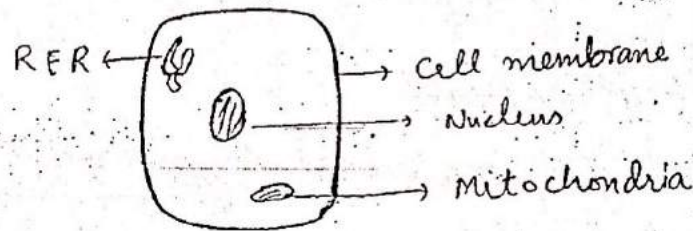


Cell Injury

4 parts of a cell which are vulnerable to injury.



Causes of cell injury

1) Hypoxia - (mc)

(a) Ischemia

Atherosclerosis

Thromboembolism

vasospasm

(b) Anemia

(c) Cardiopulmonary failure.

(d) CO poisoning

2) Infections

3) Genetic disorders

4) Hypersensitivity reactions

5) Autoimmune diseases

6) Physical agents - heat, cold, trauma, radiation

7) Chemical agents

8) Nutritional imbalances

Deficiencies (Vit., PEM)

Excess (Vit ADEK, Fats)

Outcomes of cell injury

1) Irreversible cell injury / cell death

Necrosis

Necroptosis

Apoptosis

Pyroptosis

2) Reversible cell injury

Hydrophic degeneration (cloudy swelling)

Fatty denaturation

3) Cellular adaptation

Hypertrophy

Atrophy

Hyperplasia

Metaplasia

* Dysplasia is not a cellular adaptation. It is a premalignant condition.

4) Intracellular accumulation & pathological

Proteins

Calcification

Fats

Dystrophic Cal.

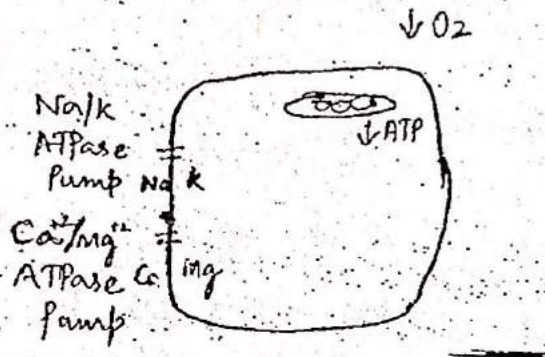
Glycogen

Metastatic Cal.

Pigments - Lipofuscin

5) Cellular ageing

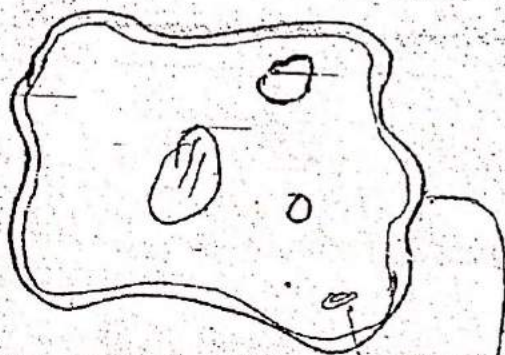
Mechanism of Cell Injury (Reversible)



(a) Pump failure due to lack of ATP

$\rightarrow$ Eflux of K^+ from cell

$\rightarrow$ Na^+ , Ca^{2+} influx into the cell



$\uparrow$ Osmotic load
(H_2O enters the cell)

