Pathology

- M/C cause of cell injury → Hypoxia → Ischemia
- Most susceptible cell to ischemic injury → Neurons
- Least chances of cell injury → Fibroblast

In presence of hypoxia cells may undergo adaptations or there can be reversible or irreversible injury.

Adaptations

Atrophy: ↓ size of the cell
→ Physiological or pathological

Hypertrophy: ↑ Size and function of cell
→ Physiological or Pathological

Hyperplasia :↑ in number of cell
→ Physiological or Pathological

Metaplasia: It refers to change in nature of cell because of reprogramming of stem cell.

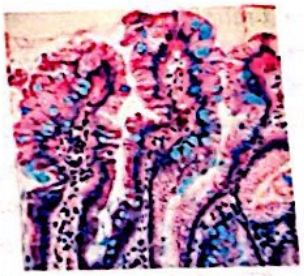
- Only **hypertrophy** is benign condition rest all **atrophy, hyperplasia** and **metaplasia** can progress into malignancy.
- At the time of pregnancy both uterus & breast undergo hypertrophy & hyperplasia.

Metaplasia: change in nature of cell in presence of stress.

- **Epithelial metaplasia** → e.g. lungs: squamous metaplasia is seen in smokers
- **Connective tissue metaplasia**→ e.g. Myositis ossificans(ossification of muscle tissue after traumatic injury)

M.C cause of metaplasia is squamous metaplasia in smokers.

- In **Barrett's esophagus** there is change of epithelium from squamous epithelium to Intestinal columnar epithelium
- Intestinal columnar epithelium shows presence of Goblet cells have Mucin (Blue colored Mucin Granules)



Presence of Goblet cells

For Identification of Mucin we use Alcian Blue

2. Myositis ossificans → In this degenerative muscle tissue is gradually ossified
↓
show presence dystrophic calcification

Dysplasia

→ Presence of disordered differentiation
→ There is presence of Intact Basement Membrane

Progression from Dysplasia → Anaplasia → Malignancy

Reversible Cell Injury:

Commonest cause – Hypoxia
1st involvement of Mitochondria is seen
↓
↓ ATP
↓
Entry of more water inside the cell
↓
"Hydropic change" (Earliest Microscopic Manifestation)

This is also presence of Myelin figures (Composition – Phospholipids)

- These are spiral structure which are seen Intra cellular more commonly and may present extracellularly also.

Irreversible Cell Injury

1. Necrosis
2. Apoptosis
3. Necroptosis
4. Pyroptosis

} Different subtypes of Irreversible cell injury

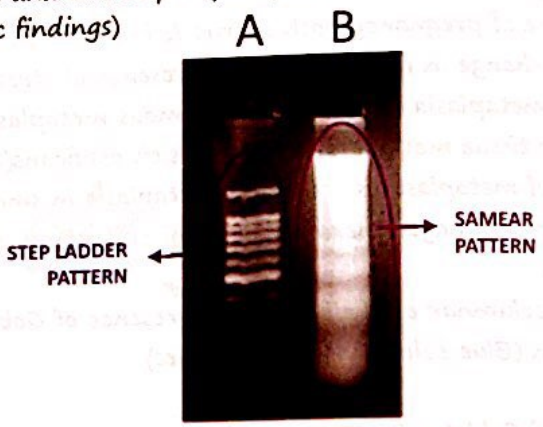
Necrosis

Commonest subtype of necrosis at microscopic level is coagulative necrosis.

→ It is seen due to Extension of Hypoxia.
→ ↓ O_2 which leads to disturbance in cell Membrane
→ Irreversible Mitochondrial Dysfunction
Reason of cell death → Excessive Ca^{+2} entry deposition mainly in Mitochondria
k/as Mitochondrial Density

- In Necrosis, there is a activation of Phospholipase and due to phospholipase there is Cell Membrane Damage (Most characteristic findings)
- There is also activation of DNAase.

Gel Electrophoresis
↓
"Smear Pattern"



Types of Necrosis

→ Coagulative
→ Liquefactive
→ Caseous
→ Fibrinoid

1.Coagulative Necrosis

- It involves all the organs of Body except CNS
- M/c reason → Hypoxia
- There is formation of Triangular structure called Infarct

→"Tombstone appearance"

e.g. Zenker's Degeneration seen in Patient suffering from Enteric fever

2.Liquefactive Necrosis → Associated with Abscess formation therefore associated with Pyogenic Infection

It is seen in CNS
A/k/a → Colliquative Necrosis.

→ A special subtype of liquefactive Necrosis → **Fat Necrosis**
In this condition there is activation of Lipase enzyme.
It is associated with Acute Pancreatitis; Injury to Omentum, Breast Tissue

3. Caseous Necrosis → "Cheese like appearance of Necrotic Material"

e.g. Tuberculosis, Systemic Fungal Infection e.g. (Histoplasma, Coccidioidomycosis) and in Bacterial infections like syphilis.

4. Fibrinoid Necrosis

M → Malignant Hypertension due to damage to Blood vessel as a result there is deposition of Pinkish material in Vessel wall

A → Aschoff Body (histological finding in Rheumatic heart disease)

P → Polyarteritis Nodosa

Fibrinoid Necrosis is associated with Immune complex disease
(Type III hyper sensitivity reaction)
↓
Immune complexes damage the endothelial cells
↓
Associated with deposition of fibrin and fibrinoid material

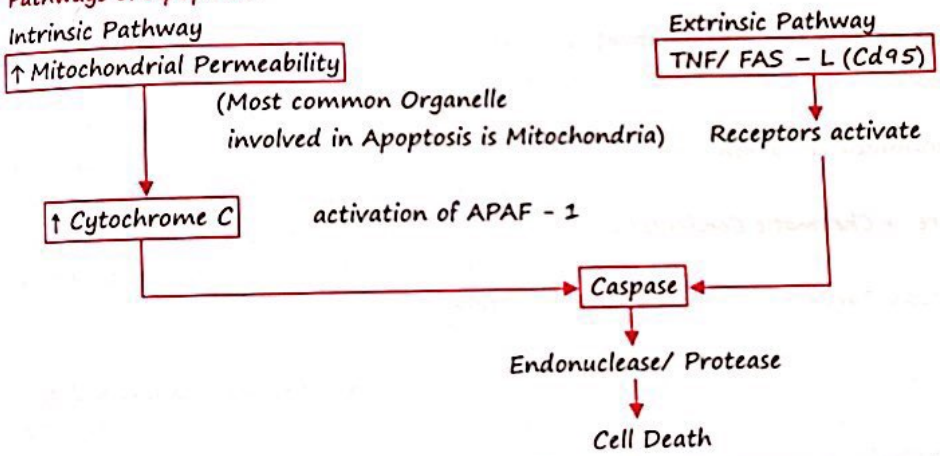
Apoptosis: Programmed cell death & is controlled by Genes

APOPTOSIS

Pro Apoptotic	Sensors	Anti Apoptotic Gene
↑ Apoptosis	It maintains balance	↓
- P53 gene	between pro apoptotic &	BCL – 2
- BAX	Anti apoptotic Gene	MCL – 1
- BAK	- BH3 genes	

- MCL – 1 Gene is responsible for Development of resistance to Anti-cancer drugs

Pathways of Apoptosis



- Caspases are enzymes which contain cysteine and causes cleavage at aspartic acid residue.
- Caspases are of 2 types
  - Initiator caspases
  - Executive caspases
- Executional caspases in common for both Pathways → Caspase 3
- Initiator caspase are different for these 2 pathways

Initiator caspases for Extrinsic Pathway is Caspase 8 and for Intrinsic pathway Caspase 9

- Protease enzyme result in ↓ size of cell So apoptosis is characterized by

Shrinkage of cells

- Endonuclease enzyme →

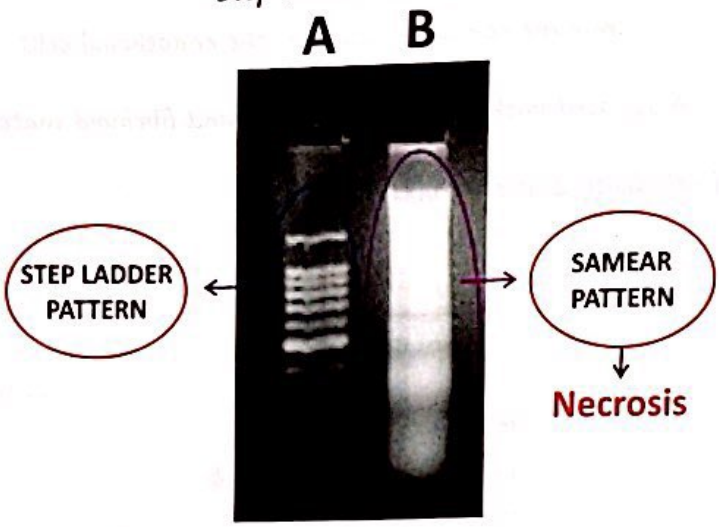
Cleave DNA at specific sites

↓

These cleaved DNA can be picked with help of TUNEL technique

↓

"Step ladder Pattern"



- Caspase are involved in majority of cells except Neurons
  In Neurons there is no presence of Caspases
  In Neurons there is presence of Apoptosis Inducing Factor (AIF)
- Apoptosis is also k/as caspase dependent programmed cell death
- There is No involvement of Phospholipase

↓

Therefore no Cell Membrane damage (No Inflammation)

High Yield

- Caspase Dependent Programmed cell death
- Inflammation is absent.
- Most characteristic feature → Chromatic Condensation
- Cell size ↓;
- Specific Marker for Apoptosis: Tunnel Technique stepladder Pattern

Dyes:

- Annexin V
- DAPI stain

- There is flipping of certain molecules.

So some Molecules which are present inside of cell and come outside

- Apoptosis can be
  → Physiological e.g. Embryogenesis
  → Pathological e.g. Viral Hepatitis, Retinitis Pigmentosa
- Councilman Bodies are Name of apoptotic Body seen in Viral Hepatitis

1. Anoikis: Loss of Adhesion between cells.

↓

"Cell death"

2. **Necroptosis**: It is combination of Necrosis and Apoptosis

↓

There is a activation of TNF but No activation of caspases

↓

Necroptosis is a/k/as → **Caspase Independent Programmed cell death**

3. **Pyroptosis**

→ Caused by Bacterial Infections
associated with formation of Multi - Molecular complex inside WBC

↓(inflammasome)

Activation of Caspase 1/11

↓

IL – 1 formation (Fever)

- Inflammation is Absent in case of Apoptosis
- Max^{m} Inflammatory changes →Necrosis
- Necroptosis has mixed feature of Apoptosis and Necrosis

↓

Presence of Inflammation seen

- **Autophagy**: It is associated with cell cannibalism

Marker = LC – 3

e.g. Cancers, TB, IBD, Alzheimer's disease, Huntington's disease.

Free radical Injury

$$O_2 \xrightarrow[\text{Oxidase}]{\text{NADPH}} O_2^{\cdot-} \xrightarrow{\text{SOD}} H_2O_2 \xrightarrow[\text{MPO}]{Fe^{+2} \rightarrow Fe^{+3}} OH \text{ Hydroxyl radical}$$

Antioxidants

→ Vit. A,C,E Proteins (Ceruloplasmin & Transferrin)

→ SOD; Catalase, Glutathione Peroxidase

Any kind of Mutation in SOD → Lead to Neurological disorder

↓

Amyotrophic lateral sclerosis(ALS)

Catalase and Glutathione Peroxidase has common function responsible for conversion of $H_2O_2 \rightarrow HO_2$

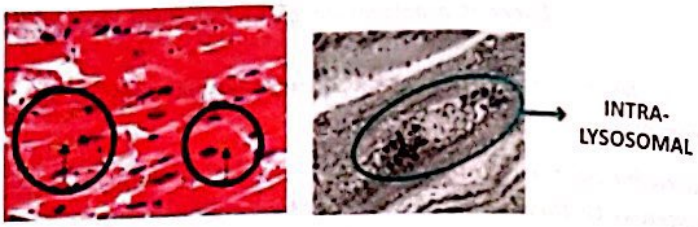
NADPH enzyme is responsible for formation of free radical and therefore responsible for killing of bacteria inside wbc.

- Free radical Injury is most important reason for ↑ Age of Individual (Aging)
- There is deposition of lipofuscin

$$H_2O_2 \xrightarrow[Fe3+]{Fe\ 2+} OH^{\cdot} \text{ Hydroxyl Radical}$$

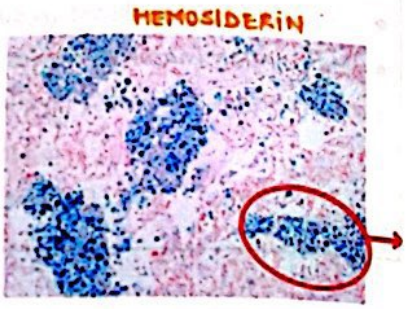
→ Reaction in which heavy metal like Iron is converted from ferrous to ferric form is called as **Fenton's reaction**

1. Lipofuscin → Free R Injury / Wear and Tear Pigmentation
Also seen in Cachexia, Cancers
Lipofuscin is a Golden-Brown pigment and also called as pigment of Aging.



lipofuscin

2. Melanin → Black in color
Identified with Masson/ Fontana Stain
3. Homogentisic Acid → Black Pigmentation seen in Alkaptonuria
• Problem in enzyme activity – Homogentisic oxidase
• Responsible for Black Pigmentation in different Parts of Body as well in Urine



→ It is associated with ochronosis.
4. Hemosiderin → Deposition of extra amount of Iron
Stain → Prussian Blue and Iron reaction
is called as pearl's reaction when Iron reacts with Prussian blue there is formation of ferric ferricyanide
E.g. Iron overload condition seen in repeated Blood transfusion, Thalassemia, Hemochromatosis

5. Calcification:

Dystrophic Calcification	Metastatic Calcification
→ Normal Ca^{+2} level → Deposited in Degenerative/ dead tissues •Calcium has max^{m} changes of deposition in organelle = Mitochondria •M.C organ affected organ = Lungs •Extra calcium deposition does not take place in parathyroid gland.	→ Hypercalcemia → Seen in living Tissue
e.g. TB •Rheumatic Heart disease •Atherosclerosis •Myositis ossificans •Tumors M → Meningioma Mesothelioma O, S, T → Papillary cancer ovary / papillary cancer of Salivary Gland / papillary cancer of Thyroid P → Prolactinoma G → Glucagonoma	E.g. CKD • Parathyroid adenoma • Milk-Alkali syndrome • William Syndrome (Hypercalcemia of Infancy) • Sarcoidosis (Over activity of enzyme α1 hydroxylase) ↓ Active form of vitamin D ↓ Calcification • Certain types of tumors which have presence of Metastasis ↓ Bone Destruction

Stain

Von-Kossa Stain commonest stain for identification of Ca^{+2}

- Tetracycline labelling Index is used as Index for Bone Mineralisation.
  Calcium deposition occur most commonly in Mitochondria except in kidney calcium deposition takes places in Basement Membrane.

INFLAMMATION

- Definition :Response of the vascularized connective tissue to the injury

→Acute

→Chronic

- Commonest pattern of Inflammation that is seen clinically is Catarrhal → Associated with leakage of mucin & fluid

Acute Inflammation has 2 Components

→Vascular changes

→Cellular changes

Vascular changes: Seen in Small vessels

Vascular changes → Vasoconstriction (earliest)

↓

Vasodilation

↓

↑ Permeability

↓

Stasis

Mechanism of Vascular leakage:

1. Endothelial Cell Contraction (Commonest Mechanism)
   A/k/a Immediate transient response e.g. thorn prick
2. Direct Endothelial cell injury → a/k/as Immediate sustained response

   ↓

   Seen in Severe Burns, septicemia
3. Endothelial Cell Retraction → a/k/a Delayed Transient.
   Seen in Cytokine mediated Injury, Hypoxia, Bacterial Infections
4. Endothelial cell damage → Delayed Prolonged leakage
   Seen in Late Sunburn & radiation

Only Endothelial cell contraction affects Venules

rest all involves Venules, Capillaries, arterioles

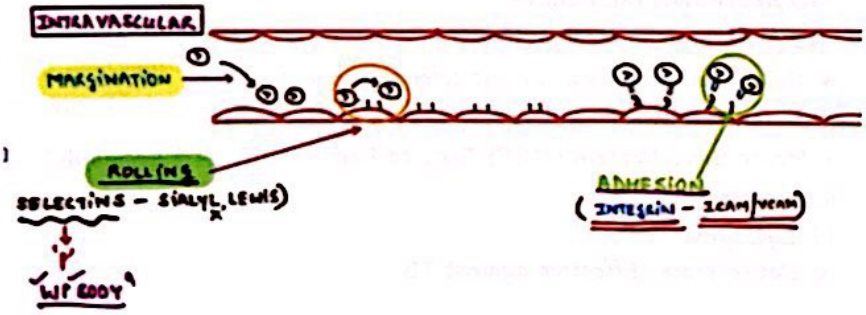
Cellular Changes

→Intravascular

→Extra vascular

Changes seen inside the cell

1. Margination: Movement of WBC from centre towards Periphery



2. **Rolling**: Loose attachment of WBC with endothelial cells

→Rolling is dependent on special molecule which is called selectin and also interaction with sialyl Lewis X.

- Example of selectins → 'p' selectin source - **Weibel Palade Body**
- Weibel Palade Body containing VWF, 'P' selectin.

3. **Adhesion**: Firm attachment of WBC with endothelial cells.

- Different molecules are need for firm attachment called as **Integrins**
- Integrins interact with Adhesion molecules like Vascular cell adhesion Molecule (VCAM) or Inter cellular adhesion Molecule (ICDM)

Leucocyte Adhesion Deficiency Disorders (LAD)

LAD 1

→ Defect of integrins (CD11 or LFA) or Adhesion Molecules

LAD 2

→Defect in selectin molecule.

→Recurrent infections are common finding to both LAD 1 and LAD 2

LAD 1	LAD 2
H/O →delayed separation of Umbilical cord	H/O → Rarest Blood group → Bombay Blood Group → Short Stature

4. **Diapedesis**: Movement of WBC across the blood vessel through basement membrane

M.C Glycoprotein component of Basement Membrane → "Laminin"

Reason of Penetration of WBC through Basement membrane is responsible for Secretion of Metalloproteases.

Metalloproteins cause easy Permeability of WBC across the Basement membrane.

- There is facilitation of Diapedesis by a molecule → CD31 (PECAM)

Chemotaxis: movement of WBC to site of Infections

Exogenous Chemotactic Molecule: Bacteria Metabolic products

Endogenous chemotactic Molecule C5a, IL8, LTB

Targeted Bacteria are killed by Process of "Phagocytosis"

Components of Phagocytosis

→**Opsonization**

→**Engulfment**

→**Killing**

1. **Opsonization** is dependent on molecules like
   Cb, IgG ,Fibrinogen ,Mannose binding Lactin ,CRP
2. **Engulfment** → Dependent on Pseudopod Extension.
3. **Killing of Bacteria is dependent upon 2 mechanism**

→**O_2 dependent mechanism**

→**O_2 Independent Mechanism**

- O_2 dependent Killing is most effective way of killing

O_2 Independent Killing is dependent on special molecules

i. Major Basic Protein (MBP) Toxic to Parasites causes ↑ Eosinophil

ii. Lactoferrin

iii. Lysozyme

iv. Cathelicidin (Effective against TB)

CHEMICAL MEDIATORS

Cellular Mediators

Pre-formed mediators
- i. Histamine
- ii. Serotonin
- iii. Lysosomal enzymes

Freshly formed
- Nitric Acid
- Cytokines
- Arachidonic acid Metabolites

Histamine → richest source → mast cell
- Derived from Histidine
- Most important chemical required in the process of acute inflammation

Serotonin → a/k/a 5HT
→ Both histamine and serotonin causes vasodilation and ↑ in permeability

Nitric oxide – It is derived from Arginine

Causes both → vasodilation
Causes both → Free radical formation

1. Arachidonic Acid Metabolites

Membrane phospholipids

Steriods ⊗ → PLA_2
(Rate limiting Enzyme)

AA

5-LOX

COX ⊗ ← Asprin, NSAIDS

5-HPETE

Leucocytes
Leukotrienes
(+) LTC_4

Cyclo-endoperoxides

Platelets
Thromboxanes
(+) TXA_2

Endothelium
Prostacyclin
(-) PGI_2

smooth muscles

Prostaglandins
(-) PGE_2
(+) PGF_2

→ TXA_2 – Causes Vasoconstriction Platelets aggregation
→ PGI_2 - Anti aggregatory for Platelets, Vasodilation
→ PGE_2 – Causes Pain and Fever
→ PGF_2 - Vasoconstriction

v. Defensin

O_2dependent Killing

O_2 —(NADPH, Oxidase)→ O_2^- —(SOD)→ HO_2 —(MPO, $Fe^{2+} \rightarrow Fe^{3+}$)→ OH Hydroxyl Radical

O_2dependent killing is most important for Bacterial Killing

→**MPO Halide system:** Formation of OH radicle due to activity of MPO enzyme.

↓

That is responsible for killing of Bacteria

- Deficiency of NADPH oxidase enzyme result in **Chronic Granulomatous Disease**

Chronic granulomatous Disease is example of condition where patient has repeated attacks of infections particularly due to **Catalase positive organisms.**

- **Diagnosis** of Chronic Granulomatous Disease **Nitro-Blue Tetrazolium Test** (NBT)
- NADPH oxidase is also k/as respiratory burst oxidase enzyme
- Defect in Molecule like **LYST Protein**

↓

Development of "Chediak Higashi Syndrome"

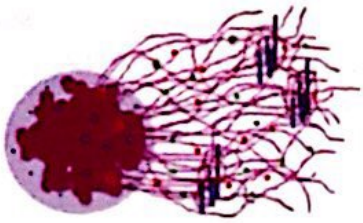
→↑ risk of development of infections

→CNS involvement neurological defects

→↑ tendency of Bleeding

→Albinism

1. Neutrophil Extracellular Trap



Septicaemia → platelets activation → activation of neutrophils.
→ nuclear material of neutrophils forms extracellular trap..

↓

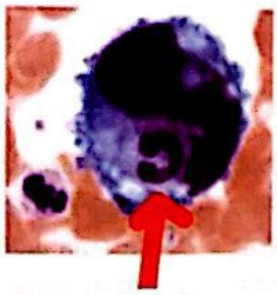
There is entrapment of bacteria and bacteria are killed.

- This process is Dependent on change of amino acids in Nuclear material structure.

i.e. Arginine → citrulline in histone

- Dependent on Platelet activation
- ↑ Risk of Development of SLE
- Death of Neutrophil

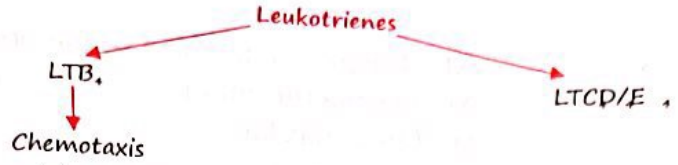
2. Emperipolesis



→ It is the presence of an intact cell within the cytoplasm of another cell

→ it is unlike phagocytosis in which the engulfed cell is killed by the lysosomal enzymes of the macrophage. Instead the engulfed cell remains viable within the other.

- It is seen in Rosai Dorfman Disease and also in myelodysplastic syndrome.



Leukotrienes are very powerful Broncho-constrictors
Leukotrienes also given name of SRS-A (Slow reacting Substance Anaphylaxis)

CYTOKINES

1. Pro-Inflammatory - IL1/IL6/TNF-α

Actions
- ↓in appetite
- Presence of Malaise
- Fever
- ↑ sleep
- ↑ acute phase reactants

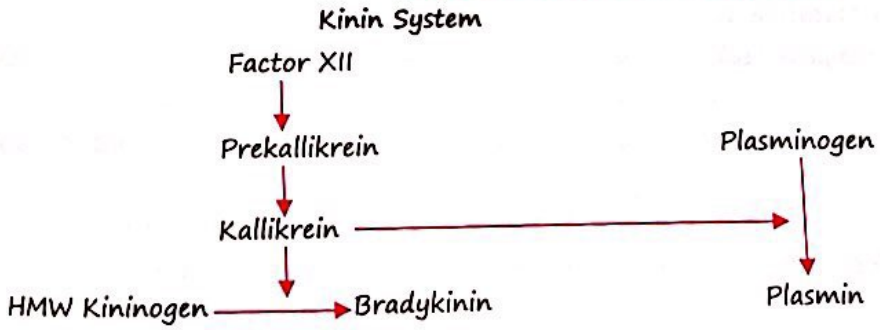
→ TNF α - responsible for causing weight loss
IL-1, IL-6 → Both have systemic effects
- IL-18 is not associated with development of fever

2. Anti-Inflammatory → IL10/TGF
TGF is most Fibrinogenic cytokines
Very important for wound healing
IL - 11 - is also Anti-Inflammatory in Nature

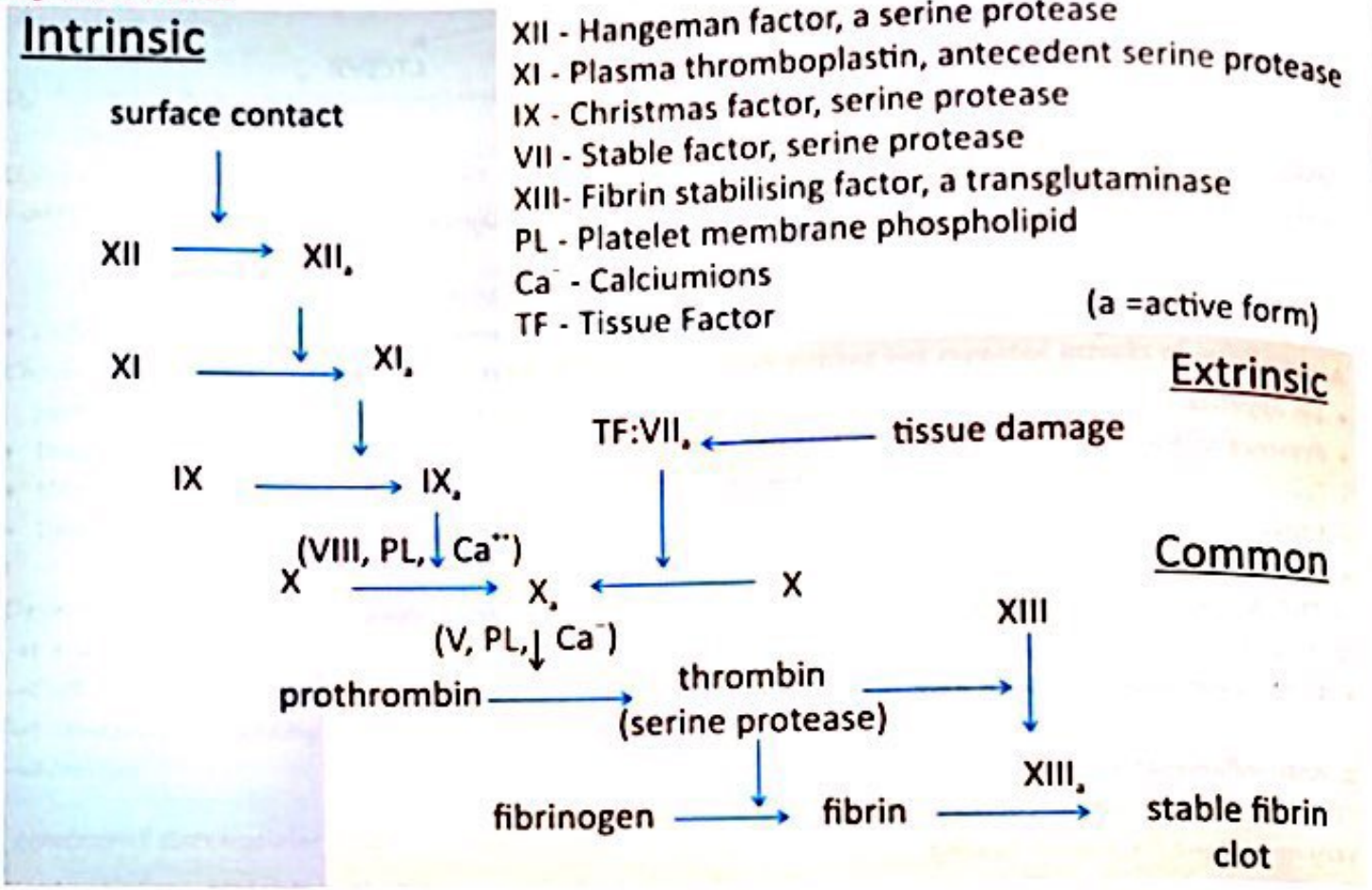
3. Dual Action - IL 4/ IL - 6
4. Interferons - IFN γ
IFN - γ is responsible for the Granulomatous Inflammation which is Component of Chronic-Inflammation and IFN- γ is responsible for activation of macrophage.

