PATHOLOGY

PG-NOTES

2017

JAIN STATIONERY

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→ CELL INJURY ←

- 4 parts of cell : More vulnerable to Injury
  - Cell membrane
  - Nucleus
  - Mitochondria
  - RER

Causes : m/c 1) Hypoxia ($\downarrow O_2$ delivery to tissues)

↓

can be due to
- → Ischaemia → m/c
  - → Thromobm bolism
  - → Atheroesclerosis
  - → Vasospasm
- → Anaemia (O_2 carrying capacity ↓)
- → Cardiopulmn Failure
- → Co poisoning

MCQ: Cell most suspectable for Hypoxia : Neuron

(die ☆ in 3-4 min in hypoxia)

. Cardiac muscle will die ☆ in 30 min (20-40 min)

2) Infections : 2nd most common cause

3) physical : Heat, cold, radiation, Trauma

4) Chemical agents

5) genetic disorders

6) Hypersensitive reactions and autoimmune diseases

7) Nutritional Imbalance

	Def	Excess
ⓟ Ⓐ	Vit & mineral PEM	Fatsoluble vits, Fat → obesity, Atherosclerosis

Outcomes of cell Injury :

i) Reversible cell Injury (Show : Hydrophic degeneration / Cloudy degeneration
Fatty degeneration

ii) Irreversable cell Injury : a) Apoptosis
b) Necrosis
c) Necroptosis
d) pyroptosis

iii) Intracellular accumulations and pathological calcification
↳ can be protein
fats
glycogen
Lipofuscin pigment

Dystrophic calcification
Metastatic calcification

iv) Cellular adaptations : Hyperplasia
Hypertrophy
Metaplasia
Aplasia

Dysplasia is not a cellular adaptation : it's a premaglignant condition.

Eg: CIN (cervical intraepithelial Neoplasia)

CIN 1
CIN 2
CIN 3 → Ca in situ

v) Cellular ageing

FIXATIVES / PRESERVATIVES :

1) 10% Neutral Buffered Formalin: mlc fixative used for Histopathological specimen

2) 2.4% Glutaraldehyde → Electron microscope
   ∂/b post fixation in osmium Tetraoxide

3) Normal saline → Immunofluoroscene Examination (Skin)

4) Albolute Alcohol (95% ethyl alcohol) → fixative for papsmear

5) Blood
   - CBC — EDTA
   - ESR
     - → Wintrobes method → EDTA
     - → Westergren method → Trisodium citrate (Standard method)

6) Coagulation Studies: Trisodium citrate

7) Sugar estimation: NaF

8) osmotic fragility test → Heparin
   - for Hereditory spherocytosis
   - Thalassaemias

9) Preservation in Giemsa stain; Methanol

STAINS:

1. Haematoxylin and Eosin (H&E): mlc stain used in Histopathology
   Hematoxylin: Blue dye (stains nucleus); Eosin: Pink dye (cytoplasm)

2. Peripheral smear and BM Aspiration smear
   - Leishman stain
   - Giemsa stain
   - Jenner stain
   - Wright Stain
   - May Grunwald Giemsa

   } Romnowsky stains (mlc)

3) Reticulocyte / Young RBC's

Supra vital stains: stains living cells: Dont add preservatives

- brilliant cresyl Blue (better) — So that living cell
- New Methylene Blue — cannot be stained

4) Heinz bodies: Denatured Hb (unstable Hb diseases)

↓ Seen in G6PD def

Stained ē metachromic stains like: crystal violet, methyl violet } also stain amyloid

dye reacts ē tissue form polymers → Produce diff color

Eg: Amyloid → Pink

5) Fats: Stains → Oil Red O (Best)

Sudan Black

Orcein (also used for co staining)

Routine processing (10-12 hrs)

Formalin (Fixation)

↓

Alcohol (dehydrating agent)

↓

Xylene < Miscible ē paraffin wax, Fat solvent

↓

Paraffin Wax (to solidify tissue) not miscible ē water

↓

Cut thin section

↓

stain with HE

• xylene disadvantage: Remove fat

so not useful for fat visualization

So frozen stain is used for fat visualization

for fat ; Tissue in formalin (fixative)
↓
then it is frozen in a cryostat (solidification of tissue)
↓
Then cut thin sections in cryostat
↓
Then stain in Toluidine Blue (or) Rapid H & E

Frozen section: Rapid test
↓ also used to detect fat
Uses: 1) Demonstration of fat in tissue
2) To differentiate Benign from Malignant in OT
3) To analyze resection margins (free from tumour or not)
4) To detect metastatic deposits in sentinel Nodes

6) Glycogen stains
- PAS
- Best carmine

PAS +ve → Glycogen appear Rose pink
Pas +ve and diastase sensitive (Amyloid PAS+ve & diastase Resistant)
(Salivary Amylase) → that Breakdown Glycogen

PAS +ve substances:

a) Glycogen
b) Amyloid
c) Collagen
d) Mucin
e) Fungal cell walls
f) bacterial cell walls
g) Basement membrane
h) Hyaline (Pink) globules
- → Yolk sac tumours
- → Hepatocytes in α_1 AT def
- → Adenoid cystic Ca: (Minor Salivary Glands)

PAS +ve diastase resistant

i) Gaucher cells: "PAS +ve" (Crumpled apperance on H&E)
↳ Genetic disorder → accumulation of Glucocerebroside mainly in Macrophage

b) ~~Gaucher cells~~ (AR) → mutation in GBA gene in chromosome 1
↓
(Glucosylcerebrosidase β gene)
even ass c parkinsonism

c) Mucins: → PAS
→ Alcian Blue (Best)
→ Mucicarmine

e) Basement Memb: → PAS
→ silver stain

g) Mast cell → Toluidine blue (metachromatic tissue stain)
→ Giemsa → also used in frozen section

Toluidine Blue → orthochromatic → stain nuclear acid
→ Microchromatic →
[Stain Mast cells & granules]

d) Collagen: Masson's trichrome (MT)

f) Reticular Fibers: Silver stain
↓
type II collagen fibers secreted by reticular fibres (fibroblasts)

) Elastine fibers: Ver Hoeff's stain
Produced by premitive mesenchymal
↓
Produce
- Connective tissue
- Skeletal "
- Blood & Lymph

) Haemosiderin: Prussian blue → doesn't stain Ferritin
↓ (Perl's reaction)

i) Calcium → Von kossa (Black)
→ Alizarini (Red)
→ Calcein

- Tetracycline labelling index → To detect Bone mineralisation

18) Melanin: → Dopa reaction
→ Masson's fontana

16) Copper → orcein
→ Rubeanic acid

17) DNA → Feulgen Reaction

18) Stain for Spirochaetes: ⟶ Warthine Stomy Silver stain
i.e, treponema pallidem

19) Fungus ⟶ Gomori's Silver methanamine
PAS
KOH - Skin infections

Mechanism of cell (Reversible cell Injury) → Hydrophic & fatty s/PLF → disrupt & mod

10% of ↓ ATP production when compared to normal

↓

Changes of reversible injury are seen

→ 1st ion involved is Na^+

→ Most imp ion involved in cell injury is : Ca^{2+}


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Deals in
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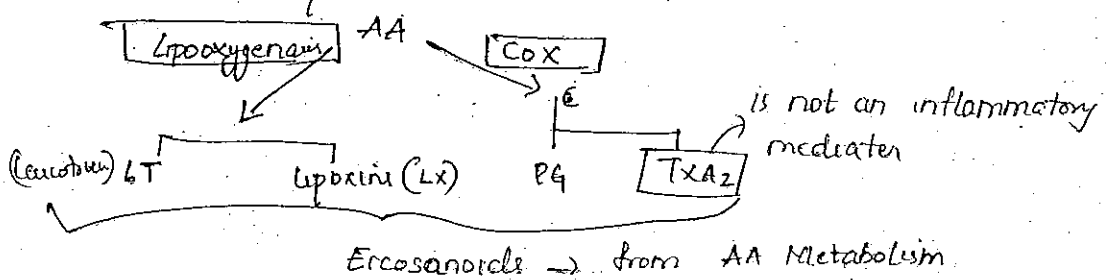
25th JUNE 2017 2nd Class

(3) Lysosomal enzymes:

⇒ Necoly

Arachadonic Acid Mediaters

1) 20 C, polyunsaturated fatty acid
2) found in phospholipid Membrane
   esterfied in Membrane in phospholipid
3) Enzyme phospholipase release AA from membrane



Ercosanoids → from AA Metabolism

Cyclooxygenase pathway

(Thromboxane) Tx

AA

↓ COX

PG

↓

PGG_2

↓

PGH_2

Prostacyclin synthetase (found in endothelium) | Tx synthetase (found in platelets)

- → PGI_2 (also called Prostacyclin) → Inflammatory mediator
  1) Vasodilation
  2) (–) platelet aggregation
- PGD_2, E_2, F_2
- TxA_2 ↓
  1) Not a inflamatory mediater
  2) Plays role in haemostasis
  3) Platelet aggregation
  → two functions

PGD_2, PGE_2, PGF_2

MCQ

1) (↑) vascular permiability
2) In addition @ PGE_2 → Responsible for pain fever
b) PGF_2, PGD_2 } Chemotactic for neutrophils
c) $PGF_{2\alpha}$ → uterine smooth muscle contraction

→ Lipoxygenase Pathway ←

AA

↓ 5 LOX (found in Neutrophils)

5HPETE

↓ (platelets) 12 LOX → Lipoxins produced (Lx)

LTA_4 ← LTB_4

LTA_4 → LXA_4, LXB_4

1) ↑ vascular permeability

2) powerful chemotactic agent for neutrophils, monocytes & macrophages

LTA_4 → LTC_4 → LTD_4 → LTE_4

LTC_4, LTD_4, LTE_4 = Slow reacting substance of anaphylaxis (SRS-A)

→
1. Vasoconstriction of larger vessel
2. Broncho constriction
3. vascular permeability

→ Lopoxins ←

Actions of Lopoxins:
- Pro inflammatory
- Anti inflammatory

} Both actions

- Inflammation: Activate monocytes & macrophages
- Anti " → Inhibit Natural killer cell activate
  Inhibit neutrophil chemotaxis

→ Platelet Activating factor

1. * Lipid mediator
2. Source: Mast cells, all leukocytes, platelets
3. Actions: a. Platelet aggregation
   b. Vasoconstriction
   c. Vascular permeability (↑)

d) In addition : Angiogenesis
cell to cell signal transaction

e) Bronchodilation

f) Vasodilatation

⟶ Neuropeptides → Newly synthesized Mediator

Eg: Substance P / Neurokinine A

a) Secreted by sensory nerves & leukocytes
In CNS & PNS

b) Action: ① transmits pain signals
② Regulate BP
③ ↑ Vascular permeability

⟶ Chemokines ⟵

a) they are short chain polypeptides (proteins)

b) Function: Chaemotaxis of various cells

c) divided into 4 category (depending on cytene placed)

① Cxc / α chemokines
↓ ↓
Cysteine cysteine

Eg: a. IL-8 : chemotactic for neutrophil
b.

② c-c / β chemokines
chemotactic for all except neutrophil

Eg: Eotaxin → eosinophil
RANTES → eosinophil & lymphocytes

MCP 1 ⟶ Monocytes & Macrophages

(Monocyte chemoattractant Protein 1)

MIP-1α ⟶ Monocytes & Macrophages

(Macrophage inflammatory Protein 1α)

③ C – / gamma chemokines

(C dash)

Eg: Chemotactic for Lymphocytes

④ CX₃C chemokines — C → cysteine aminoacid, X → other aminoacids, C → cysteine aminoacid

~~Only~~ only known example is fractalkine ⟶ Monocytes, Lymphocytes

⟶ CYTOKINES ⟵

Acute inflammation: IL-1, TNFα

Source: ① Macrophage produce them ② Dendritic cells

↳ Also produced by Tcells & Mast cells

Actions:

1) Systemic acute phage reaction :-

↓ brought about by IL 1, TNFα and IL 6 ☆

① Fever, ② ↑ sleep, ③ ↓ appetite, ④ ↑ TLC & neutrophils, ⑤ ↑ ESR

Eg: Appendicites

→ TNF also regulates energy balance by promoting lipid & protein mobilization and (↓) appetite

∴ sustained ↑ TNF levels leads to **Cachexia**

↑ TNF found (or) produced also by cancer cells

① Endothelial Activation → ↑ expression of adhesion molecules
→ ↑ production of mediator cytokines, chemokines
→ AA mediator are produced in their membrane like PG LT

③ Activation of Neutrophils

TNF → (↑) the microbicidal activity of neutrophil

④ Activation of Fibroblasts

IL-1 → fibroblast proliferation → synthesis of collagen

→ Actions of cytokines

① IL-2 → It a growth factor for NK cells & T cells

② IL-4 → It activates mast cells
→ B cell to produce IgE cells

③ IL-5 → activation of eosinophil
→ IgA from B cell

④ IL-6 → Role in pathogenesis in Multiple myeloma
systemic acute phage reaction participation
↓
Helps in inflammation (Pro inflammatory)
in some cases (Anti inflammatory)
Both Actions ∴ Cytokine (IL-6)

IL-8 ⟶ Chemotactic for neutrophils

⟶ MCQ on Inflammatory Mediators ⟵

① Fever producing: **IL-1 Most imp**
TNF α
IL 6
IFN gamma
$PGE_2\alpha$
Ciliary Neurotrophic Factor

② Pain producing: $PGE_2\alpha$
Bradykinine
Sub P → Most Imp

③ Most imp mediator of acute inflammation: TNFα

④ " " Septic shock } TNFα
⑤ " " Cancer cachexia }

⑥ Angrogenesis **VEGF → M imp**
TGF β
PAF

⑦ Fibrosis: TGF β

⑧ granuloma **IFN gamma M-imp**

⑨ Systemic Acute phase react: TNFα
IL-1
TNFα
IL-6 → M imp

⑩ Both morphogenic & Mutagenic → Bone morphogenic protein (member of TGF β family)

(iii) Anti inflammatory cytokine

IL 4
IL 13
IL 10
IL 6 → (Both Pro & Anti inflam)
TGF β

(b) Suppress Immunity → TGF β

→ Nitric Oxide ←

a) Gas

b) is produced by

L - Arginine $\xrightarrow{\text{NO synthetase}}$ NO

c) Source: only the NO synthetase enzyme when present can produce NO

Eg: Macrophages
Dendritic cells
specific neurons in brain

d) Action: — Vasodilation
— Microbicidal Gas

→ MEDIATORS DERIVED FROM PLASMA ←

(1) kinin cascade → generates bradykinin

Prekallikrein $\xrightarrow{\text{XIIa (Hagman pathway)}}$ kallekrein

HMW kininogen $\xrightarrow{\text{kallekrein}}$ Bradykinin

Actions of bradykinin : 1) (↑) vas permeability
↓
M imp action in Acute inflammatn
2). Pain
3) Vasospasm & Bronchospasm

(2) complement cascade → 20 protein
found highest conc in plasma

Three pathways for complement activation
- Classical pathway
- lectin "
- Alternate "

a) Classical pathway

* starts ~~c~~ activation of C1

* C1 is activated by Antigen-Antibody complexes

* C1
↓
C2
↓
C4 → after activation of C2 & C4 (Activate 2 & 4)

→ Activat C3 Convertase
↓
C3
↓ C5 convertase
C5
↓
C6
C7
C8
C9

C5 - 9 (MAC)
(Membrane Attacked complex)

② Lectin pathway

* C_1 activation starts the pathway
* C_1 is activated by : a) Mannose Binding lectin
  b) Bacterial lectin
* Rest of the pathway is same as the classical pathway

③ Alternate pathway

* starts with activation of C_3 (C_3 is directly activated)
* No participation of C_1 C_2 & C_4
* Directly C_3 activated by ① Lipopolysaccharide in Bacterial wall
  ② Aggregation of IgA antibody
  ③ Cobra Venom.

→ Mediators produced by complement cascade are

1) Opsonins: C_3b, C_3bi } M.imp
   C_4b
   C_4bi

2) Anaphylotoxins: C_3a
   C_5a

$\underset{\text{M Imp}}{C_5a} > C_3a > C_4a$

3) Membrane attack complex: C_5 to C_9

Osmotic lysis → ① these attach to bac membrane

Make holes of the bacterial membrane
fluid leakage

④ C5a Chemotactic for Neutrophil
and also a for Monocyte, Macrophage

→ ③. COAGULATION CASCADE ←

Intrinsic pathway (form a Blood clot) Main AIM

Inflammatory mediator:

1) Thrombin: main link b/w inflammation & coagulation
↓
Action: a) Redistribution of P selectine
b) Induce cox enzymes
↓
from endothelium & cox produce Prostglandin

2) Fibrinogen: It is an opsonin

3) Fibrinopeptides : → (↑) Vas permeability
→ Chemotactic

→ ④ FIBRINOLYTIC CASCADE ←

(break the blood clot) → Plasmin

Plasmin ← Plasminogen (inactive form of Plasmin)
↓ TPA
Blood clot UPA
↓
FDP (Fibrin degradation products)
↓
Play role in inflammation.
↓
FDP → (like Fibrinopeptide help in chemotactic)
↳ (↑) Vas permeability)

→ Neutrophil Extracellular traps (NETS) ←

Neutrophils will form traps

↓

Other way to kill bacteria

* Extracellular fibrillar network, that traps the bacteria
* formed by Nucleus chromatin of neutrophil
* Neutrophil release lysosomal enzyme in the NETs
* lysosomal enzyme kill bacteria
* Due to loss of Nucleus the Neutrophils died at the end.

→ CHRONIC INFLAMMATION ←

* Slow onset
* Lasts for long duration (weeks to months)
* Tissue is infiltrated by mononuclear cells like

Macrophages M Imp!

Lymphocytes

plasma cells

* Tissue destruction is More

↓

So more: Healing

↓

Fibrosis

* Local signs & symptoms are not prominant
* cause: ① Infection (Long standing infection)
② Autoimmunity (Hypersensitivity diseases)
③ Prolonged exposure to toxic agents

* Bone marrow → Monocytes → Macrophages → Macrophage

* Also called Histocytes * part of mononuclear phagocytic system
* Main cell of chronic inflammation
* Produced by blood monocytes
* Macrophages in dif tissue have different names

In brain : Microglial cells
in spleen : Sinus Histiocytes
Litoral cells
Lymph node : sinus Histiocytes
Liver : kupffer cells
Bone : osteoclasts
Lungs : Alveolar macrophages

* Macrophages : ① 1st chronic inflammation
↓
Tissue destruction
↓
Tissue Repair

Pathways for Macrophage activation — Classical
Alternate

Classical → kill microbe → Inflammation
Tissue destruction
↓
* Activated by ① Microbial products
② Interferon gamma (produced in Hypersensitivity immune response)
③ foreign substances like crystals

classically activated macrophages Now produce

1) NO
2) release lysosomal enzyme
3) produce free radicals by NADPH oxidase

~~save~~ will kill the offending agent and cause inflammation

Alternate Macrophage Activation (initiate tissue Repair)

* Induced by cytokines other than IFNgamma

Eg IL-4 & IL 3

↓

Activated Macrophages

↓ will produce IL-10, TGF β

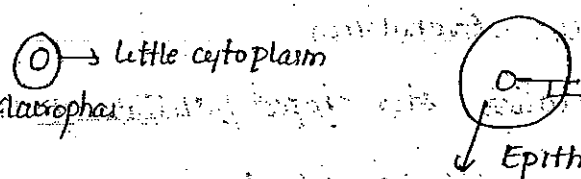
↓ GF, TGF β

↓ Tissue repair / Fibrosis

↓ Anti inflammatory effect

→ CHRONIC GRANULOMATOUS INFLAMMATION ←

* special type of Chronic inflammation
* Granulomatous formations
  ↓
* Epitheloid cells
* Granuloma (special macrophages called epitheloid cells)
* epitheloid cells - have abundant cytoplasm like epithelial cell and have slipper shaped nucleus
* epitheloid cells are surrounded by lymphocytes and plasma cells
* Old granulomas may have a rim of fibrosis outside

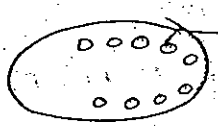


Secretory action → secrete GF & other cells like epithelial cells

* types of granulomas

1) Immune granuloma (1st type)

* IFN gamma → form this epithelioid cells
* Immune granuloma have Langhen's Giant cells



Eg: Seen in TB
Sarcoidosis
Leprosy
LGV
Cat Scratch disease

2) Caseating Granuloma

(a) Characteristic in TB
(b) Fungal infection — Histoplasmosis, Coccidioidomycosis
(c) Syphilis
(d)

3) Non caseating granuloma

seen in (a) TB (b) Hodgkins lymphoma (c) Leprosy (Tuberculoid) d) Sarcoidosis

④ Neutrophilic Granulomas

* also called star shaped / stellate granuloma

* seen in → Cat scratch disease

→ LGV

⑤ Necrotizing Granuloma

* seen in Wegner's granulomatosis

~~* Eosinophilic~~

⑥ Eosinophilic granuloma:

seen in Churg strauss (small vessel vasculitis)

⑦ DURCK granulomas:

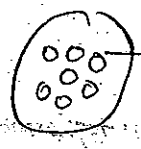
seen in: brain, cerebral malaria caused by

→ FOREIGN BODY GRANULOMA (2nd type)

* formed around foreign body

* Eg: suture material, talc, dead parasite

* Has foreign body giant cells



→ Multiple nuclei arranged (Haphazard fashion)

→ WOUND HEALING ←

Regeneration | Repair

- Dead cells are replaced by same type of cells
- Dead cells are replaced by fibrous connective tissue

3 types of tissues (Depending on regeneration)

(1) Labile tissue / actively dividing tissue

- Regenerate & replace the dead cells
- Found in G_1 phase of cell cycle

Eg: Skin
Cancer cells
Resp
GIT

① Epithelial cells: Skin, Resp, GIT
② Haemotopoitic cells:
③ germ cells
④ cancer cells

(2) Stable cells

- Low replicative potential
- Found in G_0 phase of cell cycle

these should be forced to get into G_1 phage

- Eg: parenchymal cells of organ

Hepatocytes, PCT / DCT / collecting duct cells, pancreatic acinar cells, adrenocortical cells

Mesenchymal cells
- bone
- cartilage
- fibroblast
- adipose tissue
- smooth muscle

3) Permanent / Non dividing cells

- Cannot regenerate, they left the cell cycle

Eg:
- Neuron
- skeletal muscle
- cardiac muscle

2) REPAIR

* repair occur by formation of granulation tissue

+ Granulation tissue : Pink
Moist
granular

* Composition: a) Chronic inflammatory cells (Macrophages, L, PC)
b) New blood vessels fibroprotein
c) contain proliferating fibroblast that synthesize collagen

Healing by primary intention:

* Seen in surgical incisions wound where wound edges can be approximated

0 (zero) hrs → Incision is filled with blood clot

24 hrs → ① Neutrophils from the margins infiltrate the clot and
② Mitosis in basal layer of epidermis

24 to 48 hrs → below the scab a continous thin epithelial layer is formed

Day 3 → ① Neutrophils are Macrophages
② granulation tissue appears

Day 5 → ① Max granulation tissue
② Max neovascularisation
③ collagen fibers layed down Horizontally so that they bridge the incision

* ④ Epidermis recovers full thickness i.e. surface keratinization.

2nd Week: ① (↓) inflammation
(↓) oedema
(↓) vascularisation

② (↑) proliferation of fibroblast
(↑) collagen accumulation

End of 1st month: Scar is formed

WOUND STRENGTH

1st Week: 10% of normal unwounded skin

by end of 3rd month: it is max (70 - 80%) of unwound skin

100% wound strength never be regain

→ HEALING BY SECONDARY INTENSION ←

* Seen in large defects where wound edges cannot be approximated
* large amount of granulation is formed
* large scar is formed
* Scar followed by wound contraction

↓

Scar reduced in size

* Wound contraction is brought about by (myofibroblasts)
* It is not seen in healing by primary intension

→ Connective tissue component

1) Collegen: * Most imp connective tissue component
* Triple helex

Type I collagen → a) Most abundent
b) tensile strength
c) found in skin, bone, ligaments, blood vessels

Type II collagen → a) cartilage
b) Vitreous humor

Type III collagen → a) found in uterine tissue
keloid
embryonic tissue
granulation tissue

Type IV collagen : basement membrane

→ Basement Membrane

1) Type IV collagen
2) Laminin
3) Fibronectin
4) Protoglycans

→ STEM CELLS ←

* Stem cells produce different cell lineages
* Stem cells (self Renewal) → Daughter stem cells
* Asymmetric replecation → differentiated stem cells

Stem cell → two daughter cells

* All body cells are produced by stem cells

2 types of stem cells

① Embryonic stem cells → Isolated from a blastocyst in embryo
→ they are totipotent (can produce or generate all tissues of body)

② Adult / somatic stem cells

- found in normal tissue
- found in close association to differentiated cells in specialised micro environment called "Niche"
- they can be { pleuripotent / Multipotent / Bipotent

- found in a) Bone marrow
  - i) Haemotopoietic stem cell → Pleuripotent sc → Produce all the blood cells

these cells can be isolated from
- Umbilical cord blood (Rich source)
- Bone marrow
- Phenpheral blood Flow by GM-CSF injections

ii) Marrow stromal stem cells / Mesenchymal sc

- pleuripotent
- give rise → Chrondrocytes, osteoblasts, Adipocytes, Myoblasts, Endothelial cell

b) Liver Stem Cells: also called "OVAL CELLS"

* found in canals of Hering
* Bipotent → Hepatocytes, Biliary cells

c) Neuronal stem cells / In brain

* found in

Subventricular zone — Dentate gyrus of Hippocampus

* generate → Neurons, astrocytes & oligodendrocytes

d) In skin &c

- found in Hair follicle bulge
  sebaceous glands

e) Limbus of cornea

f) Crypts of intestine

g) Satellite cells are c skeletal & cardiac muscle

→ IMMUNO-PATHOLOGY ←

Immunity
- Innate immunity (Natural) / (Natant) → First Line Immunity
  - ① prevention
  - ② eradication
- Adaptive Immunity & Second Line Immunity
  - Selective

- Innate Immunity:
  1) first line defense
  2) function: prevention
     eradication
  3) Non specific
  4) Innate Immunity does not become better c each exposure bcoz there are no memory cells

→ Components of Innate Immunity ←

1) Epithelial — Skin
GIT
Resp

a) Act as: Mechanical barriers
b) Produce antimicrobial substances
c) Intraepithelial lymphocytes

2) Cells: Neutrophils → Acute Infla } Bacteria, Fungal
Monocytes } Chr Inflam
Macrophages
Mast cell
Natural killer cells → Virally infected cells
Dendritic cells

3) Plasma protein: ⓐ Complement by alternate & lectin pathways
ⓑ Mannose binding lectin
ⓒ C Reactive protein
ⓓ Lung surfactant

- Cells that participate in innate immunity have receptors which recognise / bind to microbial components that are shared among related microbes
- these receptors are called pattern Recg receptors
- these receptors are found on ① cell membrane ② endosomal vesicles ③ cytosol

Pattern recognition receptors are;

① Toll like receptor: 11 TLRs discovered (eleven)

Toll

location ⟨ Plasma membrane
Endosomal vacle

→ NF-kB pathway activated

↓

synthesis & secretion of cytokine

↓

Inflammation (kills the microbes)

TLR - 2 → fungal infection
↓
gram +ve except leptospira

TLR - 4 → gram -ve bacteria

② NOD like Receptor (NLR's)

a) location : cytosolic Receptors

b) NLR binds to microbial products Eg: salmonella shigella
also binds to Metabolic byproducts Eg: uric acid
also sensitive to ion disturbances

c) NLR's activation ⟶ formation of inflammasome

↓

IL 1 β converting enzyme ← Activates caspase

↓

IL - 1 ⟨ Fever
Inflammation (kill microbe)

③ C type lectin Receptors
- location : plasma membrane
- Binds to fungal glycans ⟶ Inflammation

④ RIG like Receptors Eg: RIG-1
- Location : Cytosol
- Detect viral nucleic acid ⟶ produce antiviral cytokines like Type 1 Interferon

⑤ G Protein coupled Receptors
- Location : Plasma membrane
- lead to chemotaxis ⟶ it leads to phagocytosis
- these binds by N-formyl methionine on bact cell coall

⑥ Mannose Receptors : Recog Microbial sugar
lead to phagocytosis

→ Innate Immunity provides host defense by

Inflammation — Antiviral ↓ Type I INF

⟶ ADAPTIVE IMMUNITY ⟵

a) Second line of defense
b) function: Irradication of infection
c) Specific immunity
d) become better ∪ each exposure bcoz presence of Memory B&T cells
e) Components ⟵ T Lymphocytes (Cell mediated Immunity)
B Lymphocytes (Humoral Immunity)

B cell → Plasma cells → antibodies → Humoral Immunity

• Mature lymphocyte → Not encountered antigen
(Immunologically inexperienced)

↓

Naive lymphocyte

↓ ← Antigen

Effector cells — Memory cells

- Eliminate the microbe
- (Live in a state of hightened awareness)
- They rapidly kill the microbes if it returns

⟹ Clonal Selection ⟸

Lymphocyte recruited by bacteria Microbe makes its clones and all clones fight

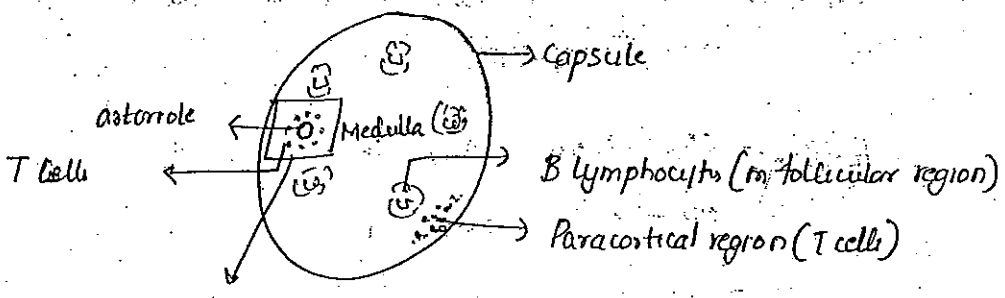
Cells of Immune system — Peripheral Blood

1) Lymphocyte
   - T cells 60-70%
   - B cells 15-20%
   - Nk cells 5-10%
2) Dendritic cells

T Lymphocyte: a) Play role in adaptive immunity (that is in cell mediated immunity)

b) Found
   - Peripheral Blood → 60 to 70%
   - Paracortical regions of lymph nodes, spleen, tonsils

Lymphoid follicle
↓
flower like arrangement



* In spleen T cells in Periarteriolar sheath
* In all other cells in Paracortical region (T cells)

T cell Markers : TCR

CD 1, 2, 3, 4, 5, 7, 8

CD 28

i) TCR Tcell receptor
↓
Antigen specific

2 types
- αβ TCR → found on 95% T cells
- γδ TCR → found on 5% T cells
  - These T cells are found in epithelial cells like skin, GIT, urogenital
  - Provide protection against microbes that enter through epithelia

(ii) CD3 → Pan cell marker
→ Function: Signal transduction

(iii) CD4 & CD8 Found on two mutually exclusive subsets of Tcells

Tcells → CD4 + Tcells 60% 2
CD8+Tcells 30% 1

CD4 : CD8 = 2 : 1

T cells

Helper cell	Cytotoxic Tcells	Regulatory T cells
• CD4 + Tcells	• CD8 + Tcells	• CD4 + Tcells
• function:	• function:	• CD25 +ve
– they stimulate B cells to produce antibodies	– kill virally infected cells	• Express FoxP3 (transcription factor)
– they activate macrophage to destroy the microbes	– kill tumour cells	• Limit immune response
		• Prevent reaction to self antigen

→ 1st line of defense against viral infection → NK cell (Innate)
2nd " " " " " " → CD8 +ve (adaptive)

