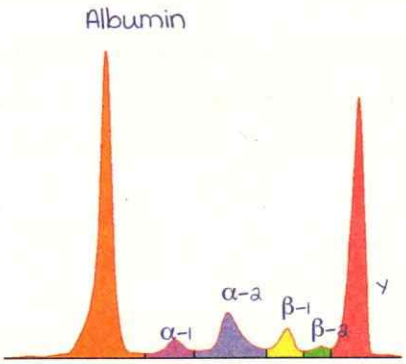
Markers on flow cytometry :

Normal plasma cells are positive for :

- CD 19 +
- CD 45 +
- CD 38 +
- CD 138 +

Cells in multiple myeloma :

- CD 19 –
- CD 45 –
- CD 38 +
- CD 138 +
- Syndecan 1 +



Active space

Prognostic factors in multiple myeloma :

Good prognostic factors include :

- t (11 : 14)

Bad prognostic factors include :

- Increased Interleukin 6.
- Increased β2 microglobulin.
- Deletion of 17p (translocation).

PB : peripheral blood. BM : bone marrow.

Plasma cell leukemia	Smoldering myeloma	MGUS	Waldenstorm's macroglobulinemia
>20% plasma cells in PB	BM plasma cells > 10%	BM plasma cells < 10%	Increased IgM
	No CRAB lesions	No myeloma defining events	
	Serum monoclonal M protein >3 gm/dl	Serum IgG < 3 gm/dl (monoclonal)	

Waldenstrom's macroglobulinemia 00:42:28

The condition is very similar to multiple myeloma. There is increased level of IgM (highest molecular weight).

Blood becomes viscous due to the heavy molecule and is called hyperviscosity syndrome.

It is usually associated with MYD 88 mutations and can be associated with lymphoplasmacytic lymphoma.

Q. A patient diagnosed with multiple myeloma develops features of restr ictive cardiomyopathy and macroglossia. Which of the following amyloid is responsible for this?

A. AL
B. AA
C. Abam
D. Acal

Answer : A. AL

AA is seen in chronic inflammatory states (rheumatoid arthritis, tuberculosis etc.)

Abam is seen in chronic renal failure or in patients on hemodialysis.

Acal is seen in medullary carcinoma of thyroid.

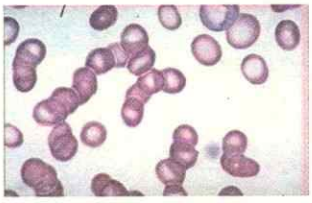
Active space

Q. A 70 year old male has a pathologic fracture of femur. The lesion appears as lytic on X ray film with a punched out appearance. The curetting from fracture is most likely to show which of the following?

A. Malignant cells forming osteoid bone.
B. Sheets of atypical plasma cells.
C. Thinned trabecular bone framents.
D. metastatic prostatic adenocarcinoma.

Answer : B.

Q. A pathologist observed the following finding in a peripheral blood smear. In patients with which of the following conditions is this seen?



1. Early HIV.
2. SLE.
3. Mycosis fungoides.
4. Hodgkin's lymphoma.
5. Multiple myeloma.

A. 1 & 4 only.
B. 2, 3 & 5.
C. 1, 2 & 5.
D. 3 and 4 only.

Answer : C. (the image shows rouleaux formation).

Sezary cell with cerebriform nuclei is seen in mycosis fungoides.

Q. A 60 year old patient's bone marrow aspirate is given below. What will be the cytogenetic change in this patient?

A. t (9 : 22)
B. Deletion of chr 13q
C. Trisomy 21
D. Myc translocation

Answer : B.

Russel body is seen in the image.

(9 :22) is seen in chronic myelocytic leukemia.

Trisomy 21 is seen in Down's syndrome.

Myc translocation is seen in Burkitt's lymphoma.

Active space

Clinical case : A 76 year old man presented for a routine health checkup. There were no physical abnormalities. Labs reveal anemia with a hemoglobin level of 8 gm%.
X ray showed lytic lesions and no fractures were seen.
Serum protein electrophoresis was done in this patient which showed increased IgG Kappa monoclonal protein.
Bone marrow biopsy showed 12% plasma cells. What is the diagnosis?
Answer : Multiple myeloma.

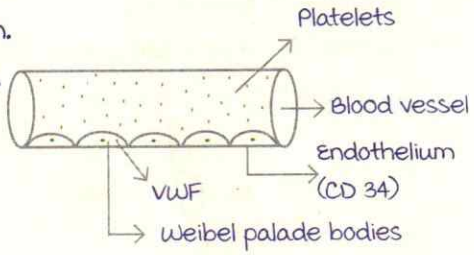
Clinical case : A 52 year old woman presented with complaints of generalized fatigue. Bone marrow showed plasma cells < 5%. Serum IgG was 1.8 g/dl. CRAB lesions were absent.
What is the diagnosis?
Answer : MGUS.

Active space

HAEMOSTASIS : PART 1

For haemostasis, 3 things are required :

1. Platelets.
2. Vascular endothelium.
3. Coagulation cascade.



Steps in coagulation cascade

00:05:17

Endothelial injury
↓
Vasoconstriction
↓
Formation of primary haemostatic plug
↓
Formation of secondary haemostatic plug
↓
Clot formation

Steps of primary haemostasis :

1. Platelet adhesion and activation :
   - Occurs by an interaction between gp Ib-IX and VWF.
   - Undergo shape change (normally, round, disc like develop spikes/protrusions : Looks like sea urchins).

Shape change
↓
Increase surface area

Phosphatidyl serine moves to the outer surface
↓
Creates negative charge
This is important for activation of coagulation cascade.

Active space

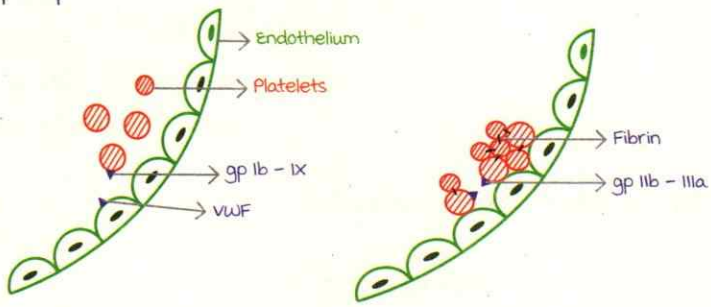
2. Platelet aggregation :

- Due to an interaction between gp IIb-IIIa.

3. Platelet secretion :

2 types of granules and their components :

- Alpha granules : P selectin, PDGF, PF 4, TGF β, fibrinogen, factor 5.
- Dense/delta granules : ADP, calcium, serotonin, epinephrine.



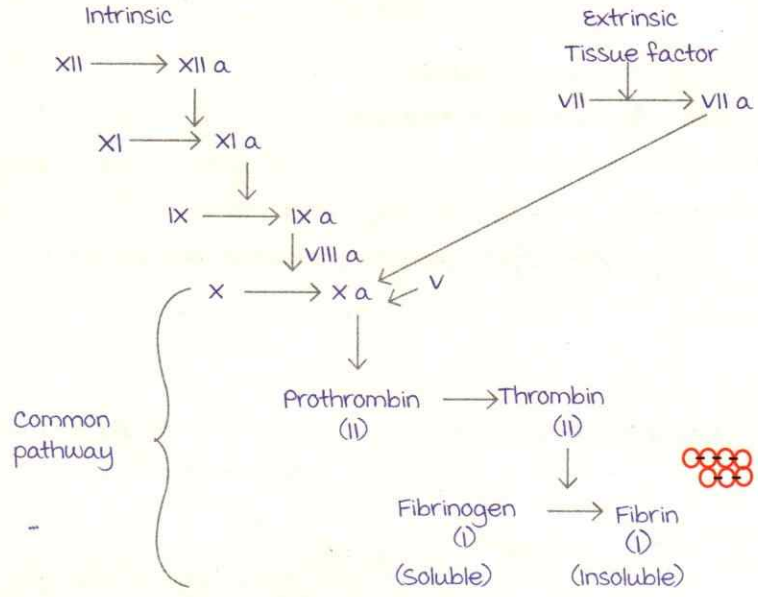
Steps of secondary haemostasis

00:11:15

Coagulation cascade :

Negative charge activates coagulation cascade.

2 pathways : Intrinsic and extrinsic.



Factor XIII : Clot stabilizing factor.

- Also known as Laki Lorand Factor.
- Deficiency of factor XIII : Umbilical stump bleeding (also seen in Glanzmann's thrombasthenia).

Active space

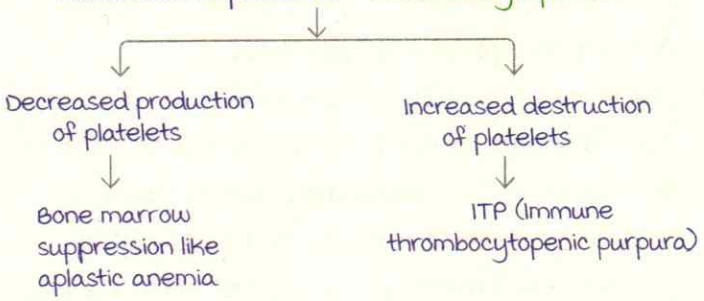
- For factor XIII deficiency : Urea clot solubility test.

Vitamin K dependent factors :

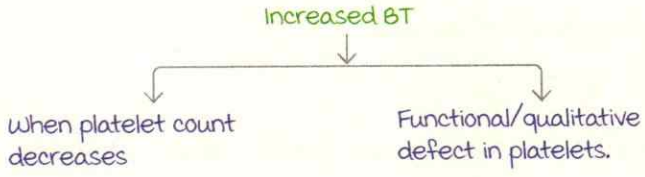
- Factor II, VII, IX, X.
- Protein C.
- Protein S.

Tests for haemostasis 00:28:00

1. Platelet count :
   - Normal platelet count : 1.5 – 4 lakhs/cumm.
   - Reduction in platelets : Thrombocytopenia.



2. Bleeding time (BT) :
   - Normal BT : 2 – 9 min.



3. Prothrombin time (PT) :
   - Normal PT : 11 – 15 sec.
   - It is the test for extrinsic and common pathways.
   - Factors in extrinsic : VII, factors in common pathway : X, V, prothrombin, fibrinogen.
   - Deficiency of these factors : PT will increase.

4. Activated Partial Thromboplastin Time (aPTT) :
   - Normal aPTT : 30–35 sec.
   - It is the test for intrinsic and common pathways.
   - Factors in intrinsic and common pathway : XII, XI, IX, VII, V, X, prothrombin, fibrinogen.
   - Deficiency of these factors : Increase in aPTT.

Active space

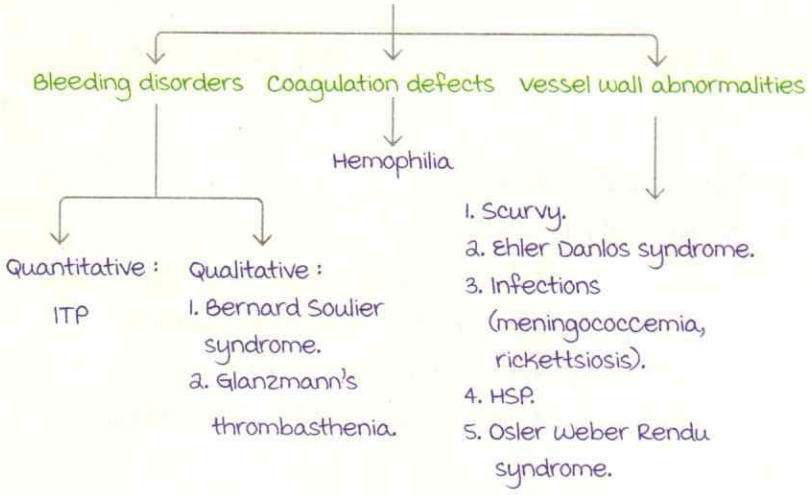
5. Thrombin time (TT) :
   - It is a test for fibrinogen.

6. Peripheral Smear (PS) :
   - Giant platelets : In Bernard Soulier syndrome, ITP.
   - Schistocytes/helmet cells/fragmented red cells : MAHA (microangiopathic Hemolytic Anemia : HUS, TTP, DIC).

Protocols for coagulation tests 00:38:49

- Platelet poor plasma to be taken.
- Store sample in room temperature.
- Testing should be done within 2 hrs of collection.
- Anticoagulant for coagulation studies : 3.2% trisodium citrate (Citrate is also used : ESR by Westergren 's method). Vacutainer with blue cap.
- Always use a plastic tube/syringe (glass tube : Negative charge activates coagulation cascade).

Disorders of haemostasis :



Osler Weber Rendu syndrome 00:47:53

- Also known as hereditary hemorrhagic telangiectasia.
- Autosomal dominant.

Active space

- Presence of mutation in TGF-β.

Bleeding disorders	Coagulation disorders
Usually autosomal.	X linked.
Male = Female.	Male >>> Female.
Clinically : Superficial bleeds (petechiae, purpura).	Clinically : Deep tissue bleeds (ecchymoses, hemarthrosis).
Lab tests : PC, BT } Can be abnormal PT, aPTT } Usually normal	Lab tests : PT, aPTTT } Can be abnormal BT, PC } Usually normal
Example : ITP.	Example : Hemophilia.

VWD and DIC : Has both bleeding and coagulation defects.

ITP (Immune Thrombocytopenic Purpura) 00:54:01

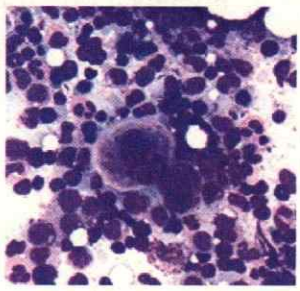
- Quantitative bleeding disorder.
- Type 2 hypersensitivity reaction.
- Pathogenesis : Caused by antibodies (Ig G) against platelet membrane glycoproteins (gpIb-IX & gpIIb-IIIa).