CHEMOKINES → α → IL - 8 (attracts neutrophil)
β → Exotoxin; Rants (Attraction of Eosinophils)
γ → Lymphotactin (attract Lymphocytes)
CXC → Fractalkaline

PLASMA CHEMICAL MEDIATORS



Coagulation cascade



The monitoring of Intrinsic Pathway is done by Parameter → aPTT

- The shorter pathway monitoring is done with (PT)
  - → For aPTT estimation; the substance is added called as "kaolin"
  - → Thromboplastin is added in platelet rich plasma when prothrombin time estimation is done.
- Coagulation cascade is Important because of multiple reasons

Formation of stable fibrin clot

- → Factor VI is not present in Coagulation cascade
- → Vit K dependent clothing factor – II, VII, IX, X
- → Anticlotting proteins → Protein C/S

Protein C/S Inhibit Clothing factor V, VIII

- Factor V mutation → Leiden's Mutation

(M.C Inheritable cause of Hyper coagulability)

aPTT/ PT estimation

Sample take is platelet poor plasma

- → Plastic syringe is used
- → Within 2 hours
- → 3.2% Trisodium citrate added

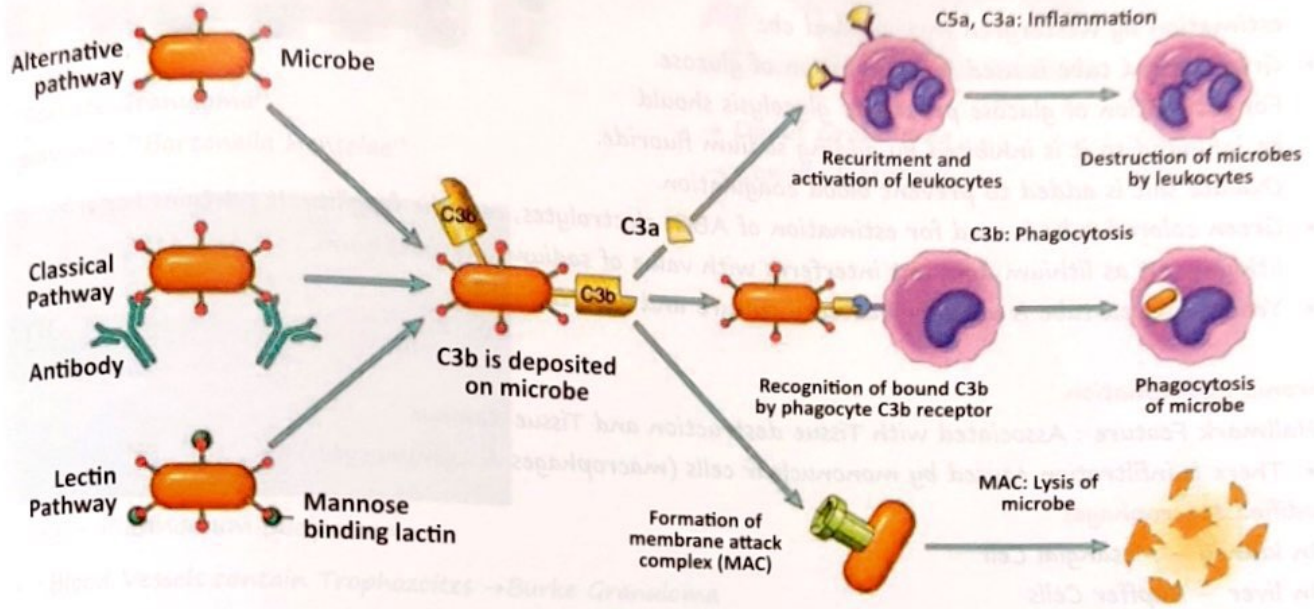
Ratio of Blood sample: Chemical

(9) : (1)

Bradykinin causes
- ↑ Permeability
- Pain development

Factor XII activates coagulation cascade & fibrinolytic pathway

Complement Pathway



Complement proteins play an important role in innate immunity as well as adaptive immunity.

There are 3 pathways:

CLASSICAL PATHWAY

ALTERNATE PATHWAY

LECTIN PATHWAY

The antibody involved in classical pathway is IgM>IgG

Alternate pathway is activated by exposure to endotoxins, lipopolysaccharide, cobra venom, IgA antibody.

Lectin pathway is activated by mannose binding protein

Deficiency	diseases
$C_1C_1C_4$	SLE
C_3	↑ Pyogenic Infections
C5/C6/C7/C8	↑ risk of infection by capsulated organism (Meningococcus, Gonococcus as well as Toxoplasma)

C_2 → Commonest complement deficiency reported in human beings

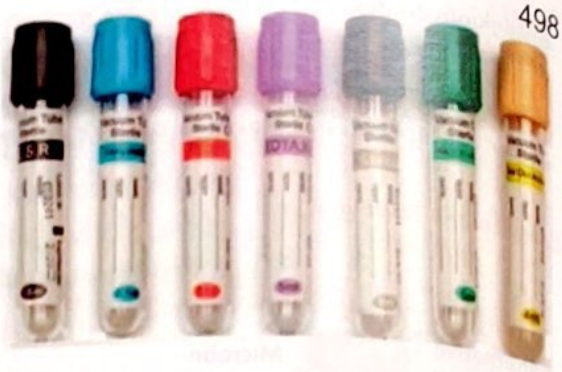
C_1 Esterase Inhibitor → Hereditary Angioedema (More commonly Females are affected, involves mucosal tissue, presence of non-pitting edema)

CD_{55}/CD_{59} → PNH (Paroxysmal Nocturnal hemoglobinuria)

Factor H; I, CD_{46} → Atypical HUS (Hemolytic Uremic syndrome)

C9 → Causing No disease

Different kinds of test tube:



- Red tube is plain tube, used for taking serum sample
- Blue color tube is trisodium citrate tube. It is used for coagulation studies and platelets study. For coagulation study platelet free plasma is used and for platelet study platelet rich plasma is used.
- Lavender colour tube contains EDTA Used for esr estimation by westergren method and cbc
- Grey colored tube is used for estimation of glucose. For estimation of glucose process of glycolysis should be inhibited so it is inhibited by adding sodium fluoride. Oxalate salt is added to prevent blood coagulation.
- Green colored tube is used for estimation of ABG, electrolytes, osmotic fragility. It contains heparin, lithium salt as lithium does not interferes with value of sodium and potassium.
- Yellow colored tube is used for bacterial culture and HLA typing.

Chronic Inflammation

Hallmark Feature : Associated with Tissue destruction and Tissue damage

- There is infiltration caused by mononuclear cells (macrophages & Lymphocytes)

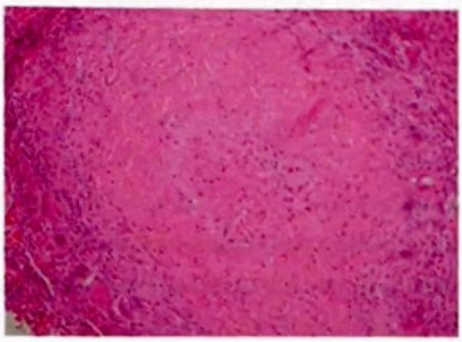
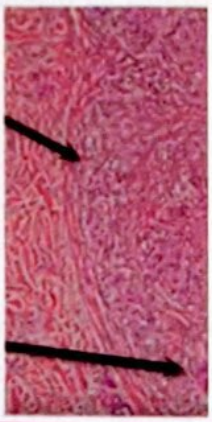
Modified Macrophages

In kidney – Mesangial Cell
In liver – Kupffer Cells
In bone – Osteoclast
In brain – Microglia / Gitter Cell
In placental tissue – Hofbauer Cell

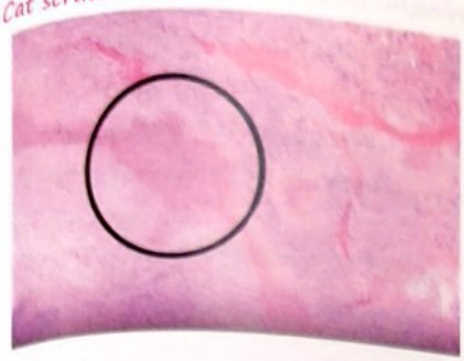
Once Macrophages are activate → they is responsible for formation of **Epitheloid cell**

- Epitheloid cell do not have phagocytic activity
- There is central area of inflammation surrounded by Macrophages, lymphocytes & plasma cells Called as Granuloma

Subtypes of Granuloma

 T.B	 Sarcoidosis
→ Presence of central necrosis & Giant cell k/a Langhans giant cell Here Granuloma is k/as soft Granuloma	→ There is no caseous Necrosis → Non-Caseating Granuloma → less mononuclear cells a/k/a naked Granuloma"

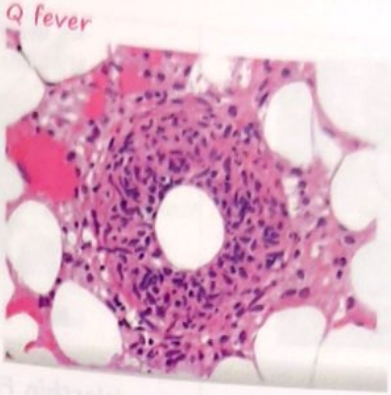
Cat scratch disease



"Stellate Granuloma"

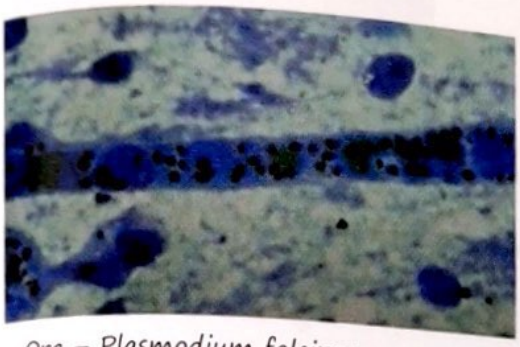
Organism = "Bartonella Henselae"

Q fever



→ Donut Granuloma

→ Coxiella Infections



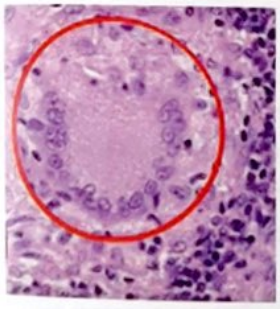
Org – Plasmodium falciparum

- Blood Vessels contain Trophozoites →Burke Granuloma

Other conditions in which granuloma is seen

- In Syphilitic infection there is Gumma
- In Crohn's disease – Granulomatous inflammation
- Giant cell arthritis
- Takayasu arthritis
- Churg-Strauss syndrome

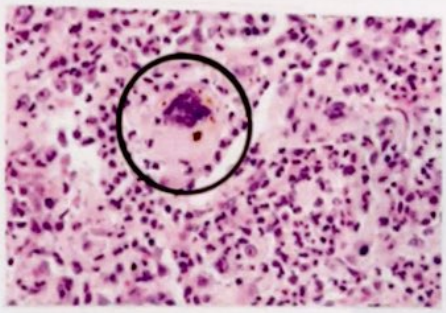
Important giant cells



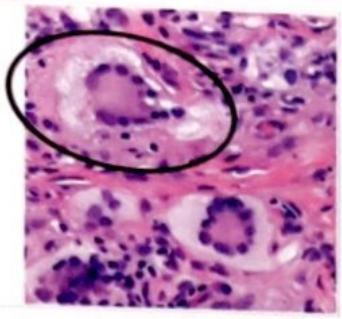
Langhans' cell

↓

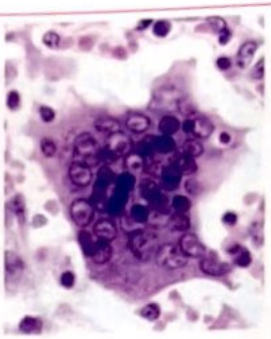
Seen in T.B



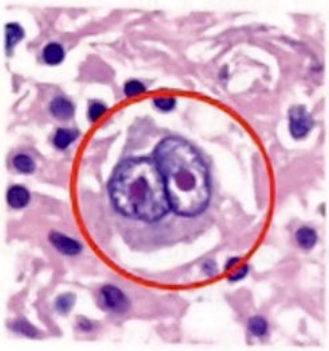
Foreign Body Giant cell



Touton Giant cell
→ seen in Xanthoma



Warthin Finkeldey cell
seen in measles



"Reed Sternberg cell"
Eg: Hodgkin's lymphoma

Wound Healing

Types
→ Primary
→ Secondary

Hallmark

1. Deposition of Granulation Tissue
2. 3 Components of Granulomatous Tissue
   → Mononuclear cells
   → Neovascularization
   → Collagen and fibrous tissue

Collagen types

Type I → Bones
Type II → Cartilage
Type III → Scar formation
Type IV → Basement Membrane

In Initial stages of wound Healing collagen III is there, and after 4 weeks there is change in collagen to type

- Primary Intension wound Healing is seen in clear surgical wounds ↓

Initially Type III Collagen → After 4 week Type I Collagen

- Vitamin required for wound Healing → Vit C

Vit C deficiency result in Impaired Wound Healing

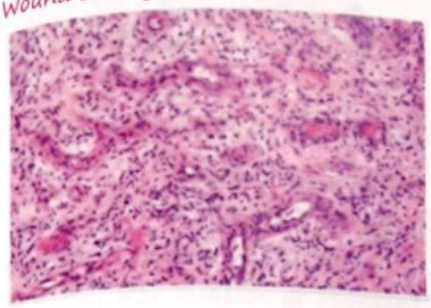
- Neovascularization is maximum on day 5 of wound Healing

Secondary Intension wound Healing

→ Wound Contraction is seen

→ Cell responsible for Phenomenon of wound contraction – Myofibroblast

Wound strength



→1 week – 10%

3 months – 70%

Never – 100%

→ Type III collagen → Pink material connective tissue is Type III Collagen

→ Type I Collagen have Thin Membrane / reticulin like appearance

Abnormal wound Healing

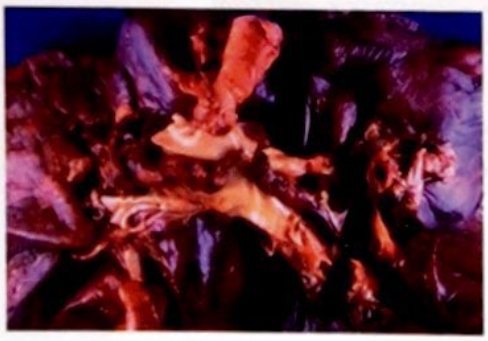
Hypertrophic Scar	Keloid
• Genetic predisposition absent	• Genetic predisposition Present
• Non Africans	• Africans
• No such site	• Skin overlying sternum is commonest location
• Spontaneous ↓ size	• No spontaneous Regression
• Within boundaries	• Overgrows wound boundaries
• Parallel Collagen	• Haphazard collagen
	• Rx = Triamcinolone

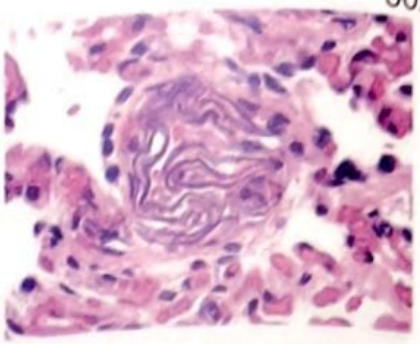
HEMODYNAMICS

1. Pulmonary thromboembolism:

- Clot in Pulmonary circulation
- Mostly asymptomatic
- Sudden death (> 60% obstruction)
- **Saddle Embolus**

→ Clot present at Bifurcation of Pulmonary Artery





2. Amniotic fluid Embolism:

- More than 80% Mortality

Presence of fetal squamous cells and mucin in maternal blood vessels

3. Fat Embolism

- Seen in Traumatic Injury after which there is release of fat globules in Systemic circulation.
- Seen in fracture of long Bones, Burn Injury

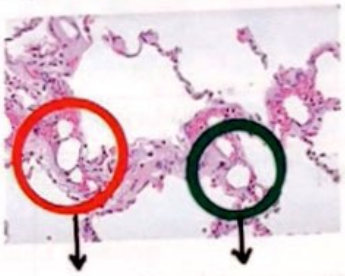
- < 10% symptomatic

Symptoms after 1-3 days

C/C

- Anemia (Sequestrations of R.B.C)
- Dyspnea
- Skin rash (due to sequestration of Platelets by Fat Globules)

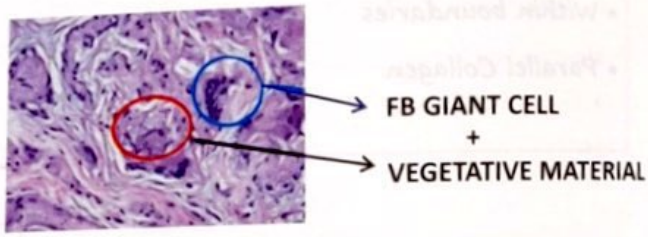
Diagnosis of Fat embolism



Clear vacuoles suggestive of Marrow fat

4. Vegetable Aspiration Pneumonia

- H/o of Aspiration
- Commonly Right Lung is involved (mostly middle lobe and Right lobe)



Histology:

- Foreign Body Giant cell
- Vegetative material

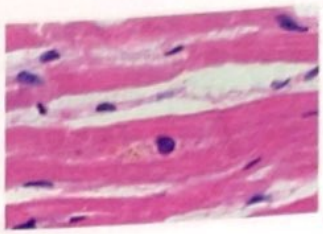
5. Chronic Venous Congestion

- Nutmeg liver
- It is associated with Cardiac Failure mostly Right Side

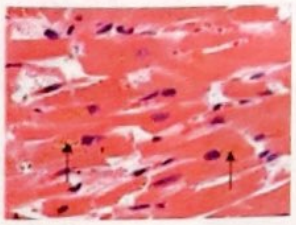
STAINS AND PATHOLOGY

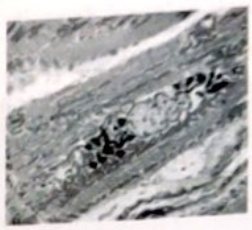
Lipofuscin

→ Yellow Brown Pigment
→ Perinuclear location
→ Lipofuscin is called as "Pigment of Aging" / Wear and Tear Pigment.



→ Associated with free radical Injury.

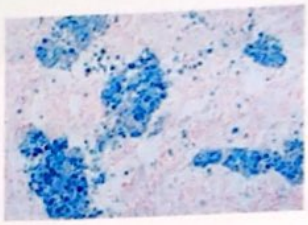




→ Seen in PEM; Cancers.
Electron Microscope Finding
→ Perinuclear location of Pigment

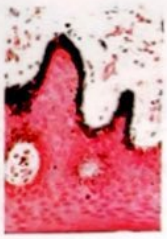
Hemosiderin

→ It is produced due to metabolism of iron
→ Iron is stored in form of molecule called Ferritin
This Ferritin is going to convert itself into Hemosiderin.
Stain: Prussian blue
Prussian blue reacts with ferritin forms **Potassium Ferrocyanide**



Reaction is known as **Perls reaction**

→ Seen in conditions where there is iron overload e.g. Hemochromatosis, Secondary iron overload (repeated Blood Transfusion)



Melanin

→ Black in colour Only endogenous Black Pigment
Identification of melanin is done by stain called Masson Fontana stain

Calcium

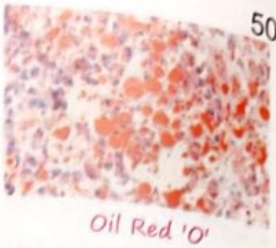
Stains:
→ Von-Kossa: best stain for Ca^{+2} in tissues.
E.g. Mönckeberg's Sclerosis: Calcium deposition in vessel Wall (Black colored)
→ Alizarine red: reddish appearance to calcium

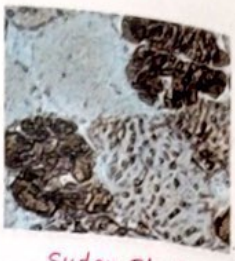
Von - Kossa Stain

alizarine red

Lipids Identification

For identification of lipids in the tissue there are multiple stains
Lipids have tendency to be washed off during slide preparation
For detection of lipids in tissues, frozen section is taken so that lipid does not get washed off.
Frozen section is called as cryostat preparation
Oil Red 'O' → Best stain for identification of lipids
Alternate stains → "Sudan Black Stain"
Black colored deposits are suggestive of lipids


Oil Red 'O'

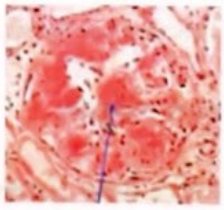

Sudan Black

Clinical Situation
Reye's syndrome: Scenario: child with viral fever + aspirin intake
↓
lipid deposition inside hepatocyte
↓
mitochondrial dysfunction
↓
hepatic failure and encephalopathy

"Oil red 'O' for detection of lipids" to see presence of Lipids in the Hepatic tissue

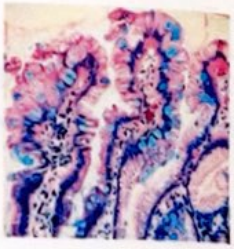
Amyloid

→ extracellular depositions.
→ Made up of Non-Branching fibrils
Commonest stain used for identification → "**Congo-red**"
→ Under Normal light - Pink - red appearance
→ Under Polarized light - Apple Green birefringence
Most Characteristic appearance

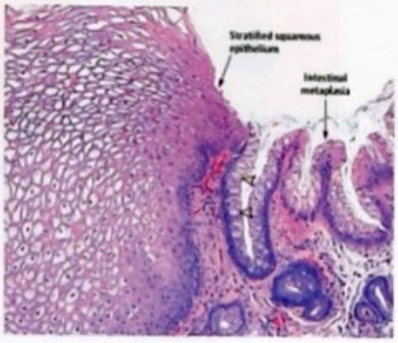


Alcian Blue:

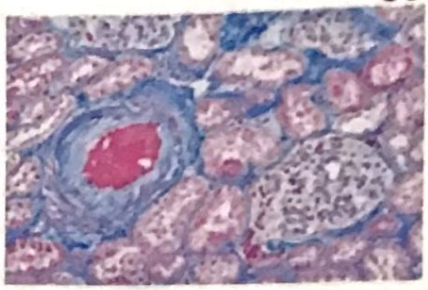
→ Alcian Blue - for mucin
blue colored appearance of mucin containing cells.
→ E.g. Barrett's esophagus
Stratified squamous epithelium → Intestinal columnar epithelium
This Metaplasia is called Intestinal metaplasia



identified by presence of Goblet cells which contain mucin



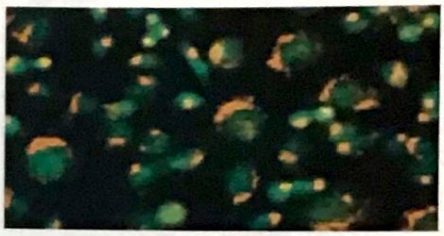
Masson Trichrome Stain:



→ for connective tissue

→ Blue colour - given by collagen
→ Red colour - smooth muscles.
→ Nuclear material is having black colour.
→ In chronic Glomerulonephritis, Glomerulus is obliterated by Presence of Collagenous material deposition so Glomerulus is seen Blue
→ In chronic Pyelonephritis - deposition of fibrous tissue (periglomerular)

Acridine Orange

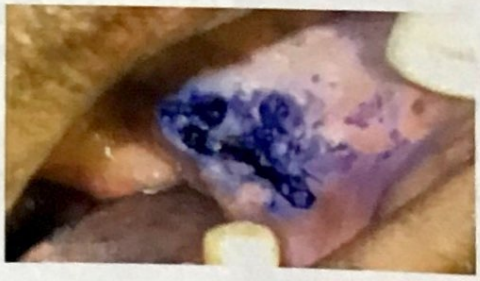


→ Used for identification of Nuclear acids (DNA, RNA)
→ It gives orange colour to the nuclear material and background is greenish colour.
→ Similar appearance seen with Feulgen stain and the reaction is called as Feulgen reaction

Toluidine Blue

→ Stains special connective tissue cells known as mast cells
→ Against a blue Background there is presence of the purple appearing mast cells.