Helper T cell further divided into three : T_{H1}, T_{H2}, T_{H17}

T_{H1} : cytokines produced are → IL-2, IFN gamma

function of IL-2 : Autocrine effect

T_{H1} → IL2 → ↑ the no. of antigen specific T_{H1} cells

function of IFN gamma ⟨ Stimulate B cell to produce Ig Gamma

- Provides protection against intracellular microbes
- ~~Deranged~~ Delayed function ↳ ass^{n} c chronic autoimmune diseases
  Eg: IBD & psoriasis

→ TH_2

a) Cytokines produced IL-4
IL-5
IL-13

b) Function :

IL-4 ⟨ Activate B cells to produce Ig E antibody
Activate Mast cell

IL-5 ⟨ Activate B cell → Ig A antibody
Activates esinophils

IL-&13 ⟨

* Protection against helminthic parasites
* Deranged function ↳ ass^{n} c allergies

→ TH 17

a) Cytokine produced ⟨ ① IL-17 M. imp
② IL-22
③ chemokines

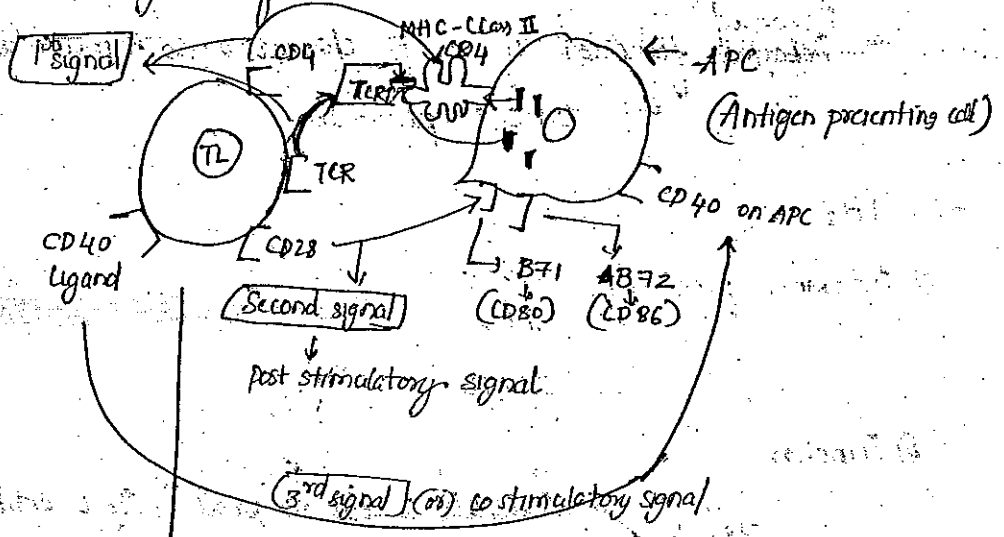
b) functions ⟨ recruitment of neutrophils & monocytes

c) - Provide protection against intracellular ⟨ bacteria
fungi

d) Deranged function → Chronic AID (Auto immune diseases)

like IBD, Psoriasis, multiple sclerosis

→ Signals for T cell Activation



After all 3 signal TL becomes TH 1

TH 1 → produce IL-2 → Helps to produce More & more TH 1

More TH 1 → More IFN gamma

IFN gamma → Activated → produce, macrophages (converted to) Epithelioidal cells → granuloma

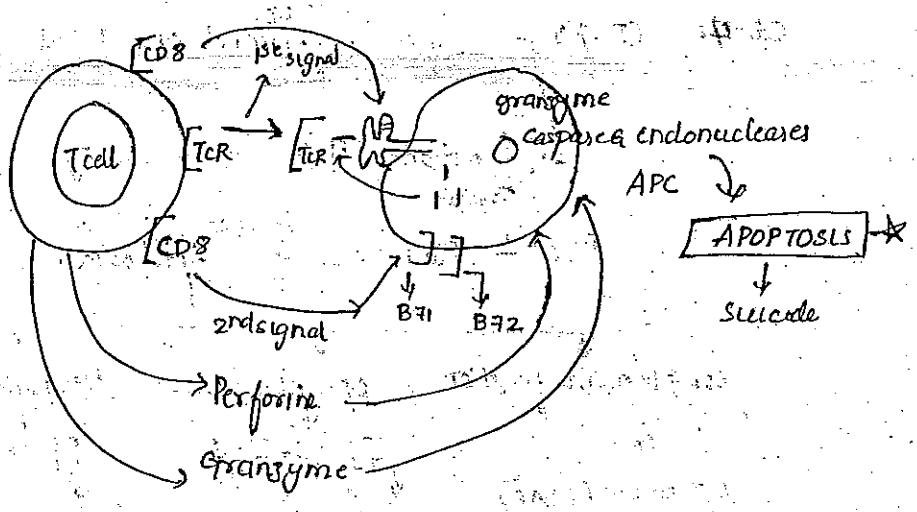
reacts to antigen → Granuloma formed

failure of signal 2 Leads to → a) Apoptosis (or) b) Energy

Intracellular Antigen (Microbes) → TH1

Helmenthic ~~Infe~~ Parasites → TH2

Extracellular Microbes → TH17



→ B cells ←

- 15-20% PB lymphocytes
- BCR (B cell receptor)

CD 19, 20, 21, 22, 23

- Igα, Igβ, & CD 40

BCR → B cell receptor

Antigen specific

Ig D (or) Ig M antibodies

↓

Monomeric Ig M

Ig α also called CD79a
Ig β also called CD79b
} signal transduction like CD3 of T cells

CD21 → Binds to complement products
↓ also called CR2
→ EBV receptors

CD40 → Binds to CD40 ligand on T cell
↓ function: Humoral Immunity
Produce ↓ B cell → Plasma cells → Produce Antibodies

1. complement fixation → C5 to C9 (MAC) → osmotic cysis
opsonisation → Ig G → opsonised bacteria → Removed by neutrophils and Macrophages
Neutralization → antibody → bacteria → antibody coats the bacteria → antibody coated bacteria cannot affect other cell

ANTIBODY PRODUCTION BY B cells

T independents mechanism
↓
ass-c polysaccharide & lipid antigen
↓
stimulate B cell to produce
↓

T dependent Mechanism
↓
ass c protein antigen
↓
B cell attach to TH cells
↓

↓ Ig M antibody (T not help of TH cell)

↓ T helps of cytokines & physical attachment

↓ TH cell produce

IFN gamma cytok. | Cytokin. IL-5 → IL-4

Ig G | Ig A | Ig E

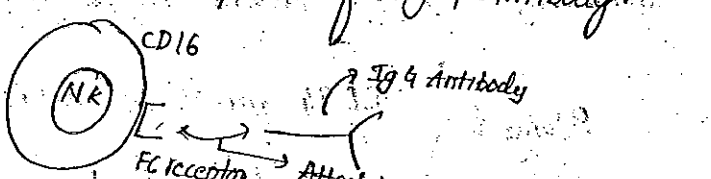
→ Isotype switching

⇒ Thu means Ig M production is stopped and produce Ig G A & E T help of Helper T cell

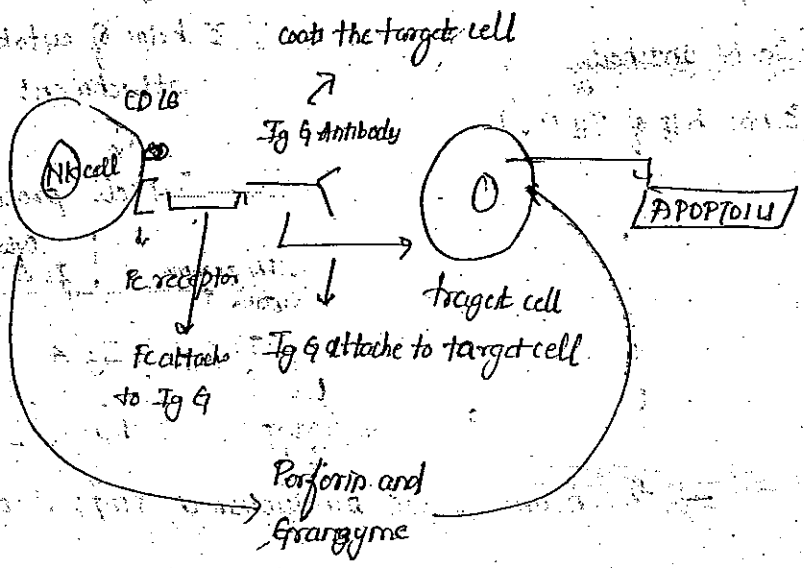
→ NATURAL KILLER CELL / NK cell ←

- 5-10% of peripheral blood Lymphocytes
- Also called → Non B, Non T cells
  - → Large granular lymphocytes
- ✱ Do not express TCR (or) BCR
- Nk cell marker cells: CD16, CD56 → function unknown

CD16 → Fc receptor for Ig G Antibody

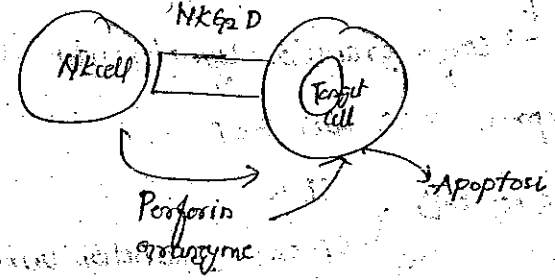


- Functions:
  - i) Innate Immunity: 1st line defense against
  - ii) Adaptive Immunity: ADCC (Antibody dependent cellular cytotoxicity)



NK cells also have 2 types of receptors

i) Activating receptor: → Activate NK to kill target cell
→ Belong to NKG2D family



ii) Inhibitory receptor: Prevent NK cell from killing Normal cell

Belongs to → CD94 family of lectins
→ KIRs (killer cell Immunoglobulin like receptors)

Cytokines that replicate NK cell activity

IL-2, IL-15 } stimulate NK cell proliferation

→ Cytokine produced by NK cell → IFN gamma

→ DENDRITIC CELL ←

→ Antigen Presenting cell (APC)

(Tcell need | APC)

Professional APC	Non Prof APC
a) Dendritic cell	a) Thymic epithelial cells
Immature / Mature (Best)	b) all glial cells
b) Macrophages & Monocytes	c) fibroblasts
c) B Lymphocytes	d) Thyroid follicular cells
	e) Endothelial cells
	f) Pancreatic islet cells

→ Dendritic Cells

a) Best APC

b) Fine hair like process which can trap antigen

c) 2 types * Interdigitating DC

1st type found in skin & interstitia of organs of lungs heart liver etc

* Immature interdigitating DC also called as "LANGERHAN CELL"

d) Site of Maturation : Lymphatics

e) Present antigen to T cell in lymphnodes (in paracortical region)

2nd type

Follicular DC:

a) found in center of lymphoid follicle

b) Present antigens to B cells

→ HYPERSENSITIVITY REACTIONS ←

Amyloidosis

- group of disease
- Deposition of abnormal proteineous substance extracellular
- H & E → Pink Homogenous appereance

→ Physical Nature

Electron microscopy → Long non branching fibrils
→ Indefinite layers
→ 75-10 nm diameter

→ X ray crystallography and infra red spectroscopy
β pleated sheet conformation (Apple green birtingence)

→ Chemical Nature

Fibrillar protein
- 95%

→ P component
- 5%
- glycoprotein
↓
raponsible for PAS +ve & diastase sensitive

→ Classification of Amyloidosis

a) Localised
↓
a) Medullary Ca thyroid → ↑Cal
b) Alzeimers disease → A β
c) Isolated Atrial Amyloelosis → ↑ ANF
d) Prion disease → Misfolded Prion particles
e) Type II DM Amyloidosis → ↑ IAPP
Islet Ass Pancreatic Peptide

b) Generalised / systemic
- Multisystemic disorders

b) Generalised / Systemic

↓

ⓐ Primary amyloidosis

- Seen in pt's of multiple mycolma
- Light chains are deposited as amyloid → A L type
- λ_3 & λ_6 are prone to deposit as amyloid
- M/c organ involved → Heart
  kidney, liver, spleen

ⓑ Secondary Amyloidosis / Reactive systemic amyloidosis

- chronic diseases → TB, OM, lung abces, bronchiectasis
  → Ankylosing spondylitis, RA, ulcerative colitis, RCC.

Liver → SAA —(Incomplete proteolysis)→ AA type amyloid

Serum Amyloid associated

Acute phase reactant

- M/c organ → kidney
  other: GIT, spleen,

ⓒ Haemodialysis Associated Amyloidosis

- Seen in pt's on Haemodialysis for CRF
- β_2 immunoglobulin is deposited as Amyloid $A\beta_2$
- Site → Joints & tendon
  → Carpel tunnel syndrome

ⓓ Senile Amyloidosis

- Old age
- Transthyretin (TTR) is deposited

- TTR → Normal tissue protein that transport ~~thran~~ thyroxine & retinol
- ATTR (Normal) → M/c. organ → Heart
  Liver

ⓔ Familial Amyloidosis

→ Familial Amyloidative polyneuropathy

- Mutant ATTR is deposited
- Site: Sensory and Autonomic Nerves
- AD disorder

→ Familial Mediterranean fever

- AR disorder
- AA derived from SAA is deposited
- Pyrin gene mutation
  - → Related to pyrexia
  - → fever, effusion

Organs involved in Amyloidosis

1) Liver → 1st site → space of Disse
   ↓
   Pressure atrophy of hepatocytes due to accumulation of amyloid

2) Spleen

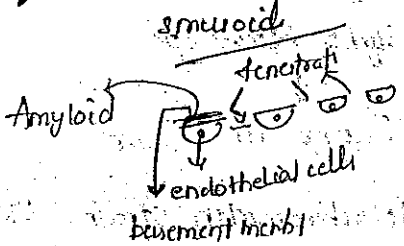
→ Cortex / White pulp
   - Lymphoid follicles – B cells
   - Paracortical region – T cells

→ Medulla / Red pulp — sinusoids

Amylordosis of spleen

In white pulp in spleenic follicles → Tapocca like granules on surface of spleen

Amyloid in Red pulp



large maps like areas of amylordosis → Lardaceous spleen

3) Heart subendocardial deposits

- Bundle branch block
- Restrictive cardiomyopathy
- CCF

4) GIT from mouth to anus

Tongue - Macroglossia

Diagnosis →

FNAC
- Abd fat aspiration

Biopsy
- Abd fat biopsy
- Rectal biopsy
- gingival biopsy
- kidney biopsy (if kidney

; strains of amyloid

1) AFE → Pink Homogenous apperence

2) PAS (+ve) diastase resistant

3) Congo Red - best strain

Light Microscope → Bright Pink color

Polarized light → Apple green birringence

4) Metachromatin strains like crystal violet & methyl violet → Pink / Magenta colored

5) Thioflavin T & S → UV Light → Secondary fluorescence

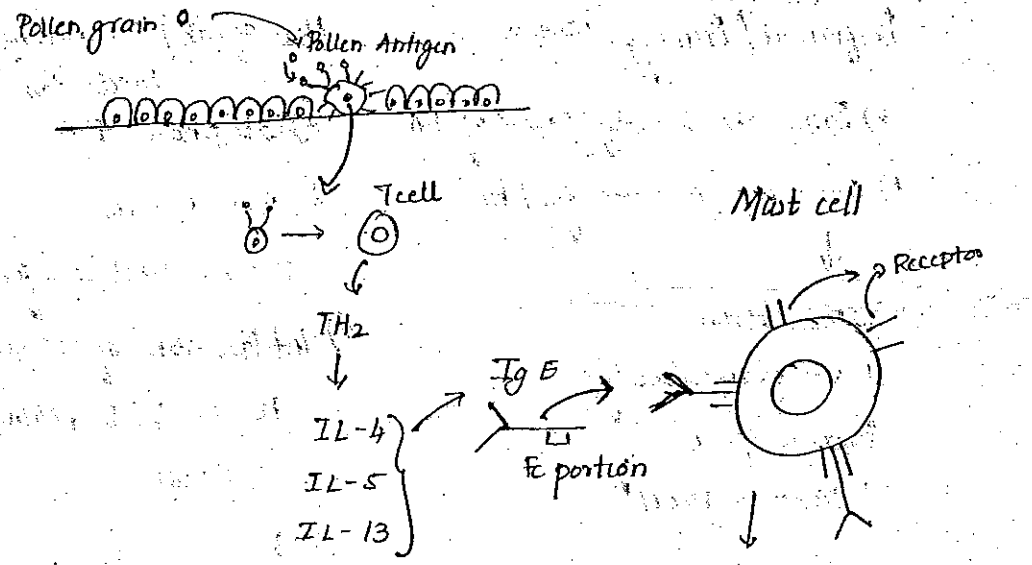
↔ HYPERSENSITIVITY REACTIONS

Def: Injurious Immune Reactions

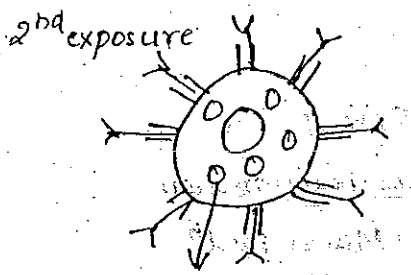
Type I HR : • Rapidly developing Reaction
• Which occurs in minutes after antigen binds to IgE antibody on the mast cells
• In a previous sensitised individual
• Examples — localised - ATOPY - genetic predisposition
  - Ex: a) bronchial asthma
  - b) Allergic Rhinitis
  - c) Allergic conjunctivitis
  - systemic
    - Anaphylactic shock
    - Penicillin
    - Antisera

④ Hay fever
⑤ Food allergies
⑥ Skin allergies

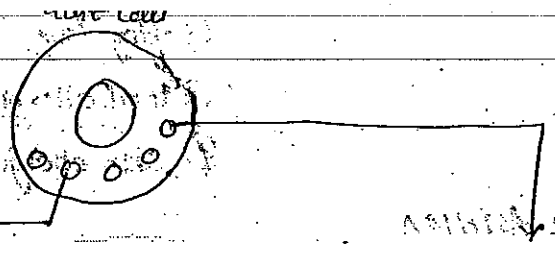
→ BRONCHIAL ASTHMA



IgE coating the Mast cell at 1st exposure called "sensitization"



Degranulates
↓
Mediators of inflammation
↓
Attack of BA



Performed / Primary Mediatory

a) Bring about early phase of BA

b) 5-30 min & lasts for 1 hr

↓

c) Vasodilation
- ↑ vas permeability
- Bronchospasm
- ↑ Mucous prodn

Neo synth / Secondary Mediators

a) Late phase BA

b) acts in 2-8 hrs and last for days

c) Infiltration of tissue by N, E, B, Monocyte & T cells

↓

Tissue destruction

Performed Mediators:

a) Early phase

b) Histamine → (↑) Vas permia
Bronchoconstriction
(↑) Mucus prodn

c) Lysosomal enzymes →
Produce { Proteases (Chymase & tryptase)
Acid Hydrolase
↓
Large tissue destruction

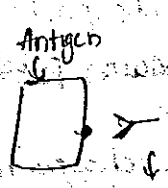
d) Eosinophilic chemotactic factor, Neutrophilic " } → Attract E & N into Bronchial Mucosa

Newly synthesized Mediators (Late phase)

a) AA mediator

- LT
  - ↓
  - LTB_4 : Chemotactic for N, E, M
  - LTC_4, LTD_4 → Bronchospasm, Vasospasm
- PG
  - ↓
  - ① PGD_2 Most abundant mediator produced
    - Bronchospasm
    - ↑ Mucus prodn
  - ② PAF →
    - Bronchospasm
    - ↑ Mucus prodn
    - (↑) Vas permea
    - Chemotactic for N & E
  - ③ Cytokines →
    - IL-1, TNFα → Systemic Acute phase reaction
  - ④ Chemokines like
    - Eotaxin, RANTES → Recruit eosinophils and lymphocytes

Type II Hypersensitivity Reactions

b) 

Dysroption of function of target cell

↑ function — Eg: Graves disease

↓ function — Eg: Myasthenia gravis, Insulin resistant DM

option (a) examples: a) Mismatched BT reaction (Hemolytic)

b) Erythro blastosis fetalis

c) Autoimmune thrombocytopenia

d) " granulocytopenia

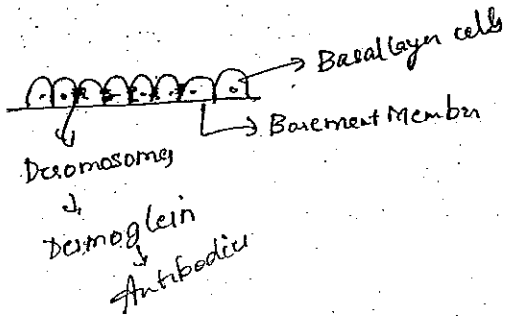
e) " themolytic anemia

f) Pemphigus vulgaris

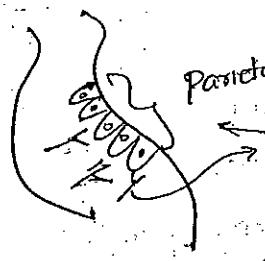
g) Pernicious anemia

h) ARHD

Pemphigus vulgaris:



Pernicious Anaemia → Antibodies to parietal
- 1) Binding antibodies
- 2) blocking antibodies
- 3) Antibodies against parietal cannicular



- No Notch → Achlorhydria
- No intrinsic factor → Megaloblastic anemia
- gastric atrophy → Metaplasia → Dysplasia → Carcinoma stomach

2) Antigen fixed on the extracellular connective tissue
Eg: basement membrane Eg: Goodpasture's syndrome

Type III Hypersensitivity Reaction
"is called as Immune Complex Disease"

Stage 1 → Immune Complex = Antigen (Ag) + Antibody (Ab)

Stage 2 → this Immune complex settles in different organs through the circulation Stage 3 → with help of complement cause tissue destruction

→ Antigen: Exogenous, Endogenous

→ Eg:
- Localized → Eg: Arthus Reaction
- Reactive arthritis → eg Yersinia
- Systemic: APSGN (Acute post streptococcal glomerulonephritis), Serum sickness, SLE, PAN, HSP → IgA antibodies

Type IV Hypersensitivity Reaction

also called Delayed HR

brought about by $CD4^+$ T cell (or $CD4^+$) — TH_1 subset plays the role

Example: a) Tuberculin reaction

b) contact Dermatitis

c) Immune granuloma → in: leprosy, syphilis, LGV, ~~scratch cat~~ cat scratch, tuberculosis, sarcoidosis

Both CD4 and CD8 cause tissue destruction Examples

→ Rheumatoid arthritis

Multiple sclerosis (Myelin sheath dysfunction)

IBD (

Psoriasis

Acute transplant rejection

Graft verses host disease

Type I DM

→ Graft Rejection ←

- HLA Matching done before organ transport
  - HLA Antigens → A, B, DR
  - Matching should be done for A, B, DR

    HLA DR more imp than HLA B & HLA A

    HLA DR > B > A
  - kidney 50% match should be done

    bone 100% match should be done

Anatomy compatability: Size of organ (Heart)
time duration (Need to minimize the time of organ storage)
severity of underlying disease

⇒ HLA Matching Not done for transplant of Heart, Liver, Lung, cornea

than 3 factor take presidence before the HLA Matching

⇒ HLA Matching a not done in Blood transfusion

Graft Rejection:

- Common complex in organ transplant: Eg: kidney transplan
- 3 types: Hyperacute, Acute, chronic rejection (MCa type of rejection)

Hyperacute Rejection:

- Occur in Mins to hrs (< 48 hrs)
- Can be seen on OT Table itself due to performed antibodies in recepient to donor kidney
- These People are those who received multiple BT developing HLA Antibodies
- Preformed Ab are seen in: a) Multiple BT
  b) people having Part H/o transplant rejection
  c) Multiparous women (exposed to fetal HLA Ag which develop HLA Ab)

on examination: a) kidney is swollen, mottled & cyanosed

b) Does not filter urine (or) filters less drops of bloody urine

Microscopic examination M/E: a) Neutrophillic infiltrate in Glomeruli, Arterioli and peritubular capillaries

b) Cortical thrombosis and infraction

this is a type II Hypersensitivity Reaction

where Antibodies come and attach to organ

Acute Rejection:

- occurs days to weeks (< 6 months)
- after immunesuppressive therapy is stopped
- 2 types { Acute cellular rejection
  Acute Humoral rejection

Acute cellular rejection

- Brought by CD 4 & CD 8 cells
- Type IV delayed HR
- Most common 3 patterns

i) Tubulointerstitial (Type I) pattern

- Tubulitis
- Interstitium infiltration by mononuclear cells

ii) Vascular (type II) pattern

Endothelitis

iii) Vascular (type III) pattern

- Endothelitis
- Necrosis in vessel wall

Rx: ↑ the dose of immunosuppressive therapy

Acute Humoral rejection

- Brought about by Antibodies after the transplant (type II) or Immune complex (type III)
  - M/c is type II
  - Does not respond to (↑) dose of Immunosuppressive therapy (IS Therapy)

  So Rx with "B cell depleting therapy"

Microscope: a) Damage to glomeruli and small vessels } they show vasculitis & fibrinoid necrosis

b) C4d depletion in vessel wall by I/F

c) thrombi in small vessels

Chronic Rejection:

- 6 months to years
- type IV HR
- M/c type of GR
- Microscope: ① Glomerulosclerosis
  ② tubular atrophy
  ③ Interstitial fibrosis
  ④ Blood vessels closed due to fibrosis called obliterative intimal fibrosis

Called as "Transplant glomerulopathy"

Complication of organ transplant

① Infections: M/c

- CMV → M/c in 6 month to 2 years
  - Owl eye intranuclear inclusions
- Polyoma BK Viral infection
  - PCT cells show basophilic intranuclear inclusion called "Decoy cells"

② Transplant Rejection

③ GVHD

④ ↑ risk of Malignancies

- ~~HHH~~ HPV → SCC skin – M/c
- EBV → Burkitt lymphoma
- Kaposi Sarcoma

→ Immunosuppressive therapy

1) Steroids: Reduce inflammation

2) Mycophenolate mofetil → (–) proliferation of lymphocytes

T cells & B cells

↓ ↓

CD4 & CD8 produce Ab

3) Tacrolimus (FK506) → Inhibit phosphatase calcineurin which is required for activation of transcription factor of NFAT

(Nuclear factors Activated T cells)

when NFAT is inhibited

↓

No IL-2

↓

T cell inhibition (No proliferation)

④ T & B cell depletion antibodies

⑤ Pooled IV Immunoglobulin (Ig)

↓

Suppress the inflammation

Graft Versus Host Disease (GVHD)

- Common complication of BMT (Bone marrow transplant)
- type IV HR
- GVHD involve all organ except Lung
- M/c organ involved is "skin"
- 2 types { Acute GVHD → < 100 days
  Chronic GVHD → > 100 days
- Recepient of BMT is "Immunocompromised"

↓

two reasons: Acute leukaemia, Aplastic anemia } Prior disease

→ Radio/Chemotherapy prior to transplant

Donor BMT

BMT
- Stem cell
- All other blood cell ← lymphocytes (T cell, B cell)

↓

Main cell in GVHD

The Donor T cell cause GVHD in BMT

- Donor is "Immunocompetent"

In GVHD → ① Skin: Acute - ulceration and
Chronic - scleroderma like fibrosis

② Deathof thymus, lymph nodes etc

③ GIT - Malabsorption, bloody diarrhoea
oesophageal and intestinal ulcers
↓
ulcer heals and form
↓
streture

④ Liver: Cholestatic Jaundice
Death of bile ducts

Complications of T cell depleted BMT

① No GVHD

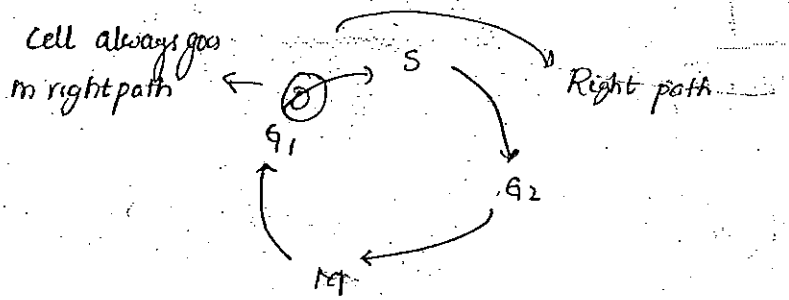
② ↑ incidence of graft failure

③ ↑ incidence of EBV related lymphomas & leukemias

④ Relapse of primary disease eg: Acute Leukemia

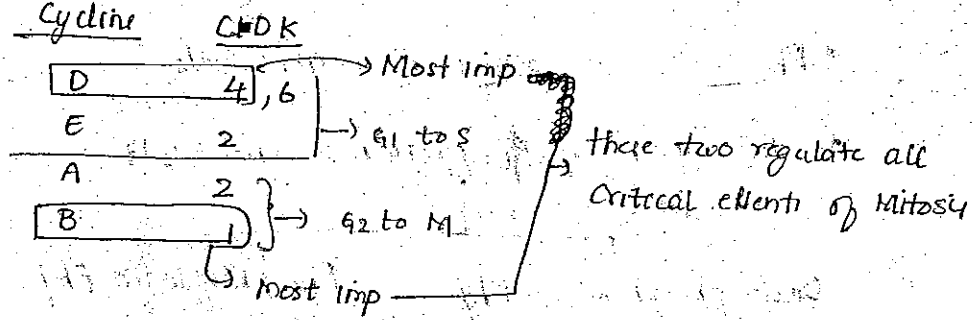
CHAPTER → NEOPLASIA ←

Normal cell cycle regulation



Cyclin (or) Cyclin dependent

Orderly progression of cell trough cell cycle is brought about by cyclins and cyclin dependent kinases



→ Inhibitor of cyclins and CDK

- Inactivate cyclene & CDK complexes
- Inhibitor belong to 2 family ← CIP/KIP family
  INK 4A/ARF family

CIP/KIP family

- P21 → Induced by P53
- P27 → " " TGF B → Non specific
- P57 →

→ INK 4A / ARF

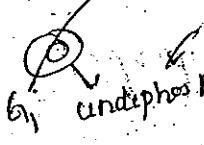
P14, P15, P16, P18 } specific inhibitors
P16 → Most imp

→ Role of Rb gene

- Tumour suppressor gene like P53
- located on Chromosome 13q14
- Rb is called { Molecule on-off switch of cell cycle / Governor of cell cycle
- Rb causes G_1 arrest of normal cells
- two forms of Rb protein on chr^{c} 13q14

Underphosphorylated Rb / Hypophosphorylated Rb	Phosphorylated Rb / Hyperpho Rb
→ Active form	→ Inactive form
Causes G_1 arrest	Causes G_1 S transport

S



Rb pocket → binds transcription factors (E2F1 DP1)
↓
so not these transcription factors
↓
these are needed in DNA synthesis
in S phase
↓

↓

now the cell become less due to death

↓

Now cyclin D & CDK 4 come and phosphorylate the underpho Rb

↓

Now cell goes G_1 to S phase

→ Loss of both copies of Rb will lead to retinoblastoma and osteogenic-sarcoma

→ Regulatory Genes:

- Regulate cell proliferate
- 4 classes of normal regulatory genes

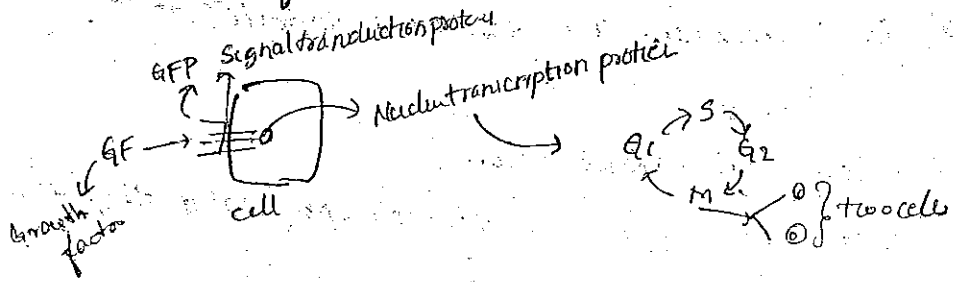
① Protooncogenes — 90 cell / 100 cells → Limit cells not exceed cell proliferation

② Tumour suppresor gene / Antioncogenes — Inhibit cell proliferation — 100 → 100 → No proliferation; remain same no.