Acute ITP	Chronic ITP
< 6 months.	> 6 months.
Sudden onset.	Insidious onset.
Male = Female.	Female : Male is 3 : 1
Usually in children.	Usually in adolescents/ adults.
Preceding history of viral infection.	No such history.
Platelet count is markedly reduced.	Platelet count is moderately reduced.
Self limiting condition.	Treatment : Steroids, IV Ig, Immunosuppressive drugs.

- Clinically : Petechiae, purpura, prolonged bleeding after injury. No splenomegaly.

Active space

- Lab tests :
    1. Platelet count : ↓↓
    2. BT : ↑
    3. PT : Normal.
    4. aPTT : Normal.
    5. Peripheral smear : Giant platelets.
    6. Bone marrow aspiration : megakaryocytic hyperplasia (large, immature with non lobulated nuclei).
    7. Positive coombs test.



megakaryocytes (in bone marrow aspiration)

- Splenectomy can resolve thrombocytopenia.

Qualitative bleeding disorders 01:04:03

1. Bernard Soulier syndrome :

- Deficiency of gpIb – IX : Defect in platelet adhesion.
- Autosomal recessive.
- Lab tests :
    1. Platelet count : Normal.
    2. BT : ↑ (due to functional defect in platelets).
    3. PT : Normal.
    4. aPTT : Normal.
    5. Peripheral smear : Large platelets /giant platelets.
    6. Platelet aggregometry.

  Platelet aggregation with ristocetin is abnormal but it is normal with ADP, collagen, epinephrine.
  Ristocetin : Enhances the interaction between VWF and gp Ib-IX.

2. Glanzmann's thrombasthenia :

- Deficiency of gp IIb-IIIa : Defect of _____
- Autosomal recessive.
- Lab tests : Only BT ↑, rest of the tests are normal.

Active space

- Platelet aggregometry :
  Platelet aggregation with ristocetin is normal but it is abnormal with ADP, collagen.

The test that differentiates Bernard Soulier syndrome from Glanzmann's Thrombasthenia : Platelet aggregometry.

Heparin Induced Thrombocytopenia (HIT) 01:11:29

2 types of HIT : Type I and type II.

Type I	Type II
more common.	Less common.
Occurs rapidly after therapy.	Occurs 5 to 14 days after therapy.
Self resolving.	Can lead to arterial and venous thrombosis.
Occurs due to the platelet aggregation effect of heparin.	Antibodies against PF 4, that lead to platelet aggregation and thrombosis.

Active space

HAEMOSTASIS : PART 2

Coagulation defects

00:02:23

Haemophilia : Also called as Royal's disease.

Types :

1. Haemophilia A : Deficiency of factor VIII.
2. Haemophilia B : Deficiency of factor IX.
   Both Haemophilia A & Haemophilia B are x-linked recessive disorders, commonly seen in males than females.
3. Haemophilia C : Deficiency of factor XI.
   Autosomal recessive disorder, occurs equally in males and females.
4. Para haemophilia : Deficiency of factor V
5. Pseudo haemophilia : Also called as von Willebrand's disease.

Haemophilia A :

X linked recessive disorder , occurs in M >>> F.

Can occur in females due to unfavourable lyonization.

Deficiency of factor VIII.

Clinically presents with ecchymoses, hemarthrosis.

Lab tests :

- Platelet count : Normal.
- Bleeding time : Normal
- PT : Normal
- APTT : Increased
- Factor VIII assay is reduced.

Classification of haemophila A :

- Mild : If factor VIII level is 6-50% of normal.
- Moderate : If factor VIII level is 2-5% of normal.
- Severe : If factor VIII level is <1% of normal.

Active space

Treatment :

Mild : Desmopressin; Release of von Willebrand factor, stabilises factor VIII.

Severe : Recombinant factor VIII concentrate, Cryoprecipitate (rich in factor VIII.

Haemophilia B :

Also known as Christmas disease.

X-linked recessive disorder, more common in males.

Deficiency of factor IX (also called Christmas factor)

Factor IX is a component of intrinsic factor.

Similar to haemophilia A, patient's APTT is high, rest of the tests are normal.

Patient clinically presents with hemarthrosis, spontaneous haemorrhages or ecchymoses.

Treatment :

- Factor IX concentrate.
- Fresh frozen plasma (all coagulation factors present).

Cryoprecipitate can't be given as it doesnt contain factor IX.

Factor IX and VIII level test can be used to distinguish between the two diseases

Von Willebrand's disease 00:13:07

most common inherited bleeding disorder.

Also known as pseudo haemophilia.

Deficiency of von Willebrand factor.

Sources of von Willebrand factor (VWF) :

- Weibel Palade bodies.
- Endothelial cells.
- Megakaryocytes.
- Liver.

Functions of von Willebrand factor :

- Platelet adhesion to endothelium, by an interaction with gp Ib-IX.
  Hence VWF defeciency can causing bleeding defect.
- VWF is a carrier for factor VIII , stabilizes factor VIII,
  Factor VIII alone, t 1/2 is 2.4 hours.
  When in combination with VWF, t 1/2 is 12 hours.

Active space

Hence vWF deficiency can cause secondary deficiency of factor VIII ⟶ Coagulation defect.

Types of Von Willebrand's disease

- Quantitative defect
  - Type 1
    - m/c (70%)
    - Autosomal dominant
    - Mild Deficiency of vFW
  - Type 3
    - Least common
    - Autosomal recessive
    - Severe deficiency of vFW
- Qualitative defect
  - Type 2
    - Four types : a, b, c, d
    - Type a is most common and is autosomal dominant.

m/c mode of inheritance of vWF : Autosomal dominant inheritance.

Clinical presentation :

- Petechiae.
- Purpura.
- Menorrhagia.
- Ecchymoses.
- Hemarthroses.

Lab tests :

- Platelet count : Normal.
- Bleeding time : Increase.
- PT : Normal.
- APTT : Increased, due to secondary deficiency of factor VIII
- Factor VIII assay : Reduced.

Specialized tests :

- RIPA : Ristocetin induced platelet aggregation : Prolonged.
- ReCOF : Ristocetin cofactor assay : Reduced.

Active space

Treatment :

Mild : Desmopressin.

Severe : Factor VIII infusions.

Thrombotic microangiopathies 00:24:45

Also called us microangiopathic haemolytic anaemia (MAHA) :

HUS : Haemolytic uremic syndrome.

TTP : Thrombotic thrombocytopenic purpura.

DIC : Disseminated intravascular coagulation.

Features of Thrombotic microangiopathies :

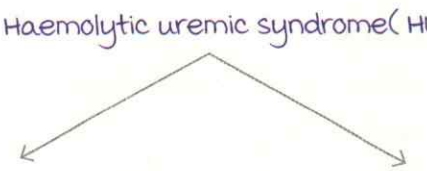
All of these are characterised by formation of thrombi in blood vessels, which consumes platelets.

- Reduced platelet count ⟶ Thrombocytopenia.
- Haemolytic anaemia ⟶ Increased reticulocyte count.
- Peripheral smear shows schistocytes/ helmet cell/ fragmented red cells.

Haemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) :

Common features (Pentad) :

1. Fever
2. Microangiopathic haemolytic anaemia
3. Thrombocytopenia
4. Renal abnormalities (more common in HUS)
5. Neurological abnormalities (more common in TTP)



Occurs due to E. coli O157 : H7, which produces shiga like toxin.

Caused due to problem in complement proteins like factor H, factor I or CD46

Active space

Patient presents :

- Renal abnormalities.
- Anaemia (microangiopathic haemolytic).
- Thrombocytopenia.

Lab tests :

- Platelet count : Reduced.
- Bleeding time : Increased.
- PT : Normal.
- APTT : Normal.
- Peripheral smear : Schistocytes.
- Reticulocyte count : Increased.
- RFT : Abnormal.
- LDH : Increased.

Thrombotic thrombocytopenic purpura (TTP) 00:32:58

Pathogenesis : Mutation in ADAM TS 13.
ADAM TS 13 is a matrix metalloproteinase which breaks down high molecular weight multimers of VWF.
In TTP, there is mutation of ADAM TS 13.
This leads to accumulation of high molecular weight multimers ⟶ Platelet activation ⟶ Thrombus formation.

Types :

- Congenital : Upshaw Shulman syndrome.
- Acquired.

Patient presents with :

- Renal abnormalities.
- Anaemia (microangiopathic haemolytic).
- Thrombocytopenia.
- Neurological abnormalities.

Active space

Disseminated Intravascular Coagulation (DIC) 00:36:46

Called as consumption coagulopathy (a lot of platelets and coagulation factors are consumed).
Pathogenesis :

Wide spread endothelial injury ⟶ Thrombosis ⟶ Platelets are consumed.
Activation of fibrinolytic pathway to break these clots.
DIC is an acquired coagulopathy.

Causes :

- Pregnancy/ obstetric complications (septic abortion, eclampsia).
- Severe toxaemia (meningococcaemia).
- Severe burns.
- Acute promyelocytic Leukaemia (AML-M3).
- Carcinoma of colon, rectum and pancreas.

Clinical features :
Features of the causative disease with major bleeding such as spontaneous haemmorhages, bleeding into cavities.

Lab tests :

- Platelet count : Reduced.
- Bleeding time : Increased.
- PT : Increased.
- APTT : Increased.
- Peripheral smear : Schistocytes.

Specialized tests :

- Fibrin degradation products (FDP) : Increased.
- D-Dimer : Increased, very specific for DIC.

Treatment : Treat the cause of DIC.

Active space

Haemostatic disorder	Platelet count	Bleeding time	PT	APTT	Extra investigations
Bernard-Soulier syndrome	Normal	Increased	Normal	Normal	Platelet aggregation with Ristocetin is abnormal. Giant platelets on PS.
Glanzmann's thrombasthenia	Normal	Increased	Normal	Normal	Platelet aggregation with ADP collagen is abnormal
Immune thrombocytopenic purpura	Reduced	Increased	Normal	Normal	PS : large platelets. bone marrow aspiration : megakaryo-cytic hyperplasia. Coomb's test : Positive.
Haemophilia A	Normal	Normal	Normal	Increased	Factor VIII assay
Haemophilia B	Normal	Normal	Normal	Increased	Factor IX assay
HUS	Reduced	Increased	Normal	Normal	RFT, Reticulocyte increased, LDH increased PS:Schistocytes
TTP	Reduced	Increased	Normal	Normal	RFT, Reticulocyte increased, LDH increased PS : Schistocytes
DIC	Reduced	Increased	Increased	Increased	PS : schistocytes D-dimer increased , FDP increased
von Willebrand's disease	Normal	Increased	Normal	Increased	RIPA abnormal, RECOF abnormal.
Vascular disorder	Normal	Normal	Normal	Normal	
Vitamin K deficiency	Normal	Normal	Increased	Increased	

Active space

Q. A 12 year old girl with dengue hemorrhagic fever is being monitored by measuring her platelet count. Spontaneous bleeding is likely to occur when the value falls below how much/ul?

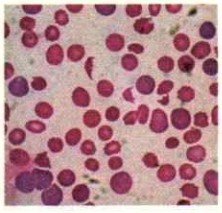
A. 3 0,000.
B. 50,000.
C. 10,000.
D. 20,000.

Q. A 72 year old man has recently had an aortic valve replacement now presents with pallor and fatigue. The red blood cell count is decreased and schistiocytes are reported on peripheral smear examination. In addition, his indirect bilirubin is significantly elevated. The cause of anemia is likely

A. Cold agglutinin disease.
B. Dietary deficiency.
C. Hereditary spherocytosis.
D. Mechanical disruption of red cells.
E. PNH.

Q. Five year old child presents with oliguria. There is history of bloody diarrhea 2 weeks ago. Coagulation tests are normal. peripheral smear is given. What is your diagnosis?

A. TTP.
B. ITP.
C. G6PD Deficiency.
D. HUS.



Q. A new born baby presented with profuse bleeding from the umbilical stump after birth. Rest of the examination and PT, aPTT are within normal limits. Most probable diagnosis is :

A. Factor X deficiency.
B. Von willibrands disease.
C. Bernard soulier syndrome.
D. Glanzmanns thrombasthenia.

Active space

Match the following :

1. Thrombotic thrombocyto purpura	A. E coli O157 : H7
2. Glanzmann thromboasthenia	B. ADAMTS 13 deficiency
3. Hemolytic uremic syndrome	C. Beta 2 glycoprotein
4. Antiphospholipid antibody syndrome	D. FDP's
5. DIC	E. Glycoprotein IIb IIIa

Answers :

1. B) 2. E) 3.A) 4. C) 5.D)

Q. A 32 year old woman presents with epistaxis, easy bruising and menorrhagia. There is no history of drug intake. Physical examination shows scattered petechiae and a normal sized spleen. Her lab investigations are given below. Antibodies against which of the following can lead to this condition?

Plc : 37,000/ul BT : 16 minutes PT : 13 sec

aPTT : 30 sec P/S : megathrombocytes

A. vWF.

B. ADAM TS13.

C. Glycoprotein IIb/IIIa.

D. Thromboxane A2.

Q. A child was brought to the emergency department with a big lesion on his forearm. As a surgery resident you decide to excise the lesion in the emergency operation theatre. Which of the following investigations will test the entire coagulation pathway?