Toluidine Blue in squamous cell cancer



→ for identification of Pre-cancerous lesions or cancerous lesions of Oral cavity lesions. E.g. Lip carcinoma; leukoplakia; Dyskeratotic lesions.

→ Toluidine Blue interacts with Nucleic acid material.

In case of Dysplastic cells and anaplastic cells there is high nuclear cytoplasmic ratio.
Due to high nuclear cytoplasmic ratio, the cells take up Blue colour in higher intensity.

→

Lugol's Iodine

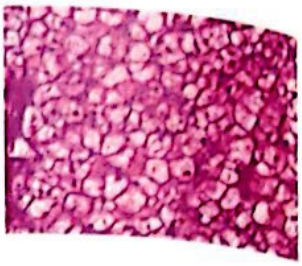
→ Lugol's Iodine is dependent on principle that it is responsible for identification of presence of Glycogen
→ In case of Normal Epithelium cells there is sufficient amount of glycogen which can be picked up with the help of Lugol's iodine.
→ In any precancerous or cancerous lesions, the amount of glycogen inside the cell is reduced

Sweet's Reticulin Stain

Reticulin fibres are predominantly made up of collagen subtype III
→ Reticulin fibres are identified with help of **sweet's Reticulin stain**
Green Background has black colored material which is suggestive of Reticulin fibres.

→Commonest tissue where this stain is used is Hepatic tissue materials

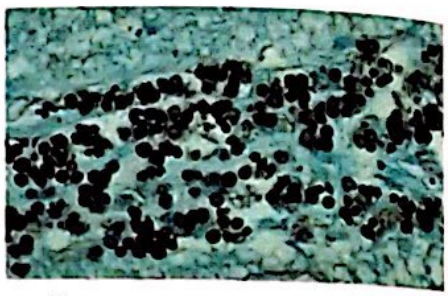
Periodic Acid-Schiff Reagent



Useful for identification of Glycogen
→When PAS is applied on Glycogen this is responsible for magenta colour
→When PAS is applied along with application of chemical or enzyme Diastase
→no magenta colour is given because diastase causes dissolution of Glycogen

PAS is responsible for identification of
→Neutral mucins.
→Basement Membrane of tissues.
→Glycogen
→Fungal cell wall.
It is not example of specific stain, but multiple substances can be identified with help of PAS.

Gomori's Methenamine Silver Stain

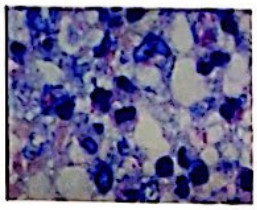


→It is useful for identification of fungi
→Fungal cell wall has brownish Blackish appearance.

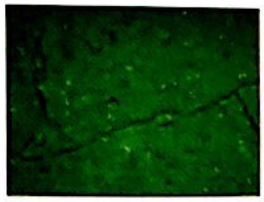
The fungi described in image is Cryptococcus.
H/o of immuno-compromised person, meningitis.
Other fungus
Pneumocystis: h/o of immune compromised person and a typical pneumonia
Pneumocystis can be identified by Gomori's methenamine silver stain.

Mycobacterium Tuberculosis

For identification of M.T.B → ZN Stain is used
→Red acid fast bacilli against blue background



ZN STAIN



Auramine Stain

Other stain → **Auramine Stains**
requires special microscope Fluorescent microscope.

Other structures which are Acid Fast
I. Mycobacterium avium intracellulare
ii. Cryptosporidium
iii. Nocardia. .

→In case of M.T.B there is h/o of cough for 15-20 days (> 2 weeks); low grade fever with hemoptysis, weight loss

↓

→ In cryptosporidium infection → causes diarrhea in immuno-suppressed individuals.
In infections by Nocardia there is brain involvement.

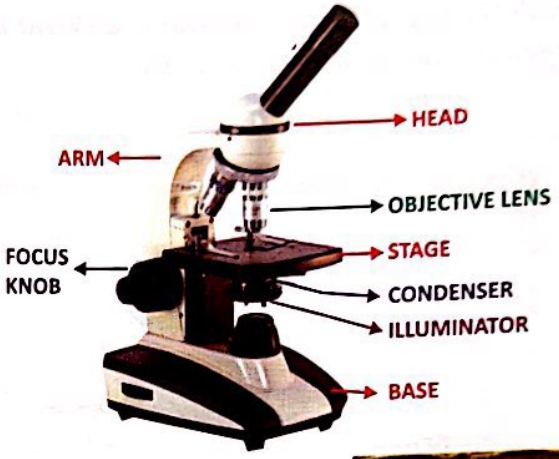
→ In infections by MAC there is pulmonary involvement.

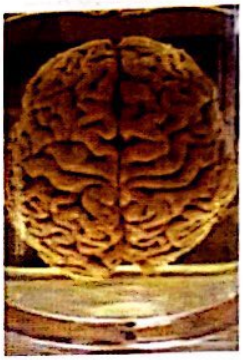
Instrument

Microscope

→ Resolving power of microscope depends on multiple components.
i. Power of eye piece
ii Power of lens
iii. Wavelength of light

→ Resolving Power of microscope does not depend on thickness of specimen



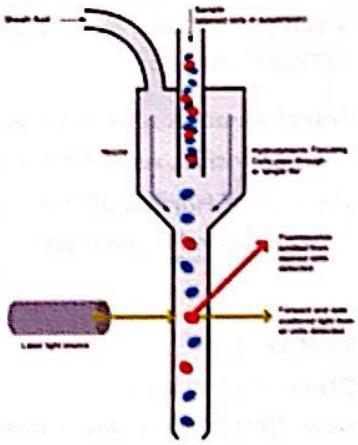


2. Preservative

Preservative used commonly for Histopath examination – **10% formalin**
Fixative: Commonest example – **4% Glutaraldehyde**

3. Flow Cytometer

These are useful for identification of substances which are expressed on the surface of cell.
In flow cytometry, sample is put from top , from side the fluid is put containing tagging molecules and then the sample is exposed to laser light source and depending upon attachment of fluorescent molecule the cell has expression.
→ It is detected with help of fluorescence emitted.



Forward Scatter:

→ It is dependent on size of cell
→ Bigger the cell size, the more is forward scatter.

Side Scatter:

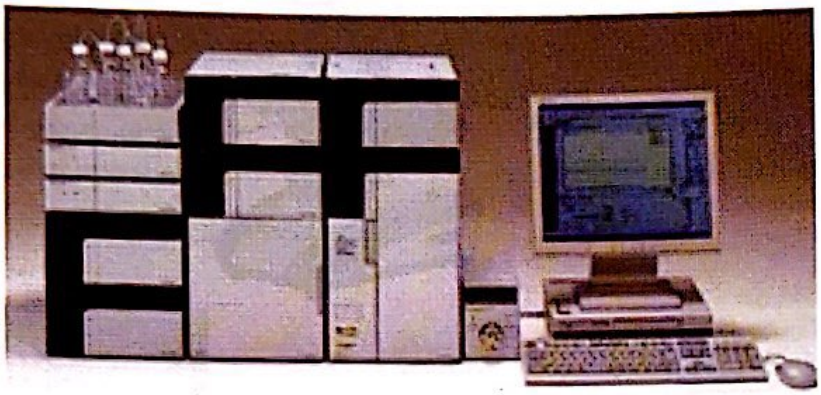
It is dependent upon granularity of cells.
Clinical uses:
i. Detection of CD molecule
ii. Detection of cancers
iii. Immunology
iv. Hematology

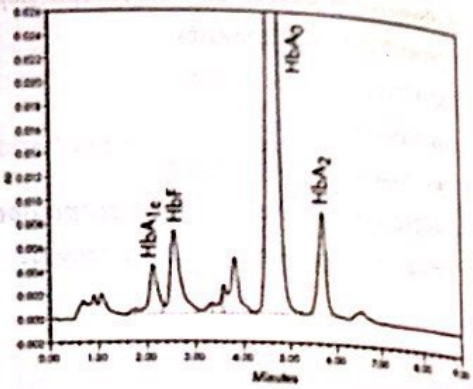
HPLC (High performance liquid chromatography)

→ Useful in diagnosing Hemoglobinopathies
– Best investigation is HPLC
e.g. Thalassemia, sickle cell anemia.

Pattern of Hemoglobin

With the help of HPLC , Patterns of different Hb subtypes is obtained.
Indicates the nature of hemoglobin





Pap Smear

→ PAP smear is responsible for identification of Presence of any kind of cervical dysplasia.
→ Ayer's spatula is used for taking sample.
→ sample is taken from squamo-columnar junction (Transformation zone)

Transformation zone helps in analysis of benign conditions like cervicitis, neoplastic disorders, hormonal disorders.

→In case of Hormonal status, the smear has to be taken from lateral vaginal wall.

Fixative: 1:1
Other: 95% ethanol
Now, Better technique is available for detection of cervical dysplasia k/a visual inspection after application of Acetic acid.

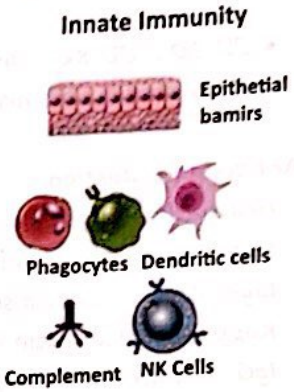
IMMUNITY PATHOLOGY

Immunity

- **Innate Immunity**
  - Non Specific
  - No Memory
- **Adaptive Immunity**
  - Specific
  - Memory Present

Components of Innate Immunity

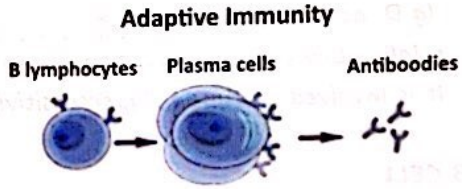
1. **Barriers** : Anatomical – Skin
   Physiological – Secretions from Sweat, Saliva etc.
2. **Cells** : Neutrophils / Macrophages / NK cells
   NK Cells are only Lymphocytes which are component of Innate immunity
3. **Complement Proteins:** Alternate Pathway Proteins
4. **Dendritic cells**
5. **Receptors** :
   TLR → responsible for activation of NF-Kβ → which is responsible for secretion of Cytokines
   Inflammasome: Recognition of Microbes, dead cells and release of IL – 1



Components of Adaptive Immunity :

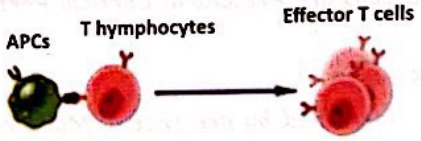
- **B cells** – effective against extra cellular organisms
- **T Cells** → Effective against intracellular microbes
  Eg – Viruses, fungi

Classical Pathway of Complement Activation
→ T lymphocytes are dependent on APCs for formation of Effector T- Cells



Salient Features of Cells

1. **Lymphocytes:**
   → T- Cells → Markers
   - CD 3 → (Pan T-Cell Marker)
   - CD28 → Co- Stimulatory Molecule



T Cells

- **Helper T-Cells** (CD_4 T Cells) (Master regulator of Immune System)
  - TH_1
  - Th_2
- **Cytotoxic T-Cells** (CD_8 T Cells)
- **T Regulatory Cells** responsible For secretion of Anti inflammatory Cytokines (IL10, TGF - B)

• $CD_4 : CD_8$: 2:1

→ **Location of T Lymphocytes:** Peri Arteriolar Lymphoid Sheath, Paracortex of L.N, intra epithelial lymphocytes.

B Cells

- There is Expression of Pan B Cell Marker CD 19
- Additionally there is also expression of CD 40.
- CD 40 Present on B cell is interacts with CD40 ligand on T Cell.
- CD 80 / CD 86 – Interacts with CD 28 molecule which is expressed on T cells.

Activated B Cells are converted into plasma cells which are responsible for Secretion of antibodies.

Antibody Production

Heavy Chain: light chain ratio is 2:2
Heavy Chain has 5 Sub Types G, A, M, D, E
Light Chain: has two subtypes → Kappa and Lambda
Kappa: Lambda ratio is 2 : 1
IgG – Maximum Concentration
– Crosses Placental Barrier
– Act as opsonin Protein
– Activation of Classical Pathway of complement System
Ig A: First line of defense Antibody
: Present in Mucosal tissue
Ig M: Maximum Molecular weight
Aka Millionaire Antibody
→ Produced as a Component of Primary immune response
→ also act as B cell receptor
Ig D: acts as B cell receptor
- **IgE** – Lowest Concentration

It is Involved in Type I Hypersensitivity reaction

B CELL

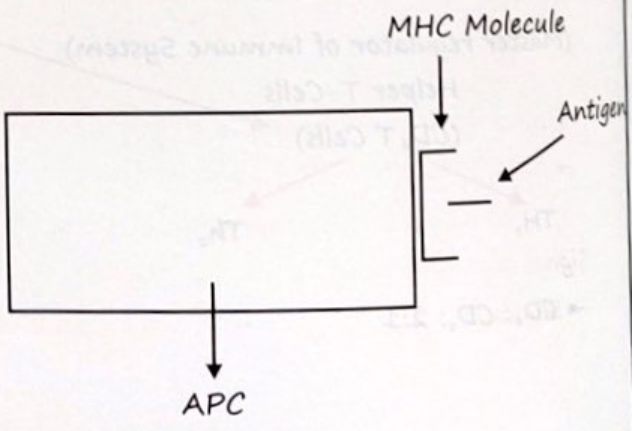
B cells are Present in Cortical Portion of L.N, MALT tissue of GIT (ileum)

NK cells

Identified by presence of Marker CD16 & CD56
Unique Property of NK cells is MHC Unrestricted killing
It act as first line of defense against (i) Cancer cells
(ii) Virus infected cells

APC's (Antigen Presenting Cells)

→ Process the Antigen, Phagocytize it and express on their surface
→ They have MHC on their surface
& MHC molecule have high expression of B7 molecules which has expression of two important forms CD 80/ CD 86
CD80 / 86 interact with CD28 on surface of T cell

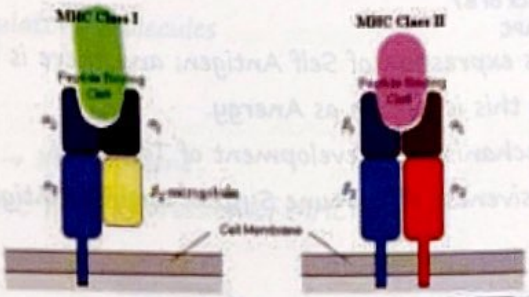


Types of APCs

Professional APCs	Non – Professional APCs
Examples: → Dendritic cells e.g. Langerhans cells which are Present in skin, interstitial tissue → Macrophages → B Cells	Examples: → Fibroblasts (Skin) → Glial Cells (brain) → Pancreatic Beta Cells. → Thymic Epithelial Cells → Thyroid Epithelial Cells → Vascular Endothelial Cells

Physiologically most important antigen presenting cell in human body is dendritic cells

MHC Types:-



MHC 1 → Goes and Stimulate CD 8 Cells

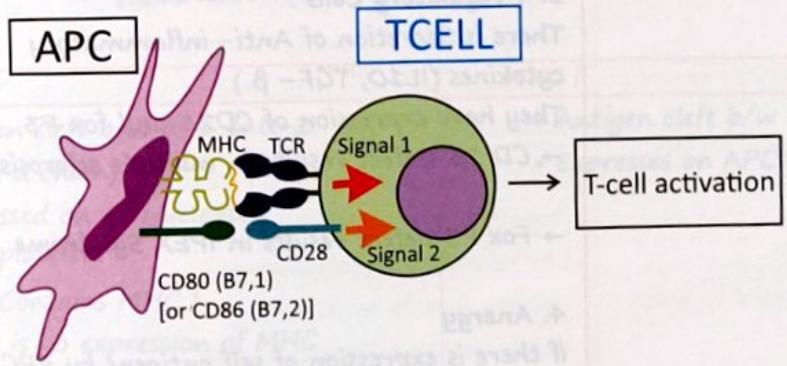
MHC 2 → Goes and Stimulate CD 4 T Cells

CD4: CD8 ratio is 2:1

Structure MHC 1 and MHC2

- In MHC 1 molecules Antigenic Binding peptide is present in alpha 1 and alpha 2 domain.
- In MHC 2 Molecules Antigen binding peptide is present between alpha 1 and beta 1 domain

Pathways



→ Most important example of Physiological APCs is dendritic cell.

→ MHC Molecule on APC interact with T-Cell Receptor on T-Cells which is responsible for generation of Signal 1

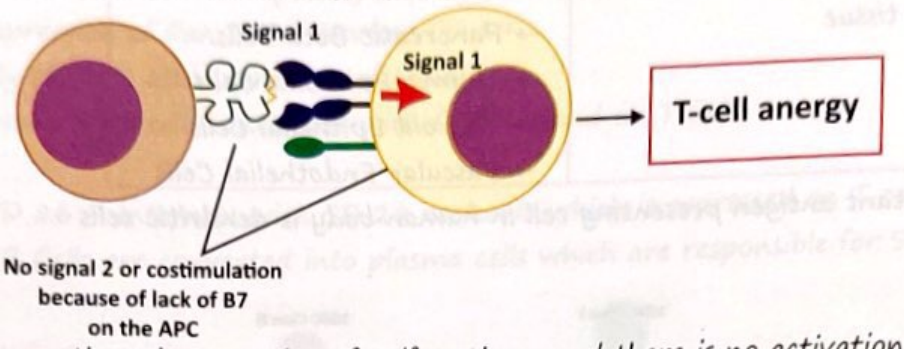
Signal 2 → Generated with CD 80 / 86 on surface of APC interact with CD28 present on surface of T cells.

→ Signal 2 is also k/as Co-stimulatory Signal

→ Only if there is presence of Co-Stimulatory pathway, only then T-cell activation occurs (Need Signal 1 as well as signal 2)

→ Signal 2 is generated only in case of exogenous antigens

→ In situation where APC is Presenting Endogenous Antigens ; Signal 2 is Not Generated



→ In this diagram, there is expression of Self Antigen; and there is no activation of T cell as there is only Signal 1 & no Signal 2; this is known as **Anergy**.

→ Anergy is important Mechanism of development of Tolerance

→ Tolerance is Non responsiveness of Immune System against Antigens.

Tolerance

It is reduced response of Immune System to self-Antigens

Types

Central tolerance	Peripheral Tolerance
1. Due to negative Selection ↓ Self-reacting B and T cells get destroyed - Gene Causing Negative Selection of T cell is **Aire Gene** - Defect in Aire gene causes Autoimmune Polyendocrinopathy 2. **Receptor Editing** Applicable for B cells	Mechanism 1. Apoptosis 2. **Immune Privilege** **Example** • Brain, • Eyes (e.g. Cornea, Retinal Pigment + epithelial cells) • Testicular tissue eg: (Seminiferous Tubules) These are the sites where antigens are hidden → k/as Antigen sequestration 3. **T regulatory Cells** : There is Secretion of Anti- inflammatory cytokines (IL10, TGF- β) They have expression of CD25 and fox P3 → CD 25 Defect results in **multiple sclerosis** → Fox P3 defect results in **IPEX Syndrome** 4. **Anergy** if there is expression of self antigens by APC cells ; T cells are not activated k/a Anergy T cell Anergy seen due to ↓ CD28 B cell Anergy ↓ CD40

Auto immunity

Loss of Tolerance

Most Important Gene involved in Auto immunity is PTPN – 22 Gene

Other Gene: NOD – 2 Gene

Polyclonal B cell Activation

→ In viral Infection (HIV, EBV) Responsible for causing auto immune disorders due to Polyclonal B Cells activation.

Molecular Mimicry

→ Similarity b/w external antigen and normal antigen of body is responsible for causing auto-immunity

Spread of Cryptic Epitope : Hidden antigen starts expressing itself seen in patients with Rheumatic heart disease

Infection – higher expression of Co-stimulatory molecules

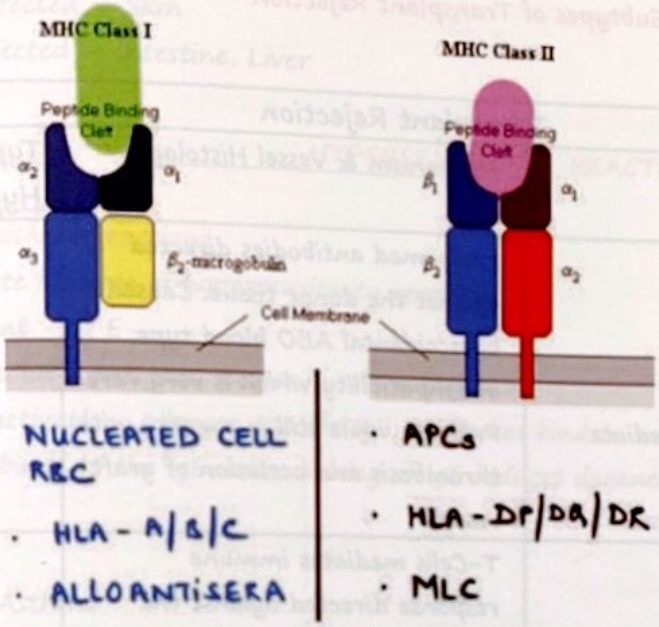
MHC

Genes are located on 6 p

Sequence of Gene in Structure : MHC I → III → II Gene

Expression of MHC I → Expression of MHC III → Expression of MHCII

Features



NUCLEATED CELL
R&C
- HLA - A/B/C
- ALLOANTISERA

- APCs
- HLA - DP/DQ/DR
- MLC

MHC I	MHC II
• Antigen cleft b/w α-1 & α-2 (distal α chain) • Expressed on all Nucleated cells, platelets • RBC Contains MHC I • There is no expression of MHC on the surface of RBC.	• Antigen cleft b/w α-1 & β-1 • Expresses on APCs
Components	**Components**
• HLA A,B,C • Identification by Allo Anti sera • Activate CD 8 T cell	• HLA DP/ DQ / DR • → identified by MLR • Activate CD_4 T cell

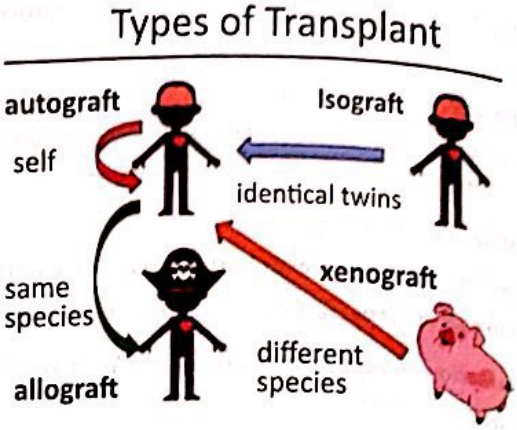
MHC III: Responsible for coding of some complement protein

↑ risk of development of SLE.

HLA Typing: Important in organ Transplantation
HLA – DR is most important Gene which should match Donor and Recipient

Types of Transplant

1. **Autograft** Donor and Recipient are same e.g. Hair transplant, skin Graft
2. **Isograft or Syngraft:** Transplant b/w Identical Twins (individual having same kinds of Gene)
3. **Allograft:** Transplant b/w 2 different individual of same species
4. **Xenograft:** Transplant b/w animal and human Being (different species)

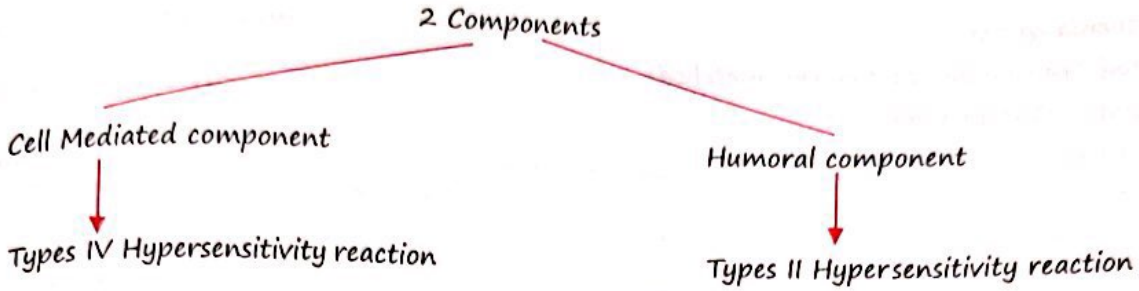


Subtypes of Transplant Rejection

	Transplant Rejection			
	Type	**Onset**	**Mechanism & Vessel Histology**	**Type of Hypersensitivity**
"Host vs Graft"	Hyperacute	Immediate	Preformed antibodies directed against the donor tissue. Caused by accidental ABO blood type incompatibility which is very rare. Presents while still in surgery with thrombosis and occlusion of graft vessels	II
	Acute	Weeks to months	T-Cells mediates immune response directed against the foreign MHC. Inflammation and leukocyte infiltration of graft vessels results. Most common type.	IV
	Chronic	Months to years	T-Cells mediated process resulting from the foreign MHC "looking like" a self MHC carrying an antigen Results in intimal thickening and fibrosis of graft vessels as well as graft atrophy	III & IV
Graft Vs Host		Varies	Donor T-cells in the graft proliferate and attack the recipient's tissue. Most commonly seen in bone marrow transplants. Presents with diarrhea, rash and jaundice.	IV

→ Important Points

Acute Transplant rejection:



Acute Humoral rejection → Take place due to activation of complement system.

Marker: Cd4

Graft vs. Host Disease → Classically Seen after Bone Marrow Transplant also called Runt Disease.

Acute	Chronic
(< 100 days)	(> 100 days)

Earliest organ effected → Skin

Other organs affected → Intestine, Liver

HYPERSENSITIVITY REACTION

Type I Hypersensitivity reactions

a/k/a immediate subtype of hypersensitivity reaction

Immune reactant – Ig E

Antigen form: soluble antigens, helper T cells subtype 2

Mechanism of activation: Allergen specific IgE antibodies bind to mast cell via their Fc receptors. When the specific allergen binds to the IgE, cross linking of IgE induces degeneration of mast cells.

Examples

A – Atopy

B – Bronchial Asthma

C – Casoni's Test

D – Drug induced hyper sensitivity reaction

Prausnitz – Kustner reaction

Type II Hypersensitivity reaction

Antibody mediated Hypersensitivity reaction

Immune reactant: IgG or IgM

Antigen form: cell Bound Antigen

Mechanism of activation: IgG or Ig M Antibody Bind to cellular antigen, leading to complement activation and cell lysis.