③ Genes for Apoptosis

④ Genes for DNA Repair

↳ if possible repair (✓) otherwise kill the cell



Molecular basis of cancer cell:

i) DNA damage lie at the heart of carcinogenesis.

ii) DNA damage cause damage to regulatory genes

iii) Regulatory gene damaged cell a called transformed cell

iv) transformed cell enter the cell cycle

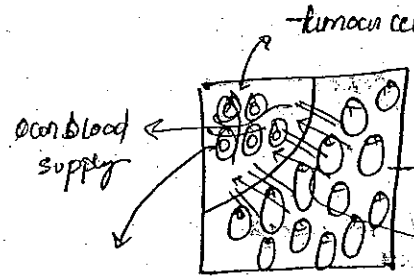
↓ 30 pop doublings

1 gm of cancer forms (10^9 cells)

↓ 10 population doublings

1 kg cancer (10^{12} cells) [Largest cancer mass compatible life]

kinetics of cancer cell cycle



Angiogenesis → local invasion → distant Metastasis

Phenotypic Attribute of cancer cells

they always acquired in a stepwise fashion

so cancer produce → VEGF, bFGF, PDGF → establish their own blood supply

Provide Nutrients, O_2, washing away the toxin, Metastasis

v) Local invasion and distant metastasis

(1) Protooncogenes:

- Cause cell proliferation
- When protooncogenes activated (or) upregulated they form

"oncogens" that cause cancer cells

- oncogenes in Acute trans-forming retroviruses
  ↓
  Discovered by Varmus & Bishop
  ↓
  Nobel price

Protoncogens

4 Mechanisms
1. Point mutation
2. translocation (from one chromosone to another)
3. Amplification (Gene amplification → ↑ in no) ↳ in 1 chrom more no of genes
4. over expression

Oncogenes

GROWTH FACTOR

SIS → Normal GF in astrocytes in brain

a) SIS gene → Astrocytes
   over expression ↓
   Astrocytoma

b) HST 1 —over expres→ Ca stomach

c) INT-2 —amplification→ Ca bladder, ca breast
   ↓
   GF for epithelia of bladder, breast

d) HGF —over expres→ HCC, Thyroid ca
   Hepatocyte Growth factor

② GROWTH FACTOR RECEPTOR

a) ERB B_1 —Overexpression→ SCC Lung

b) ERB B_2 —Amplification→ Ca breast

↓ other name (Her 2 neu)

Epidermal growth factor receptor

c) FMS —PM→ Leukaemia

***d) RET —PM→ MEN 2A
MEN 2B
Med Ca thyroid

↓

Gain of function → Lead to tumour

Loss of function → Lead to HISSRPRUNG'S Disease

e) KIT —PM→ GIST

CD117

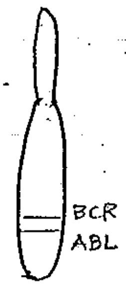
f) ALK —Translocation→ Adenoca Lung

3) SIGNAL TRANSDUCTION PROTEINS

a) ABL —Transloca (9:22)→ CML
ALL

Chromosom 9

ABL → encodes for a protein ☆ tyrosine kinase activity



Pheladelphija chromosome

BCR ABL fusion gene is formed
↓
Produce protein c̄ very high thyrosine kinase activity (or) signal transduction activity

- If this translocation occurs in lymphocytes

Lymphoid cells	Myeloid
↓	↓
ALL	CML
190 kD	210 kD kilodelton protein
Ph +ve Poor prognosis	good prognosis

→ RAS → GIT binding protein

- K RAS —Pt M→ Colon, Lung, Pancreatic Ca
- H RAS —PM→ Bladder & kidney tumours
- N RAS —P.M→ Malignant melanomas

- M/c (oncogenic Mutations) found in Human cancer are RAS Mutations
- M/c ~~muta~~ (gene mutations) forming cancer in human
  - P53

→ β casenin —PM→ HCC / Hepatablastoma

→ BRAF —PM→ Melanomas

→ tumour soppersor gene P16 responible for Hereditory Melanomas

→ oncogenes for Melanomas NRAS
BRAF

→ Nuclear transcription Protein ←

C-MYC —t(8:14)→ Burkits lymphoma

L-MYC —Amplicatn→ small cell carcinoma lung

(N)-MYC —Amplication→ (N)euroblastoma

→ Cyclins & CDK's ←

cyclin D —t(11:14)→ Mantle zone lymphoma

cyclin E —over express→ Ca breast

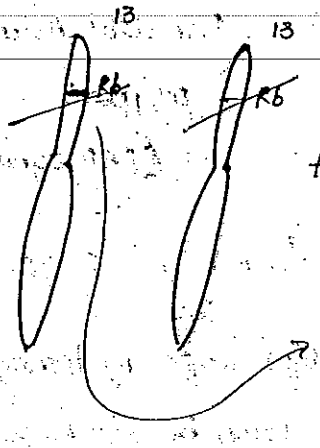
CDK4 —PM/Ampli→ glioblastoma

→ Second catogory of Regulatory genes
Tumour soppressor Genes / Antioncogens

- Inhibit cell proliferation
- loss of function mutation of both copies of tumour suppresion genes cause canca production

Loss of Heterozygocity (LOH)

LOH :



1 copy loss
↓
Heterozygous of Rb gene
↓
one allele gene in both is lost

Loss of Heterozygocity
↓
both copies lost
↳ cancer

i) E Cadherin —LOH→ Ca stomach
↓
Glue like subst in b/w cell

ii) TGF β —LOH→ Ca Colon

iii) NF-1 gene (Chr 17) ⟶ NF-1 Synd
↓ encodes for
Neurofibromin protein → RAS
↓
stop signal to transducts
↓
if lost
↓
More signal are transducted and cell proliferated more
↓
RAS singnal tranduction

NF-1 Synd
↓
also called Von Recklinghausen's disease → Neurofibroma
Cafe au Lait spots
In Iris → Lisch nodules
other - brain tumour like
→ Meningiomas
→ Ependymomas
→ CMML (Chron myelomonocytic leukemia)

iv) NF-2 gene ⟶ NF-2 synd
↓ encodes MERLIN
↓
cytoskeletal stability
found on Chromosome 22

- B/L acoustic schwannoma Synd
- Neurofibroma
- Meningioma

v) APC gene → Familial Adenomatous polyposis (FAP synd) *

Chromo 5

Inhibit ST by WNT pathway

↓

lost

↓

excess signals

Adenomatous polyps (Tubular adenomas)

- polyps appear by teenage
- Ca colon by 35–40 yrs of age
- risk of progression = 100% if no Rx

vi) PTEN — LOH → Cowden synd

Chrm 10 → Endometrial & prostate Ca

vii) Rb gene — LOH → Retinoblastoma

Chrm 13 → Osteogenic sarcoma

viii) p53 gene — LOH → Li fraumeni synd c

Chr 17 P13.1 → multiple carcinomas & sarcomas

ix) P16 — LOH → Hereditary Melanomas

x) WT-1, WT-2 — LOH → Wilm's Tumour

Chrm 11

xi) VHL gene → VHL syndr

chr 3

- clear cell RCC *
- cerebellar Hemangioblastoma
- pheochromocytoma

XII) BRCA 1 ⟶ Hereditary breast and ovarian Ca
chromosome 17 ✱ Prostate & pancreatic Ca

XIII) BRCA 2 ⟶ Hereditary breast ovarian Ca
Chr 13 ✱ Hereditary male breast Ca

Genes for Apoptosis

i) BCL 2 $\xrightarrow{t(14:18)}$ Follicular Lymphoma

GENES FOR DNA REPAIR

- loss of these genes result in ↓ DNA repair defect synd
- loss of both copies cause ⟶ " " " "

⟶ DNA repair synd

1) Ataxia Telangectasia
2) Xeroderma pigmentosa
3) Bloom's synd
4) Fanconi's Anaemia

} Autosomal Recessive

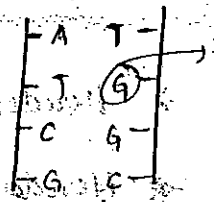
5) Lynch synd / HNPCC ⟶ Autosomal Dominant

⟶ 3 types of Genes

① Mismatch repair Genes
"spell checkers" when a strand of DNA is replicating

→ replication error phenotype

Mutation in DNA strand



mutation

↳ DNA ~~strand~~ strand produced

↓

unstable

↓

transformation

↓

Lynch synd

• polyps (FAP synd) → Min 100 polyps to diagnose FAP synd

• Ca colon

② Nucleotide Excision Repair Genes (NER genes)

- NER genes remove UV light induced pyramidine dimers
- UV light damage DNA by forming pyramidine dimers
- loss of NER gene → Xeroderma pigmentosa

↓

① Autosomal Recessive

② Photosensitivity

③ Neurological defects

④ 200 times ↑ risk of developing cutaneous cancers ← SCC, BCC, Melanoma

③ Genes for repair by Homologous Recombination

- They repair Double strands DNA breaks which can be produced by Ionizing Radiation

a) ATM gene – sensor of DNA damage
– can recognize : single strand DNA breaks
double " "

Loss → Ataxia Telangectasia
AR disorder
Cerebellar ataxia
Oculocutaneous Telangectasia
Def of IgA antibody → Repeated infection → loss main cause of deaths
↑ risk of developing lymphoreticular malignancies

b) Bloom synd : AR disorder
loss of gene producing enzyme
BLM helicase (needed for repair of double stranded DNA breaks)
↓
growth retardation
↑risk of lymphoid malignancies
Neurological abnormalities

c) Fanconi's Anemia – AR disorder
– Repair of double stranded DNA
– Hereditary aplastic anaemia
→ They have → Hypoplastic thumb & radii
Hypoplastic kidneys & spleen
– (↑) risk of developing Acute Leukaemias

CARCINOGENS

Cancer causing agents

- Chemical
- Biological
- Radiational

Chemical carcinogens:

- Initiator: Are substance that cause DNA damage → transformed cell
- Promotors: Substance that cause proliferation of DNA damaged cells
  - stimulate genetically damaged cell to proliferate
  - Example: saccharin
    - Hormones (estrogen, DES)
    - phenol
    - phorbal esters

Complete carcinogen: capable of both initiation and promotion

Carcinogens
- direct acting
- Indirect acting

Direct acting: Eg: alkalyting agents
- Active form

Indirect acting: Eg- aromatic amine → cytochrome P450 dep monooxygenase convert

Eg: ① Arsenic → Lungs & Skin Ca

② Asbestos → Lung
Mesothelioma
oesophagial Ca
gastric Ca
colonic Ca

③ Benzene – AML

④ Vinyl Chloride – Hepatic Angrosarcoma

⑤ Aromatic amines like β naphthalamine

⑥ Azodyes → HCC

⑦ Nitrosamines & Nitrites → Gastric Ca
oesophagial Ca

AMES TEST:

used to detect Mutagenic potential of a chemical by its ability to induce Mutation in salmonella typhimurium

Radiational → Ionizing Radiation
UV Light

→ Ionizing Radiation

- Mlc cancer → leukaemia
  all leukaemias except CLL
- Papillary Ca thyroid
- Breast Ca, Lung Ca, Mucoepidermoid Ca of salivary gland

~~Open tum~~

UV light : UVL Asso & induction of cutaneous cancer → SCC, BCC, Melanomas

Biological Carcinogens

Viruses	Bacteria
1) Adenoviruses - Causes cancer in animals	1) H pylori → gastric Ca, gastric lymphoma → MALT lymphome of stomach
2) HPV → ~~70 subtt~~ 70 serotypes	

Low risk serotypes 6, 11

Intermediate " " 31, 33

High risk serotypes 16, 18

Low risk serotypes → Venural warts (or) condyloma acuminatum

keratinocyte tumours of anogenital region

Intermediate & High Risk Serotypes

→ Ca Cervix
Ca anogenital region
Ca penis
Ca Vulva
Ca Vagina
Ca larynx
Ca ~~oroph~~ oropharyngeal

Viral DNA gets integrated into Human DNA

↓

this virus produced two protein

↓

encodes two viral protein

↓

E6 → Degrades P53

E7 → Degrades Rb

EBV → DNA Virus

a) CD21 on B cells is the EBV receptor

b) Causes Infectious mononucleosis → benign condition
Oral Hairy leukoplakia in HIV pt's

Tumours: Nasopharyngeal

Hodgkin's lymphoma

Burkett's "

— B cell lymphoma

EBV encodes two viral protein

LMP-1 } uncontrolled cell
EBNA2 } proliferation

HBV = Hepatitis B Virus → HCC

Repeated cycle of injury and regeneration of Hepatocytes lead to accumulation of Mutations that lead to cancers

RNA Viruses

HTLV-1 Virus

- Causes Tropical splastic paraparesis] benign
  Arthritis, Uveitis

Tumour: Adult T cell leukaemia/lymphoma

HTLV 1 encodes for "TAX protein" that leads to uncontrolled cell proliferation

~~HCV~~ ~~Virus~~

HCV → HCC
→ Splenic marginal zone lymphoma

→ Hallmarks of Cancer

a) Self sufficiency of Growth signals
   Cancer cell proliferate ~~coz~~ stimuli due to oncogene activation

b) Insensitivity to Growth inhibitory signals

c) Altered cellular metabolism
   Warburg Effect: Discovered by OHO WARBLY
   Noble prize
   - Also called as "aerobic glycolysis"
   - Provides rapidly dividing cancer cells with metabolic intermediates that are needed to

④ Evasion of Apoptosis

⑤ Limitless replicative potential due to Telomerase activation

⑥ Sustained Angiogenesis

⑦ Ability to invade & Metastasis

⑧ Ability to evade post immune system

PARANEOPLASTIC SYNDROME

1) Hypercalcemia: M/c paraneoplastic synd

- Due to production of PTH related protein by tumour cell.

Tumour — SCC Lung
Breast Ca
RCC
Adult T cell lymphoma/ leukaemia

② Acanthosis Nigricans → Skin become thick & pigmented

Due to prodn of Epidermal GF by tumour cell

tumour — gastric Ca
Lung Ca

③ Trousseau synd:

also called Migratory thrombophlebitis

tumour — Pancreatic Ca, Lung Ca

④ Paraneoplastic Endocrinopathy

ⓐ cushing → ACTH prodn

Tumour - small cell Ca lung

Pancreatic Ca

Neural tumour

(b) SIADH → Due to ADH / Atrial Natriuretic ion by tumour cells

tumour - scc lung

(c) Hypoglycemia - Due to prodn of insulin / Insulin like substain

tumour - fibrosarcoma, HCC

(d) Carcinoid synd:

Due to prodn of serotinin (∞) bradykinin by tumour cell

tumour - HCC, bronchial carcinoid, Pancreatic Ca

(e) Polycythemia - Due to EPO prodn

tumour → RCC, HCC, cerebellar Hemangioblastoma

(f) Pure Red cell Aplasia : seen ∞ thymic tumour

(g) Myasthenia → Ca lung

Immunologic

(h) Cerebellar degeneration : seen in Hodgkin's lymphoma

(i) Nephrotic synd : Marrow cancer

(j) Non bacterial thrombotic endocarditis, also called as (Marantic endocarditis) → Veg on heart valves

↳ seen in Advanced cancer
Chronic debilitating diseases

→ SERUM TUMOUR MARKERS

1) Hormones

a) Calcitonin – Medullary Ca thyroid

b) β HCG – Trophoblastic tumours eg: Choriocarcinoma

c) Catecholamines – Pheochromocytoma

2) oncofetal antigens

a) AFP → normally produced in fetal liver, Yolksac and gut
Alpha fetal protein

(↑) AFP → Yolksac tumour
HCC
Hepatoblastoma

b) CEA → normally produced by fetal liver, pancreas & gut

(↑) CEA → Ca colon, stomach, pancreas, lung & breast

3) Isoenzymes

a) Prostate Acid phosphatase : Ca prostate

b) Neuron specific enolase → Neuroblastoma & SCC lung
(NSE)

4) Specific protein

a) PSA → Ca prostate

b) Ig → Multiple mycoloma

5) ~~Mucins~~ Mucins →

CA 125 – Surface epithelial tumours of ovary

CA 19.9 – Colonic & Pancreatic Ca

CA 15.3 → Ca breast

Tumour Markes detected by IHC

Immunohistochemistry

1) Carcinoma → Cytokeratin (all Ca have cytokeratin)
→ EMA epithelial Memb Ag
→ CEA

2) Lymphoma LCA (CD 45)
Lymphocyte common Ag

3) Sarcoma → Vimentin

Rhabdomyosarcoma ↓ also +ve for Desmin
Myo D

Leiomyosarcoma " " " Smooth Muscle Actin (SMA)

Ewings Sarcoma " " " CD99

Synovial " " " " CD90
EMA

ostcosarcoma -u also +ve for → osteopontin, osteocalcin, osteonectin

Chondrosarcoma " " " "

4) Mesothelioma → cytokeratin 5/6, MESOTHELIN, CALRETENIN, WT-1

5) Melanoma → S 100, HMB45, Melan A

6) Neuroblastoma, SCC Lung, carcinoid → NSE, chromogranin, Synaptophysin

7) Schwann cells → S-100
↓
Schwanoma &
Neurofibroma

8) HCC → Hep Par 1, Arginase 3

9) Adeno Ca ~~Alveola~~ Lung, Thyroid Ca → TTF-1

10) LCH (Langerhans cell Hepatosis) → CD1a, S-100, Langerin

11) squamous cell carcinoma → P63 & P40

HEAMATOLOGY

Haematopoiesis → • formation of blood cells

- begins in 3rd week of intrauterine life in Yolk sac
- 3rd month of IUL → Liver
- 4th month of IUL → Bone marrow
- From birth upto puberty: all bones have Red marrow and therefore involved in Haematopoiesis
- After puberty Red marrow in only flat bones and ends of long bones i.e. Haematopoiesis occur in their sites.

Bone Marrow

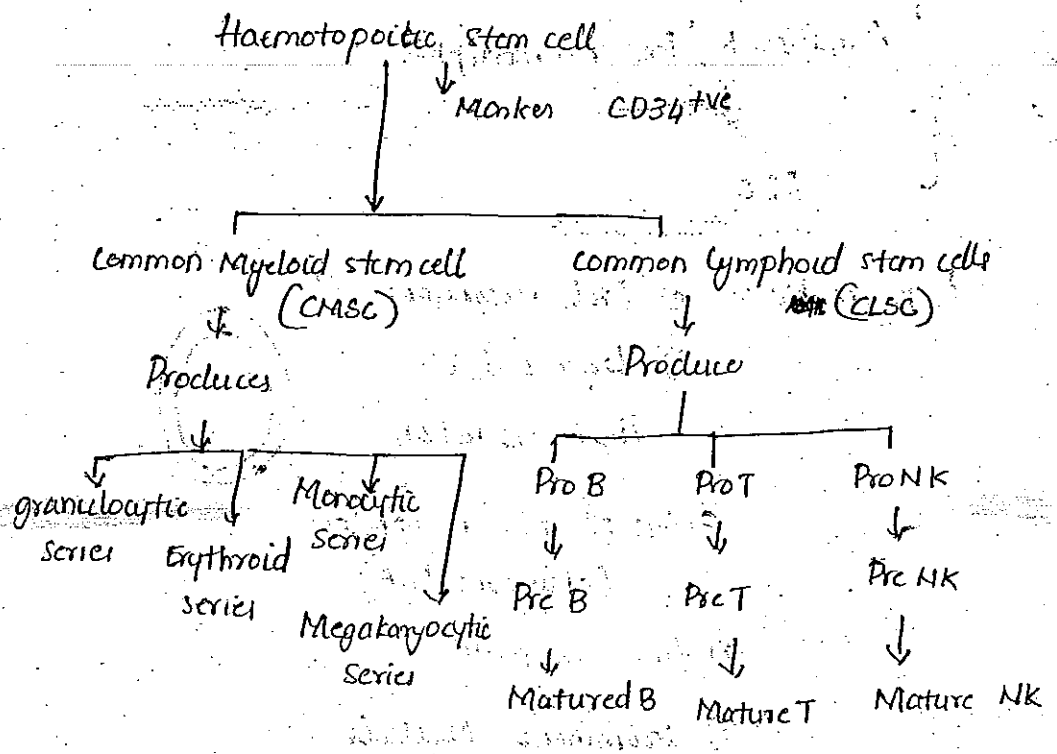
	Haematopoietic cells	Fat	
	HC	Fat	100 − Age
IN CHILDREN	75%	25%	
Adults →	50%	50%	
old age →	25%	75%	

In Haematopoietic cells: -

granulocytic series | Erythroid series | Monocytic series | lymphoid series | Megakaryocytic Series

Max cells → granulocytic > Erythroid series

Myeloid series : Erythroid series = 2 to 3 : 1 [2:1]



Erythroid series :

All cells look alike

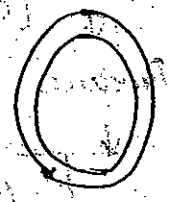
HSC
↓
CMSC
↓
CFU - E
(colony forming unit erythroid)
↓
BFU - E
(burst)
↓
Pronormoblast (1st recognisable cell that can give RBC)
↓
Early normoblast / Basophilic normoblast
↓
Intermedia Normoblast / Polychromatophilic Normoblast
↓
Late / orthochromatic Normoblast

① Pro RBC Precursor
② is found in Bone marrow
③ all cells have nucleus

↓

Non nucleated { Reticulocyte / Polychromatophil
↓
RBC

Pronormoblast: a) First recognisable cell



b) Large cell ⊂
High NC ration

c) Cytoplasm ⊍ basophilic
(abundant RNA)

d) fine chromatic

e) Prominent Nucleoli

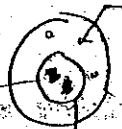
Early Normoblast: / Basophilic Normoblast

smaller than Pronormoblast

→ cytoplasm ⊍ basophilic due to abundant RNA
↳ blue in color
→ No nucleoli
→ Chromatin clumping (starts)

Intermediate / Polychromatophylic Normoblast

Smaller than Early

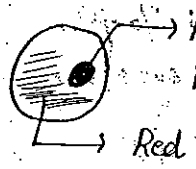


→ few red dots
Checkerboard chromatic
Cytoplasm : Basophilic (RNA)
↳ Blue

By { My light microscopy Haemoglobin ⊍ seen in Intermediate
My electron " " " " " Pronormoblast stage

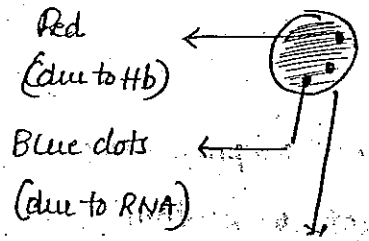
↓

Late / orthochromatic Normoblast



↓

When the cell loses its Nucleus it is called Reticulocyte / polychromatophil



Reticulocyte in circulation stays for 1-2 days

RBC ◯

- smaller than a reticulocyte
- No blue dots (No RNA)

RBC Count { 4.5 to 5 million/cumm in Female
5 to 5.5 million/cumm in Male

Reticulocyte count → 0.5 - 2 %

Absolute Retic count → should have Retic %

$$\frac{\text{Reti \%}}{100} \times \text{RBC count}$$

Corrected Reticulocyte count ⇒

Count is corrected for degree of anemia

Eg: Retic count is 6 %

Hb → 6 gm/dl

Pt is 25 yrs old

Corrected retic count is counted by

$$6 \times \frac{Pt\ Hb}{(N)\ Hb\ \%\ for\ that\ age\ \&\ sex}$$

$$6 \times \frac{6^{1}}{12_{2}} = 3\%$$

$$18 \times \frac{Pt's\ PCV}{(N)\ PCV}$$

$$6 \times \frac{Pt\ RBC}{(N)\ RBC}$$

→ Presence of Nucleated RBC in the peripheral smear is a abnormal condition except in newborn

HSL
↓
CMSC
↓
CFU
↓
Myeloblast → May (or) maynot have granules
↓
Promyelocyte
↓
Myelocyte
↓
Metamyelocyte
↓
~~Beta~~ Band / Stab form

① found in BM
② granulocytes
③ Nucleated

Peripheral blood → (N) (E) (B) granulocytes

Shift to left: "presence of unmatured cells of myeloid lineage in PB is called"

In Peripheral smear:

Shift to left + nucleated RBC

nRBC

↓

Called as

"Leukoerythroblastic blood picture"

↓

Reason

Causes ① It is seen in myelophthisis anaemia

↓

Marrow failure due to space occupying lesion that replaces the normal marrow elements

Causes: ① Granulomatous diseases

Example: TB

sarcodosis

fungal infection etc

② Metastasis of Ca lung, breast, prostate

③ Myelofibrosis

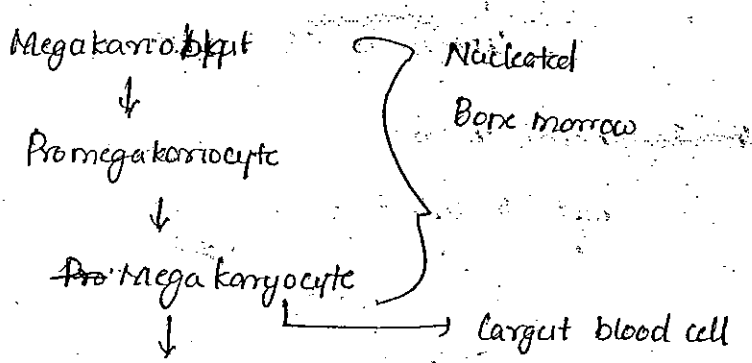
Leukoerythroblastic blood picture causes

② ④ Severe Haemolytic anaemia

Monocytic series

Monoblast ↓ Promonocyte ↓ Monocyte → PB — BM

Megakaryotype series



Haemoglobin

		Anaemia
Birth →	16.5 g/dl	< 13 g/dl
0–6 month →	11.5 g/dl	
6 months – 6 yrs →	12.5 g/dl	
6 – 12 yrs →	13.5 g/dl	
Adult female →	13.5 g/dl	< 12 g/dl
Adult male →	14.5 g/dl	
In pregnancy →	12.5 g/dl →	< 11 g/dl

Mild	Anaemia	9–12 g/dl
Moderate	"	7–9 gm/dl
Severe	"	< 7 g/dl

TLC → 4000 – 11,000 cells/cumm

DLC → N → 60-70% → 4000-6000 cells/cumm

L → 20-40% → 2000-4000 "

E → 1-6% → 40-440 "

M → 1-10% → 100-1000 "

B → 0-1% →

Platelet count 1.5 to 4 lak/ul

RBC indices

⇒ MCV = $\frac{PCV}{RBC} \times 10$

PCV also called Haemotocrit

PCV — 42% female
— 45% Male

Normal : 80-100 fL (Normocytic RBC)

<80 fL (Microcytic)

>100 fL (Macrocytic)

⇒ MCH

MCH = $\frac{Hb}{RBC} \times 10$

↓

(N) 27 to 32 Pg Picograms

<27 Pg (Hypochromic RBC)

>32 Pg

⇒ MCHC

$$MCHC \ \frac{Hb}{RBC} = \frac{Hb}{PCV} \times 100$$

↓ (N) 32-38g/dl

(↓) MCHC in anaemia

(↑) MCHC in Sickle cells
Spirocytes

⇒ RDW (Red cell Distribution Width)

Indicator of degree of anisocytosis

Anisocytosis : Variation in "size" of RBC

Poikilocytosis : Variation in "shape" of RBC

(N) Value is 12-14%

⇒ RBC

Life span of RBC → 120 days

" " spirocytes → 10-20 days

" " Sickle cells → 20 days

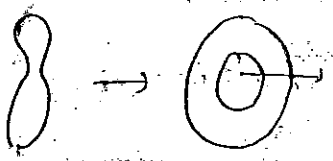
Shape: Biconcave discs → More surface area / More memb and less volume → Deformable

Size : 7.5 μ

Loss of membrane & Vol content

Spherocytes → Not deformable
→ removed prematurely by spleen
& its soon

(N) RBC



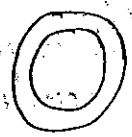
1/3 central pallor

↓

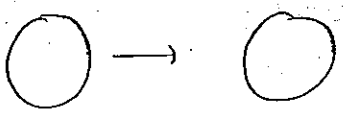
if center ↓ > 1/3 pallor

↓

Hypochromic RBC



spherocyte :



No central pallor

spherocytes seen in : ① Hereditary spherocytosis

② Autoimmune Haemolytic Anemia

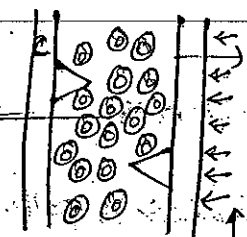
③ Alloimmune " " "

④ G6PD Def

⑤ PNH

Haemolytic Anaemia :

- Premature destruction of RBC leading to anaemia
- Haemolysis can be ⟨ Intravascular
  Extravascular ⟨ Liver
  Spleen
- (↑) Serum unconjugated bilirubin
  ↓
  lead to pigment type of Gall stones
- Anaemia → Tissue Hypoxia → (↑) Erythropoietin in kidney → Bone marrow → Erythroid hyperplasia in the bone marrow



Erythroid hyperplasia

Medula expand out

↓

Cortex will be thined

↓

fractures occur (cortical fractures)

↓

Healing occurs from outside (New bone formation)

↓

thus gives the appearance of Hair on End (or) crew cut appearance in X ray

Reticulocytosis

↓

In P/s nucleated RBCs

- CRISIS of
  - Haemolytic crisis
  - Aplastic crisis : caused by Parvo B 19 viral infection

- In sickle cell anemia

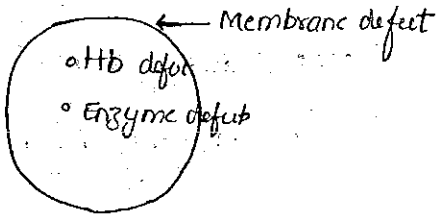
SCA
- Aplastic crisis
- Haemolytic crisis
- Sequestration crisis
- Vaso-occlusive crisis

- Intravascular
  - Hb
  - Haemoglobinemia
  - Haemoglobinuria
- Extravascular
  - Spleenomegaly
  - Hepatomegaly
  - ↑ S.unconjugated bilirubin

- Heamosiderinuria
- ↓ serum Heptoglobin levels and ↓ serum Haemopexin
- Small Hb ↓ Oxidised ↓ Methyl Hb ↓ Methalbuminemia

Classification OF HAEMOLYTIC ANEMIAS

Intrinsic / Intracorpuscular defect



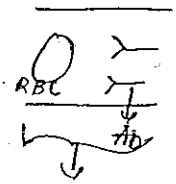
→ Memb defects: Hereditary spirocytosis
" Elliptocytosis
" Pyropoikilocytosis
" Stomatocytosis

✱ PNH → acquired defect

→ Enzyme defects: Inherited ← { Pyruvate Kinase Def, Hexokinase Def, G6PD Def

→ Hb defects / Haemoglobiniopathies

Extrinsic / Extracorpuscular Defect



① Immune Haemolytic Anemia
↓
they can be Autoimmune
Alloimmune

② Microangiopathic HA
thrombi are found in small vessels, RBC strike against the thrombi and breaks
↓
I.V. Haemolysis
↓
P/S Schistocytes (or) Helmet cells

Hb defects

Quantitative defect
- Thalassaemia

Qualitative / structural defect
- HbS
- Hb C
- Hb D
- Hb E
- Unstable Hb ducan

Causes:
- HUS
- TTP
- DIC
- 3) Vegetations on heart valves seen in a) SABE
  b) Marantic endocarditis (NBTE) Non bacterial
- 4) Prosthetic heart valves
- 5) Malaria
  - Intravascular Haemolysis
  - Extravascular
- 6) Toxins: snake venom, C. welchii toxin
- 7) severe burns
- 8) MARCH Haemoglobinuria
  soldiers while they march.

