India Connecting Continents (ICC)

Study materials for FMGE

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PATHOLOGY

Cell injury, Adaptation, Cell death

Stress → Adaptation

* Homeostasis → Stable steady state of a cell
* Adaptation → New but stable state

Cell —Stress→ Adaptation —Mild injury→ Reversible injury —Severe/Persistent→ Irreversible injury.

* Cell adaptation will be of 4 types:
  - Hypertrophy
  - Hyperplasia
  - Metaplasia
  - Atrophy

(No dysplasia, it is malignancy)

* Type of injury to cell MC is ~~Hy~~ Ischemia, Hypoxia

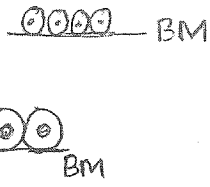
* Irreversible injury:
  - Necrosis
  - Apoptosis
  - Necroptosis
  - Pyroptosis

Hypertrophy

- Tissue which cannot divide
- ↑ size
- ↑ synthesis of structural protein
- Stimulus is ↑ work load

Hyperplasia

- Tissue which can divide
- ↑ in number
- ↑ cell proliferation
- ↑ work load along with ↑ growth signal



- DNA content of each cell ↑
- Physiological >> Pathological
- Skeletal muscle (bodybuilders) Cardiac muscle (HTN) Uterus (in pregnancy) Breast (preg, puberty & lactation)

- DNA content of each cell remains the same.
- Both physiological and pathological
- Under the effect of estrogen – Endometrial hyperplasia
- Androgen – BPH (Benign prostatic hyperplasia)
- Skin warts – HPV
- Uterus – Pregnancy
- Breast – Puberty & Pregnancy

* Breast: Lactation → Only hypertrophy
* Both ~~pathology~~ trophy & plasia

Breast (preg, pub) > Uterus (preg) → mainly hypertrophy

Tortous in hyperplasia to accomodate all ~~urine~~ content

- Metaplasia → change in phenotype because of "chronic irritation"

Types
- Epithelium
  - Squamous
  - Columnar
- Connective tissue → Myositis ossificans (muscle replaced by bone)

* Mc type of metaplasia - Squamous

Squamous metaplasia

* Any other epithelium is replaced by squamous epithelium.

* eg: Respiratory epithelium → Smoking, Chr. bronchitis, Vit A defi

  - GIT → Bile duct, Pancreatic duct } Infection or stones
  - Urinary bladder → Stone & infection like Schistosomiasis

* Resp. system → normally psuedo stratified columnar epithelium

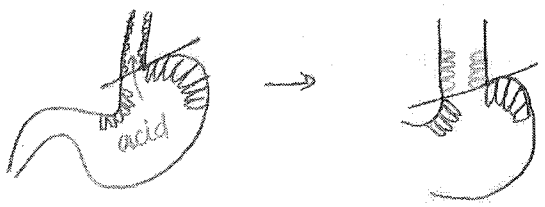
~~* In GIT called as columnar metaplasia~~

Columnar metaplasia

* Any other epithelium is replaced by columnar epithelium.

eg: Barrett's oesophagus

* Normal oeso - Squamous, stomach-columnar




Goblet cell

* Goblet cells secretes mucin (mucus)
* So when acid from stomach goes to oesophagus, oesophagus changes from squa → columnar → Barrett's oeso.
* It is an intestinal type of metaplasia (goblet cells - only in small intestine, so not gastric type. Stomach mucus by fove
* Barrett's oesphogus progress to dysplasia → to adenocarcinoma (adeno-gland)
* Goblet cells are the hallmark of Barrett's oesophagus.

Atrophy

* ↓ in size or ↓ in no: of cells.
* Types
  - Physiological
  - Pathological

* Physiological
  ↓
  Embryogenesis

Pathological
↓
- Disuse
- Denervation
- Ischemia
- Pressure
- Nutritional

* Alzheimer's disease - Cerebral atrophy
  Gyri → narrowed
  sulcus → widened
* Skeletal muscle atrophy: Spinal muscular atrophy

Reversible injury

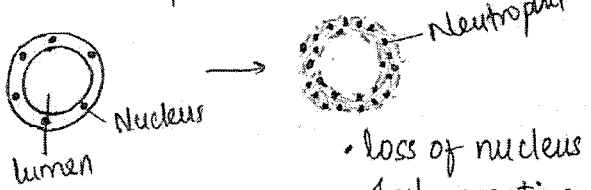
* Mild ischemia → leads to mild hypoxia → ↓ ATP (Glu $\xrightarrow{O_2 \times}$ Lactic acid & ↓ ATP pdtn) → Na^+/K^+ ATPase pump function ↓ → ↑ Na^+ inside cell → H_2O in ECF moves in to cell → Cell swelling / cloudy swelling / hydropic change → Organelle swelling : Mitochondria & ER swells → to prevent cell bursting → cytoplasmic bleb formation
* ER swelling → Ribosomal dettach → ↓ protein synthesis
* ↓ ATP & ↓ protein in cell → so cell try to break TG to free fatty acids → inside the cell we can see plenty of lobules in fat.
* Also ↑ lactic acid → ↓ pH → chromatin condensation.
* In light microscope can see → cell swelling, chromatin condensation & fatty change → indicates reversible cell injury (MCQ)

Irreversible injury

* Severe ischemia → severe hypoxia → ATP depletion → stop functioning of Na^+/K^+ ATPase → ↓ K^+ inside cell → ↓ Ca^{2+} moving out of cell (K^+ helps in it) → so ↑ Ca^{2+} inside the cell → Ca^{2+} gets deposited as large amorphous density (seen in electron microscope) → Ca^{2+} is co-factor of some enzymes → it activates some enzymes : (APE)
  - ATPase
  - Protease
  - Phospholipase
  - Endonuclease
* ATPase → ↑ ATP depletion
* Protease → plasma membrane damage
  Phospholipase ↑ ↓
  Also lysosomal damage
  ↓
  releases some enzymes which damages the tissue. Also it has DNA ase & RNA ase → damage cell nucleus → Nucleus appears blue, so here ↓ blue colour → called as ↓ basophilia
* Damage to tissue → neutrophilic infiltration
* Endonucleases causes
  - Pyknosis (condensation)
  - Karyorrhexis (fragmentation)
  - Karyolysis
* In light microscope → ↓ basophilia, ↑ pink colour, neutrophil infiltration, karyolysis (no nucleus)
* Morphological types:
  - Necrosis
  - Apoptosis
* Necrosis :
  1) Coagulative necrosis

Coagulative necrosis

* Cell outline is preserved (due to collagen)



- loss of nucleus
- Inflammation (neutrophils)

* eg: Ischemia in all solid organs except brain (no collagen)
  - Thermal injury
  - Zenkers degeneration (Typhoid)

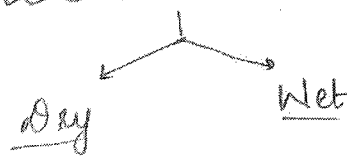
Liquifactive necrosis

* Cell outline is not preserved
* Ischemia to brain (eg)
* Other eg:
  - Coag necrosis + Bacterial infection

Caseous necrosis

* "White cheese like" deposition
* It is a type of coagulative necrosis
* eg:
  - Tuberculosis
  - Histoplasmosis

Gangrene



* Dry → ↓ blood supply → ischemia → coagulative necrosis → anaerobic decomposition → foul smell & black tissue.

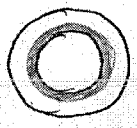
* Dry gangrene + Bacterial infection
  ↓
  Wet gangrene (Liquefactive necrosis)

Fatty necrosis

* Damage to adipocytes
* It can be ~~chronic~~ traumatic or enzymatic damage.
* Traumatic → Breast, buttock, abdomen
* Enzymatic → Acute pancreatitis
* Acute pancreatitis → Lipase release → TG → FA + Ca^{2+} (combines) → Chalky white deposits → called as saponification
  (TG - Triglycerides, FA - fatty acid)

Fibrinoid necrosis

* Fibrin like → homogenous pink colour



* eg: Malignant HTN, Vasculitis, Immune complex injury, inside Ascoff body.

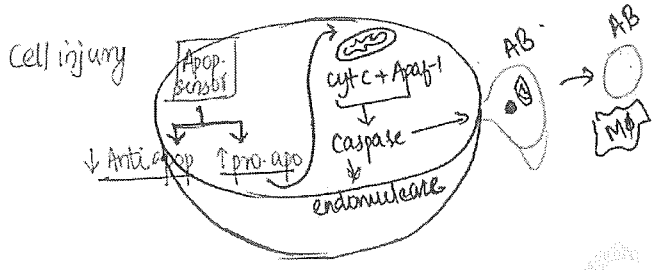
Apoptosis

* Programmed cell death (naturally occuring)

Apoptosis	Necrosis (Toxins, infection, trauma)
• Single cell	• Group of cells
• Physio > Patho	• Pathological
• shrunken cell	• Swollen cell
• Cell outline is intact.	• Cell outline is lost here.
• Condensed (blue) chromatin	• Karyolysis
• Inflammation is absent	• Inflammation always present

* Most characteristic change is chromatin condensation.
* Most imp. difference is inflammation
* Pathways
    1) Intrinsic pathway
    2) Extrinsic
* Intrinsic pathway (mitochondrial)
* Extrinsic (Death receptor pathway)

Intrinsic pathway



* Cell injury → sensed by cell - Apoptotic sensor (Bim / Bid / Bad) → it will stimulate ~~anti~~ pro apoptotic genes (BAK, BAX) → inhibits anti apoptotic genes (Bcl, Mcl) → (l in Bcl & Mcl: longevity) → BAK, BAX acts on mitochondria → releases cyt. c & Apaf-1 (Apoptotic activating factor-1) → They both activates caspase → breaks proteins → starts act on cell membrane → CM swells outside → called as apoptotic bodies → then it pinches out → apoptotic body contains any organelle it want to kill → macrophage engulf the apoptotic body → this completes the process of apoptosis.
* Caspase also activate endonucleases

Extrinsic pathway

* eg: CD8 T cell killing.
* CD8 T cell on its surface has FAS-ligand (go & attaches to FAS on Ag)
* Ag on its surface has FAS ~~receptor~~
* FAS is also called as CD 95 / TNF-R family (R-receptor)
* FADD (FAS associated death domain) receptor on Ag
* FAS & FADD together activates Caspases (FAS combines with FADD)
* Caspases → Apoptosis

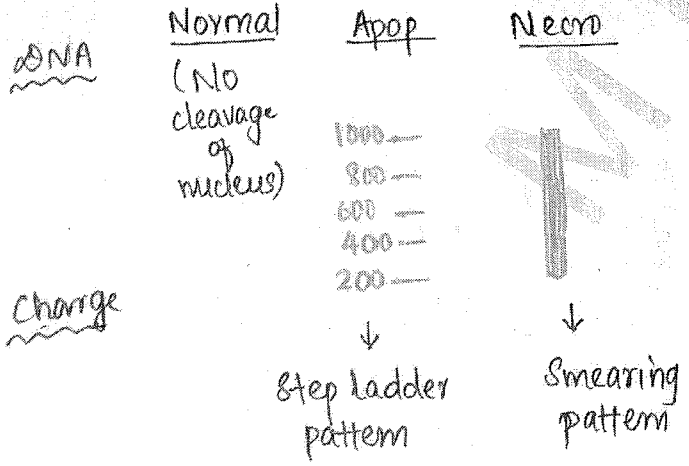
Caspases

* Enzyme
* C + asp + ases
* composed of
    - cysteine aminoacid
* cleave after (ases): Aspartic acid (Asp)
* eg:
    - Initiator
    - Executioner
* Initiator → 8 (Extrinsic pathway)
  9 (Intrinsic pathway)

  (Eight → Extri)
* Executioner → 3, 6
  (Both extri, intrin)
* 8, 9 stimulates 3, 6
* In intrinsic pathway: Caspase 9 will activate 3 & 6
* In ext, caspase 8 → activates 3, 6

Diagnosis of Apoptosis

* On histology → cell outline is maintained, chromatin condensation, inflammation absent
  ↓
  Apoptosis
* Most specific stain for apoptosis is Annexin V.
* Also confirm apoptosis by using Agargel electrophoresis
* Electrophoresis – seperation of anything by mass / charge.
* DNA of apoptosis is cleaved in to multiples (multimers) of 200 bp (bp-basepair) (200, 400, 600 ----)
* But in necrosis → kanyolysis → 1, 2, 3, 4 --- bp



* Step ladder pattern in Apoptosis
* Smearing pattern in Necrosis.

* In wet gangrene → above the gangrene there is superimposed infection → infection causes release of many enzymes → that is why appears wet.

FREE RADICAL INJURY

eg: H_2O_2 (hydrogen peroxide)
$OCl^{\cdot -}$ (hypochlorite)
$OH^{\cdot -}$ (hydroxyl)
$O_2^{\cdot -}$ (super oxide)

* Free radical is an element with free electron in outermost orbit.
* Injury by FR → by both necrosis & apoptosis
* They can damage any tissue
  - Protein
  - Lipid
  - Phospholipid
  - DNA.
* Protein damage → Misfolding
  Lipid " → Peroxidation
  PL " → Cell membrane damage
  DNA " → Mutation
* Production of free radical:
  - Inflammation
  - UV rays & X-rays
  - Fenton's reaction

$$Fe^{2+} + H_2O_2 \rightleftharpoons OH^{\cdot -} + Fe^{3+}$$

(Fenton said iron combines with H_2O_2 can produce FR → OH^- & Fe)
↓
He also said reaction is reversible.
(So FR produced are H_2O_2 & OH^-)

- Heberweis reaction:

$$H_2O_2 + O_2 \rightarrow H_2O_2$$

Removal of free radical (Scavengers)

eg: • Vitamin E, A, C
• Transferrin, Ferritin, Ceruloplasmin
• Catalase & Peroxidase

$$H_2O_2 \longrightarrow H_2O + O_2$$

• Superoxide dismutase (mainly in brain)

$$O_2^{\cdot -} \xrightarrow{SOD} H_2O_2$$

[Site: Mitochondria & cytoplasm
Co-factor: Mito. SOD → Mn
Cytop. SOD → Cu

• Glutathione peroxidase

$$H_2O_2 \longrightarrow H_2O + O_2$$

GSH → GS-SG

(G → Glutathione
GSH → reduced, GS-SG → oxidised)

$$H_2O_2 \longrightarrow H_2O + O_2$$

GSH → GS-SG
NADP ← NADPH

mcq
⇒ SOD is not a best example of scavenger. Because it is removing a free radical & at the mean time producing another free radical

$$O_2^{\cdot -} \xrightarrow{SOD} H_2O_2$$

Cellular accumulation

* FR can deposit on
• Proteins
• Glycogen
• Calcium
• Pigments
• Lipid ← TG, FA, Phospholipid

Stains

• Lipid → Sudan Black B, Oil Red O
• Glycogen → PAS (Per-iodic acid Schiff)
Best carmine (complete name not best one is carmine)
• Calcium → Von Kossa

Calcification

Dystrophic
↓
Tissues – Dead, degenerated
Serum Ca^{2+}: Normal
eg: R – Rheumatoid nodule
A – Atheroma
T – Tuberculous lesion
T – Tumor (Psammoma body)

Metastatic
↓
In living tissue.
Raised
eg: Hyperpara-thyroidism
• Vit D intoxication
• Sarcoidosis
• Milk alkali syndrome

* Ca^{2+} deposits in tumor → Psammoma bodies

* Psammoma bodies seen in :
  - M - Meningioma
  - P - Prolactinoma
  - P - Papillary cell carcinoma (Kidney, Thyroid, Ovary)
  - G - Glucagonoma

* Ovary → Papillary cell carcinoma is called as serous cyst adenoCa

* Metastatic calcification :
  - Hyperparathyroidism
  - Vit D intoxication
  - Sarcoidosis
  - Milk alkali syndrome
  - Chronic renal failure (Renal osteodystrophy) → here not dystrophic, it is metastatic calcification

* Living tissue undergoing calcification
  - MC in alveoli
  - BM kidney
  - Gastric mucosa
  - Vessels

* Calcification begins in mitochondria.
* Stain used → Von Kossa. of calcification

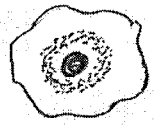
Pigments

* Can be exogenous or endogenous
* Endogenous (inside body)
  1) Melanin : Melanoma
  2) Iron : Iron overload
  3) Lipofuscin : Cell ageing.

* Stain for melanin → Mason fentana
* " iron → Perl stain, Prussian blue
* " lipofuscin → long Z-N stain

* Exogenous
  1) Carbon deposition in alveoli (Carbon laden macrophages)
  2) Tatooing. (Carbon deposition on skin → produces black spots on the skin)

* Lipofuscin : Cell ageing pigment (Brown colour deposition around nucleus. So also called as brown atrophy)



* Any cell undergoing free radical injury causes lipofuscin deposition around the nucleus.
* Also indicates cell get aged.

Cellular ageing

* Caused by
  - Free radical injury
  - Protein misfolding
  - DNA mutation
  - Senescence.
* Senescence → decreased replication potential.

Telomere (at end of chromosome)

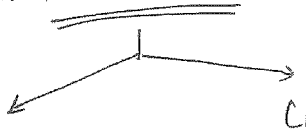
Telomere (Helps in replication)

* With each division → telomere length decreases → it lost → no replication → ageing.

Delay cell ageing

* Cell replicates when glucose enter a cell & glu. stimulates replication
* Natural way in delay of cell ageing is calorie restriction → ↓ replication of cell → so telomere is not shortened
* Sirtuins (Present in Red wine)
  - → decreases cell metabolism
  - → increase telomere length
  - → decreases apoptosis

INFLAMMATION



Acute

* Time: Minutes to few days
* Mediator: Neutrophil
* Outcome: Self limiting condition

Chronic

* Weeks-months
* Macrophage
* Progressive (does not ends)

Acute inflammation

* Cardinal signs of inflammation
  - Redness — Rubor
  - ↑ temp — Calor
  - Pain — Dolar
  - Swelling — Tumor

  } Given by Celsus

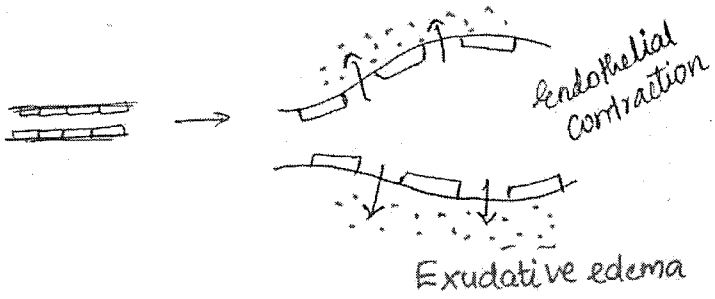
* Rudolf Virchow said 5th one as loss of function : Functio laesa

Events

a) Vascular
b) Cellular

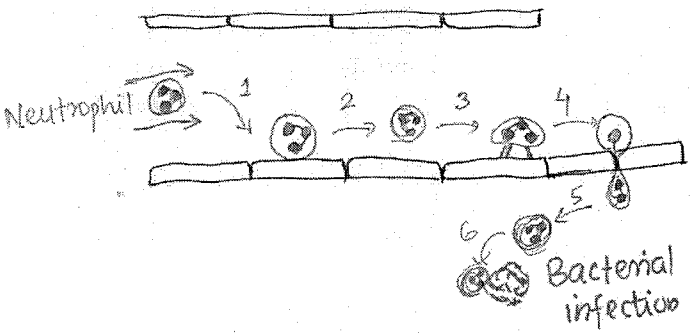
Vascular

* Transient vasoconstriction (Reflex)
* Vasodilatation (Histamine - from mast cells)
* Increased vascular permeability
  - (by Histamine)
  - Histamine affects post capillary venules
  - It is an immediate transient response



* Mechanism → Endothelial contraction
(gap b/w endothelium → fluid comes out → exudative edema)

Cellular events



1) Margination (neutrophil at centre of blood flow comes to margin)
- Vasodilation
- Selectins

2) Rolling → Has some receptors on endothelium & WBC
- Endothelium: Selectin (E-selectin & P-selectin)
- WBC: Sialyl lewis X-glyco protein
(Both E & P-selectin acts on it)

3) Adhesion → Need receptors on the endothelium & WBC
- Endothelium: CAM (Cell adhesion molecules)
  - CAM → I CAM
  - V CAM
- They interact with molecules on the WBC (β-2 integ-
  - I CAM → LFA-1 & MAC-1
  - V CAM → VLA-4 (β-1 integrin)
    ↓
    WBC molecules.
    Also called as Integrin

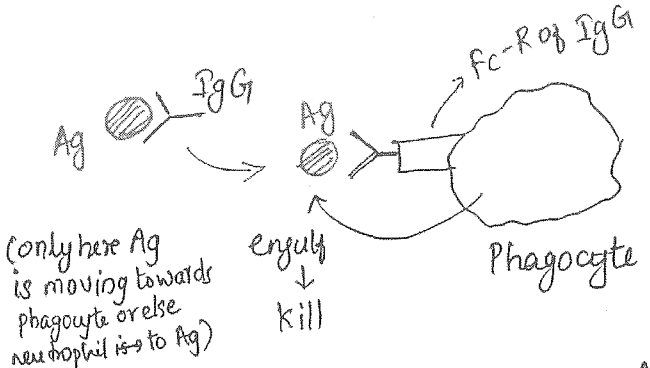
4) Diapedesis / Transmigration

Endo	WBC
CD 31 (PECAM-1)	CD 31 (PECAM-1)

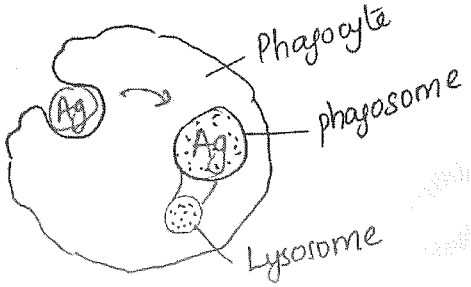
5) Chemotaxis: Unidirectional movement towards a known stimulus.
↓
Stimulus which attract WBC as Chemokines
↓
eg: Interleukin 8 (IL-8), C5a, LTB4, Bacterial products

6) Phagocytosis:
(i) Recognition - of bacteria by receptors such as
eg: Scavenger-R
Mannose-R

(ii) Opsonization - ↑ efficiency of phagocytosis (makes tasty)
↓
by Opsonins
eg: C3b, CRP (C-reactive protein), Fibrinogen, C4b, C5b, IgG

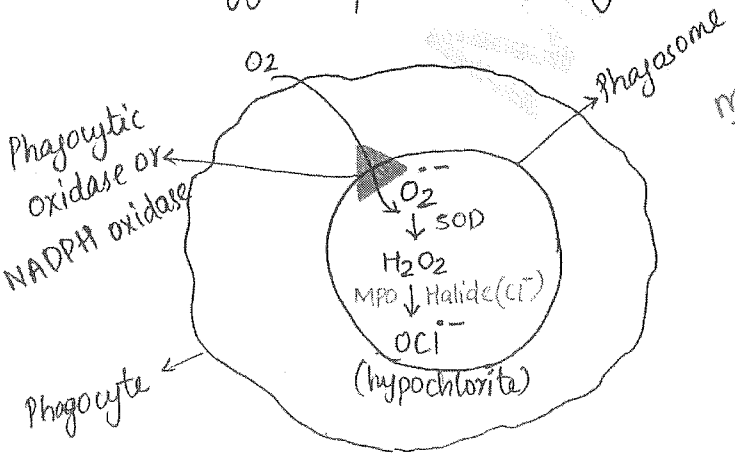


(iii) Engulfment → To engulf an Ag, phagocyte makes a pit → Ag moves inside → now pit closes → Ag inside a vacuole - phagosome → phagosome activates lysosome and fusion of both → phagolysosome



7) Killing : done by 2 pathways

(i) Oxygen dependent killing



MCQ • Strongest bactericidal free radical / most efficient bactericidal free radical → OCl^- hypochlorite

MPO (Myeloperoxidase)

MCQ • Most efficient bactericidal system (produces OCl^-) is H_2O_2 - MPO - Halide

(ii) O_2 independent killing:
done by enzymes in the granules of neutrophil.

Granules

(i) Primary (Azurophilic)
- MPO (Myeloperoxidase)
- Defesin
- Lysozyme
- P - protease (proteinase)
- N - Neutrophil elastase
- G - Cathepsin-G

Secondary (Specific)
- Alkaline phosphatase
- Lactoferrin
- Transcobalamine II

* Here no need of O_2
* But in O_2 dependent, from O_2 free radicals are produced.

MCQ
* In primary / azurophilic granules, MPO is needed for oxygen dependent killing.

Mediators of inflammation

* Helps in inflammation

Plasma derived
- Complements
- Kinins
- Coagulation system

Cell derived
- preformed
- newly syn

Cell derived

Pre-formed
- Histamine
- Serotonin
- 1° & 2° granules

Newly synthesised
- Arachdonic acid metabolites
- Platelet activating factor (PAF)
- Nitric oxide
- Interleukins and cytokines

Complements
* C_{5a} → Chemokine
* C_{3b}, C_{4b}, C_{5b} → Opsonin
* C_5 - C_9 → Membrane attack complex (MAC)

Kinin
* Bradykinin ⇒ Cause vasodilation, ↑ vasular permeability, Pain.

Coagulation system
* In inflam. → activation of factor XII → Coagulation pathway.

Pre-formed
* Histamine : from mast cells
* Serotonin : from Enterochromaffin cells & Platelets
* Both histamine & serotonin has same function.
- Vasodilation
- ↑ permeability
- Bronchoconstriction

* 1° & 2° granules of neutrophils (Azurophilic & Specific)

Newly synthesized (Synthesized de Novo)

* Arachdonic acid metabolites :

Phospholipid (in CM of neutrophils) (cell membrane)
↓ P. lipase
Arachdonic acid
COX → Prostaglandin PGG2 → PGI2, TXA2, PGD2, PGE2, PGF2
LOX → LTB4 ↓ (produces) LTC4, LTD4
LOX → Lipoxin

Prostacyclin
* PG I_2 : ~~Prostaglandin~~ → ↓ plat. agg
* TX A_2 : Thromboxane A_2 → vaso. const
* PGD_2, E_2, F_2 : Prostaglandin → Vasodila, ↑vasular permeability.
* LTB4 - Chemokine
* LTC_4, LTD_4 - Most potent spasmogenic agent → causes broncho constriction

MCQ
* PGF_2 - Prostaglandin which causes vasoconstriction (all others vasodilation)

MCQ
* Lipoxin → Anti-inflammatory mediator.

PAF
* Source: Mast cell & Endothelium
* Causes vasodilation, ↑ permeability and bronchoconstriction, activates platelets.