A. Activated partial thromboplastin time.

B. Prothrombin time.

C. Thromboelastography.

D. Bleeding time.

Active space

BLOOD BANKING AND TRANSFUSION MEDICINE

Blood groups

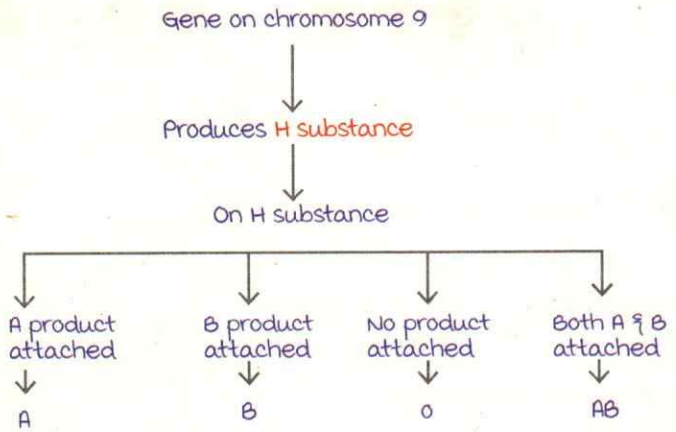
00:00:46

They are the glycoproteins present on the surface of RBCs.
39 blood group systems exist.
Major blood group system → ABO & Rh system (MC used).
Discovered by Landsteiner.
Minor blood group system → Kell, Duffy, Kidd, MNS.
ABO & Rh systems follow codominance, meaning both will be expressed concomitantly whenever they are present.

Difference between ABO & Rh system :

ABO system	Rh system
Gene on chromosome 9.	Gene on chromosome 1.
Expressed as A, B, AB, O.	Expressed as positive or negative.
Present in saliva, semen, sweat.	Not present.
IgM, naturally occurring.	IgG, do not occur naturally.

Formation of A, B, O blood groups :



Active space

Blood grouping analysis

00:07:33

Forward grouping	Reverse grouping
Test for presence of antigens on RBC surface.	Test for presence of antibodies in patient's plasma.

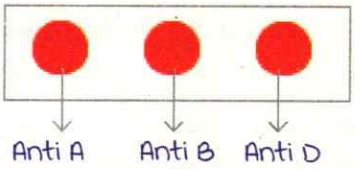
Procedure :

Take a glass slide.

Put 3 drops of blood.

Add anti A, anti B & anti D each to each drop.

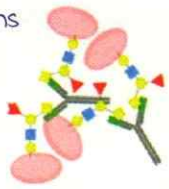
If antigen is present, agglutination occurs.

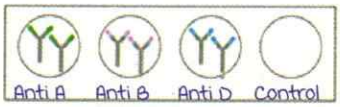


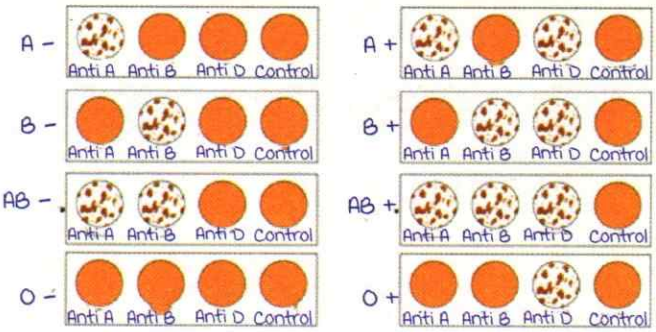
Look for agglutination.

Eldoncard blood type test : The spots have antibodies (agglutinates) stuck on them.

If the blood added has the matching antigens (agglutinogens), the mix will clump up (agglutinate).







If clumps are seen in the control, the test is invalid.

O +ve → MC blood group in India.

Bombay blood group/Phenotype :

Person lacks H substance.

No antigens to H, A, B.

Active space

Antibodies with A, B & H present.

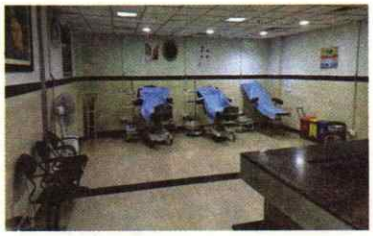
This blood can be transfused to anyone.

But people with Bombay blood group cannot be transfused with A, B or O blood.

Can be transfused only with Bombay blood.

Blood Banking :

October 1st → Blood donation day.



Blood donation hall

Blood donation hall :

Blood Bag :

Volume of one blood bag : 350 mL.

Triple blood bag

Triple bag : To make components like packed RBCs, platelets.

Volume : 450 mL.

Anticoagulants in blood bag

00:19:53

Anti coagulants	Full form	Shelf life
ACD.	Acid citrate dextrose.	21 days.
CPD.	Citrate phosphate dextrose.	21 days.
CPD A (mc)	Citrate phosphate dextrose + adenine.	35 days.
SAGM.	sodium adenine glucose mannitol. (Longest shelf life)	----------

Shelf life : The duration for which the stored blood products remain good and transfusable. If exceeds shelf life, the blood product is expired and shouldn't be transfused. It depends on the anti coagulant present.

Active space

Functions of the anti coagulants :

Component	Function
Citrate	Anti coagulant by chelating calcium.
Phosphate	Acts as buffer & helps in maintaining pH.
Dextrose	Provides nutrition.
Adenine	Provides substrate for ATP synthesis. (Increased shelf life).

Features of a blood bag :
Anticoagulant is written on top.
CPDA → 350 mL.
Date of Collection (DOC) :
19/02/2021 (e.g.,)
Date of Expiry (DOE) :
DOC + 35 days.

After collecting blood from the donor, it must be screened for 5 infections before it can be transfused.

5 diseases for which all donated blood is screened :
HIV, Hepatitis B, Hepatitis C, Malaria & Syphilis.
Hepatitis C → M/C transfusion transmitted infection.
Malaria can be transmitted by all blood products.

Components of blood

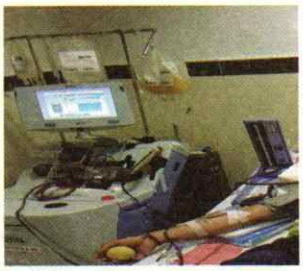
00:29:44

From whole blood, components must be separated within 6 hours of blood collection.

Active space

Blood product	Volume	Temperature	Shelf life	Uses
Packed RBCs.	350 ml.	2 – 6 °C.	CPD A : 35 days. SAGM : 42 days.	Severe Anemia. 1 unit = 1g % Hb or 3% hematocrit.
Fresh frozen plasma/ FFP : Deficient in Factor V & VIII.	200 ml.	≤ – 30°C.	1 year	multiple coagulation factor deficiencies. DIC. Chronic liver disease. Hemophilia B.
Cryoprecipitate : Centrifuged FFP. Rich in factor VIII, XIII, von Willebrand factor (vWF) & fibrinogen.	10 to 20 ml.	≤ – 30°C.	1 year	Factor XIII deficiency. Hemophilia A. Hypo fibrinogenemia. Von Willebrand's disease
Platelet rich plasma (PRP) :				Platelet defects. Thrombo cytopenia.
2 types : Random donor platelets (RDP).	50 to 70ml.	Room temp. / 20 – 24°C with agitation to prevent clumps.	5 days.	1 unit RDP = 10,000 cells/ cu.mm.
Single donor platelet (SDP).	200 to 300 ml.	20 – 24°C with agitation.	5 days.	1 unit SDP = 30 – 50,000 cells/cu.mm.

Random Donor Platelets (RDP) :
Blood taken from different individuals, centrifuged & PRP produced and transfused.
Single Donor Platelets (SDP) :
Platelets taken from a single person by apheresis. much more effective & expensive.


Apheresis machine

Active space

Advantage of RDP over SDP :
RDP can be used to make other blood components as well.

Life span of transfused RBCs → 50 – 60 days.
Product which is most susceptible to bacterial contamination : Platelets.

Transfusion protocols :

- Do not transfuse blood immediately after retrieving it from its storage at cold temperature.
- Patient will develop hypothermia.
- Warm or thaw it before transfusing.
- Transfusion should commence within 30 minutes of taking the product out of fridge.
- Transfusion should be finished within 4 hours.
- Size of micropore filter → 170 microns.
- Size of needle used → 18 – 19 G.

Blood transfusion reaction 00:48:56

Two types :

Immediate	Delayed
• Allergies. • Febrile Non Hemolytic Transfusion Reaction (FNHTR) : m/c. Prevent by using leuko depleted blood products. • Febrile hemolytic blood transfusion reaction. • TRALI → Transfusion related acute lung injury.	• Graft Versus Host Disease (GVHD). • Delayed hemolytic transfusion reaction. • Post transfusion purpura. • Infections.

Massive Blood Transfusion (MBT) :

Active space

Definition : Transfusion/ replacement of patient's whole blood volume within 24 hours.
SL (approximately 15 – 20 Units).

Ratio of RBC : FFP : Platelets → 1 : 1 : 1.

Complications :

Mnemonic → CATCH.

Coagulopathies : Disseminated intravascular coagulation (DIC).

Alkalosis : metabolic alkalosis due to formation of HCO^{3-}.

T : Hypothermia.

C : Citrate toxicity. Manifests as tingling, numbness.

H : Hyperkalemia (due to lysis of RBCs) leading to arrhythmia; Hypocalcemia.

m/C cause of death following MBT : DIC due to coagulopathy.

TRALI

00:57:05

Transfusion Related Acute Lung Injury (TRALI).

Definition : Development of fever, dyspnea, respiratory symptoms within 6 hours of blood transfusion.

m/C cause of death due to blood transfusions.

Usually occurs due to antibodies against HLA 2 or anti neutrophilic antibodies.

More common with plasma products like FFP.

Differential diagnosis :

ARDS/TRALI : In both conditions, Chest X ray shows bilateral pulmonary infiltrates/White out appearance.

TACO/TRALI : Blood pressure is high in TACO.
(TACO : Transfusion Associated Circulatory Overload).

MCQs :

Q. All of the following are true about TRALI except :

A. Most commonly seen after sepsis and cardiac surgeries.
B. Develops within 12 hrs of blood transfusion.
C. Usually due to plasma product transfusion.
D. It's a cause of non cardiogenic pulmonary edema.

Active space

Q. The given product is used in which indication?

A. Factor V deficiency.
B. DIC.
C. VWD.
D. Hemophilia A.

Q. A CKD patient had to undergo dialysis and his Hb was 5.2 gm/dl. Two blood transfusions were to be given. The first bag was completed in 2 hours. The second was started and in the midway, he developed shortness of breath and hypertension. BP was 180/120mmHg and PR was 110/min. what is the cause ?

A. Allergic.
B. Transfusion related circulatory overload.
C. TRALI.
D. Febrile non haemolytic transfusion reaction.

Q. A patient with thalassemia developed pallor and dizziness 1 week following blood transfusion. His lab reports are LDH increased and haptoglobin decreased. Which of the following is seen in this condition?

A. Direct coombs test negative, IgG mediated.
B. Direct coombs test positive, IgG mediated.
C. Direct coombs test negative, IgM mediated.
D. Direct coombs test positive, IgM mediated.

Active space

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PRACTICAL HEMATOLOGY

Vacutainers

00:00:23

Colour coding of vacutainers :

Vacutainer	Cap colour	Content (anti-coagulant)	Use
	Purple/ lavender	EDTA (Ethylenediamine-tetraacetic acid)	CBC, peripheral smear, ESR determination by Wintrobe's method
	Grey	Sodium fluoride	Blood sugar estimation
	Red	No additive	For serum studies like enzymes, proteins, hormones
	Yellow	Gel which enhances serum separation	For serum studies like enzymes, proteins, hormones
	Blue	Citrate	Coagulation testing & ESR determination by Westergren's method
	Green	Heparin	ABG, osmotic fragility test, immunophenotyping.

Active space

Instruments

00:06:53

Bone marrow aspiration needle :

Salah bone marrow aspiration needle

Jamshidi's needle

Most common site for bone marrow aspiration in adults : Iliac crest, anterior superior iliac spine or, posterior superior iliac spine.

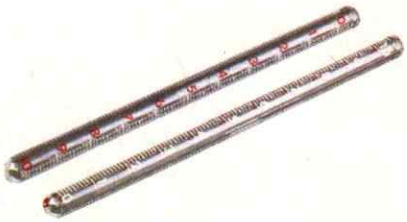
Most common site for bone marrow aspiration in children : Shin of tibia.

Conditions where dry tap is seen :

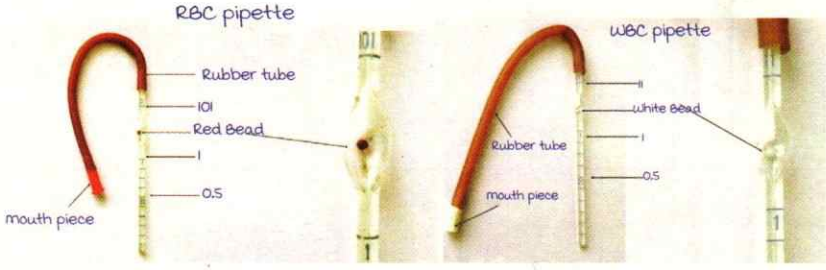
- Aplastic anemia,
- Hairy cell leukemia,
- myelofibrosis.

Westergren's tube : Used for ESR determination.
Open from both ends. 30cm in length.

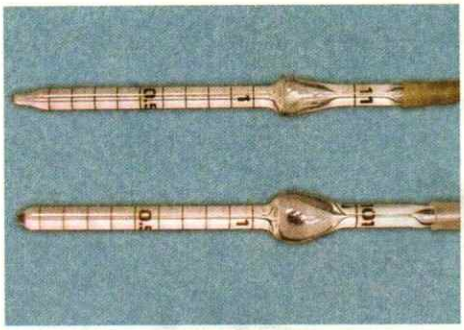
Wintrobe's tube : Used for ESR determination.
Closed from one end.