→ Types of Haemoglobins ←

(After 6-9 months of birth)

In Adults: HbA → 2α & 2β ($\alpha_2\beta_2$) ≅ 95%

HbA_2 → α_2 delta 2 < 3.5%

HbF → α_2 gamma 2 < 2.5%

In fetal life: embryonic Hb

Gower 1	zeta 2	epsilon 2 (Yolk sac)	< 5-6 wks
Gower 2	α_2	"	4-13 weeks
Portland	zeta 2	gamma 2	4-13 weeks

(predominant) HbF $\alpha_2\gamma_2$ gamma$_2$ Liver starts at 3 Sols of IUL

- Continous upto 6-9 month after birth

HbA $\alpha_2 B_2$ Bone marrow Starts @ 9 weeks of IUL

→ HbA_2 is not found in fetal; HbA_2 starts after 4 months of age (Adult levels)

At birth HbA → 5-45%

HbF → 50-95%

↓(ultimately)

HbA are ↑ed

HbF are ↓ed to <2.5%

PNH Parasoxemal Nocturnal Haemoglobinuria

- Acquired Memb defect
- Stem cell disorder

bac osmolysis (bac) → complement (MAC)

GPI anchors: which anchors of CD55, 59 on R, W, P

CD55 (DAF)
CD59 (MIRL)
Protective umbrella

RBC WBC Platelet

CD55 → It breaks C3 & C5 convertases ↑ decay accelerating factor (DAF)

CD59 → Protects these 3 cells (RBC WBC platelet) from MAC & other complements

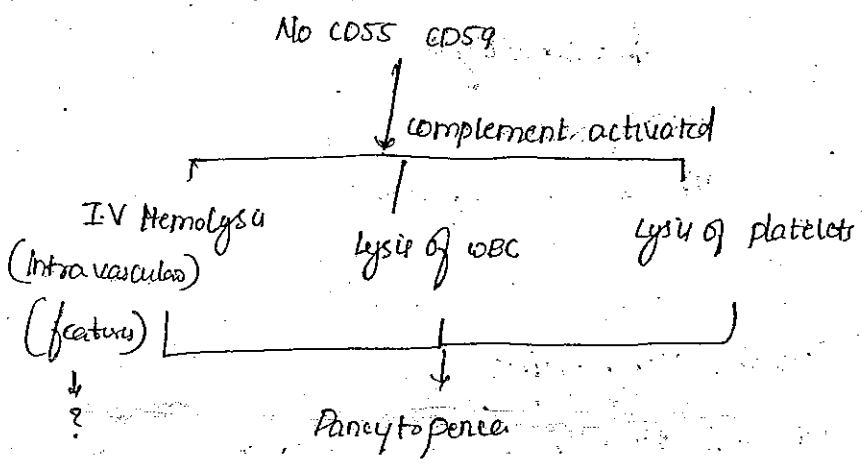
Memb inhibitor of reactive components -lysis ↓ (MIRL)

It breaks MAC

→ GPI anchors are encoded/produced by PIGA gene

- Stem cell disorders → Mutation of PIGA gene
  ↓
  No anchors GPI
  ↓
  No GPI anchor linked proteins CD55 CD59

- complements can triggered also by Resp distress that lead to acidosis



Haemolytic anemia → IV. haemolysis

1) Episodes of IV haemolysis occurring more at night → ~~classical~~ clinical picture seen only in 25% pt

2)

3) Leucopenia → Rpt-infections

4) Thrombocytopenia → Bleeding

5) Thrombosis - (Venous thromboses > Arterial)
   Hepatic vein thrombosis called (Budd chiari) in the

most common cause of death in PNH:

Budd chiari Synd.

① PNH
② Pregnancy
③ Polycythemia rubara vera
④ other CMPD

⑥ PNH can involve into aplastic anaemia

⑦ " " " " Acute leukemia

PNH triad of: Pancytopenia, HA, Thrombosis

⇒ 5-10% cases of PNH can present at birth (congenital PNH)

P/s: ① Microcytic Microchromic (due to chronic blood loss)
② Reticulocytosis
③ nRBC on P/c
↓
nucleated

BM Aspiration: → BM is hypercellular & erythroid Hyperplasia
→ BM can be hypocellular due to evolution to aplastic anemia

M : E myeloid : Erythroid cells

2-3 : 1

↓

More in bone Marrow

M1 cell (High)

RBC cells (low)

↓

P/S RBC more (120 day)

WBC less (~10 days)

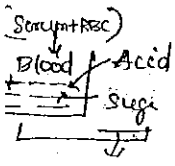
E/P of WBC is much less

→ LAP Score

↑ cd	↓ cd
• Leukamoid reaction	• CML
• Polycythemia rubra Vere	• PNH
• Aplastic anemia	
• blast crisis in CML	

(↑ in comparative)

Tests : 1) Hams test / Acidified serum test



activate the complimentsystem

↓

Haemolysis

2) Sucrose lysis test / Sugar water test

3) Flow cytometry (Gold standard for Dsu)

↓

directly seen the CD55 cells in which are they present & absent

→ HEREDITORY SPHEROCYTOSIS ←

- 75% cases are AD
- 25% cases are AR
- Inherited disorder
- Due to def of memb protein

M/c ① Ankyrin

2nd common ② Band 3 (also called: anion trans post protein)

3rd " ③ spectrin

4th " ④ Band 4.2 (also called: Palladin)

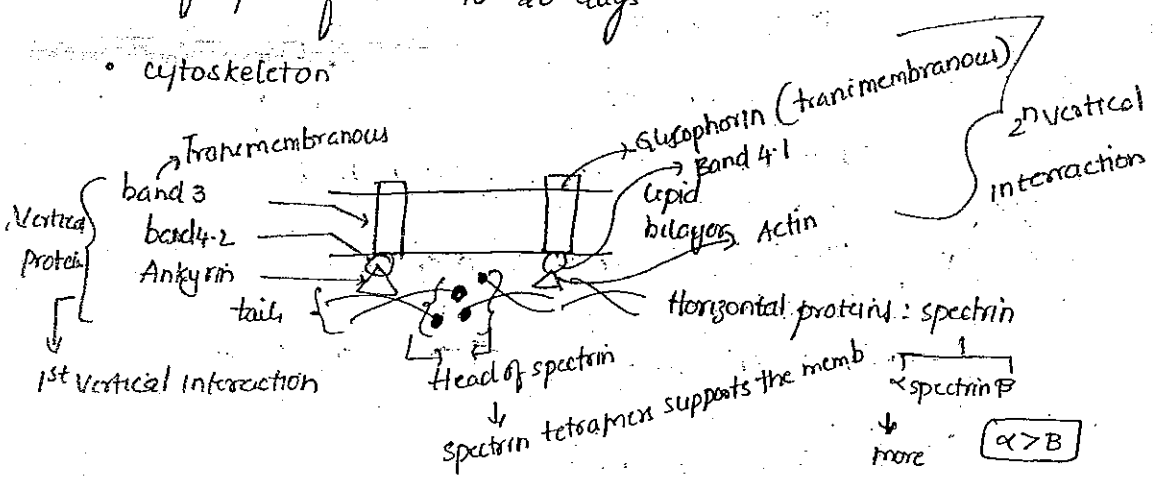
- M/c cause is Ankyrin def
- Most severe form of HS is due to spectrin def

↓

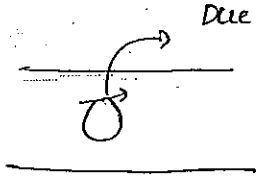
bcoz spectrin is most abundent

Protein in RBC membrane

- Life span of HS: 10-20 days
- cytoskeleton



pathogenesis: Def of cytoskeletal protein: loss of Memb support



Due to shearing stress of blood

↓

there is loss of RBC membrane in ⊖

↓

spherocytes are formed

↓

Not at all deformable

↓

Removed prematurely by Splenic macrophages

↓

(Predominantly) by Hepatic cells (extravascular Haemolysis)

LAB tests: Hb ↓

MCV → (N) or ↓

MCH → (N)

MCHC → ↑

Reetic count → ↑

S. bilirubin → (↑) unconjugated bilirubin

P/s: Spherocytes → Slightly smaller than RBC

Reticulocytes → ↓ Lack central pallor

nRBC (may be present)

TEST: Osmotic fragility test:

- (N) RBC are isotonic to 0.9% NaCl
- Haemolysis starts at 0.5% NaCl

- Haemolysis completed by 0.3% NaCl
- Spherocytes: Haemolysis starts at >0.5%
  (they have ↑ed osmotic fragility: very fragile)

⟹ Blood in NaCl (N saline) = RBC intact

↓

Blood in NaCl + water = ~~Haem~~ water enter into RBC

↓

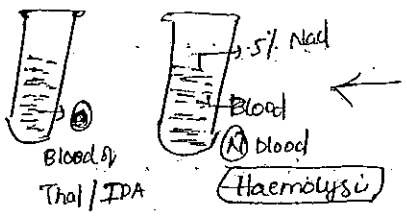
RBC bulge

↓

Lysis (0.3)

Microcytes seen in Iron Def Anemia & Thalassemia

have ↓ osmotic fragility



NESTROF — Reddell

Naked eye single tube ~~Red~~ osmotic fragility test

Thal NESTROF is a screening test for β Thal trait

↓

but not conformatory test

MCQ: Proteins which are integral part of RBC memb are Glycophorin AND Band 3

H-Spherocytosis ← Anemia, Jaundice, Splenomegaly

↓

Heptamegaly may also be there

↓

Haemolysis → extravascular

Crises ⟨ Haemlysu crii
⟨ Aplastic crisis → Parvo B19 viral infection

⇒ they may have gall stones

→ HEREDITARY ELLIPTOLYSIS ←

- AD disorder
- Def of protein band 4.1
- Pt's usually asymptomatic
- P/s : >15% Elleptocytes
  (usually they have 50-90% elliptocytes)

→ AUTOIMMUNE HAEMOLYTIC ANEMIAS ←

- Test for Δsq → Coombs test / Antiglobulin Test

AHIA

warm cold type

↓

More common > cold

Worm ~~AHI~~ AIHA

① Rh (D) → Ag

~~Anti~~ IgG → Ab

temp → 37°C

(thermal amplitude) → ⊖

→ opsoning antibody → opsonized RBC → are removed by spleen → extravascular Haemolysis

Causes of Warm AIHA are:

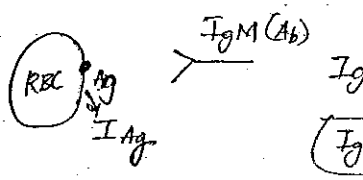
1) Idiopathic
2) Chronic lympho proliferative disorder
   - CLL (MCQ) (10% pt of CLL have Warm AIHA)
   - Hodgkin's lymphoma
3) AID → SLE (MCQ), Rheumatoid Arthritis, ulcerative colitis
4) Drugs → α Methyl dopa (MCQ), Penicillin, cephalosporins, Quinidine

COLD AIHA

Classical cold (or) Cold Agglutinin disease

PCH (paroxysmal cold Haemolysin disease) (or) cold Haemolysin disease

→ Cold agglutinin disease



IgM (complement fixation)

IgG (also comple fix)

temp
- In vitro = 4°C
- In vivo = <31°C

In peripheral parts of body like Hands & feet in winter season

from peripheral to central trunk (In warm temp of trunk i-e 37°C)

↓

In trunk (In warm temp) central part

↓

IgM dissociate from RBC

↓

(Complement in halfway through) RBC comes coated c̄ · C3b C3bc

↓

(predominant) Opsonized RBC are removed prematurely by splenic macrophage (extravascular H)

↓

Some Intravascular H occurs

Causes: ① Idiopathic
② Infectious mononucleosis
③ Mycoplasma pneumonia
④ Drugs
⑤ Lymphoproliferative disorders → lymphoplasmocytic lymphoma

PCH / cold Haemolysin Disease

RBC — P(Ag) Minor blood Sp — IgG (complement fixing cold cAb)

↓

Complement — In vitro 4°C
In vivo <31°C in peripheral parts of body like hands & feets

↓

then go to trunk (warm temp)

↓

does not dissociate from RBC (warm & cold reactant)

↓

RBC coated c MAC

↓

MAC cause I.V Haemolysis

Causes of PCH : i) syphilis

ii) Mycoplasma pneumonia

iii) Following viruses like — Measles, Mumps, Rubella

~~b)~~

⟹ IgG Ab of PCH — Donath Landsteiner antibody, Biphasic antibody

P/s : ① Normocytic Normochromic c reticulocytosis (↓ polychromatophils)

② spherocytes are seen

③ Microc/Micron → in case of chronic Haemolysis

④ nRBC

→ MICRO ANGIOPATHIC HAEMOLYTIC ANEMIAS ←

→ Thrombi are formed in small blood vessels

→ RBC strike against the moving → IV Haemolysis

→ P/s — Schistocytes OR Helmet cells

→ Thrombi are composed of

- platelets in ┌ TTP
                └ HUS } →

- Platlet + Coag factors → DIC ┌ Thrombolysis
                               └ Coagulopathy

→ HUS

2) Types

① Typical HUS children

. Due to verocyotoxins producers E-coli (O157 : H7)

- E coli produces shiga like toxin that causes endothelial damage

② Atypical HUS : Due to defn of Alternate complement pathway inhibitors : Eg : Factor H & CD46

↓
Inherited
Acquired (Autoantibodies)

HUS Clinical features : fever
Thrombocytopenia
kidney involvment
IV Haemolysis
Neurological signs & symptoms

⇒ Kidney is more prominent in HUC

In TTP:
- fever
- thrombocytopenia
- I.V haemolysis
- CNS & ANS → (more predominant)
- kidney involvment:

→ G6PD Def ←

- Glucose 6 phosphate dehydrogenase Def
- G6PD participate in HMP shunt pathway → ~~Reduced~~ Generates Reduce Glutathione → which inactivates free radicles → thus it protects RBC's from oxidative stress

RBC
G6PD

① lipid peroxidase damage of Memb
② Nucleus damage

- G6PD Def is X linked recessive disorder

⇒ Most of the intrinsic diseases are Hereditory
" " " Extrinsic " " Acquired

- G6PD enzyme

(1) RBC
No G6PD → No glutathione ← free radicles
↓
they attack ① Memb
↓
Lipid peroxidase of memb
↓
Intravascular Haemolysis

② Free radicle attacks Protein

↓

Hb

Hb is denatured

↓

Hb is oxidised (denatured)

↓

Hb is attached to RBC memb (Heinz body)

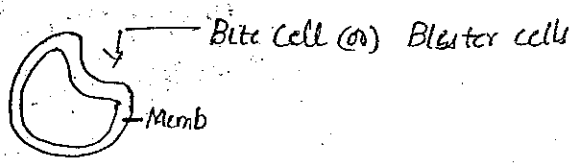
↓

When the RBC goes to spleen

↓

spleen bits off the Heinz body along with part of the memb

↓



↓

ultimately spherocytes are formed

↓

spherocytes undergo splenic Haemolysis (Some component of extravascular H)

P/s: ① M/c M/c anemia

② Reticulocytosis, nRBC

③ spherocytosis, bite cells

④ Metachromatic stains → Heinz bodies in RBC

test: Methylene Blue Reduction test

↓

Screening test

Confirmatory test : Quantification of enzyme by chromatography

⇒ two common def variants are

A⁻ type	Mediterranean type
• Mild enzyme def	• Severe enzyme def
• only old RBC go Haemolysis	• Both young & old RBC undergo Haemolysis

→ Sickle cell Anemia ←

- Abnormal Haemoglobin
- HbS – substitution of Valine for GA at 6th position of β chain

HbC – lysine for GA at 6th posn.

HbE – Valin for GA at 26th position

HbD – Glycine for GA at 121st position

Sickle cell synd's : AR disorder

Mutation in

sickle cell trait : Heterozygous trait (One gene is mutated)

↓

Asymptomatic HbS – 25–40%

Sickle cell disease: Homozygous trait

↓

Symptomatic Hb – 90–95%

~~Cf~~ Chronic haemolytic anemia ⊂ hyperbilirubinaemia and reticulocytosis

C/F : 1) Vaso occlusive crisis - Sickle RBC clog the vasculature of various organ → organ infracts

a) Bone infracts
- Small bone of hand & feets
  - ↓ severe pain called : Dactylitis
- Avascular necrosis of head of femour

b) Vertebral infracts → produce Fish mouth deformity

c) Lung infracts

d) Liver "

e) Splenic infracts → Repeated

f) Brain & retinal infracts

Rpt splenic infracts → Autosplenectomy (loss of splenic function)

↓

Repeated infections to capsulated organism

eg : Strep; pneumococcus, H. influenza

• DM caused by salmonella

3 Emergencies : i) Acute chest synd :

- Clogging of pulmn vasculature
- they have Fever, chest pain, cough

Xray - B/L pulmn infiltrates

ii) Hand and foot synd :

- Infracts in bone of hands & feets

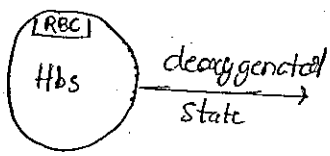
- Seen in children and (severe pain in digits)

iii) Priapism: • Penile vessels are clogged
• Painful erection

- Hemolytic crisis
- Aplastic crisis: Parvo B19 viral
- Sequestration crisis: seen in children

Sequestration of spleen blood in spleen
↓
Hypovolemia
↓
Shock

- ↑ risk of developing medullary Ca of kidney



Hbs forms polymers
↓
Reversibly sickled
↓
oxygen
↓
RBC

Irreversible sickled RBC ← Rpt episodes of sickling & unsickling ←

↓
Removed by spleen (prematurely)
Extravascular haemolysis

⇒ Factors effecting sickling

1) Deoxygenation promotes sickling
2) Acidosis (↓ pH → ↓ O_2 & ↑ CO_2) → CO_2(↑) → sickling.

3) ↑ 2,3 DPG → promotes sickling

4) Interaction c other Hb

called → HbC + HbS, HbD + HbS → ↑ed sickling episodes

→ HbSC → Highest incidance of Bone infracts and proliferative retinopathy

Irrevisible sickled RBC

↓

Memb damage

↓

Open K^+ channel

↓

efflux: K^+ & H_2O

↓

Intracellular dehydration

↓

↑MCHC

TESTS: Lab test:

① Screening test → 2% Sodium meta Bisulphate test / Dithionate test

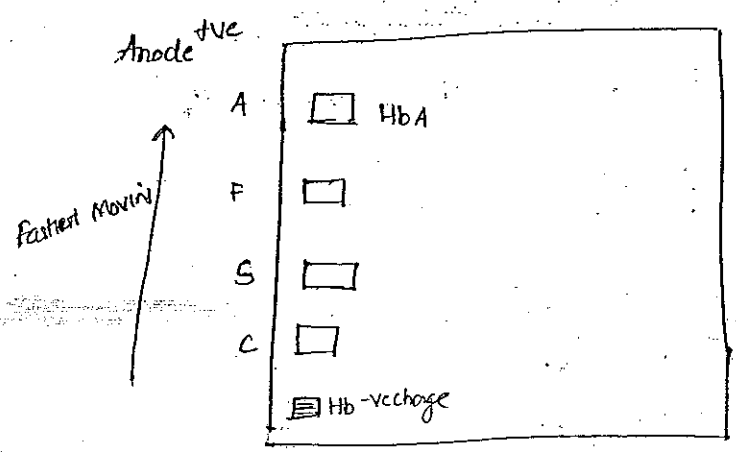
Creates deoxygenated state

this screening test cannot differentiate sickle cell trait from SC disease

② Confirmative test: → Hb electrophoresis / HbLC (Best)

Hb electrophosis: it seperates different Hb's on basis of their charge and more imp a size

- Carried out at an alkaline pH (8.6) on citrate agar (or) agarose gell (or) cellulose acetate



band in S region: due to HbS, HbD, Hb G (SDG)

band in C region: due to (CEO) HbC HbE HbO HbA_2

↓

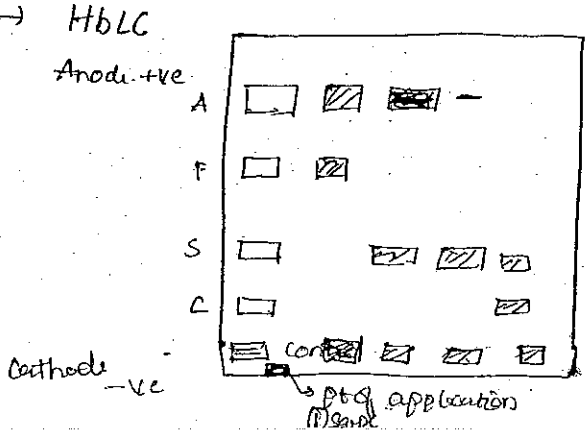
Rpt Hb electrophasis in an acidic PH (6-6.5) on citrate agar (or) agarose gell

↓

It helps to separates HbS from HbD & HbG

It also separate HbC from HbE, HbO, HbA_2

→ HbLC



Fastest moving : HbH and Hb_{Bart}

→ High performance

- Separate Hb based on their elution time

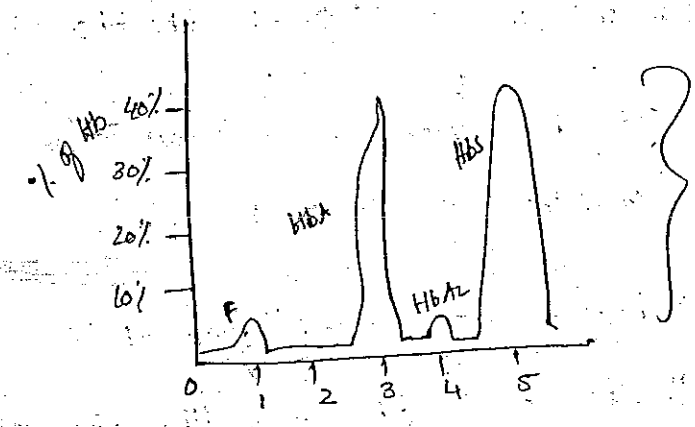
1 min

2.5 min — HbA

3-3.5 min — HbA_2

4-5 min — HbS

5 min — HbC



SC Trait

→ THALASSEMIAS ←

- AR disorder
- ∝ Thal β Thal

↓∝ chain producth ↓ β chain producth

- pathogenesis : ∝ Thal

↓ed ∝ chain producth

↓

β_2 chain form tetramer (will bind -c somebody else)

↓

β_4 (Tetramers)

Bone Marrow

- β_4 deposit in erthroid precusors in BM

(Rbc)

↓

killed by BM

→ Ineffective erythropoisis in BM

β_4

escapsed β_4 from BM

↓

Captured by spleen

↓

Removed by spleen

↓

Spleen macrophage/ Extravascular Haemolysis

→ Anemia ←

↓

Erythroid Hyperplasia in BM

↓

flat bone are hypertrophied

↓

∝ ray show crew cut

Rpt Blood transfusion

↓

Complications of Iron Overload

↓

Chipmunk facies / Mongoloid facies

* Hepatosplenomegaly (due to extravascular H)

α THALASEMIA

- Due to ↓ed α chain production
- α thalasemia can present both prenatally & postnatally

↓

beos HbF(α_2 Gamma$_2$)

↓

α Thal

⇒ β thal appears after 6 to 9 months of ter birth

- 4 genes on chromose 16 encodes for α chains

Chro 16 — chro 16 } (N) genotype

αα — αα

↓

both produce 100% α chains

1 lost → 25% α lost

- α Thal is due to {gene deficiency}

1st synd: Silent Carrier

- one gene is deleted $-\alpha/\alpha\alpha$ } 25% reduction in α chains
- Normal individuals (No anemia)

- Difficult to pick them up

2nd synd: α Thal Trait / α Thal Minor

- 2 genes are deleted (Trans deletion)
  - → $-\alpha/-\alpha$ (Transdelection) Africo Americans
  - → $--/\alpha\alpha$ (cis deletion) South East Asian
- 50% reduction in α chains
- Mild microcytic Hypochromic Anemia
  - Mild anemia

3rd synd: HbH disease

- $--/-\alpha$ 75% redn in α chain
- Moderate to severe anemia
- Life long BT

  B4 are called HbH

4th synd: Hydrops fetalis

- all 4 genes are deleted (No α chains)
- No HbF is formed during fetal life so it leads to IUD of fetus

  in fetal life ∠ Death in IU
  Severe anemia, Jaundice, ascites, HSM.

- In HB. F

α_2/γ_2

$-/\gamma_2 \rightarrow$ of form tetramers

↓

[Hb bart]

HPLC / Hb electrophoresis

Hb A → (↓)

Hb A_2 → (↓)

Hb F → (↓)

Hb H
Hb bart → Detected

β THALASSEMIA

- Due to pnt mutation in β globin gene

- m/c → in Splicing region Promoter region

- Chro 11 chromosome 11

β / β ... (N) genotypes

- β^0 → β zero (severe mutation, No β chain is encoded by this gene) zero production

β^+ → Reduction in the β chain

1st synd: β Thal trait / β Thal minor

- Mild M/c M/c anemia
- Genotype β / β^+ → Mild redn in β chain

Screening test: NESTROF TEST

- No Blood transfusions required

2nd synd: β Thal Intermedia

- Moderate M/c H/c anemia
- May require BT in special circumstances like preg
- Genotype → β / β^+ → marked redn in β chain
  → β^+ / β^+ →

3rd synd → β Thal major / Cooley's Anemia

- Severe redn in β Chain
- Severe M/c H/c anemia
- Life long BT

β^+ / β^T, β^0 / β^+, β^0 / β^0

Null type (rare)

B Thal Minor: D/D for Iron def anemia

P/S ↓

- M/c H/c anemia ⓒ Mild anisocytosis
- Reticulocytosis
- n RBC
- Presence of Target cells
- RDW <16% [12-14%]
- Rectic count is (↑ed)

↓

- M/c H/c anemia
- Pencil cells: ⬭ ↓ eliptical cells
- Pessary cells / leptocytes → Little bit Hb rim at periphery
- Rectic count is ↓ed

ID Anemia → Iron

Aplastic anemia

Megaloblastic anemia → FA & B12

Food for Hb & RBC ↓ Young RBC's will not come ↓ Rectic is (↓ed) ↓ & treatment Rectic (↑ed)

- RDW : >16%

→ Hb electrophoresis / HPLC

- B Thal Minor
- HbA = ↓
- HbA2 = ↑ <3.5% → B Thal trait 3.5-8%
- HbF = may (ⓒ) may not ↑ (ⓒ) slightly ↑

β Thal Intermedia / β Thal Major

- HbA = ↑↑
- HbA_2 = (N)(∞) slightly ↑ed
- HbF = ↑↑

→ β Thal ~~Major~~ Minor

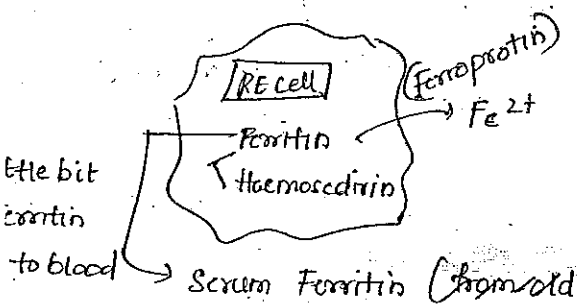
	β Thal Minor	Iron Def Anemia
1) PIs	Reticulocytosis Target cell nRBC	1) PIs ↓ Reetic count Pencil cells Pencil cells
2) RDW 12-14%	< 16%	2) > 16%
3) RBC count	> 5 million/cumm	3) RBC Count < 5 million/cumm
4) RDW index $\frac{MCV}{RBC} \times RDW$	< 220	4) > 220
5) Mentzer index $\frac{MCV}{RBC}$	< 13	5) > 13
6) Serum Iron Studies	(↑ed)	6) (↓ed)
S. Ferritin	(↑ed)	(↓ed)

Fe^{3+} in blood

Liver → stored in hepatocytes in form of Ferritin

Mostly to BM → to Erythroblasts → RBC produced → 120 days → die → Iron is released → stored in RE cells of spleen, liver, skeletal muscle, BM as Ferritin and Haemosiderin

Skin, gut, endometrium → Iron is lost by shedding of cells



Serum Ferritin (from old RE cells to blood)

↓

Excellent reflection of storage Ferritin

Normal Value 50 - 200 µg/L

Ferroportin : Transports Iron from cells to blood

1) Duod epithelial cell to Blood

2) RE cell to blood

→ Stages of Iron Def

1) Prelatent stage: storage iron is reduced

to asses the stores: we can measure

① S. ferritin (N) 50-200 ug/L

② BM Aspiration ⊼ Prusian blue

(↓ Prusian blue stainable iron)

2) Latent stage: Circulating iron is reduced

S. Iron (N) 50-150 ug/dL

TIBC → 300-360 ug/dL

⇒ In Iron def ↓ anaemia (↑ed)

% Sat → (N) 30-50%

⇒ In IDA (↓ed)

3) Clinically evident stage: 1st ↓MCV (1st to appear)

pt present ⊼ IDA: M/C HMC anemia

↓ MCH

↓ MCHC

↑ RDW

Serum Iron studies:

S. Iron ↓ed

TIBC ↑ed

% : ↓ed

S. ferritin ↓ → (<12 ug/L is highly specific for iron def anemia)

- Free Erythrocyte p'roto prophyrin

FEP / RBC proto porphyrine

(N) 30-50 µg/dL

↑↑ < Iron def Anemia
Lead poisoning ↑↑↑

Haem has many biosynthesis which can be inhibited by lead poisoning especially in last step.

Lead Inhibit → Iron → into Prophyrin Rings

↓

empty prophyrin rings

Response to Rx

- Symptomatic improvement within 24 hrs

↑ Reticulocyte Hb ← 3-4 days ↑

↑ Reticulocyte count — 5-7 days ↑

↑ RBC count — Transient

↑ Hb — Start Teal in after 3-5 wks of Rx

(N) Value reached by 2 months

But Rx is given upto 6 months to replenish the iron stores.

ANEMIA OF CHRONIC DISORDERS

Seen in pts ~~c~~ long standing collagen dis. in malignancy.

P/S — MC/HC
NC/HC

MIC | HC

Causes:

① Chronic ~~Microbial~~ infection
- a) UTI
- b) Lung Abscess
- c) SABE
- d) TB
- e) HIV

MIC | HC
- Iron def (M/common)
- Thal
- ADCD
- Sederoblastic

② Chronic AID — SLE, Rheumatoid ~~Arthritis~~, IBD

③ Neoplasms — ca lung, heart, prostate; Hodgkin's lymphoma

S Iron studies

S. Iron ↓
TIBC ↓
% Sat ↓
S. Ferritin ↑

Pathogenesis :

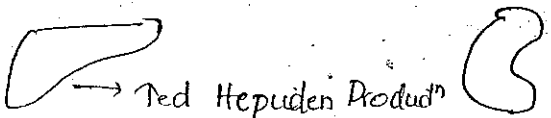
Chronic diseases / Malignancy

↓

Inflammatory mediator

↓

IL-1 / TNF



→ ↑ed Hepcidin Produ^{n} ↓ EPO

↓ed Transferrin Product^{n}, ↓

Hypoproliferative anemias

Hepcidin : Protein produced by LVer

↓

causes (↓) iron absorption

↓

Hepcidin degrades Ferroprotein

i) in duodenum no transport into blood

a) in RE cell no transport outside

↓

S. Iron ↓ ed

TIBC of transferrin (TIBC ↓ ed)

Sat % ↓ ed

S. ferritin ↓ ↑ed

→ SEDIROBLASTIC ANEMIA ←

P/s : M/c H/c anemic, dimorphic anemia { M/c H/c / N/c N/c

- Ineffective iron utilization by erythroblasts for haeme synthesis due to enzyme deficiency

Causes:
1. Drugs : Anti TB drugs
2. Alcohol consumption
3. Cu deficiency

} Reversible

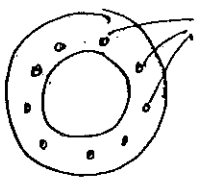
4. MDS
5. Genetic: Def of enzyme ALA synthetase
   ↳ X Linked dominant disorder

Serum Iron studies:

1. S. Iron is ↑ed
2. TIBC is Normal
3. % sat is ↑ed
4. S. Ferritin ↑ed

} Iron overload in the body

Bone Marrow: shows Ringed sideroblasts



Iron granules like ring around nucleus (seen in mitochondria)

→ APLASTIC ANEMIA ←

- Stem cells ~~dies~~ dies
- peripheral blood shows "pancytopenia"
- Causes: 1. Idiopathic
  2. Drugs : a) cytotoxic drugs like cyclophosphamide

b) anticonvulsants : Hydantoin
→ Carbamazipine.

c) NSAID's – Ibuprofen, phenyl

d) Antibiotics – Chloromphenicol
Sulphonamides

e) Chloroquine

③ Radiation

④ Viral infections – HIV, HCV, Parvo B19
CMV, EBV

Hereditary aplastic anemia

P/s : Pancytopenia ∵
Rectriculocytopenia

BM biopsy : Hypocellular ∵
↑ BM fat.