Nitric oxide (NO)

Arginine —NOS→ Citruline + NO

(NOS: Nitric oxide synthetase)

* Causes vasodilation, ↑ permeability, smooth muscle relaxation

Interleukin / cytokines
* eg: ~~IL-8~~, IL-1, IL-8, IL-6, IL-4, TNF-α
* Most imp: IL-1 & TNF-α
* Functions of both are same:
  (i) Activate macrophage
  (ii) Activate neutrophils
  (iii) Activate endothelium
  (iv) Help to synthesis acute phase reactants.
  (eg: CRP- C reactive protein, Fibrinogen, Ferritin, Haptoglobin] ↑ in inflam.
  Albumin, Transferrin] ↓ in inflam.
  (v) Causes fever (pyrexia)

* Albumin & Transferrin ↓ at the time of inflamm. so called as Negative acute phase reactants
* All others → ↑ in acute infla → there is ↑ ESR
  Positive acute phase reactants

Anti-inflammatory mediators
↑ → TGF β (Transforming growth factor)
I → IL-10
L → Lipoxin

MCQ
* IL-4, IL-13 ⇒ Both are pro-inflam- mediators & anti-inflammatory.

Types of acute inflammation

1) Catarrhal
* ↑ mucin production
* eg: Sinusitis

2) Serous
* Accumulation of fluid in a cavity
  eg: Effusions (pleural, pericardial, ascites)

3) Sero sanginous
* Accumulation of fluid & blood (eg: Hemothorax, hemopericarditis)

4) Purulent
* Pus (necrotic tissue + neutrophils)

5) Fibrinous

* Deposition of fibrin like substances (pink colour)

eg: Bread & butter pericarditis (seen in acute rheumatic carditis)

mcq

⇒ MC is Catarrhal

Chronic inflammation

* Shelf life of neutrophil : 6 days
* » macrophage : Years
* When It is defined as a condition where tissue injury & attempts to repair. They both occur simultaneously
* Ag provokes are
  - ~~Ag~~ Persistant Ag
    eg: silica, TB
  - Hypersensitivity causing Ag
    eg: Talc, TB, Beryllium infection
    ↓
    (industrial chemical)
* Mediators → Macrophages
  (Shelf life is months to years)

[Monocyte : Shelf life is 1 day]

[Lymphocytes : » week-months]

* Mechanism → when neutrophil can't remove the Ag → Mϕ acts → chronic inf

GRANULOMA

* Huge Mϕ → Giant cell (multinucleated)
* Modified Mϕ → Epithelioid cell
* When neutrophil can't remove Ag → Mϕ comes and surround the Ag → → some Mϕ fuse to form giant cells which are multinucleated → some Mϕ modified in to epithelioid cells → they are slipper like cells → they also surround Ag after Mϕ → lymphocytes also comes and get b/w them → all these together forms the granuloma.
* Examples of granuloma:

Granuloma

Immune (involves T-helper cell)
- Infective
  - TB
  - Leprosy
  - Cat scratch disease
  - Syphilis
  - Lymphogranuloma venerum (LGV)
  - Histoplasmosis
  - Coccidiodomycosis

  (LGV - by Chlamydia)
- Non-infective
  - Sarcoidosis
  - Crohn's disease
  - Rheumatoid arthritis
  - Berryliosis
  - Wegener's granulomatosis
  - Churg straus syndrome

Non-immune (No T cell involved)
- Talc
- Silica
- Suture

Repair & Regeneration

* Repair is the incomplete restoration of orginal tissue with or without fibrosis
* Regeneration is complete restoration of orginal tissue, without fibrosis
  eg: Liver
* Skin → heals.
  Organ → repair.

■ Cells according to division capacity

- Labile cell
- Stable cell
- Permanent cell

* Labile → continous dividing cell
* Stable → Quiscent (divide when required)
* Permanent → Non dividing cells
* Cell cycle:
  - Labile → G_2-M
  - Stable → $G_0 \rightarrow G_1$
  - Permanent → $G_0 \nrightarrow G_1$
* egs:
  - Labile → Hematopoeitic stem cell (HSC), skin epithelium, mucus membrane of GIT & respiratory tract; Germ cells, epithelium of ducts of exocrine gland (eg: bile duct)
  - Stable: eg: Liver, Kidney, skin fibroblasts
  - Permanent: eg: Neurons, skeletal muscle, cardiac muscle

Stem cells

* Divided according to new updates
  - Embryonic stem cell
  - Adult stem cell.
* Embryonic stem cells are totipent
  eg: Inner cell mass of blastocyst (gives endoderm, ectoderm and mesoderm)
* Adult stem cells:
  1) HSC → WBC, RBC, platelets
  2) Mesenchymal stem cells → Muscles, Bones, Cartilage & Vessels.
* HSC & Mesenchymal stem cells are both present in bone marrow.
  3) Localized stem cells → Niche
  - Skin (around hair follicle & sebaceous gland)
  - Liver
  - GIT
  - Eye
  - Skeletal system
* Liver → canals of Hering
* Eye → Limbus
* Skeletal system → Bones
* GIT → Krypts of Liberkuhn

* Order of healing: Neutrophils → Macrophage → Granulation tissue → ~~Epithelisation~~. Collagen.

Healing of Skin

* Types
  1) Primary intension.
  2) Secondary intension.

* Primary
  - Clean cut wound
  - No loss in surface area

* Secondary:
  - Loss in surface area
  - Wound contamination

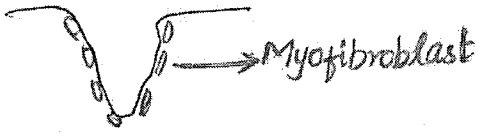
Primary intension healing

* Day 0 → Blood clot
* Day 1 → Neutrophilic infiltration
* Day 2-3 → Thin epithelization (but no clinical significance)
* Day 3 → Neutrophils replaced by
  - macrophages
  - Granulation tissue (fibroblast + blood vessels) mcq
  - Collagen appears
* Day 5 →
  - Macrophage infiltration
  - Granulation tissue ++
  - Collagen; bridges the gap in the wound.
  - Angiogenesis (new vessels)
  - Thick epithelization

mcq
* Epithelization occurs in day 5
* Thin epithelisation: 2_{2-3}
* Up to 1st month → ↑↑ collagen deposition
  (Collagen - triple helix)
* After 1st month (+ Vit C)
  - Cross linking of collagen fibrin
  - Replacement of collagen III to collagen I (more strong)
  - Both ↑ strength of wound.
  - To replace collagen, we need collagenases (MMP: Matrix Metallo proteinase)
  - Co-factor of MMP is Zn & Cu.

Secondary intension healing

* Loss in surface area



* Hall mark of 2° intension healing
  Myofibroblast
* They can → contract & secrete collagen
* Myofibroblast causes mcq
  - Fibrosis
  - Wound contracture
* Granulation tissue is more prominant

* Inflammation is also more prominent.

Wound strength

* At the end of 2nd week 10% of original
* At the end of 1st month 30% of original.
* At the end of 3rd month. 70% of original (maximum wound strength)

Complication

1) Delayed wound healing.

- Local factors
  - Foreign body
  - Wound contamination
  - Ischemia
  - Denervation
  - Improper immobilization eg: joint wounds (continously moving)
  - Large hematoma
- Systemic factors
  - Immunosuppresion (HIV, steroid)
  - Sepsis
  - Diabetes
  - Marfans syndrome & Ehler Danlos syndrome (collagen defect)
  - Vit C, A, E deficiency
  - Zn & Cu deficiency.

2) Excessive granulation tissue deposition (it also delays healing) mc → K/a Proud flesh.

3) Deficient collagen deposition → ↓ wound strength

4) Excessive collagen deposition - Scars

Scar

Hypertrophic	Keloid
• On the ~~bone~~ surface	• Away from bone surface
• Within 2 months	• After 2m.
• Superficial	• Deep
• Regress	• Never regresses
• No site favourable	• Sternum, ear lobes, shoulder
• —	• MC in Afro-American race

IMMUNE SYSTEM

Diseases of Immune system

Immune System

Innate	Adaptive
* Active before Ag exposure	* Active after Ag exposure
* ~~Specific~~ Not specific	* Specific
* Short lasting	* Long lasting (produces memory cells)

Innate

* Lag time ; Short (to activate immune system - time)
* eg: Skin epithelium, Mucosa of GIT & resp. system, WBCs like Neutrophil, Basophil, Monocyte, Eosinophil, NK cells (Natural Killer), Complements, pattern recognition receptor (PRR).

Adaptive

* Lag time: Longer (24 hr)
* eg: Lymphocyte (T & B), Plasma cells, Antibodies

Innate Immunity

1) Natural Killer cells (NK cells)

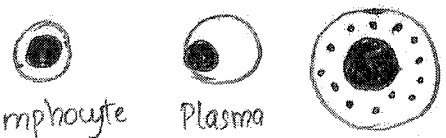
* It is a type of lymphocyte
* Lymphocyte → B, T, NK cells

B : ~~70%~~ 10-20%

T : ~~20%~~ 60-70%

NK cells : 10-15 %

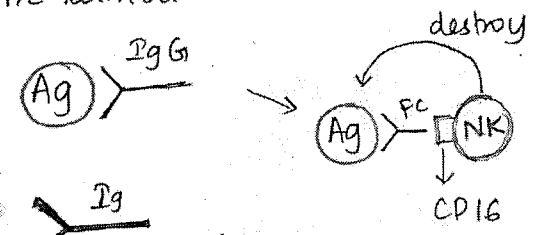
* But in our body, maximum is T cells

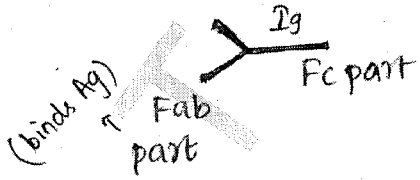


Lymphocyte (B / T) | Plasma cell | Large granular lymphocyte (LGL) or NK cell

* Receptors on NK cells
  - Lympho B → CD 19 +
    T → CD 3+
    NK → CD 19⁻, CD 3⁻
    (initially k/a → (null cell)
  - But NK have CD16, CD56
  - CD16 + → Fc-R of IgG
    CD 56 + → NCAM (NK cells Adhesion molecule)

* MOA :
  - Kills virus infected cells and the tumour cells.





  - Ab dependent cell mediated cytotoxicity (ADCC)
    (Ab - IgG, cell - NK cell)

MCQ
  - ADCC is shown by NK cells
    (Ag - Virus, tumour cells)

MCQ
  - MHC-I on Ag inhibit NK cells
  - All cells with nucleus has MHC-I (so MHC-I prevent NK cell from killing normal body cells)

MCQ
  - So NK cells kills an Ag without MHC -I

2) Pattern Recognition Receptor (PRR)

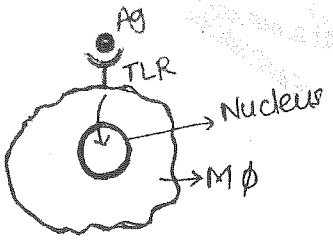
* Pattern is a type of molecular structure on Ag.
* Patterns are of 2 types
  - Damage associated } molecular
  - Pathogen associated } pattern

  DAMP & PAMP

* DAMP → are necrotic cells
* PAMP → are shown by micro-organism
* Ag have pattern, body have pattern like recognition receptor (PRR)
* Types of PRR:

  eg: Toll like Receptor (TLR)
  (they identify DAMP or PAMP)

* MOA of TLR – present on surface of the cell.



* Ag to TLR → signal to nucleus → ↑ interferon regulatory factor (IRF) & nuclear factor Kβ (NFKβ) ↑ in ~~nucleus~~ nucleus → both can destroy Ag. (K-Kappa, β-beta)
* Different Ag has different TLR
* Only types of TLR changes according to organism, otherwise same mechanism
  (ie, release of IRF & NF Kβ → Ag destruction)

Types of TLR	Organism identified
• Type 2	→ TB
• Type 3	→ DNA / RNA virus
• Type 4	→ Gram -ve bacteria, Chlamydia.
• Type 5	→ Flagella (five)
• Type 9	→ Protozoa

Adaptive immune system

* It is basically lymphocytes

Lymphocyte

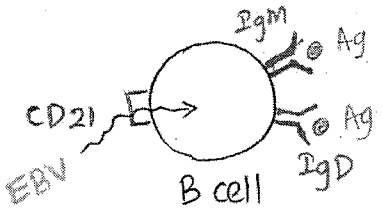
B	T
• 10-20%	• 60-70%
• Produced in bone marrow	• Produced in bone marrow
• Matured in bone marrow	• Matured in Thymus.

* Basic function of 'B' lymphocytes
  - (B) cell → produces → Plasma cell → produces ↓ Ab
  - 1st Ab produced is IgM
  - Then IgG, IgD, IgA, IgE

IgM → Kla (Class switching) → G, D, A, E

B-cell receptor

* B cell has IgM & IgD receptor
* Ag acts on IgM / IgD

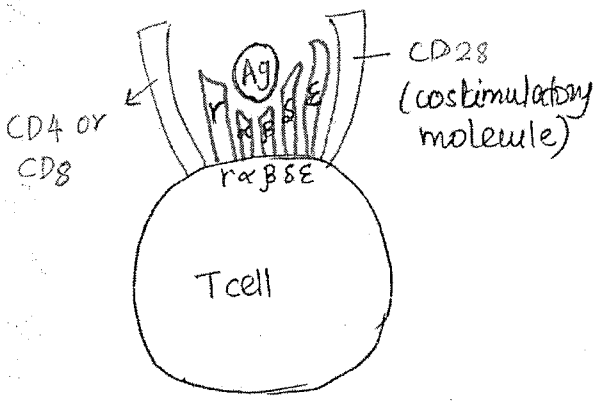


* CD21 (Complement receptor-2) (CR-2)
* B cells identify Ag by IgM & IgD
* But, EBV virus enters B cells by CD21 (EBV – Ebstein Barr virus)
* As immune system ↓, it starts proliferating. (EBV enters)

mca
* If CD_{21} is absent, EBV infection does not occur.

T-cell receptor (TCR)

* Have 7-8 receptors on surface
* $\alpha, \beta, \gamma, \delta, \varepsilon$, CD28, CD4, CD8



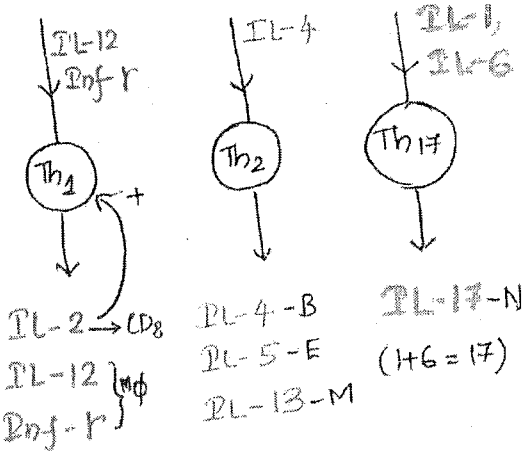
* α, β – 95% of TCR
* γ, δ – 5% of TCR
* If it has CD_4 – Helper T cell, if CD_8 +nt – Cytotoxic cell

T-lymphocytes

* Types:
  - ⇒ CD-4 → Helper T cell
  - ⇒ CD-8 → Cytotoxic T cell
  - ⇒ CD-25 → Regulatory T cell
  - ⇒ γδ T cell → Mucosa of intestine (gamma delta T cell)
* Regulatory T cell prevents auto-immunity.

CD_4 helper T cell (Th cell)

* Th_1, Th_2, Th_{17}



* IL-2 activates → CD8
* IL-12, Inf-γ → activates Mϕ
* IL-4 activates → B lymphocyte
* IL-5 ↑ Eosinophil
* IL-13 ↑ mucin production

* IL-17 activates neutrophils
* Th_1 activates CD_{28} & Mϕ
* Th_2 activates B lymphocyte, eosinophils
* Th_3 activates neutrophils
* IL-2 activates Th_1 itself.

CD8 T cells (Cytotoxic T cells)

* Kills other cells like
  - Virus infected cells
  - Tumour cells
* MOA : CD_8 T cells → secretes Perforin & Granzyme → cause apoptosis of the Ag

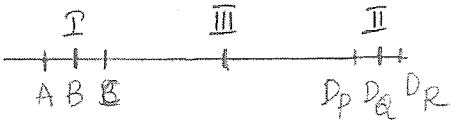
⇒ Ag presenting cells will activate CD_4 & CD_8 T cells

Ag presenting cells (APC)

* Cells which presents Ag to CD_4 or CD_8.
* MCQ * eg: Langerhan cells, Mϕ, dendritic cells, B-lymphocytes, Mucosal (M) cells.
* All have both MHC-I & MHC-II

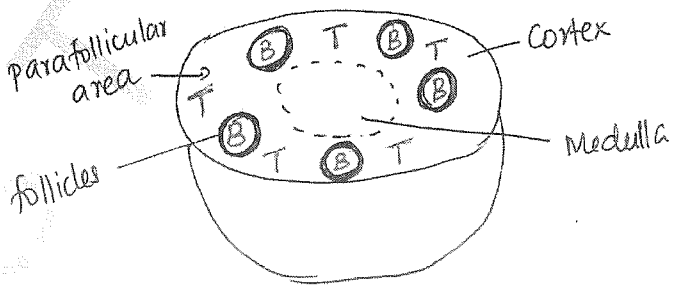
MHC

* Major histocompatibility complex
* MHC is present in chromosome 6 short arm (chr 6p)
* 3 genes on MHC : I, II, III (III b/w them)
* Subtypes of MHC I : A, B, C
  " MHC II : D_P, D_Q, D_R

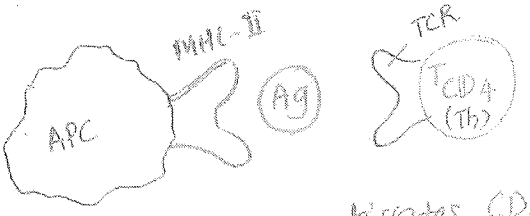


* Site : All nucleated cells + Platelets. (MHC-II)
* MHC-II present in all Ag presenting cells (APC)

Lymphnode



* In cortex → follicles → in b/w them → parafollicular area
* Follicles has B cells
* Parafollicular area has T cells.
* Ag is brought to LN via lymphatics.
* Interaction of APC with T cells
  - Rule of 8 – states MHC x CD = 8
    eg: MHC II x CD4 = 8
    " I x "8 = 8



- MHC I → activates CD8 } rule of 8
- MHC II → " CD4 }

mug
* CD_4 T cell kills extracellular Ag
eg: Bacteria

mug
* CD_8 T cell kills intracellular Ag
eg: Virus

* T cell dependant Ag:
- Protein Ag
* T cell independant Ag (ie, depends on B cells)
- Carbohydrate (glucose)
- Lipids

• (Ag with protein in surface is T cell dependant)
• Ag with glucose / lipid on surface is T cell independant / B cell dependent.

goes to infection site & acts against Ag.
• Th_2 activated → secretes IL-4, IL-5, IL-13 → which activates B lymphocytes, eosinophils, mucin production (sputum in cough) → B-lym activates plasma cell & produce Ab - it goes to infection site → Eosinophil (allergens) also goes to infection site.
• Th_3 activated → secretes IL-1, IL-6 → activates neutrophil → goes to infection site and again against infection.
• so all these activation are strong enough to remove the Ag.

Summary

• Cut in hand → infection → vascular & cellular events of acute inflammation → neutrophils predominates → if can't clear the Ag → Ag is taken by lymphatics & go to lymph node → in the LN, in paratollicular areas has T cells → T helper cell - Th_1 activated → ~~secretes~~
• T helper cell can promote various reactions to clear the antigen.
• Th_1 activated → secretes IL-12, Interferon γ, IL-2 → which activates CD_8, Th_1 itself and Mϕ → CD_8 causes Ag killing → activated Mϕ

Hypersensitivity Reaction

* It is defined as excessive and misdirected immune response to exogenous or endogenous Ag

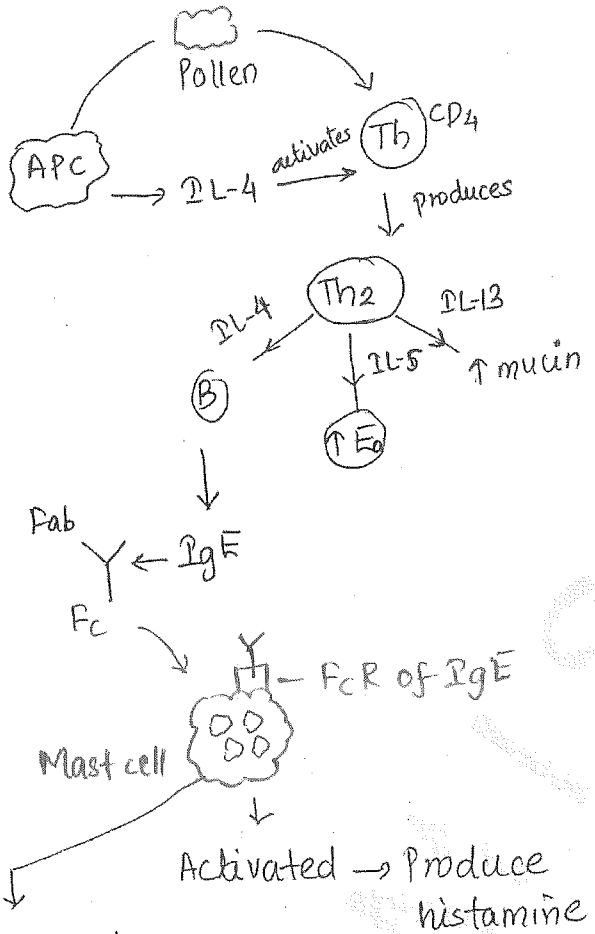
* Types

1) Type 1 - Anaphylaxis / Immediate type
2) Type-2 - Cytotoxic / Ab / Humoral
3) Type 3 - Immune complex
4) Type 4 - Delayed / cell mediated

(ACID)

Type 1

* Anaphylaxis
* eg: Allergy, Asthma.



Plasmamembrane
↓
made of phospholipid
↓ P. lipases

Arachidonic acid

COX | LOX

COX → PGD_2, E_2, F_2

LOX → LTB_4 ↓ LTC_4, LTD_4 } Bronchoconstriction

* After 1 day (24 hrs)

(Eo)

- IL-5 → activates Eosinophil
  ↓
  ↑ Eo
  ↓
  comes from Eo (Major basic protein (MBP)
  Eo cationic protein (ECP))

- IL-13 → ↑ mucin → ↑ cough
- MBP & ECP → damages ciliated columnar epithelial cells → comes out in cough.
- MBP & ECP → damages respiratory epithelium.
- ↑ Eo → Charcot Leydin Crystal
- MBP & ECP → Resp. epi. damage
  ↓
  Creola body
- ↑ mucin → Cirschman spirals

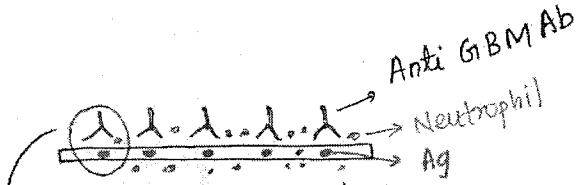
(CCC)

* eg: Allergy, Anaphylaxis, Asthma, Atrophy, Urticaria, Casonis test (Hydatid cyst)

Type 2

* cytotoxic, Ab mediated.

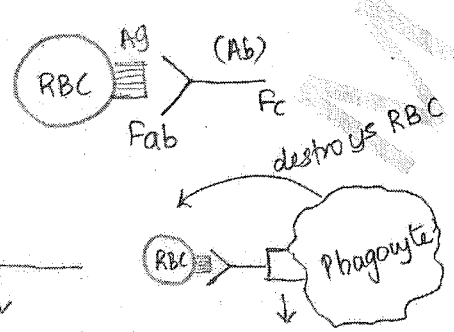
a) Inflammatory type :



Ag-Ab complex → ↑ complements → C5a → Neutrophilic infiltration & damage to tissue

eg: Good Pasture Syndrome

b) Phagocytic type :



Immune hemolytic anemia
(destruction of RBC by the phagocyte)

eg: Hemolytic disease of new born (HDN)
- Rh incompatibility
- ABO incompatibility

- Immune thrombocytopenic purpura (ITP)

c) Receptor dysfunction :

* If Ab is activating / inhibiting the receptor.

Thyroid-receptor

eg: Grave's disease

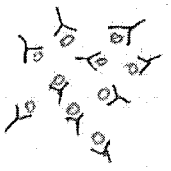
ACh-receptor

eg: Myasthenia gravis

* Ab is common in both
* So they are specific (acts on particular cell only)

Type 3

* Immune Complex
* Step 1 : Formation of immune complex



- Ab is produced against an Ag
- They combine and forms immune complex.

Step 2 : Deposition of immune complex.

↓

It will activates complement

↓

C_5a

↓

Step 3 : Inflammatory damage

C_5a

↓

Neutrophilic infiltration + Damage.

eg :- All glomerulonephritis except Good pasteur which is type II

- SLE
- PAN
- Arthus reaction
- Serum ~~sickness~~ siderness
- PSGN
- Membranous glomerulonephritis
- IgA nephropathy
- HSP (Henoch scholein purpura)

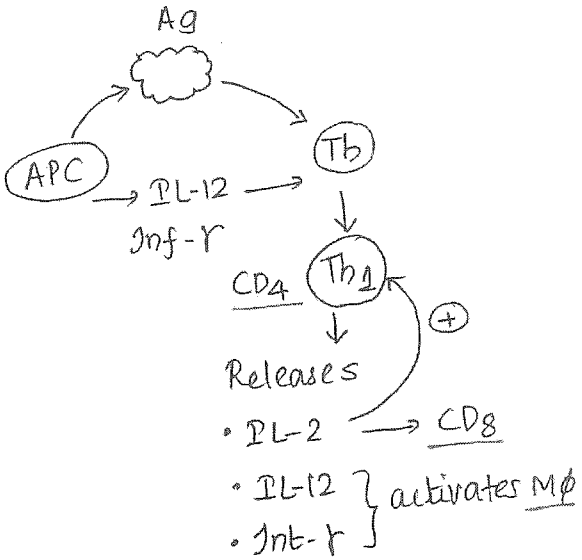
* The immune complex can travel in body & get deposited in areas where high filtration is present like kidney & joints (cause glomerulonephritis & arthritis)

CONCEPT

⇒ Type II : Ab are produced against a particular cells & destroys them only. No harm to other cells.