Ig G can also mediate ADCC with cytotoxic T cells, NK cells, macrophages and Neutrophils

Example:

Mnemonics

My – Myasthenia Gravis

Blood – Blood Transfusion reaction (mismatched)

Group – Good – Pasture syndrome

Graves' disease

Is – Immune Hemolytic Anemia

Immune Thrombocytopenia

R – Rheumatic Heart disease

H – Hyper acute Transplant rejection

Positive - Pemphigus vulgaris

Pernicious Anemia

Type III Hypersensitivity reaction

a/k/a **Immune complex disease**

It is associated with fibrinoid Necrosis.

Immune reactant: IgG and IgM

Antigen form: soluble antigen

Mechanism of Activation: Antigen-Antibody complexes are deposited in tissues, complement activation provides Inflammatory mediators and recruits neutrophils. Enzymes released from neutrophils damage tissue

Example

S - SLE

H – Henoch – Schonlein Purpura

A – Arthus Reaction

R – Reactive Arthritis, Raji's Assay

P – Polyarteritis Nodosa

Type IV Hypersensitivity reaction

Cell mediated Hypersensitivity Reaction

aka Delayed Type Hypersensitivity reaction.

Immune reactant: T cell

Antigen form: Soluble or cell Bound antigens

Mechanism of activation: CD_8 T cell Activation.

Example

Rheumatoid Arthritis

Mantoux test, Tuberculin Test

Lepromin test

Multiple sclerosis

Contact Dermatis

CD_8 T cell Activation → Damage of cancer cell, virus infected cells.

Classification of Amyloidosis:

Amyloid is extracellular material made up of **non-branching fibrils** leads to development of tissue dysfunction and organomegaly.

Types

Systemic (Generalized Amyloidosis)

Localised Amyloidosis

CLASSIFICATION OF AMYLOIDOSIS

Category	Associated Disease	Biochemical Type	Organs Commonly involved
A. SYSTEMIC (GENERALISED) AMYLOIDOSIS			
1. Primary	Plasma cell dyscrasias	AL type	Heart, bowel, skin nerves, kidney
2. Secondary (Reactive)	Chronic inflammation cancers	AA type	Liver, spleen, kidneys, adrenals
3. Hemodialysis-associated	Chronic renal failure	$A\beta_2M$	Synovium, joints, tendon sheaths
4. Heredofamilial			
i. Hereditary Polyneuropathies	-	ATTR	Peripheral and autonomic nerves, heart
ii. Familial Mediterranean fever	-	AA type	Liver, spleen, kidneys, adrenals
iii. Rare hereditary forms	-	AApoAI, AGel, ALys, Afib, ACys	Systemic Amyloidosis
B. LOCALISED AMYLOIDOSIS			
1. Senile cardiac	Senility	ATTR	Heart
2. Senile cerebral	Alzheimer's transmissible encephalopathy	Aβ, APrP	Cerebral vessels, plagues, neuro billary tangles
3. Endocrine	Medullary carcinoma type 2	Procalcitonin	Thyroid
	Diabetes mellitus	Proinsulin	Islets of Langerhans

Primary amyloidosis: Associated with multiple myeloma

Secondary Amyloidosis → Commonest cause R.A in world and TB in India.

It is associated with RCC, Hodgkin's lymphoma

Familial Mediterranean fever: It is associated with substance pyrin which is Responsible for fever development

- In Medullary carcinoma chemical nature of Amyloid is A-Cal
- Type 2 D.M - chemical Nature of Amyloid is AIAPP

Organs Involved in Amyloidosis

- Commonest and most severely affected organ involved is Kidneys
- Maximum involvement in Kidney is seen in mesangium

Cardiac Tissue

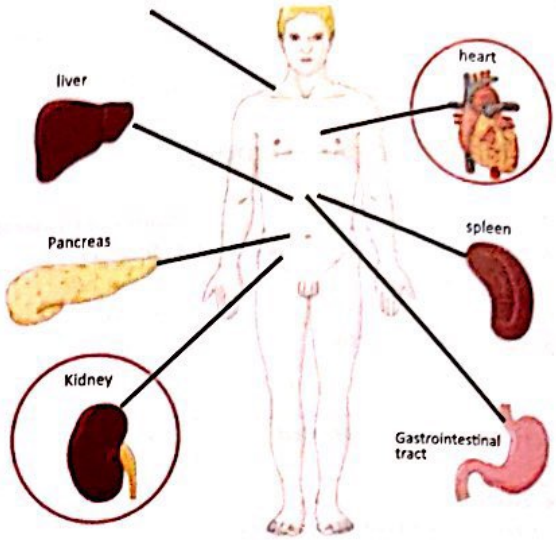
Development of Restrictive cardiomyopathy, Arrhythmia 1st site of deposition of Amyloid in Heart → subendocardial area

Hepatic tissue → first affected area → Space of Disse

- In Space of Disse → Ito cells are present
- Ito cells are involved in Vit. A metabolism

Spleen:

- Red pulp → Lardaceous spleen
- white pulp → sago spleen



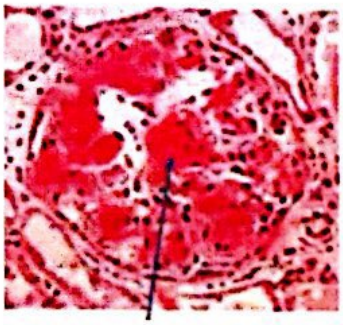
- **Skin:** Amyloid deposition in Perivascular area → Pinch Purpura
- **Joints:** Development of Carpel Tunnel syndrome Knee joint are also involved

GI Tract – Tongue ↑↑ (Macroglossia)
Oral mucosa as well rectal mucosa involved

- Abdominal Fat Aspiration is Best for Diagnosis of Amyloidosis in multiple organ involvement

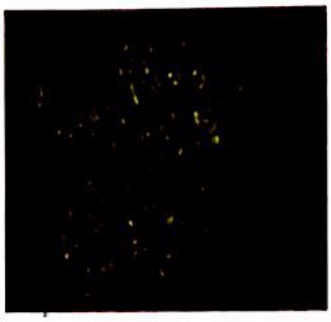
Rectal Biopsy > > > oral Biopsy
Stain used: **Congo-red**

Normal light



Pink red appearance

Polarized light



Shiny appearance apple Green Birefringence

Other satins:

- PAS
- Thioflavin → T / S

- **Electron Microscopic Examination** → Non-Branching fibrils seen
  Spectroscopy: → Amyloid Shows -Pleated structure

NEOPLASIA

→Tumor cells are examples of Monoclonal Growth
→But in inflammatory condition there is polyclonal growth
→**Features:**

1) **Anaplasia:** Hallmark of Malignant Transformation
   →Definition- Loss of Differentiation
   →Nucleo-cytoplasmic reaction 1:1
   →Presence of Abnormal mitotic spindle- presence of TriPolar or quadripolar
   → spindles.

→It is example of Irreversible change
→Loss of Polarity
→Note:
→i. Metaplasia is Reversible change
→e.g. Myositis ossificans (connective tissue metaplasia), squamous metaplasia (epithelial metaplasia) in smokers.
→ii. Dysplasia is example of Partial Irreversible change (reversible initially)
→iii. Anaplasia Irreversible change

2. **Rate of Growth:** Warburg effect is responsible for high rate of growth of cancer cells (Cancer cells utilize O_2 by Aerobic Glycolysis)
- Clinical Significance: "18 FDG" used in PET Scan is → example of Non-Metabolizable Glucose. It can tell different sites of Tumor cells localized in different Parts of Body
→Note - To detect the Smallest clinically detectable mass of Tumor 10^9 cells ~ 1 gm of tumor is required.

	10^9 Cells	10^{12} Cells
Tumor Mass	1 gm	1 kg

→ Carcinoma in situ → Basement Membrane is not affected
→Carcinoma → Basement Membrane is affected

3. **Invasion:**
→ Invasion is dependent on Presence of localized Network of new blood vessel ie Neovascularization/Angiogenesis

4. **Metastasis** - Most Reliable Feature of malignancy
→- Dependent on Angiogenesis
→- Factors required for Angiogenesis: VEGF
: BFGF (basic fibroblast growth factor)

If factors like VEGF and BFGF are inhibited
↓
Lesser number of Blood vessels
↓
Metastasis cannot take place effectively.

All tumors metastasize. Exceptions:
Glioma (CNS tumor)
Basal cell Carcinoma
} Very Malignant Tumor but no Metastasis is seen

Note:- Thyroid Tumor types :-
→ Follicular Adenoma
→ Follicular carcinoma
→Both cannot be differentiated on the Basis of Histology. This differentiation is done on the basis of Vascular invasion. If there is involvement of Blood Vessels in Capsule - Malignant tumor e.g. (Follicular

Carcinoma). These both cannot be distinguished by FNAC also.
→ similar is true between benign and metastatic pheochromocytoma

Pathways of tumor spread:

Lymphatic Spread
Hematogenous spread
Body Cavity

1) **Lymphatic Spread** → Seen in Carcinoma
   → Clinical Significance - Sentinel Lymph node is the first Lymph Nodes involved in Metastasis.
   → It is highly effective in deciding the extent of surgery and prognosis of patient
   → Clinically seen in patient of Breast cancer
      If cancer arises from upper-outer Quadrant → sentinel LN is Axillary LN
      If cancer arises from inner Quadrant → sentinel L.N is Internal Mammary LN

Extra:-Special Names given to L.N in special cancers.
→ Gastric adenocarcinoma - left Supra Clavicular LN (**Virchow's L.N**).
→ left side Axillary L.N involved – **Irish LN**
→ Metastatic deposits around Periumbilical skin area -**Sister Mary Joseph Nodule**
→ Peritoneal area around the rectum is involved → known as "**Bulmer's Shelf**'

Note:-Synovial sarcoma/ alveolar Rhabdomyosarcoma – lymphatics are involved

2. **Hematogenous spread**- Involvement of Blood vessels are seen in **Sarcoma**
   → veins are more commonly involved than arteries due to thin walls
   → any organ with more perfusion/ blood supply or dual blood supply has a higher chance of getting involved e.g. lungs/liver

Eg - Renal cell carcinoma
- Hepatocellular carcinoma

3. **Direct spread** :-
   → Commonest Body cavity involved – Peritoneal Cavity
   → malignant ascites is seen
   → Pseudo-myxoma Peritonei (peritoneal cavity filled with mucinous fluid) is associated with
      - In females – Ovarian Cancer
      - In Males / females – Appendix Cancer

Important Terms:

1. **Choristoma**: Normal tissue present at Abnormal site
2. **Hamartoma**: Disorganized mass of tissue present at Normal site.
   - Commonest Site → Lungs (associated with Popcorn Calcification –

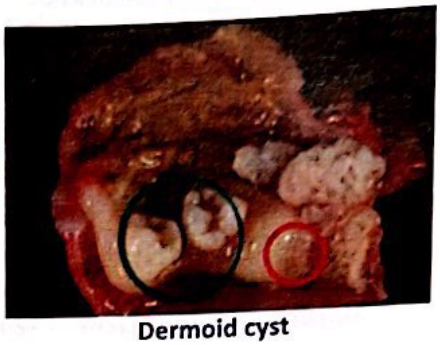
Pre-Neoplastic lesions

3. **Desmoplasia**: Fibrous tissue deposition due to secretion of cytokines & growth factors
4. **Teratoma**: Cell of Origin – Totipotent Cell
- can be Benign / Malignant and It arises from more than one germ cell layer.
   → Commonest site → **Gonads**
   → MC extra gonadal site → **Mediastinum**
   → In Male Teratomas are usually **Malignant**
   → In Female Teratomas are usually **benign**

Dermoid cyst

(Presence of tooth, Cartilage tissue, muscle, Adipose tissue, Hair like structure)

- Usually Dermoid cyst is benign
  but if dermoid Cyst contains skin tissue and malignancy arises then shall lead to squamous cell carcinoma.



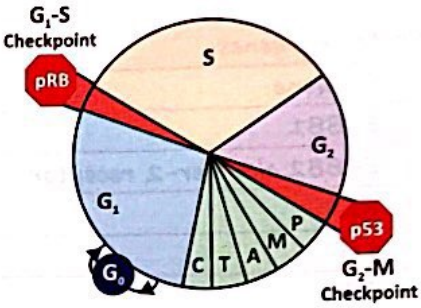
Dermoid cyst

CELL CYCLES & REGULATION

G0 → G1 → S → G2 → M

↓ Resting phase of cycle

↓ (doubling of DNA Material) aka- Point of no return of cell



Checkpoints

- G_1-S Checkpoint - controlled by RB Gene
- G_2-M Checkpoint - controlled by p53 Gene
- P53 Gene is responsible for controlling both Checkpoint
- Predominant checkpoint on which P53 exerts its inhibitory action -GS_1 Checkpoint
- Cell cycle is affected by molecules called as cyclins

Cyclin	Cyclin Dependent Kinases
D	4;6
E	2
A	2;1
B	1

→ Most important cyclin which is required for replication of cell is Cyclin D because it is first cyclin which activated.

RB Gene- Molecular on/off switch of cell a/k/a Governor of cell replication

↓

Tumor suppressor gene

But when RB Gene is phosphorylated

↓

inactive

↓

Cell Cycle Proceeds

→ Transition of G1 → S

Role of p53 Gene - Guardian of genome (New guardian of genome- PTEN)
Normally wild type is present in the cells but which is Non Mutated.

Inhibitors of Cell Cycle: p21/p27/p57 → Activity of these is stimulated by p53 and inhibit the replication of damaged cell

Genes Involved in Carcinogenesis:-

Proto-oncogenes:- these are normal genes.

- Only when they get mutated i.e. get Hyperactive / associated with gain of function → act as Oncogenes
- Even a single mutation can cause cancer

Tumor Suppressor Genes:

Involved in – Cell differentiation

- DNA repair
- ↓ replication of cell
- Mutation of Both Gene is required for development of cancer aka Double hit theory → Given by Knudson

Proto oncogenes

Sis Gene	Brain Tumor – Astrocytoma
ERBB1	Lung Cancer
ERBB2 aka Her-2 receptor	Breast Cancer
RET	MEN II Syndrome
KIT	GIST
RAS K-RAS	Bladder cancer, kidney cancer Colon cancer, Pancreatic cancer
ABL (Chr 9) - Non-receptor associated Tyrosine Kinase activity	- CML - Good Prognosis - ALL -Bad prognosis
MYC Gene → C-MYC Gene → N-MYC Gene	 Burkitt Lymphoma (Max Mitotic Rate) - Starry sky pattern Neuroblastoma
Cyclin D_1	MANTLE Cell Lymphoma

Note: If mantle cell is not having cyclin D, Then Diagnosis is done by Marker SOX - 11

Tumor Suppressor Genes:

1) Rb Gene (Governor of Cell replication; molecular on/off Switch of cell)
   ↓
   Location (13q 14)
   a/w Retinoblastoma
2) NF-1 (17q) - associated with Neurofibromatosis -1 (a/k/as Von-Recklinghausen's Disease)
   NF-2 (22q) - associated with Acoustic Neuroma
3) APC Gene (5q) - Gate Keeper of Colonic neoplasia
4) VHL Gene (3p) - Associated with Von-Hippel landau Syndrome
   ↓
   - Associated with RCC
   - High risk of development of Pheochromocytoma
   - Cerebellar Hemangioblastoma, Retinal Angioma
5) CDH1: Associated with defect in Protein Cadherin associated with Familial Gastric Carcinoma Syndrome
6) BRCA 1/2 - DNA Repair Activity.

- BRCA 1 associated with Breast cancer in Females. Higher risk of endometrial cancer
- BRCA 2 associated with Breast Cancer in males; Higher risk of Prostate cancer

Apoptosis Regulation:

P53 Gene (Pro-apoptotic)

- Commonest Gene mutation a/w Human cancer - Causes Li-Fraumeni syndrome.

BCL 2(anti apoptotic gene) → Gene defect causes → Follicular Lymphoma (Non- hodgkin's lymphoma)

DNA Repair Genes

i. Mismatch Repair defect - Associated with Lynch Syndrome

- AD
- C/E/O syndrome (↑ risk of colon, endometrial, ovarian cancers)
- Proximal part of colon involved commonly

ii. Nucleotide Excision Repair – a/w Xeroderma Pigmentosum

- Due to exposure to UV light there is DNA Damage.

iii. Homologous Recombination Repair:

- Bloom syndrome
- Fanconi Anemia
- Ataxia Telangiectasia

Only Lynch Syndrome is AD rest are AR

AUTOSOMAL RECESSIVE CONDITIONS

B – Bloom Syndrome
I
G
F – Fanconi Syndrome
A – Ataxia Telangiectasia
X – Xeroderma Pigmentosa

Chromothrypsis – There is Chromosome shattering as a result, chromosomes are broken into smaller segments and they rearrange in defective pattern

↓

activation of proto-oncogenes

↓

Underactivity of tumor suppressor Gene → Cancer

- associated with ↑ risk of Osteosarcoma / Glioma

Oncogene addiction:-

Tendency of Tumor cells to totally dependent on Growth factors provided because of mutation e.g. CML

- CML is associated with Philadelphia Chromosome
- First cancer for which Targeted Chemotherapy done (by tyrosine kinase inhibitor)

Due to overactivity of tyrosine kinase enzyme tumor cells are totally dependent on tyrosine kinase and if there because of any reason there is decrease in tyrosine kinase tumor cells will be not able to survive.

Differentiation Therapy

- seen in AML – M3 (Acute promyelocytic leukemia)T(15;17)

↓

on administration of All-trans-Retinoic-acid (ATRA)
as a result there would be no

Epigenetic Changes

influence the activity of other genes
Therefore interfere with the activity of proto oncogenes and tumor suppressor genes.
These changes are associated with DNA methylation.

Tumor Lysis Syndrome

Seen in Burkitt's Lymphoma >ALL

↑ K^+
↑ Uric Acid
↑ Phosphate
↓Ca^{+2}

→ electrolyte disturbances

ETIOLOGICAL FACTORS

Carcinogens –**Ames Test** (carcinogenic test / mutagenic test): oncogenic potential of a substance.

- Organism used – S. Typhimurium

EXAMPLES OF CARCINOGENS

1) **Aflatoxin** – development of hepatocellular carcinoma
   → Aflatoxin is example of toxin produced by fungus (Aspergillus flavus) on contaminated peanuts
2) **Nitrosamines** - Causes GIT malignancy
   - Esophageal cancer
   - stomach cancer
3) **Asbestos** – associated with mesothelioma, bronchogenic carcinoma
   - M.C cancer due to asbestos- bronchogenic carcinoma
   - Most specific cancer due to asbestos – mesothelioma
4) **Vinyl chloride**
   - Associated with angiosarcoma of liver
   - Note: seen in exposure to thorotrast, arsenic, polyvinyl chloride
5) **Diethyl stilbestrol** associated with vaginal carcinoma,
6) **Cigarette smoking** lung cancer, kidney cancer, urinary bladder cancer as well
   Urinary bladder cancer can also be seen because of specific chemical
   β naphthylamine .

Radiation U.V.B rays exposure causes Skin cancer

- If there is defect in nucleotide excision repair gene causes Xeroderma Pigmentosa .

Ionizing radiation causes
i. Leukemia (CLL is not associated)
ii. Thyroid (papillary thyroid cancers)

Microbes

- Human T- cell leukemia/lymphoma virus
  - It causes adult T cell leukemia and CD4 T cell are affected

- HCV
- HCV + HBV

} Causes Chronic inflammation
↓
Hepatocyte injury
↓
↑ Regeneration rate of hepatocytes which causes mutations as result there is development of cancer

HBV → due to HBx protein causes DNA damage

- EBV – Hodgkin's lymphoma, Non-hodgkin's lymphoma, Burkitt's lymphoma, Nasopharyngeal carcinoma
  - Due to expression of LMP 1 there is predisposition to tumor is seen
- HPV- secretes E6 and E7 protein .E6 protein decreases RB gene activity and E7 protein causes decrease in P53 gene activity.
  - It causes Cervical cancer, Anal canal cancer, Oral cavity cancer.
- HHV 8 and HIV – KSHV (Kaposi sarcoma associated herpes virus)
- HIV – Primary CNS lymphoma

Non-Hodgkin's lymphoma

M.C extra nodal site for NHL in immunocompetent individuals is GIT (Stomach)

- M.C extra nodal site for NHL in HIV patients – CNS

H. pylori secretes CAG protein and responsible for MALToma (site stomach) and Gastric adenocarcinoma

Schistosoma- Bladder Cancer

Paraneoplastic syndrome

- Hypercalcemia – squamous cell carcinoma, breast cancer
- Cushing syndrome – small cell variant of lung cancer
- Polycythemia – RCC/HCC / CNS – cerebral hemangioma,fibromyoma
- SIADH – small cell lung cancer
- Hypoglycemia – fibrosarcoma, liver cancer
- Acanthosis nigricans – Stomach cancer, lung cancer
- Myasthenia gravis – THYMOMA
- Lambert Eaton syndrome – Small cell lung carcinoma
- Lesser Trelat sign (multiple seborrheic keratosis)

Seen in stomach cancer, pancreatic cancers

Diagnosis of cancers

1. FNAC – 22-26G needle
   does not differentiate between follicular adenoma and follicular carcinoma
   - Blood vessels in capsular thyroid are checked, If invasion is seen then neoplastic .
2. Exfoliative cytology: Pap smear
   Fixative → Ether +95% ethanol
   Site of taking biopsy is squamo-columnar junction.
   higher risk of contamination is seen in solid cancers biopsies.
3. IHC (Immunohistochemistry):Diagnosis, origin, prognostic and therapeutic significance.

E.g. Her 2/neu – it is molecule associated with breast cancer

Prognostic – if there is high expression of her 2/neu in tumor cells i.e. they have high proliferative rate (poor prognosis)

Therapeutic – Herceptin: drug targeting her 2/neu receptor.

4. Lymph node imprinting:- Useful for diagnosis of malignancy

5. Tumor markers – not for confirmation of diagnosis .

- **CA 125**: Diagnosis of ovarian cancer
- **CA 19-9**: Diagnosis of pancreatic cancer
- **CA 15-3**: Diagnosis of breast cancer
- **Calcitonin** : Diagnosis of medullary thyroid cancer

Note: If calcitonin negative medullary thyroid cancer CEA is used as marker

- β- HCG- Diagnosis of choriocarcinoma
- α- subunit has resemblance with other molecules like FSH, LH so Non – specific.
- VMA – diagnosis of pheochromocytoma
- Arginase- diagnosis of HCC
- CEA- diagnosis of colon cancer, pancreatic cancer.
- Immunoglobulins – diagnosis of multiple myeloma
- C-Kit (CD117) GIST; CML
- Current GIST is detected by more specific marker – DOG 1
- NSE - Diagnosis of neuroblastoma

Note: Synaptophysin, chromogranin, NSE – Tumor markers associated with neuroendocrine tumor

- CD99 (mic 2) - Ewing's sarcoma
- HMB - 45 - Melanoma

HMB - 45 is most specific marker for making diagnosis of malignant melanoma

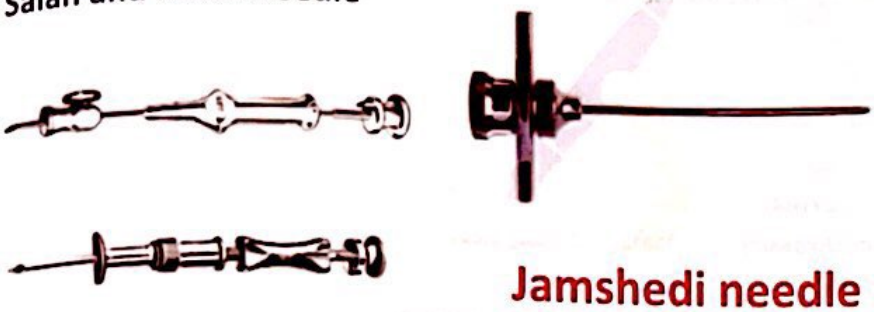
- Most sensitive marker of melanoma S - 100
- TTF- 1
  - Thyroid cancer
  - Lung cancer
- TTF- 1 is expressed in particularly adeno-carcinoma of lung

Intermediate Filaments

Cytokeratin → carcinoma
Vimentin → sarcoma
Desmin → Rhabdomyosarcoma
GFAP → Astrocytoma

1. Bone marrow examination

Salah and Klima needle



Jamshedi needle

Bone marrow examination can be done by 2 techniques

i. Bone marrow aspiration

ii. Bone marrow biopsy

→ Site of taking bone marrow tissue in adults is post-superior iliac spine

→ Site of taking bone marrow tissue in children is Tibia

Bone marrow aspiration:

It can be done by Salah and Klima needles

Bone marrow biopsy can be done by Jamshedi needle/Trephine biopsy needle

Differentiation between Salah and Klima needle

→ Salah needles have screw present on side

→ Klima's needle is straight needle, no screw on side of needle.

Reticulocyte

→ It have reticulin fibres

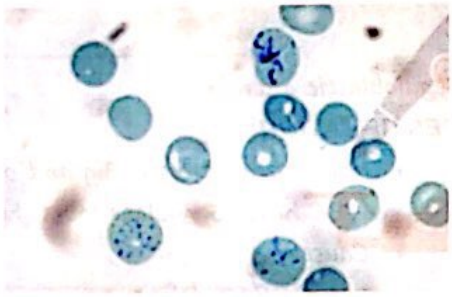
→ Presence of meshwork which is seen because of presence of Ribosomal RNA

→ This cell can be identified only in living state So k/a supra vital staining

→ Normal % of cells = 0.2-2%

→ It requires 1-2 days of maturation to become fully functional adult red blood cell.

→ Best stain for identification is new methylene blue.



Normal peripheral smear

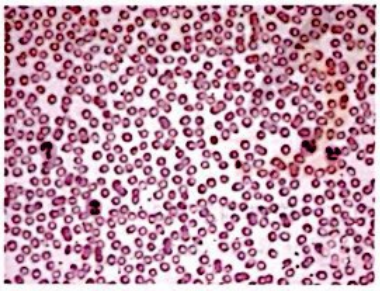
IDENTIFICATION:

→ Greater number of RBC are present

→ Presence of some types of WBC's

→ Dot like structures are present which represent platelets

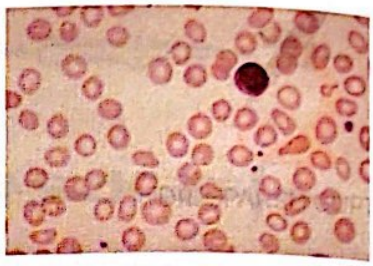
→ Normal RBC's have central 1/3rd pallor. This is due to distribution of hemoglobin



→ RBC parameter
- MCV
- MCH
- MCHC

→ In hereditary spherocytosis there is increased MCHC.