~~BM fa~~

CRITERIA : 1) BM cellularity <25% of normal
2) ANC → <500 cells / cumm.
Absolute Neutrophil count
< 200 → severe aplastic anemia
3) PC → <20,000/cumm
4) Corrected retic count <1%

→ MACROCYTIC ANAEMIA ←

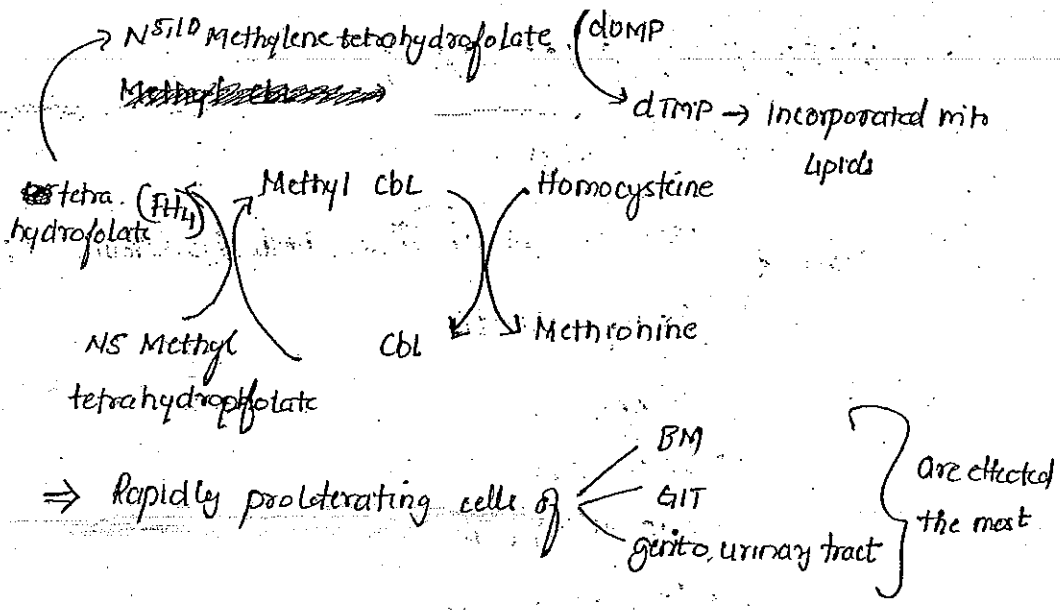
MCV >100fl

Causes
- Megaloblastic anaemia - both B12 & folic acid Def
- Non megaloblastic
  - Alcohol
  - Liver disease
  - Hypothyroidism
  - Post splenectomy
  - Haemolytic anaemia

* VIT B12 (cobalamine)

- Daily requirment 2-3 µg / Day
- Site of absorption → Terminal ileum
  ↓
  Intrinsic factor (parietal cells of stomach)
- 2 forms of B12
  - Methyl cobalamin → DNA syn
  - Adenosyl CbL → Needed for syn of neural lipids

Methyl, melonyl CoA —(Adenosyl CoA)→ Succinyl CoA
↓
Incorporated into neural lipids



⇒ Rapidly proliferating cells of { BM, GIT, Genito urinary tract } are effected the most

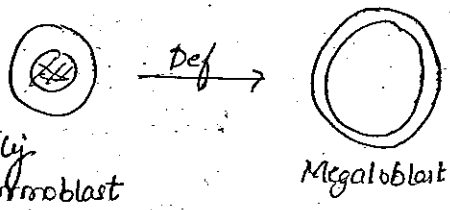
→ Folic Acid

- Site of absorption: Jejunum
- Daily requirment: 50 - 200 µg/day
- Functions: 1) DNA syn
  2) 1 carbon transfer

Histadine —FH4→ Glutamate

- Bone marrow: BM is Hypercellular & erythroid Hyperplasia & presence of Megaloblasts

Erythroid series



Megaloblasts: they have fine sieve like chromatin

⇒ Sevie like chromatin → Immature chromatin

Nuclear - Cytoplasmic Asynconi

↓ ↓

Normal Maturation takes place ∴ (N) Hb

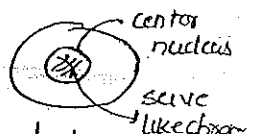
Nuclear maturation does not occur due to def of Vit B_{12} & Folic acid, the chromatin lack behind

MCQ Late normoblast

↓

eccentric

MCQ Last megaloblast →



↓

Change is best appreciated in Last normoblast.

Granulocytic series: Nuclear maturation defect

↓

giant metamyclocytes & Giant stabes

Megakaryocytic series: Also show nuclear abnormalities

Bone marrow shows ineffective Haematopoiesis

P/s : • Pancytopenia

• RBC's are macrocytic (MCV ≥ 110 fl)

• Macrovalocytes: characteristics of megaloblastic anemia

• Leuc "

• WBC Series: Leukopenia

" Hypersegmented neutrophills "

(N) neutrophil

→ blue colour Nucle

pink granules in cytoplasm

eosinophils

→ brick red nucleus

basophil  → No nucleus is seen which is covered and granules look in blue

⇒ >5% neutrophils with 5 lobes, even single neutrophil with 6 lobes indicate

⇒ Hypersegmented neutrophils persists 14 days after therapy start of therapy

⇒

Other Lab tests:

① S. LDL levels: (N) 300 – 1000 ng/L

↓

(↓ed)

② (↓) S. folate levels: 6 – 20 ug/L

③ (↓) Red cell folate levels: 160 – 640 ug/L

↳ Not influenced by immediate folate intake

↓

(so better test)

④ ↑ S. homocysteine levels

⑤ ↑ Serum & urinary methyl analonyl CoA level

⑥ FIGLU excreation ~~from~~ for FA deficiency

- FIGLU ↑ed
- It is a intermediate product forming during conversion of histidine ~~to~~ glutamate requiring FH_4

⟹ Schilling test: Measures Vit B_{12} absorption

~~Labell~~ ~~Vit B_{12}~~

Oral labelled Vit B_{12} to pt is given

↓

1 µg ^{57}Co

followed by overnight fast

↓

Next give flushing dose of ~~non~~ labelled Vit B_{12} given IM

↓

urine collected after 24 hrs

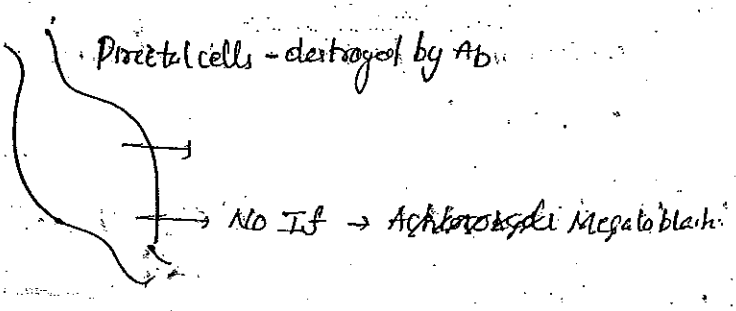
>10% of oral labelled Vit B_{12} is excreted	<5% of oral labelled Vit B_{12} is excreted
↓	↓
Absorption (N)	Absorption defect

⟹ If absorption defect is intrinsic factor then

Vit B_{12} + intrinsic factor = defect is corrected

→ PERNICIOUS ANEMIA ←

In this the pt's have



→ TUMOURS OF HAEMATOPOETIC CELLS

1. Lymphoid tumour
2. Myeloid tumour
3. Histiocytic tumours

→ LYMPHOID NEOPLASMS

1) Precursor B cell Tumour
2) Precursor T/NK cell Tumour
3) Peripheral B cell Tumour
4) Peripheral T/NK cell Tumour

} NHL — Non Hodgkins Lymphomas

5) Hodgkins Lymphomas

→ HODGKIN'S LYMPHOMA

- Cell of origin : Germinal center (B)
  post Germinal center B Lymphocyte

, Paraneoplastic synds

1) Cerebellar Degeneration
2) Nephrotic synd
3) Hypercalcemia
4) AI Hemolytic -Anemia, Granulocytopenia, AI thrombocytopenia

Clinical Features C/F :

1) Involves single group of Lymph Nodes and spread to adjacent node in a continuous fashion

   M/c ↙

2) Extranodal involvement is rare
3) Tonsils & Waldeyers ring - not involved
4) B symptoms — Fever Pel-Ebstein fever
   - Night sweats
   - wt loss

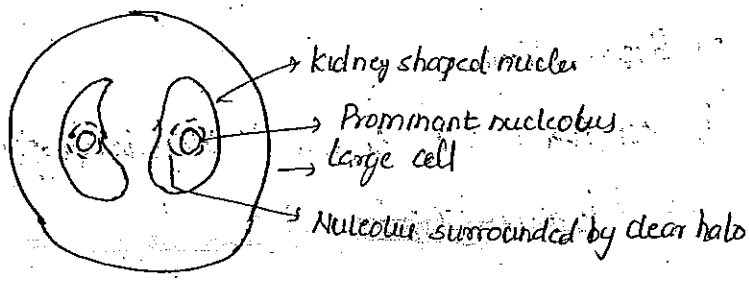
Pel-Ebstein fever: fever lasts for days to week followed by afebrile interval then reoccurance of fever.

Hodgkin's lymphoma — clinical subtypes
- Nodular Lymphocyte Pred HL

Classical subtypes

i) Classical Reed Sternberg cells (RS cells)

Or their mononuclear variants



Nuclei are called "Mirror image" Nuclei

RS cells have "Owl eye" apperance

a) Markers
- CD15
- CD30
- PAX5
- BOB1
- Oct 2

+ve

CD45RO : Marker for memory T cells

⇒ RS cells are found in a background of reactive cells (non neoplastic cells)

- Lymphocyte
- Plasma cell
- Eosinophil
- Neutrophils

(a) Nodular sclerosis: mlc subtype in the world

- LN separated by fibrous tissues.
- Nodules contain:
  - Lacunar cells (mononuclear variant of RS cells) & don't have cytoplasm
  - Classical RS cells
  - L, E, N, PC in background
- EBV → No association
- Good prognosis

(b) Lymphocyte rich HL

- Classical RE cells in a background of numerous lymphocytes
- EBV +ve
- Rare subtype
- Good prognosis

(c) Mixed cellularity

- Mlc subtype in India
- Mlc " " HIV pts
- EBV +ve
- Intermediate prognosis
- Classical RS cells & their mononuclear variants in a

in a background of L,E,PC,N

d) Lymphocyte depleted

- Worst prognosis
- EBV +ve
- M/c Numerous pleomorphic RS cells in a background of very few lymphocytes

Nodular Lymphocyte pred HL:

- Best prognosis HL
- No EBV association
- Microscope: pop corn (or) called L&H cells
  - Lymphocytic & Histiocytic cells
  - Background of Numerous Lymphocytes
  - No E & N in the background
- Markers:
  - LCA, CD45, CD20 } +ve
  - CD15, CD30, PAX5, BOB-1, Oct 2 } -ve for these markers

Prognostic factors :

Poor prognostic factors

1) Age : > 45 years
2) Stage IV disease
3) Hb < 10.5 g/dL
4) TLC > 15,000 cells/cumm
5) DLC Lymphocytes < 8%

Absolute lymphocytic count < 600 cells/cumm (1)

6) Hypoalbuminemia

LANGERHAN CELL HISTIOCYTOSIS / HISTIOCYTOSIS X

* tumour of langerhan cells
* Immature dendritic cells
  ↓
  Interdendritic cells
* these are Antigen presenting cells
* Markers for these cells : CD 1a
  S-100
  Langerin (CD207)

- LCH is of 3 types
  1) Letterer Siwe disease
     - Acute disseminated disease
     - Seen in children < 3 yrs of age
     - Poor prognosis

C/F :
- Lytic bone lesion : especially in skull bone
- Pancytopenia due to BM involvement
- Sebhorrhoic dermatitis due to Skin involvement
- HSM, LNpathy

Microscopy M/c :
- Numerous langerhan cells
- "coffee bean nuclei"
- Numerous eosinophil

(2) Eosinophilic granuloma : children, Adults

- Lytic bone lesion
  - In Biopsy (Bx) — langerhan cells, Eosinophils
- Good prognosis

(3) Hand Schuller Christian disease

Triad of
- Lytic bone lesion (in skull bone
- exophthalmus
- Diabetes insipidus

→ Pictures

Caseous necrosis : In lung
- due to TB → granuloma

Fat necrosis : Chalky white areas (due to calcification)

Fibrinoid necroses :

① Quincken cells ② Amyloidosis — cardiac amyloid, kidney "

③ Leiomyoma

5) Adenocarcinoma = form glands

6) Squamous cell Carcinoma

7) Rhabdomyosarcoma

8) Metastasis in the liver: umbilication

a) falciparum, P. Vivax

b) Onion (hyaline enterolob PAS stain)

c) Myocardial infraction

Plasma cell Tumours → CD38, CD138, Syndecan

1-7 → CD19, CD20, Surface Ig } +ve

1) CLL/SLL
2) Hairy cell / Leukemia → Hair like projections
3) Marginal zone lymphoma
4) Mantel zone lymphoma

} Small lymphoid cells

1,2,4 are not easily differentiated

	CD5	CD23
CLL/SLL	+ve	+ve
Marginal zone	+ve	-ve
Mantel zone	-ve	-ve

⇒ All tumour that arise from germinal center are marked by Germinal center markers

Markers are: CD10, BCL6 } ← Burkitts, Follicular, DLBCL

BCL6 → Germinal center; Post Germinal center

1) CLL / SLL

Chronic lymphocytic leukaemia

Small cell lymphocytic lymphoma

CLL: ~~see in~~

Small mature lymphocyte cells in the blood

In CLL ↑ in number >5000

Lots of lymphocytes in P/S

↓

Causes: Viral infection (or) by tumour

↓ ↑

all cell are polyclonal origin

In tumours the cell will monoclonal cells

Criteria for CLL/SLL:

1) Absolute monoclonal lymphocytes count >5000 cells

2) BM ≥ 30% lymphocytes

↓

in viral no ↑ in BM lymphocytes

3) Monoclonal lymphocytes have CLL phenotype ✓ CD19, CD20, Sufaab, CD5, CD23 } flc

4) Lymphocytosis should be there atleast 3 months.

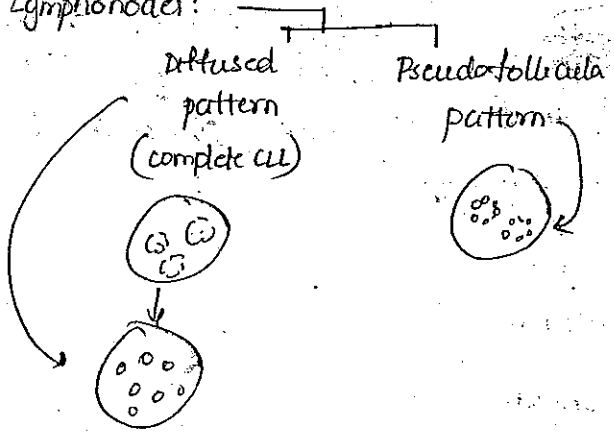
P/S → ↑↑ TLC : 20,000 – 2 Lac/cu

- Numberaces small lymphoid cells
- Smudge cells / Parachute cells
  - (CLL cells ~~are~~ cytoplasm a very fragile)
- Prolymphocyte — large cell → <11%
  - Nucleus & Nucleoli

	Prolymphocytes
CLL	<11%
CLL/PLL overlap	11-55%
PLL	>55% (poor prognosis)

Prolymphocytic leukaemia

Lymphonodes:



Cytogenetic abnormalities: Chromosome 11 q deletion
12 q trisomy
13 q deletion good prognosis
17 P deletion

Clinical features: ① Old age
② 7 decade
③ Male > Female
④ Spleenomegaly
⑤ Rpt infections (lymphocyte → plasmacells → Ab → immune)
⑥ 10% pts → warm AIHA
⑦ AI Thrombocytopenia + CLL → Evans synd

from CLL to AI Thrombocytopenia

8) CLL a low grade lymphoma

↓ can go ← (RICHTER TRANSFORMATION)

High grade lymphoma

9) CLL can have secondary malignancies: Hodgkin lymphoma
skin cell cancer
solid tumour

2 Staging of CLL ① Rai staging } In these 2 stages the
② Binet staging } pt's if developed anemia (or) thrombocytopenia

→ poor prognosis

→ Poor prognostic factor

1) Anemia Hb < 11gm/dl

2) Thrombocytopenia < 11ac/ul

3) Expression of CAP 10

4) 11q del, 17 p deletion

5) ↑ S. β_2 microglobulin levels

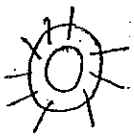
6) Rapid lymphocytic doubling time

Hairy cell Lykaemia

- Trauma to memory B cells
- C/F: 1) Age 6th decade
2) Male > Female (5:1)
3) Pt infections esp: mycobacterial infection
4) Spleenomagaly: Rep. pulp of spleen is involved
- Cytochemistry, ~~cyto~~ TRAP +ve

cyto →

- P/S pancytopenia & presence of hairy cells



small ~~cell~~ lymphoid cells

Round / kidney shaped nucleus

Hair like structures projection of cytoplasm

But visualised by PHASE CONSTRAST MICROSCOPE

- BM Aspiration: Dry Tap
- BM biopsy: Atic

Hairy cells are immersed in fine reticulin fibrin → Fried egg appearance.

- ~~Cell~~ Markers

CD19, CD20, Surface Ig } +ve

CD11c, CD25, CD103

(Annexin A1 +ve) But marker

- DD → splenic marginal zone lymphoma → Annexin A1 +ve

→ Marginal Zone Lymphoma ←

- Arise from marginal zone B cells
- ~~Nodal~~ 3 types
  - Nodal MZL
  - extraNodal MZL / Maltoma MALToma (Mucosa as lymphoid)
  - Splenic MZL
    - DD of hairy cell leukaemia
    - Assc HCV infection

M/c is extranodal M2L / MALToma

- m/c site : Stomach
- Arise in 2 settings :

1) Chronic infections (m/c)

H. pylori → gastric MALToma

Borelia → Cutaneous "

Chalmydea → orbital "

2) Chronic AID

Thyroid → Hashimoto's MALToma

Salivary gland → Sjogren's "

1st line of Rx is antibiotics :

↓

due to infections (m/c)

⇒ Cytogenetic abnormalities ⇒ Chemotherapy

t(11:18), t(1:14), t(14:18)

Mantle zone Lymphoma :

→ seen characteristic t(11:14)

Chromosome 11 → cyclin D1 gene

chro 14 → Ig H gene

- Involve LN & extranodal like GIT
- High grade Lymphoma

Germinal center Tumour ⇒ Markers

CD19
CD20
Surface Ig } +ve

Germinal center tumour markers { BCL6, CD10 }

1) Burkitt's arise from follicular B blasts in germinal center

t (8:14) chr 8 - CMYC gene
t (2:8)

2) 3 types

i) Endemic / African type: children & young adults

→ Jaws / facial bones
BM and meninges

→

ii) Non endemic / American type

- 15% EBV assoc
- Abd < GIT → ileocaecal region mass found
  kidney
  gonads, breast, BM, CNS

iii) Immune deficiency type

- 30% EBV assoc
- Involves only lymph nodes

BM / PB → large cells ± slightly clumped
nuclear chromatin 3-5 prominent nucleoli
cytoplasm: Deep blue ± vacuolation in it

LN / Tissue involved in GCT
↓
Seen by H&E

- Medium sized lymphoid cells
- Starry sky apperance: Due to interspersed tingible body macrophages
- Most rapidly growing human tumour ± doubling time of tumour cell ≤3 days

→ Follicular lymphoma ←

- Tumour of centrocytes: small cleaved cells

centrocyte: ↗
centroblast: large noncleaved cell

centrocyte > centroblast

- Involves LN, extraLN involvement V. Low
- Richter transformation present
- t (14:18)
  chro 14 → Ig H gene
  chro 18 → BCL2 gene

CD marker: CD 19, CD 20, surface Ig, CD 10, BCL6, BCL 2 } +ve
↓
most imp

→ DLBCL: Diffused large B cell Lymphoma

- m/c NHL in the world
- High grade lymphoma
- Well responds to chaemotherapy
- Site: LN, extranodal
  ↓
  common: m/c: GIT
  others: Testis
  bone
  thyroid
  salivary gland
- Median age: 7th decade
- origin — Germinal center / the
  Post " " " "

Markers { CD 19, CD 20, surface Ig, CD 10, BCL 6 } +ve
BCL 6 ↓ most imp

- 2 variants of DLBCL:
  1) Immunodef type: Seen in setting of severe T cell
     Immunodef — HIV (AIDS) pt
     Allogeneic BMT

- EBV (+ve)

Immunodef pt develop: DLBCL
Burkitt

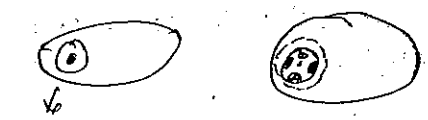
4) Body cavity lymphoma / primary effusion lymphoma
↓
pt presents with effusion like pulmn. »

- HIV (+) / Elderly
- HHV 8 / KSHV (8) +ve

→ PLASMA CELL TUMOURS ←

Multiple myeloma:

- Tumour of Plasma cells
- Monoclonal Plasma cells present → produce monoclonal Ab ↓ but cannot fight the infections



Monoclonal Ab
(M component)
- Found in serum
IgG - mlc
IgA

Bence Jone protein
↓
these are monoclonal light chains
↓
Found in serum excreted in urine

IL-6
↓
Need for monoclonal proliferation
↓
Osteoclast activating factor
↓
bone reabsorption
↓
Lytic lesions in Bone
↓
Hypercalcaemia
↓
calcification

C/F : 1) Bone pains and pathological factures

↓

In xray : Lytic lesions

common bone : Vertebral coloumn then ribs, skull, pelvis, femur, clavicle, scapula
(flat bones)

lesion starts in medullary cavity of bone

2) Rpt infected : due to lack of ⓝ polyclonal Ab

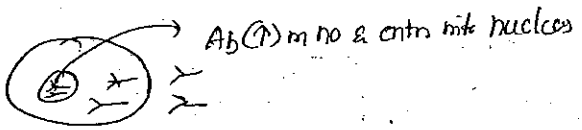
m/c cause of death in multiple mycoloma

3) Sign & symptoms of : Hypercalcaemia and Metastatic calafication.

4) Renal insufficiency : due to AL type of amylordosis
Nephrocalcinosis

Bence Jones are toxic to

BM findings : • Shows monoclonal PC >10%.
• Plasmablasts & ~~Plasm~~ Binucleate plasma cells are present
• PC → Russel bodies
Dutcher "



Flame cells : PC ⊂ fiery Red cytoplasma

Mott cells : PC ⊂ grape like vacuole in cytoplasm

P/S : → M/c N/c Anemia
→ • Rouleaux formation

⇒ Plasma cell leukaemia : ≥ 20% of plasma cells in PB

- Serum = M component
  - → β_2 monoglobulin level (↑)
  - → ↓ Serum ~~globulin~~ albumin level

A:G ratio = Reversal

Staging: 1) International myeloma staging
↓
2 parameters

S. β_2 microglobulin : Higher the level, poorer the prognosis

S. Albumin : Lower the level, poorer the prognosis

S. β_2 Microglobulin < 3.5 mg/L

S. albumin > 3.5 g/dL

2) Durie Salmon staging
(Clinico pathological) staging

- M component in serum
- Lytic bone lesions
- Hb, S. Ca levels
- S. Creatinine

WHO criteria : Symptomatic myeloma

1) BM monoclonal PC > 10%
2) M component in serum & urine

IgG → >30gm/L

IgA → >25gm/L

Bence Jones protainuria >1gm excreted in 24 hrs

>1gm/24 hrs

3) Related organ and tissue insufficiency (ROTI)

C - Hypercalcaemia
R Renal insufficiency
A Anemia
B Lytic bone lesions

- Rpt infection
- Hyperviscosity synd
- Amyloidosis

→ SMOLDERING MYELOMA/ ASSYMPTOMATIC MYELOMA

⇒ Lab criteria is met but Assymptomatic

good followup is required bcoz

10% / year progress to Multiple mycoloma

→ Non secreatory mycoloma

⇒ Cretoria 2 & not met (No M component in serume urine)

⇒ λ_2 & λ_6 → prone to cause amyloidosis

IgA IgG3 IgM → lead to Hyperviscosity synd

→ MGUS (monoclonal Gammopathy of undetermined significance)

1) Monoclonal PC <10%

2) M component IgG <30/L

3) Bence Jone protein <1gm/24 hrs

3) No hypercalcaemia

4) No renal insufficiency

5) No anemia

6) No lytic bone lesion

7) No other B cell lymphocytic disorders

⇒ Risk of progression to MM is 1% per year

→ WALDENSTRON'S MACROGLOBULINEMIA

(Lymphoplasma cytic lymphoma)

Monoclonal plasma cell

- M component → IgM Ab
- Bence Jones proteinuria
- No IL-6 → No lytic bone lesion → No hypercalcaemia

- Involves lymphnodes, LN, BM ① Monoclonal PC ② " Lymphocyte ③ Plasmacytoid lymphocytes

- Their IgM can
  - ① cold AIHA
  - ② Cryoglobulin : PPt at cold temp → Raynaud's phenomena
  - ③ Hyperviscosity syndrom : sluggish blood flow
  - ④ to vital organ eg: brain, retina → Neurological symp, Visual disturbance

→ 4) IgM Ab forms complexes ⊂ coagulation factors

coagulation factor(s) → Bleeding in pt

→ OSTEOSCLEROTIC MYELOMA ←

POEM synd

P- Polyneuropathy

O- Organomegaly

E- Endocrinopath

M- Monoclonal gammopath

S- < Skin cancer
osteosclerotic change in BM

Pempheral T-/NK cell Tumours

1) Adult Tcell leukemia/lymphoma

- As
-
-
- As ⊂ Hypercalcaemia

↳ B/M

→ Flower cells / clover leaf cells

HSM, LN pathy, Skin involvement

2) Mycosis Fungoides:

- Arises from CD4+Tcells
- PAS +ve
- Cutaneous lymphoma

Micro/c
- Epidermotropism: malignant T cell have tropism for epidermis
- Pautrier's micro abscesses: collection of Malignant T cells in epidermis

⇒ SEZARY SYND
- cutaneous involv + involv of BM & PS


"Cerebriform nuclei"

3) Anaplastic large cell lymphoma
- Also called as "Hall cell lymphoma"

↓
Hall Mark cells / Doughnut cells

DD. - Carcinoma

Markers:
- LCA +ve
- CD3 +ve
- CD30 +ve
- EMA +ve
- ALK +ve (Anaplastic lymphoma kinase protein)

↓
Good prognosis

4) Extranodal NK/T cell lymphoma
- Also called "lethal Midline granuloma" (A) Angiocentric lymphoma } usually arises from NK cell ↓ fatal / lethal

- EBV (+ve)

- Angiocentric : lymphoma cell invade blood vessels

- Site : Nasopharynx

5) Large Granular cell lymphoma

Ass c Felty synd

RA — splenomegaly — Neutropenia

others : 6) Hepatosplenic lymphoma
7) sprue ass lymphoma
~~8) Angioblastic~~
8) Angioimmunoblastic lymphoma

→ MYELOID NEOPLASMS ←

1) Acute myeloid leukaemia
2) Myelodysplastic syndrome (MDS)
3) Chronic myeloproliferative disorder
4) Myeloproliferative / Myelodysplastic disorder

→ Atypical CML
- Chronic myelomonocytic leukaemia (CMML)
- Juvenile myelomonocytic leukaemia (JMML)

CMPDs

1) CML

2) Polycythemia Rubra Vera

3) essential thrombocythemia

4) Idiopathic myelofibrosis

5). Chronic Eosinophilic leukaemia

6) " Neutrophilic "

7) Systemic mastocytosis

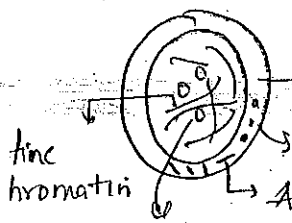
Acute Myeloid Leukaemia:

Acute Myelogenous leukaemia

Dx: ≥ 20% myeloid blasts in BM & PS

Myeloid blasts → 4 types

a) Myeloblast:



large cell & large N:C ratio

→ Moderate amount of cytoplasm

granules ↓ Contain granules

fine chromatin

→ Auer Rods: Composed of dysplastic lysosomes

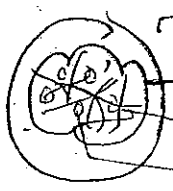
2-3 nucleoli

Cytochemistry: MPO +ve V imp

Sudan black B +ve

CD marker: CD13, CD33, CD117

b) Monoblast:



→ Large cell & high N:C ratio

→ Nucleus may show folding / cleaving

→ Very fine chromatin

→ 3-5 nucleoli

Cytochemistry: NSE (non specific esterase) +ve

Markers: CD 11c, CD 14, CD 64, Lysosome } +ve ⇒ atleast 2 out of 5 must be +ve

c) Erythroblasts — PAS +ve, glycophorin A

d) Megakaryoblast
- MPO ±
- CD 41, CD 42, CD 61

FAB classification: 8 subtypes (M0 - M7)

AML M7 → • Acute Megakaryocytic leukaemia
• ≥ 20% blasts of megakaryocytic lineage
• Acute
M/C AML in down's synd

AML M6 → called Acute erythroleukaemia

Erythroid/Myeloid	Pure erythroid leukaemia
• ≥ 20% myeloblasts + ≥ 50% erythroblasts	• > 80% erythroblasts

~~• Marker~~

AML M5 → Acute Monocytic leukaemia
• ≥ 20% Monoblasts ± promonocytes

- PB Monocyte count @ >1000 cells/cumm
- ~~Lysosome~~ * ↑ serum & urine Lysozyme Levels
- HSM, LN pathy, tissue deposits
  ↙ also called
  chloroma / Granulocytic Sarcoma
- Gum Hypertrophy

AML M4 : also called Acute Myelomonocytic leukemia

- Both myeloblasts & Monoblasts
  ↙
- Serum & urinary Lysozyme level (↑)
- HSM, LN pathy, tissue deposits, Gum Hypertrophy
- 2nd M/c AML
- commonly
  inversion of chromosome (16) → good prognosis + eosinophilia

AML M3 : Acute pro-myelocytic leukemia

- ≥ 20% promyelocytes ± Myeloblasts
- Characteristic cytogenetic abnormality here is
  t(15:17)
  chro 15 – RARA (retinoic Acid Receptor Alpha)
  chro 17 – PML gene
  t(15:17) → PML – RARA gene
  encodes abn Retinoic acid receptor

Rx: All trans retinoic acid

↓

they differentiate into neutrophils

↓

Short life

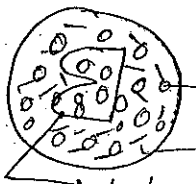
↓

they die

complication: DIC

APML

- Hypergranular APML (common)
- Microgranular APML (M3V) rare



→ Numerous granules covering all the cell

→ Numerous Auer rods in cytoplasm (FAGGOT cells)

→ kidney / Buttock shaped nucleus

→ MPO(+ve), they express CD13, 33 myeloid markers CD117

AML M0 (Minimally differentiated AML)

AML M1 (AML without maturation)

AML M2 (AML with maturation) → M/c AML

→ ≥90% myeloblasts

≤10% maturing myeloid component

→ t(8:21) good prognosis

→ Highest incidence of granulocytic sarcoma

≥20% ~~Mature~~ Myeloblasts

+

≥10% Maturing Myeloid component

WHO Classifications

1) AML ō genetic aberation:

t(8:21) good

t(inv (16) good

t(15:17) ō good prognosō

Chr 11q deletion ō poor

(N) cytogenetic & Mutatad nucleoformine (NPM)

2) AML ē MDS like feature (Poor prognosō)

3) AML therapy related; (very poor)

- Alkylating agent therapy(or) Radiation:

2-8 yrs latency period

- Topoisomerase II inhibitor 1-3 yrs

4) AML NOS (Not otherwise specified)

include FAB classification

CHRONIC MYELO PROLIFERATIVE DISORDERS

- they are tumours of matured cell of mycloid lenage
- BM shows panmyelosis And a BM Aspiration cannot deferrenciat one from the another
- Splenomegaly
- Basophilia → Histamine release → pruritis, peptic ulcers

- Evolve into acute leukemia and complication into narrow myelofibrosis

1) CML (Chronic Myeloid leukemia)
(or)
Chronic granulocytic leukemia

cytogenetics: t(9:22)

Chro 9 : abl gene

chro 22 : Bcr gene

* Bcr - abl fusion gene is formed

- Syn - 210 kD

* chro 22 - Philadelphia chromosome

C/F: 3-4th decade of life

Splenomegaly (Massive)

P/s: • TLC ↑↑

• avg TLC is 3-4 lac/al

• shift to left in myeloid series

• Max cells on P/s are myelocytes
metamyelocytes
granulocytes

→ They have Neutrophilia
eosinophilia
Basophilia
Blasts <10%

Chronic phase
↓
1st presentation of pt

LAP scores ↓↓

⇒ Chronic phase lasts for 2-3 years

In platelet count → Thrombocytosis

Accelerated Phase:

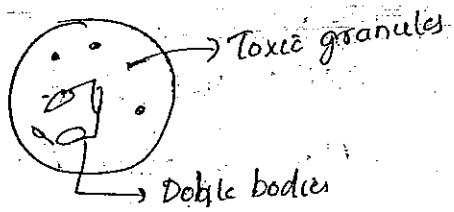
- Running towards Acute leukemia
- Blasts are 10-19%
- Basophils >20%
- TLC Not responding to Rx
- Spleen size Not " " "
- Platelet count → Thrombocytopenia ↓ (platelet → <10 lac/ul) ↓
  Thrombocytosis ↓
  Platelet count >10 lac/ul

~~Accelerated~~

Additional cytogenetic ~~chrom~~ abnormality: duplication of the chromosome / Trisomy 8

- Blasts crisis ← 2/3rd AML, 1/3rd ALL
- ≥ 20% Blasts in BM and PS
- Development of granulocytic sarcomas
- D.D ↓ leukemoid reaction

CML	Leukemoid Reaction
• Tumour	• Infections
• TLC >50,000 cells/cumm	• 50,000 cells/cumm
• Basophilia	• Not seen
• ↑ platelet count	• (N) platelet count
• Lap score ↓↓↓	• ↑↑↑
• BM → Sea blue Histiocytes Panmyelopathy	



→ POLYCYTHEMIA RUBRA VERA ←

- also called 1° polycythemia
- it is CMPD
- ** JAK 2 Mutations are seen
- PB: ↑↑ RBC → ↑↑ PCV (>65%)
  ↓
  ↑↑ Hb (>20 gl/dL)
- ↑↑ RBC → stasis of blood → Thrombo embolic episodes
- ↓↓ S. erythropoietin levels
- TLC ↑ (will be thousands)
- Platelet count ↑
- Splenomegaly is present

- evolved into → Acute leukemia
  → Myelofibrosis
  ↓
  Burntout face

Criteria

Major: a) Hb → >18.5 g/dl - males
>16.5 g/dl - female

or any other evidence of ↑ Red cell Mass

2) JAK-2 Mutation (+)

Minors: 1) BM is hypercellular c panmyelosis

2) S. EPO level are markedly low

3) Endogenous erythroid colony

Rx of Choice: Phlebotomy

Chemotherapy only to the pts not responding to Phlebotomy.