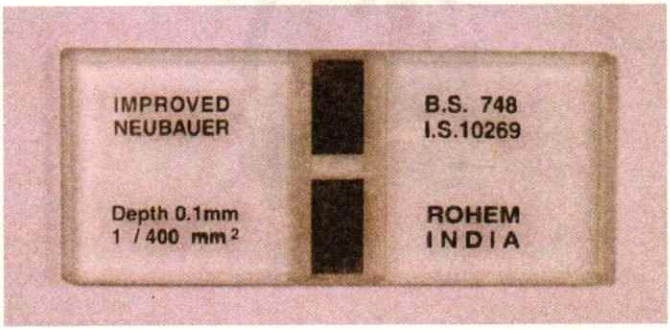


RBC & WBC pipette :

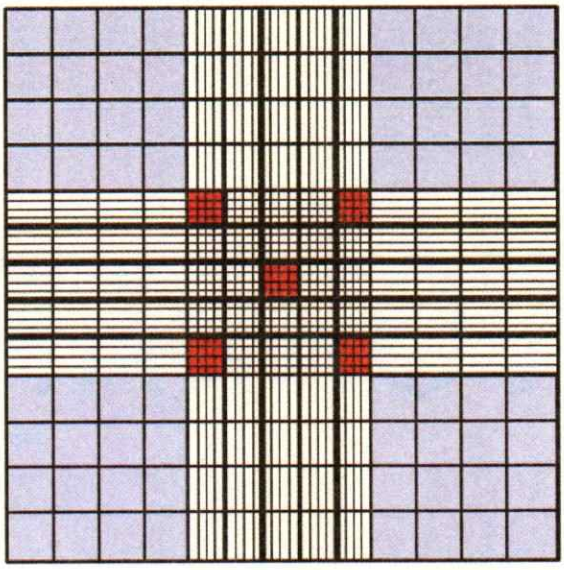


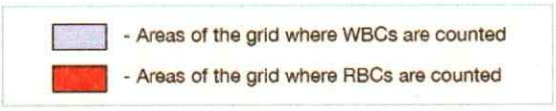
Active space





Improved Neubauer's chamber :





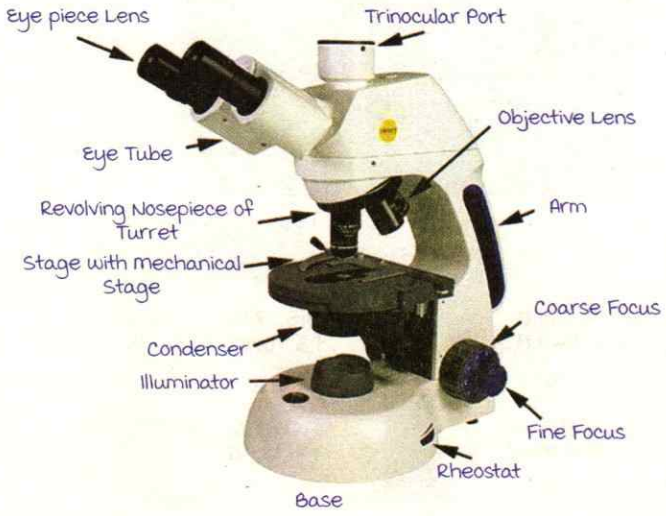
Various diluting fluids :

- WBC diluting fluid : Turk's fluid.
- RBC diluting fluid : Hayem's and Dacie's fluid.
- Platelet count fluid : Rees and Ecker diluting fluid.

Active space

Microscope

00:15:46



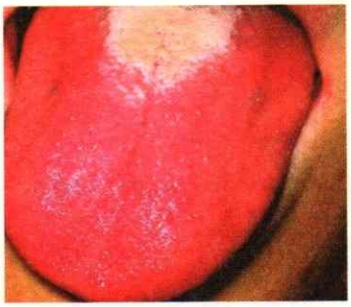
Active space

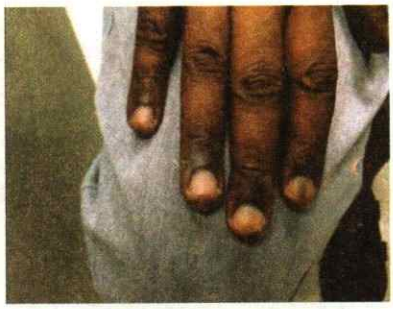
HEMATOLOGY CLINICAL CASE DISCUSSIONS

Case 1

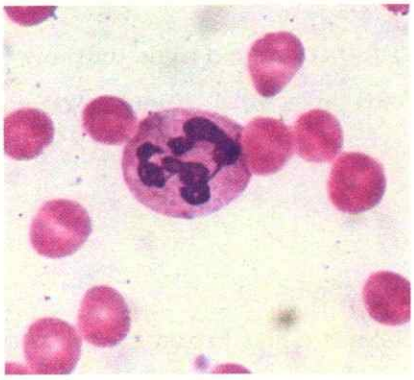
00:00:52

Q. 30 year old, alcoholic, tiredness, weakness. On examination

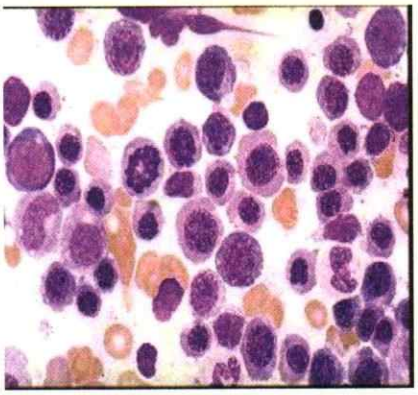




Peripheral smear examinaton :



Bone marrow examination :



Tongue → Beefy consistency.

Hands → Pigmentation present on knuckles.

Peripheral smear shows Hypersegmented neutrophils.

Bone marrow examination shows megaloblasts with sieve like chromatin.

Blood count showed →

Decreased Hb, TLC, PLC levels.

Active space

MCV → 125 fL with normal MCH & MCHC levels.

Indicates macrocytic anemia.

D/D for macrocytic anemia :

- Liver disease.
- Hyperthyroidism.
- Megaloblastic anemia due to vitamin B12 deficiency.
- Cytotoxic drugs.

Diagnosis → Megaloblastic anemia due to deficiency of vitamin B12.

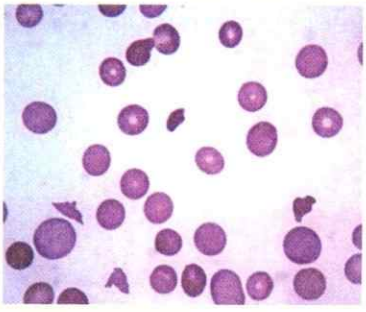
Treatment → Vitamin B 12 therapy.

Monitoring the response to therapy → Reticulocyte count.

Case 2

00:05:06

Q. A 73 year old male with aortic valve replacement presents with pallor and fatigue. RBC count is decreased while P/S is shown. Cause of anemia?



P/S shows :

Helmet cells/ Fragmented red cells/ schistiocytes.

Diagnosis → Micro angiopathic hemolytic anemia.

D/ D :

- Hemolytic uremic syndrome.
- Thrombotic thrombocytopenic purpura.
- Disseminated intravascular coagulation.

Schistiocytes is also seen in prosthetic cardiac valves.

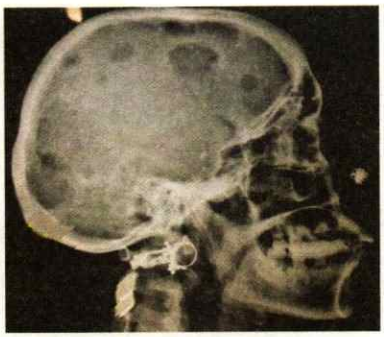
Anemia occurs because of intravascular hemolysis & mechanical destruction of RBC'S.

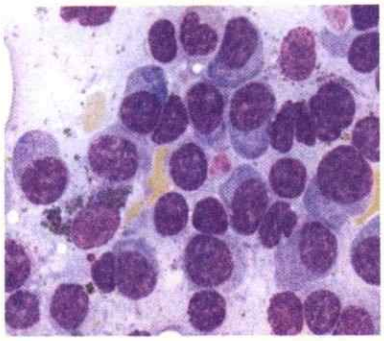
Case 3

00:07:30

Q. 70 year old man, severe bone pain, respiratory infections. X ray skull and bone marrow aspirate was done.

Active space





X ray shows lytic lesions.

Bone marrow shows plasma cells.

Diagnosis → multiple myeloma.

Investigations :

- Peripheral smear shows rouleaux formation.
- Elevated ESR.
- Serum calcium levels raised.
- serum albumin globulin ratio reversed.
- Serum/ Urine electrophoresis : Increased IgG.

Treatment → Chemotherapy.

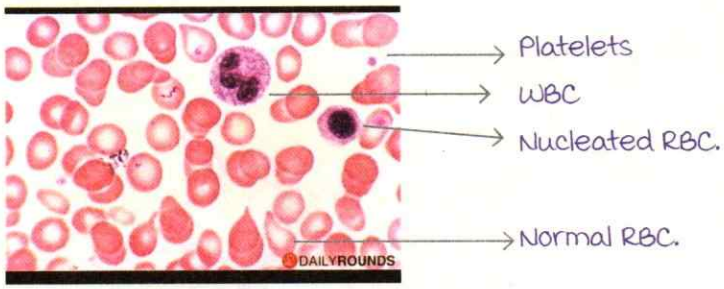
Case 4

00:10:25

Q. A 55 year old male on chemotherapy presents with pallor and dyspnea. Also complaints of frequent infections and petechiea.

CBC shows pancytopenia.

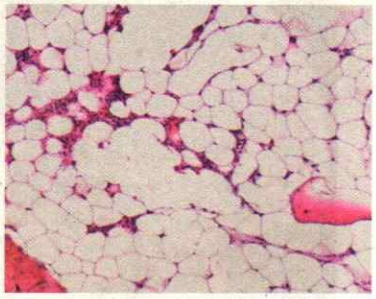
Peripheral smear shows :



Bone marrow aspirate showed dry tap.

Active space

Bone marrow biopsy :
Shows increased fat.



Chemotherapy drugs lead to pancytopenia & aplastic anemia.

Diagnosis → Aplastic Anemia.

Splenomegaly is never seen in aplastic anemia.

History of :

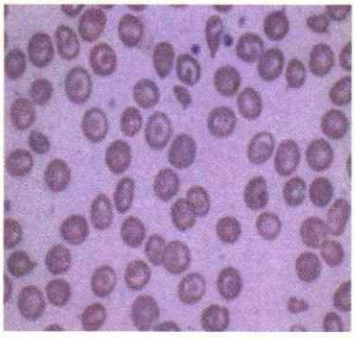
- Treatment with chemotherapeutic drugs.
- Parvovirus B19 infection.
- On radiation.
- Viral infections like hepatitis B, HIV, Epstein Barr virus & so on.

Inherited cause of aplastic anemia → _____

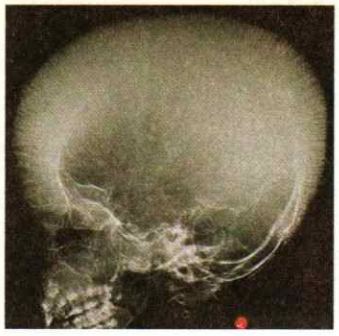
Case 5

00:13:19

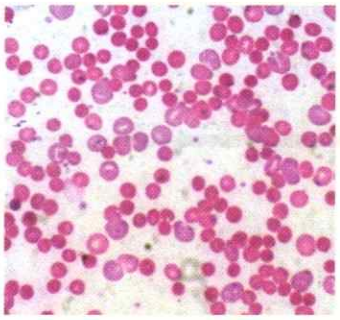
Hemoglobin 5%



P/S → Target cells



X ray → Crew cut/Hair on end appearance.



P/S → Polychromatic

Active space

Hb electrophoresis → Increased HbF.

Confirmation done by HPLC (HbF : 23%)

Blood parameters :

MCV, MCH & MCHC decreased.

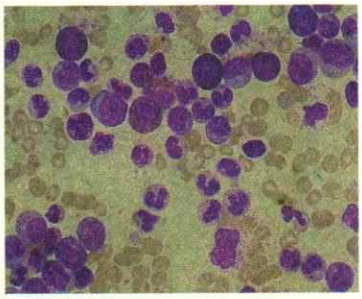
RDW normal.

Diagnosis → Beta thalssemia major.

Case 6

00:16:37

Q. 45 year old woman, massive splenomegaly. TLC was 60,000/μL. Next investigation ?



Patients with splenomegaly usually presents with dragging sensation in abdomen or abdominal discomfort.

D/D for massive splenomegaly :

- Malaria (India).
- Kala azar (Bihar).
- Myeloproliferative disorders (CML, Polycythemia vera, myelofibrosis).
- Hairy cell leukemia.
- Storage disorders (Gaucher's disease).

High total leucocyte count.

Peripheral smear shows all stages of myeloid maturation.

Bone marrow aspirate → very high myeloid to erythroid cell ratio.

Fluorescent insitu hybridization (FISH) :

t (9 : 22) translocation (philadelphia chromosome)

which is present in 95 % cases of CML.

Diagnosis → Chronic myeloid leukemia.

Treatment → Imatidine mesylate.

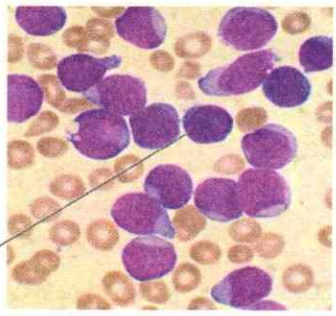
Active space

Case 7

00:20:20

Q. 3 year old boy with fever and epistaxis. Mutiple petechiae are seen with palpable splenomegaly and lymphadenopathy.

- Hb → 8g %.
- Plc → 80,000/cu. mm.



Peripheral smear shows blast like cells with coarse chromatin & no nucleoli.

Lymphoblasts.

PAS stain showed block positivity.

Diagnosis → Acute Lymphoblastic Leukemia (ALL).

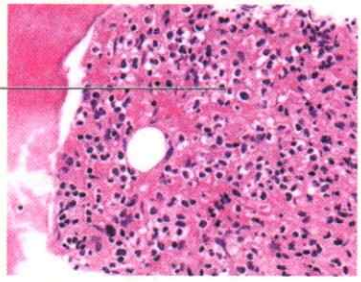
Flowcytometric analysis gave a diagnosis of B ALL.