Red blood cell



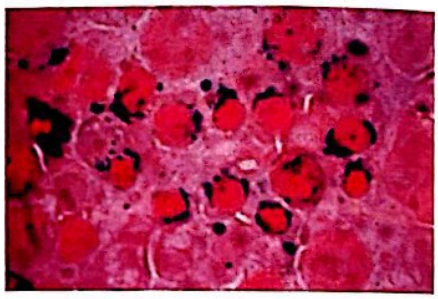
1. Microcytic hypochromic anemia

Diagnosis on peripheral smear:-

• Centre pale area as compare to normal
Which has only 1/3rd pallor (**hypochromic**)
• Cells are small in size (**microcytosis**)
M.C cause of microcytic hypochromic anemia – Iron deficiency anemia
• Anisocytosis (variability in cell size)
• Poikilocytosis (variability in cell shape)

→ To differentiate iron deficiency anemia and thalassemia trait we use – Mentzer Index.
→ Another reason of development of microcytic hypochromic anemia is anemia of chronic disease
In anemia of chronic disease normocytic normochromic anemia is more common than microcytic hypochromic anemia.

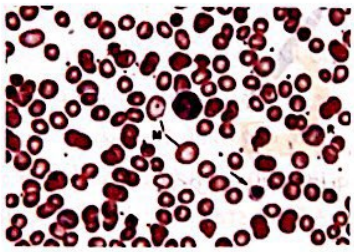
Sideroblastic anemia



Sideroblast in bone marrow examination

→ It is associated with lead poisoning, alcohol intakes, anti-tubercular therapy drugs.
→ Sideroblast cells have iron deposition in perinuclear area.
→ Sideroblast can be seen in following conditions
  i. Sideroblastic anemia
  ii. Myelodysplastic syndrome

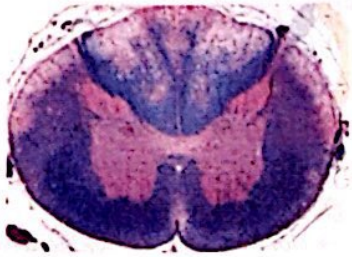
Megaloblastic anemia



IDENTIFICATION

→ Macro ovalocytosis (Big and oval RBC's)
→ WBC has > 5 nuclear lobes (hyper segmented neutrophil)
→ Causes
  - B12 deficiency
  - Folic acid deficiency
  - Administration of certain drugs

IN B12 deficiency there is demyelination affecting dorsal column of spinal cord

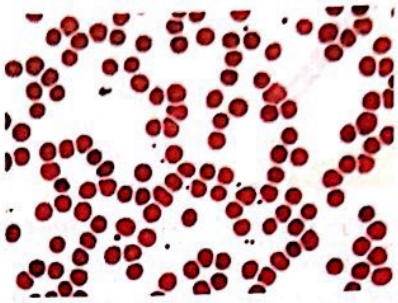


K/a sub-acute combined degeneration of spinal cord.

→ Presence of megaloblastic anemia with neurological manifestations diagnosis goes in favor of B12 deficiency
→ Presence of megaloblastic anemia without

neurological manifestations diagnosis goes in favor of folate deficiency .

Hemolytic anemia



1. Spherocytosis

Identification of spherocytes

- Spherical shape of cell
- No central pallor

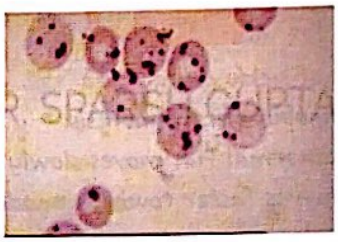
Causes:

- Autoimmune hemolytic anemia (M.C)

Genetic cause: Hereditary spherocytosis (due to defect in membrane protein ankyrin)

G6PD deficiency

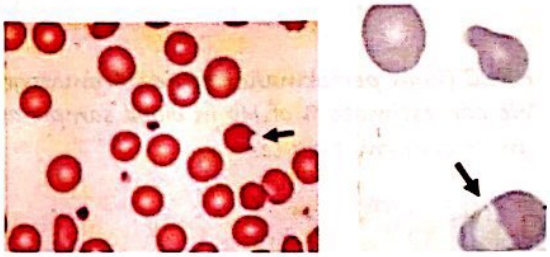
→ RBC more prone to oxidative damage .



HEINZ BODIES

→ Following any oxidative stress there is denaturation of hemoglobin which is going to result in precipitation of hemoglobin inside the RBC.
These bodies are called Heinz bodies
Heinz bodies can be detected by supra vital staining

→ RBCs with heinz bodies when pass through splenic circulation, macrophages try to eat up that part of RBC giving rise to bite cells



BITE CELLS

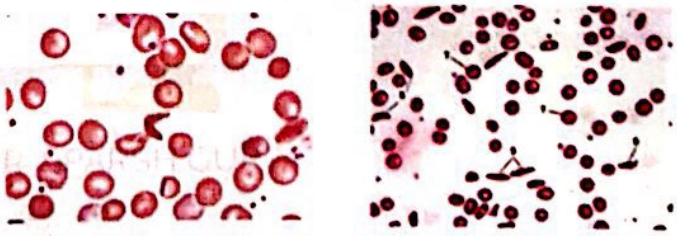
→ RBC membrane become stretched so responsible for formation of Blister cell

1. Heinz bodies are detected with supravital staining
2. Bite cells
3. Blister cells
4. spherical RBC in peripheral smear
5. Both intra vascular and extra vascular hemolysis is seen

→ No treatment is required as it is self-limiting condition

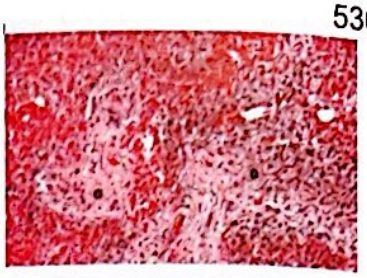
Sickle cell anemia

In Peripheral smear → Sickling of cells is seen

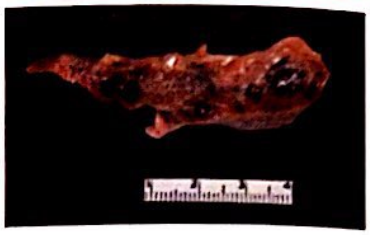


→ Sickling is not easily seen in sickle cell trait so chemical is added k/a Na meta bisulphide so that sickling can be observed.

→ There is also presence of Fibrotic areas in spleen
→ Which are having calcium deposition k/a
"Gandy gamma bodies"

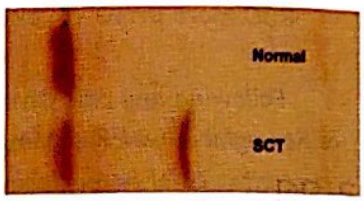


In initial stage there is ↑ in size of spleen; at later stages there is fibrosis of spleen k/a auto splenectomy
it is caused due to hemoglobinopathy that is resulting because of point mutation .

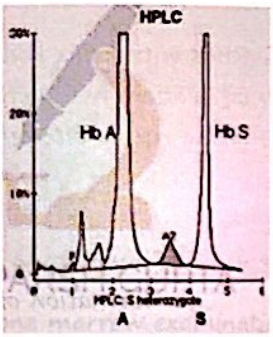


Diagnosis of sickle cell anemia

I. **Hemoglobin electrophoresis:-**
Hb S (abnormal Hb) moves slowly and
Hb A moves faster towards anode

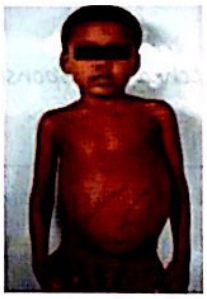


ii. **HPLC** (high performance liquid chromatography)
We can estimate % of Hb in blood sample and it is most confirmatory test.



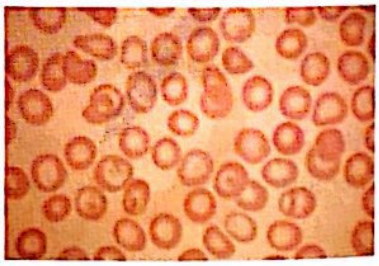
THALASSEMIA:

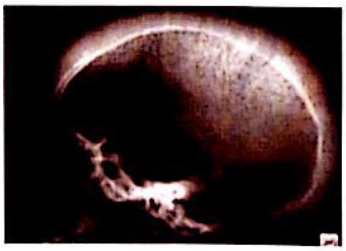
There is Presence of hepatomegaly and splenomegaly



Peripheral smear:

→ Presence of microcytic hypochromic cells (>1/3rd central pallor)
→ Target cells / deposition of Hb inside RBC
→ Severe anemia
→ Crew cut/hair on end appearance Due to expansion of diploic spaces



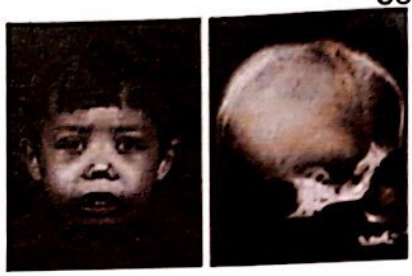


Crew cut/hair on end appearance

Extra medullary hematopoiesis:-

→ Characteristic facial appearance

.Bones of nasal, maxilla and jaw become prominent along with malocclusion of teeth and prominent forehead.



Types

Thalassemia trait

↓

Nestrof of test is done - screening test

Thalassemia major

→ RBCs which are affected in case of thalassemia are relatively resistant to osmotic fragility Therefore they not able to lyse easily so the black line is not visible

→ Black line is visible in the control

The test is K/as naked eye single tube red cell osmotic fragility test

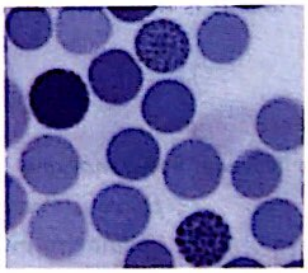
Diagnostic test in thalassemia trait and thalassemia major is made by HPLC

→ In thalassemia trait there is >3.5 gm. of HbA2

→ In thalassemia major - >% of Hb F. (fetal hemoglobin)

Alpha Thalassemia;

→ In alpha thalassemia sometimes there is presence of inclusions associated with precipitation of Hb H This kind of Hb H is responsible for granularity on surface of RBC described as Golf Ball appearance.



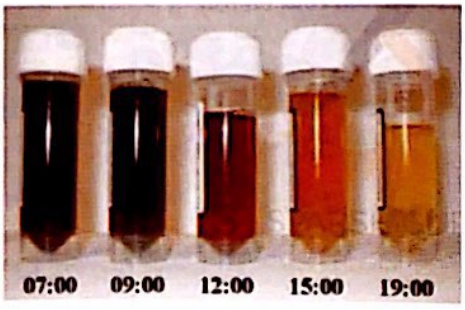
PNH - (paroxysmal nocturnal hemoglobinuria)

→ PNH is only important example of acquired intracapsular hemolytic anemia

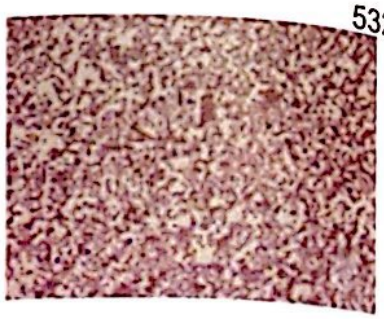
→ There is Defect in GPI linked protein, causing decreased functioning of CD59/CD55 and complement related protein

→ Due to presence of nocturnal intravascular hemolysis patients have hemoglobinuria and early morning sample is darkest sample.

Subsequently the sample becomes normal till night.



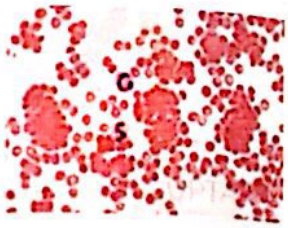
→ PNH in not seen in infancy
→ It is a/w myelodysplastic syndrome
→ also a/w leukemia as well as aplastic anemia



Cold Agglutinin Disease:

Following any kind of exposure to cold, RBC have tendency to agglutinate

- sample of patient is taken on a chilled slide and viewed under high power magnificatin
  Agglutination of RBC is seen

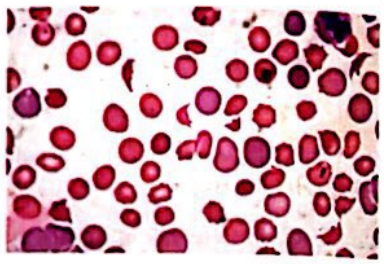


Classical antibody seen is IgM

→ It is Associated with infectious mononucleosis, mycoplasma infections and Waldenstrom macroglobinemia .

Angiopathic hemolytic anemia

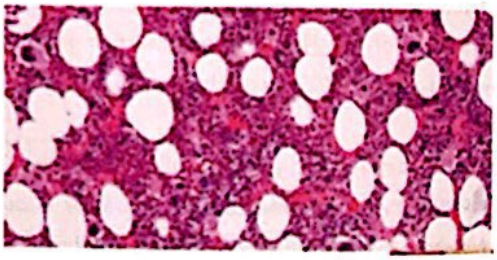
→ Characterized by deposition of clot in the blood vessels which is responsible for causing physical damage to RBC .
→ fragmented RBC (Schistocytes - helmet shaped) appear in blood



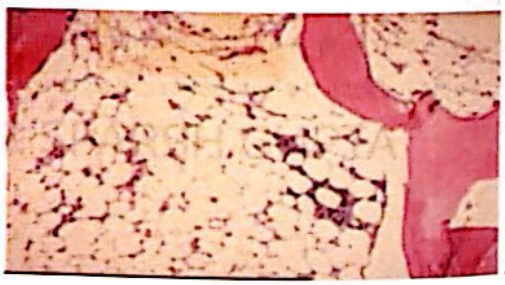
→ M.C condition associated with **microangiopathic anemia** is DIC and it is mosty commonly seen in patient who have undergone cardiac valvular replacement.

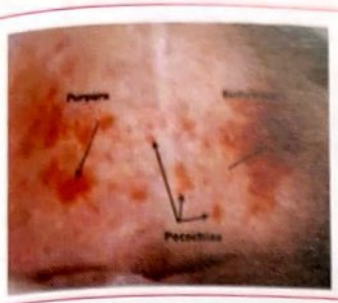
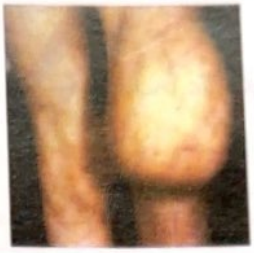
Aplastic anemia

→ Normal bone marrow
  - there is Presence of empty areas and there is 50% cellularity and 50% presence of fat cells.



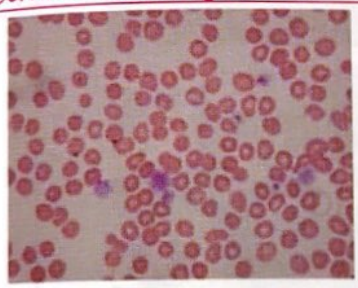
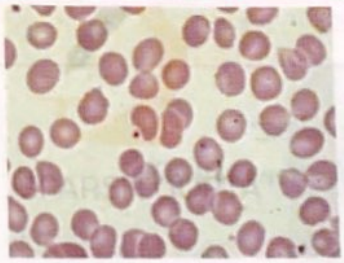
In aplastic anemia there is Hypocellular marrow and Extensive infiltration of fat cells
IOC: bone marrow biopsy.



	
In Platelet disorder - there is involvement of superficial skin C/C Purpura, petechia, ecchymosis	in Clotting factor defects - there is massive bledding in muscles or joints (Hemarthrosis)

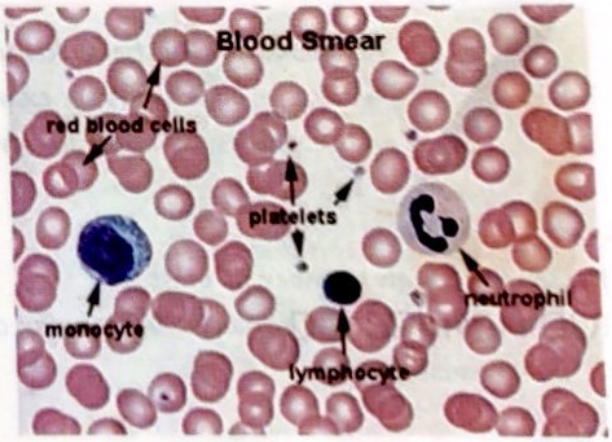
→ Investigation for platelet disorder
  ○ Platelet count, bleeding time
→ Investigation for clotting disorders
  ○ APTT, PT value

Platelet disorders

Bernard soulier syndrome	Wiskott Aldrich syndrome
	
• In this condition Giant platelets are seen and platelets size comparable to normal RBC	• Platelets are less in number • Extremely small

White blood cells

Normal peripheral smear
→ Neutrophil – 3-4 nuclear lobes
→ Lymphocytes – longest living W.B.C round nucleus
→ Monocyte – kidney shaped nucleus
Basophil and eosinophils are relatively less in number so may not be visible on peripheral smear
Variations

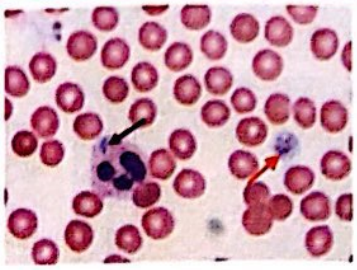


1. May Hegglin anomaly

findings :

i. Giant platelets

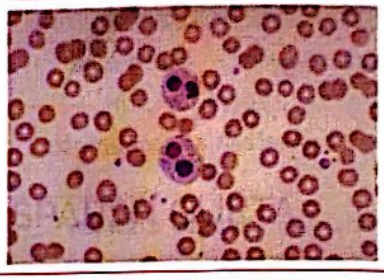
ii. Neutrophils have basophilic inclusions



2. Pelger – Huët anomaly

→ Neutrophil has only 2 nuclear lobes

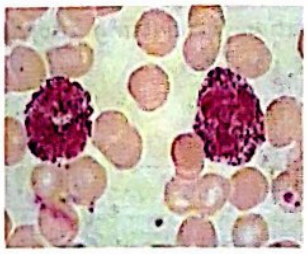
→ Pseudo Pelger anomaly is seen in myelodysplastic syndrome



3. Alder- Reilly anomaly

→ W.B.C has- dense eosinophil granules

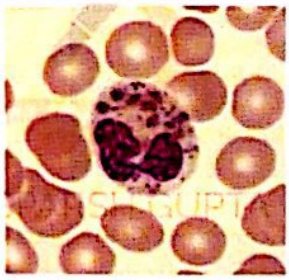
→ This condition Is associated with patient suffering from mucopolysaccharidosis



4. Chediak Higashi syndrome

→ Presence of giant granules inside W.B.C

→ ↑ Bleeding tendency, ↑ risk of infections, albinism due to lysosomal transfer protein.



Acute leukemia

Acute lymphoblastic leukemia

→ I.O.C – bone marrow examination

→ >20% blast – acute leukemia

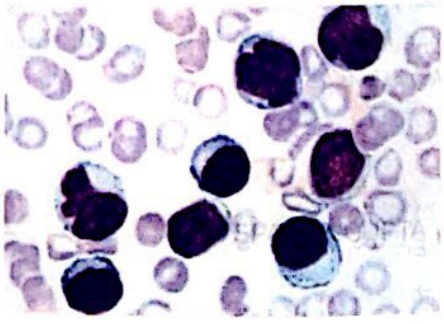
Acute myeloblastic leukemia

Lymphoblast

Presence of high number of blast

i. No granules is cytoplasm "Agranular cytoplasm"

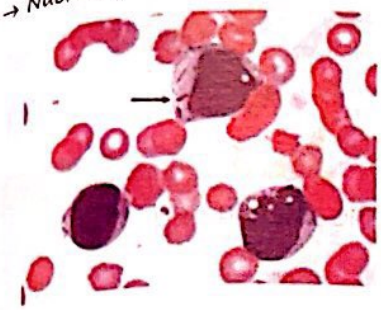
ii. No nucleoli



Myeloblast

→ Presence of granules in cytoplasm

→ Nucleoli present

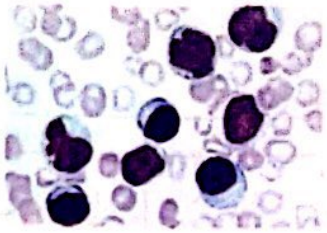


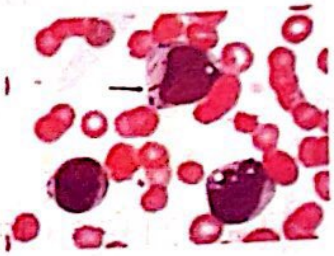
Lymphoblast Vs myeloblast

→ Stains for lymphoblast- PAS and TDT

→ Stains for myeloblast -Myeloperoxidase, Sudan black V

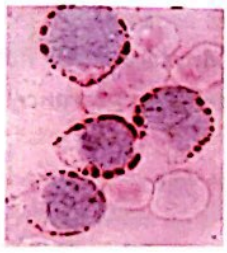
→ In some subtype of Acute myeloblastic leukemia (M6, M7 variant) – PAS positivity can be seen





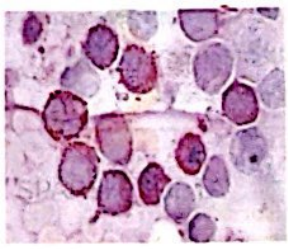
PAS staining

Block like staining



Seen in lymphoblast, granularity is seen

Diffuse staining



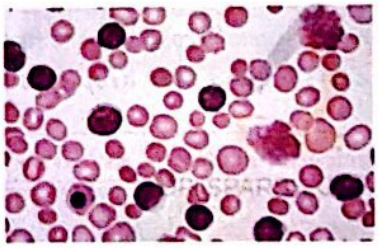
Seen in erythroblast; M6 variant of AMC (Diffuse staining)

Chronic leukemia

→ Cells have crushed up appearance

→ "smudged up appearance"

Seen in CLL

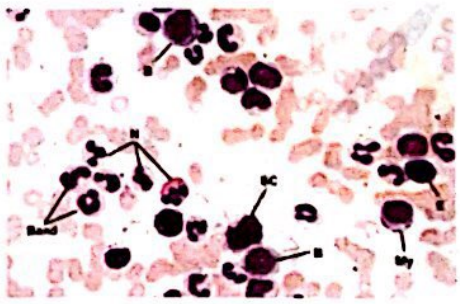


Commonest blood cancer in adults

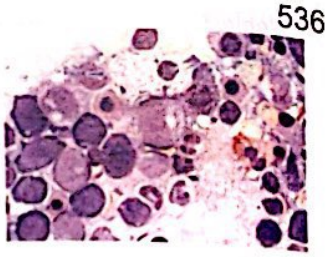
→ I.O.C – flow cytometry shows presence of CD molecule on neoplastic cells.

→ presence of precursor cells, band cells, myeloblast, promyelocyte, eosinophils, Erythroblast.

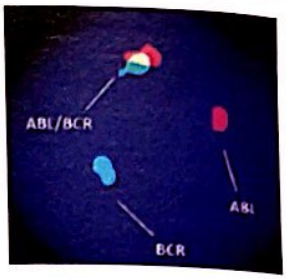
→ Different stages of maturation of WBC in peripheral smear seen



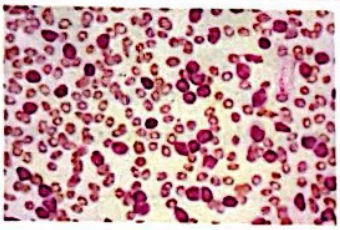
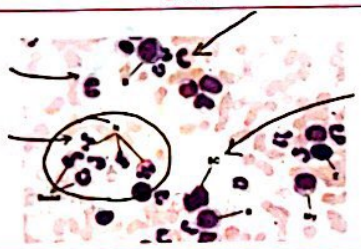
→ Combination of basophilia and eosinophilia in peripheral smear seen in CML
→ Sometimes there may be presence of cell k/aPseudo-Gaucher cells
They have foamy appearance.



I.O.C – FISH Technique
In this technique Different dyes are used to detect Philadelphia chromosome
In this translocation of chromosome 9 and 22 is seen.

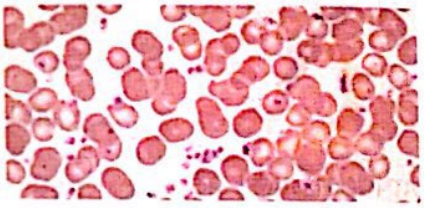


Peripheral smear examination CLL vs CML

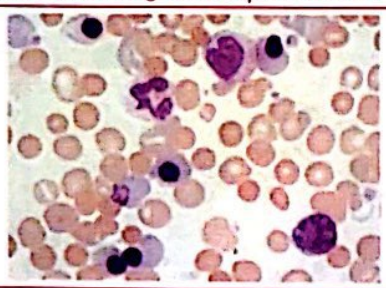
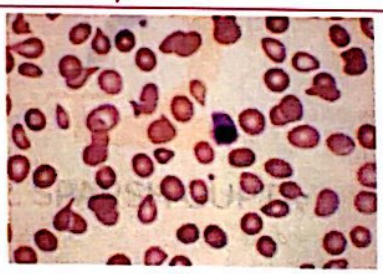
CLL	CML
	
All tumor cells have same appearance → convent girl appearance or "Smudged appearance"	Different types of stages are present College girl appearance or flowers in "garden appearance"

Myeloproliferative disorders

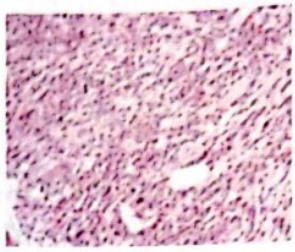
1. Essential thrombocytosis
   → Platelets are present predominantly
   → Big size platelets & ↑ in number



Primary myelofibrosis : there are nucleated erythroid precursors and tear drop cells seen.