3) Essential / Thrombocythemia :-

- JAK 2 Mutations
- P/s ↑ platelet cell (Avg >10 lac/cumm)
  ↑ TLC c Basophilia
  → Aquagenic pruritics
- platelet function defect → bleeding
  → thrombo embolic episodes

→ Criteria

1) PC > 4·5 Lac/μl
2) JAK 2 mutation (+)
3) Bcr-ABL (neg)
4) Not meeting the WHO criteria for other myeloproliferative disorder
5) ↑ megakaryocytes in BM
   ↓
   Mature & larger than (n)

Idiopathic Mycelofibrosis / Chronic Mycelofibrosis

- Fibrosis of BM occuring over a period of years
- This disease passes through 2 stages
  Hyper and Hypocellular stages
- Hypercellular stage:
  a) Panmyelosis
~~b)~~ Hypocellular stage: Myelofibrosis

⇒ Spleen takes over the function of marrow so Haematopoiesis in spleen (extramedullary haemotopoiesis) → Massive splenomegaly

- P/S: a) leukoerythroblastic blood picture
  ↓
  (n RBC + shift to left)

b) Tear drop RBC

BM Aspiration : Dry Tap

BM Bx : fibrosis in BM

→ Causes of Myelofibrosis

1) Granulomatous disorder < TB / Sarcoidosis

2) Metastasis in BM

3) Idiopathic MF

4) AML M7

→ BLEEDING DISORDERS ←

Causes : ① Vascular disorder

② platelet disorder < thrombocytopenia / platelet function disorder

③ Coagulation disorder

VASCULAR DISORDER

Causes: 1) Infections:

2) Drug Reaction: Ab produce IC deposits in vessel wall → damage, → bleeding

3) Collagen deficiency in vessel

Vessel wall def of collagen { Scurvy, Ehler Danlor synd

4) Amyloidosis in vessel wall

5) Hereditary haemorrhagic telangectasia:

AD disorder

Abn dilatation of BV → bleeding

Coagulation tests:

1) Prothrombin time (PT)

test for extrinsic & common pathway

↓

7a + Tissue factor

↓ Ia

X → Xa

Prothrombin → Thrombin

Fibrinogen → Fibrin clot

Common pathway (any one in this missing prolongs PT)

Co) rabit

Trisodium citrate is the anticoagulant

(N) Value → 12-14 sec

→ Causes of prolonged PT

1) Def of cagualation factors of extrinsic (a) common pathway

[factor 7 has shortest t1/2.]

7a
V
X
Prothrombin
Fibrinogen

2) Liver disease

PT is prolonged due to factor 7

3) Vit k Def

function: activation of 2, 7, 9, 10

[Vit k needed for carboxylation of glutamic acid residues of 2, 7, 9, 10, protein c & protein S]

4) Vit k antagonists:

pt's on antrcoagulants

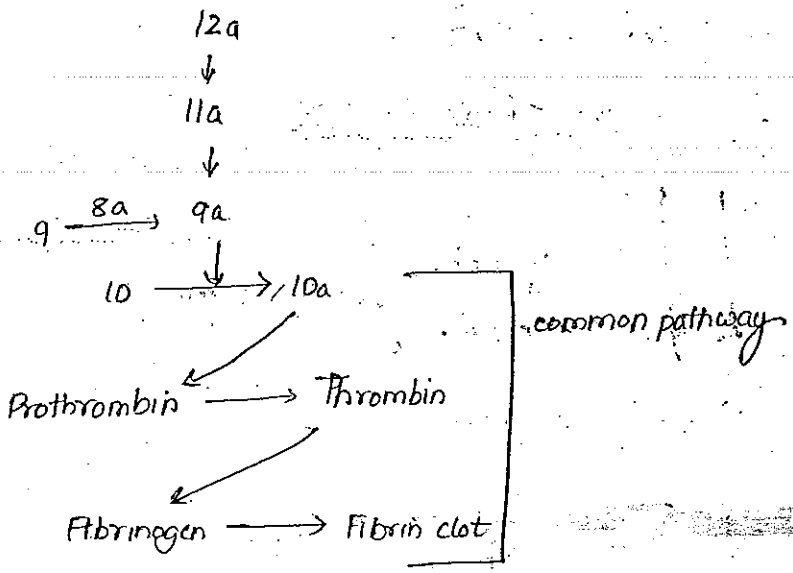
5) DIC

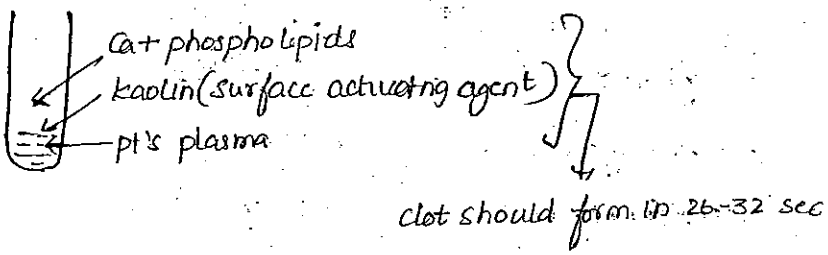
Second test: Activated partial thromboplastin time (APTT)

(a) PTTK

Kaolin

test for intrinsic and common pathway





Causes of prolonged APTT

1) Def of coag factors of intrinsic & common pathway

~~12, 11, 10, 9, 8, 5, prothrombin, fib~~

12, 11, 10, 9, 8, 5, prothrombin, fibrinogen

2) DIC

3) Liver disease (PT > APTT)

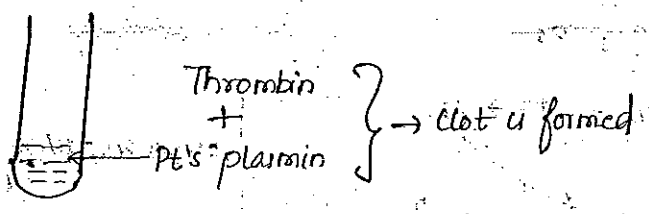
4) Haemophilia $\begin{cases} A - \text{factor VIII def} \\ B - \text{factor IX} \ " \end{cases}$

5) VW disease

6) Heparin therapy

Third test: Thrombin time (TT)

for adequate fibrinogen levels



(N) Value = 15-19 sec

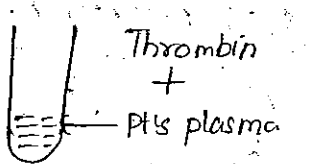
Causes for prolonged TT:

1) fibrinogen def

Inherited	Acquired
• Afibrinogenemia	• DIC
• Hypofibrinogenemia	• Liver disease
• Dysfibrinogenemia	

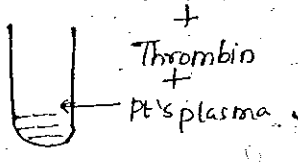
2) Heparin overdose

Reptilase time test / Ancrod time test



fibrinogen Def — Heparin overdose

→ Rpt TT



→ TT is still prolonged (Fibrinogen Def)

→ TT is corrected (Heparin overdose)

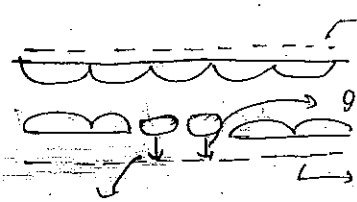
Initially caused prolonged TT

C/F :	Platelet disorder ↓	Coagulation disorder
① Petechiae (Characteristic of Platelet disorders)		Not seen
② Echymosis →	small multiple superficial	Large solitary Deep
③ Hemarthrosis →	Absent	Present
④ Dissecting hematoma →	"	characteristic
⑤ Bleeding after trauma →	Immediate	Delayed
⑥ Bleeding from superficial cut →	~~min~~ present	minimal

→ Platelet Disorders ←

Function: 1° Haemostatic Plug

Steps : ① platelet adhesion

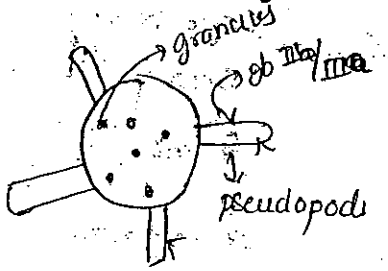


VWF factor
↓
attache to collagen
↓
Single layer is formed
(but this is not enough to bleed to stop)

Subendothelial collagen exposed to blood
↓
platelets in blood will come
↓
Glycoprotein platelets expressed
↓
Glycoprotein "gp Ib/IX"
↓
attach to subendothelial collagen
with the help of VWF

2) Platelet activation

Platelet change shape



Disc → spherical shape → pseudopods on their surface → express gp IIb/IIIa

↓

platelet release contents of their granules

granules

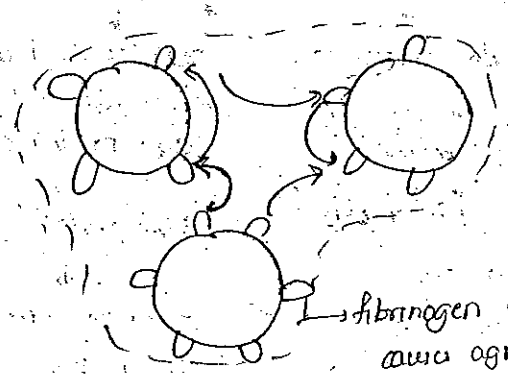
Alpha granules
- Fibrongen
- Fibrohelin
- Factor V
- VWF

(synthesis in liver)

Dense bodies
- ADP
- Ca
- serotonin

⇒ Platelet produce TXA_2 → helps in platelet aggregation

3) Platelet aggregation



∴ It is called 1° Haemostatic plug

↓

coagulation cascade constructed

↓

Fibrin is deposited around the platelets

→ PLATELET FUNCTIONS DEFECTS ←

1) -Adhesion defects

a) Bernard soulier synd

AR disorder

- Def of gp $Ib/_{IX}$ complex
- gaint platelets are seen in

gaint platelets

(1) bernard soulier synd

(2) Idiopathic (ITP)

(3) CMPD → CML, ET, PRV

(4) AML M7

test: platelet function test: Platelet fails to aggregate (agglutination in response to ristocetin)

b) Von willebrands disease

Functions of VM factors: (m/c inherited bleeding disorder in human)

- Need for platelet ~~addition~~ adhesion
- carrier for factor VIII

VWF + factor VIII → Half life 10-12 min

factor VIII → 2-4 min

Type I VWD : m/c

- >70% cases
- AD
- Mild def of VW factor

Type II VWD (Qualitative defect)

- AD

Type III VWD : - AR
- Severe def of VW factor

Lab tests :

1) Platelet function test :
We will see platelet agg fails to agglutinate in respound to Ristocetin

2) Coagulation tests :
PT (N)
APTT (↑)

Rx : Mild disease : Desmopressin
Severe " : → Cryoprecipitate
→ FFP

⇒ Defect in Aggregation ⇐

c) Glanzman's Thrombasthenia :-
- AR disorder
- Def of IIb/IIIa

PF Tests → platelet agglutination in response to ristocetin is normal

Platelets fail to aggregate in response to aggregating agents - ADP, collagen, TXA_2, Serotonin

(b) Fibrinogen Def

Inherited	Acquired

- Afibrinogeremea
- Hypofibrinogeremea
- Dysfibrinogenemia

Afibrinogen:
- AR disorder
- fibrinogen levels 200-400 mg/dl
- complete absence of fibrinogen

Hypofibrinogenemea
- AR
- ↓ fibrinogen levels (20-110 mg/dl)

Dysfibrinogenemei
- AD
- Qualitative Defect

Test:

1) PFT: Plat agglutination in response to ristocetin is normal

→

Coagulation test:

PT ↑

APTT ↑

TT ↑

3) Defects in Platelet secretion

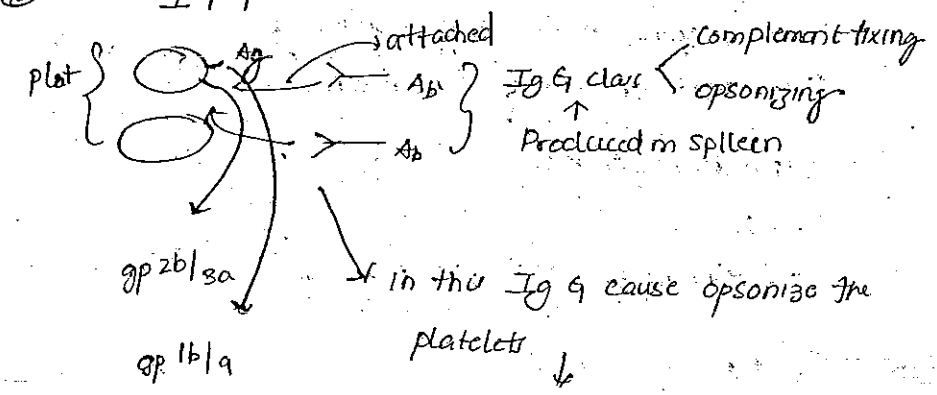
ⓐ Gray platelet synd

Def of Alpha granules

ⓑ Storage pool disease:

Def of dense bodies

ⓒ ITP



⇒ No spleenomegaly in ITP

Acute ITP — Chronic ITP

- Resolves spontaneous in 2-8 wks
- Remission spontaneously
- Platelet count fall docon, <20,000/cu
- F/b viral infection
- in children
- Sudden onset
- Age 2-10 yrs

chronic ITP : Insidious onset

- No H/o viral infection
- Adult 20-45 yrs
- Female > males
- Underlying : ALD = SLE
- Duration : Months to years
- Plat count : 30,000 to 50,000/μl

→ ***COAGULATION DEFECTS***

Hemophilia A → X linked recesive disorder

- Pred affects males
- Symptoms will vary according to factor VIII levels

<2 % factor VIII activity = severe deficiency

2-5 % factor " " = Moderate "

5-50 % " " " = Mild "

C/F

tests : PT (N)

APTT Prolonged

TT (N)

factor 8 assay ~~done~~

Rx : 1) Recombiant factor VIII

2) ↓

Factor VIII concentrate

↓

Cryo ppt

↓

FFP

Haemophilia B / Christmas disease

- Factor IX def
- XR disorder
- clinically identical to Haemophilia A

test :

→ Factor X def ←

Inherited	Acquired
• AR disorder	• DIC • liver disease

- can present c active bleeding
- Umbilical cord bleeding

test : PT ↑

APTT ↑

TT N

- factor X assay & confirmatory

Rx: No factor V replacement products

↓

So give, FFP

→ Factor 13 deficiency ←

Function: a) to stabilise the fibrin clot

b) needed for wound healing

c) " " trophoblast implantation

factor XIII
- Inherited (AR)
- Acquired
  - AML
  - Amyloidosis

C/F 1) Bleeding : severe

2) Umbilical cord bleeding

3) Delayed wound healing

4) Habitual abortion

test: PT (N)

APTT (N)

TT (N)

When everything comes (N) then do

Clot solubility test / Urea lysis test

↓

Clots formed in presence of Factor XIII are stable for atleast 1 hr in 5 mol/L urea solution

Confirmatory: factor XIII assay

→ DIC

Always secondary to another disorder

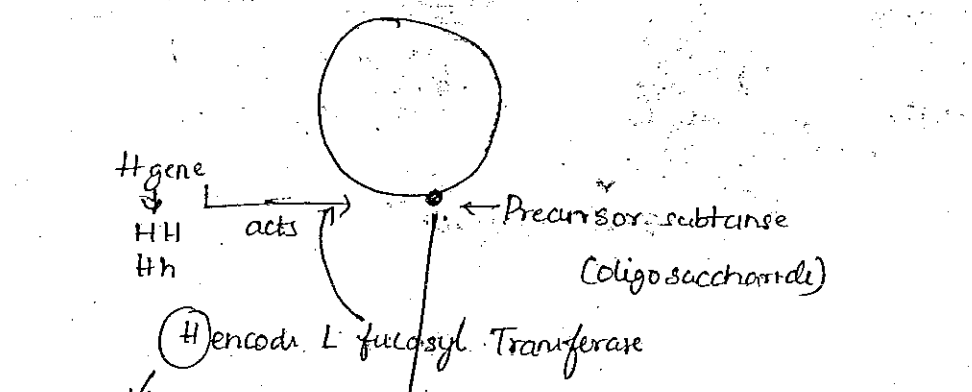
Causes: Obstructive complications
Tumour → AML M3
Mucinous

Lab tests: Plat count ↓
PT, APTT, TT } Prolonged
S. fibrinogen → ↓↓
S. FDP → ↑↑
D. Dimer → +ve More specific for DIC

→ BLOOD GROUP ←

chro 19 → gene encoding for H antigen

2 alleles



hh

No enzyme

L fucosyl Transferase → No H substance

↓

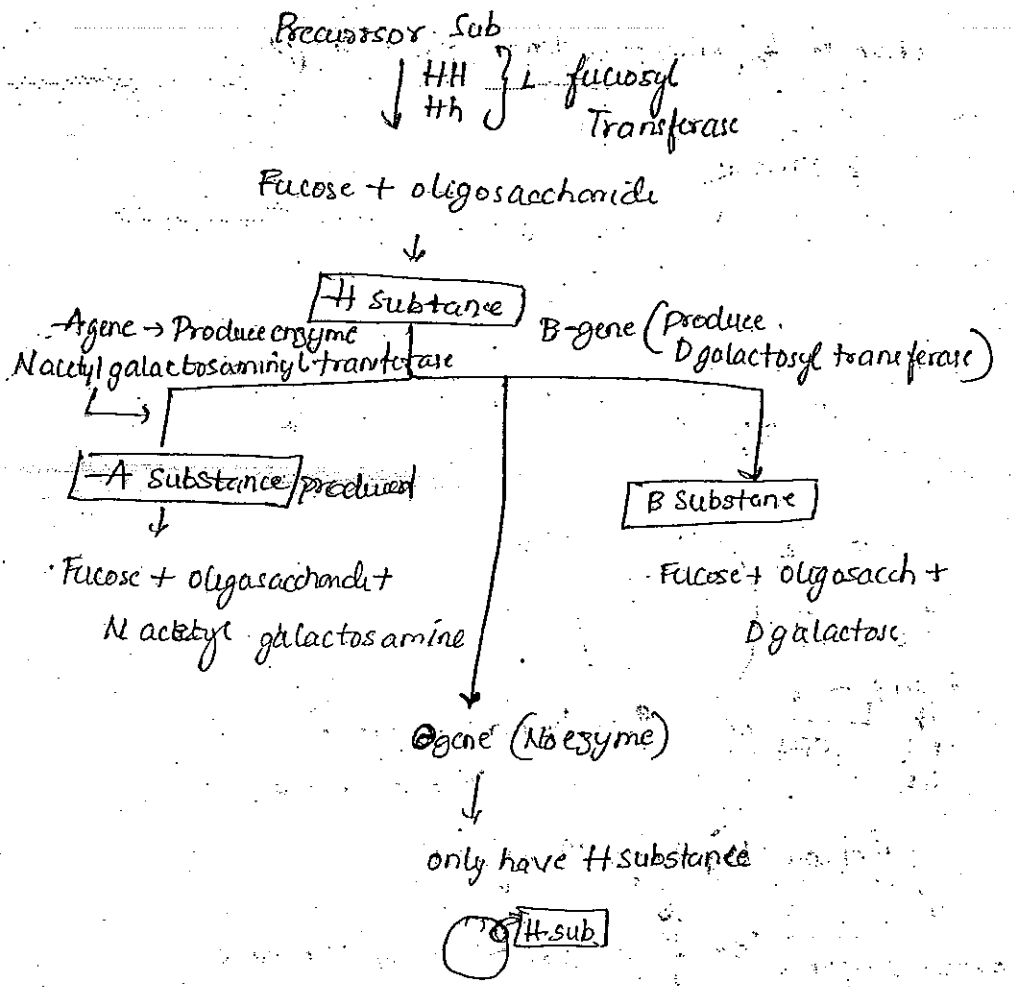
On RBC

↓

On A, B & O Antigens can be attached

↓

Bombay blood group



Blood group	Antigen	Antibody
A	A, H	Anti B
B	B, H	Anti A
AB	A, B, H	No antibodies
O	H	~~A, B~~ Anti A & B
Bombay	—	Anti A, B, & H

AB ⇒ universal receipient

O ⇒ universal Donors

⇒ A, B, H antigen expression start in fetal life but they are not fully developed at birth

⇒ complete development occurs by 1 year of age

⇒ Antibodies to blood gp antigens, they are produces 3 to 6 months after birth And they naturally occurring Ig M class.

⇒ some group O individuals, who have Ig M also have Ig G in low titers

→ Rh system ←

- genes of Rh antigen are found on chromosome 1
- 3 gene { Cc, Dd, Ee } → Rh antigen → c antigen, D Ag, E Ag
  D Ag → more immunogenic
- Rh +ve → express D antigen on RBC
  → 85% population
  → genotypes: DD, Dd
- Rh -ve → No D antigen on RBC
  → 15% population
  → genotype dd
  d = donot produce antigen
- Rh Null type: No Rh antigen on RBC
  ↓
  c, D(e) E
  also ⊂ hereditary Homatocytosis

⇒ Antibodies to Rh antigens are always

IgG class

⇒ They are found in individuals who have been exposed to Rh+ve blood

→ ABO antigen & Diseases

① gp 'O' individuals have 1.5 times ↑ed risk of "peptic ulcer"

② gp 'A' " ↑ed risk of "peptic ulcer"

③ gp O → lowest levels of VWF

H/b A, B, & AB — max levels

④ gp 'A' — A_1, A_2 (when A gene get mutated from A_2)

A_1 80%

A_2 20%

⇒ Mutation in A gene → A_2 gene formation

→ A_2 (reduced enzyme activity)

∴ antigen expression is weak

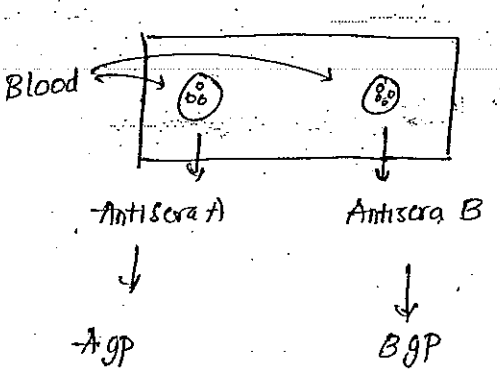
A_2 is weaker than A_1

A_2 expression is further weaker in A_2B individuals

→ Blood Grouping ←

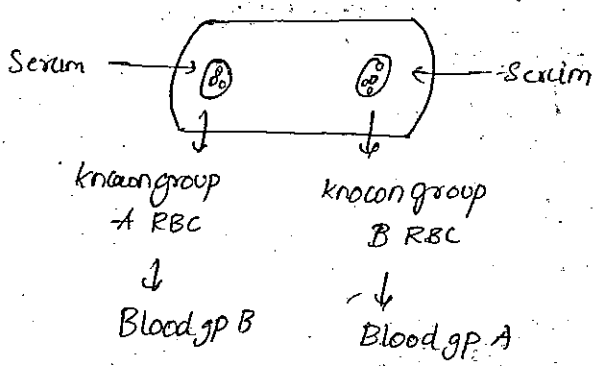
- forward grouping → Detects antigen on RBC
- Reversal grouping → Detects antibodies, then on serum
- Gel Card Technique

forward grouping



No aggl ⁻ⁿ anti A & anti B → O/Bombay blood gp

Reverse grouping: Detect antibodies in the serum



→ Agg ⁻ⁿ both grop A & gp B → O/Bombay

→ No Agglu

→ Feto maternal incompatibility ←

ABO groop — Rh incomp

↓

- more common
- Does not produce severe disease
- Mother gp O → Anti A & Anti B of IgM & IgG class
  baby gp A & B
- Mild disease: does not require Rx
  Jaundice appear 24-48 hrs after birth
- Can occur in 1st preg also

→ Rh incompactability ←

Mother → Rh -ve

Father → Rh +ve

1st pregnancy → No disease

→ Fetal blood enter the maternal circulation

↓

Mother produce IgG class of Anti Rh antibodies

↓

2nd pregnancy of subsequent preg →

IgG cross the placenta &

destroy fetal RBC (Rh+ve) →

Severe HDN

↓

Jaundice occure b/o 24 hr (N) child

from in Jaundice ↓

↓

Rx: Anti-D ☐ in 72 hrs after the delivery

↓

Anti D

↓

Neutralize Rh +ve antibodies

NACO guidelines

1) Age - 18-60 yrs
2) wt - >45 kgs
3) Hb - >12.5 g/dl
4) No H/o suggestive of HIV, HCV, HBV
5) Refferal for 1 year — who have received Hep B Immunoglobulin
   Anti Rabies Immunoglobulin
6) Deffered for 6 months if undergone major surgery
7) b/w two donation Interval → 3 months
8) Donar is deffered for 1 month if he has received live attenuated vaccine.
9) Donar should not have consumed any antibiotics (or) Ayurvedic drug in last 48 hrs
10) Donor last 24 hrs of alcohol
11) Permanent disqualification — HIV, Hep B, Hepc
    Age >60 yrs

Preservatives used for blood collection

1) ACD : Acid citrate Dextrose

citrate : Anticoagulant
chelates Ca^{2+}
Dextrose : Nutrition to RBC

Shelf life : 21 days

Draw back : low levels of 2,3 DPG
↓
low O_2 delivery

2) CPD = Citrate phosphate Dextrose
↓
Sodium dihydrogen phosphate
↓
NaH_2PO_4 — Buffer
— ↑ 2,3 DPG levels ↑ O_2 delivery

Shelf life 21 days

3) CPDA
Adenine → ↑ ATP level of RBC
↓
Shelf life is increased
↓
Shelf Life : 35 days

4) CPD - SAGM
S - Saline
A - Adenine
G - Glucose (Nutrition), ↑ ATP generation
M - Mannitol

Saline + Mannitol → prevent Haemolysis of RBC

Praervative of Choice : CPD - SAGM

shelf life : 42 days

BLOOD COMPONENTS

whole blood

Plasma components

- FFP
- cryoprecipitate
- cryosupernant

Whole blood : 450 ml of blood + 63 ml anticoag

850 ml of blood + 49 ml anticoag

Store 1 - 6 °C

shelf life ACD/CPD - 21 days

Indications : (1) exchange transfusion of whole blood (2) Acute blood loss (>25% of total vol)

(3) Hypovol shock

(4) Surgical procedure (loss > 500 - 700 ml)

~~(5)~~

Drawback of whole blood

(1) fluid overload

(2) factor 5, factor 8 } Usable factor ↓ readily lost from stored blood

(3) after storage >24 hrs WBC & platelets become
nonfunctional ⇒ Rate of transfusion 2-4ml/kg/hr
completed in 4 hours

(4) Plasma components: Unit ⇒ raise Hb by 1gm%

1) FFP (Fresh frozen plasma)

250ml * plasma is seperated from whole blood
& in 8 hrs of collection and then
plasma is frozen

temp: −18°C

Shelf life: 1 year

Thaw the FFP
↓
keep it at 2-6°C
↓
use it & in 24 hrs

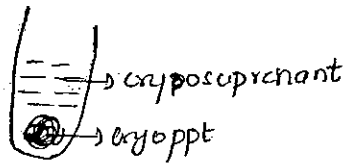
→ constituent of FFP
(1) fibrinogen (200-400mg)
(2) All clotting factors (1 IU/ml of all clotting factor)
(3) Indication: a) Multiple clotting factors Def
eg: Liver disease (Cs) in DIC
b) factor 5 def
c) Reversal of warfarin overdose

4) Contain protein C & protein S

2) Cryoprecipitate

1 unit = 10-15 ml of cryo ppt

FFP → taken → centrifuged →



Cryoppt contain

① Factor 8
② Factor 13
③ Fibrinogen
④ VWF

Indication: 1). Hemophilia A

3) Cryosoppernant: also called · cryoppt depleted FFP

Indications also depleted of largest multimers of VWF

↓

so it is indicated in TTP treatment

TTP: Def of ADAM TS 13

↓

It is an enzyme that degrades multimers of VWF

↓

No ADAM TS 13

↓

Multimers of VWF persists in blood and cause platelet aggregation

↓

Thrombosis

→ CELLULAR COMPONENTS ←

1) RBC concentrates / Packed cells

temp 1-6°C

Shelf life → APC CPD 21 days

CPDA 35 days

CPD SAGM 42 days

Contents → 65-80% RBC alone & leukocytes & platelets

20-25% plasma

Indications: (1) Anemia & Impending cardiac failure

(2) Haemolytic anemias like

Sickle cell Anemia

Thal

(3) BM infiltrative disorders → leukaemias

(4) Aplastic anemia

2) Granulocytes concentrates

obtained by apheresis

1 unit → 1×10^{10} granulocytes

- temp → room temp (20 - 24 °C)
- Infused ē in 24 hrs of collection

- Indications: ⓐ Cancer pt on ┬ Chemo
  Radiotherapy
  ⓑ Neonatal sepsis
  ⓒ Septicaemia not responding to antibiotics
  ⓓ Neutrophil function defects
  ⓔ Neutropenia

(ii) Platelet concentrate

Single donor platelets	Random donor platelets
↓	↓
obtained by apheresis	obtained from 5 donors and the collected platelets by ~~centrifugal~~ centrifuge
↓	
donor by apheresis	
↓	
Milk is given after	
↓	
~~Ca~~ Ca^{2+}	
1unit = 3×10^{11} plat suspended in 200ml plasma	1unit → 5×10^{10} platelets
1unit raises plat count by 25,000 to 75,000/ml	1unit raises the pt count by 10,000 - 12,000/cmm
1 unit SDP = 6 unit RDP	temp 20-24°C ē continous agitation (movement of pack)
single donor pl-count	donot form clump

Indications: (1) Active bleeding

(2) Prophylactic platelet transfusion

when platlet ≤ 20,000/mL

↓ Malignancies (leukemia)
Prior to major surgery

Count brought upto 50,000 - 1 lac/mL

Rate of plat

FROZEN RBC

shelf life → 10 years

Solution in which stored : Glycerol

temp → -65°C

Indications : Freezing of rare blood groups

→ BLOOD TRANSFUSION REACTIONS ←

(1) Febrile Non Hemolytic transfusion reactions
(F NHTR)

- Pt has fever & chills
- occurs in 1/2 → 1 hour of BT
- Due to

- M/c complication of BT

2) Haemolytic Transfusion Reaction

3) Urticaria 2nd common complication

Type I Hypersensitivity reaction

rarely anaphylatic shock

cau N/K

4) TRALI :- Transfusion related Acute Lung Injury

- occurs ≤ in 6 hr of transfusion
- Cause : Donor blood / plasma

↓

contain Anti HLA - Antibodies

↓

cause agglutination of WBC in pulmn vessels

↓

pt complaint of resp distress

5) Circulatory Overload

In elderly & preg women → Cardiac failure

c) Transfusion siderosis

occurs in multiple transfusion

1 unit → 200 mg iron

7) Transfusion ass GVHD

Graft vs Host

T cells in donor blood lead to GVHD

in immunocompromised receipients

Complications of Massive BT

→ > 5 liters ℂ in 24 hrs

→ > 50% vol, replacement ℂ in 4 hrs

a) Hypothermia M/c complication

b) Hypocalcemia → due to citrate toxicity

c) Metabolic acidosis

d) Metabolic alkalosis : more common alkalosis

↓

excess citrate → goes to liver → ↓

metabolised to HCO_3

↓

↑ HCO_3

↓

alkalosis

9. Hyperkalemia

RBC rupture

↓

K^+ comes out

↓

Hyperkalemia

Dilutional coagulopathy.