⇒ Type III : Ab are produced against a cell & but damage occurs in kidney & joints (Glomerulonephritis & arthritis)

Type IV



* Cell mediated hypersensitivity (Cells → CD_4, CD_8, Mϕ)

* Activation of cells needs 24-48 hrs

* So k/a delayed type of hypersensitivity.

* Activated Mϕ → causes ↑ phagocytosis → engulf Ag

* If can't remove Ag → granuloma formation & remove

* eg: Infective & Non-infective
  - granuloma (written in previous notes)
  - Type I Diabetes Mellitus
  - Multiple sclerosis
  - Lepra I
  - Tuberculin test (TB test)

Amyloidosis

* Deposition of Amyloid
* Amyloid → 95% fibrils
  → 5% "P" component (P is mucoprotein)
* It is an insoluble deposit.
* Classification

Primary — Multiple Myeloma

Plasma cells → produces light chain [by κ (kappa) and λ (lambda)]

↓

(AL)

Secondary — secondary to

1) Chronic inflammation
2) Malignancy
3) Auto immune conditions

↓

Stimulates liver

↓

Liver produces (AA) (amyloid associated) (1A → 1°, 2A → 2°)

* Types of deposition of amyloid

1) Localised deposition: (to an organ only)

Disease (remember amyloid disease)	Organ	Amyloid
• Alzheimer's	Brain	Aβ
• Medullary cancer thyroid	Thyroid	Acal (Calcitonin)

2) Systemic Amyloidosis:

eg: Familial Mediterranean
- fever (deposition of SAA)

[SAA – Systemic Amyloid Associated]

- Senile / Familial amyloidosis (deposition of ATTR)

[TTR → Transthyretin]

* In these 2 conditions, amyloid is deposited all over the body.

* Amyloidosis is diagnosed by Tissue specimen: Rectal biopsy
* On H&E stain (Hematoxylin & Eosin)

↓

Homogenous pink colour

* On special stain: Congo Red (polarized)

↓

MCQ Apple green birefringence

* MC organ involved in Amyloidosis
  Kidney
* MCC of death is:
  Arrythmia
* Amyloid can deposit in the spleen. If in
  - Red pulp → Lardeceous spleen
  - White pulp → Sago spleen

(red - lal, white - saphed in Hindi)

GENETICS

Mutation

* Defined as permanent change in the DNA.

Types

A) Genes

B) Chromosome

Gene mutation

Point mutation

Frameshift

- It is replacement of nucleotide

ATC CGG
↓
ACC CGG
⇓

Mis sense | Nonsense | Silent

* Mis-sense → change in aa produced by the codon.
* Nonsense → change in aa to stop codon/termination codon
* Silent → No change in aa
* Stop codons → UAA, UAG, UGA

Frameshift

* Defined as either deletion or insertion of nucleotides

- ATC CCG CGC
  ↓ (if T deleted)
  ACC CGC GC
- ATC CCG CGC
  ↓ (insertion of A)
  ATC CAC GCG C

B) Chromosomal mutation

* It can be change in number (numerical) or structural (change in structure)
* n = 23, 2n = 46 (diploid)

Numerical

Euploidy

If total no: is exact multiple of n = 23

eg: 3n (Triploidy)
4n (Tetraploidy)

Aneuploidy

If total no: is not an exact multiple of n = 23

eg: 2n+1 (47)
2n-1 (45)

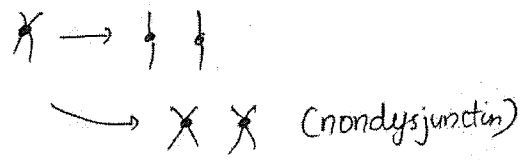
* 47 → Trisomy
* 45 → Monosomy

Causes of Aneuploidy

* Main cause is non-disjunction during meosis.
* Non-disjunction during mitosis

Mosaicism

* Non-disjunction means no seperation



* Mosaicism → Mixture of nomal and abnormal cells.

46 < 46 < 46 / 46 (mitosis)
46 < 46 < 47 / 45 47

Mosaicism

* ≥2 sets of chromosomes in the same person

46, 47

* Eg. of Aneuploidy (Important)
  - Trisomy (47)
    - Autosome
      - Tri 13 - Patau's
      - 18 - Edwards
      - 21 - Downs
    - Sex chromosome
      - 47 XXY Klinefelter
  - Monosomy (45)
    - Autosome: Not known
    - Sexchromosome: 45XO Turner's syndrome

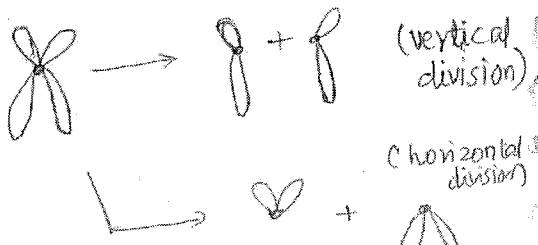
Monosomy (45)

Structural mutations

(1) Deletion (del)
- del 5p : Cri du chat syndrome
- del 22q : Velocardio facial defect + Digeorge syndrome → combinely k/a CATCH 22

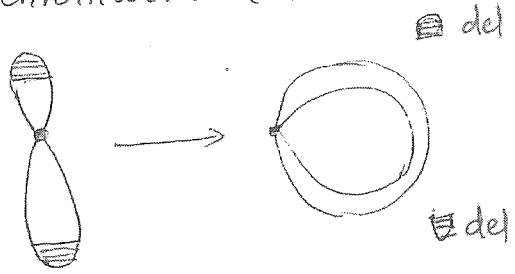
(p - short arm, q - long arm)

(2) Duplication
(3) Insertion
(4) Inversion.
(5) Isochromosome (i)
(iso = same in size)



If plane of division is ⊥ to normal axis → Isochromosomes

6) Ring chromosome (r)



7) Translocation (exchange)

a) Balanced

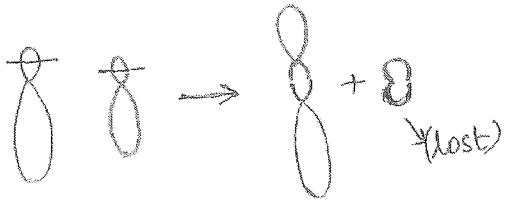
MCQ b) Robertsonian : 2 acrocentric chromosome

- Centromere at centre
  - Metacentric

- Subs& metacentric (away from centre)

- Acrocentric (towards end)

- Telocentric (Absent in humans) (at end)



(Robertsonian)

↓

2 centromere → k/a dicentric chromosome

Inheritance pattern of Mutation / diseased

- Mendelian (classical)
- Non Mendelian (Non classical)
- Multigenic

* eg: of
  - Mendelian:
    - Autosomal dominant (AD)
    - Autosomal recessive (AR)
    - x linked dominant (XD)
    - x linked recessive (XR)
  - Non Mendelian:
    - Trinucleotide repeats
    - Mitochondrial inheritance
    - Gonadal mosaicism
    - Genomic imprinting
  - Multigenic (multiple genes causes disease)
    - Diabetes
    - Obesity
    - HTN
    - Cleft lip / cleft palate

Mendelian Inheritance

* Phenotype = Clinical features
* Genotype = Genetic representation of the phenotype.
* Allele = Alternative form of the genotype.

1) Autosomal dominant

* MC
* eg: Marfan's syndrome
  M - Normal allele
  m - mutated allele
* Genotypes are:
  MM - Normal
  Mm - Diseased
  mm - Diseased
* Autosomal dominant is defined as diseases which manifest even in heterozygous condition.
  eg: Mm
* But sometimes all Mm need not to be diseased.
* It is defined by penetrance
* Penetrance = $\frac{\text{Patient who are diseased}}{\text{Pt. who inherited one abnormal allele.}} \times 100$

100 Mm

30 diseased — 70 nondiseased

Penetrance = $\frac{30}{100} \times 100$

= 30 %

* Here mutation may not be complete so only some are not diseased.

2) Autosomal recessive

* Defined as diseases which manifest only in homozygous condition.
* eg: Gaucher's disease
  (deficiency of β-glucocerebrosidase)
  ↓
  accumulation of β-glucocerebroside.
  ↓
  accumulates in liver, spleen and bone marrow
  ↓
  C/C: Hepatosplenomegaly (L&S)
  Growth retardation (BM)
  ↓
  Bone marrow specimen shows
  - MΦ of BM enlarged
  - Tissue paper crumbled appearance
  - cell is called as Gaucher cell
* Genotypes:
  G → Normal
  g → mutated
  } allele

  GG - Normal
  Gg - Normal
  gg - Diseased
* Expressed only in homozygous condition.

AP → Mm (diseased) MM (normal)

AD → Mm MM

MM mM MM mM
(N) (Dis) (N) (Dis)

Rule of Dominance:

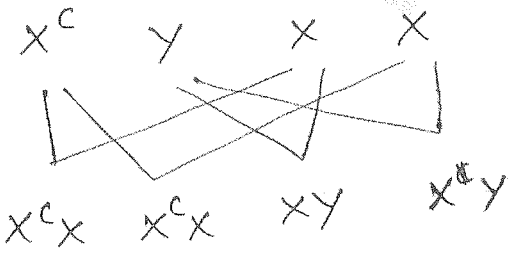
If a child is diseased then 50% of parents are diseased.
(1 of parent should be diseased)

3) X-linked recessive

* eg: Colour blindness
  X – Normal allele.
  X^c – Mutated allele.

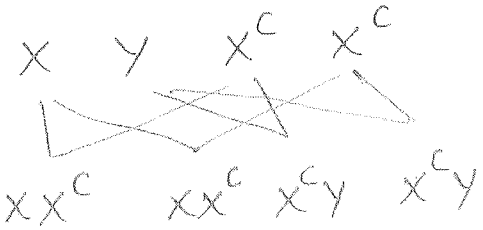
(Diseased male) (Normal female)
⇒ X^cY XX

①



(Normal male) (Diseased ♀)
⇒ XY X^cX^c

②



* In case ① father never transmits to son
* In case ② mother transits to son and also to daughter.
* In case ① father transmits to daughter

Rule of X-linked recessive

Father never transmits to son

* In case ② – Criss cross inheritance.

4) X-linked dominant (Rare)

eg: Red – Reth's syndrome
Rose – Rickets
for – Fragile x-syndrome
All – Alports
Children – Charcot Marie tooth disease.

Eg: of AD: (HEAVY DOMINANT)

H – Hereditary spherocytosis, hyper cholesterolemia
E – Ehler Danlos syndrome.
A – Achondroplasia
V – von Willebrand disease
Y

D – Distrophica myotonia
O – Osteogenesis imperfecta
M – Marfans syndrome.
I – Intermittent porphyria
N – Noonas Syndrome

A - ADPKD (Autosomal dominant polycystic kidney disease)
N - Neurofibromatosis
T - Tuberous sclerosis

* eg: of AR → All enzyme deficiencies (ABCDEFG)

A - Alkaptonuria
B - β-Thalasemia
C - cystic fibrosis
D - sensori Neural Deafness
E - Emphysema (α_1-Antitrypsin defi)
F - Fredrich's ataxia
G - Gaucher's disease

* Eg: of XR

Lady - Liesch Nyhan syndrome
Hardinge - Hemophilia
College - Chronic granulomatous disease
Girls - G6PD deficiency
Dont - Duschenes Muscular dystrophy
Care - Colour blindness
About - Brutons X-Agammaglobinemia
Foolish - Fragile x-syndrome
Words - Wiscott Aldrich syndrome.

Non-Mendelian Disorder

1) Trinucleotide repeats

eg: GAA GAA GAA

* Eg: of repeats can be seen in coding & non-coding genes of DNA

Repeats

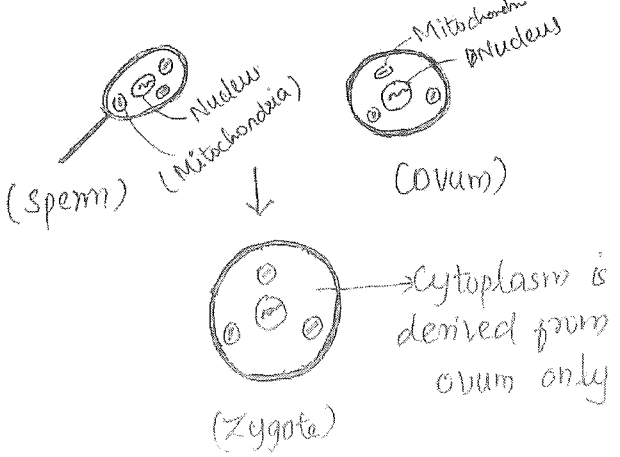
Coding region (codes for protein)
→ Huntington's disease (CAG)
(Hunter: Cage)

Non coding region
→ F: Fragile X-syndrome (CGG)
F: Fredrich's ataxia (GAA)
M: Myotonia dystropica (CCTG)

* Fredrich's ataxia → Ataxia: Gait → GAA
* myotonia → CTG
* No: of repeat is increasing in these diseases.

2) Mitochondrial Inheritance

* Also k/a Maternal Inheritance



* Mitochondria transmits the disease
* Mother transmits the disease (as cytoplasm of zygote is derived only from ovum) → Maternal inheritance.

eg: K L M N O P
- Kearn Sayre Syndrome
- Leigh syndrome
- MERRF
- MELAS
- NARP
- Chronic Progressive Opthalmoplegia
- ~~Pearsan syndrome~~
- Pearsan syndrome

3) Genomic Imprinting

* Means genomic silencing.
* ie, gene does not express
* It is explained by epigenetics

ATC → (mutation) → TTC → Disease

ATC → (remains same) → ATC → Disease

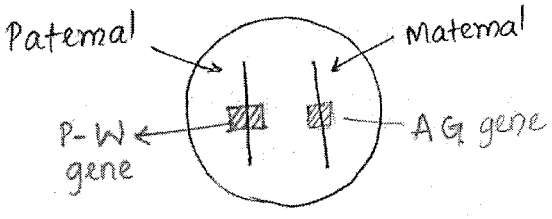
* Epigenetics is defined as change in DNA without change in sequence.
* Mechanism ⇒ Hypermethylation of a gene which causes gene silencing.

(No change in DNA → but change in chemical composition (hypermethylat^n) which makes it unable to express (silenting)

eg: Praderwilli syndrome
Angelman syndrome.

Mechanism (of both)

1) Silencing
2) Deletion
3) Uniparenteral disomy



Praderwilli syndrome	Mechanism	Angelman syndrome.
Paternal	1) Silencing 2) Deletion	Maternal
Maternal	3) Uniparental disomy	Parental

* P-W gene is coming from paternal → so if it is absent → Praderwilli syndrome.
* ~~Angelman syndrome~~ AG gene is coming from maternal → if it is absent → Angelman syndrome.
* In case of uniparenteral disomy, either paternal ~~or~~ or maternal (both are same - from parental/maternal)

absent → if ~~parental~~ both are maternal then no PW gene & causes Praderwilli syndrome.

4) Gonadal mosaicism:

* Somatic genes → Normal - Phenotypically normal
* Germ cell genes → mutated ↓
  Children will be diseased
* Person himself is normal but can transmit the disease to his children

eg: Tuberous Sclerosis
Achondroplasia

* This will not follow rule of dominance (~~50%~~ chi If child is diseased then 50% of parent is diseased → But here parent is normal)

Diagnosis of Genetic disease

* For diagnosis use karyotyping

(1) * Karyotyping → study of chromosome
* For karyotyping, arrange chromosome in decreasing order of size
  Largest → Chromosome 1
  Smallest → Chr 21

(2) FISH : Fluorescence insitu hybridization.

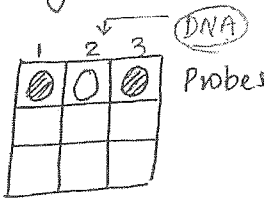
* If want to diagnose chr 5p deletion
* make flourescent probe against the 5p → normally can find fluorescent probe → if 5p is deleted → ~~no~~ can't find fluoresant probe.

mcq

* FISH is done for known genetic mutation only.

(Unknown mutation → cannot make probe → so can't do FISH)

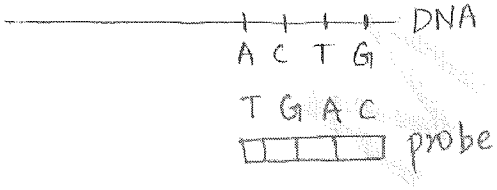
3) Micro array : Reverse hybridization



Probe	DNA
1	Normal
2	Mutated
3	Nomal

* Microarray can study multiple genes in single reaction

* Probe → small unit of a DNA.



* Probes are arranged in the micro array → Add DNA → if it binds - normal → not bind - mutated.

Samples for genetic analysis

- Antenatal samples
- Post natal samples

* Antenatal samples:
  - Chorionic villi sampling (CVS) (9-11 wks)
  - Amniocentesis (14-16 wk)
  - Cordocentesis (18 wks)

* Postnatal samples.
  - All WBCs except monocyte
  - Skin fibroblast
  - Bonemarrow aspiration

* Antenatal sampling method has a risk of abortion

mcq * So recently used → Fetal DNA in Maternal ~~blood~~ serum.

(No risk of abortion but expensive)

NEOPLASIA

* Neo + plasia → New + growth
* So process of new growth is neoplasia.
* Anlage: Primitive tissue from which an organ develops
  eg: Renal anlage → Kidney
  Hepatic anlage → Liver
* 2 developmental anomalies
  - Choristoma
  - Hamartoma
* Choristoma → Normal tissue & abnormal location
* Hamartoma → Abnormal tissue & normal location.

meq
* Since abnormal tissue, hamartoma is a premalignant condition
* eg: of choriostoma:
  Pancreatic tissue in gastric mucosa
* eg: of hamartoma:
  Bile duct abnormal proliferation
  (Von mayerburg complex)
  ↓
  Bile duct hamartoma

Nomenclature of a tumour:

* According to tissue of origin:

1) Epithelial tissue
   - Squamous epithelium
   - Glandular epithelium

(Malignant → Add carcinoma)

* Squamous epithelium.
  - Benign: Squamous papilloma
  - Malignant: Squamous carcinoma
* Glandular epithelium:
  - Benign: Adenoma
  - Malignant: Adenocarcinoma

2) Mesenchymal tissue
   → Benign: — oma
   → Malignant: — sarcoma

   eg: Bone
   Osteoma, Osteosarcoma
   Muscle
   Myoma, Myosarcoma
   Vessels
   Angioma, Angiosarcoma

3) Mixed tumor

a) Epithelium + mesenchymal tissue
   eg: Pleomorphic adenoma (salivary glands)
   Wilms tumor (kidney)

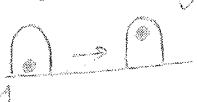
b) Ectoderm + Mesoderm + Endoderm
   (Teratoma)

Microscopy of a tumour

* Differentiation : Extend to which a tumor resembles tissue of origin
* It can be well differentiated & -poorly differentiated
  - Well D → Good prognosis
  - Poorly D → Poor prognosis
* Dysplasia : Disordered growth
* Anaplasia : Loss of differentiation (all different)

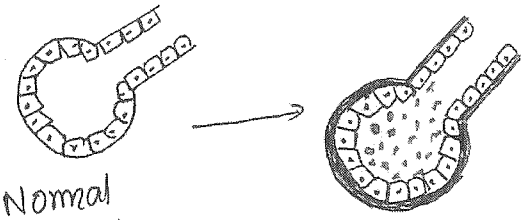
	Dysplasia	Anaplasia
• Rate of proliferation	↑	↑↑↑
• Pleomorphism	+	++
• Hyper chromatism	+	++
• Loss of polarity	+	+
• Mitotic rate	↑	↑↑↑
• Reversibility	Partially reversible	Irreversible

* More no: of cell → Proliferation
* Pleomorphism → All cells have different size & shape
* Hyperchromatism → Darkly shaded nucleus than normal.
* Loss of polarity → nucleus from base (normal) goes to apex



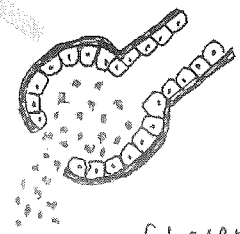
BM

* Hallmark of ~~neoplasia~~ malignancy
  Anaplasia
* Carcinoma in situ (CIS)
  eg: Breast, Cervix, Skin



Normal gland

Tumor cells infiltrate. But have intact basement membrane
↓
K/A CIS



Invasion (basement membrane ruptures & tumor cells comes out)

* Malignancy

Features are

1) Anaplasia
2) Invasion
3) Metastasis

- Hallmark of malignancy - Anaplasia
- Surest sign of malignancy is Metastasis

Hallmarks of cancer:

S - Self sufficiency in growth signal (activation of oncogenes)

T - Tumor suppresor gene. (inactivation of tumor suppressor gene)

E - Evasion of Apoptosis

A - Altered Cellular Metabolism

L - Limitless replication potential

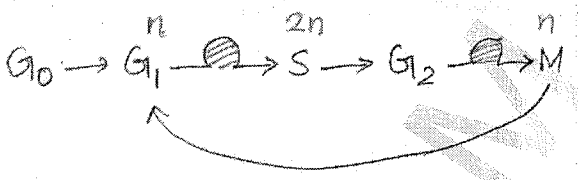
A - Angiogenesis

T - Evasion of immunity

M - Metastasis

Cell cycle

* Sequence of events leading to cell division



* Check points:
  - G_1-S
  - G_2-M
* G_0 → ~~Synthetic phase~~ Resting phase
* G_1 → Pre-synthetic phase
* S → Synthetic phase
* G_2 → Pre-mitotic phase
* M → Mitotic phase
* Chromosome no: doubles at S phase

* Checking points → Checks for mutation.
* Checkpoints → Check for mutation
  ↓ if present
  Repair
  fails (−) → Apoptosis
  (+) success → Cell cycle

* Controll of cell cycle:

(a) Cell cycle proliferators

(Helps in continue cell cycle)

Proteins → Cyclins

Enzymes → Cyclin dependent kinases (CDK)

D	combines with	CDK 4	G_1-S
E		2	
A		2	G_2-M
B		1	

* Cyclin D combines with CDK 4
* ~~CDK 4, CDK 2~~
* D-CDK4, E-CDK-2 → In G_1-S
* A-CDK_2, B-CDK_1 → In G_2-M

(b) Cell cycle inhibitors (p-protein)

(Helps to stop at checking points)

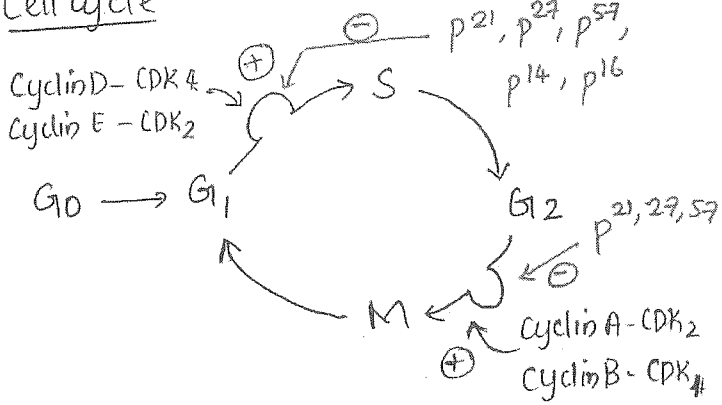
Cip/Kip	INK 4a
p21	p14
p27	p16
p57	

Cip - CDK interacting protein

Kip - Kinase inhibitory protein

* Cip/Kip inhibits both G_1-S & G_2-M
* INK 4a inhibits only G_1-S

Cell cycle



* Proliferators initiate cell cycle at check points
* Inhibitors inhibit cell cycle at the check points.

⇒ Hallmark of cancer (STEAL ATM) acts on cell cycle by acting on this proliferators & inhibitors

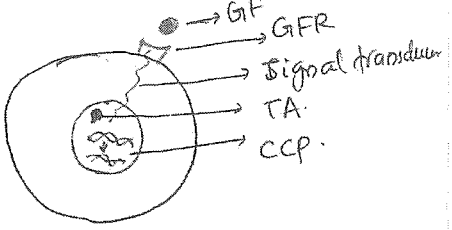
Regulation of cell cycle

1) Proto-oncogenes : Physiological genes.
   * Function → Cell growth, cell division, inhibits apoptosis.
   * When undergo mutation → transforms to oncogenes, which are cancer causing genes. (pathological genes)
   * Oncogenes → releases proteins k/a onco proteins

Proto-oncogenes : Physiological genes
Oncogenes : Pathological genes

Family of proto-oncogenes

* Growth factor → acts on its receptor → send signal to nucleus - signal transducer → activates transcription factor - transcription activators.



* Transcription → DNA → RNA → proliferates - cell cycle proliferator
* 5 family of proto oncogenes.

Proto oncogenes	Tumor (mutation)
1) Growth factor (GF)	
PDGF	Astrocytoma
FGF	Osteosarcoma, Fibrosarcoma
HGF	Hepato cellular carcinoma (HCC)
2) GF receptors	
• PDGFR	Glioma
• EGFR-1	Adenocarcinoma lung
EGFR-2 (Her 2 neu)	Breast Ca (Ca - carcinoma)
• RET	MEN (Multiple Endocrine Neoplasia)
• KIT	GIST (Gastro intestinal stromal tumour)

3) Signal transducer

- ✓ K-RAS → Colon cancer
- H-RAS → Bladder & Kidney tumor
- N-RAS → Hematological malignancy
- ✓ A-ABL → Chronic myelogenous Leukemia
- B-BRAF → Hairy cell leukemia
- C-Catenin → Hepatocellular Carcinoma (HCC)

4) Transcription Activator:

- C-myc → Burkitt lymphoma
- n-myc → Neuroblastoma
- l-myc → lung carcinoma

5) Cell cycle proliferators:

- Cyclin D_1 → Mantle zone lymphoma
- CDK 4/6 → Breast & Ovarian cancer.

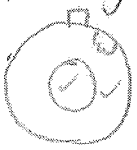
=) Astrocytoma is a type of Glioma.

= MC protooncogene causing cancer
MCQ K-RAS

2) Tumor suppressor gene

* Function → Cell repair, ↓ telomerase activity, Apoptosis.