Nucleated erythroid precursors	Tear drop cells
	
These are seen due to Presence of fibrosis in marrow	→ RBC gets stretched and as a result it appear as 'Tear drop' a/k/a dacryocytes

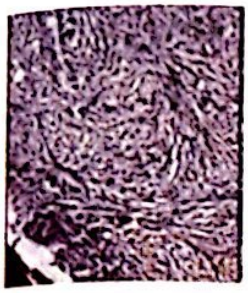
BM biopsy of primary myelofibrosis



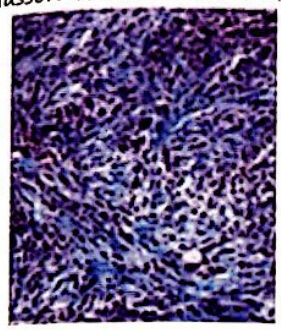
Biopsy findings

- Abnormal precursors seen
- Deposition of reticulin fibres
- Presence of fibrous tissue & Collagen

For detection of reticulin fibres stain used is **"Gomori stain"**



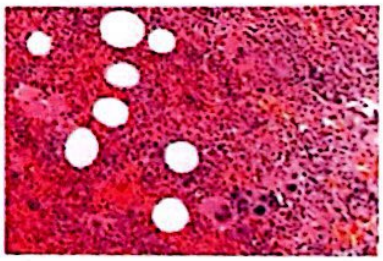
→ Masson Trichrome stain is use to detect fibrous tissue



Polycythemia vera

→Characterized by change in Amino acids

→ There is replacement of valine by phenylalamine



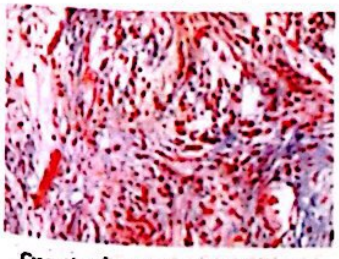
Mutation = **JAK 2 Mutation**

→ In early stage there is proliferation of all cell lines k/a Panmyelosis.

→In this image there is increased cellularity this is seen due to proliferation of all cell lines.

However in later stages due to excessive fibrosis in marrow which is Called as spent phase.

In this image blue colour depicts fibrosis of marrow k/a spent phase.



Spent phase in BM biopsy

1. **Myelodysplastic syndrome**

→It can progress to acute leukemia

→In children it is associated with monosomy 7

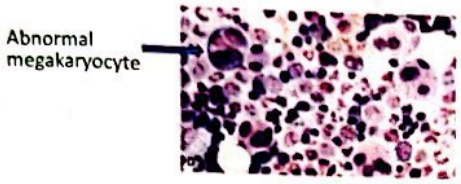
→In adults it is associated with 5q deletion

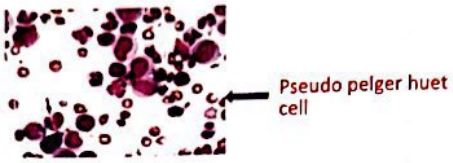
BM examination

→ There is Presence of Abnormal RBC, WBC and platelet precursors

WBC – has presence of 2 nuclear lobes k/a **pseudo Pelger Huët cell**

Platelets: abnormal megakaryocyte have fragmented nuclear lobe k/a **'pawn ball megakaryocyte'**

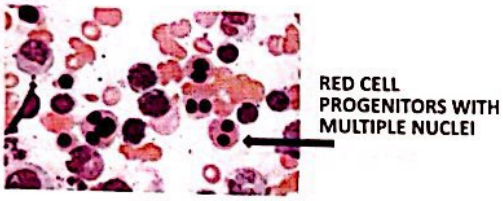


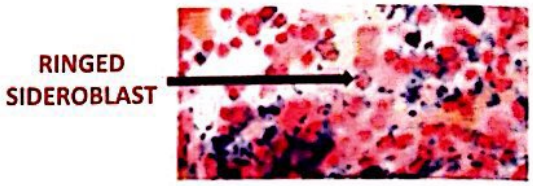


→ Erythroid precursor – red cell progenitors with multiple nuclei

→ Perinuclear deposition of iron – **ring sideroblast**

→ **Ring sideroblast** can also be seen in lead poisoning, administration of anti tubercular drugs mainly isoniazid, sideroblastic anemia





MDS

RBC	WBC	Platelets
Ringed Sideroblastic	pseudo-Pelger Huët cells	Pawn Ball megakaryocytes

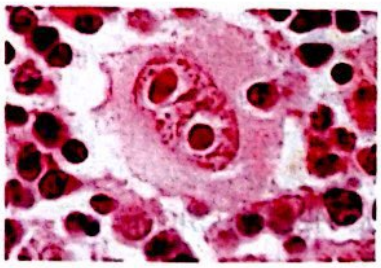
Lymphoma's

Hodgkin's lymphoma

Classical Cell- RS cell (Reed Sten Berg cells)

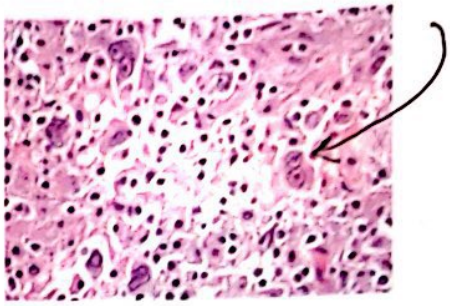
RS cell has 2 nuclei with prominent nucleoli

- "owl eye appearance"

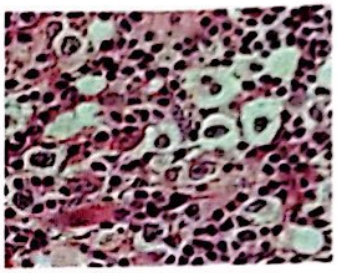


→ To make diagnosis of Hodgkin's lymphoma – there should be classical Reed Sten berg cells along with Black ground of other inflammatory cells

→ Only reed Stenberg cell is not sufficient for making diagnosis of hodgkin's lymphoma.

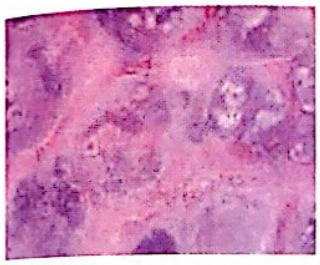


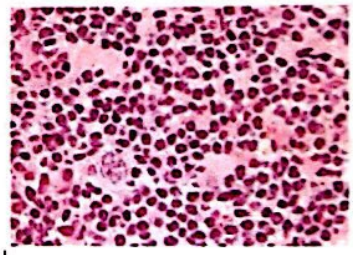
Classical RS cell has markers like CD 15 and CD 30
Variant of RS cell
↓
Associated with absence of CD 15 /CD 30 markers k/a "Non -classical RS cell" or popcorn cell" or LH cell.



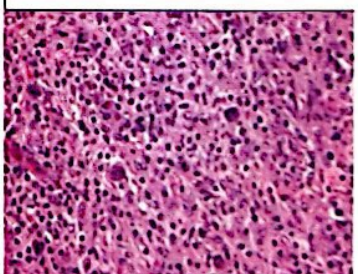
RS cell variants:

1.Lacunar cells-
Nucleus is present in empty area or lacuna is k/a lacunar cell.
associated with release of TGF-beta which is responsible for deposition of fibrous tissue so there is formation of nodules
Seen in "nodular sclerosis Hodgkin's lymphoma



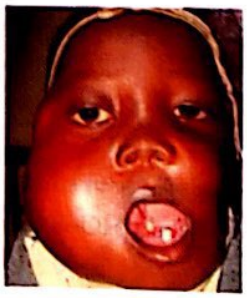


2.Non classical RC cell
→Nuclear membrane have indentations responsible for "popcorn cell appearance".
→Seen in lymphocyte – predominant Hodgkins lymphoma
→This subtype has **Best prognosis**
→Popcorn cell are identified with help of **BCL6, Cd20**



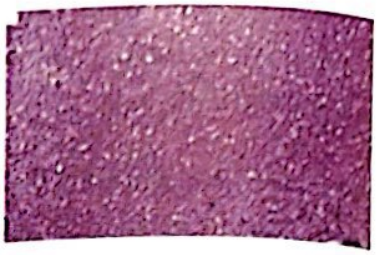
3. Mononuclear RS cells
→Background of inflammatory cells like plasma cells ,lymphocytes , eosinophils etc.
→Seen in mixed cellularity Hodgkin's lymphoma
→Commonest type of Hodgkin's lymphoma in India is mixed cellularity Hodgkin's lymphoma

- **Commonest type of Hodgkins lymphoma in word is nodular sclerosis Hodgkins lymphoma.**



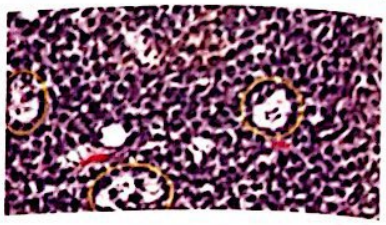
Non-Hodgkin's lymphoma
1. Burkitt lymphoma
→ Associated with over activity of C-Myc gene

→ Associated with chromosomal translocation
classically t(8;14) but there can be also other
→ translocation as well like: t (2:8)
→ Endemic sub variant of Burkitt lymphoma seen in African children
classically involving jaw.

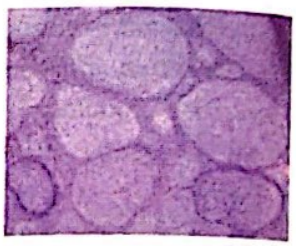


Biopsy findings

→ There is Presence of empty looking area against dark
Colored tumor cells.
→ empty looking area are representative
of macrophages.

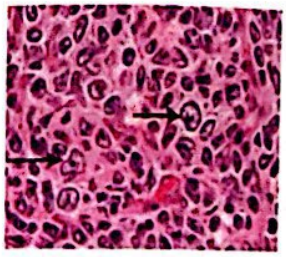


Appearance of **Starry Sky**

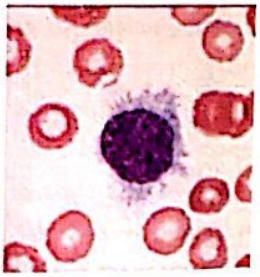


Follicular lymphoma

→ **Non- Hodgkins lymphoma**
o There is Presence of follicles.
→ It is due to chromosomal translocation between
chromosome 14 and 18which is responsible for
causing ↑↑ BCL 2 (anti-apoptotic gene) and
overexpression of bcl2 is responsible for formation of
low grade tumor which is associated with formation of follicles.

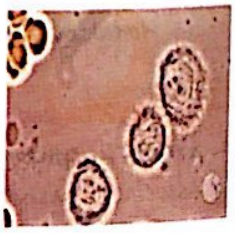


Microscopic findings
There are 2 subtypes of tumor cells
- Centroblast
- Centrocyte or buttock cells
Bigger cells are centroblast which are having presence of nucleoli.
→ Most common subtype of non-Hodgkin's lymphoma
is Diffuse large B cell lymphoma .
→ Some patient having follicular lymphoma progress to
diffuse large B cell lymphoma K/as "**Richter's Transformation**"

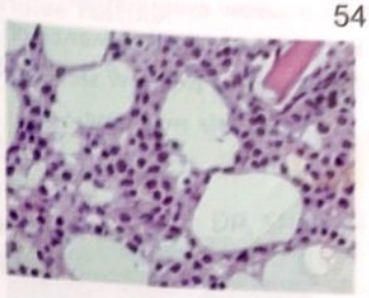


Hairy cell leukemia

→ Hair like projection are seen which arises from the surface of cells.
→ It is B cell Tumor
→ Best appreciated under phase contract microscopy in which
Hairs like projections are seen.
→ It involves Bone marrow and spleen .
→ Bone marrow aspiration gives dry Tap
→ I.O.C = Bone marrow biopsy



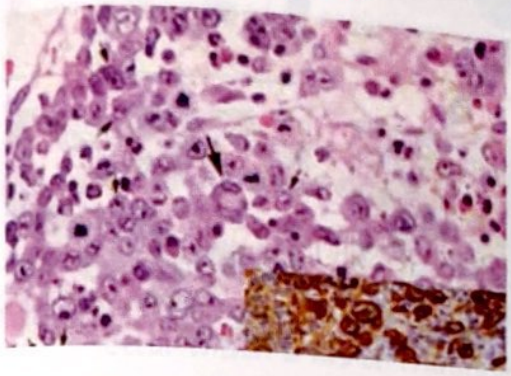
Bone marrow biopsy



tumor cells give **Honey Comb appearance.**

→ Around nucleus of tumor cells there are empty spaces giving fried egg appearance

Anaplastic large cell lymphoma

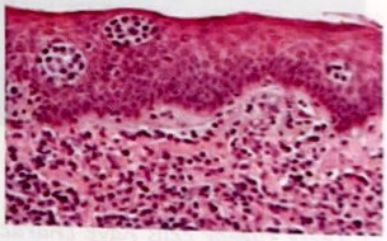


- **T cell tumor**

→ Most characteristic finding is tumor cell with "Horse shoe nucleus" or Embryoid nucleus known as **hallmark cells**

→ Positive immuno staining for ALK

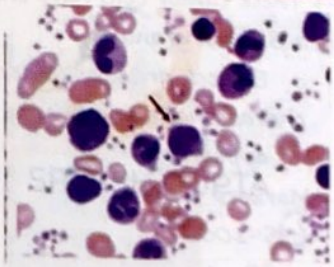
Albert – basin disease



→ It is another name given for skin involvement in Patient suffering from **mycosis fungoides.**

→ Mycosis fungoides is CD4 T cell tumor

→ Tumor cells infiltrate into epidermis - Pautrier micro abscess



→ There neoplastic cells can be seen in blood as well When they are seen in blood they are k/a Sezary cells Nucleus have convoluted appearance K/a **"cerebriform nuclei"**

Plasma cell neoplasia

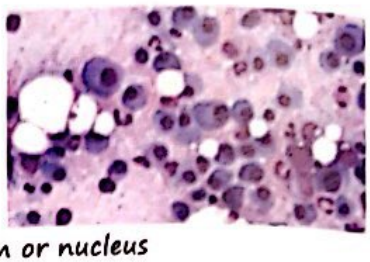
→ Plasma cell identification

→ Presence of eccentric nucleus due to large amount of endoplasmic reticulum.

→ Nucleus has cart wheel appearance

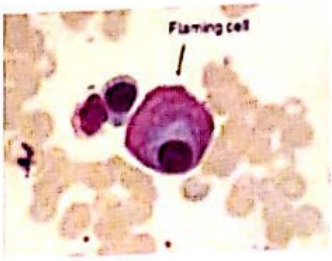
Bone marrow examination

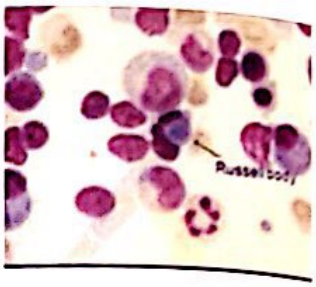
→ There is Predominance of plasma cells in the bone marrow seen in plasma cell neoplasia E.g. multiple myeloma.

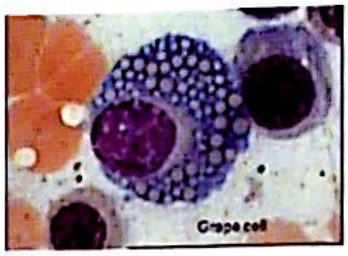


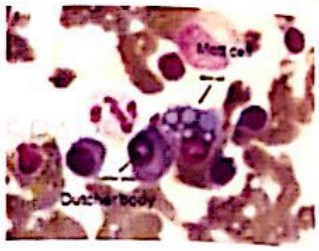
→ Histological finding due to immunoglobulin deposition either cytoplasm or nucleus

1. Flame cells –immunoglobulin deposition giving pinkish appearance.
2. Russell body -cytoplasmic deposition of Immunoglobulin inclusions.
3. Mott cell – inclusions are deposited in form of grape like appearance
4. Dutcher body -intra nuclear inclusions





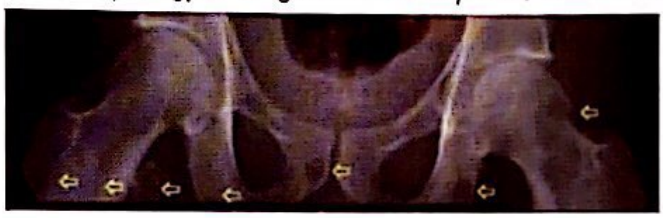


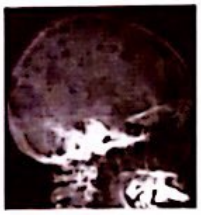


Radiological findings

→ Presence of punched out lesions in x- ray skull

→ Multiple types of lytic lesions in pelvis, femur head and vertebral column



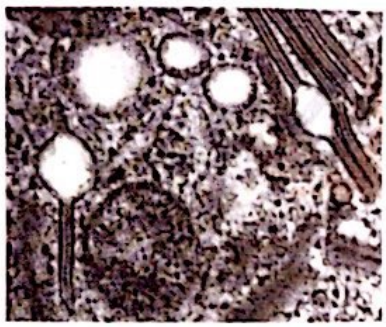


Langerhans' cell histiocytosis

→Presence of tumor cells

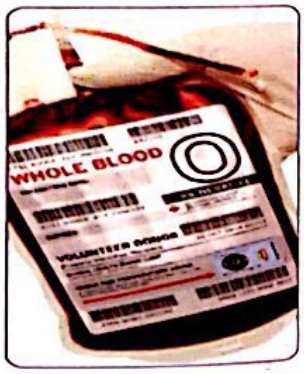
→ These tumor cells have characteristic granules k/a Birbeck granules

- Birbeck granules under electron microscope have characteristic appearance k/a Tennis racket appearance



→Markers:-

- S-100
- CD- 1a
- HLA -DR



Blood Bank

1. Whole blood

Storage temp- 2-6 degree C

Shelf life- 42 days

Anticoagulant added – SAgM

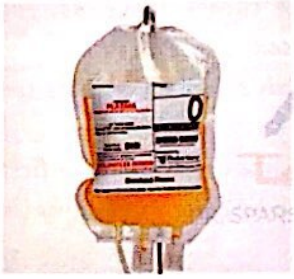
Blood transfusion should be started within 30 minutes and it should be finished within 4 hrs.

→ Commonest blood transfusion reaction is febrile non- hemolytic transfusion reaction

→ Mismatched BT reaction is mostly due to clerical error i.e wrong blood group is mentioned on blood bag
- It is associated with fever, loin pain in conscious patient
- In unconscious patient there is bleeding oozing from surgical site

2. Transfusion set
→ 2 components
I. Transfusion needle
→ Size= 18-19G
→ Size of filters= 170-180 microns
→ Transfusion of fresh frozen plasma or cryoprecipitate should be started as early as possible and finished within 20 min .

Fresh frozen plasma;
→ Fresh frozen plasma indication
i. Active bleeding due to deficiency of clotting factor
ii. Storage - -18 degree C to -30 degree C
- Shelf life- 1 year



Complication: Transfusion related acute lung injury
- Occur within 6 hrs of Transfusion

Cryoprecipitate: Temp- -18 degree C to -30 degree C
- Shelf life- 1 year

It should be transfused as early as possible and finished within 20 minutes
Difference between cryoprecipitate and fresh frozen plasma
Cryoprecipitate is rich in certain factor I, VIII, XIII and von Willebrand factor

Indication of cryoprecipitate
- Hemophilic A
- Von Willebrand disease

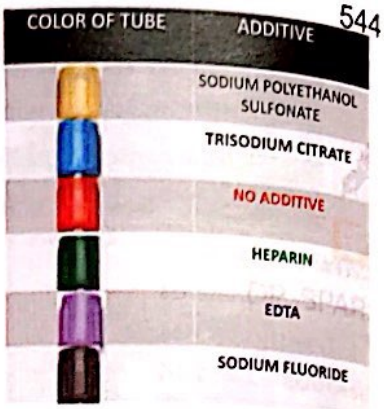
In hemophilia B. FFP is required

→ Platelets
→It should be kept at 20-24C
→Shelf life- 5 days
→M.C component of blood which is associated with transfusion related infections is platelets.

Platelet donation
- Single donor platelets
- Random-donation platelets

When there is platelet donation the blood sample is taken from donor, then it goes to processing unit where the platelets are separated and rest of the blood is transfused back causing perioral numbness/tingling. because blood that is re-infused contains citrate and it causes transient hypocalcemia.

Lab Additives



1. **Yellow tube** contain Na poly ethanol sulfate
   →Used for bacterial culture
2. **Light blue tube** – Contains Trisodium citrate (3.2%) which is Used as anticoagulant
   → Used for Estimation of ESR, platelet study, coagulation study

Trisodium citrate: Blood ratio 1:9

Red Tube → contains no additive
   →Used for serum analysis

Green Tube → contains Heparin

Used for estimation of serum electrolytes, osmotic fragility test, ABG
   →Lithium salt of heparin is preferred for serum electrolytes (light green colour tube)
   →Na salt for other purposes (dark green colour tube)

EDTA tube – (Lavender color tube)

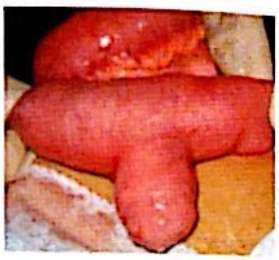
- Used for CBC, PCR

Greyish color – Contains sodium fluoride which inhibits process of glycolysis used for glucose estimation

Sequence of sampling – first in yellow tube → blue color → red tube → green → lavender → grey
→ Yellow color tube sampling is done first because of least chances of getting contaminated.

Gastrointestinal tract

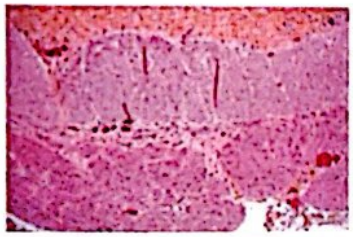
Congenital Anomalies



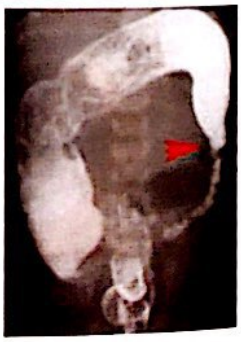
1. MECKEL'S DIVERTICULUM

Rule of "2"

→ Seen in 2% of population
→ Presents in males
→ Presentation of child <2yrs of age
→ Location: 2 feet Proximal to ileocaecal value
→ 2 inches in length
→ It is True diverticulum
→ Sometimes, there is presence of ectopic Gastric mucosa, and if there is ulceration in ectopic Gastric Mucosa, the children can have right iliac fossa pain



2. HIRSCHSPRUNG DISEASE



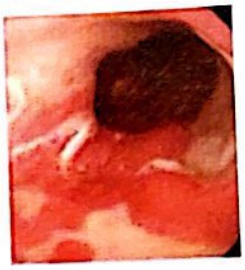
→ Associated with RET Gene Mutation
→ There is defect with migration of Neural crest cells as a result of which there will be Absence of Ganglionic cells both in submucosa as well in muscle layer.
→ Due to Absence of Nerve cell the affected part which is mostly rectum does not contracts properly.
→ The part proximal to affected area will be dilated and affected area will become constricted.
→ Diagnosis is made on clinical Presentation and rectal Biopsy

→ Intra operative frozen sections can be taken which can be used for demonstrating the presence of Acetyl choline esterase activity in the Biopsy section.

ESOPHAGUS

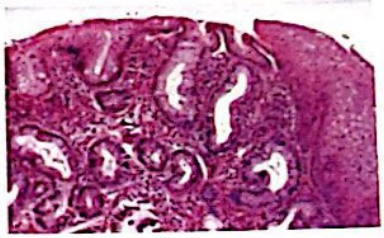
1. BARRETT'S ESOPHAGUS

→Endoscopically, barrett's esophagus is identified by presence of Reddish mucosa which can be seen in comparison to the pale Normal Mucosa.



Microscopic findings:

→ Normally Esophagus is lined by Stratified squamous epithelium.
→ In Barrett's Esophagus, the stratified squamous epithelium is gradually replaced by intestinal columnar epithelium.
→ At Microscopic level, intestinal columnar epithelium is identified with the help of Goblet cells.
→ There is change in nature of epithelium which is called as Metaplasia
→ If this condition is present for long of time it increases the risk of development of **Adenocarcinoma of Esophagus**
Anatomically, the Adenocarcinoma of Esophagus arises from lower 1/3rd of esophagus.
→ Identification : Goblet cells are having presence of mucin And mucin can be stained with the help of stain called as **Alcian Blue** .

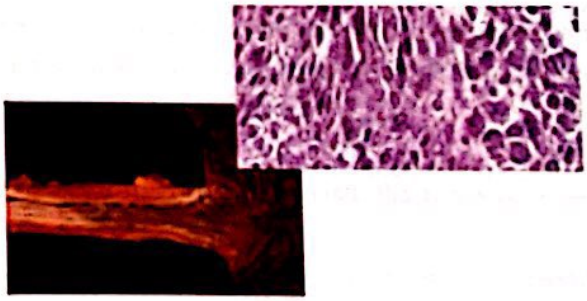


Barrett's with malignancy

→ Patients having Barrett's Esophagus have higher risk of development of Adenocarcinoma Esophagus.
→ Mass projecting in lumen of Esophagus in Patient with Barrett's suggest adenocarcinoma of Esophagus.

2. HERPES ESOPHAGITIS

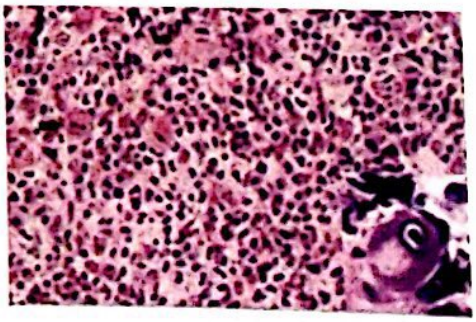
→ Presence of sharp delineated ulcers that are located in lower part of Esophagus also called as "Punched out" ulcers.
→ Microscopically, there is intracellular substance k/a ground glass appearance.



3. CMV ESOPHAGITIS

→ Commonly seen in Patients with
- Transplant
- Immunosuppressant drugs

→ "Owl eye appearance" is characteristic Feature of CMV Esophagitis.



4. ACHALASIA CARDIA

→ There is selective loss of inhibitory Neurons, particularly affecting the lower part of Esophagus.

→ Affected part is having Narrow lumen and proximal part is having dilated Esophagus.

→ Appearance on Barium Swallow: **Bird Beak appearance**

- Chronic achalasia cardia increase the risk of Squamous cell carcinoma.
- Cancer in achalasia cardia arises from lower 1/3rd Esophagus.