↓

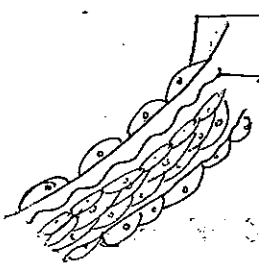
• M/c cause of death in Massive BT


JAIN STATIONERY
Deals in Medical Book & Notes
Ph.
9654691327
9811982449

JESUS SAVES

7th Aug 2017

BLOOD VESSELS



*** ARTERIOSCLEROSIS

- Hyaline
  - MCQ
  - found in benign HTN
  - ↓
  - >180, chronic
  - H&E:
  - pink, amorphous material present in vessel wall
- Hyperplastic
  - Pt's c malignant HTN
  - H&E:
  - Hyperplasia of wall
  - ↓
  - a. onion skin apperance
  - b. Fibrinoid necrosis

Different onion skin in Medicine

a. L/M of Malig. HTN

b. Electron microscopy of Tay Sachs dis

c. nerve Bx of CIDP

Chr Inflla Demelyneting Polyneuropathy

d. xray of Ewings sarcoma

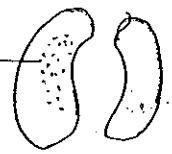
e. SLE (Spleen capsule)

f. L/M of primary Biliary cirhosis

* Malignant Nephrosclerosis

Flee bitten kidney

petechial Haemorrhage



→ ATHEROSCLEROSIS ←

Risk factors :

Non modified	Modifiable
• Male gender	• DM
• Family History	• HTN
• Age	• Sedentary life style
• Type A personality	• Obesity
	• Hyperlipidaemia
	• Cigarette smoking
	• Hyperhomocysteinemia

↓

(ass ↑ risk of MI Atherosclerosis)

Modifiable — Non modifiable

↑ risk of Atherosclerosis
- CMV
- Herpes
- chlamydia

Pathogenesis

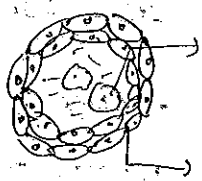
MCQ M/c vessel affected by atherosclerosis : Abd aorta

Response to Injury Hypothesis

Atherosclerosis is a result of endothelial injury

Risk factor
↓
Endothelial gets injured
↓
the smooth muscle cell migrate and from media to intima & starts proliferating there

process = Neointimal Hyperplasia
↓
leads to formation of plaque



→ Lipid laden macrophages
⇓
Foam cells

→ Fibrous cap
⇓
shoulder

Atherosclerotic plaques = 2 types

Stable plaque
↓
Most of plaque is composed of Fibrous cap

Vulnerable plaque
↓
Mostly composed by Necrotic core
↓
Dangerous

VASCULITIS

Large Vessel	Medium Vessels	Small vessels
• Gaint cell	• PAN	• Wegners
• Takayasu	• Kawasaki	• M/s polyangiitis
	• Bergers	• chrug straus synd
		• HSP

ANCA
- C ANCA – cytoplasm
- P ANCA –

P ANCA	C ANCA
• Anti MPO	• Anti PR3
• +ve in Microscopic polyangiitis (MPA) and chrug straus synd	• +ve in Wegners (G) granulomatosis
thin	• ANCA is neither very sensitive nor very specific. It can be raised in other autoimmune dis
	thick(G) diffused

GAINT CELL ARTHRITIS

* Temporal arthritis
* Age > 50 yrs
* M/c vessel infected superficial temporal artery
* M/c vasculitis in adults

Clinical features

- Severe Head ache
- Jaw pain
- Jaw Claudication (M/specific symptom)
- Fever, wt. loss
- ophthalmic artery = visual loss of Blinding

Diagnosis

- H & E = 1. Granulomatous inflammation
  2- Giant cells
  3. Fragmentation of internal elastic lamina

TAKAYASU ARTHRITIS

- Also known as "pulseless disease" = loss of pulse in upper extremities
- M/c/Vessel "Subclavian artery"
- Age <40 years (Diff btw giant cell & Takayasu = Age)

H & E: Granulomatous inflammation
Transmural inflammation

POLYARTHRITIS NODOSA [PAN]

- Medium Vessel
- Pelvic the pulmn vessels & lung
- Can affect: Liver
  GIT
  kidney
- kidney can be affected but ⊖ Glomerulonephritis ∴ Not seen.

- * 30% pts are HBsAg +ve
- Type 3 Hypersensitivity reaction

- H & E : 1. Fibrinoid necrosis
  2. All stages of inflam : Acute lesion
     Healing lesion
     Healed lesion
     can be seen in a single Bx simultaneously

→ KAWASAKI DISEASE ←

- Age < 5 years
- also known as Mucocutaneous lymphnode synd
- Usually seen in Japanese children
- M/c/Vessel affected coronary artery
- M/c/c of death Cardiac complications like MI etc
- Clinically : Mucocutaneous lesions
  conjunctivitis
  oral ulcers (or) inflam
  Red Lips
  Strawberry tongue
  Skin rash
  Cardiac complications

CRASH & Burn :
conjunctivitis (non purulent)
Rash
Adenopathy (cervical & commonly unilateral)
Strawberry tongue
Hands (Palms & soles) & Burn (Fever lasting for 5 day & more)

H/p:

1. Transmural inflam
2. Anti endothelial Ab +ve (can be +ve)

BURGER'S DISEASE (Thromoangitis obleterans)

- Seen in middle aged male smoker
- Clinically: 1. Intermittent claudication
  2. Rest pain
  3. gangrene
- H/p: 1. granulomatous inflam
  2. Microabscess in vessel wall

→ KLEGNER'S ←

- Granulomatosis & Polyangitis
- 95% cases are C-ANCA +ve
- triad:

lesions in the upper resp tract	lesion in the Lower resp tract	kidney lesions
• Sinusitis, polyps	• Bl. pneumonitis • Granuloma in lung	• focal proliferative glomerulo nephritis • rapidly progressive glomerulo nephritis

→ MICROSCOPIC POLYANGITIS

- Similar to PAN except:
  a) small vessels
  b) lung can be involved
  c) glomerulonephritis can be seen
  d) P ANCA +ve

CHURG STRAUSS SYND

- PANCA +Ve
- Bronchial Asthma
- esinophilia

m/specific Vasculitis in children = kawasaki

M/c vasculitis in children = HSP

→ List of Granulomatous Vasculitis ←

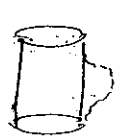
1. Gaint cell
2. Takayasu
3. wegner's granulomatosis
4. Chraag strauss synd
5. Burger's synd

→ ANURYSMS ←

- Dilatation of vessel due to weakening

- M/c/c of aneurysm formation = Atherosclerosis

True	False/ Pseudo
• Involves all layers of wall	• Not a acutual bluge • Due to a extravascular Haemotoma communicating b intravascular space



Q

* Syphilitic Aneurysm

- Seen in tertiary syphiles, Gumma
- Usually affects the ascending aorta
- Tree bark Apperance

→ TUMORS ←

- Tumours

Benign	Borderline	Malignant
Haemangioma	kaposi's sarcoma	Angiosarcoma
Lymphangioma	Mes	

HAEMANGIOMA

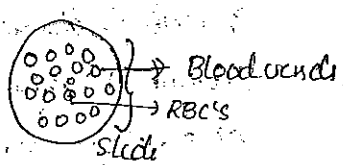
Capillary Haemangioma

Usually in infants & children

Usually self regressing

effects the skin

H&E: proliferation of large no of small blood vessels



→ CAVERNUS HAEMAGEOMA ←

- Adults
- Deeper organ like liver
- Notself regressing Q
- HGE: proliferath of large ~~blood~~ vessel dilated vascular spaces

→ KAPOSIS SARCOMA ←

Causative factor: HHV-8 Q

HGE: spindle spaced cells & slit like vascular spaces

→ ANGIOSARCOMA ←

Risk factor: angiosarcoma of liver = Q Polyvinyl chloride (PVC)

→ Immuno Histo Chemistry Markers

VWF
factor VIII
VEGF
CD 31
} for blood vessels

β myosin - Hypertrophic cardiomyopath
Spectrin → Hereditary spherocytosis
Fibrillin → Marfan's synd
CFTR → cystic fibrosis
Dystrophic → Duchin muscle

BLISTERING DISEASES

Ls or Bullous

- Subcornial → Pemphigus foliaceous
- Suprabasal → P. Vulgaris = Row of tombstone
- Subepidermal → Bullous pemphigoid

TUMOURS OF THE SKIN

- Squamous Cell Carcinoma [SCC]
  ↓
  H&E: 1. any where in the Body shows: keratin pearls
  2. Desmosomes: Intercellular bridges
  Seen when cells are seperated bcoz of Cancer
  3. Marker for SCC (or) any epithelial cancer
  cytokeratin (or) CK

- Basal cell carcinoma
  Also called: Rodent ulcer
  ↓
  Like rat: Do not metastatic = Glioma
  H&E: 1. Nodules of Basaloid cell → peripheral palisading (Hallmark)
  2. the individual cell are small & scanty cytoplasm
  Hyperchromatic nuclei
  ↓
  parallely arranged cells

→ MALIGNANT MELONOMA ←

- Massen Fontanna : stain for melanin
  - ↓ black colour
  - brown color
    - ↓ Haemosclerin
    - Lipofuscin
- Markers : 1. HMB-45
  2. Melan A
  3. S-100

***→ Imp Antibodies In Medicine ←

Condition	Antibody
1. M/specific for SLE	Anti smith (SM)
	anti ds DNA
M/sensitive	Anti nuclear
2. Drug induced lupus	Anti Histone
3. Neonatal lupus	anti SS-A (RO)
4. Sjogren synd	Anti RO (SS-A)
	La (SS-B)
5. Limited scleroderma	Anti centromere
6. Diffuse "	Anti topoisomerase I (SCL-70)
7. Inflam myopathies	Anti JO 1 (RNA hystadyl transferase)
8. Caeliac disease	antigliadin
	anti tissue transglutaminase (TTG)

9. Ulcerative cholitis ⟶ P-ANCA
10. Chrons ducase ⟶ Anti saccharomyces cerevisae Ab
11. kawasaki dis ⟶ Anti endothelial
12. Hashimotos thyroiditis ⟶ Anti Thyroglobin, Anti microsomal

⟶ HEART / CVS ⟵

Valvular Heart Disease

RHD:

- Type 2 HR
- occurs after 2-3 wks streptococcal sore throat
- age 5-15 yrs
- mlc valve affected - Mitral
  Llc " " = Relmn
- acute RF = MR
  Chronic RHD = MS
- Joner criteria

Morphology of Heart:

1. Aschoff Bodies / Aschoff Nodules (Most pathognomic in RHD)
   Consists of lymphocytes, plasma cells, fibronoid necrosis + macrophages & slender, wavy ~~bone~~ Ribbon like nucleus (W)

2. Caterpillar / Anitschow cells

Max seen in myocardium (Ⓝ seen in all layers)

3. Grossly Bread & Butter pericarditis

4. Mccallum plaques / sub endocardial Jets

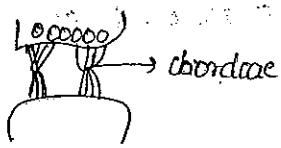
↓

Bacs of regurgitation

5. Chronic RHD ← Fish mouth

Button hole stenosis

6. Small, warty, sterile, Non destructive, along the lines of closure valve leaflets



INFECTIVE ENDOCARDITIS

Acute	Subacute
• previously Ⓝ Heart valve	• occurs in previously damaged
• staph aureus (highly virulent)	• Streptococci (low virulent)

M/c IE in intravenous drug abusers = Staph aureus

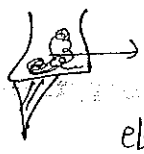
- Duke's Criteria used
- IOC : Blood culture

- Clinically : Fever
  Spleenomegaly
  Roth's spots (Retinal haemorrhages)
  Osler's nodes (SC nodules in pulp of digits)
  Janeway lesions (Splinter haemorrhages in palm & sole)

- large, friable, infective, destructive veg alone the line of closure of valve leaflets

→ LIBMANN SACHS ENDOCARDITIS ← ~~LUPUS~~

- Cardiac manifestation in SLE
- Small - medium, non destructive, veg along the both side of valve leaflets



→ more on the undersurface.
elsewhere in the endocardium

→ NON BACTERIAL THROMBOTIC ENDOCARDITIS ← (NBTE)

- Veg in pts c debilitating dis like metastatic cancer

→ MYOCARDIAL INFRATION ←

Transmural	Subendocardial
• Involved all 3 layers	• only subendocardial zone ↓ least perfusion
• ST segment elevation Infract	• Non ST segment elevation infract

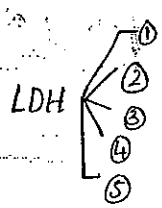
- M/c/ vessel affected in MI: LAD > RCA > LCx
- Clinically: Dyspnea
  Chestpain radiating to (L) shoulder
  diaphresis (sweating)
- Biochemical Markers for MI

1. Myoglobin raise in 1 hr
   - Non specific ↓ peaks in 12 hrs
   - Earliest marker Falls in 24 hrs

2. CPMB
   - Indicative of Reinfraction
   - Falls in 2-3 days

3. Troponine I & T
   - Most specific Marker = Trop I
     Falls in 7-10 days

4. LDH (Lactate dehydrogenase)



(N) people LDH2 > LDH1

After MI

LDH1 > LDH2

LDH flip (or) flipped LDH ratio

5. ** AST

Stain for Heart

paint the cut surface of Heart with triphenyl tetra zolium chloride (TTC)

(N) Heart	Infracted Heart
↓	↓
Retain Brick red colour	pale/ yellow
bcoz of dehydrogenase activity	loss of dehydrogenase activity

→ Morphological changes of Heart after MI

→ CARDIOMYOPATHY ←

1. Dilated CMP (DCM)

causes: a. Idiopathic *& post partum

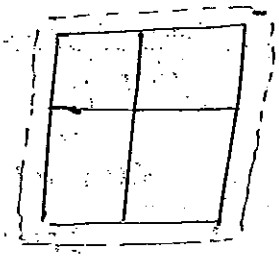
b. Genetic factors

*c. Alcohol

*d. Cardiotoxic drugs like
doxorubin
Adriamycin

*e. Myocarditis

Grossly



dilatation of all 4 chambers

HOCM

2. Hypertrophic cardiomyopathy (HOCM)

- M/c/c of ~~Sud~~ sudden cardiac death in young athletes
- Causes: 1. M/c of the cases are due a Genetic cause like

Mutation in sarcolemmal protein

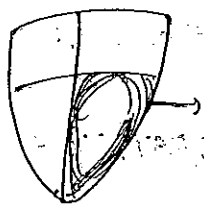
↓

Troponin

Tropomyosin

2. M/c/protein affected: β myosin Heavy chain

- Grossly Heavy



Hyperplasia of wall

↓

Banana split

- H&E: Myofiber disarray and Hypertrophy

3. Restricted Cardiomyopathy

- Causes: Idiopathy
  - Metastatic cancer
  - Haemochromatosis
  - sarcoidosis
  - Amyloidosis → (ATTR protein)
  - Loeffler's endomyocarditis

→ ENDOMYOCARDIAL BIOPSY ←

- M/c Biopsied chamber of heart: Rt Ventricle
  ↓
  easy to approach
- Indication of Biopsy
  * 1. to look rejection in cardiac transplantation
    ↓
    we do as followup
  2. To conform doxorubicin & Adriamycin toxicity.

→ TUMOURS OF HEART ←

- M/c tumour: Secondaries
- M/c 1° tumour: Myxoma
- M/c tumour in children: Rhadomyoma

Myxoma:

- Arise from (Lt) Atrium (usually)
  Lt Atrial Myxoma
  ↓
  produces Ball Valve obstraction
  H&E: stellate cells in a acid mucopolysaccharide background

Myxoma
↓
Myxoid
↓
Mucopolysaccharide

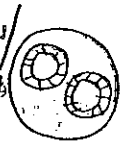
→ Rhabdomyoma :

- ↑ risk in children c/ tuberous sclerosis
- Spider cells → H&E
- Marker : Myogenin
  ↓ Desmin
  Rhabdomyoma Myo D1
  Rhabdomyosarcoma

→ ENDOCRANE PATHOLOGY ←

→ THYROID GLAND

⇒ HASHIMOTO'S THYROIDITIS

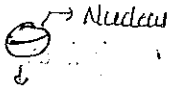
1. Lymphoid follicles / Lymphoid Aggregates 

2. Hurthle cells / oncocytic change 

   cells c/ Abundant, eosinophillic granular cytoplasm (Due to excess mitochondria)

3. H Hypothyroidism
   A Autoimmune disorder
   S Synthroid txt
   H Hurthle change
   I Initial Hashitoxicosis
   M Marginal zone NHL
   O goiter
   T TPA (Antimicrosomal) & anti Thyroglobulin Ab
   D Lymphocytic infiltration

→ TUMOURS OF THYROID ←

1. Papillary cancer of Thyroid
   - M/c thyroid Malignancy
   - Best prognosis
   - Young Females (usually)
   - Usually metastasis by lymphatics
   - Can produce cervical lymphnode enlargment
     young ♀ ⇒ cervical LN enlargment
   - Ionizing radiatn (Risk factor)
   - H&E : Testicular } Never biopsied
     Thyroid }
     ↓
     1. papillae → 
        ↓ ↑
        Lined by fibrovascular core
     2. Lined by cells optically clear nuclei
        ↓
        ⇒ orphan Annie Eye nuclei
     3. Nuclear Grooves  → Nucleus
        ↓
        Coffee bean nuclei = Granulosa cell tumour
     4. Nuclear pseudoinclusion
     5. ~~Psammoma~~ Psamomma Bodies

Follicular Variant of papillary cancer

Cells arranged in follicles

but nuclear features are those of papillary cancer

2. Follicular cancer of thyroid

- 2nd m/c thyroid cancer
- Middle - elderly age
- Usually metastatised by Haematogenous route
- Can produce Bone metastasis
- Risk factor: Long standing goiter
  Iodine deficiency
  Hypothyroidism
- FNAC, is not useful in diagnosis
  ↓
  becoz it cannot differciate follicular adenoma from follicular carcinoma.

→ Follicular adenoma

- Cells arranged in follicles

Follicular carcinoma

- Cells arranged in follicles
- capsular and/or vascular invasion
- Histopathological examination is Asst of thyroid follicular ca

3. Medullary Carcinoma of thyroid

- Arise from paratollicular (or) C cell of Thyroid
- Can be ass c "RET" on chromosome 10 mutation.
  ↓
  oncogene
- Can be ass c MEN-II Synd (Multiple endocrinal neoplasm)
- produces: Amyloid (Acd)
- Tumour marker: Calcitonin

4. Anaplastic Carcinoma of thyroid

- Hc thyroid malignancy
- Worst prognosis

MEN II: Multiple endocrine neoplasm

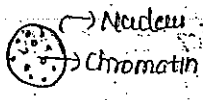
Men I	Men IIa	Men IIb
NEET	↓	↓
↓	SIPPLE	men IIa
WERMER	2P's parathyroid	+
3P's: pituitary	Pheochromocytoma	marfanoid Habitus
pancreatic	Medullary Ca of thyroid	+
parathyroid		mucosal ganglioneuroma

→ PHEOCHROMOCYTOMA ←

- HM: Cells arranged in "Zell Ballen" pattern
  ↓
  Characteristic of pheochromo

Nests

- cells ⊂ Salt & papper chromatic



- Marker for any neuroendocrine tumour
  1. NSE (Neurone specific enolase)
  2. Chromogranin
  3. Sinaptophysin
- E/M electron microscope = Dense core neurosecretary granules
- Example of neuroendocrine tumours
  1. pheochromocytoma
  2. Carcinoid tumour
  3. Small cell ca of lung
  4. Paraganglioma
  5. Carotid body tumour

→ Imp Bodies in Pathology ←

Body	Condition
1. HEIN2	G6PD def.
2. Howell Jolly	Asplenia, megaloblastic Anemia
3. pappenheimer	Sid Anemia
4. Dohle	Sepsis
5. Russel	MM

6. Dutcher — Multiple myeloma MM

7. ∝ D — Leishmaniasis

8. Counedman — Hep B

9. Gamma gandy — cong splenomegaly

10. Asteroid — Sarcoidosis

11. Schauman — "

12. Asbestos / Ferruginosa — Asbestosis

13. Verocay — schwannoma

14. Negri — Rabies

15. Lewy — Parkinson

16. Hirano — Alzheimers

17. Schiller Duval – yolk sac tumour

18. call exner – granulom cell tumour

19. Psamomma – 1. papillary Ca thyroid
2 " RCC
3. meningioma
4. Serous cystadeno carcinoma ovary
5. prolactinoma

20. Mallory Hyaline – Necro NASH
Indian childhood cirrhosis
W Wilson's
A Alcoholic liver dis
T tumour like HCC
C cirrhosis " PBC
H

→ Inherited cancer syndrome ←

	Gene	Chromosome	Tumour
1.	NF-1	17	Neurofibroma optic glioma N. gliomas
2.	NF-2	22	Schwannoma
3.	BRCA-1	17	Br Ca Ovarian Ca
4.	BRCA-2	13	Male Br Ca Prostate Ca
5.	APC	5	FAP
6.	WT 1	11	Wilm's tumour
7.	Rb	13	Retinoblastoma osteosarcoma
8.	P53	17	Li, Fraumeni synd
9.	VHL	3	Clear cell RCC cerebellar haemangioblastoma
10.	RET	10	Medullary Ca thyroid MEN II Synd
11.	PTEN	10	endometrial ca prostate ca cowden synd
12	AMLH1		HNPCC

MSH 1 MSH 2

→ Bone marrow Findings in Various Disorders ←

Disease	Bone Marrow Aspiration	Bone Marrow Bx
1. ALL	>20% lymphoblast	
2. AML	>20% myeloblast	
3. CML	Pseudogaucher cells sea blue Histiocytes	
4. CLL	↑ Lymphocysts	
5. Aplastic anemia	Dry tap	↑ Fat ↓ cellularity
6. Hairy cell leukaemia	Dry tap	Fried egg Honey comb
7. Multiple myeloma	>10% plasma cells Flame cells Mott cells Russel body Ductcher body	
8. Myelofibrosis	Dry tap	↑ Fibrosis
9. Megaloblastic anemia	Erythyroid Hyperplasia megaloblasts	
10. ITP	↑ no of mature & Immature megakaryocytes	
11. Gaucher's	Gaucher's	
12. Leishmaniasis	L D Bodies	

→ RESPIRATORY ←

1. Emphysema

Centri acinar	PAN acinar	distal acinar	Irregular
M/c smoking ass emphysema	Ass c α_1 Antitrypsin deficiency		

Pathogenesis:

1. Mucus membrane gland Hypertrophy + Hyperplasia
2. Goblet cell metaplasia
3. ↑ Mucus production
4. REID'S INDEX (MCQ) (N) RI = 0.4

RI = ratio of thickness of mucus gland layer to the thickness of wall b/w epithelium and cartilage

RI = ↑ in chronic Bronchitis

BRONCHIAL ASTHMA

- Type I Hypersensitive Reaction

Cytokines Imp = IL4 IL5

Imp cells = Oeinophils
Mast cell

Imp mediator = Hurtamine
↓
Toludine Blue stain

Sputum microscopy in Asthma

3 Cs

- CURSCHMAN SPIRALS: whorles mucus pulgs
- Charcot leden crystals: Eosinophil memb protein called as galectin 10
- Credla bodies: Sloughed epithelium (Creola)

⇒ Adam. 33, 5

they are MMP's (matrix metalo protease)

ADAM TS 13 = TTP

IL 13 =

BRONCHIECTASIS

- Causes
  - Q KARTAGENER SYND
  - Obstruction
    - Tumour
    - FB
  - Infection

↓

A/E/A Immotile cilia syndrome (or) primary ciliary dyskinesia

↓

problem in dynein arm of cilia

- Situs inversus
- Situs inversus
- Bronchiectasis
- Infertility

} Triad

Normal

Probe = stops 4cm before the pleura

Bronchiectasis

Probe = Almost reaches pleura

Complication: - Amyloidosis

↓

type : AA

RESTRICTIVE LUNG DISEASE

Pneumoconiosis:

- Pathogenesis of pneumoconiosis depends on size of particles 5 microns.
- Solubility of particles
- Duration of exposure
- Other synergetic factors: smoking
- Affects upper lobes

Coal macule → Nodule → Progressive massive Fibrosis

- Caplan synd = coal workers pneumoconiosis + Rheumatoid A

Silicosis:

- Mc occupational lung dis in the world
- Caused by biterengial silica particle (SiO_2)
- X ray show Egg shell classification
- It is synergetic to TB

Abestosis:

- Usually affects Lower lobes
- More in construction worker
  shipyard "
  Plumbers

- Asbestor fiber

Serpentine	Amphibole
Flexible	Amorphow fibres
Curled Fibres	↓
	more pathogenic

- Diseases caused by asbestosis

a. pleural plaques (m/c/lesion)

b. pleural effusion (.

c Lung carcinoma (m/c malig caused)

d. malig mesothelioma (m/s specific malignancy)

- H&E of Asbestos

Abestos bodies / Ferruginous bodies

Asbestos fibres coated c iron

(Beaded, fusiform body)

Malignant Mesothelioma

- H&E Biphasic pattern

Spindle shaped cells

Epithelioid cells

- Marker: Calretinin

- Electron microscopy: Low straider microvilli Tonofilament

Byssinosis = Cotton toxicity

Bagassosis = Sugarcane toxicity

Baritosis = Barium toxicity

SARCOIDOSIS

- F >> M
- multisystem Invasion: liver, skin, lungs, lymph node salivaglands, Eye etc.
- ↑ ACE levels
- 95% Hilar lymph node enlargment
- ↑ S. Ca^{2+}
- H & E = ① Non caseating granuloma / ~~Hal~~

  Naked granuloma

  ↓

  Lymphocytic collar is absent

  ② Asteroid Bodies

  ↳ Starshaped

  ③ Schuman bodies

Heart failure cells: they are, Haemosiderin labelled macrophages seen in the lung of a pt ⊂ CHF

Stain = ~~Heart~~ failure cell = (Perls iron blue)

Lymphnode Biopsy : 3 images

Reign stanberg cell

Stary skin cell (burkitt lymphoma)

Granuloma

HISTOPLASMOSIS

- Histoplasma capsulatum
- M/c in pigeon breeders / Bird breeders
- Grossly = Tree bark apperence
- H&E = Leaseating Granulomas (dfd of TB)

PNEUMONIA

- Infection of lung parenchyma
- Lobular
  ↓
  entry lobe affected

Lobular
↓
patchy involvement

- 4 path stages
  1. congestion : Last for 1-2 days
     lung full of RBCs

2. Red Hepatisation: last 3-4 days

Lung red in colour due to RBC

Hepatisation = liver like consistancy

3. Grey Hepatisation: 5-7 days

Disintegration of RBCs

lung is grey

liver like consistancy

4. Resolution: >7 days

M/C outcome

TUMOURS OF LUNG

1. SCC of lung m/c lung cancer in Males

Smoking associated

Centrally Located

Paraneoplastic syn = Hypercalcaemia due PTH, P

can produce cavitatory lesion

H&E: keratin pearl, Desmosomes

Marker: cytokeratin (Ck)

Adeno carcinoma : • m/c/ Lung cancer in Women

• m/c/ Non-smokers

• perripherally located

• H&E = Glands lined by malig cells

• called as : Adeno Ca insitu

Tumour cell grow along bronchoalveolar Lining → Butterflies on a pence / Filigree pattern / lepidic pattern