Case 8

00:23:39

Q. 55 year old male, abdominal fullness. On examination : massive splenomegaly. Bone marrow Aspirate : Unsuccessful. Bone marrow biopsy shown below. Cells were positive for TRAP.

Fried egg appearance



Splenomegaly.

BMA → Dry tap.

Diagnosis → Hairy cell leukemia.

Immuno histo chemical (IHC) markers positive :

(CD 25, IIc, 103, Annexin AI).

Best marker → Annexin A 1

Case 9

00:25:35

Q. A 45year old male with splenomegaly, gum bleeding.

Hb → 7 g%.

TLC → 15,000/cu. mm.

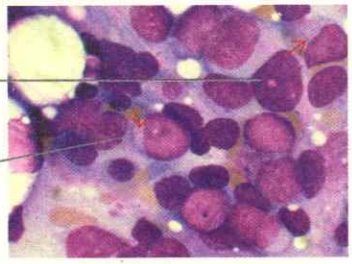
Platelet count → 60,000/cu. mm.

Active space

Peripheral smear shows :

Large cells with granules in cytoplasm.

Auer rods.



BMA → Showed myeloblasts.

Stains like myeloperoxidase (MPO), Sudan black positive.

Flow cytometric markers (CD 13, 33) → Positive.

Diagnosis → Acute myeloblastic leukemia (AML).

Case 10

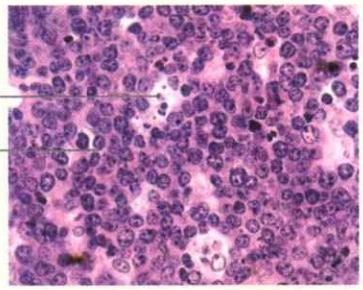
00:28:25

Q. 10 year old boy, abdominal mass. CT showed retroperitoneal lymph nodes. Biopsy was done.

Starry sky appearance.

Histiocytes (stars)

Sky



Diagnosis → Burkitt's lymphoma.

A young child, African origin with jaw swelling or an abdominal swelling usually indicate Burkitts lymphoma.

Translocation → t (8 : 14) OR amplification of c-myc gene.

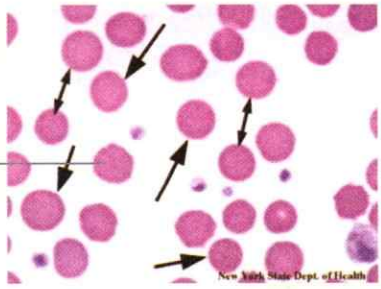
Case 11

00:30:19

Q. 14 year old boy, fatigue, jaundice, splenomegaly. Coombs test is negative.

Peripheral smear shows :

Spherocytes



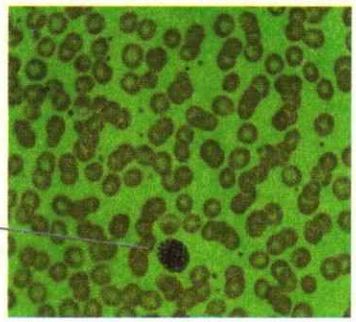
Active space

Osmotic fragility test → Curve shifted to right.
Flow cytometric analysis confirmed diagnosis.
Diagnosis → Hereditary spherocytosis.

Case 12

00:32:06

Q. A 40 year old male with below BMA.

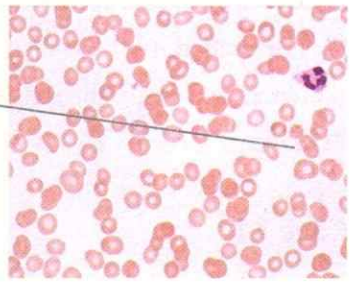


Diagnosis → Multiple myeloma.

Case 13

00:32:53

Q. A 10 year old girl, pallor and weakness. Congenital anomalies seen. Family history of cancer. Short stature, absent radius, microcephaly, epicanthal folds.



Bone marrow aspirate → Dry tap.
Bone marrow biopsy → Increased fat & decreased cells.

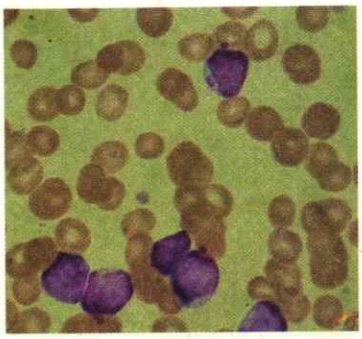
Diagnosis → Fanconi's anemia.
(Congenital anomalies + Pancytopenia).

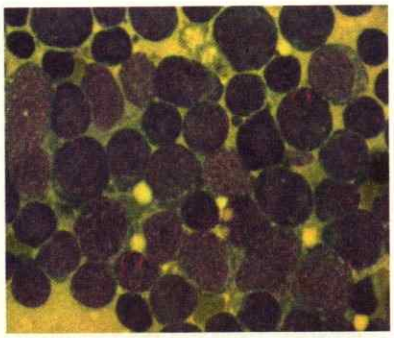
Case 14

00:34:29

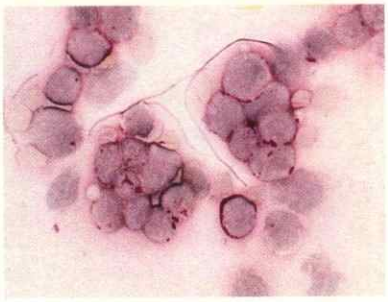
Q. An 8 year old child, fever and fatigue. On examination, generalized lymphadenopathy.

Active space





PAS Stain



Peripheral smear shows lymphoblasts.

PAS stain → Block positivity.

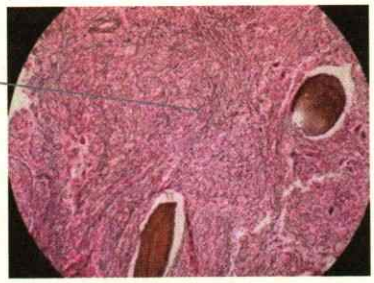
Diagnosis → Acute Lymphoblastic Leukemia (ALL).

Case 15

00:35:42

Q. A 55 year old male, massive splenomegaly. Bone marrow aspirate shows a dry tap. Bone marrow biopsy is given below.

Increased reticulin fibrosis.



Diagnosis → myelofibrosis.

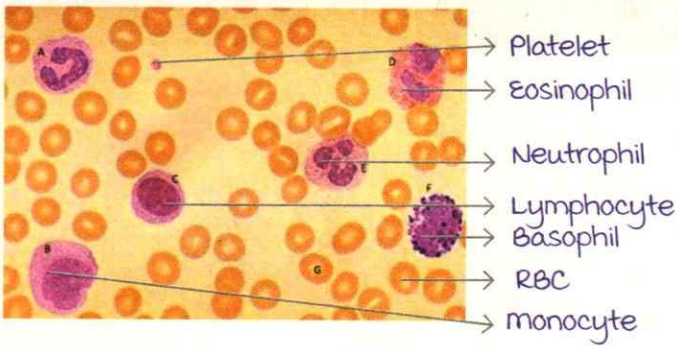
Active space

HEMATOLOGY IMAGES

Normal studies

00:00:53

Normal peripheral smear :



RBCs : Round cells with central 1/3rd pallor.

Platelets : Appears as pinkish spots.

WBCs 5 types :

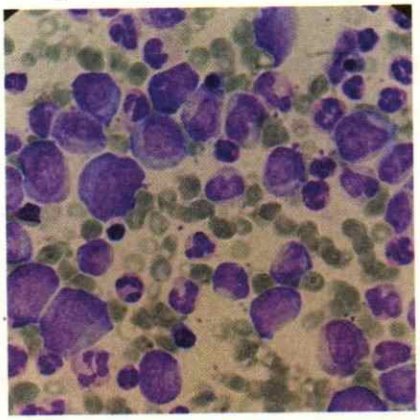
- Neutrophils : Nucleus has 3 to 5 lobes.
  Small sparse granules in the cytoplasm (granulated cell).
- Basophils : Nucleus is obscured by dark blue granules (< 1% in quantity).
  Basophilia is an indication of Chronic Myeloid Leukemia/ CML or any myeloproliferative disease.
- Lymphocyte : Small round cells with a small nucleus.
  It is an agranulocyte.
- Monocyte : Largest cell in the blood.
  It has a horseshoe/ kidney shaped nucleus.
  It is an agranulocyte.
- Eosinophils : Brick red granules in the cytoplasm.
  Bilobed nucleus.

Normal bone marrow aspirate :

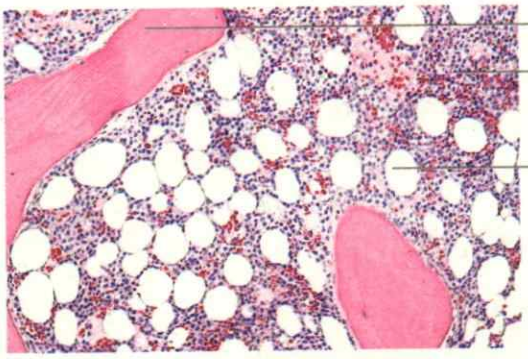
Has all cells of erythroid series, myeloid series and megakaryocytic series in various stages of maturation.

Active space

Normal myeloid : Erythroid ratio / M:E = 3 : 1 to 15 : 1.



Normal bone marrow biopsy :



% cellularity is used to determine if the patient is normocellular, hypocellular or hypercellular.

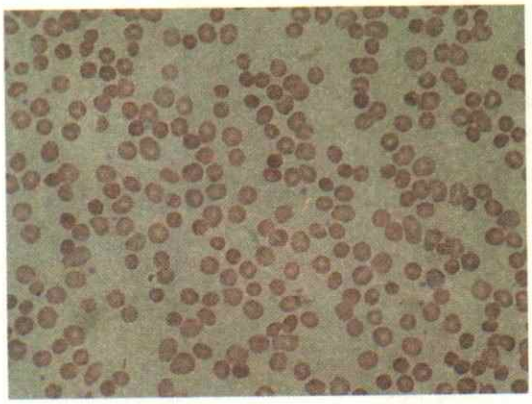
% cellularity of bone marrow = 100 − Age of the patient.

E.g : At age 40, % cellularity = 100 − 40 = 60% cells, hence 40 % fat.

Abnormal cells

00:06:02

Spherocytes :



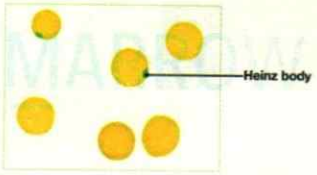
Spherical cells without central pallor.

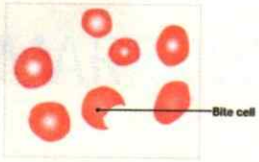
Active space

Seen in :

- Hereditary spherocytosis.
- Autoimmune hemolytic anemia (most common cause).
- Blood transfusion reaction.
- Burns.

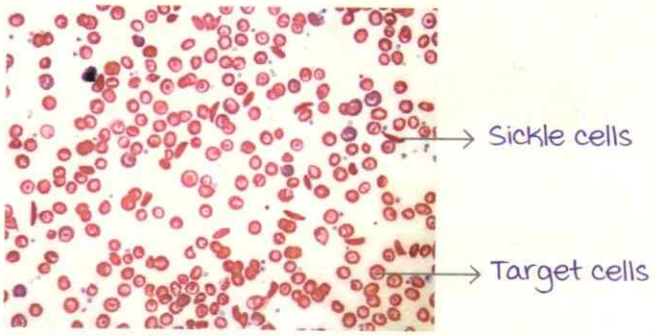
G6PD deficiency :



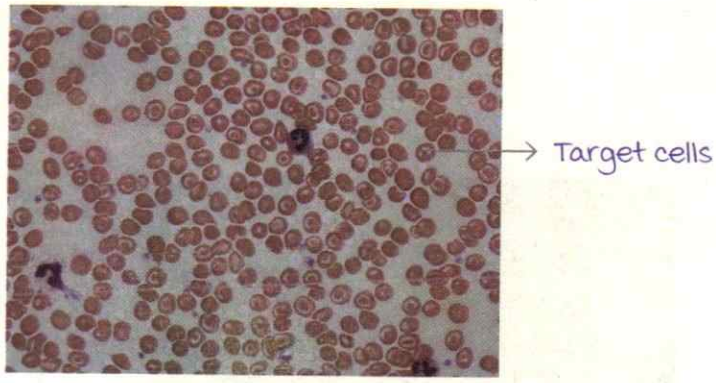


Heinz bodies and bite cells are seen.

Sickle cell anemia :



Contains sickle cells and target cells.



Target cells are seen in thalassemia and liver disease.

Basophilic stippling: RBCs with bluish dots.
Seen in lead poisoning.

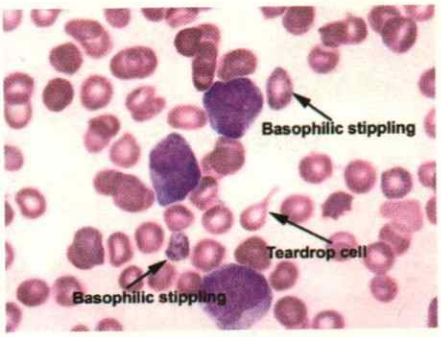
Active space

Tear drop cell is also called dacrocyte.

Seen in :

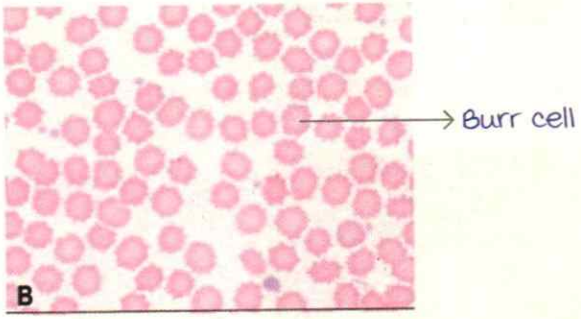
myelodysplastic syndrome.

myelofibrosis.