* Family of tumor suppressor gene (location)



(1) On cell surface
(2) Under cell surface
(3) Cytoplasm
(4) Nucleus

Tumor suppressor gene	Tumor (inactivation)
1) On cell surface	
TGF-β	→ Colon Ca, Breast Ca
2) Under cell surface	
MCQ ~17q NF-1	→ Neurofibromatosis I
~22q NF-2	→ " II
3) Cytoplasm	
P-PTEN	→ Cowden syndrome ♂: Prostate Ca ♀: Endometrial cancer
~~A-APC~~	
~~S-SMAD~~	
A-APC	→ Familial adenosis polyposis coli (Colon Ca)
S-SMAD	→ Pancreatic Ca

4) Nucleus:

MCQ

~17p	p^{53}	→ Li Fraumeni syndrome
~13q14	Rb	→ Retinoblastoma, Osteosarcoma
~11p	WT-1	→ Wilms tumor
~17q	BRCA-1	→ Breast Ca, Ovarian Ca
~13q	BRCA-2	→ Breast Ca (male), prostate Ca, gall bladder Ca

* MC ~~tumor suppressor~~ gene causing tumor is p^{53}

* MC oncogene causing cancer is K-RAS

* p^{53} on chromosome 17 p → it codes for 53 KDa protein (kilodalton-kDa)

* MOA of p^{53}:

Cell damage → activates tumor suppressor gene - p^{53} → cell cycle arrest at $G_1S > G_2$-M → repair → if successful then go back to cell cycle → if repair not successful then apoptosis (BAK, BAX)

= Repair by GADD 45

* Other name of p^{53} is policeman of cell cycle.

* Tumors due to p^{53} mutation:

(BLAST)

B - Breast, Brain
L - Lung
A - Adrenal
S - Stomach
T - Tumour.

} all comes under common tumor → Li fraumeni syndrome → at young age

* Rb gene → Called as Governor of proliferation

Growth factor → brings together (Cyclin D – CDK 4) → they add multiple PO_4 groups to Rb gene → (Rb → Rb-P-P) → proliferation → acts on both G_1-S > G_2-M.

* Mutation of Rb gene causes
- Retinoblastoma
- Osteosarcoma
- pineoblastoma

* Bilateral retinoblastoma + pineoblastoma (in brain) ↓ Kla Trilateral retinoblastoma

Other hallmarks of cancer

3) Evasion of apoptosis
- Causes apoptosis - BAK, BAX
- Inhibit apoptosis - BCl 1, 2, 6, MCl-1, BCl-XL

* L → Long life (no apoptosis)

4) Altered Cellular metabolism:

* Normal cell → glucose → glycolysis → pyruvate → Krebs cycle → NADH, FAD → ETC → ATP

* Tumor cell → glucose entry ↑↑↑ → makes lactic acid instead of pyruvic acid → lactic acid makes building blocks - glucose, protein, lipid, nucleotides → ↑↑ no: of tumor cells.

* Tumor cell → 10% to pyruvic acid → ATP → but rest 90% to lactic acid

* Warburg effect : Hunger for glucose / glucose hunger.

↓

Main end product of tumor cell will be lactic acid instead of pyruvate to make more tumor cells.

5) Limitless replication potential :

* Tumor cell → inhibits the tumor suppressor genes (TSG) (eg : p^{53}) ↛

* Also tumor cell → activates telomerase → maintain / ↑↑ telomere length → it causes unlimited replication.

6) Angiogenesis :

* New vessels

(tumor cells) —up to 2mm→ Invasion

—to move > 2mm→ Invasion + Vessel. (for glucose)

* Pro angiogenic factors :

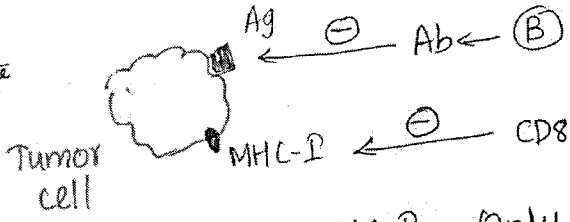
eg : VEGF, TGF-β, Angiogenin

7) ↑ : Evasion of Immunity

* Adaptive cells in body → B & T lymphocyte

* B-lymphocyte → Ab production

* T-lymphocyte → CD_4, CD_8 T cells.



(CD_8 → MHC-I, Only CD_8 kills)
(CD_4 → MHC-II)

* Tumour cell becomes → Ag negative & MHC-I negative → so evade immune system.

(If normaly cell has Ag → B cells produces Ab & kill Ag → if cell has MHC-I → CD_8 T cells activated & acts on it → kills → but tumour cells since Ag-ve & MHC-I-ve can't kill by B-lym. & CD_8 T all))

8) Metastasis :

* Discontinous spread of tumour cells.

* Step 1 → loss of attachment

• Tumor cells attached to each other by a protein - Cadherin

• For loss of attachment → cadherin mutation.

* Step 2 : Dissolution of basement membrane

• By release of collagenases

* Step 3 → Spread out through various routes.

(i) Blood / Hematogenous by Sarcoma

(ii) Lymphatic - by Carcinoma

(iii) Direct spread by Ovarian cancer.

* Step 4 → Attachment to new site

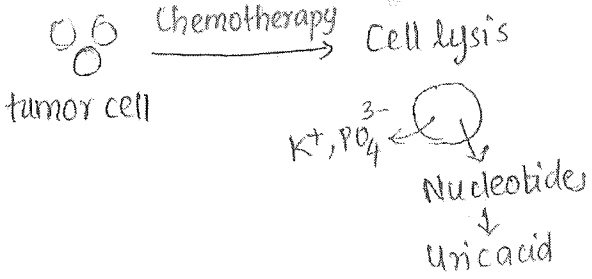
*

⇒ Exception: Renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) spread by hematogenous route.

Clinical features of tumor

1) Cachexia (weight loss)
Pyrexia (fever)
- Mediator : TNF-α, IL-1

2) Tumor lysis syndrome:



↑ • Hyperkalemia (↑ K^+)
↑ • Hyperphosphatemia (↑ PO_4^{3-})
↑ • Hyperuricemia
* ↓ • Hypocalcemia (↑ PO_4 causes ↓ Ca)

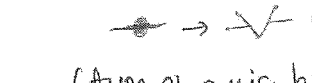
3) Paraneoplastic syndrome:
Some clinical features which cannot be explained by
- Anatomical location
- Spread of tumor

eg: Most common - Hypercalcemia (seen in many tumours including lung cancer)

Hypercalcemia → ↑ PTH (due to) So ↑ PTH activity in lung cancer → can't link → paraneoplastic synd)

Tumor diagnosis:

1) Tissue specimen
- FNAC
- Biopsy (better - Large amt of tissue)
→ incisional biopsy (part of tumor out)
→ excisional biopsy (entire tumor out)
→ Wedge biopsy



(type of excis. biopsy)

2) Fixation : 10% Formalin

3) Stain : H & E stain (Hematoxylin & Eosin)

4) Tumor markers : Basically used for screening. But also gives information about
- Prognosis
- Recurrence
- Tumor load

Imp MCQ

eg: Hormones (3C)

C - Calcitonin ⟶ medullary Ca thyroid

C - catecholamines ⟶ Pheochromocytoma

C - β-hCG ⟶ Germ cell tumor

(eg: Embryonal carcinoma, Choriocarcinoma)

Enzymes

LDH ⟶ Ewings Sarcoma (mcq), Lymphoma

Prostate acid phosphatase ⟶ Prostate cancer

Alkaline phosphatase ⟶ Bone : Osteosarcoma

Placenta : Seminoma.

Protein

✓ CEA ⟶ Ca lung, pancreas, colon

(asked many times) ✓ αFP (feto protein) ⟶ Hepatocellular carcinoma.

β2 microglobulin ⟶ Multiple myeloma

CA (mucoprotein)

CA 125 ⟶ Epithelial ovarian cancer

CA 19.9 ⟶ Lung, pancreas Ca

CA 72.4 ⟶ Stomach

CA 15-3 ⟶ Breast Ca

(CEA : Carcino Embryonic Antigen)

RENAL SYSTEM AND ITS DISORDERS

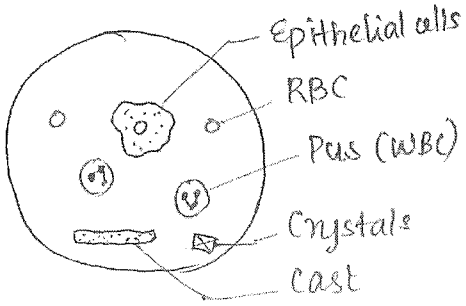
Renal Function Test

*

- Glomerular function → Measure GFR → Done by
  - Inulin excretion test
  - Creatinine clearance test. (Best one used)
- Tubular function → Measure specific gravity.

Urine Routine Microscopy

* Take 5ml of urine → centrifuge it → with sediment do microscopy → will get some RBC, WBC, epithelial cells, cast, crystals.



* Hematuria → >3 / hpf (high power field) or >5 RBC / ~~mm~~ µl (microlitre)
* Pyuria → >5 WBC / hpf

* Microscope → 3 power
  1) 10× (~~low~~ low power)
  2) 40× (high power)
  3) 100× (oil immersion)

* Sterile pyuria : Non growth on culture media eventhough has pus
  eg: Mycobacterium TB
  (It does not grow in that ~~specific~~ particular media → grow in other specific media.)

* Crystals :
  - Acidic urine pH:
    - ⇒ Calcium oxalate (diamond like)
    - ⇒ Uric acid (rectangular)
  - Alkaline urine pH:
    - ⇒ Triple phosphate (coffin lid appearance)

* MC is calcium oxalate
* Triple phosphate is k/a Struvite

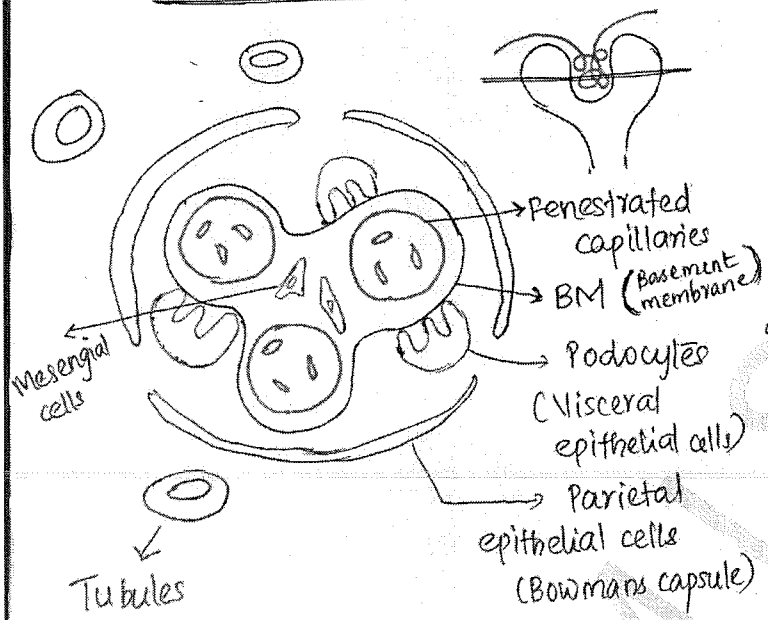
* Casts :
  - ⇒ Tubular in shape
  - ⇒ Deposit in DCT
  - ⇒ Types of cast - RBC casts, WBC casts, Hyaline cast
  - ⇒ RBC cast : In glomerulonephritis
    eg: PSGN
    RPGN
    HSP

⇒ WBC cast : 
Pyelonephritis
Tubulo interstitial nephritis

⇒ Hyaline cast : In proteinuria
eg : Nephrotic syndrome
Pregnancy
Dehydration

(no cells inside)

Structure of Glomerulus



MCQ
- Podocytes are visceral epithelial cells
- Bowmans capsule is parietal epithelial cells
- Basement membrane (BM) are cell type IV
- Mesengial cells are modified macrophages (MΦ) of glomerulus

PSGN - Post streptococcal glomerulo nephritis

Glomerulonephritis

* Inflammation of glomerulus
↓
Mechanism

Type II hyper sensitivity reaction
eg: Good Pasteur syndrome.

Type III hyper sensitivity reaction
eg: All glomerulo nephritis like
↓
- PSGN
- MGN
- MPGN
- IgA nephropathy

* Clinical features :

	Nephritic	Nephrotic syndrom
Proteinuria	< 3.5 g/day	> 3.5 g/day
Edema	Mild	Severe
Hypertension	++	+
Uremia	++	+
Hematuria	++	+
eg:	1) PSGN 2) RPGN 3) IgA nephropathy 4) MPGN	1) Minimal change disease 2) MGN 3) FSGS 4) IgA nephropat 5) MPGN

RPGN - Rapid progressive GN
MPGN - Membrano proliferative GN
MGN - Membranous GN
FSGS - Focal segmental glomerulo sclerosis.

mcqs

* MCC of nephritis in children
  PSGN
* MCC of nephrotic in children
  minimal change disease
* MCC nephritis in adult
  IgA nephropathy
* MCC nephrotic in adult.
  FSGS

Nephritic Syndrome

1) PSGN

* Post streptococcal glomerulo nephritis
* Etiology: Group A β ~~strept~~ hemolytic streptococcus (12,4,1) (strains)
* Age: 5-10yr
* C/F: Cause hematuria 7-21 days (1-3wks) after sore throat or pyoderma.
* Prognosis: Very good.
* Antibiotics have no role in prevention (because it is immune related)

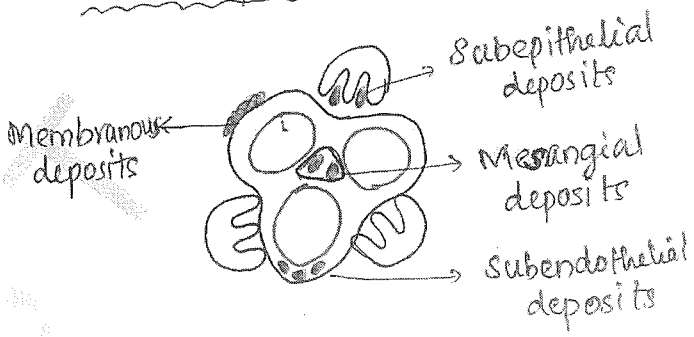
*

* on kidney biopsy:

⇓

LM	FM	EM
(Light microscopy)	(fluorescence microscopy)	(Electron microscopy)
↓	↓	↓
Endo & Exo capillary proliferation	Granular deposits	* Subepithelial deposits "humps"

Immune complex deposits



* eg: of subepithelial deposits:
  PSGN, MGN
* mesangial deposits:
  eg: IgA nephropathy
* Subendothelial deposits:
  eg: MPGN-I
* Membranous deposits:
  eg: MPGN-II

2) RPGN

* Rapidly progressive glomerular nephritis.
* It is rapidly progressive to acute renal failure within 4 wks
* Classification:
  1) Type I → Anti GBM Ab
  2) Type II → Immune complex
  3) Type III → Pauci immune.

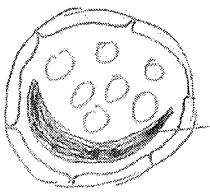
* Type I
  eg: Good Pasture syndrome

* Type II
  eg: MPGN, MGN, PSGN, IgA nephropathy.

MCQ
* Type III / Pauci immune due to small vessel vasculitis (inflammation)
  eg: Wegeners granulomatosis
  Microscopic polyangiitis
  Churg strauss syndrome.

* Morphology kidney → gross finding
  - Petechial hemorrhage spots
  k/a "Flea bitten kidney"

- Microscopic:

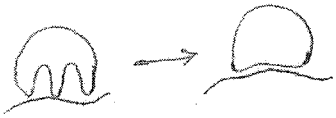


* Crescents – proliferation of
  Parietal epithelial cells + WBC + Fibrin.
* Crescents compresses glomerulus
* No: of crescents ∝ Poor prognosis

Nephrotic syndrome.

1) Minimal change disease (MCD)

* MC nephrotic in children
* Age: 5-15 yr
* C/F → No prior history (sudden proteinuria)
  ↓
  often selective proteinuria
* Excellent prognosis
  99% cases will resolve
* Kidney biopsy:
  - LM (light microscopy)
    ✓ No findings
  - Fluroscent microscopy
    ✓ No findings
  - Electron microscopy
    ↓
    Loss of foot process of podocytes. ⇒ Effacement of foot process.

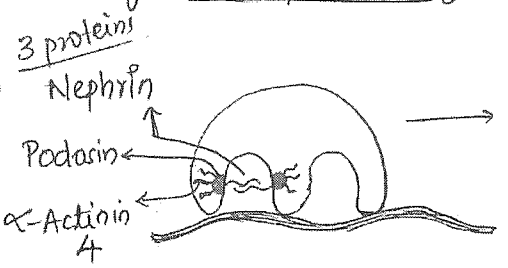


- Protein lost in Nephrotic syndrome:
  * 1st → Albumin, Transferrin, Vit D binding protein, thyroglobumin, protein C, S, Antithrombin-III ⇒ Selective proteinuria
  - Last → Globulin ⇒ Non-Selective proteinuria

2) FSGS

* Focal segmental glomerulosclerosis
* Etiology : Reflux nephropathy, iv drug users, sickle cell anemia, post renal ~~failure~~ surgery, HIV, congenital nephrotic syndrome.

Congenital nephrotic syndrome



Type 1 : Finnish type (good prognosis)

this proteins helps podocyte foot process to attach links with BM.

* Nephrin, podosin, α-actinin 4 (Absence of any 1 protein → Congenital NS)

Mutation of	Gene	Inh.	Chr.	Kid. ds
Nephrin	NPHS-1	AR	19	Minimal change disease
Podosin	NPHS-2	AR	1	FSGS

* MCQ
NPHS-1 Type 1 → MC, good prognosis, Kla Finnish type

(Inheritance - Inh, AR - Autosomal recessive, Kid. ds - Kidney disease)

* Mutation of NPHS-1 → No nephrin.
* Steroid resistant nephrotic syndrome.

3) Alports syndrome

* X-linked dominant disease.
* Also Kla hereditary nephritis
* Cause → Defective collagen type IV (Basement membrane defect)
* collagen in basement membrane.

* C/F in :

Alport's triad
- Kidney → Proteinuria, Hematuria
- Eye → Anterior lenticonus
- Ear → Sensory neural hearing loss

* Kidney biopsy :
  - LM (light microscopy)
    - Thin GBM (glomerular basement membrane)
    - Foam cells (Lipid laden macrophage)
  - Fluroscent microscopy
    No immune complex deposits
  - Electron microscopy :
    Spliting of GBM
    ↓
    "Basket weave appearance"

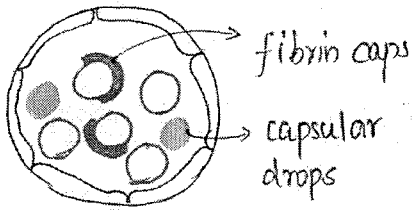
Secondary cause of Nephrotic syndrom

Diabetic Nephropathy

* Screening : Microalbuminuria
  (small amount of albumin in urine)
  ↓
  - 30 - 300 mg / 24 hrs (Best)
  - 30 - 300 mg/gm of creatinine (MC)
    (spot urine sample)
    (Albumin - creatinine ratio: ACR is done here)

* Microalbuminuria is first finding in Kidney involvement in Diabetes mellitus
* 30-300 mg/24 hr needs 24 hr urine samples which is difficult so not used)

* Kidney biopsy: (MC finding)
  1) Diffuse glomerulonephropathy
     - Diffuse GBM thickening
  2) Nodular glomerulosclerosis
     - Collagen deposition (sclerosis)



Fibrin caps + Capsular drops } Kimmelstein Wilson lesion.

- Fibrin caps – fibrin deposits around capillaries like a cap
- Capsular drops – collagen deposit in capsule.

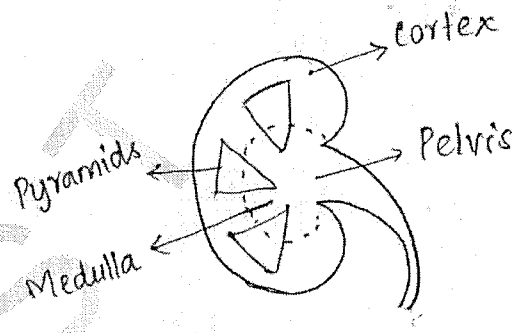
  - Most specific in Diabetes mellitus is Kimmelstein Wilson lesion

3) Glycogen deposition in PCT k/a Armani Ebstein crystals.

Disease of Tubules & Interstitium

1) Tubulo interstitial nephritis
2) Pyelonephritis

* Tubulo interstitial nephritis
  Inflam. of tubules + interstitium
* Pyelonephritis:
  Inflam. of tubules + interstitium + pelvis



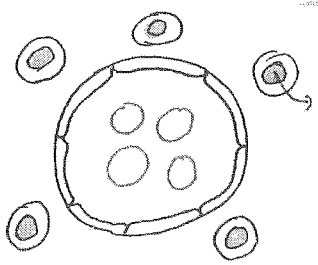
Tubulo interstitial nephritis

* C/F
  - GFR : Normal
  - Concentration of urine ↓ ses.
  - Salt wasting nephropathy (↑ NaCl in the urine)

Pyelonephritis

* Types:
  1) Acute
  2) Chronic
* Inflammation of tubules + interstitium + pelvis.
* UTI ⇒ E.coli > Proteus

	Acute	Chronic
Etiology:	UTI + Ascending infection	UTI + Reflex nephropathy or Obstractive nephropathy.
Gross:	Cortical abscess on kidney	Granular contracted kidney.
M/e : (Microscopy)	Neutrophil infiltration + Interstitial edema	• Thyroidization of tubules. • Hyaline arteriosclerosis • Periglomerular fibrosis • Late; FSGS
Complication:	3P - Papillary necrosis - Pyonephrosis - Perinephric abscess	- Xanthogranulomatous pyelonephritis (yellowish plaque on cortical kidney) • Proteus > E.coli (Etiology)



~~Thyroid kit~~ Colloid like substance inside tubules
↓
Thyroidization of tubules

Renal tumors

* Benign → Renal angioma
  Angio lipoma
  Oncocytoma
* Malignant → Renal cell carcinoma

Renal cell carcinoma

* Etiology :
  - Smoking (Most common)
  - ↑ Estrogen exposure (ocp use)
  - Asbestosis
  - Benzene dyes
* ↑ risk of RCC:
  - Chronic Kidney Disease
  - ESRD (End stage renal disease)
  - Prolonged dialysis
* Classification:

Clear cell Ca (80%)
- Origin: PCT
- Gene mutation VHL gene
- Focal lesion (one)
- m/e: Vacuole - lipids, glycogen

Papillary cell Ca (10-15%)
- 20CT
- MET gene
- Multiple lesion
- m/e: finger like projection filled by tumour cells

* Other types: (of RCC)
  - Chromophobic
  - Belini duct Ca.

* C/F: (RCC)
  - Painless hematuria (most consistent)
  - Loin pain
  - Abdominal mass

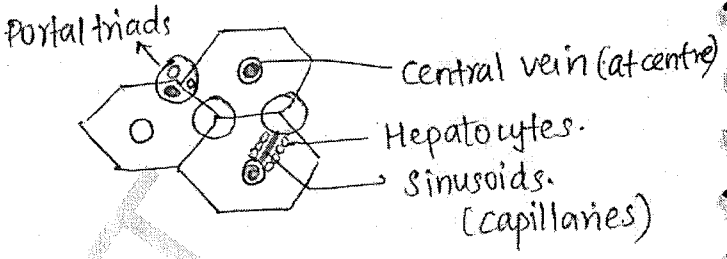
* Paraneoplastic syndrome of RCC:
  - Hypercalcemia & Cushing's syndrome is rare in RCC
  - Hypertension, ↑ESR
  - ↑ Erythropoesis → Polycythemia
  - Amyloidosis
  - Eosinophilia
  - Stauffer's syndrome (Hepatic dysfunction in RCC)

LIVER & ITS DISEASES

* Microscopy of liver:
  - Lobular structure (hexagonal)

* Weight : 1.4 – 1.6 kg

* Blood supply:
  1) Portal vein (70-80%)
  2) Hepatic artery (20-30%)



PV
HA
BD
} Portal triads

* Maximum oxygenated blood around portal triad k/a Zone I.
* Least oxygenated – around central vein k/a Zone III
* B/w Zone I & III → Zone II
* Zone I : Periportal (most oxygenated)
  Zone II : Mid zonal
  Zone III : Centrilobular. (b/w lobules)
* Blood flow → from portal triad towards central vein.
* MCC of necrosis → toxins than O_2 ↓

Necrosis of liver

1) Zonal necrosis:

Z I	Z II	Z III
• Periportal	• Mid	• Centrilobular
↓	↓	↓
- Phosphorus poison	Yellow fever	- CCl_4 poison
- Eclampsia (PE)		- Chloroform poison
		- Cardiogenic shock (3C)

2) Confluent necrosis:

* Involves ≥ 2 zones
* Halothane poison, Acetaminophen poison

3) Bridging necrosis:

* Zone I to II to III spread
  eg: Viral hepatitis

Apoptosis of liver

MCQ
* Counsilman body indicates apoptosis
* They are apoptotic hepatocyte

Congestion of liver

* Accumulation of blood.
* Zone III → less O_2 blood → so most affected.
  (Happens in ~~cong~~ block ~~aft~~ somewhere ~~in~~ after zone III → causes congestion)
* Block → Zone I is pushing blood towards zone III → but blood pooling around zone III due to block in front → so zone III appear red → zone I is still pushing blood towards zone III so it will undergo fibrosis & appear white → Thus in chronic stage alternate red & white appearance

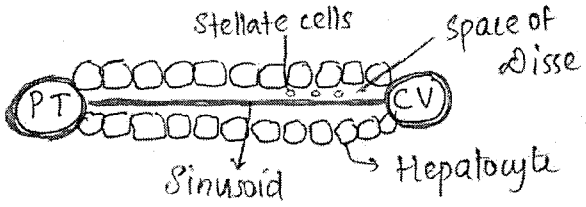
Acute	Chronic
• Shows centilobular fatty change	(Right heart failure) • Sinusoidal dilatn around central vein (red) • Periportal fibrosis (white) Nut meg liver

Cirrhosis of liver

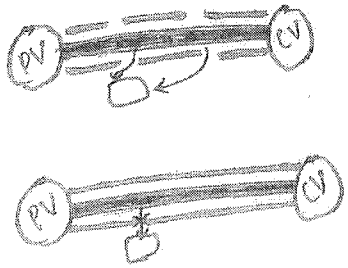
* Etiology:
  - Alcoholic liver disease (ALD)
  - Non alcoholic fatty liver disease (NAFLD)
  - Hepatitis B, C
  - Biliary: PBC, SBC
    PSC (Sclerosing cholangitis)

- Metabolic – (Chronic etiology)
  - Wilson's disease
  - Hemochromatosis
  - α_1 antitrypsin deficiency

* Pathophysiology of cirrhosis:



- Space of Disse → b/w sinusoid and hepatocytes
- It contains Stellate cells (Ito cells) which are myofibroblasts
- Sinusoids have Kuffer cell. (they are MΦ)
- In cirrhosis → chronic etiology → stimulates Kuffer cells → releases ET-1 (endothelin 1) → stimulate stellate cells → they release PDGF & TGF-β → deposits collagen in extracellular matrix
- Normal collagen around sinusoid is collagen type IV (not continous)
- In cirrhosis → becomes collagen type I & III which is continous



- In cirrhosis → sinusoids converts to capillary k/a capillarisation of sinusoids
- Later on it leads to bridging fibrosis.