CLARA cells

Small cell carcinoma

• M>>F

• strongest ass c smoking

• can be ass c (Loss MYC mutation)

MyC
- CMyc - Burkitt
- NMyc - neuroblastoma
- LMyc - lung (small cell Ca)

• centrally located can go peripherally

• Worst prognosis

• Highly chemosensitive

- also known as Oat cell cancer
- Produces / Max paraneoplastic synd = like cushings
  SIADH etc
- H&E: Bells & salt & pepper
- Marker: 1. Chromogrenin
  2. NSE
  3. synaptophysin
- E/M = Will show Dense core neurosecretory granules

Large cell carcinoma

Carcinoid tumour

Clinically: sweating
flushing
diarrhea

H&E: Salt & pepper Chromatin

Marker: NSE
Synaptophysin
Chromogrenin

Lung cancer at the Apex = PANCOS TOMOURS

- It compresses the cervical sympathetic chain
  ↓
  Horner's synd

punjabi = ptosis

M = Miosis

E = Enophthalmos

A = Anhydrosis

L = loss of ciliospinal reflex

MALE GENITAL SYSTEM

- m/c/ indication of Testicular Bx = Infertility
- m/c/ fixative for Histopath and L/M =

  10% Neutral Buff. Formalin
- m/c/ fixative for E/M = Glutaraldehyde
- m/c/ fixative of Testis = Bouin's fluid

  ↓

  ~~does~~ contain picric acid

  Formalin = spoils sperm

- HPV infection

  H&E/ pap smear

  ↓

  Shows: koilocytes

  ↓

  cells ± thick memb; Resin like nucleus and perinuclear halo

TESTICULAR TUMOURS

- Germ cell Tumour
  - Seminomatous
    - Includes Seminoma
      - Dysgerminoma
        - ↓
        - In Female
    - Non seminomatous
      - Include yolksac
      - Embryonal
      - Teratoma
      - choroca
- Sex cord stromal Tumours
  - ↓
  - Lidig cell tumour
  - sertoli cell tumours

Seminoma	NSGCT
1. Age : 2nd 3rd decade	1. Elderly
2. Radiosensitive	2. Radioresistant
3. Usually metastasize by lymphatics	3. Usually Haematogenous

SEMINOMA

H&E = 1. cells arranged in Nodules

- Nodules separated by fibrous septe
- septae are infiltrated by lymphocytes *
- cells have round to polygonal c thick memb and sometime they have perinuclear halo
- Marker : PLAP +ve (placental
  - HCG +ve
  - OCT 3/4 } New
  - NANOG }

YOLK SAC TUMOURS

- Also/knocon/IS (A/K/A) Endodermal Sinus tumour
- H&E: Schiller duval Bodies (Glomerulus)
- usually seen in children
- Marker: AFP (Alpha feto protein)
- Teratoma:

  Derivative of all 3 Germ layers

  Ectoderm

  Endoderm

  Mesoderm

- Grossly: Hair

  teeth

  Bone

  Cartilage etc

- H&E:

  - Mature
  - Immature
    - presence of Neural element
    - poorer prognosis

CHORIOCARCINOMA

- Metastasis by Haematogenous
- So lung involve leading to canon ball apperance
- H&E : malignant syncitiotrophoblastic cells
- Marker : HCG

LYDIG CELL TUMOUR : Reinke's crystals (+ve)

SERTOLI CELL TUMOUR : marker : Inhibin

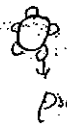
~~CALL~~ GRANULOMA CELL TUMOUR : Call Exner bodies (+ve)

****

⇒ Peripheral smear Findings In Various Diseases ⇐

P/S finding	condition
• RBC	
1. microcytic MCV < 80 fL	S Sid Anemia I Iron Def n T Thalsemia A An of chr dis
2. Macrocytic MCV > 100 fL	L Liver dis H Hypothyroidism M Megaloblastic Anemia C - cytotoxic drugs
3. Sickle cell anemia	SC Anemia
4. Pencil cell	Fe def anemia

5. Tear drop cell ⟶ Myelofibrosis
Dacrocyte

6. Burr cell  ⟶ CRF/ Uremia
Projection

7. Acanthocyte  ⟶ A Betalipoproteinemia

8. Schistocyte/ Helmet/ Frag. Red cell △ ⟶ MAHA → HUS, TTP, DIC

9. Spherocyte ● ⟶ 1. HS
2. AIHA
3. Blood transfusion Reaction

10. Target cell ◎ ⟶ Thalsaemia
Megaloblastic Anemia

11. Cabot rings ⟶ Megaloblastic Anemia

12. Basophilic stippling ⟶ lead poisoning
Thalasemia

13. Rouleaux ⟶ Multiple myeloma

14. Bite cell ⟶ G6PD deficiency

15. Heinz bodies ⟶ G6PD "

16. Jolly Body ⟶ Asplenia, megaloblastic Ane

14. Pappenheimer ⟶ Sid Anemia

18. Polychromasia ⟶ Heamolytic Anemia

White Blood cells

19) Hypersegment Neutrophil ⟶ Megaloblastic Anemia

20) Dohle bodies ⟶ sepsis

21. Smudge cell/ ⟶ CLL
Basket cell/
parachute cell

22. Pseudo pelger Huet cell ⟶ MDS
bilobed Neutrophil

→ Types of Amyloid ←

condition	Type of Amyloid
1. Primary amyloid (MM)	→ AL (light chain)
2. Sec chr inflam condition (RA)	→ AA
3. Familial mediterranean fever	→ AA, Apyrin
4. Familial amyloidotic polyneuropathy	→ ATTR
5. Senile / cardiac	→ "
6. Alzeihmers	→ Aβ
7. CRF / long term dialysis	→ Aβ2M (Aβ2 Microglobulin)
8. Medullary Ca thyroid	→ ACal (Calcitonin)
9. Prion disease	→ APr

Pathology :

Prion P_C —Mutation→ Pr P_{SC}

α helix → β plated

↓

$A P_r$

HCEF spongi change

→ TUMOURS OF CNS ←

Glioma > meningioma > astrocytoma

H&E of brain Tumour

1. Cellularity
2. Degree of pleomorphism
3. Mitotic number
4. % of necrosis
5. endothelial vasc proliferation

} all these ↑

6.

Astrocytoma

WHO I Pilocytic astrocytoma

II Diff Fibrillary "

III Anaplastic "

IV Glioblastoma multiforme

(4 BM)

H&E: 1. Mild ↑ cellularity

2. No pleomorph
3. " mitosis
4. " Necrosis
5. " vascular proliferatn

3. Rosenthal fibers

4. Microcysts

② Diff Fib Astrocytoma

Middle elderly

cerebral Hemisphere

H&E : ↑ cellularity by fibrillary process

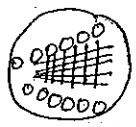
Mild pleomorphic

" necrosis ↑ mitosis

No necrosis, No proliferation

Anaplastic Astro

H&E =		
	cellularity ↑↑	++ +++
	Pleomorphism	++ +++
	Mitosis	++ +++
	Necrosis	++ Necrosis = Geographical/ Serpentain
	Vascular proliferation	++



tumour cells around necrotic area

Best prognosis

Glomeruloid bodies

(BL vessels proliferate in circular pattern)

Worst prognosis

→ OLIGODENDROGLIOMA ←

- Middle to elderly age
- Cerebral Hemisphere commonly involved

*** H&E 1. cell c central nucleus
- perinuclear Halo
∴ " FRIED EGG APPEARENCE "

2. CHIKAN WIRE Blood Vessels
↓
Anastomosing & spreadout

3. Calcification

→ EPENDYMOMA

H&E : perivascular pseudorosette
↓
Rose like / flower like

→ Blood vessels
→ tumour cells

→ MEDULLOBLASTOMA

- Exclusive child tumour
- " in post fossa / cerebellum
- H&E = Sheets of small round blue cells c scanty cytoplasm + → tumour cell, → central space

Rosettes = Homer Wright Rosette

↳ Small Round Blue cell tumour of childhood

*** List of small Round Blue cell tumours of childhood

1. Retinoblastoma
2. Medulloblastoma
3. Hepatoblastoma
4. Neuroblastoma
5. Nephroblastoma (Wilm's tumour)
6. Ewing's sarcoma
7. Primitive neuroectodermal Tumour (PNET)
8. Lymphomas
9. Rhabdomyosarcoma

Homer Wright < medullo / Neuro

Flexner Wintorstein : Retinoblastoma

Perivascular Pseudorosette : Ependymoma

→ Meningioma : Psammoma bodies

→ VVVImp SCHWANOMMA

- Ass c NF2 on chr 22
- Arises from Vestibulocochlear Nerve Interior
- H & E : Hypocellular Areas of "Antoni A pattern"

Hypocellular area = Antoni B pattern

Acellular area = Verrocay body

Tumour/cell of origin	Marker
1. Haemopoietic stem cell (HSC)	CD 34
2. B lymphocyte	CD 19, 20, 21, 22
3. Pan B lymphocyte	CD 19
4. Recc for EBV on Bcell	CD 21
5. T lymph	CD 1, 2, 3, 4, 5, 7, 8
6. Pan T "	CD 3
7. NK cell	CD 16, 56
8. R-S cell	CD 15, 30
9. Pop corn	CD 20, 45, bcl 6
10. Myeloid marker (AML)	CD 13, 33, 117
11. Mantle cell lymphoma	cyclin D1, CD 5+, CD 23
12. CLL	CD 5+, CD 23+
13. Burkett's lymphoma	bcl 6+
14. follicular "	bcl 2+
15. Hairy cell leukaemia	Annexin A1, CD 25, CD 11c, CD 103

16. LCH ⟶ CD1a, Langerin, S-100

17. Apoptotic ⟶ Annexin V

18. Malig melanoma ⟶ HMB 45, MELAN A, S100

19. " mesotheleoma ⟶ Calretinin

20. Ewing's sarcoma ⟶ CD 99 (mic-2)

21. GIST ⟶ DOG 1, CD117 (C kit) CD34

22. Medullary Ca of thyroid ⟶ calcitonin

23. Seminoma ⟶ PLAP, HCG, Oct 3/4

24. Chorio Ca ⟶ HCG

25 Yolk sac ⟶ AFP

26. Sertolicell tumour ⟶ Inhibin

27. Epithelial origin ⟶ Cytokeratin (CK)
(any carcinoma)

28. Mesenchymal origin (sarcoma) → Vimentin

29. Smooth Muscle origin ⟶ SMA (smooth muscle Actin)
(leiomyoma)

30. Skeletal mus origin (Rhabdo) → Desmin, Myogenin, MyoD

31. Glial origin ⟶ GFAP
(Glioma) (glial Fibrillary acidic protein)

32) Neuro endocrine ⟶ NSE
(Pheochroma) synaptophysin
chromogranin

33) Vascular origin ⟶ vWF, factor VIII,
(Angiosarcoma) CD31, VEGF

34) Hepatic origin (HCC) ⟶ Hepar 1, AFP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STOMACH

12 Aug 2017

H. PYLORI

- Gram -ve bacilli
- PUD (peptic ulcer dis)
- Gastric Adenoca
- Maltoma
- pathogenesis : 1. produce urease

urea ⟶ ammonia

↓

contract acidity of stomach

urea

2. It has flagellin
3. 2 Toxin : VacA & CagA
4. Antral Biopsy : H. pylori colonize there in antrum
5. H&E : Intraepithelial Neutrophils and Subepithelial plasma cells
6. H. pylora is seen floating on mucosa. It doesnot penitrate mucosa
7. Spl stain : Warthin Starry Silver Stain (for H pylori)

Gastro Intestinal Stromal tumour (GIST)

- M/c. mesenchymal tumour of stomach
- Arises from Interstitial cells of Cajal. (these are gut pacemaker cells)
- Can be assc Ckit mutations
- Markers: DOG 1 (latest marker)
  CD 117 (C kit) → 99% +ve = Most specific
  CD-34 60% (+ve)

Gastric Adenocarcinoma

- Very common in Japanese people bcoz of smoked fish
- Food Rich in preservatives → Nitrosamines
- Blood group A
- smoking
- Lauren's classification

Signet Ring cell → Intracellular Lumin → Lysin → pushes the nucleus

Intestinal	Diffused	Linitis plastica
- Polypoid lesions Not involve all layers	- Infiltrative lesion - usually involves all layers	leather bottle appearance
• H & E: ~~Glands~~ ~~lepe~~ can be assc Glands lined by malignant cells.	Loss of E-cadherin (CDH-1 Mutation) → Lead to cancer Adhesion cells H&E - Sheet of signet ring cells	

* Most Imp pregnostic factor for oesophagal adenoca
↓
Depth of Invasion of tumour cells

1. Virchow's Node : Lt supraclavicular lymph Node
2. Sutar mary Joseph Nodule : periumbilical Nodule of metastatic Adenocarcenoma
3. Krukenbergs tumour : Gastric cancer metastasis to ovaries

COELIAC DISEASE :

- also known as Gluten sensitive enteropathy
- cannot have Gluten in Diet
- cannot have B Barley
  R Rye
  O Oats
  W wheats
- can Eat : Rice
  Maize
- HLA DQ_2 ; DQ8 Association
- ↑ risk of Dermatitis Hepatiformis
  " " " T cell lymphoma
- Anti gliadin
  Anti Tissue transglutaminase
  Anti endomysial

- H&E = 1. Villous Atrophy
  2. Crypt Hyperplasia
  3. ↑ Intra epithelial lymphocytes (IEL)

- MARSH scoring = Coeliac

  Gleason score = prostate adenoma

  Bloom richardson score (BR score) = Breast Ca

→

WHIPPLE'S DISEASE

- It is caused by Trophyrema whipplei
- H & E : Lamina propria is infiltrated by macrophages & are studded by Pas +ve material (organisms)

→

CROHN'S DISEASE	ULCERATIVE COLITIS
1. A/k/A Regional enteritis	1. A/k/A Backwash Ileitis
2. M/c site → Ileum	2. M/c site = Rectum
3. Smoking is a risk factor	3. Smoking = protective
4. ~~Antibodies~~ Anti Saccharomyces Cerevisiae Ab is +ve	4. PANCA (+ve)

5. Barium :	string sign of Kantor	Lead pipe / Hose pipe apperence
	GROSSLY	
6.	Skip lesions : +ve	skip lesion -ve
7.	Cobblestone apperance of mucosa +ve	-ve
8.	Creeping fat +ve	-ve
9.	Ulcer : deep knife Leve	ulcer : superficial broad base
10.	Pseudopolyps : absent	present
	Microscopically	
11.	Granuloma : +ve	-ve
12.	Transmural	Submucosal
13.	Crypt to Crypt abscess } less common → more neutrophil	Cryptitis → Neutrophil in crypt } more common Crypt-dil
	Complication	
14.	More risk of Fistula	Less Risk
15.	More risk of sinus	"
16.	Less risk of malignancy	More Risk

→ POLYPS < Sessile = no stalk = more malignant (bcoz no stalk)
pendunculated

↓ Histological classificatn < Tubular
Villous
Tubulo villous

Polyp

Neoplastic — Adenomatous

Non neoplastic — Hyperplastic
Inflammatory
Hamatomatous

PEUTZ ZHEGHER SYND

- Multiple Hamartomatous polyps + Mucocutaneous Hyperpigmentation + ↑ risk of colon & pancreatic cancer

GARDNER SYND

Bone tumours like osteomas
+
Epidermoid & dermoid cysts

TURCOT SYND

Multiple polyp
+
Brain tumour (like medulloblastoma)

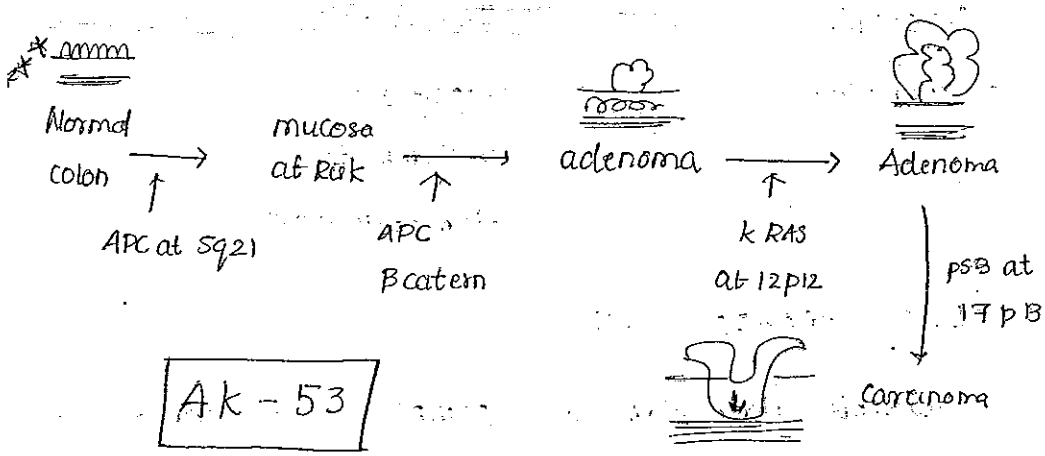
→ COLO RECTAL CANCER

Pathogenesis: Most cancers are due to

Apc gene mutation on chr 5

↓

(Familial Adenomatous polyposis) FAP ↓ colon Ca } Adenoma Carcinoma Sequence



Ak - 53

FAP:

- Cased by >100 polyps in the intestine
- Most cases progress to colorectal ca
- Mutation of hMLH1 / MSH-1 / MSH-2

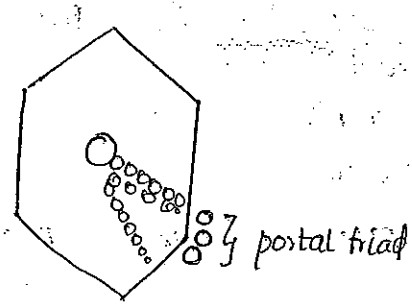
  k/as Miss match repair genes
- Defects are k/as Micro satellite Instability defects (MSI)

  ↓ leading to

  HNPCC
- H&E in colon Ca: glands lined by malignant cells

  Tumour marker: CEA, CA 19-9

→ LIVER ←



Cirrhosis: Destruction of liver architechture & formation of fibrotic nodules

Micro nodular = < 3 mm

Macro nodular = > 3 mm

Causes: Hepatitis B and C

Alcoholic liver disease

Non Alcoholic steatohepatitis (NASH)

Indian childhood cirrhosis

Heamochromatosis

Wilson's disease

α_1 anti trypsin deficiency

Various drugs and toxins

HEPATITIS

	A	B	C	D	E
1.	Feco oral	Sexual parenteral Vertical			Feco oral
2.	RNA Virus	Hepadna DNA ↓ Most Carcinogenic	RNA	RNA	RNA ↓ Max mortality in pregnancy
3.					

H&E of Hep B:

Acute:

1. Ballooning Degradation
2. Neutrophilic Infiltration
3. Ballooning Degradation
4. Councilman Bodies (Apoptotic)
5. Lymphoplasmacytic Infiltration
6. Minimal periductular infiltration

Chronic

1. Lymphoplasmacytic Infiltration
2. Ground glass Hepatocytes
3. Periductular infiltration
4. Fibrosis (Bridging Fibrosis = B/w central vein & portal triad)

→ H&E of Hepatitis C ←

Lymphoid aggregate (or) follicles

Alcoholic Liver Disease :-

- Steatosis
- Hepatitis
- Cirrhosis

• Fatty change

- Microvascular Steatosis
- Macrovesicular steatosis

Q MALLORY Hyaline bodies

↓

• composed of Intermediate Filaments like CK 8, CK 18

• these bodies are seen in New - NASH
Indian - Indian childhood cirrhosis
W - Wilson's dz
A - Alcoholic liver dz (most specific)
T - Tumour like HCC
C - Cirrhosis like PBC
H

→

(NASH) Non alcoholic steato Hepatitis

• No H/o alcoholic intake

• Seen in pts of obesity
Metabolic syn
Insulin resistance
Hyperlipidaemia

WILSON'S DISEASE:

- A/k/A: Hepatolenticular Degeneration
- ~~Ece~~ Excessive Copper Association.

Pathogenesis: Mutation of ~~ATP7B~~ gene leading to

↓ced copper excretion ↓ceruz incorporation into ceruloplasmin

Clinically

1. Eye: kayser Fleisher Ring on the descements membrane of cornea
2. Liver
3. Neuro psychiatric manifstn

Spl stain for Cu = Rhodamine stain

→

HAEMOCHROMATOSIS

Excessive Iron overload

patho: HPE gene mutatn
↓
↓ Hepcidin
↓
↑ Fe

Bx: Brownish pigment on level bx

spl stain = Prussian blue / Pearls

Clinical features: Bronze disease

↓

Bronze like pig of skin

↓

but it is due to Melanin

Affects: pancreas

Joints

genitals

Heart = Restrictive CMP

→

α1 Anti Trypsin Deficiency (α1 AT Def)

- AR
- Deficiency of α1 AT enzyme
- Def of enzyme lead to

↓

↑ neutrophil elastase activity

lung — liver cirrhosis

Pan acinar emphysema

- H&E: globules & are PAS +ve

Glycogen
Mucin
Amyloid
Fungal org
Basement Memb

} PAS +ve

REYE'S SYNDROME

- usually children
- After aspirin intake
- Viral infection
- H&E: Extensive microvesicular steatosis

→

HEPATIC ADENOMA

- OCP use
- HCC
- H&E = Pleomorphic cells
  Absence of portal triad
  Vascular invasion
- Markers = Hep par 1
  Alpha feto protein

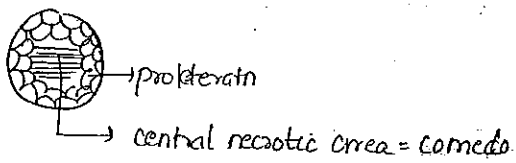
Chr venous congestion of liver = NUT MEG LIVER

→ BREAST ←

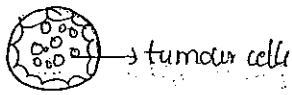
DCIS (Dultal Ca Insitu)

- Can lead to Invaerve carcinoma

1. comedo DCIS



2. Cribriform DCIS



3. Solid DCIS

4. papillary DCIS

5. Micropapillary DCIS

→ Ca Breast

- Invasive Ductal carcinoma → No special type (NST)
  ↓
  M/c breast ca

- lobular ca of breast
- Mucinous ca of breast
- Medullary ca of breast

- IDC – NST = M/c

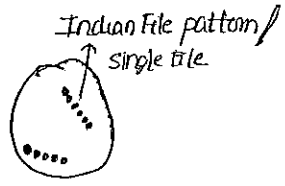
- H & E : 1. Ducts / Tubules
  2. Lined by pleomorphic cells
  3. Mitosis No

- BR score Bloom Richardson score = % tubule or duct
  % pleomorphism
  no of mitosis

- Poor prognosis

Lobular ca of Breast

- usually B/L
- usually multicentric
- H & E : small, dyscohesive cells ⊼
  scanty cytoplasm arranged
  one after another

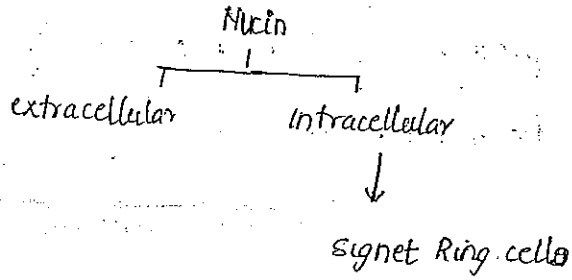


↓
bcoz loss of E cadherin

- Excellent prognosis

Mucinous Ca of breast

- H&E = tumour cells floating on pool (or) lakes of mucin



- Excellent prognosis
- Colon Mucin = Poor prognosis : Diff type of mucin

Medullary Ca of Breast

- H&E : *1. Sheets of highly pleomorphic cells
  2. Mitosis
  *3. Lymphoplasmocytic infiltration
  *4. Pushing Borders

BRACA 1 positive tumour = usually have medullary like features

- Poorer prognosis but still better than IDC-NST

Prognostic factors in Breast Ca

* 1. M/Imp prognostic factor in Ca Breast

Axillary LN status in the absence of metastasis

2. M/Imp prognostic factor in presence of metastasis

Hormonal receptor status { ER estrogen recep; PR progesteron recep; Her 2 neu

3. Stage
4. Size
5. type
6. Lympho vascular invasion

Tamoxifen ← { ER, PR } Nuclear

↓ S/E endometrial Hyperplasia

Her 2 neu = memb

↓

Trastuzumab / Herceptin

poor prognosis

** Latest Molecular classification of Breast Cancer

Gene expression profiling ← ER, PR, Her 2 neu

1. Luminal A : m/c/type
   - ER+ve, PR +ve, Her 2 neu (-ve)
   - Good prognosis
   - Well differentiated tumour

2. Luminal B

- ER +Ve PR +Ve Her 2 neu +Ve
- triple +ve breast Ca
- Well dettierentiated ē good prognosis

3. Basal like

- ER -Ve PR -Ve Her 2 neu -Ve
- triple -Ve breast Ca (Worst progno)
- poorly differenciated ē poor prognosis

4. Her 2 neu positive tumours

- ER -Ve PR -Ve Her 2 neu +ve
- poorly differentiate, poor prognosis

→ NEPHROLOGY ←

Kidney Bx = glomerulonephritis

How to Read a kidney Biopsy

1. Count the No of glomeruli (min 10)
2. Focal = <50% glomeruli out of all are involved

   Diffuse = >50%

   segmental = Portion of the glomerular affection

   Global = entire Glomerular Affected

   Polaferative = ↑ cellularity
   ↓
   By epithelial cell
   inflam cells
   mesangial cells

URINE EXAMINATION

URINE MICROSCOPY
↓ ↓ ↓
cells casts crystals

- All casts are composed of tamm Horspall protein produced in ascending limb of loop of Henle

Casts		condition
1. Hyaline cast	⇒	physiological cast Fever stree
2. RBC cast	⇒	Glomerulonephritis
3. WBC cast	⇒	pyelonephritis
4. Broad/waxy cast	⇒	chr renal failure
5. Muddy brown granular cast	⇒	Acute tubular necrosis
6. Fatty/lipid cast	⇒	Nephrotic synd

Nephrotic syndrome

- Massive proteinuria (>3-5gm/24hrs)
- Hypoalbuminemia
- Oedema
- Hyperlipidemia
- Coagulopathies

Nephritic synd

- proteinuria
- edema
- Haematuria
- Hypertension
- Azotemia

- M/c/cause of nephrotic syn in children ↓ Minimal change dz
- M/c/c nephrotick in Adults: -FSGS
  In elderly: membranous

- M/c/c of nephritis in children PSGN
  Post strepto glomerulonephritis
- M/c/c in adults: IgA nephropathy
- M/c/c glomerulo nephritis world wide

Post streptococcal Glomerulonephritis (PSGN)

- Age 5-15 yr
- Usually (after Inf. ⊂ Group A β streptococci)
  Strain = 1, 4, & 12
- Type 3 Hypersensitivity reaction
- cola colored urine
- Light/Microscopy: enlarged Hypercellular glomeruli
  ↓
  by inflam cells
  Max endocapillary proliferation
- Electron/Microscopy: sub epithelial Humps
  ↓
  usually Immunoglobulin
  = Hump sign
- Immunofluorence = lumpy bumpy

Type II Hypersensitivity Reaction

Eg: my myasthenia gravis
blood Blood Trafuse Reaction
group Grave's dis, Good pastures
IS ITP, Immune haemolytic anemia
R RH fever
H Hyperacute graft rejection
+ positive pernicious anemia, pemphigus vulgaris

Type II Hypersn reaction

S - serum sickness, SLE

H - Hypersn pneumonitis

A - Arthus reaction

R - Reactive arthritis

P - PSGN

polyarthritis nodosa

→

RPGN (Rapidly progressive glomerulo nephritis)

- L/M = >50% Glom show = Crescents
  ↓
  formed by proliferath of parietal epithelial cells fibrin and macrophages
  ↓
  M/Imp
- More no of crescents = poorer the prognosis
- RPGN

Type I	II	III
Anti GBM	Immune complex	pauci immune
Eg: Good pasture syndrome	Eg: SLE, HSP	M/c type Eg: Wegener's granuloma

Good Pasteur's synd

- α_3 chain (@), collagen type IV
- Type II Hypersensitivity Reaction
- 1st organ affected: lung (Haemoptysis)
  ↓
  kidney (m/c/c of death)

Lupus nephritis

- kidney manifestation of SLE
- WHO grades
  - I min mesangial
  - II mesangio proliferation
  - III focal proliferative
  - IV diffused proliferative
  - V membranous
  - VI Dense-sclerosing = Worst prognosis
- M/c/ type of Lupus nephritis = type IV
  ↓
  H&E = Wire loop lesions

Alport Synd

- X linked dominant inheritance
- $\alpha 5$ chain of collagen type IV ← Antibodies

- Triad
  - Eye: lenticonus, subluxation
  - Sensorineural deafness
  - kidney: Hematuria

- E/M is Astic: thinning of ~~memb-bran~~ basement memb
  - thickening → rupture
    - Basket weave apperance

→

MINIMAL CHANGE DISEASE

- LM = (N) Glomeruli
- EM = effacement of podocyte foot processes
- malignancy of m/c ass. with ⊆ GN = membranous
  In AIP m/c GN is = membranous

→

Membranous GN

LM = capillary BM Thickening

EM = spike and dome apperance on silver stain

→

Effacement of podocyte foot process

1. Membranous
2. MPGN (membrano proliferative)
3. FSGS

4. Diabetic nephropath

5. minimal change disease

⟶

MPGN — I
II
III

• L/M = • Duplication/ splitting of BM Double contours

↓

"Tram track/Appearance"

• Sub endothelial deposits

⟶

FSGS: Focal segmental

• Can be ass c 1. sickel cell anemia
2. Reflux Nephropathy
3. Heroin abuse
4. Hypertensive nephropathy
5- HIV pt

• L/M = <50% glomeruli

• E/M = effacement

⟶

DIABETIC NEPROPATHY

• depends upon the duration of disease

• L/M = earliest finding = 1. capillary BM thickening
2. Diffused glomerular sclerosis
↳ m/c finding

3. Nodular glomerulosclerosis } Kimmelstiel Wilson (KW lesion)
   PAS +ve " } ↓ M/s specific finding

4. Fibrin caps

In poorly controlled DM

PCT have vacuoles contain glycogen = Pas +ve
(Armani Ebstein cells)

on examination of kidney

papillary Necrosis : Necrotizing papillitis

Common causes of papillary necrosis

1. DM
2. Analgesic nephropathy
3. Sickel cell anemia
4. Acute pyelonephritis
5. Urinary obstruction

CYSTIC DISORDERS

polycystic kidney disease complications

1. Liver
   Spleen } other organ
   pancreas

2. Cysts are not seen in
- rarely
  - Lung — 3rd answer
  - Brain — 2nd answer
  - Intestine — 1st answer

3. Colonic diverticulosis

4. Berry aneurysm

TUMOURS OF KIDNEY

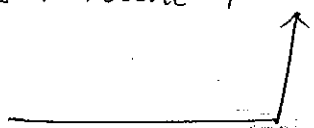
Clear cell RCC	Papillary RCC	Chromophobe RCC	Collecting duct / Belini duct Ca
M/c renal cancer and Poor prognosis can be assc with VHL gene on chromo 3 · polycythemia produced · H&E = Sheets of cells with clear cytoplasm	1. Most angio invasive 2. can be assc with dialysis assc kidney disease 3. H&E a) papillae b) Foamy macrophages c) Psammoma bodies	1. Arise from collecting duct 2. Best progn 3. H&E's abundant eosinophilic cytoplasm Hale's colloidal iron (stain)	1. L/e 2. poor prognosis

WILM'S TOMOR

- Can be assc : 1. Loarg synd
  2. Denysh drash synd
  3. Beckwoiru weidman synd

- H&E small round blue cells + Rosettc +

Epithelial
meechymal
Blastomer



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