5. ESOPHAGEAL CANCER

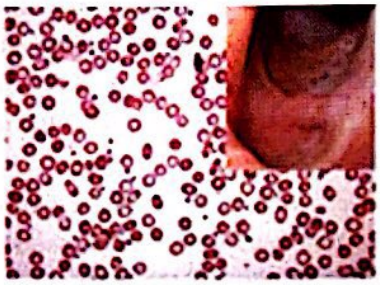
Risk factor

→ Tobacco intake orally or smoking

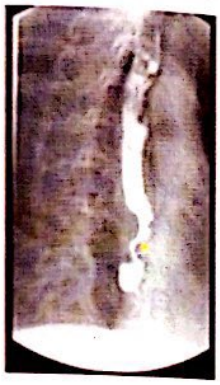
→ Alcohol intake

→ Nutrient deficiency

→ Female having iron deficiency anemia with esophageal webs presence of atrophic glossitis is associated with **Plummer Vinson syndrome**



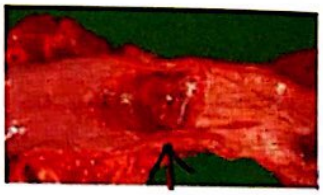
→ Esophageal web is mucosal protrusion in upper part of Esophagus, so if these patients are having development of Esophageal carcinoma, the site is upper 1/3rd of Esophagus



→ If patient is having cancer secondary to Barrett's Esophagus, the location is lower 1/3rd.

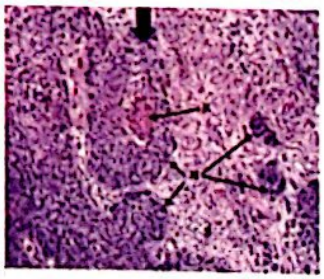
→ This cancer gives zig zag appearance called as "Rat Tail appearance".

→ M.C location of esophageal cancer in India is Middle 1/3rd



Histology

→ Squamous cell carcinoma M.C subtype



Identification of SCC:

- "Nest like structures"
- "Presence of Keratin"

ESOPHAGEAL ADENOCARCINOMA

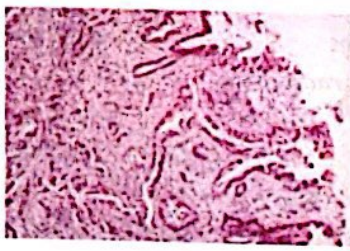
→ Associated with Barrett's esophagus

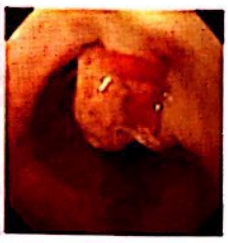
→ Red velvety mucosa

→ Abnormal exophytic mass.

Microscopically

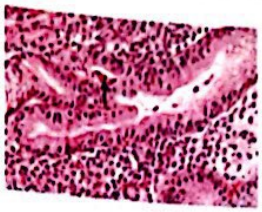
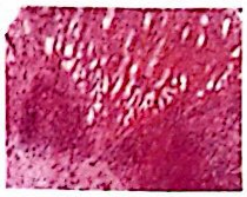
Glandular structure is seen which have poorly differentiated cells





1. H. PYLORI GASTRITIS

M.C cause of chronic gastritis is caused by H. Pylori.

Microscopically

i. Presence of Neutrophils in lamina propria

ii. Presence of lymphoid aggregation with subepithelial plasma cells.

Special stain to identify H. Pylori is silver stain

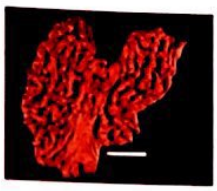
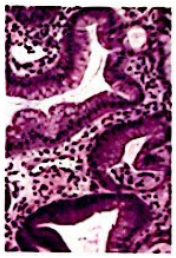
2. MENETRIER DISEASE

→ Grossly, it is associated with Prominent Gastric rugae folds

→ It is characterized by over secretion of TGF-

Histologically

→ Foveolar cells Hyperplasia.

C/F

→ Abdominal Pain

→ Diarrhea

Patient with Ménétrier's disease have high risk of carcinoma stomach.

3. GASTRIC CARCINOMA

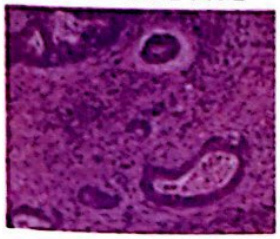
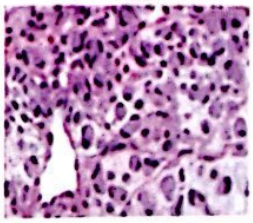
→ M.C site (India): Antrum

→ In Developed countries, M.C SITE: Proximal stomach.

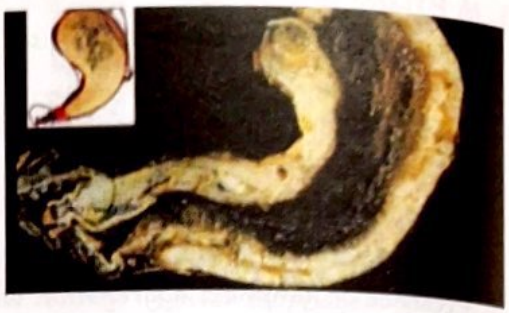
Microscopically:

- Adenocarcinoma

lauren's classification

Intestinal subtype	Diffuse subtype
→Presence of Tumor cells which result in Gland formation → They separate out **INTESTINAL TYPE** 	→ Tumor cells do not adhere to each diffuse involvement of stomach → Diffuse subtype is associated with E-cadherin genetic mutation **DIFFUSE TYPE** 

→ Gastric carcinoma can also be classified as
i. Early Gastric Carcinoma – Cancer involve mucosa and submucosa
ii. Late gastric carcinoma – Goes beyond submucosa
(involved of muscle layer or involvement of serosa layer)



→ Diffuse subtype is also associated with Desmoplastic response, Whenever there is desmoplastic response it is sometimes Associated with thickening of stomach wall k/a **Leather Bottle appearance of stomach.**

4. GASTRIC LYMPHOMA (MALTOMA)

→ It is extra Nodal Lymphoma
→ M.C Extra Nodal site for development of Lymphoma – GIT (m.c Stomach)

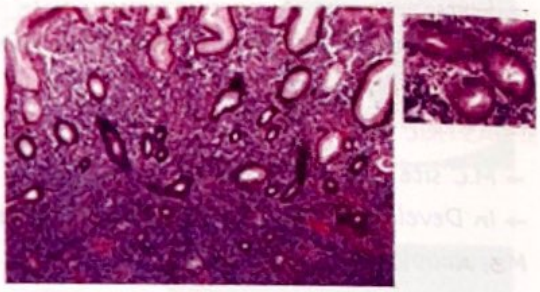
Risk Factors

i. H. Pylori infections
ii. t (11, 18)

Management

If Tumor is caused by H. Pylori – only Antibiotics are sufficient
→ If tumor is associated with Translocation (11,18) antibiotics will not work .

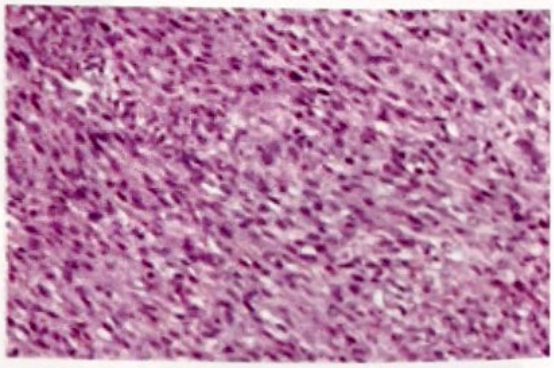
Histology



→ Lymphoepithelial lesions
→ Infiltration of Gastric Glands
→ Gastric lymphoma is example of B cell Tumor
→ In case of Patient who has received Immunosuppressant drugs (e.g. cyclosporine) after organ transplantation the commonest site of development of lymphoma is Bowel.
→ Immunosuppressive therapy cause "Selective down regulation of T cell" therefore, patient have higher chances of B cell lymphoma.

5. GASTROINTESTINAL STROMAL TUMOR

→ Commonest mesenchymal Tumor of stomach
→ It arises from Interstitial cells of kajal
→ On Microscopy there is Presence of spindle cells.
→ 2nd variant of GIST has epithelial like cells
→ 3rd variant has both spindle cells and epitheloid cells.
→ C/F: Mucosal ulceration (Bleeding)



Markers

→ Most specific marker → DOG 1 marker
→ CD 117 marker/ C-KIT
→ CD 34 marker

→ ↑ Tyrosine Kinase Activity

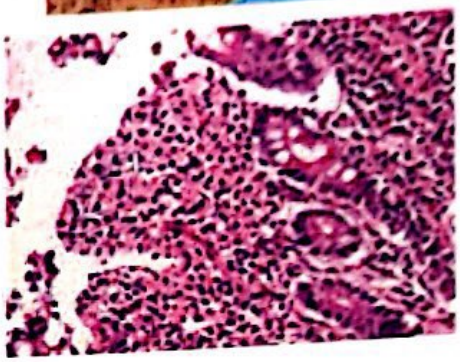
Treatment:

- IMATINIB - Tyrosine kinase

INTESTINAL ULCERS AND INFECTIONS

1. TUBERCULOSIS

i) Primary TB due to ingestion of infected milk (M. Bovis)
ii) Secondary TB is due to ingestion of infected sputum and intestine is affected (m.c site is ileum)
→ Transverse ulcers are seen in TB (90 degree to long axis of intestine)



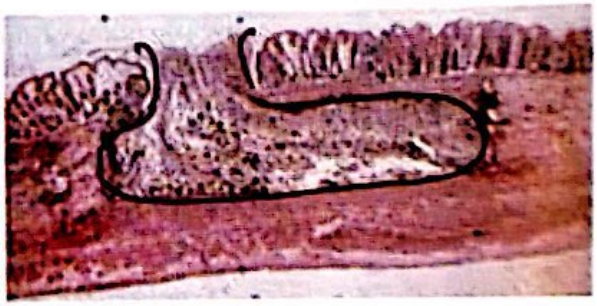
2. ENTERIC FEVER

Mode of Transmission: feco-oral route
→ Commonest area: Ileum
→ Ulcerations of Peyer's patches is seen
→ Ulcer is along long axis of intestinal (**Longitudinal ulcer**)
→ Microscopic findings
→ Presence of RBC inside Macrophages
Called as Erythrophagocytosis

TB	Typhoid
Transverse	Longitudinal Ulcer
Stricture formation	No stricture formation

3. AMOEBIASIS

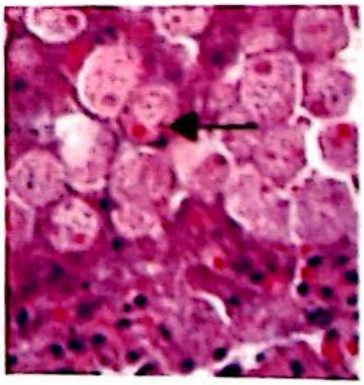
→ Organism: Entamoeba Histolytica
→ Commonest site affected: Caecum >> Sigmoid colon
→ Ulcer have narrow neck & broad base
called as "**Flask shaped ulcers**"



Route of Infection:
→ Due to intake of contaminated water containing cyst.
- These cyst changes into trophozoite in gastric lumen

→ On Biopsy: Presence of E. Histolytica
- Appearance is similar to macrophages
- Some of them have RBC inside them

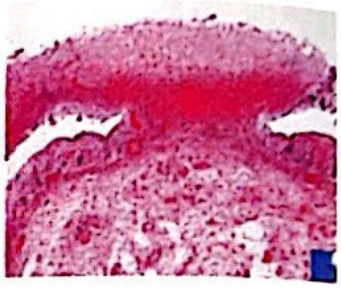
→ The Trophozoite can migrate from G.I.T Tract into liver and over there they form Amoebic liver abcess
→ Characteristic features of Amoebic liver abcess in - **Anchovy Sauce Pus**



4. PSEUDO MEMBRANOUS COLITIS

→ Causative organism: Clostridium difficile
→ Most commonly seen in patient taking 3rd Gen. Cephalosporins
→ Toxin released by C. difficile is responsible for Pseudo membranes (as made up of inflammatory cells and necrotic debris)

Microscopic findings



→ Presence of Necrotic Debris and Neutrophils arising from epithelium giving "Mushroom like appearance" or "Volcanic eruption"

Treatment

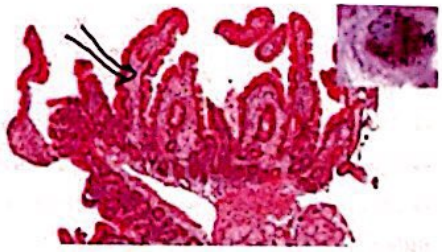
- Vancomycin
- Metronidazole
- Fidaxomicin

MALABSORPTION DISORDERS

1. WHIPPLE DISEASE

→ It is Infectious Malabsorption disorder
→ Causative organism: **Tropheryma whippelii**
→ Due to this infection there is Influx of macrophages and as a result is the accumulation of macrophages in intestine causing compression of Lymphatics.
→ Due to compression of lymphatics there is malabsorption

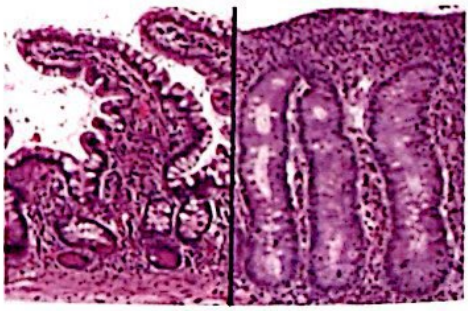
Biopsy



→ Presence of foamy macrophages and these have Bacilli inside them.
→ These Bacilli are "Rod shaped Bacilli"
→ a/k/as Pas Positive Diastase resistant Granules'
→ These Bacilli are also present in infection caused by Mycobacteria
→ To distinguish between Tropheryma whippelii and mycobacterium
→ Mycobacteria are acid Fast Bacilli where T. whippelii is not acid Fast.

2.CELIAC SPRUE

Autoimmune condition
Activation of CD_4T Cells
It is due to intake of certain cereals which contain a protein called Gliadin
→ Cereals like wheat, oat, Barley and Rye causes this condition



Microscopic feature

i) villous atrophy
ii) Crypt Hyperplasia

iii) Positive serology

Biopsy

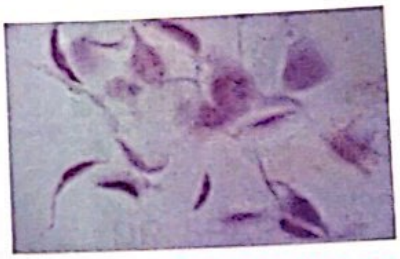
Site: Duodenal Biopsy

Treatment

i) Withdraw offending cereals

ii) Safe cereals are given mainly maize and rice

→ Celiac sprue has higher chances of development of Enteropathy T cell lymphoma and adeno carcinoma of small intestine



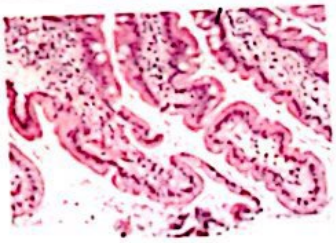
3. Giardiasis

→ a/k/as – Grand old man of intestine

→ It is Discovered by Leeuwenhoek

→ Identification of Giardia lamblia Pear shaped appearance

- Presence of Di-nucleus



Intestinal Biopsy:

→ Presence of sickle shaped organism "Giardia"

→ It is not associated with mucosal invasion

→ M.C cause of Infectious Malabsorption

INFLAMMATORY BOWEL DISEASE

1. CROHN'S DISEASE

COBBLESTONE MUCOSA

→ "Skip lesions"

- Patchy involvement of intestine

→ M.C location of Crohn's disease – Ileum

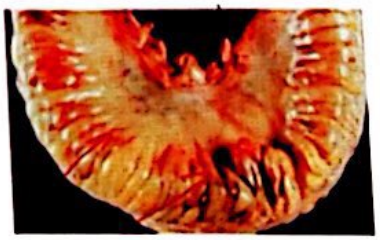
→ site not involved – Rectum

→ Cobble stone mucosa

→ Transmural involvement of intestinal

→ Due to presence of mucosal edema, the mucosa is having rough texture called as cobble-stone mucosa.

→ Due to Presence of ulcers, heal by fibrosis and pulling up of surrounding area of mesentery, therefore mesenteric fat enters bowel called as creeping fat



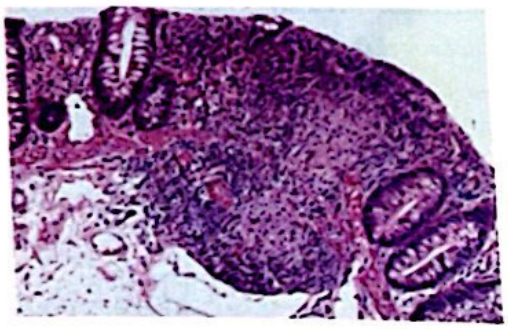
Antibody: ASCA +ve

Histology

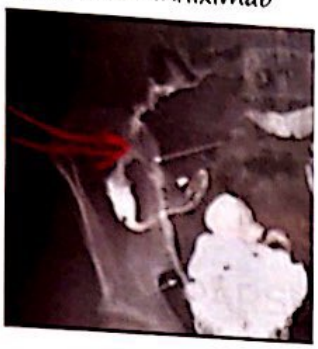
→ Transmural inflammation

→ Granulomatous inflammatory Disorder

→ Because of Transmural inflammation, the patient has higher risk of Stricture and Fistula formation



Radiological Appearance :String sign of Kantor
Treatment: infliximab

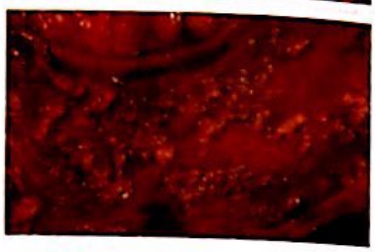


2. ULCERATIVE COLITIS

Characteristic Findings

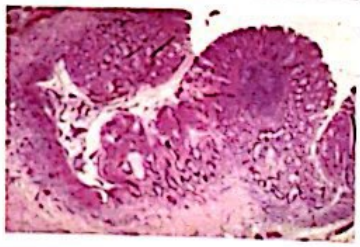
→ Involve colon in retrograde manner
→ First involve rectum and then progresses backward and sometimes there is complete involvement whole large intestine k/a pancolitis .

→It only involves mucosa and submucosa & Sometimes there may be regenerating mucosa projecting in lumen k/a pseudopolyps.



Histology

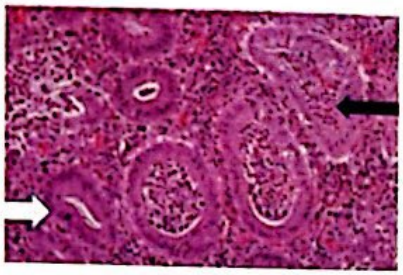
It only Involves mucosa and submucosa
→ Absence of Granuloma
→ Non Granulomatous superficial Inflammation
→ Antibody: P-ANCA
→ Hepatobiliary condition associated with ulcerative colitis is primary sclerosing cholangitis.



→ Ulcerative colitis is more likely to associated with colon cancer as compared to Crohn's disease

Histology

there is presence of neutrophils in the crypts k/a crypt abscess.

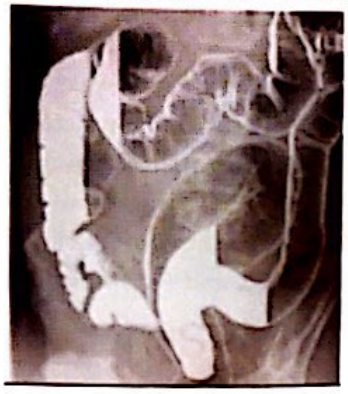


Radiological feature

"Lead Pipe" appearance
→ Calprotectin is marker for severity of inflammatory bowel disease

Treatment

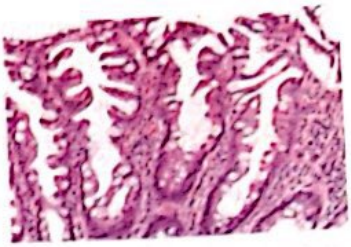
→ 5 Amino – salicylic Acid
→ Sulphasalazine
→ Steroids



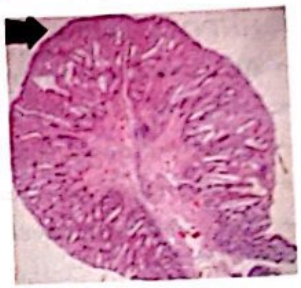
COLONIC POLYPS

Two Types

a) NON-NEOPLASTIC POLYPS

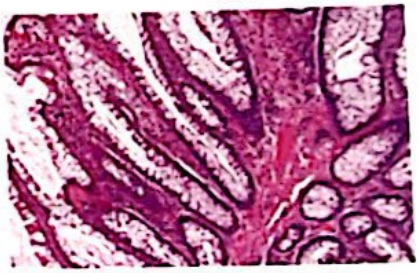


1. Hyper plastic Polyps:
   - → Benign polyp
   - → Serrated appearance due to overcrowding of cells
   - → arises more commonly from left side of colon
2. Inflammatory Polyp
3. Juvenile polyp
   - → Pedunculated polyps



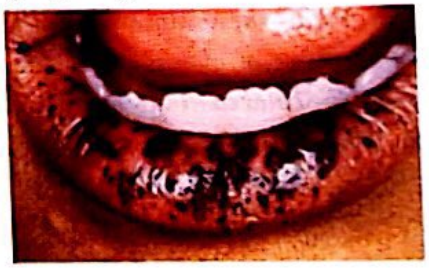
It is spontaneous or associated with syndrome
It is seen is children <5 yr of age
→ C/F – Rectal Bleeding

Microscopically
- → Pedunculated
- → Cystic space presents – filled up with mucin
- → Isolated Juvenile polyp is Benign
- → If Juvenile Polyp is associated with syndrome is called as Juvenile polyposis syndrome
- → Juvenile Polyposis syndrome is associated with SMAD – 4 Gene
- → These patients have very large number of Juvenile polyps

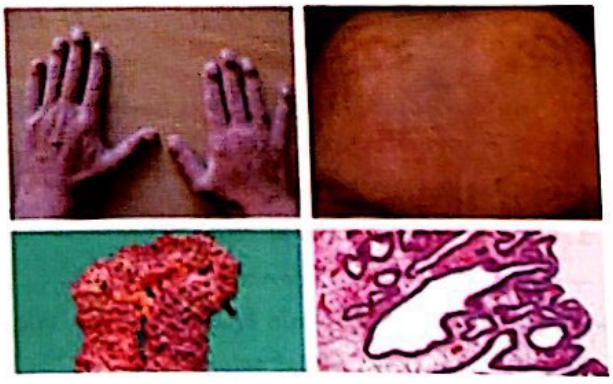


Therefore resulting in massive bleeding
There is definitive risk of development of colon cancer

4. PEUTZ- JEGHER POLYP
   - → It is hamartomatous polyp
   - → It may occur sporadically or associated with syndrome
   - → Sporadically it is located in Jejunum
   - → Most characteristic Finding is Presence of arborizing network of lamina propria glands, smooth muscles and connective tissue
   - → Isolated Polyp is Benign



Peutz Jegher syndrome
- → It is associated with development of malignancy
- → Multiple hamartomatous polyp
- → Mucocutaneous pigmentation
- → Positive family history
- → In peutz jegher polyp there is mutation in tumor suppressor gene k/a STK 11 (serine, threonine kinase) which is responsible for malignancy in peutz jegher syndrome.



Cronkhite Canada syndrome
- → Presence of multiple GIT Tract Polyps
- → Presence of cachexia, alopecia, Nair atrophy, skin manifestations, anemia
- → These are at higher risk of development of colon cancer.

Cowden syndrome:
- → It is associated with mutation of gene called PTEN gene
- → ↑ risk of multiple types of cancer

B →Breast tumor
E → Endometrial tumor
S → Skin tumors (Benign)
T → Thyroid tumor
Only skin tumors are benign and rest are malignant.
5. ADENOMATOUS POLYP

b) NEOPLASTIC POLYP

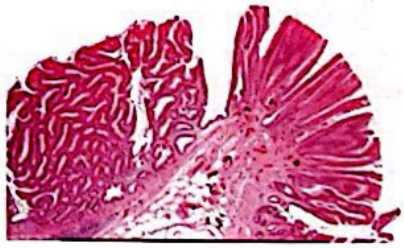
Higher risk of Development of Adenomatous Polyp in 2 conditions

1. HNPCC/ lynch syndrome
→ Autosomal Dominant
→ Defect in DNA repair gene
→ Adenomatous polyp are less in Number
→ There polyps are characterized by "Microsatellite Instability"
→ These Patients develop cancer in Proximal colon at early age.

2. Familial adenomatosis polyposis
→High number of Adenomatous Polyp
→ Mutation in APC- Gene (chromosome square)
Minimum number of polyp should be 100 to make diagnosis

Variants of FAP are:
1. Classical FAP – associated with multiple adenomatous polyp as well as retinal pigment hypertrophy
2. Turcot syndrome – adenomatous polyp along with CNS tumors
3. Gardner syndrome- Adenomatous Polyp + Cystic lesions + Tumors like osteoma fibroma

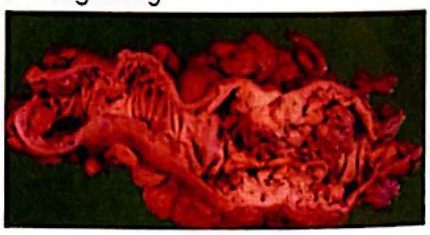
Histology of adenoma:
3 Important subtypes
1. Tubular adenomatous polyp
→ Presence of glands
→ Pedunculated
2. Villous adenomatous polyp
→ Villi like projections
3. Tubular villous:
→ Tubular component as well as villous component



→ M.C subtype – tubular adenomatous polyp
→ Polyp associated with maximum chances of dysplasia/ malignancy – villous → adenomatous polyp
→ Polyp associated with development of diarrhea with hypokalemia and hypoproteinemia-Villous adenomatous polyp
→ Any adenoma of > 4cm – is having higher chances of progression into malignancy

COLON CARCINOMA

Grossly it has 2 important presentations
1. It can affect proximal colon
→ Ulcerative type of cancer
→ Associated with chronic bleeding and result in development of anemia
2. It can arise from distal colon



→ Exophytic in nature
→ Circumferential involvement of colon
→ "a/k/a Napkin ring appearance"

Factors which ↓ development of colon cancers
1. Dietary fibres
2. Drug – aspirin

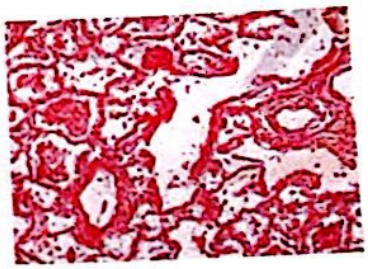
Microscopic findings
→ As it arises from columnar epithelium it is adenocarcinoma
→ Presence of hyperchromatic cells suggestive of malignancy
→ Presence of mucin which pushes the nucleus on one side it is called signet ring appearance

Radiological finding
→ In barium enema narrowing of lumen
→ Apple core appearance

Tumor marker: Carcinoembryonic antigen

LUNGS

1. Adult Respiratory Distress syndrome



→ Initiating event in ARDS is Endothelial cell Injury.
→ Due to Endothelial cell Injury there is release of Inflammatory cytokines and there is damage to TYPE I and TYPE II pneumocytes.