* Morphology in cirrhosis
  - = Gross → liver shrinks in size because of fibrosis, nodules on surface (Nodular cirrhosis)

Size
- < 3mm → Micronodular cirrhosis
- > 3 mm → Macronodular cirrhosis

* On microscopy (m/e)
  - Hepatocyte destruction
  - Deposition of collagen (ECM - extracellular matrix)
  - Capillarization of sinusoids. (Hall mark)

Hepatitis

* It can be
  - → Bacterial
  - → Parasitic
  - → Viral
* MC is Viral → by Hepatotropic virus (Hepatitis A → E)
* Cytomegallo virus, Ebstein barr virus (EBV), Parvo, Rubella
  - ↓
  - Other ~~RNA~~ viruses causing hepatitis

* Hepatitis A → E : All are ~~viral~~ RNA virus except HBV → DNA virus

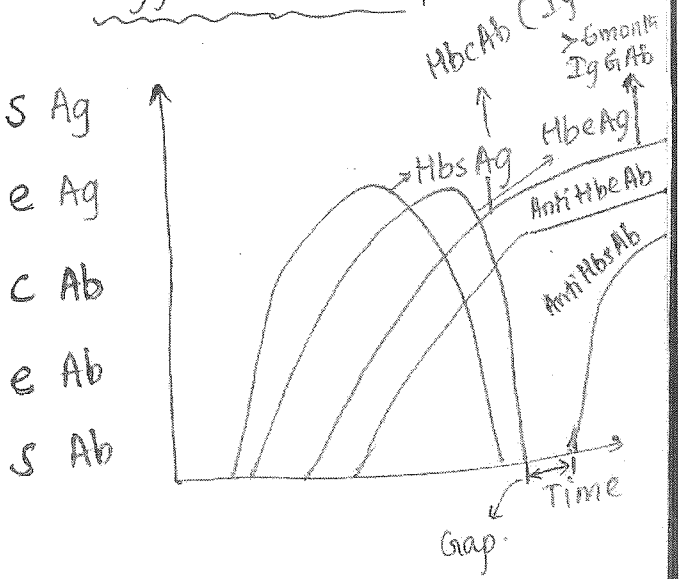
Hepatitis A

* Incubation period : 4-6 wks
* Mode of transmission : Fecooral > Percutaneous
* Prognosis - Good
* Low risk of chronic cirrhosis, hepatocellular carcinoma.
* Diagnosis :
  - HAV in stool
  - Anti HAV Ab (IgM)

Hepatitis B

* Incubation period : 4-26 wks
* MOT : Horizontal (Blood products)
  Sexual
  Vertical (mother to child)
* MC in India → Horizontal
* Antigen in HBV :
  - Surface Ag (HbsAg)
  - Core Ag (HbcAg)
  - Envelope Ag (HbeAg)
* In core Ag → 2 parts → C Ag & pre C Ag
* C Ag codes for ~~core Ag~~ "c" Ag
* pre C & C Ag → codes for ~~envelop Ag~~ "e" Ag.
* ~~Core~~ "c" Ag never appears in patients serum
* ~~Envelope~~ "e" Ag is the infective Ag appears in blood.
* Patient produce Ab against both "c" & "e" Ag.
* DNA virus → ds ~~circular~~ incomplete circular DNA
* DNA has DNA polymerase activity
* DNA has gene HBX
* HBX gene mutation → ↑ risk of hepatocellular carcinoma.

Serology of acute Hep. B



* Acute Hep. B shows HbsAg, HbeAg, HbcAb
* Chronic Hep B → HbsAg for 6 months, IgG HbcAb

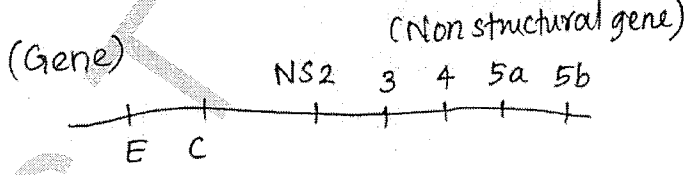
* Acute Hep.B
  - HbsAg ⊕
  - IgM HbcAb ⊕
  - HbeAg ⊕ (infective)
* Chronic Hep.B
  - HbsAg > 6 months
  - IgG Hbc Ab ⊕
  - HbeAg ⊕ (infective)
* Recovery:
  → HbsAg ⊖
* Recent recovery
  - IgM HbcAb ⊕
* Past (Remote) recovery
  - IgG Hbc Ab ⊕
* Vaccination:
  → Anti Hbs Ab ⊕
  → Protective level ≥ 10 mIU/ml
  → If less than this level then give booster dose.
* Window period:
  - HbsAg ⊖
  - Anti Hbs Ab ⊖
  - IgM Hbc Ab ⊕
  - HBV DNA ⊕

(If IgM Hbc Ab ⊕ → Core window period)

Hepatitis C

* Incubation period 4-40 wks
* MOT: Horizontal (most common) → Blood products
  Sexual
  Vertical (mother to child)
* Risk of chronicity in HBV
  10-20% MLA
* Risk of chronicity in HCV
  80%

Structure of HCV



* NS 5b changes structure frequently
* So Ab cannot neutralize Ag.
* Thus risk of chronicity is 80%.

* Diagnosis → Anti HCV Ab test
  → HCV RNA level (Best)

Hepatitis δ

* δ < Dependent virus (on HBV)
  Defective virus (lacks surface Ag)
* Types of infection:
  - With HBV → k/a co-infection
  - After HBV → k/a super infection → High risk of fulminant hepatitis (MCQ)

* Fulminant hepatitis → Acute liver failure occuring within 6 wks of infection

Hepatitis E

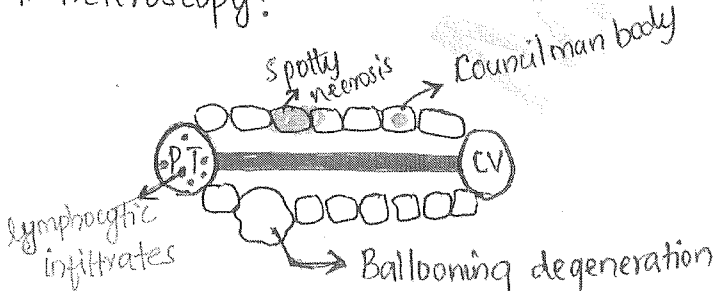
* Incubation period 4-6 wks
* MOT : Fecooral
* Prognosis – Good (except in pregnancy)
  ↓
  ↑ risk of fulminant hepatitis

MIB

* HEV is most common sporadic hepatitis in India.
  (Sporadic → some people in some area infected)

* Morphology:
  - Gross → Initialy swollen
    Later shrinks

* Microscopy:



1) * Lymphocytic infiltrates / mononuclear cells in portal triad.
2) * Ballooning degeneration of hepatocyte
3) * Kuffer cell hyperplasia
4 * Spotty necrosis
5 * Councilman body.

⇒ In late stages + bridging necrosis (from portal triad to central vein)
↓
Loss of liver architecture.

Chronic Hep B

* HBV > 6 months
* Normally hepatocytes stains + granular & pink staining of cytoplasm due to glycogen.
* HBV > 6 months consumes all glycogen → stains pale smooth & pink in colour
  ↓
  k/a ground glass appearance
  Hallmark of chronic Hep B
* Then bridging fibrosis → progress to cirrhosis.

Alcoholic liver disease (ALD)

* Dose > 60 g/day for 10-15 yrs (Alcohol) → Alcoholic hepatitis
* > 160 g/day for 10-15 yrs
  ↳ Alcoholic cirrhosis
* Only 20% of alcoholics to alcoholic cirrhosis.

* ↑ risk

MCQ
- Concurrent Hep B, C infection
- Concurrent Iron overload
- Female > Male.

Stages

1) Fatty liver (steatosis) (Completely reversible)
↓
accumulation of fat globules inside hepatocytes

Microvesicular steatosis

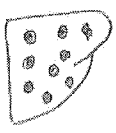
Macrovesicular steatosis

2) Steatohepatitis
   i) Ballooning degeneration of hepatocytes
   ii) Neutrophil infiltration in portal triads.

(Alcoholic : Neutrophil
Viral Hep : Lymphocyte)

   iii) Malori hyaline / malori denk body (pink coloured inclusion inside hepatocyte)

3) Alcoholic cirrhosis:
Gross morphology is a shrunken liver with many globules / nodules on surface
↓
Hob Nail liver / Lennac cirrhosis



(microscopy)
* m/e → perisinusoidal fibrosis
(fibrosis around the sinusoid)
↓
causes portal hypertension in liver cirrhosis.

MCQ

Differential diagnosis of Malori hyaline body

WAIT IN PHC

W - Wilson's disease
A - Alcoholism
I - Indian Childhood Cirhosis
T - α_1 Anti-trypsin deficiency
P - Primary biliary cirrhosis
HC - Hepato cellular carcinoma.

Non-Alcoholic fatty liver disease (NAFLD)

* 2nd Mcc of fatty liver (1st - Alcohol)
* Etiology : Consumes alcohol < 20 g/wk.
  - Hyperlipidemia
  - Metabolic syndrome (syndrome X)
* ↑ risk :
  - Obese (Central)
  - Diabetes

Stages

1) Steatosis (fatty liver)
2) Steatohepatitis (NASH – Non Alcoholic Steato Hepatitis)

* MCC of death in NAFLD is Cardiovascular complications.

Biliary diseases

* PBC - Primary biliary cirrhosis
* SBC - Secondary biliary cirrhosis
* PSC - Primary sclerosing cholangitis (MCQ)

(of above 3)

c/f : Obstructive Hepa Jaundice (MCQ)
↓
Clay stool, pruritus,
Lab: ↑ conjugated bilirubin, ↑ ALP, ↑ ggt (gamma glutamyl transferase)

PBC

* Involves intrahepatic bile duct
* Mostly autoimmune
* ♂ : ♀ = 1 : 6
* Diagnosis ⇒ Anti mitochondrial antibody (AMA)
* Biopsy - Florid duct lesions, lymphocyte infiltration in bile ducts

SBC

* Extrahepatic bile duct
* ⁂ 2° to bilestones, bile infections, carcinoma pancreas (head)
* ♂ : ♀ = 1:1
* No Ab.
* Cholestasis,

PSC

* Both intra & extrahepatic BD.
* Autoimmune
* ♂ : ♀ = ~~1:6~~ 2:1
* Atypical p-ANCA.
* Onion skin appearance

⇒ Associated with inflammatory bowel disease : PSC
⇒ Associated with HCC, bile duct Ca

PSC > PBC > SBC

⇒ Malori hyaline body (eosinophilic inclusion within hepatocyte)

PBC

Tumor like lesion in liver

1) Peliosis hepatitis - Sinusoidal dilatation
2) Von Mayerburg complex - Bile duct hamartoma

Tumors

* MC : Metastasis (lungs) > HCC (malignant)
* Benign → Hemangioma (MC)
  H. adenoma.

HCC

* Hepatocellular carcinoma
* Etiology:
  - ALD (MC) (Alcoholic liver disease)
  - NASH (Non Alcoholic Steato Hepatitis)
  - Hep C, B
  - Aflotoxin
  - Metabolic → Wilsons, α-AT deficiency, hemochromatosis
  - Biliary diseases
    PSC > PSBC > PBC
  - Congenital tyrosenemia
* MC type is adenocarcinoma (tumor of gland)
* Gene mutation → β catenin (high risk)
* Tumor marker → α-feto protein
* Stain → Glypican

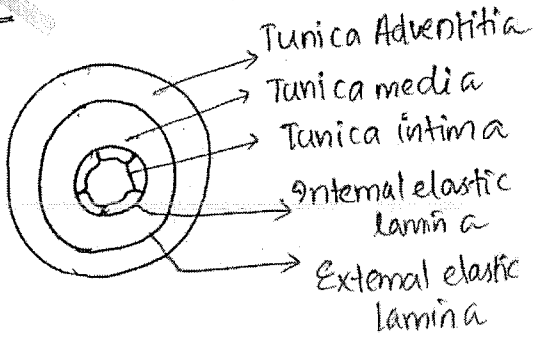
	HCC	HCC-fibro lamellar variant
♂:♀	3:1	1:1
Age	70-80yr	20-30yr
α-feto protein	↑↑↑	Normal
Prognosis	Poor	Good

⇒ Neurotensin is tumor marker for HCC-fibrolamellar variant.

HCC | HCC-fibro lamellar variant.
♂:♀ | 3:1 | 1:1
Age | 70-80yr | 20-30y
α-feto protein | ↑↑↑ | Normal

VESSELS & DISORDERS

Artery

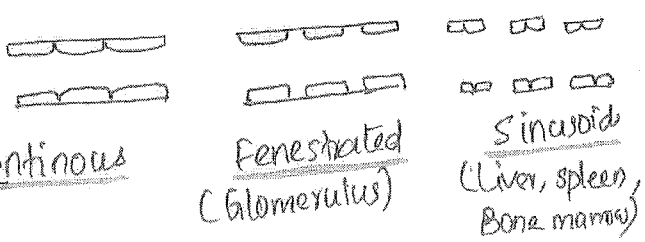


* Tunia media has smooth muscles which provides elasticity to artery

Veins

* 3 layers are not well developed
* Tunica media under developed
* Valves present.

Capillary

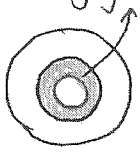


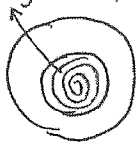
Vascular sclerosis

* Thickening of vessel
* Types

1) Arteriosclerosis

	Fibroelastic	Hyperplastic
Etiology:	Benign HTN	Malignant HTN (SBP > 180 mmHg)
Morpho:	Layer of fibrin + proteoglycan	Collagen deposit
	(smooth pink)	Onion skin appearance





2) Monkeburg medial calcific sclerosis:

Calcific deposition in tunica media → dystrophic

① calcification in T. media → ↓ elasticity → Because of calcification - can palpate arteries
② like bones → Lumen remains
③ normal.

↓

Actually senile change (80-90 yrs) ♂ : ♀ = 3:1

3) Atherosclerosis

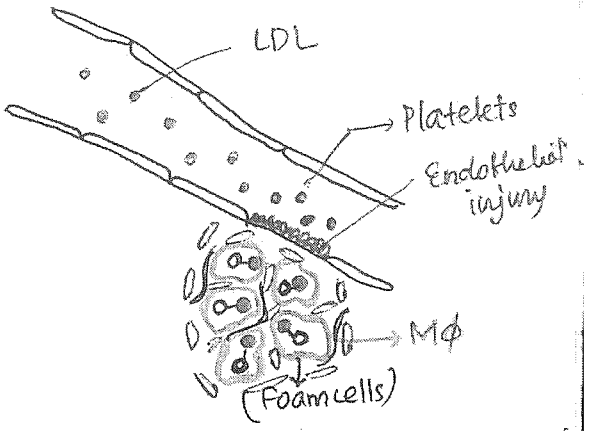
MCQ

- Starts with endothelial injury

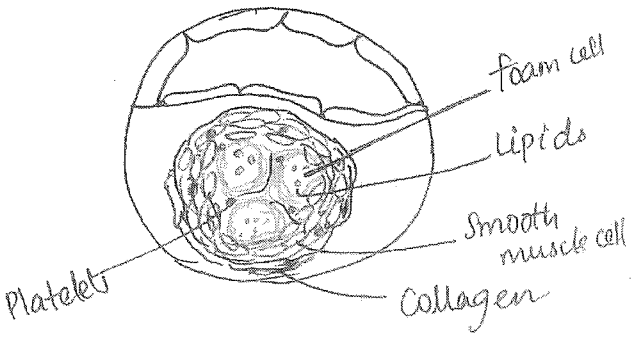
↓

- Smoking
- HTN
- Diabetes mellitus
- Hyperlipidemia

- Theory ⇒ Response to injury hypothesis.
- Pathophysiology:



* LDL → LDL-oxidised (LDL-O) → free radical
→ engulfed by macrophages (Mϕ)
→ forms foam cells → foam cells + platelets → PDGF & TGF-β → deposits in the extracellular matrix (smooth muscle cells + collagen)



Fibroatheroma

(Lipid core, fibrous cap)

- Foam cells + Lipids + Platelets + Collagen
~~Lipid~~ + Smooth muscle cell
↳ Fibroatheroma

* Single foam cells – Fatty dots
* Multiple foam cells – Fatty streak
* Fibrous cap
  - ↳ Thick : stable
  - ↳ Thin : Vulnerable to rupture MCQ

* Complications of fibroatheroma
  1) Rupture of plaque
  2) Thrombosis
  3) Embolism
  4) Aneurysm
  5) Dissection (b/w layers of vessel)

Aneurysm

* Dilatation of vessel wall
* Types → 2
  - Fusiform (along axis of vessel)
  - Saccular (along lateral axis)

* Etiology
  - MC → Atherosclerosis
  - Syphilis (Ascending aorta)
  - Takayasu's ~~aorta~~ arteritis (Arch)
  - Mycotic aneurysm
  - Cystic medial necrosis (Asc. aorta)
    eg: Marfans
    Ehler Danlos syndrome

(Pyogenic infection)

Mycotic aneurysm (Not fungus)

↓

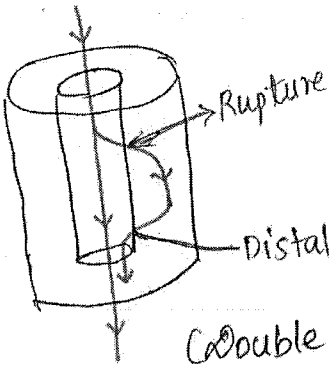
- Staph aureus (Ascending aorta)
- Salmonella (Abdominal aorta)

MCQ

* MC site : Abdominal Aorta (b/w renal arteries & bifurcation of iliac arteries)

~~Aorta~~ Dissection

* Rupture of internal elastic lamina so that blood lies in the tunica media.
* Etiology:
  - Hypertension (MC)
  - Atherosclerosis



(Double barrel vessels)

↓

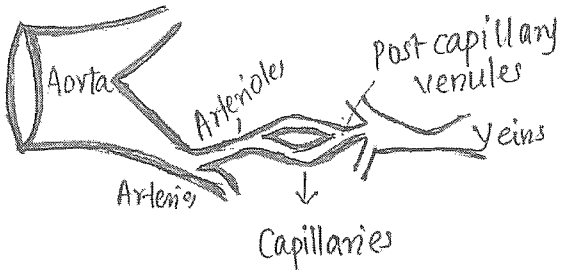
(Two flow channels in same vessel)

MCQ

* Double barrel vessel is a complication of dissection

Vasculitis

* Inflammation of vessels.



Types of vasculitis

Large vessel V

↓

Aorta & its major branches

- Subclavian arteries
- Temporal arteries

↓

eg: • Giant cell arteritis
• Takayasu arteritis (GT)

Medium vessel V

↓

Arteries

↓

eg: • Poly arteritis Nodosa (PAN)
• Kawasaki disease (PK)

Small vessel vasculitis

(due to) Immune complex deposition

↓

- HSP
- SLE
- Cryoglobinemia

(due to) Pauci immune

↓

- Wegeners granulomatosis
- Microscopic polyangitis
- Churg strauss syndrome

⇒ Small vessels involves: capillaries + post capi. venules

Large vessel vasculitis

1) Giant cell arteritis:

* C/F are
  - Headache
  - Blurring of vision
  - Pain while mastication [Jaw claudication] (chewing)
* Diagnosis
  - Biopsy → from temporal artery
  - m/c → Vasculitis + Giant cell (multinucleated cell)

2) Takayasu arteritis:

* Involvement of subclavian artery.
* C/F: Pulse less disease (↓ pulse at radial artery)
  - Pain in hand while working [Hand claudication]
  - Arch of Aorta aneurysm.

Medium vessel vasculitis

1) PAN

* Poly Arteritis Nodosa
* Ag + Ab complex deposition
* Usually Ab is against HbsAg
* So usually immune complex is HbsAg + Anti HbsAb
* Vessels involved → Renal artery (MC)
  RA ≥ GIT > Limbs
  ↓
* Causes renal hypertension
* Pulmonary artery is not involved (MCQ)

2) Kawasaki disease:

* ≥ 5 days of fever + CREAM
  - C – Conjunctivitis
  - R – Rash
  - E – Edema
  - A – Adenopathy
  - M – Mucosal involvement (Strawberry tongue)

Small vessel vasculitis

1) HSP

* Henoch Scholein Purpura
* MCC of vasculitis in children
* C/F : Glomerulonephritis + Arthritis + Purpura (palpable)
* Immune complex deposition
* C/F :
  - Glomerulonephritis (IgA nephropathy)
  - Arthritis
  - Purpura (palpable)
  - Mesentric Ischemia (Abdominal pain)

2) Pauci immune

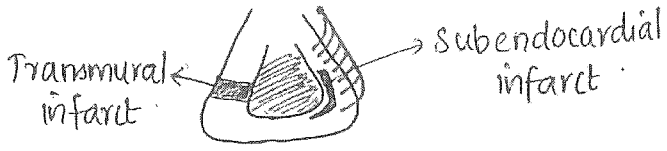
	Churg Straus syndrome	Wegeners granulomatosis	Microscopic polyangitis
Asthma	+	–	–
Granuloma	+	+	–
Glomerulo nephritis	+	+	+

* Due to ANCA mediated.
* ANCA : Anti Neutrophilic Cytoplasmic Ab.

ANCA
- cytoplasmic → C-ANCA → • Wegeners granulomatosis
- Perinuclear → P-ANCA →
  - Churg Straus syndrome
  - Microscopic polyangitis
  - Ulcerative colitis

HEART

Myocardial Infarction:



Transmural	Subendocardial
↓	↓
• Focal	• Multicentric
• Complete occlusion of arteries	• Incomplete occlusion or Cardiogenic shock.

Diagnosis

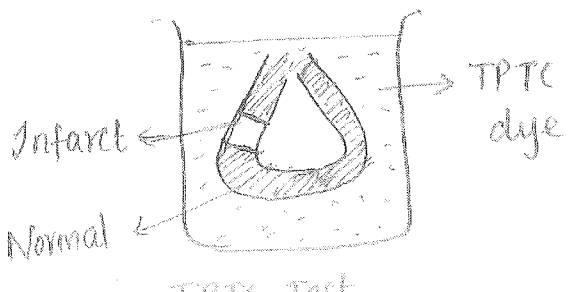
* Diagnose MI in dead person
* Heart is put in a beaker filled with a dye ↓

mca

Triphenyl tetrazolium chloride (TPTC)

* If LDH +nt → stains red
* If LDH −nt → white colour

(LDH is present inside muscle normally. LDH is absent in the infacted area)



TPTC Test

Time elapsed after MI

* Reversible injury → < 30 min
* Irreversible injury → > 30 min

Changes in heart in MI

Time	Gross	LM	EM
< 30 min	—	—	• Mitochondrial swelling • Relaxation of myofibrils
30 min to 4 hrs	—	Waviness of myofibrils	• Large Amorphous density • Myelin figures
Day 1	Red infarct	• Necrosis starts • Neutrophil appears	—
Day 1 - 3	Red to Yellow (bilirubin)	Necrosis ++ Neutrophils - Brisk (max.)	—
Day 3 - 7	Yellow	MΦ ++ (Macrophages)	—
Day 7 - 14	Red	Granulation tissue (Blood vessel + fibroblast)	—
> Day 14	Silvery white	Collagen appear	—

changes in heart in MI

Time	Gross	Light microscope	Electron microscope.
< 30 min	—	—	• Mitochondrial swelling • Relaxation of myofibrils.
~~30-40~~ 30 min – 4 hrs.	—	Waviness of myofibrils	• Large amorphous density • Myelin figures.
Day 1	Red infarct	• Necrosis starts • Neutrophil appears	—
Day 1-3	Red - Yellow (bilirubin)	• Necrosis +++ • Neutrophils - Brisk (maximum)	—
Day 3-7	• Yellow	• Mϕ (+++) (macrophages)	
Day 7-14	Red	• Granulation tissue (Blood vessel + Fibroblast)	—
> Day 14	Silvery white	Collagen appear	—

MI

* Coagulative necrosis (Contraction Band necrosis)

Vegetations

* Growth on the valve.
* Seen in –
  a) Rheumatic carditis
  b) Non bacterial thrombotic endocarditis (NBTE)
  c) Libman sach endocarditis
  d) Infective endocarditis

* Libman sach endocarditis is seen in SLE.

Rheumatic carditis

* Etiology : Grp A β & hemolytic streptococci (1,3,5,18) (strains)
  (PSGN → 12,4,1)
* Age : 5–15 yr (PSGN : 5–10 yr)
* C/F : 7–21 days after sore throat (PSGN – Also pyoderma)
* Antibiotics can prevent rheumatic carditis (PSGN – No role)
* HSN : Type II (Hypersensitivity reaction) (PSGN – Type III)

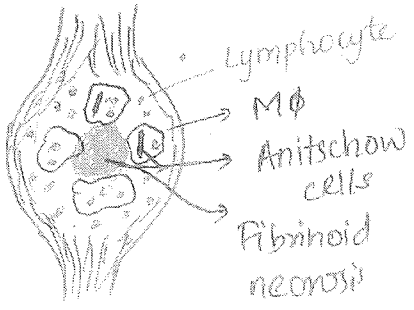
* Pathogenesis :
  Ab produced against "M" protein of streptococci
  Cross reacts with
  - Myocardium
  - Valves
  - Skin
  - Joints

* This type of cross reaction is k/a Molecular mimicry.

Morphology

* Causes pancarditis (involves all 3 layers of heart)
  ↓
  (1) Pericarditis (pericardium involved & it sticks to myocardium
  ↓
  Bread & Butter pericarditis (Adhesive pericarditis)

  (2) Myocardium
  ↓
  Aschoff bodies (inflammatory nodule)
  ↓
  Have MΦ, at centre has fibrinoid necrosis, long chromatin – Anitschow cells, lymphocytes.



Anitschow cell → Caterpillar like chromatin inclusions.

3) Endocardium

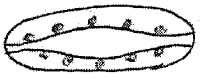
- Wall → Thickened patch > Mc cullum patch
- Valve → Vegetation (MC → Mitral valve)

MCQ

*

Chronic carditis

* In acute carditis it has multiple nodules around valve



* In chronic carditis → ends has large nodules → slit like opening in valve → k/a fish mouth appearance.