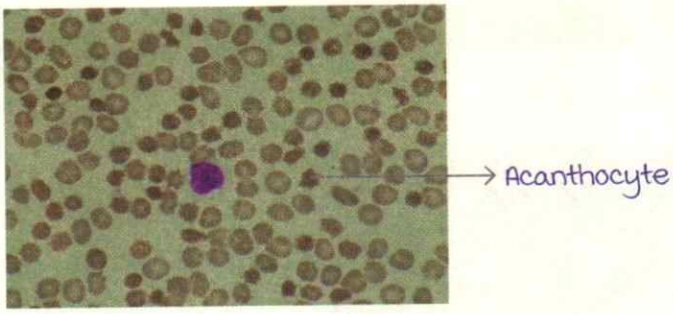
Burr cells : RBCs with blunt projections.

Seen in : Uremia.



Acanthocytes: RBCs with sharp projections.

Seen in : Abetalipoproteinemia.

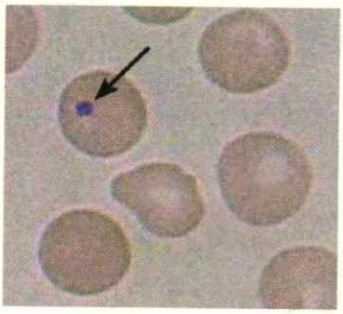


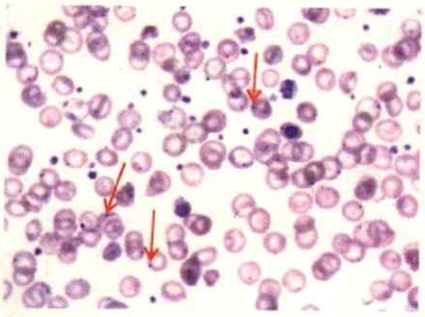
Howell Jolly bodies : Remnant of the nucleus.

Seen in :

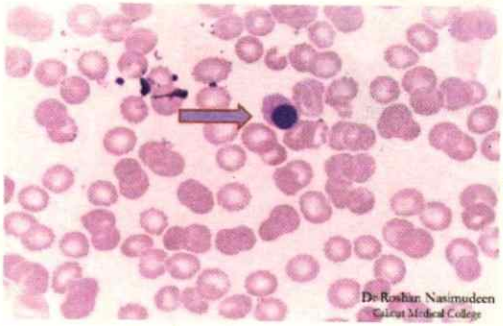
- Asplenia.
- Megaloblastic anaemia due to B12 deficiency.
- Thalassemia.

Active space



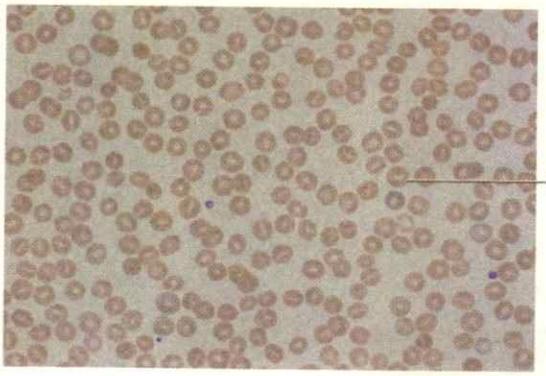


Howell Jolly Body



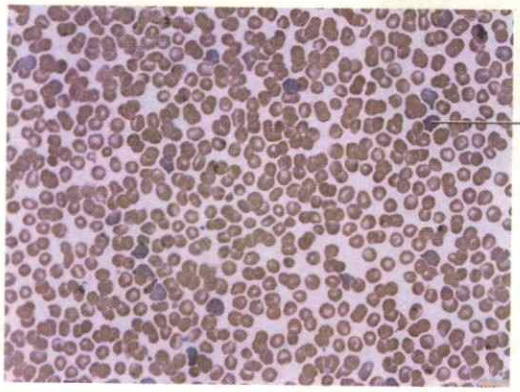
Nucleated RBCs (NRBCs). Can be seen in any hemolytic anemias.

Stomatocytes: RBCs with slit- like pallor.



Stomatocyte

Polychromasia :



Polychromasia

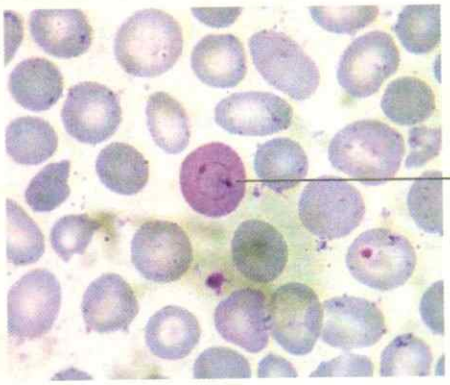
RBCs with both pinkish and bluish hue.

Seen in hemolytic anaemia due to destruction of red blood

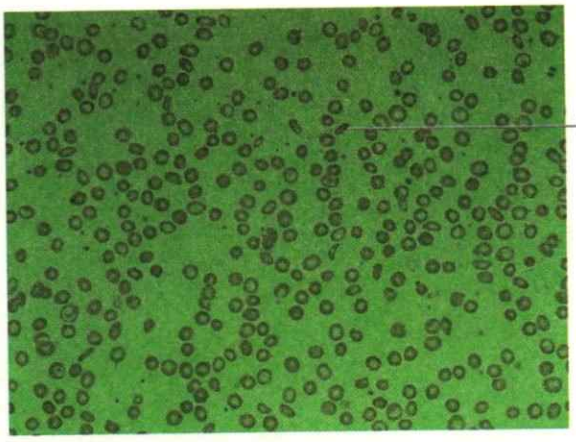
Active space

cells.

Cabot ring :
Ring-like structure (figure of 8) produced by microtubules.
Seen in megaloblastic anaemia due to deficiency of Vitamin B12.

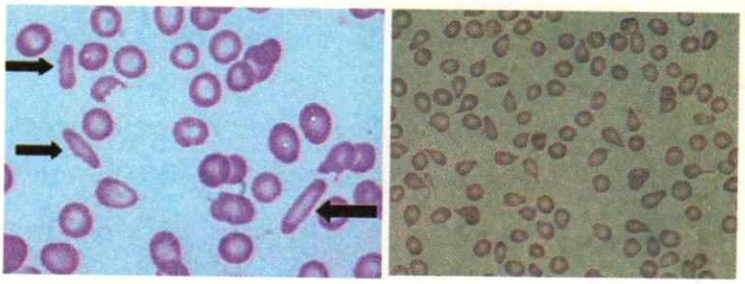


Microcytic Hypochromic RBCs : Small RBCs with more than 1/3rd pallor.
MCV is low
Seen in : Mnemonic : SITA
Sideroblastic anemia.
Iron deficiency anemia.
Thalassemia.
Anemia of chronic disease.

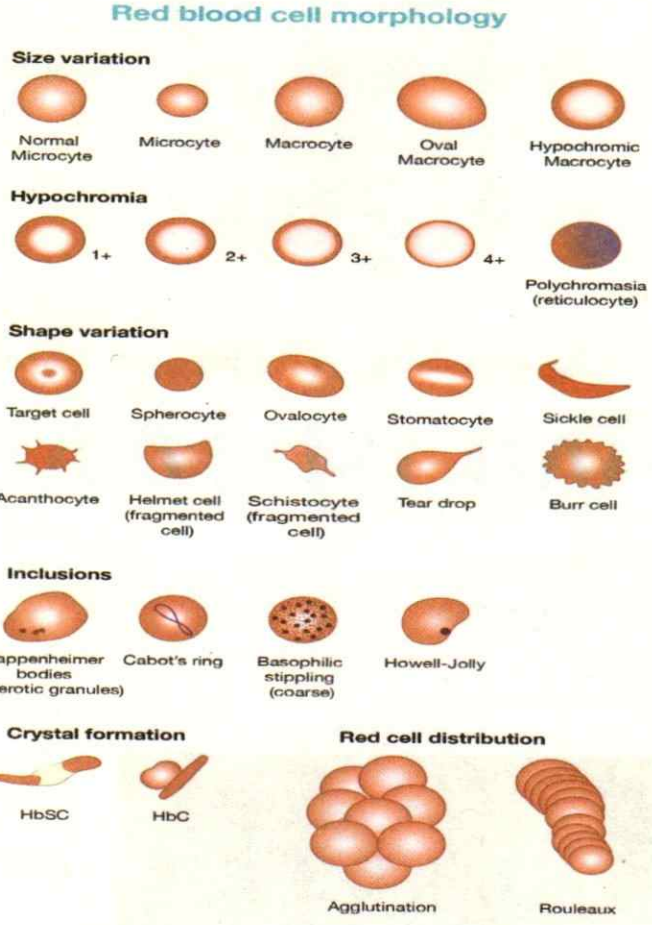


Peripheral blood smear also shows the presence of pencil cells seen in iron deficiency anemia.

Active space



Pencil cells Tear drop cells



Rouleaux formation :

RBCs arranged like a stack of coins.

Seen in multiple myeloma.

Reticulocyte :

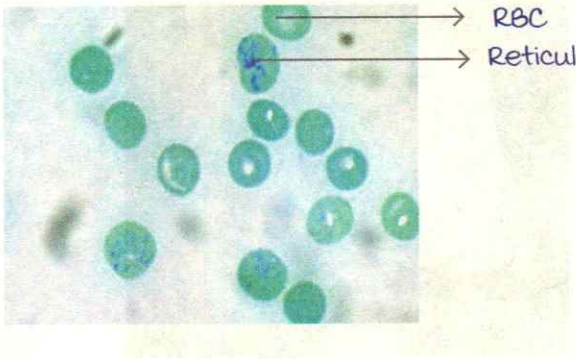
Has a bluish meshwork formed by RNA/ ribosomes.

Normal reticulocyte count : 0.5 to 1.5 %.

Cause of increased counts / Reticulocytosis : Hemolytic anemia.

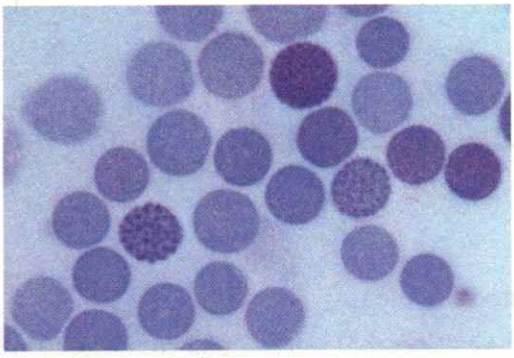
Active space

Stain used is vital stain / supra vital stain : Brilliant cresyl blue / New methyl blue.

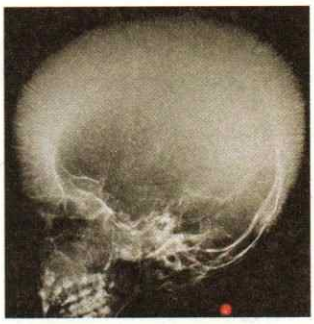


Blue stains :
Brilliant cresyl blue / New methyl blue : for reticulocytes.
Prussian blue stain for hemosiderin.

Hemoglobin HbH inclusions / Golf ball inclusions : RBCs with bluish inclusions.
Seen in HbH disease : 3α gene deletion.



Crew cut / Hair on end appearance :
X-ray skull showing a spiky look.
Due to extramedullary hematopoiesis in the skull bone.
Seen in Thalassemia > Sickle cell anaemia.

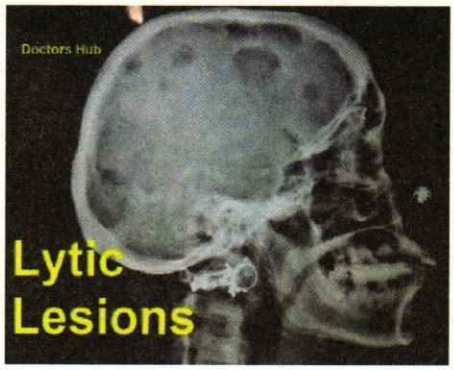


Lytic lesions :
Seen in multiple myeloma.
Clinical features of multiple myeloma includes :
Patient presents with hypercalcemia.
Increased number of plasma cells.

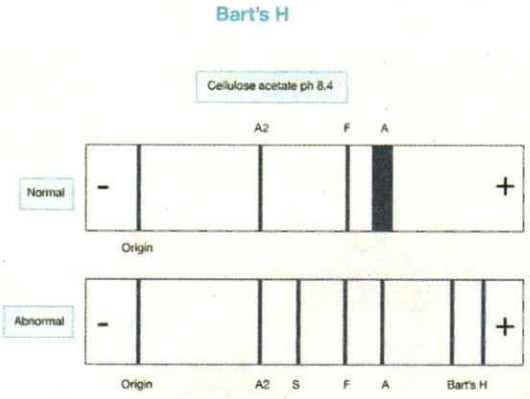
Active space

Pathological fractures.

Bone pain.



Hemoglobin electrophoresis :



Done for hemoglobinopathies like :

- Sickle cell anaemia : Abnormal sickle cell haemoglobin will be raised.
- Thalassemia major : Increased levels of fetal haemoglobin.
- Thalassemia minor / trait : Increased levels of HbA2.

Normal levels : 2 to 3.5 %.

If 4 to 8 % : Diagnostic of Beta thalassemia minor.

Normal electrophoresis

3 types of Hemoglobin :

HbA : 95 to 97 %.

HbF : < 1 %.