Microscopic features:
→ There is diffuse alveolar damage so there is presence of certain alveoli which are distended and certain alveoli are collapsed.
→ Due to endothelial cell injury there is deposition of protein fibrin and this fibrin is responsible formation of membrane → k/a Hyaline Membrane
→ These Patients do not have good response to O_2supplementation due to hyaline membrane formation and damage to Pneumocyte.

Treatment
→ Treat Etiological factors
→ Give Positive end expiratory Pressure

2. Lung Abscess

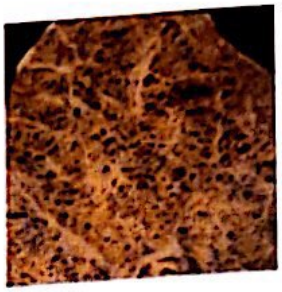
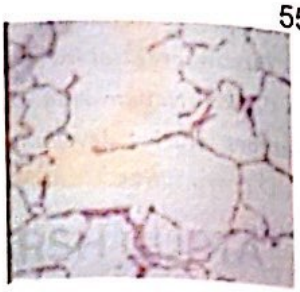
→ There is presence of areas which are associated with necrosis.
→ It is most commonly associated with aspiration of any material .
→ organisms associated are mixed flora
→ Most important organism responsible for development of Lung abscess is Staph. aureus
→ Chest x-ray shows Presence of air fluid levels

OBSTRUCTIVE LUNG DISORDERS

Hallmark finding: Reduction in ratio FEV_1 FVC

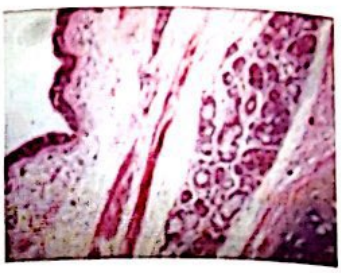
1. EMPHYSEMA
→ There is Involvement of acinus
→ Etiological Factor: M.C seen is Smoking (Upper lobes of lung are involved)

→ Other: α, Anti trypsin deficiency - Pan acinar emphysema ;
Lower lobes of lungs are involved
Microscopically: Distension of Alveoli due to damage
Complication:Long term complication of emphysema is Pulmonary Hypertension

2. CHRONIC BRONCHITIS

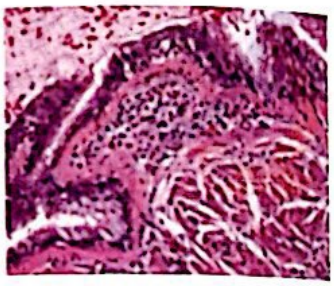
→ Most commonly associated with Smoking
→ Clinical Definition: Presence of Productive cough for a duration of at least 3 months in 2 consecutive years.
→ There is Mucous Gland Hypertrophy (↑ Thickness in Mucous Layer)
→↑↑ in value of Reid's index



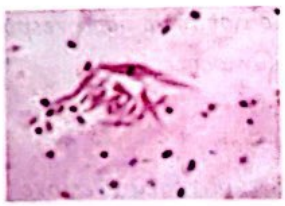
→ Chronic Bronchitis is not associated:
1. With Amyloid deposition
2. Very less no. of patient are at risk of development of Bronchogenic carcinoma.

3. ASTHMA

→ Reversible airway inflammatory disorder
Histologically
→ There is Airway Remodeling
→ Smooth Muscle Hypertrophy
→ Eosinophilic Infiltration
→ Goblet cell hyperplasia



Sputum examination
3C's
C → Charcot laden Cells – Composition Gallatin 10
C → Curschmann spirals
C → Creola Bodies
→ Best Protein which related to severity of Asthma in Patient is YKL – 40




Variants of Asthma

Extrinsic Asthma	Intrinsic Asthma
→ Type I Hyper sensitivity reaction → ↑↑ IgE→ Exposure to viruses	→ Exposure to viruses → Intake of drugs like NSAID's and Cold temperature exposure

4. BRONCHIECTASIS

→ Characterized by abnormal permanent dilation of Airway to an extent that can be traced till the surface of lung

→ More commonly lower lobes of lungs are affected

→ More commonly affects the left lung

Risk Factors

1. Obstruction
   → Foreign body
   → Tumor
2. Infections

Two important examples of Special conditions

1. Bronchiectasis complicate the disease like cystic fibrosis
2. It can also be seen in a patient having Kartagener syndrome

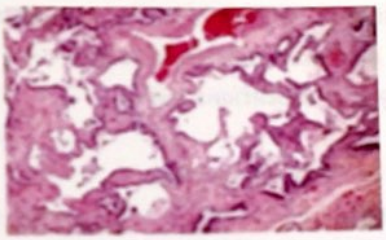
→ Amyloid deposition can be seen in Bronchiectasis

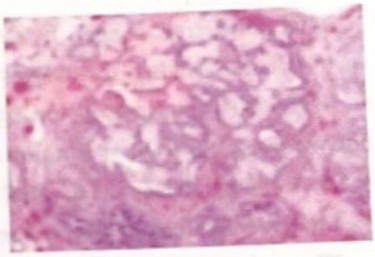
→ It never proceeds to lung carcinoma.

RESTRICTIVE LUNG DISORDERS

→ It is characterized by restriction to expansion of lung.

1. USUAL INTESTINAL PNEUMONIA





→ It is used to describe the histological hallmark finding of patient suffering from Idiopathic Pulmonary fibrosis

→ associated with advancing age of person

→ Affects the Gene coding for surfactant

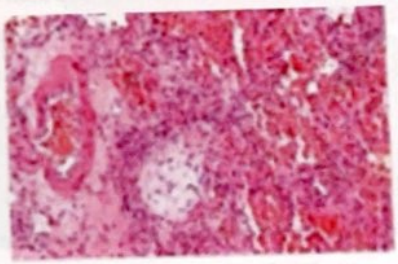
→ Environment factors like smoking are also associated

Histological Findings:

→ Patchy, Fibrosis, Interstitial (Hallmark feature)

→ Honey Comb Pattern

2. CRYPTOGENIC ORGANIZING PNEUMONIA



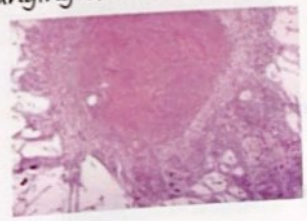
→ Loose wall of connective tissue in alveolar spaces k/a **Masson's Bodies.**

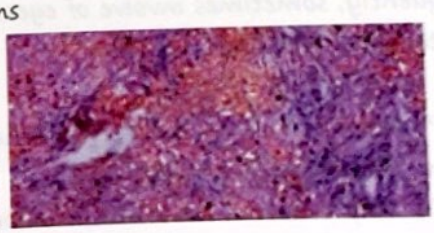
→ Not Associated with "Honey Comb Pattern" of Lung

→ Not associated with interstitial fibrosis.

3. PNEUMOCONIOSIS (Occupational lung Diseases)

→ It is due to Inhalation of dust particles ranging b/w 1 – 5 microns





1. Silicosis

→ Involvement of upper lobe of lung.

→ ↑ risk of Infection with TB

→ Commonest Pneumoconiotic Disorders

Microscopically

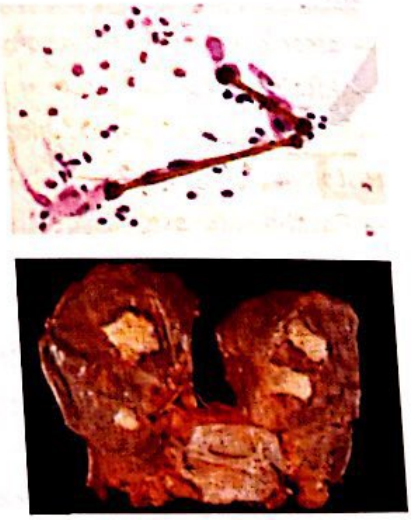
→ Presence of Bundles of collagen deposited k/a silico Nodules
→ Presence of Birefringence which is suggestive of silica crystals.
→ Radiography of chest X-ray: there is Presence of hilar lymphadenopathy is seen with outer surface of Hilar lymph nodes calcified k/as Egg shell calcification

2. Anthracosis

→ Seen due to inhalation of Coal Dust.
→ asymptomatic
→ Gradually Patient develops more severe fibrotic reaction
→ when the disease progresses further & becomes chronic it is called as Progressive massive fibrosis.
→ Since patient working in coal mine is exposed to coal dust over long period of time so lungs turn black k/a **black lung**
→ Some of Patients of Anthracosis, might as well have **Rheumatoid Arthritis**; co-existence Anthracosis with rheumatoid arthritis is called as Caplan's syndrome

3. Pleural Plaque

→ This condition is seen in Patients who are exposed to Asbestos
→ It is used in ship industries and insulation industries.
→ There are many Pulmonary manifestations but commonest is Pleural Plaques.
→ It involves Anterior as well as Posterior surface
→ Other Manifestations: Interstitial Fibrosis
→ There is presence of Dumbbell shaped structure having proteinaceous coat and also deposition of iron and calcium k/as Asbestos Body or ferruginous body.
→ Particles of asbestos are heavy, therefore more commonly involving the lower portion of Base of Lung
→ Any Patient having exposure to Asbestos is always at higher risk of development of malignancy
→ M.C lung cancer associated with Asbestos Bronchogenic Carcinoma
→ More specific Lung Cancer → Mesothelioma (Malignant Mesothelioma)



GRANULOMATOUS DISORDERS

1. SARCOIDOSIS: Autoimmune disorder

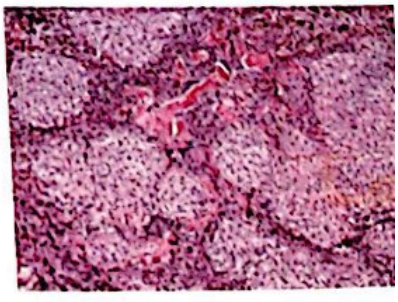
→ Multiple organs are involved: Lungs, L.N are involved very frequently, sometimes involve of eyes, spleen.

Histological findings

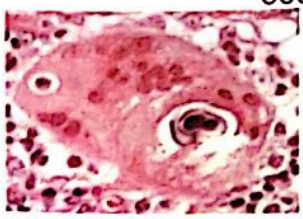
→ Presence of Non - Caseating Granuloma

Other Histological Findings

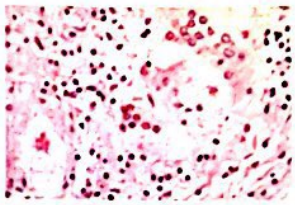
→ Ca^{+2} deposition in concentric fashion inside giant cell



k/as Schaumann Body
→ Presence of star shaped or stellated inclusions k/as Asteroid Body
→ Some of patients have residual body
→ Immunological Defects: High CD_4: CD_8 ratio b/w 5:1 to 15:1
→ Sample: Bronchoalveolar Lavage
→ Hypercalcemia is also seen
→ ↑ Activity of enzyme :1α hydroxylase, ACE Enzyme.

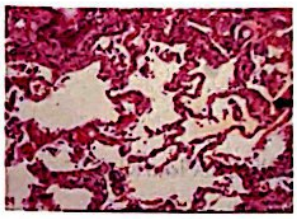


Treatment:
→ Spontaneous remission
→ Steroids



2. HYPERSENSITIVITY PNEUMONITIS

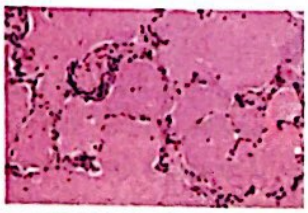
→a/k/a Extrinsic Allergic alveolitis.
→Certain conditions included in Hypersensitivity pneumonitis.
i. Humidifiers lung
ii. Pigeon lung
iii. Bird fancier's lung
iv. Farmer's lung
→It is mixed Hypersensitivity reaction
→ Presence of immune complexes as well as Granuloma formation: Type III and Type IV Hypersensitivity reaction
→ Type IV > type III Hypersensitivity reaction.

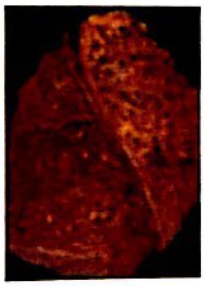


Histological Findings:
→ Granulomatous inflammation is seen in the interstitial tissue.
→ Example of Non- caseating granuloma

3. PULMONARY ALVEOLAR PROTEINOSIS (PAP)

→ Surfactant is degraded by macrophage
→ Macrophage differentiation is dependent on GM-CSF factor
→ Most common association: autoimmune disorder
→ Auto Antibodies are directed against GM-CSF macrophages;
→ surfactant accumulate in the intra-alveolar and bronchiolar spaces.
→ PAP can have association with transport of surfactant seen with multiple types of Gene defect surfactant C; Surfactant B; ATP Binding Cascade Protein (ABC3 Gene)
→ Most common gene defect: ABC3 Gene
→ Lamellar Bodies with electron dense cores is finding of PAC with ABC3 Gene defect.





PNEUMONIA

→ Exudative solidification of Lung

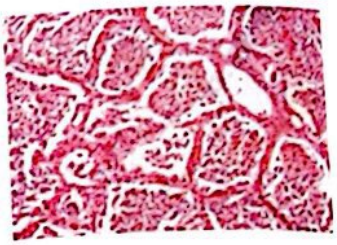
Typical Pneumonia

1. Lobar Pneumonia (Extensive involvement of complete lobe)

Organisms

→ Staphylococcus Aureus
→ Streptococcus Pneumoniae
→ H. Influenza

2. Broncho Pneumonia (Patchy involvement of Lung)

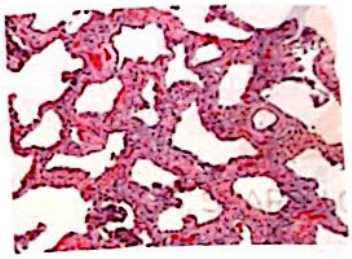


→ Bronchopneumonia is seen at extreme ages (Children, old)

Histological Findings:

→ Typical Pneumonia/ Air space Pneumonia
→ It is characterized by Alveolar exudates and neutrophilic infiltration

Atypical Pneumonia:



Commonest organism

→ Mycoplasma
→ Chlamydia
→ Virus and fungi
→ Histological Findings
  No alveolar exudates
  Interstitial Tissue Inflammation

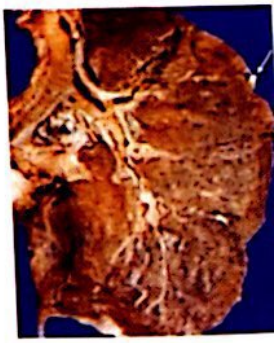
C/F

→ Low grade fever
→ Dry cough

Symptoms are ↓ Signs ↑

TUBERCULOSIS

→ 1st involvement of lung caused due to droplet infections
→ Involvement of Sub pleural area k/as (Ghon's Focus)
→ If draining lymphatics and lymph nodes are involved along with Ghon's Focus k/a Ghon's Complex



→ Whenever Immune System gets activated this focus is reduced to Calcified nodules
→ Best detected with Chest X ray
→ Calcified Ghon's focus is k/as Ranke's complex
→ In majority after Primary Pulmonary Tuberculosis, bacilli gets inactivated.
→ whenever immunity is low, reactivation of bacilli leads to development of Secondary Pulmonary Tuberculosis

MILIARY T.B

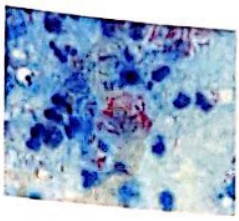
→ In Immunosuppressed Individuals, there are multiple areas of lungs affected giving millet like appearance k/a Miliary T.B.

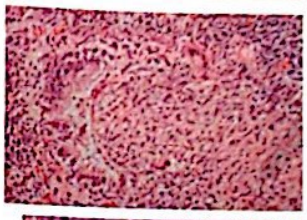
Sputum Examination

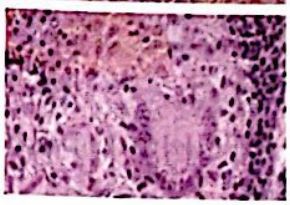
Acid Fast Bacilli Seen

Microscopic Findings:

1. Presence of granulomatous inflammation and 'Caseous Necrosis' k/as 'Caseating Granuloma'
2. Presence of Giant cells present in U pattern Langhans Giant Cell.







PULMONARY VASCULAR DISORDERS:

1. Pulmonary Thromboembolism

→ In most of individuals, pulmonary emboli are silent, few patients are symptomatic.

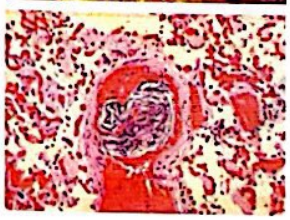
→ If there are Big clots then it may lead to Obstruction of pulmonary vasculature, sometimes due to big clots there is occlusion of branching point of Pulmonary Artery k/as saddle Embolus.

Diagnosis: D- Dimer assay & can also be performed for DIC.

2. Amniotic Fluid Embolism: Sometimes due to rupture of Membranes during delivery, there is entry of Amniotic fluid in systemic circulation

Histology Findings:

→In Pulmonary vessel of mother there is having presence of fetal epithelial tissue.



3. Fat Embolism:

→ Seen after Trauma or accidents

→ associated with long bones fractures; marrow releases fat , it moves into systemic circulation & then in lungs.

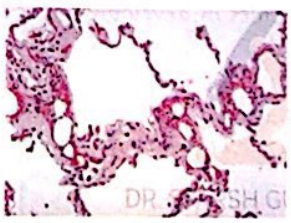
→ presence of Round Halos in Lungs

C/F

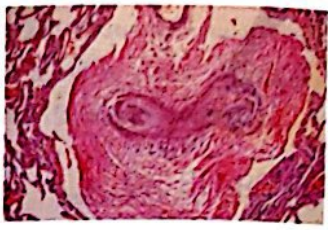
→ Skin Rash

→ Anemia

→ Tachypnea



4. Pulmonary HTN



→ ↑ in pressure of Pulmonary circulation

Findings

→ Plexiform Lesions

→ In pulmonary vessel there is tuft of Capillaries

→ Smooth muscle hypertrophy

→ Due to Pulmonary HTN, there is ↑ in workload on right Side of heart, Resulting in Right sided heart failure

→ Right ventricular failure secondary to Pulmonary HTN k/a Cor Pulmonale

LUNG TUMORS

Bronchogenic Carcinoma:

→M.C Primary Malignant Tumor affecting lung

Etiology

→ Smoking cigarette for long duration

→ Exposure to air pollutions

C/F

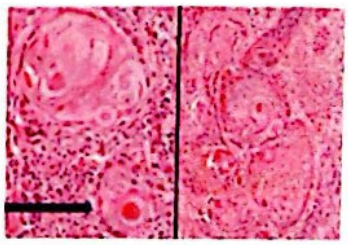
→ Cough

→ Weight loss

→ Hemoptysis

Important Biopsy Findings of Different type of Lung cancer

1. Squamous cell Cancer:



→ Squamous cells are responsible for secretion of Keratin

→ keratin pearls seen – Diagnostic Findings

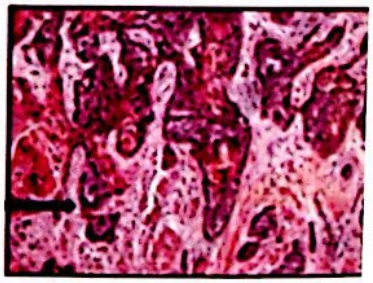
→ M/C is males, smokers.

→ Central location near Hilum

→ Presence of cavitation

→ Paraneoplastic Syndrome associated is Hypercalcemia (due to secretion of PTH related peptide)

2. Adenocarcinoma of lung



→ Females >> Males

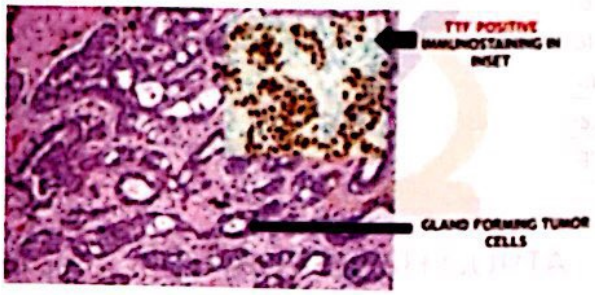
→ Non smokers

→ Adenocarcinoma has peripheral location.

→ Tumor cells are characterized by Presence of glands

→ Adenocarcinoma of lung is responsible for secretion of mucin, results in development of thrombophlebitis.

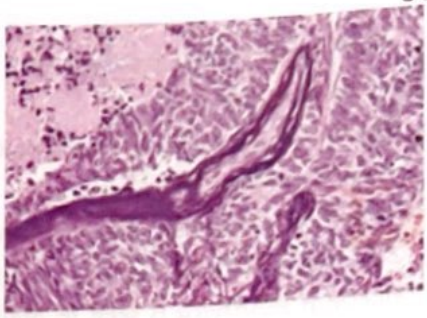
Diagnosis



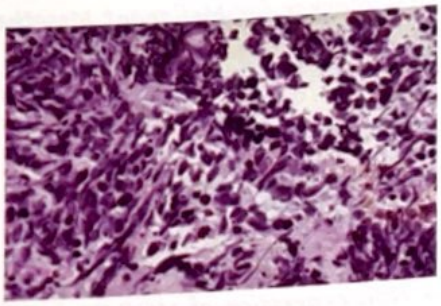
→ TTF Positive

→ Napsin A Positivity

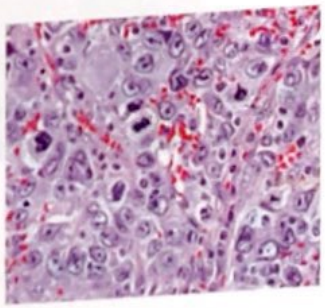
3. Small cell lung carcinoma
→ Males; Smokers
→ Central Location
→ Best Response to
- Chemotherapy
- Radiotherapy
→ Worst Prognosis



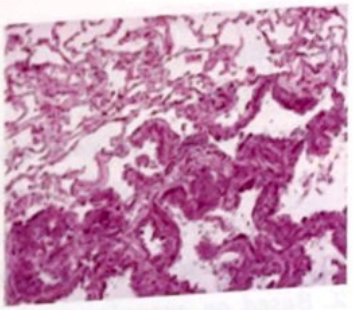
Microscopic Findings
→ Presence of Neurosecretory granules tumor cells are Hyperchromatic, sometimes chromatin Material from Tumor cells leak out → giving Blueish color to Vessel Walls.
→ High expression of BCL – 2
→ Oat cell cancer
→ Small cell carcinoma has maximum Paraneoplastic Syndrome
i. Hypocalcemia
ii. SIADH
iii. Crushing Syndrome



4. Large Cell Cancers
No characteristics findings. It is diagnosis of exclusion.
Tumor cells are responsible for secretion of Estrogen
→ Patients develops gynecomastia.

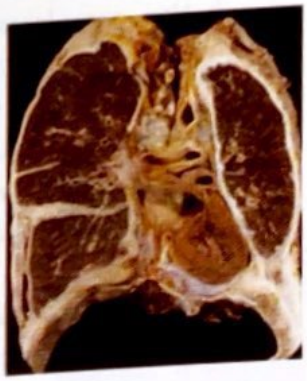


5. Adenocarcinoma in situ
→ Tumor cells do not penetrate basement membrane, so tumor cells are restricted anatomically along alveolar septa.
→ From one septa tumor cells can spread to other septa
→ Aerogenous Spread



6. Mesothelioma:
→ Arise from Pleura surface
→ Variant

Benign	Malignant
Pleural fibroma	Associated with
No association with Asbestos	Asbestos exposure, Smoking
Keratin Negative	Keratin Positive
CD 34: Positive	CD 34: Negative



3 Types

1. **Epithelioid Type**: Sarcomatoid
2. **Mixed Variant**
3. **Epitheloid Type**: Tumor cells resemble epithelial cells.

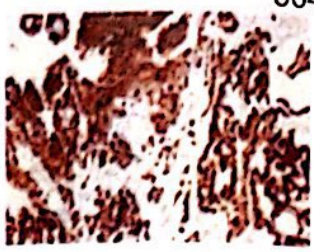
→ Commonest type

→Tumor cells mimics Adeno carcinoma of lung

→ Distinguish b/w Malignant Mesothelioma and Adenocarcinoma

Calretinin Positivity is seen in Malignant Mesothelioma

(Best Marker for Malignant Mesothelioma)



Other Markers:

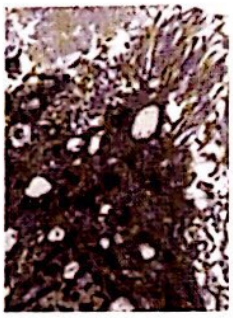
→ Cytokeratin 5 and 6

→ B240

→ WT 1

→ Non expression of MOC 31 in Malignant Mesothelioma

→ MOC 31 Positivity is associated with Adenocarcinoma of lung.



Electron microscopic Examination

Mesothelioma: Microvilli are lung and thin

Adenocarcinoma: Short Microvilli

CVS

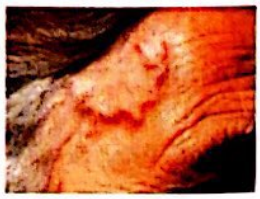
BLOOD VESSELS

Vasculitis

Classification:-

1. **Based on size of blood vessel affected**
   - a. Large vessel vasculitis:
   - b. Medium vessel vasculitis:
   - c. Small vessel vasculitis :
2. **Based on granuloma**
   - a. Granulomatous vasculitis
   - b. Non-granulomatous vasculitis

TEMPORAL ARTERITIS:-



→ Large vessel vasculitis.

M.C vasculitis disorder in adults

It is associated with inflammation of superficial temporal artery

C/F

→ Headache, jaw claudication

→ Polymyalgia rheumatica