Infective Endocarditis

* Inflam. of endocardium

Types

MCQ

Acute

Valve: - Native

Etiology:- Staph. aureus

Subacute

- Prosthetic
- Streptococcus viridans

MCQ

* Special cases:
  - i.v users → S. aureus > pseudomonas > Candida
  - i.v catheter → Staphylococcus epidermidis (Coagulase negative staphylococcus ↳ CONS)
  - Dental carries → Streptococcus mutans

⇒ If nothing mentioned, MCC Staph. aureus

Vegetations in

	Rheumatic carditis	NBTE	Libman Sach	IE
Types:	Small, warty, friable		Medium to large	Large, bulky, friable
Site:	Lines of closure of valve		• under surface or • Mural endocardium	On the valve cusp
Sterile: (no growth in culture media)	✓	✓	✓	* Not sterile (will grow)
	✗	✗	✗	* Destructive
	Non destructive			

*

⇒ Maximum embolism caused by Infective Endocarditis

Tumor of Vessels

Benign (-oma)	Border line	Malignant (-sarcoma)
• Hemangioma • Lymphangioma	Kaposi sarcoma	• Hemangio sarcoma • Lymphangio sarcoma

Kaposi sarcoma (MCQ)

* MC tumor in HIV infected patients
* Causative : HHV-8 or KSV (Kaposi sarcoma virus)
* Types :

Types
- Classical → Old age → Skin
- Endemic → Africans
- Epidemic → HIV pts
- Sporadic → Post organ transplant

Endemic, Epidemic, Sporadic → Lymphnodes & Visceral organs (site)

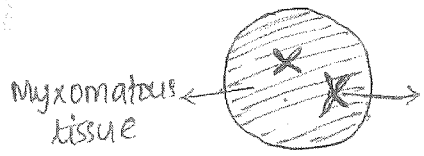
* Rx :- Surgical excision + Anti viral therapy + Retroviral therapy
* Kaposi sarcoma is purely vascular tumor.

Tumors of Heart

* MC → Metastasis
* MC 1° tumor → Myxoma
* » in children → Rhabdomyoma

Myxoma

* Morphology → Gel like mass in the left atrium
* C/F → Ball valve obstruction (blood flow obstruction)
* m/c → Pinkish myxomatous tissue with typical butterfly shaped cell – k/a stellate cell / lepedic cell.



* Recent : PRKAR-α gene mutation

Carney's complex → Myxoma, Endocrinopathy, Spotty pigmentation

* Carney's triad is seen in GIST (gastro intestinal stromal tumour)
  - GIST
  - Paraganglioma
  - Pulmonary chondroma

Protein loss in Nephrotic synd.

1st protein: Albumin

* Then Transferin, Vit D binding protein, thyroglobulin, protein C,S, Antithrombin - III

causes selective proteinuria.

* Last: Globulin
  ↓
  Non selective proteinuria.

* Protein C,S, Antithrombin III loss
  ↳ causes thrombosis.

* Globulins loss in urine causes
  ↳ increase infection

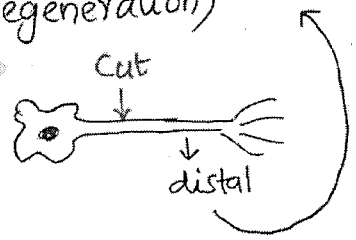
CNS injury

Response to CNS injury:

1) Nerves → Most prone cells to ischemia

* Acute injury (Irreversible injury)
  ↓ (pink colour)
  Red Neurons

* Subacute injury:
  Wallerian degeneration.
  (when a nerve is cut, distal segment undergoes Wallerian degeneration)



2) Glial cells (response k/a Gliosis)

(i) ~~Glial cell~~ Microglial cells:

- Accumulate lipids
  Gitter cells
- Accumulate iron
  Siderophage

(ii) Macroglial cells:

a) Astrocytes – Star shaped
   ↓
   - Makes BBB
   - Metabolize toxins
   - Response to CNS injury
     – Rosenthal fibers

CNS

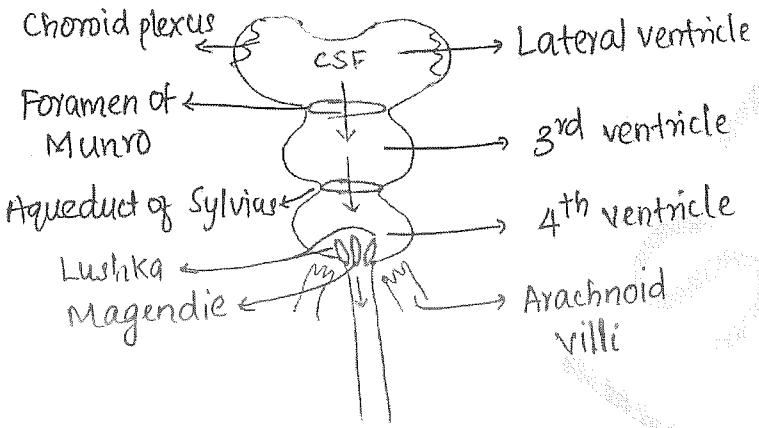
Cells

- Nerves
- Supporting cells (Glial cells)
  - Microglial → Modified MΦ in CNS
  - Macroglial →
    - Astrocytes
    - Oligodendrocyte
    - Ependymal cells.

- Rosenthal fibers are eosinophilic inclusion inside astrocyte (pink coloured)
↓
Also seen in Astrocytoma, Alexanders disease.

Hydrocephalus

* Dilation of Ventricles



* Causes:

1) Choroid plexus tumor:
eg: Papilloma

2) Obstructive hydrocephalus
MCC → Aqueduct Sylvius stenosis

3) ↓ absorption by Arachnoid villi
- TB
- Bacterial infection.

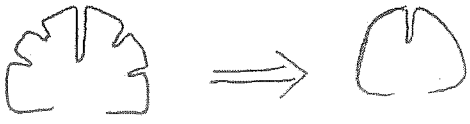
4) Cortical atrophy
- Alzheimers disease
k/a Hydrocephalus ex-vacuo.

Congenital Anomalies of CNS

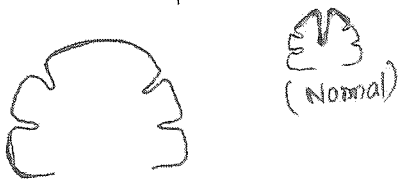
a) Forebrain anomaly
b) Neural tube defect
c) Posterior fossa anomaly.

Forebrain Anomaly

1) Micro encephaly (small brain)
2) Megalencephaly (large brain)
3) Lissencephaly (loss of gyri and sulcus)
↓
Smooth outline contour

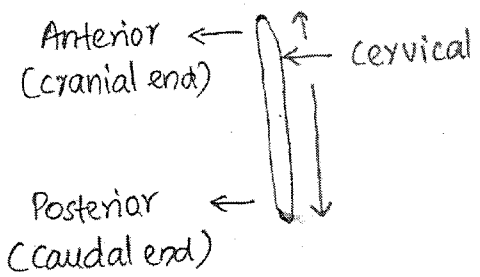


4) Holoprosencephaly:
Incomplete seperation of cerebral hemisphere.



5) Agenesis of corpus callosum:
Commissural (connecting) fibres b/w cerebral hemisphere
↓
On MRI: Bat wing deformity (no corpus callosum)

Neural tube defect



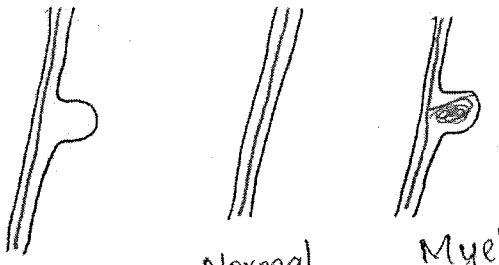
* Fusion of neural tube
  - starts → 21st day
  - completed → 28th day
* Fusion starts at cervical part
* Folic acid → to prevent it.
* Least common site of defect
  Cervical
* MC site of defect
  Caudal
* Folic acid is given to prevent NTD in periconceptional period (0.5 mg dose)

1) Spina bifida

* Failure of fusion of neural tube

Types
- Occulta → Small vertebral defect
- Aperta → Large vertebral defect.

2) Meningocele / ~~meningo~~ Myelomeningocele.



Meningocele	Normal	Myelo meningocele
(Translucent swelling)		(Opaque swelling)
↓		↓
CSF inside swelling		Nerves & CSF in swelling

* Swelling at back

3) Syrinx:

* Fluid filled cyst inside the spinal cord.
* MC site is Cervical

4) Anencephaly

* Failure of formation of cranial end of neural tube

Posterior fossa anomaly

1) Arnold Chiari malformation
2) Dandy Walker syndrome.

Arnold Chiari malformation

- C - Cerebellar, pons, medulla

H - Herniation

↓ foramen magnum

S.C

- Post. fossa volume ↓

(SC - Spinal cord)

Dandy Walker syndrome

- D - Dilatation of 4th ventricle

(A B C D
1 2 3 4)

- Cerebellar hypoplasia (large cyst in the post. fossa) (pressing)
- Post. fossa volume ↓

- Very poor prognosis

2) TB

* Releases heavy basal exudates
↓
Block arachnoid villi
↓
Hydrocephalus (dilated ventricles)

* On m/c shows granuloma
* Healed granuloma is k/a Tuberculoma.

CNS infection.

1) HIV:

* Systemic HIV —monocytes→ CNS
* Involvement of CNS causes:
  - White matter degeneration (palor)
  - Microglial nodules
  - Peri vasculitis (infla. cells around vessel)

* Spinal cord involvement causes
  - Vacuolar degeneration → in microscope → vacuoles
    Spongiform degeneration

* HIV in brain causes
  1° CNS lymphoma
  ↓
  - m/c : Diffuse large B cell lymphoma
  - Infected with : EBV (Ebstein barr virus)

3) Rabies

* 100% fatal if not treated
* Diagnosis:
  - Corneal smear
  - Brain ~~smear~~ biopsy

* Corneal smear → Can do
  - Viral culture
  - RT-PCR (Reverse transcriptase)
  - Direct fluorescence Ag (dFA) → MC done

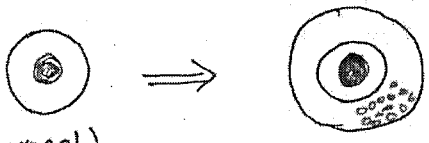
* Brain biopsy → shows Negri bodies (inside the nerves)

* Negri bodies: Intracytoplasmic eosinophilic inclusions

* MC neve → Purkinje cells of cerebellum & Hippocampus

4) Cytomegalovirus (CMV)

* Cell size increases
* Inside nucleus → dark basophilic inclusion
* In cytoplasm → eosinophilic inclusions



(Normal) ⟹ Owl Eye appearance

[Hodgkins lymphoma → Owl Eye (2 eyes)
CMV → Owl eye (1 eye)]

5) Herpes :
Intranuclear Cowdry A body

6) Measles:
* Late complication : SSPE
* m/c → Intranuclear + intra cytoplasmic ~~cellular~~ inclusion

Neurodegenerative disease

1) Alzheimers disease
* Localized amyloidosis (Aβ)

APP ⟶ Aβ
(protein in chr 21)

* In Down syndrome (Trisomy 21)
→ ↑APP → ↑Aβ
↓
So early onset Alzheimer disease

* Morphology :
1) Gross → Cortical atrophy, causes hydrocephalus. ex-vacuo
2) m/c → Brain biopsy shows
(i) Diffuse amyloid plaque (deposition of amyloid)
(ii) Senile plaque (Aβ amyloid at centre + dystrophic neures)
Amyloid destroys nerves around it & causes memory loss / dementia

Senile plaque → Pathognomic for Alzheimers

(iii) Neurofibrillary tangles
- Tau proteins (elongated proteins)

Tumors of CNS

- MC tumor → Metastasis (Lung > ~~Rose~~ Breast)
- MC 1° tumor → Meningeoma > Glioma > Astrocytoma > Pilocytic astrocytoma.
- MC 1° malignant tumor in
  - Adult → Glioblastoma
  - Child → Medulloblastoma

* Glioma: Tumor of macroglial cells
  1) Astrocytoma
  2) Oligodendrocytoma glioma
  3) Ependymoma

* Astrocytoma → 4 Grades
  Grade 1: Pilocytic astrocytoma
  Grade 4: Glioblastoma

* cerebellum → Medulloblastoma
* covering → Meningeoma.

Gliomas
1) Astrocytoma
2) Oligodendroglioma
3) Ependymoma

Astrocytoma
- Grade I: Pilocytic astrocytoma
* Grade II: Atypical
* Grade III: Anaplastic
- Grade IV → Glioblastoma
* Pilocytic
  - Localized
  - Best prognosis
  - Rx: Surgical excision only
* Glioblastoma
  - MC malignant in adult
  - Poor prognosis
  - Rx: Surgery + Chemo + Radio

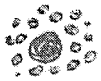
Other brain tumors

1) Meningioma
* From brain covering
* Arises from Arachnoid cap cells

* C/F: Localizing sign MCQ
  ↑ size during pregnancy
* m/c → Psammoma body (calcification)

2) Medulloblastoma
* Grade IV WHO tumour
* Most malignant
* Poor prognosis, metastasis common
* Rx: Sx + Chemo + Radio

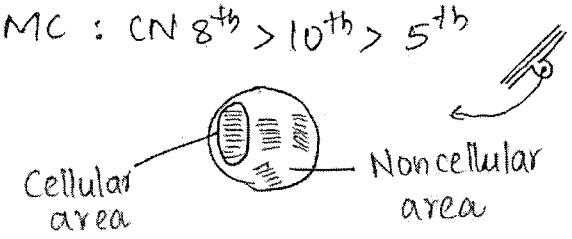
* m/c : Homer Wright Rosette



(Pinkish deposition around e tumour cells present)

3) Schwannoma :

* Peripheral nerve sheath tumor
* MC : CN $8^{th} > 10^{th} > 5^{th}$



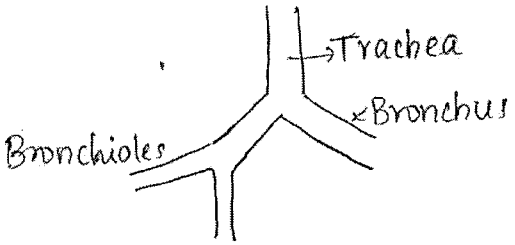
* Cellular area k/a (cells one over other)
Verocay body

4) Vascular tumor :

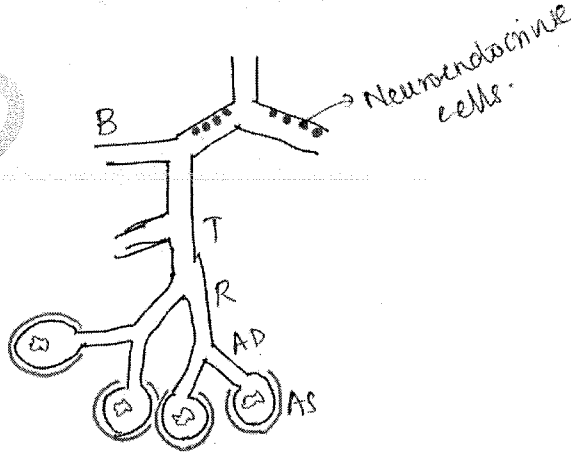
* MC → Cerebellar hemangioblastoma
* Often associated with
VHL gene mutation - chr 3
(Von Hippel Lindau)
H - Hemangioblastoma
I - ↑ risk of RCC (clear cell)
P - Pheochromocytoma
P - Port wine stain (ectasia)
E - Eye lesion
L - Lung cyst

(ectasia : Swelling of vessel)

LUNGS



* Trachea → bronchus → bronchioles → terminal bronchioles → respiratory bronchioles → alveolar duct → alveolar sac.



* Acinus → Airway distal to the terminal bronchiole.
* Blood vessels around alveolar sac. (pulmonary capillaries)
* MΦ inside alveoli k/a
Alveolar MΦ (Dust cell)

mcq
* Bronchus has neuroendocrine cells → secretes serotonin, calcitonin, bradykinin
(Serotonin : Vasodil, Bronchoconst, ↑ GI secretion)

* Lungs develop from ventral part of the ~~bronchus~~ foregut.

Congenital anomalies

1) Foregut cyst: It can be
   - Bronchogenic cyst MCQ
   - Esophageal cyst
   - Enteric cyst

2) Sequestration:
   * Discrete mass of lung tissue
   * No connection to main lung.

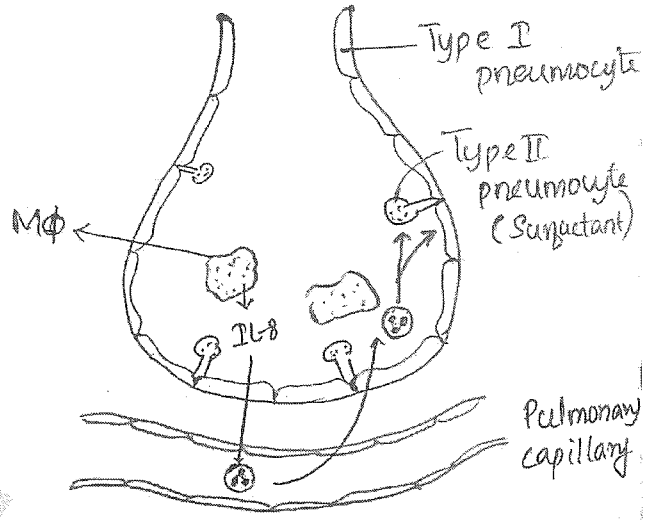
3) Lung / Pulmonary hypoplasia:
   * Failure of development of the ventral part of foregut.

4) Congenital cystic adenoid malformation (CCAM):
   It is a lung hamartoma MCQ

ARDS

* Acute Respiratory Distress Syndrome
* Also k/a Hyaline membrane disease or Shock lung.
* Etiology →
   - Aspiration
   - Sepsis
   - Pulmonary infection
   - Head trauma.

* Pathophysiology:



* Etiology → activates MΦ → release IL-8 → ~~attracts~~ neutrophils activated → reach alveoli → releases protease & IL → damages type I & II pneumocytes
* Type I damage → causes respiratory distress → also fluid gets in → edema k/a non-cardiogenic pulmonary edema.
* Damage to type I & II pneumocytes → diffuse alveolar damage
* Giving O_2 cannot resolve → k/a shock lungs
* ↓ type II → ↓ surfactant production
* Damage → sealed by fibrin / hyaline → k/a ~~fibrin~~ hyaline membrane disease
* Later ~~collagen~~ hyalina

* Healing stage: Hyaline deposition in damaged alveoli → Hyaline membrane disease
* Later → Pulmonary fibrosis

Most important
- IL → IL-8
- Mediator → Neutrophil
- Cell damage → Type 1 > 2 pneumocyte
- Histopathological → Diffuse alveolar damage (DAD) + Hyaline membrane disease (HMD) + Neutrophil infiltration of in alveoli

Chronic Pulmonary Disorders

- Obstructive (COPD)
  - eg: Emphysema, Asthma, Bronchiectasis, Chronic bronchitis
- Restrictive
  - Chest wall disorder
    - Trauma
    - Scoliosis
    - Polio
  - Lung parenchyma
    - Fibrosis (interstitial)
    - Granulomatous disease
      - Sarcoidosis
      - Wegeners
      - Churg straus syndrome
    - Smoking
    - Pneumoconiosis

Left Ventricular heart failure

↑ pulmonary capillary wedge pressure
↓
RBC to alveoli : Pulmonary hemorrhage
↓
Mϕ engulfs RBC & removes it. Hb inside RBC → Mϕ filled with dark coloured iron particle
↓
k/a Hemosiderin laden Mϕ / "Heart failure cells" (Mϕ + Fe)

Emphysema

* Dilatation and destruction of small airway (acinus)
* Types of emphysema:

Centri acinar (MC)	Pan acinar
• Proximal acinus	• Both proximal and distal acinus
• Due to smoking	• α_1 antitrypsin deficiency
• At apex	• At base
• Most common (MC)	

Asthma

* Type I hypersensitivity
* Sputum m/c → 3C
  - C - Cirshman spiral (impacted mucus plug)
  - C - Charcot Leydin crystal (Eosinophil crushing artefact)
  - C - Creola body (shed out resp. epi. cells)

Bronchectasis

* Dilatation and destruction of large airway
* Etiology:
  1) Infection (TB, Staph. aureus) (Aspergillus) MC*
  2) Autoimmune disease (SLE, Rheu. arthritis)
  3) Foreign body
  4) Congenital causes:
     - Cystic fibrosis
     - Kartagener syndrome (1° ciliary dyskinesia)

     ↓

     Triad
     - Bronchectasis
     - Situs inversus
     - Sinusitis.

     (50% infertile) but not a part of triad

* Morphology
  - Gross → large, dilated, destroyed airway

"Honey comb appearance"

Mostly seen in bilateral lower lobe.

Chronic bronchitis

* ≥ 3 months of productive cough in last two consecutive years.
* Pathogenesis ⇒ Persistent infection causes ↑ mucin production (IL-13)

  ↓

  ↓ airway clearance

  ↓

  due to that again infection
* Ratio of mucin gland layer thickness to epithelial layer thickness. ↓

  $\frac{MGL}{EL}$ increases

  ↓

  MCQ

  K/a Reid Index.
* Reid index ↑ in chronic bronchitis.

Restrictive lung disease

Pneumoconiosis

Types

~~Anthracosis~~ Anthracosis (coal worker) | Silicosis | Asbestosis

* MC is Silicosis

mcq

AC	S	Asb
• Upper lobe	• U.L	• Lower lobe
• No gross finding	- Bilateral hilar LN - Egg shell calcification	• ~~Pulmonary~~ - Pleural effusion - Pleural plaque - Interstitial fibrosis
• m/c has coal macule (coal + MΦ) 	• Non immune granuloma 	• Sheek kebab appearance  Asbestes body (beaded rod)
• No TB risk	• TB ↑	• No TB risk
• Lung Ca NO	• Lung Ca ↑	• Lung Ca ↑↑↑

Lung Tumors (Important)

* MCC of cancer related mortality Lung tumor.

+ Etiology:
  - Smoking (Squamous cell Ca > Adeno carcinoma)
  - Asbestosis
  - Silicosis
  - Radon exposure
  - Genetic mutations like
    - p53 → Squamous cell Ca
    - Rb gene → Small cell Ca
    - EGFR 1, KRAS } Adeno Ca

(EGFR2 → Breast Ca)
[Her-2 neu]

Classification

Small cell Ca (SCC) | Non small cell Ca (NSCC)

eg: SCC

eg: Adeno Ca
Squamous cell Ca

Squamous cell lung Ca

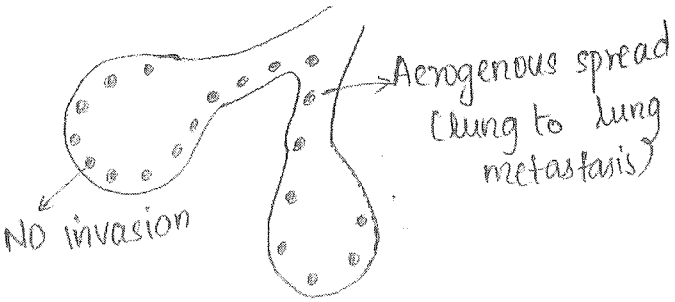
* MC — India
* MC — Smokers
* MC — Hypercalcemia
* C/F :
  - Sites : Brochus
  - Cavitory lesions

MCQ

MCQ
* m/c → Keratin pearls

Adeno Ca lung

* MC lung Ca throughout the World
* Best prognosis
* MC lung cancer in
  - Non smokers
  - Young age
  - Females
* Site : Peripheral in location (ie, in the alveoli)



Lepedic pattern (Butterfly)

Neuroendocrine tumor of lung

eg: 1) Carcinoids
2) Small cell Ca

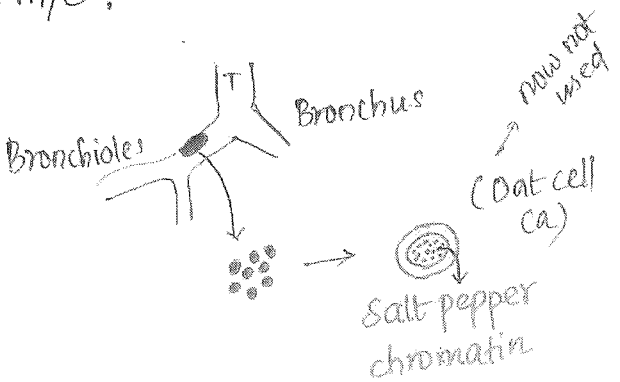
(Neuroendocrine cells → in bronchus → secretes ~~secre~~ serotonin → causes vasodilatation, bronchoconstriction, ↑ GI secretions → ie, cyanosis, diarrhea, flushing)

* Site : Bronchus (Neuroendocrine cells)
* They secrete serotonin which causes
  - Diarrhea
  - Flushing
  - Cyanosis

  } k/a carcinoid syndrome

Small cell Ca (SCC)

* Site : Bronchus
* MC lung Ca with paraneoplastic syndrome (except hypercalcemia) (ectopic hormones)
  (hypercalcemia seen in squamous cell Ca)
* m/c :



* Stains → Synaptophysin, Cromogranin

Tumors of Pleura

Malignant mesothelioma

* from pleura
* Malignant in nature
* Often associated with asbestor exposure (10-15 yr)

MCQ
* No ↑ in risk with smoking
* SV 40 (Simian virus 40) coinfected
* Poor prognosis

Lung Cancer in Asbestosis

- Adeno carcinoma ✓
- Squamous cell Ca ✓

Pleural Ca in Asbestosis

- Malignant mesothelioma ✓

GIT

Malabsorption syndrome:

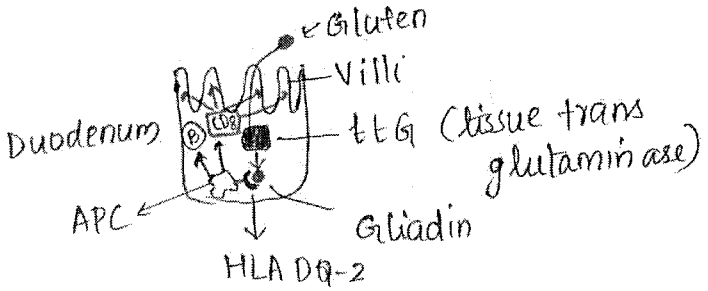
1) Celiac disease
2) Tropical sprue
3) Whipple's disease

Celiac disease

* Not an infection
* It is hypersensitivity to gluten

Gluten seen in (Wheat ka Bora)
- Wheat
- Barley
- Oat
- Rye

* Patient who have HLA-DQ-2 +ve
* Site: Duodenum
* Pathophysiology:



Gluten → via villi absorbed → digested by ttg in to gliadin → presents APC with HLA DQ-2 binds to it → to T_H → will activate B cells & CD8 → CD8 destroys the villi → B cells produce Anti endomysial Ab

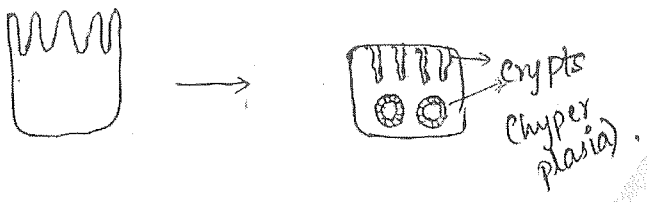
(T_H: T helper cell)

* Diagnosis : Malabsorption

Ab used → Anti endomysial Ab
Anti ttg Ab

(Both will be +ve)

* Biopsy : Duodenal biopsy → loss of villi in duodenum; Crypt hyperplasia.