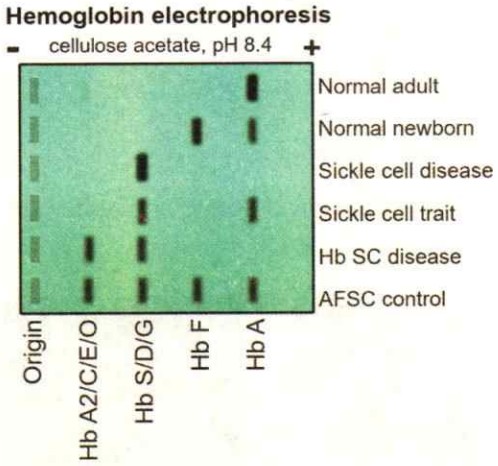
HbA2 : 3 to 5 %.

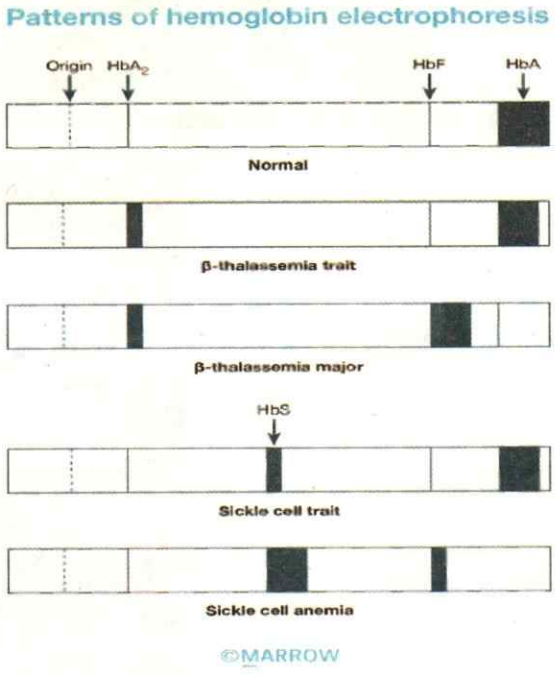
Sequence from (+) to (−) is HAFSA :

Active space

H band → A → F → S → A2.

Abnormal : All haemoglobins are raised
In this sample of the given example.
Patterns of Hemoglobin electrophoresis :
Levels of HbA 2 is high : β–thalassemia trait.
Both HbF and HbA 2 is high : β– thalassemia major.
HbS and HbA high : Sickle cell trait.
If only HbS is high : Sickle cell anemia.





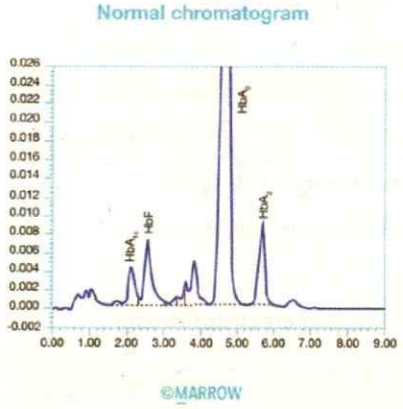
Normal Chromatogram :
HPLC : High performance/ pressure liquid chromatography.

Active space

It quantifies the various types of hemoglobin.

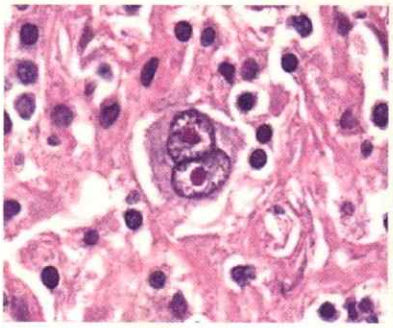
E.g : % of HbF = 3%.

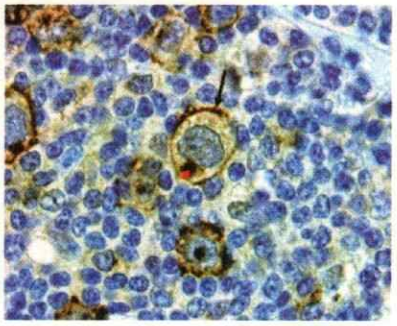
% of HbA = 96%.



Reid Stenberg cells / RS cell :

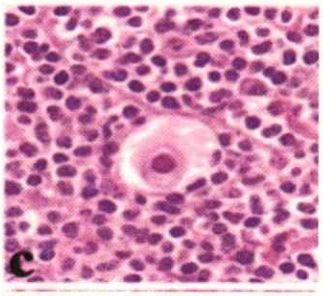
Binucleate cell with prominent nucleoli : Owl's eye appearance.





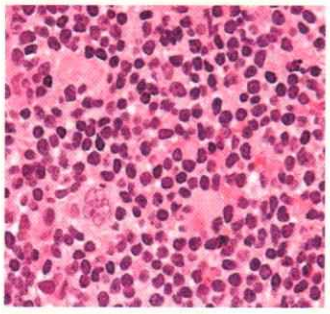
Lacunar RS cells: Empty space around the cells

Seen in nodular sclerosis Hodgkin's lymphoma.

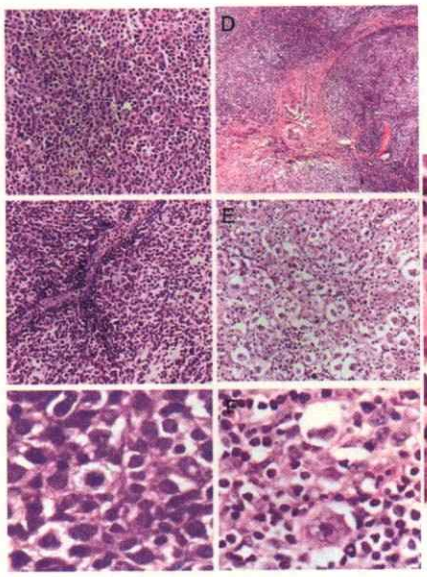


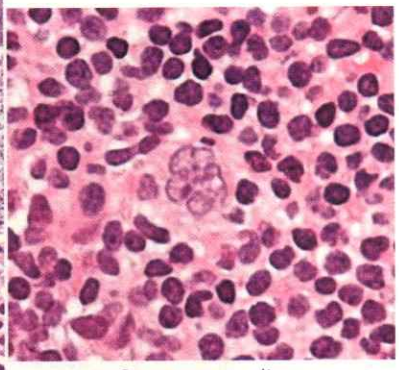
Popcorn / L-H RS cell :

Seen in NLPHL / Nodular lymphocyte-predominant Hodgkin's lymphoma.



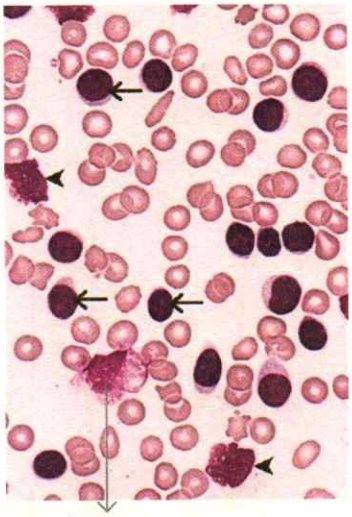
Active space





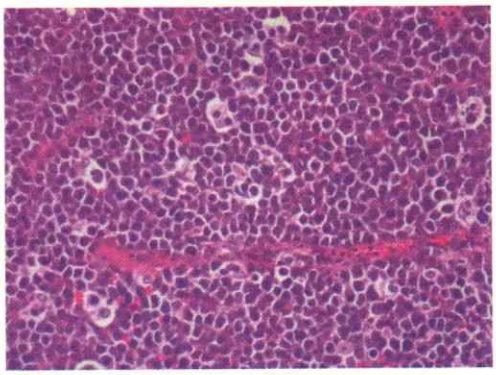
Popcorn cell

Clinical scenario :
65 year old man who presents with fatigue and pallor. On examination lymph node examination is present. Peripheral smear is shown below. What is the diagnosis?
WBCs seen arel ymphocytes, which are high in number.
Hence CLL / Chronic Lymphocytic leukaemia in the elderly is suspected.
Also seen are the smudge cells/ basket cells/ parachute cells.



Smudge cell

Given is the lymph node biopsy of a five-year-old African boy with a jaw/ mandibular swelling.What is the genetic mutation seen in the child ?
A. RB.
B. P53.
C. C myc.
D. N myc.
Burkitt's Lymphoma is suspected in African males with jaw swelling.

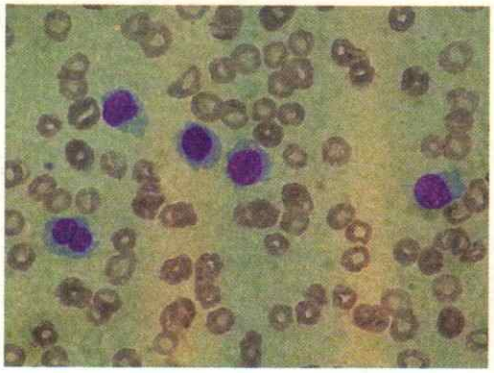


Active space

Seen as a starry sky appearance.

Lymphocytes are sky, histiocytes/cacrophages are stars

Genetic mutation seen: C-myc or t (8: 14).



Hairy cell leukemia : hair like projections

Bone marrow needles :

Salah's needle.

Klima's needle.

Jamshidi's needle.

Jamshidi's needle

Jamshidi's needle :

Both biopsy & aspiration can be done.

The most common site for bone marrow aspiration or biopsy

In adults :

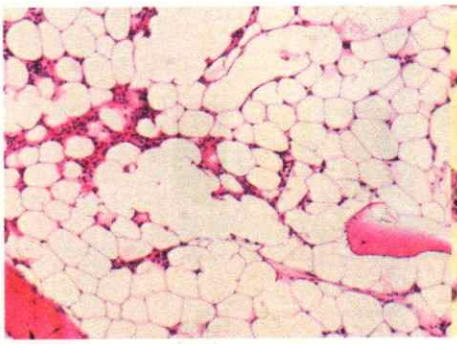
Posterior superior iliac spine.

Iliac crest.

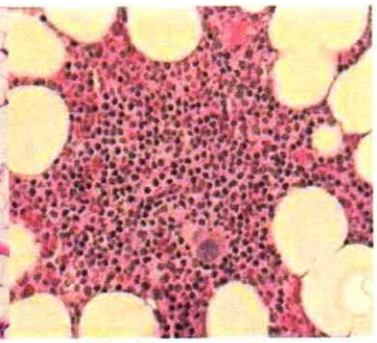
Anterior superior iliac spine.

In children : _ _ _ _ _ _ _ _ _ _ _ _

Active space



Bone marrow biopsy of a 30year old with excess fat and bony trabeculae



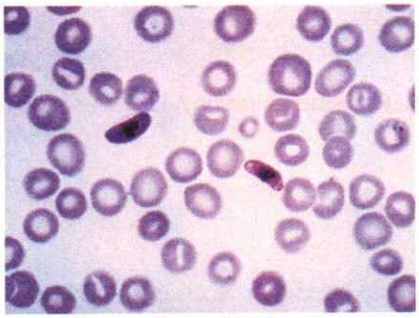
Normal bone marrow biopsy

Diagnosis : Aplastic anemia.

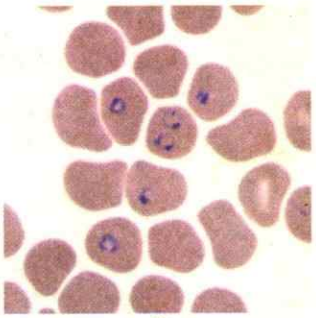
Aspirate gives a dry tap.

Bone marrow biopsy is the investigation of choice.

Splenomegaly is never seen.



Plasmodium falciparum gametocyte



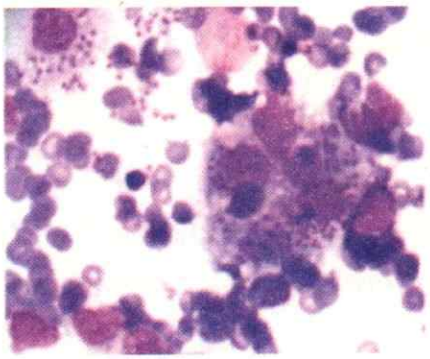
Ring form

Leishman Donovan bodies / LD bodies :

Small purplish dots in macrophages.

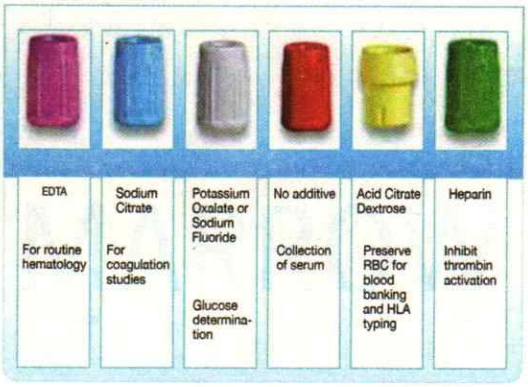
Double dot appearance.

Seen in leishmaniasis.



Active space

Color coding of vacutainers



©MARROW

Purple/lavender :
Anticoagulant used : EDTA.
Used for routine hematology.

Blue :
Anticoagulant used : Citrate.
For coagulation studies and ESR determination by Westergren method.

Grey :
Anticoagulant used : Potassium oxalate or sodium fluoride.
Used for : Glucose determination.

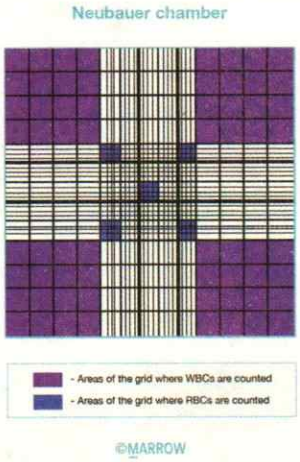
Red : No additive. Some gel separator can be present.
Used for : Collection of serum.
Serum studies like LFT, RFT.

Yellow :
Anticoagulant used : Acid citrate dextrose.
Used for : Preserving RBC for blood banking and HLA typing

Green :
Anticoagulant used : Heparin.
Used for : Inhibit thrombin activation.
Arterial blood gas analysis/ ABG, Immunophenotyping or osmotic fragility test.