PAS +ve diastase resistant bacteria (partially digested) in the lamina propria layer.

↓

Whipple's disease.

* Most important differential diagnosis Intestinal TB

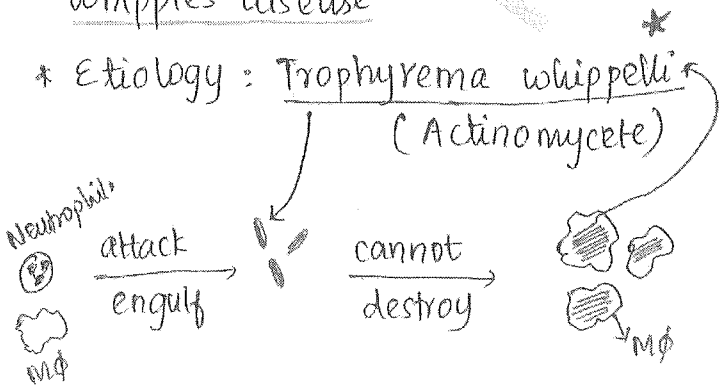
* TB is ZN stain +ve (zein nelson stain → or acid fast stain)

Tropical sprue

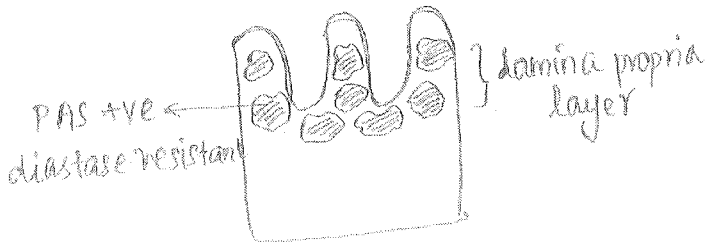
* Infective etiology : E.coli
* Biopsy → Mild loss of villi
Mild Crypt hyperplasia

Whipple's disease

* Etiology : Trophyrema whippelli (Actinomycete)



* Diagnosis : Duodenal biopsy



HEMATOLOGY

* Hematopoesis → Formation of blood cells
* Starts with yolk sac at 3rd wk of intrauterine life.
  ↓
  then liver at 3rd month of intrauterine life
  ↓
  to bonemarrow at 4th month of intrauterine life.
  ↓
  Bone marrow is the site of hematopoesis throughout the life.
* At birth all bones produces hematopoesis.
* At adult → only flat bones (sternum, iliac crest, spine, vertebra)

Formation & development of blood cells

Hematopoetic stem cells (HSC) in bone marrow

- Erythroblast (bone marrow) → (periphral) RBC (4-4.5 million/μL)
- Myeloblast → WBC (TLC = 4000-11000 /μL)
- Megakaryocyte → Platelets (1.5-4.5 lacs/μL)

WBC

(TLC = 4000 - 11000 /μL)

↓

Differential count (DLC)

- Granulocytes
  - Neutrophil (50-75%)
  - Basophil (≤1%)
  - Eosinophil (<400/μL) MEA
- Non granulated
  - Monocytes (<8%)
  - Lymphocytes (25-40%)

MEA ⇒ Normal no: of eosinophil <400 /μL

⇒ Leucocytosis : WBC > 11000 /μL

1) Neutrophilia (>75%)
   - Infections
   - steroids
   - Stress : MI
   - Myeloproliferative disease
     (CML - Chronic myeloid leukemia
     PCV - Polycythemia vera

2) Eosinophilia (>400/μL)
   - Asthma
   - Allergy, hay fever, urticaria
   - Parasitic
   - Drug reaction
   - Tumors

* Parasitic : Hook worm, Filaria, Ascariasis

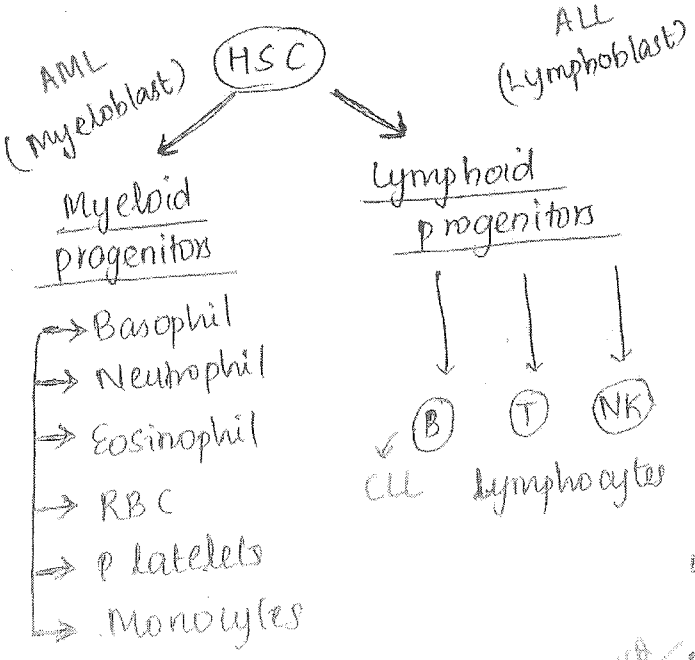
- Tumors (ALL, AML, Hodgkin's lymphoma)

3) Basophilia: (> 1 %)
- Ulcerative colitis
- CML, Systemic mastocytosis

4) Monocytosis (> 8 %)
- Infection (Infectious mononucleosis, TB, Kalazar)
- AML - M_4 / M_5
- Ulcerative colitis

5) Lymphocytosis
- Infections (TB, Pertusis)
- Viral infections
- Malignancies like lymphoma
  eg: CLL
  (Chronic lymphocytic leukemia)

WBC & its disorders



(Progenitor → blast → mature cell)

* Only B-lymphocyte → CLL
* Myeloblast → AML
  Lymphoblast → ALL
* All mature myelocytes → CML
* Only B-lymphocyte → CLL

Acute Leukemia (ALL & AML)

* MC tumor in children: ALL (B)
  (Acute lymphoid Leukemia) B type
  ALL (B) > Brain tumor
* C/F: ↑ blast proliferation
* Normal % of myeloblast (MB) in bone marrow
  5 %
* ↑ blast proliferation → ↓ mature cells
  - ↓ erythroids - Anemia
  - ↓ myeloids - Neutropenia
  - ↓ thrombocytes - Bleeding

	ALL	AML
1) CNS infiltrat"	+ +	+ / −
2) Testes infiltration	+ +	+ / −
3) Mediastinal LN	+ + (T-ALL)	+ / −
4) Gum hyperplasia	+ / −	+ +
5) Chloroma	+ / −	+ +
6) Auer Rods	− (absent)	+ +

MLA

* Hallmark of AML (only in AML)
  Auer rods

Cytogenetics

Good prognosis
t (12, 21)

Poor prognosis
t (5, 14)
t (9, 22)

(t : translocation)

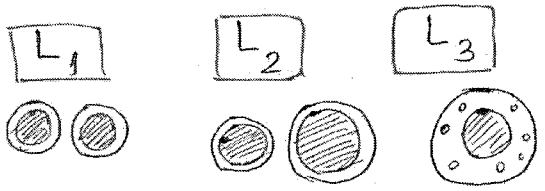
AC lassification

1) ALL

* Acute lymphoblastic leukemia

(a) FAB classification

French, American, British } Basis of 1) Morphology 2) staining.



L_1	L_2	L_3
• Small Homogenous	• Heterogenous	• Cytoplasmic vacuoles
• PAS ⊕	• PAS ⊕	• PAS ⊖ SBB ⊕ (Sudan Black B)
• Good prognosis	• Intermediate prognosis	• Poor prognosis

(b) WHO classification:

1) ALL with recurrent cytogenetic abnormality.
(based on cytogenetics)

AML

* Acute myeloid leukemia

a) FAB classification (based on ~~MORT~~
- Differentiation
- Lineage

FAB

Differentiation

- M_0 - AML ⊂ out different (minimal)
- M_1 - AML ⊂ diff.
- M_2 - AML ⊂ maturation
- M_3 - ~~Acute~~ Acute promyelocytic leukemia

Lineage

- M_4 - Ac. myelomonocytic leukemia
- M_5 - Ac. monoblastic leukemia
- M_6 - Ac. erythroid leukemia
- M_7 - Acute megakaryocytic leukemia

MCQs

* MC AML → M_2
* Max. Auer rods → M3
* Chloroma → M_2
* MC showing gum hyperplasia
  M5

* MC asso. c̄ Down's syndrome
  M_7
* Worst prognosis → M_0
* DIC (Disseminated Intravasular Coagulation) MC seen in
  M_3 (APML) [Medical Emergency]
* Monocytosis shown by → M_4, M_5

b) WHO classification:

(1) AML with recurrent cytogenetic abnormality

Cytogenecity

Good prognosis
- t (8, 21) → M_2
- t (16, 16) or invesion 16 (M_4)
- t (15, 17) → M_3

Poor prognosis
- FLT-3 gene mutation

(2) AML-therapy related
* Can be seen in post: Alkylating agents, Topoisomerase II inhibitors
* Both have poor prognosis

(3) AML - Myelodysplasia (disordered growth is dysplasia)
* Poor prognosis
* Cytogenetics: MC: Monosomy 5, Del of 5q (5q-)

(4) AML in Down's syndrome:
* Good prognosis

(5) AML: Not otherwise specified (NOS)
* It includes M_0 to M_7 except M_3

Diagnosis
* On CBC (Complete Blood count)
  - ↓ Hb
  - ↑↑↑ TLC (↑ blasts)
  - ↓ platelets
    - if % blasts ≥ 20% then it is Acute leukemia
    - if % blasts < 20% → do bonemarrow aspiration
      → needle used
      eg: Salah
      Klima
      Jamshedi
      → site: eg: Adults - post. sup. iliac spine
      Children → tibial tuberosity
      → staining:
      1) PAS (Periodic acid schiff)
      2) MPO (myeloperoxidase)
      - PAS → Lymphoblast (ALL)
      - MPO → Myeloblast (AML)

CD markers : (Best way)

* MCQ

Cells	CD markers
1) Blasts	CD 34, tdt (only in lymphoblast)
2) All WBC	CD 45 (common leukocyte Ag)
3) Myeloid cells	MPO
4) Lymphoid cells :	
B cells	CD19, 20, 21, 22
T cells	CD3, 1, 2, 4, 5, 7, 8
NK cells	CD 16, 56
5) Monocyte (4)	CD 14, 64

MCQ

⇒ Cells +ve for both

* ① CD34 → Blast
MPO → Myeloid

AML

② CD34 - Blast
tdt - Lymphoblast
19 - B

B - ALL

Chronic Leukemia

* Myeloid mature tumor
(from mature myeloid cells)
(Neu, Mono, Bas, Eo, RBC, Plate)

(1) CML (Chronic myeloid Leukemia)
(2) PCV (Polycythemia vera)
(3) ET (Essential Thrombocythemia)
(4) PMF (Primary myelofibrosis)

CML

* Defined as ph chromosome +ve
t (9q : 22q)
ph → philladelphia chromosome

* On chr 9 → gene ABL (Abelstein)
chr 22 → BCR (Break point cluster region)

* main problem in CML is translocation of BCR-ABL
t (BCR - ABL)
↓
Activates tyrosine kinase receptor
↓
causes CML

* Imatinib inhibits tyrosine kinase receptor → Rx CML

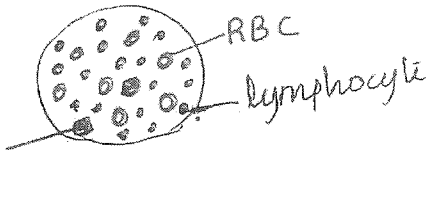
Diagnosis

* CBC & PS → ↑↑ TLC → ↑ Basophil, ↑ myelocytes, Blasts +/-
  (peripheral smear)

- Differential diagnosis
  (1) CML
  (2) Leukemia like reaction
  K/a Leukemoid reaction
- Leukocyte Alkaline phosphatase score (LAP score)
- LAP score ↑ in Leukemoid reaction
  LAP score ↓ in CML

* Diagnosis

* CBC & Peripheral smear
  → Lymphocytosis



* LN biopsy (lymphnode)
  → ↑ lymphoid proliferation

* Prognosis of CLL - Good
* Poor prognostic markers:
  CD 38 ⊕, ZAP 70 ⊕

Tumors of lymphoid origin

* B → CLL
  T
  NK

Hodgkins Lymphoma (Important)

* Tumor of lymphoid origin
  (B, T, NK)
  ↓
  None of them
* Unknown origin

CLL

* Chronic lymphocytic leukemia
* MC chronic leukemia of adults
* Never arises after radiation toxicity

	CLL	CML
♂ : ♀	3:1	3:1
Age	50-60 y	50-60 y
C/F	Asymptomatic (Lymphadeno pathy)	Hepato-splenomegaly → Abd pain

Classification

Classical

- CD 20 ⊖
  (B cells - CD 20)
- CD 15/30 ⊕

Non classical

- CD 20 ⊕
- CD 15/30 ⊖

* Characteristic cells: Reed Sternberg cell (RS cell)

Binucleate owl eye (both eyes)

Hodgkin type	R-S cell	EBV (Ebstein Barr virus)	Prognosis
Classical type			
1) Mixed cellularity	MCQ Mononuclear	70%	Good
2) Nodular Sclerosis	Lacunar	0% MCQ	Very good
3) Lymphocyte rich	Classical	40%	Very good,
4) Lymphocyte depleted	Reticular	90% MCQ	MCQ Poorest
Non Classical type			
5) NLPHL (Nodular lympho predominant hodgkins lymphoma)	Popcorn MCQ	0%	MCQ Best

MCQ

⇒ MC in India
Mixed cellularity

MCQ

⇒ MC worldwide
Nodular sclerosis

C/F of Hodgkins

MC feature

A (Asymptomatic) → MC: cervical lymphadenopathy

B ("B" symptom)
- Night sweat
- Weight loss
- Fever (Pel Ebstein)
  (1 wk fever, 1 wk normal, next wk fever continues)

RBC

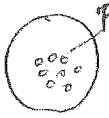
Bone marrow

Proerythroblast
↓
Basophilic (early) erythroblast 
↓
Polychromatic (intermediate) erythroblast 
↓
Orthochromatic (late) 

↓
Nucleated RBC (nRBC) → nucleus → Spleen

Peripheral blood
↑
Mature RBC
↑
Reticulocyte

⇒ Hb first appears in polychromatic (intermediate) erythroblast

⇒ Reticulocyte has RNA inside them 

Anemia
↓
CBC, PS, ~~Reti~~ Retic %

↙ Retic % ↑↑
↓
Hemolytic anemia

↘ Retic % ↓↓
↓
Hypoproliferative anemia.
eg: Aplastic Anemia, pure Red cell aplasia

Reticulocyte

* Immature RBC
* Contains ribosomal RNA (rRNA)
* Statin : Supra vital stain

Hemat stains

- Giemsa } eg: of Romanowsky stain
- Lieshman }

Eosin + Methylene blue

* eg: of supravital stain
  - New Methylene blue
  - Brilliant cresyl blue.
* RBC appears grey in them
* % reticulocyte = Reticulocyte / 100 RBC
* (N) % → < 2% adult
  < 5% children
* Hb - 8 gm%, % retic = 9 %
  ↓
  Hemolytic anemia
* % Retic = 0.1 %
  ↓
  Hypoproliferative anemia

RBC indices

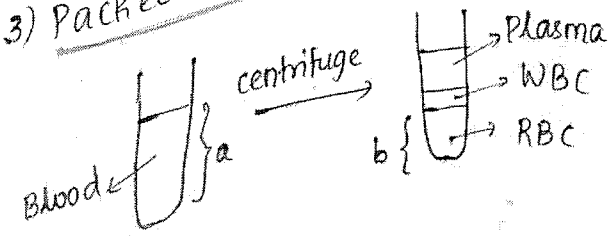
1) Mean corpuscular volume (MCV)
   Volume of single RBC
   (N) : 80-100 fl (femtoliter)

2) Mean corpuscular Hb (MCH)
Amount of Hb in each RBC

$$MCH = \frac{Hb}{RBC\ count}$$

(N) : 30 ± 2 pg (picogram)

3) Packed cell volume (PCV)



$$PCV = \frac{b}{a} \times 100\ \%$$

4) Mean corpuscular Hb concentration (MCHC)

Hb per unit packed volume.

$$MCHC = \frac{Hb}{PCV}$$

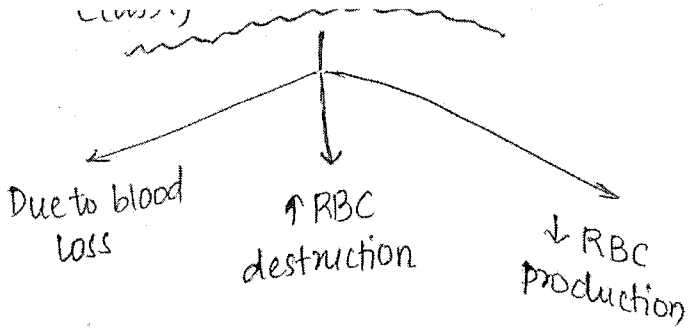
(N) 32 ± 2 g/dl

5) RDW (Red cell distribution width)

Measure of anisocytosis (variation in the size)

(N) : 12 - 16

• If RDW = 25 → indicates anisocytosis



Blood loss

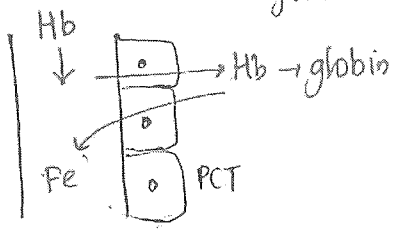
- Acute
  eg: Trauma surgery
- Chronic
  eg: Ulcer, Carcinoma, Parasitic infection
  ↓
  - Hook worm → Iron defic. anemia
  - Diphyllobothrium latum → Pernicious megaloblastic anemia

↑ RBC destruction ↓

Hemolytic anemia

- Intravascular (inside vessel)
  Free Hb
  ↓
  * Findings:
    - Hemoglobinemia
    - Hb + Haptoglobin → (liver) → Haptoglobin level ↓
- Extravascular (inside spleen)

- Hb → Urine (Hemoglobinuria)
- Tubular cells absorbs Hb & converts to globin + Fe



Hemosiderinuria (Fe in urine).

- ↑ bilirubin (unconjugated)

Jaundice

Extravascular hemolysis

* MΦ in spleen absorbs Hb
* So no hemoglobinemia, normal haptoglobin level, no hemoglobinuria, no hemosiderinuria.
* But can ↑ bilirubin (unconjugated)
  - Causes spleenomegaly.

* ⇒ Jaundice is a common feature of both intravascular & extravascular hemolysis

Eg:

- Intravascular H
- Extravasc. hemolysis
  - RBC membr: • Hereditary spherocytosis / Hereditary elliptocytosis
  - RBC enzyme: • G6PD deficiency, pyruvate kinase defi
  - RBC Hb: • Thalasemia, Sickle cell anemia
    - Warm AIHA

- Hereditary elliptocytosis also in extravascular hemolysis.

- Eg: of intravascular hemolysis
  - PNH (Paroxysmal Nocturnal hemoglobinuria)
  - PCH (Paroxysmal cold hemoglobinuria)
  - cold type AIHA (Auto immune hemolytic Anemia)
  - Angiopathic hemolytic anemia
    eg: Vasculitis,
    - DIC,
    - HUS (Hemolytic uremic syndrome)
    - TTP (Thrombotic thrombocytopenic purpura)
    - March Hemoglobinuria

Hereditary Spherocytosis (HS)

* Autosomal dominant
* Shape: Biconcave

- ↑ surf. area / volume
- can change shape while pass through spleen

MC

* Patho: Defect in Ankyrin

Ankyrin > Band 3 > spectrin

(RBC membrane proteins)

Defect 

↓

loss in surface area

↓

becomes spherical ○

↓

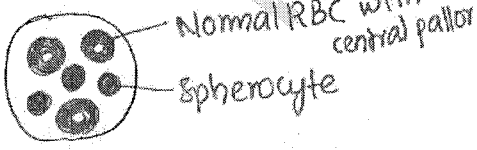
when pass through sinusoids of spleen, it wont allow them

↓

destruction of RBC in spleen (Extravascular hemolysis)

* C/F :
  - Splenomegaly
  - Jaundice
  - Pigmented gall stones
  - +ve family history (hereditary)

* Diagnosis : CBC with retic %
  - Retic % ↑
  - CBC shows spherocytes



* Spherocytes ~~also~~ seen in
  - H.S (Hereditary spherocytosis)
  - Immune hemolytic anemia
  - Severe burn
  - Toxin

* Confirmatory :
  OFT (Osmotic fragility test) NEET

G6PD deficiency

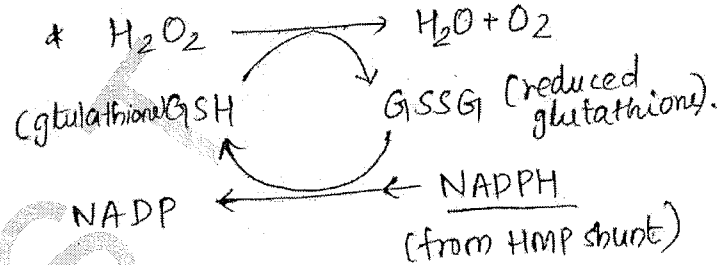
* In HMP shunt

G6P

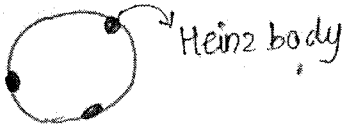
NADP ⇄ NADPH | G6PD ↓

6-p-gluconolactone

* NADPH is a reducing substance
* In RBC → ↑ H_2O_2 → oxidise & precipitate Hb



* G6PD deficiency → ↓↓ NADPH → ↑ H_2O_2 → oxidize & precipitate Hb k/a Heinz body (on the RBC surface)



* When this pass through spleen → it removes heinz body → now bite cell formed → continues → destruction in spleen → extravascular hemolysis


(Bite cell)

* Bite cell seen in G6PD deficiency

Diagnosis

* Screening → Methylene blue reduction assay
* Confirmatory → G6PD enz assay

Hb abnormality

- Quantitative
  - ↓ ↓ ↓ quantity
  - Thalasemia
    - eg: α-thalasemia, β-thalasemia
- Qualitative
  - defective structure
  - Hemoglobinopathy
    - eg: Sickle cell anemia (HbS)

(N) ($HbA = \alpha_2\beta_2$)

Thalasemia

- α
  - Autosomal recessive
  - ↓ α chain
  - β excess
- β
  - AR (autosomal recessive)
  - ↓ β chain
  - α excess

* Pathogenesis of β-thalasemia

Bonemarrow → Erythroblast → has excess of α chain → it will destroys some of the blast in bonemarrow → those not destroyed comes out → those RBC have α excess → pass through spleen → it destroys it - extravascular hemolysis

C/F → Severe anemia
Severe jaundice
Spleenomegaly

* Also ↓ β chain → excess α → combines with ε, γ → $\alpha_2\varepsilon_2$ ↑ (HbA_2↑), $\alpha_2\gamma_2$ (HbF)↑ → HbF has high O_2 affinity, does not deliver O_2 to tissue → tissue hypoxia → ↑ erythropoeitin → erythropoesis from bonemarrow & liver (intramedullary & extramedullary ~~eryt~~ hematopoesis) → intramedullary H.P causes skeletal deformity → extra MHP causes hepatosplenomegaly.