Active space

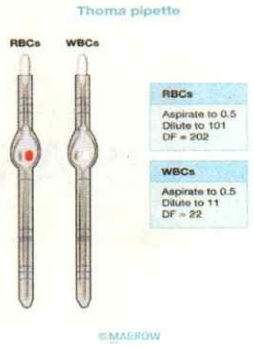
Sahli's Hemoglobinometer : used for rough estimation of hemoglobin.



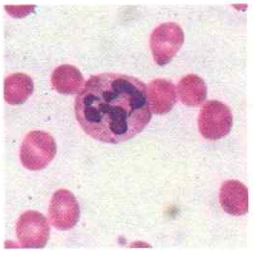
Improved Neubauer chamber

RBC pipette :
Has a red bead.
markings are till 101.

WBC pipette :
Has a white bead.
markings are till 11.



Hyper segmented Neutrophil :
Normal neutrophil has 3 to 5 lobes.
In hypersegmented neutrophil, there are more than 5 lobes.
Seen in megaloblastic anemia due to deficiency of Vitamin B12.



Active space

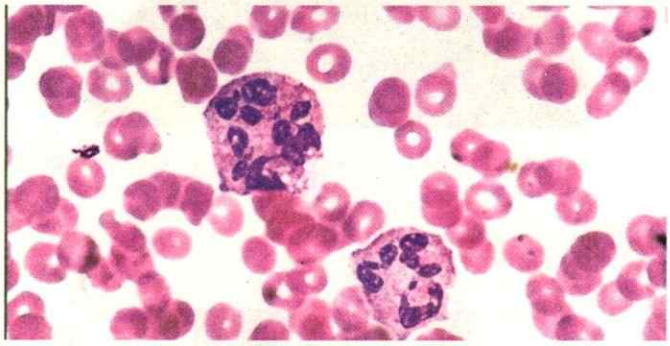
Seen in : Mnemonic : LHMC (Lady Hardinge Medical College).

Liver disease.

Hypothyroidism.

megaloblastic anaemia.

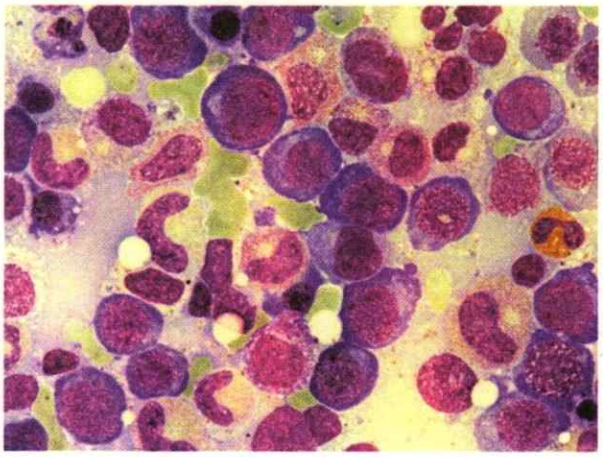
Cytotoxic drugs.



Hypersegmented neutrophils with macro- ovalocytes

Bone marrow aspirate of a patient with megaloblastic anaemia:

It is called megaloblast because the erythroid precursor is large and sieve-like chromatin.



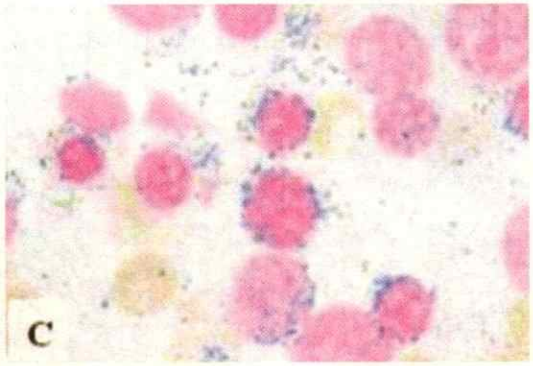
Ring Sideroblasts : Erythroid precursors with bluish dots which look like a ring around them.

Seen in :

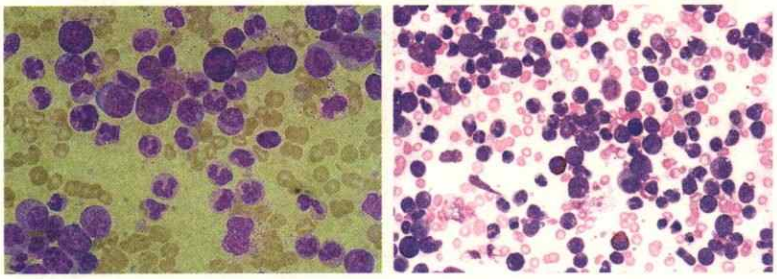
Bone marrow aspirate of sideroblastic anemia.

It is composed of iron granules in a perinuclear location.

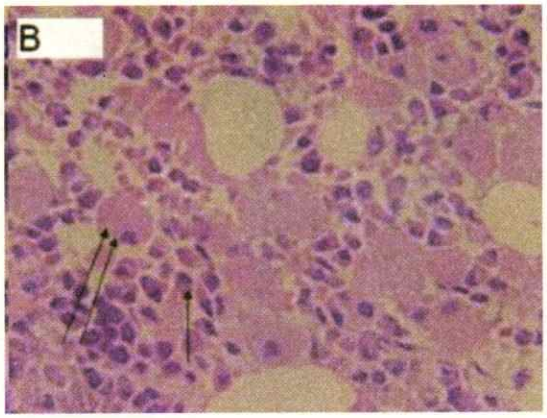
Active space



65 year old female with massive splenomegaly. TLC is very high. Periperal smear is given below. What is the most likely translocation ?



Peripheral smear looks like a bone marrow with cells at different stages of myeloid maturation and basophilia.
Hence, diagnosis : CML / Chronic Myeloid Leukemia.
Translocation : t (9 : 22).
Bone marrow aspirate in CML :
Shows psuedogaucher cell with wrinkled tissue paper appearance in the cytoplasm.
Gaucher cell has a crumpled tissue paper appearance in the cytoplasm.



Active space

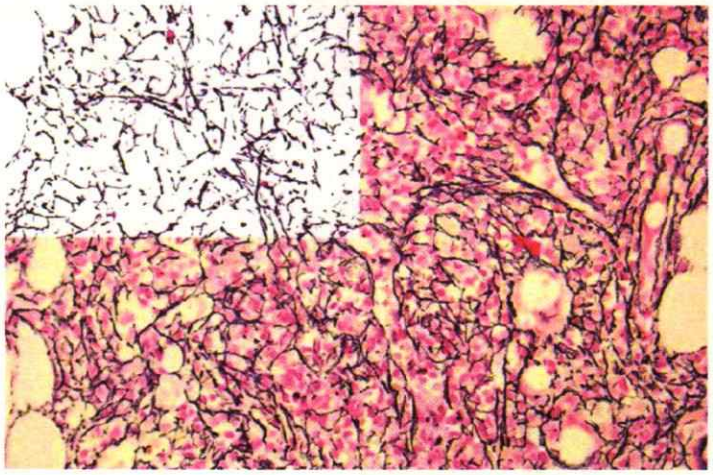
Bone marrow biopsy of myelofibrosis :

Shows blackish fibres : Fibrosis. Not much fat.

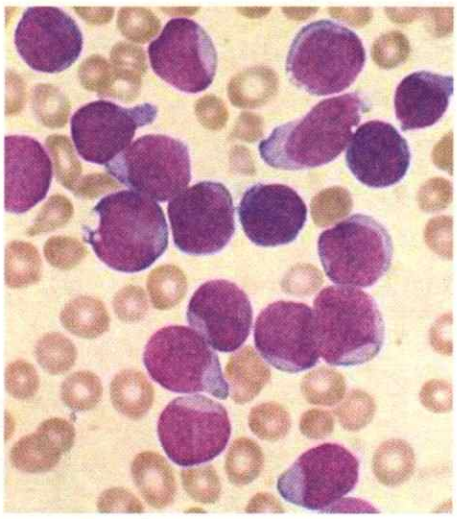
Stain used : Reticulin stain.

History : Massive splenomegaly.

Peripheral smear finding : Tear drop cells / dacrocytes.



An 8 year old child presents to the clinic with petechiae and bone pains, examination reveals splenomegaly. Hemoglobin is 6gm%, Total counts is 3000, Platelet counts is 80,000. Peripheral smear is as shown. What is the provisional diagnosis?



Peripheral smear shows :

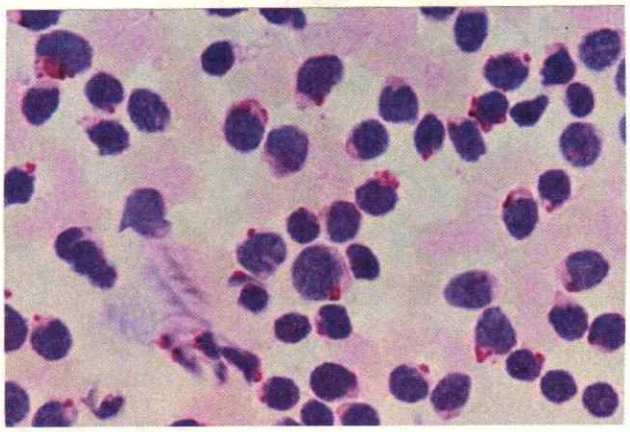
Lymphoblasts: Larger than lymphocytes, which are precursors of lymphocytes (lymphoblasts), with no granules in the cytoplasm. Very dark/ coarse chromatin with no prominent nucleoli.

Hand mirror cells : Some cells which show hand mirror morphology.

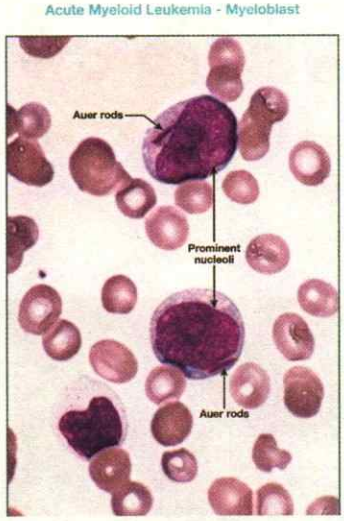
On staining with PAS : positive. Shows block positivity.

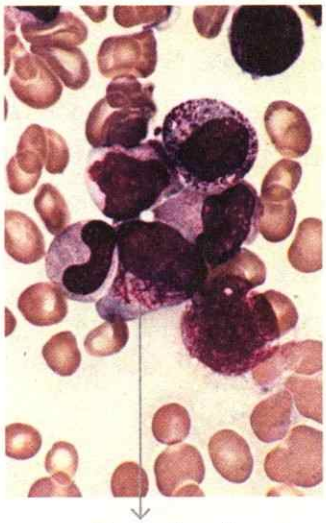
ALL/ Acute lymphoid leukemia.

Active space



If the patient had AML :





Faggot cell

Myeoblasts :

Cells with moderate amount of cytoplasm, with granules.

Rod like structures in cytoplasm : Auer rods.

Cells with bunch of Auer rods : Faggot cells.

Chromatin in pinkish : Homogenous / glassy chromatin.

Myeloblast has 3 to 5 prominent nucleoli.

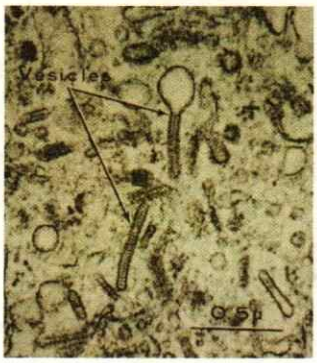
Stains : Myeloperoxidase, Sudan black, oil red O positive.

Tennis racket cells :

Contains Birbeck granules.

Seen in_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Active space



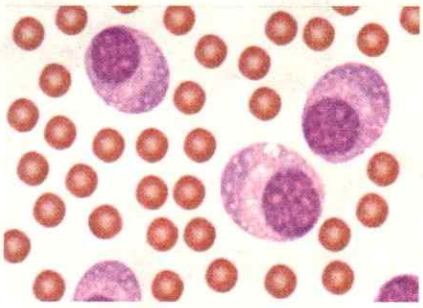
Plasma cells :

Oval cells with eccentric nucleus.

Perinuclear hoff/ halo : Empty space around the nucleus.

Cart wheel chromatin : The chromatin pattern looks like a clock face or bullock cart wheel.

Increased number seen in multiple myeloma.

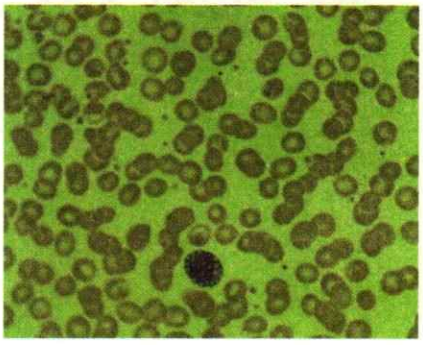


Mott or morula cell :

Seen in multiple myeloma.

Grape like cluster in cytoplasm.

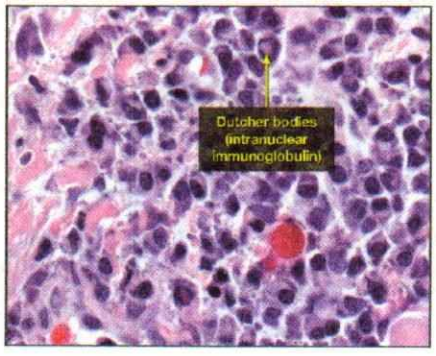
Seen due to abnormal immunoglobulins which precipitate in the cytoplasm.



Intra nuclear inclusion bodies in multiple myeloma called as Dutcher body.

Russel body : intracytoplasmic inclusion.

Multiple myeloma - Dutcher bodies



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