Skeletal deformity → X-ray: Hair on end appearance, Crew cut appearance

* Diagnosis:
  - Peripheral smear & retic %
  - Retic % low (becoz of destruction in bonemarrow)
  - Anisopoikilocytosis
  - Microcytic/hypochromic RBCs

[RBC ↓ central stain → Target cell

Normal RBC

Target cell

Howell jolly body

Basophilic stipling

Cabot rings

* Confirmatory: Hb-HPLC
  (High performance liquid chromatography)
  - HbA ($\alpha_2\beta_2$) ↓
  - HbA_2 ($\alpha_2\delta_2$) ↑
  - HbF ($\alpha_2\gamma_2$) ↑

Sickle cell Anemia (HbS)

* Point mutation : β chain 6th position glutamic acid replaced by valine.
* Structure of Hb

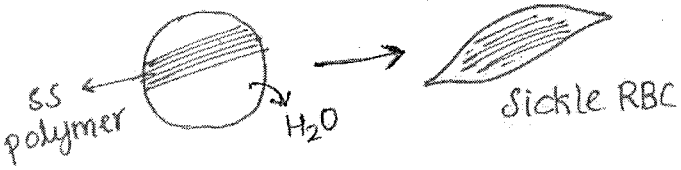
* Initially:

Blood flow ↓
↓
Kla vaso occlusive crisis

eg: • Painful dactylitis (pain in hand & foot – Hand foot syndrome)
• ↑ infection in
  – lungs (Acute chest syndrome)
  – bones (osteomyelitis)
    Salmonella

* Later on → HbS makes a polymer : Hb polymer

* HbS polymer (SS polymer) inside the RBC → destroys RBC membrane → all H_2O leaks out → takes shape of polymer kla sickle RBC



* When passes through splenic sinusoids → extravascular hemolysis
* Diagnosis:
  Peripheral smear c̄ Retic %
  (PS)
  - Retic % ↑
  - Sickle RBC in PS

* Sickling test
  Sodium metabisulphite →

changes normal looking RBC to sickle RBC (any RBC ⊆ has tendency to sickle)
- It is a reducing substance

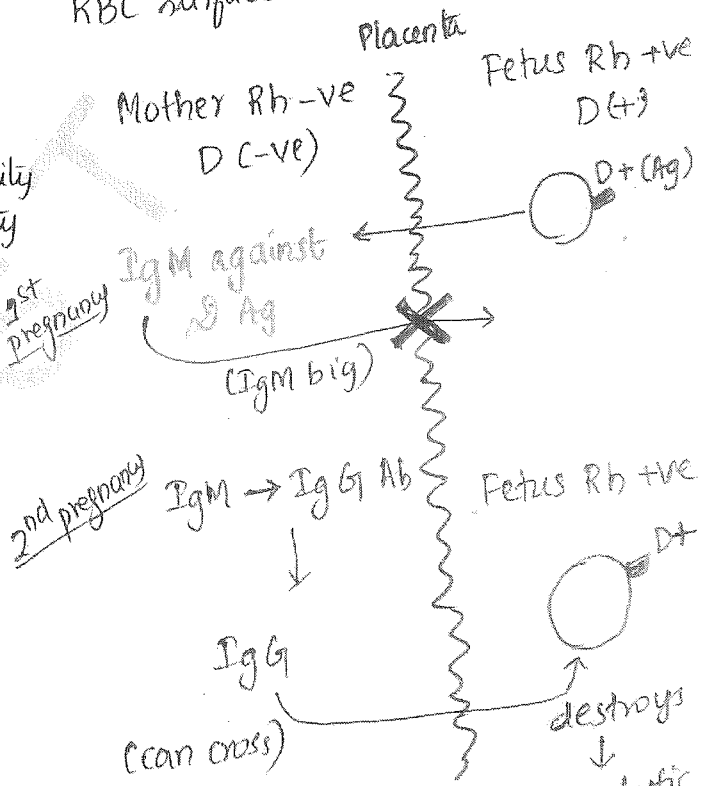
Immune Hemolytic Anemia

- **Auto immune** → Ab against self Ag
  - **Warm Ab**
    - IgG
    - 1° → Unknown cause
    - 2° - due to
      - drugs - ∝ methyl dopa, Penicillin
      - Autoimmune disease
      - Lymphoma : CLL
  - **Cold Ab**
    - IgM
    - 1° - Unknown cause
    - 2° due to
      - Infection : Myco-plasma, Chlamydia
      - Multiple myeloma
      - PCH (Paroxysmal cold hematuria)
- **Allo immune** → Ab against foreign Ag
  - eg: ABO incompatibility, Rh incompatibility

* Diagnosis : Peri. smear ⊂ retic %.
- Retic % ↑
- Spherocytes in PS

* To differentiate b/w HS & (immune) Coomb test ⊕ ve in hemolytic anemia

Coomb test
- **Direct (DCT)** → detects Ab on RBC surface
- **Indirect (ICT)** → detects Ab free in serum



* K/a Erythroblastosis fetalis / Hemolytic disease of new born.

- In Mother → do ICT (Indirect coombs test)
- In baby → do DCT (Direct Coombs test)

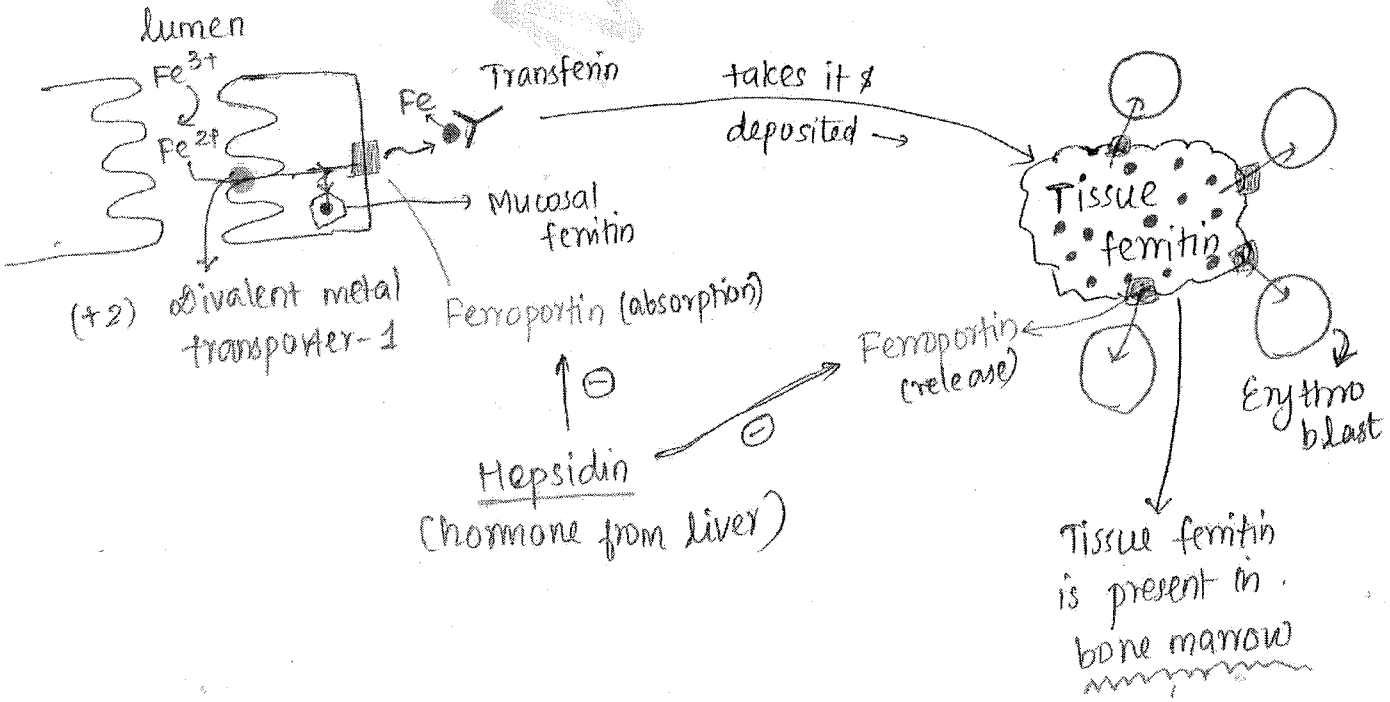
Decrease in RBC production

- Nutritional anemia
  - eg:
    - Iron deficiency anemia
    - Vit B_{12} def
    - Folic acid def
    - B_6 def
- Hypoproliferative anemia
  - eg:
    - Aplastic
    - PRCA

Iron deficiency anemia (IDA)

* MC anemia in India
* Site of iron absorption:
  Duodenum + Proximal jejunum
* Mechanism: Iron in food < Heme (MC)
  Fe^{3+}

- Heme can directly get absorped
* In food iron as Fe^{3+} → but absorped as Fe^{2+} so converted to Fe^{2+} → abs. by DMT-1 → some part of Fe^{2+} stored as mucosal ferritin → rest ~~carries~~ transported by ferroportin on from basolateral surface → transferrin transport Fe to tissue ferritin & deposit there → erythroblast need Fe → ~~take~~ Fe^{2+} is stored in tissue ferritin in bone marrow → erythroblast takes Fe^{2+} from bone marrow → tissue ferritin.
* Bone marrow needs ferroportin to deliver iron to erythroblast.
* Ferroportin is -vely regulated by a hormone from liver: Hepsidin.
* Ferroportin (function) → Transport & Release (↑absorption)
* If deficiency → ↓ hepsidin / ↑ ferroportin.



Serum iron study

	Nomal	Iron def. anemia	Anemia of chronic disease
• Serum iron (transferrin bound)	50-150 µg/dl (100)	↓	↓
• Serum ferritin	50-150 ng/ml	↓	↑↑
• % transferin saturatn	33%	↓	↓
• Total iron binding capacity (TIBC)	300 µg/dl	↑	↓

Microcytic / hypochromic RBC

Ferritin $\propto \frac{1}{TIBC}$

ACD

+ Anemia of chronic disease.
+ Etiology:
  - Chronic inflammation
  - Alcoholic liver disease
  - Malignancy

↑ IL 6, 1, TNF-α
↓
stimulates liver
↓
↑ Hepsidin
↓
↓ ferrotonin
(↓ absorption & delivery of Fe^{2+})

↓ transport absorption
↓
↓ serum Fe
↓
↓ saturation

↓ delivery
↓
↑ ferritin (tissue)
↓
-ve feedback to transferin (↓ transferin)
↓
TIBC ↓

★ Common in IDA & ACD.

- ↓ serum iron
- ↓ % transferin saturation.

★

	IDA	ACD
S. ferritin	↓	↑
TIBC	↑	↓

(first start with in IDA S. ferritin always ↓, others just opposite)

Ferritin $\propto \frac{1}{TIBC}$

* Most sensitive:
  Serum ferritin
* Most specific:
  Tissue ferritin
* Tissue ferritin → Perls/Prussian blue (stain)

* 30 yr ♀ → fatigue. Hb: 8.5 gm%, RBC - microcytic/hypochromic RBC

50-150	S. iron -	20	30
33%	% sat -	12%	16%
50-150	S. ferritin -	30	600
300	TIBC -	600.	30
		↓	↓
		Iron deficiency anemia	ACD (Anemia of chronic disease)
		F↓, TIBC↑	F↑ TIBC ↓

Ferritin ↑ → TIBC ↓

In both,
IDA + ACD

↓ S. iron
↓ % transferrin saturation

Ferritin ↓	Ferritin ↑
TIBC ↑	TIBC ↓
IDA	ACD

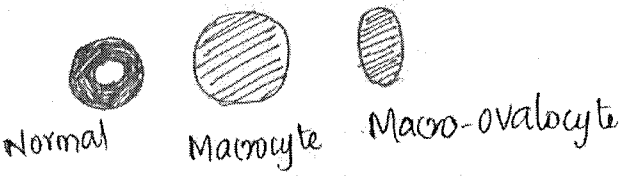
Macrocytic anemia:

* MCV > 100 fl (femti liter)

Megaloblastic	Non megaloblastic
↓	↓
Bone marrow has large size blast	Bone marrow has normal size blasts
↓	
eg: Folic acid deficiency, Vit B_{12} deficiency	eg: Alcoholism, Reticulocytosis, Hypothyroidism

Diagnosis:

* CBC with PS (peripheral smear), Retic %
* Retic % → (N)
* PS → Anisopoikilocytosis
  ↓ size + ↓ shape variation



↓ seen in
- Thalasemia
- Post splenectomy

↓ seen in myelofibrosis

★ Pancytopenia + Hypercellular bone marrow

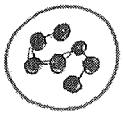
Imp

seen in Megaloblastic anemia

(Because large size blast inside bone marrow so appear hypercellular, since large, can't come out so defi. outside → pancytopenia)

WBC

* Has hypersegmented neutrophils (>6 lobes)



Lab investigation

* ↑ serum homocysteine level
* ↑ s. methyl malonyl coA level

↑ in B_{12} def only

↑ in B_{12} & folic acid def.

Hypoproliferative anemia

* in both retic % ↓
* M:E ratio (myeloid : Erythroid) 3:1 (N)

	Aplastic	Pure red cell aplasia
Retic %	↓	↓
M:E	(N)	↑

Etiology

Inherited

- Fanconis Anemia
- Dykeratosis congenita
- Diamond Schwachman syndrome.

MCQ

- Diamond Blackfan syndrome

Aquired causes

- Infection (Parvo B19 virus)
- Radiation
- Drugs
- Pregnancy
- PNH
- Tumor

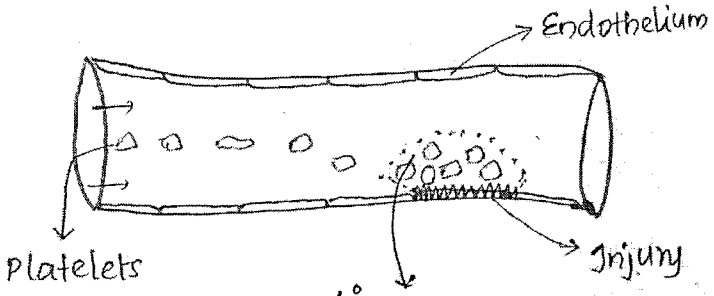
- Infections (Parvo B19)
- Tumor (Thymoma)
- Drugs.

(Drugs → Chloramphenicol, Azathioprine, Phenytoin)

Aplastic A → Pancytopenia + Hypocellular bone marrow

Pure red cell aplasia → Severe anemia + Absence of erythroids in the bone marrow

Hemodynamics:
Bleeding & Coagulation

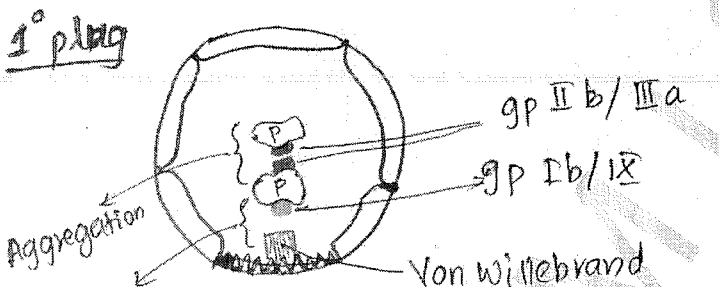


1° hemostatic plug (unstable)

↓

fibrin accumulates & forms:
2° hemostatic plug (stable plug)

1° plug



* Injured endothelium → express vWF → platelet comes and gp Ib/IX to vWF → platelet adhesion.
* gp IIb/IIIa of platelet to other → platelet aggregation

Defect in 1° plug

Quantitative

Thrombocytopenia (↓ count)

Qualitative

Platelet function defect

Thrombocytopenia

* Platelet count < 1.5 L/dL

↓ production

* Aplastic anemia
* Chemotoxic drugs
* Radiation
* Bone marrow suppression
* Myelofibrosis

↑ destruction

Immune

* Immune thrombocytopenic purpura (ITP)
* Auto immune disease
* Drugs
* Dengue.

Non immune

* HUS
* TTP
* Hypersplenism
* DIC

ITP

* Immune thrombocytopenic purpura.
* Ab's against gp Ib/IX & IIb/IIIa on platelets →

causes platelet destruction.

* Rx :
  - steroids
  - i.v Ig (blocks Ab's)
  - Plasmapheresis
  - splenectomy (Best Rx but only for chronic cases)

HUS

* Hemolytic uremic syndrome

* ↓ platelet count
+
Microangiopathic hemolytic anemia (MAHA)
+
Renal failure
↑ s. urea
↑ s. creatinine

TTP

* Thrombotic thrombocytopenic purpura.

* ↓ platelet
+
MAHA
+
Neurological manifestations
eg: confusion, unconsciousness

Platelet function defects

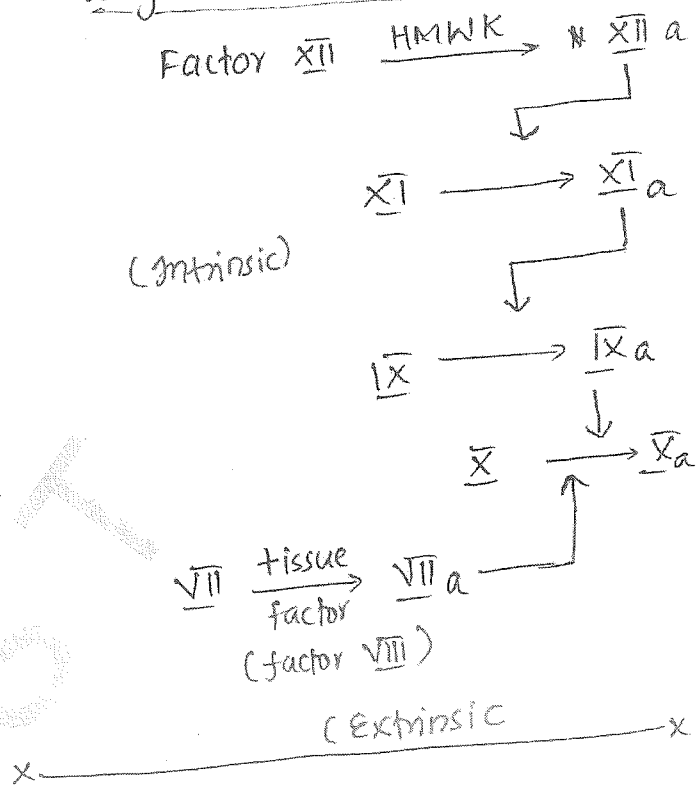
Deficient	Defect	Disease
VWF	P. Adhesion	VWD (disease)
gp Ib/IX	P. Adhesion	Bernard Solier syndrome
gp IIb/IIIa	P. Aggregation	Glanzman thrombesthenia

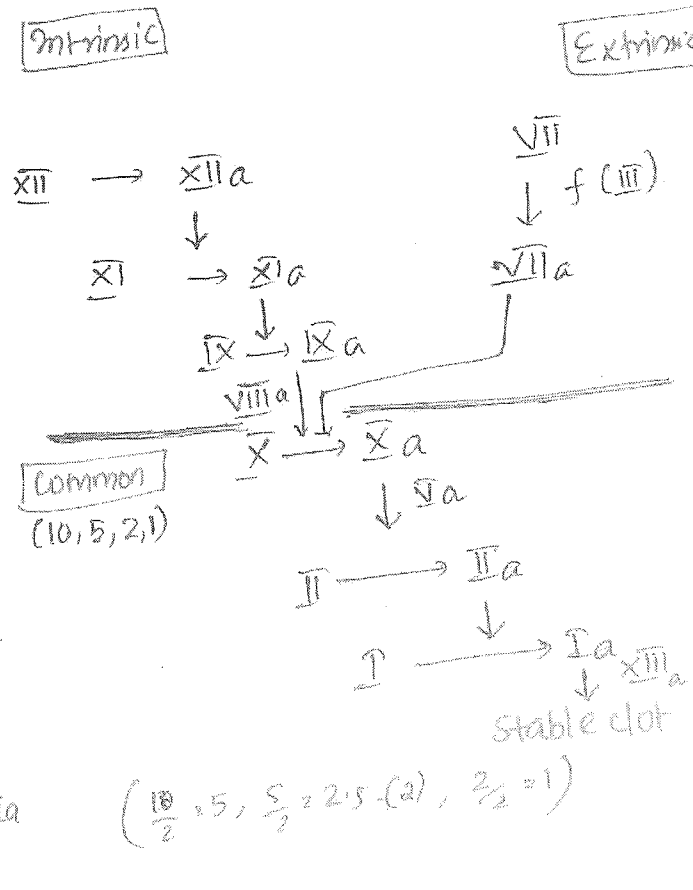
Imp ★

P: Platelet

2° plug formation

* Formation of stable plug.
* Coagulation cascade





IIa : Thrombin

Ia : Fibrin

XIIIa : Clot stabilising factor.

* Deficiency of coagulation factor
↓
Bleeding (severe)

* Coagulation tests:
→ PT (Prothrombin time)
→ aPTT (activated partial thromboplastin time)

PT	aPTT (long name long path)
* Extrinsic + common pathway	* Intrinsic + common pathway

Case 1

PT ↑, aPTT n → F VII def (extr), Vit K def

Case 2

PT n, aPTT ↑ → F XII, XI, IX, VIII def (intr)

Case 3

PT ↑, aPTT ↑ → F X, V, II, I def (common pathway)

Vit K dependent factors

* F 2, 7, 9, 10 } Inactive in plasma
* Protein C & S. }

↓

To liver, in liver with help of Vit K ← ⊖ warfarin

↓

Activated 2, 7, 9, 10

* In Vit K def → factor 7 ↓ first ($t_{1/2}$: 4 hr which is shortest)

So only PT ↑↑↑ here.

* Warfarin inhibits activation in the liver (inhibits Vit K dependent factor activation)
* So warfarin causes ↑PT. (anticoagulant)
* Adjust dose of warfarin by measuring PT.
* Normal PT is 12-16 sec
* INR : International Normalized Ratio.

MCQ

$$INR = \left(\frac{PT \text{ of patient}}{PT \text{ of control}}\right)^{ISI}$$

ISI : International standardized index.

* Instead of measure PT, we measure INR.

THROMBOSIS

* Thrombosis theory by Virchow
* Virchow's triad:
  - Endothelial injury
  - Turbulence
  - Hypercoagulability of blood.

* Role of endothelium to prevent clot formation

Antithrombotic (not allow clot to form)

- Glycocalyx clot (repels platelet)
- NO, PAF } Vasodilation
- PGI_2 → ↓ platelet aggregation
- Antithrombin III (Inhibits factor II) (II is thrombin)
- Thrombomodulin (converts protein C to active protein C)

APC (prot S) → inhibits activation of F V & VIII

Fibrinolytic (dissolves the clot if formed)

↓

Endothelium releases

↓ MCQ

Plasmin

↓ (breaks stable clot)

Fibrin monomer (clot dissolved)

FV → ✕ V a X

F VIII → ✕ VIII a X

PAF: Platelet activation factor.

⇒ Thrombomodulin converts protein C into active protein C → protein S acts on this active protein C (APC) → then inhibits activation of factor V & VIII.

Etiology of thrombosis

Inherited causes

1) F V ~~leiden~~ mutation: leidin

* Here F V is not inactivated by APC & protein S

2) AT III
3) protein C
4) Protein S

} deficiency

(AT: Antithrombin)

Acquired causes

1) OCP / Estrogen containing pills
2) Diabetes mellitus, Atherosclerosis, Smoking
3) Nephrotic syndrome
4) Prolonged surgery, immobilization

5) Tumors:

S → Stomach
L → Lung
A → Adenocarcinoma of
P → Pancreas

6) APLA (Anti phospholipid Ab syndrome)
(Anti β_2 gp I Ab)

Types of Thrombosis

Arterial

* Seen in atherosclerosis
* Site: Cerebral, coronary
* White in color as contains platelet
* Mural (on walls only)
* Spread:
  - Towards heart
  - Retrograde spread (backward direction)

(Carries away from heart)

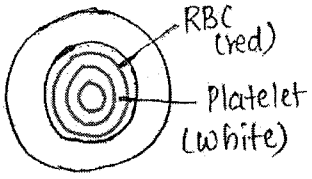
Venous

* Seen due to stasis
* Phlebothrombus (lower legs)
  eg: DVT
* Dark red as it contains RBC + fibrin
* Occlusive (complete block)
* Spread:
  - Towards heart
  - Anterograde (forward) (veins to heart)

★ MCQ

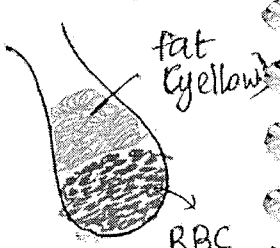
Clot

Antemortem (before death)



↓
Lines of Zahn (in microscopy)
↓
seen in the vessel

Postmortem (after death)



↓
Chicken fat appearance (gross)
↓
Large clot.

Fate of Thrombus

D → Dissolve
O → Organize
P → Propagate
E → Embolize

Embolization

* Spread of solid, liquid or gas through vessels to distant sites.

eg: Pulmonary Embolization
(1) - MC type of embolization
- Source: DVT

(DVT: Deep vein thrombosis)

2) Systemic thromboembolism
3) Fat embolism (in long bone # femur)
4) Air embolism (in Caisson's disease)
5) Amniotic fluid embolism. ↓ (decompression sickness)

Shock

* Defined as decreased blood flow to organs causing ischemia.
* Types:
  1) Cardiogenic shock
  2) Hypovolemic
  3) Neurogenic
  4) Anaphylatic
  5) Septic

Cardiogenic shock

* Cardiac pump failure
  eg: MI, Arrythmia, CHF

Hypovolemic shock

* ↓ blood volume
  eg: Blood loss / Hemorrhage
  Burns
  Severe dehydration

Neurogenic shock

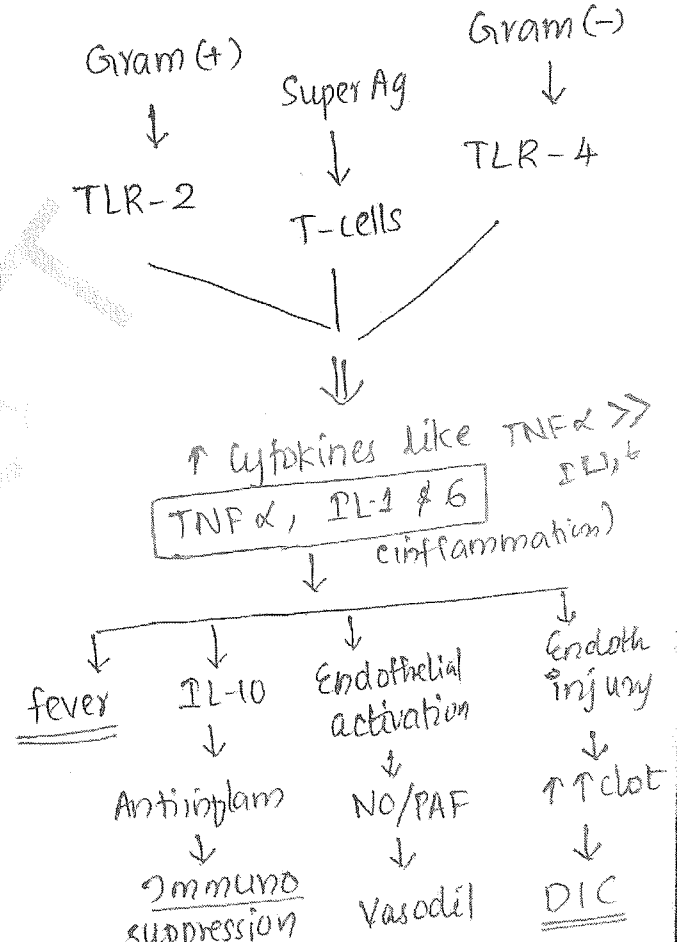
Spinal cord injury

Anaphylatic shock

Type I hypersensitivity
(vasodilatn → less flow to distal)

Septic shock

* Gram (+) > Gram (−)
* Pathophysiology:



• DIC: Disseminated Intravascular Coagulation
• TLR: Toll like receptor

Blood Banking

* Blood donated : 350 ml (♀)
  450 ml (♂)

* Tests done:
  - HIV
  - HBV
  - HCV
  - Malaria
  - Syphilis

* components prepared:

	stored	Used
1) PRBC (Packed RBC)	2-8°C	Anemia
2) Platelets	22-24°C	Thrombo-cytopenia
3) Fresh frozen plasma (FFP)	-4 to -20	All coagulatn factors
* 4) Cryoprecipitate (vWF, factor VIII)	-20°C	• vW disease • Hemophilia-A

Hemophilia A → def. factor 8
Hemophilia B → def F 9
Hemophilia C → def F 11