Cellular swelling

Hydrophilic changes

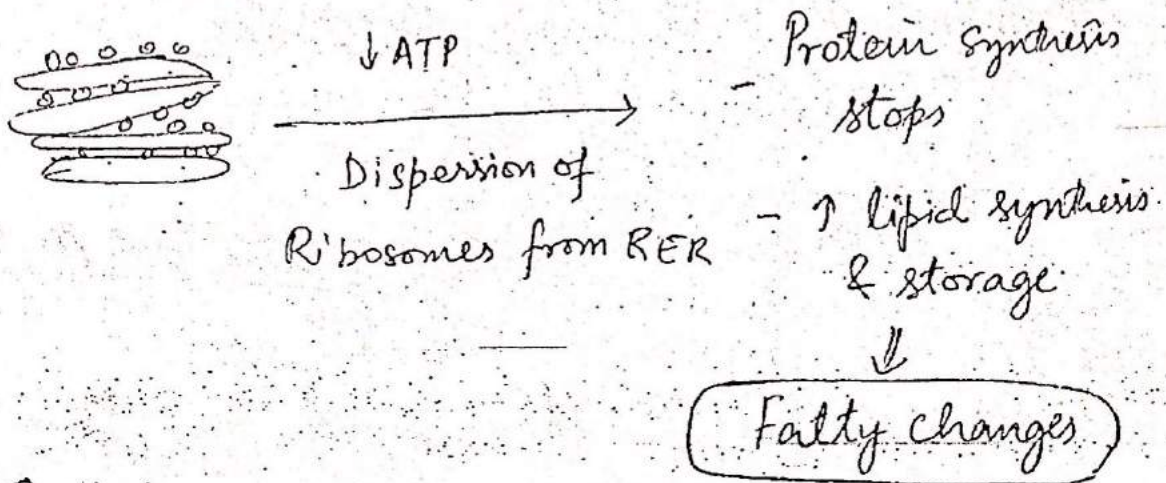
Organelles also swell up.

$\rightarrow$ Cell membrane blebs are formed

$\rightarrow$ Murkin figures are formed

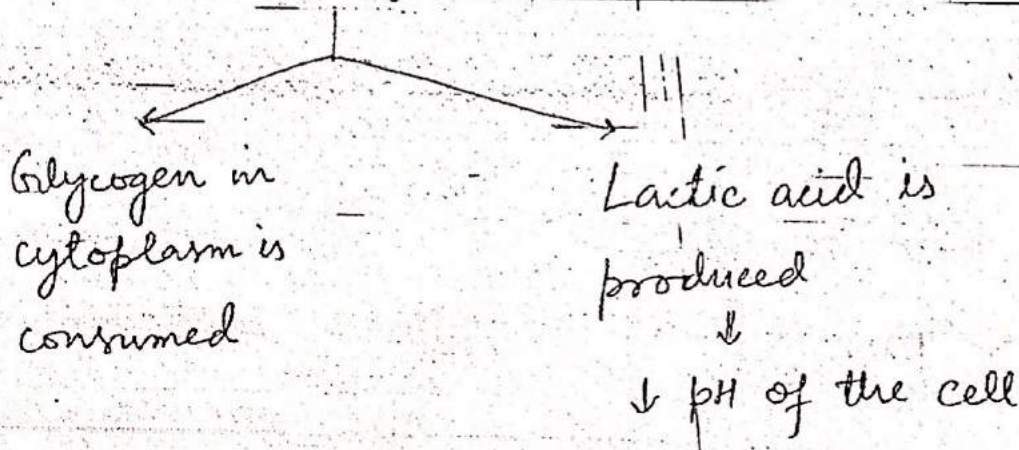
$\rightarrow$ Due to accumulation of water b/w membrane phospholipids

(b) If ATP is absent - Protein synthesis stops.



Switch over

(c) to Anaerobic glycolysis



Nucleus



↓ pH



Clumping
of Nuclear chromatin

Mechanism of Irreversible cell injury

1) Severe mitochondrial damage

Important feature of irreversible cell injury:-

① $\Rightarrow$ NO ATP production by mitochondria

② $\Rightarrow$ Large amorphous flocculant densities in mitochondrial matrix

Composed of
Calcium &
phospholipids

2) Severe membrane damage

$\uparrow$ permeability of plasma membrane

leakage of important intracellular enzymes & proteins.

Influx of Ca^{++} into the cell

3) Release of lysosomal enzymes

$\downarrow$ pH
 $\uparrow \uparrow$ Ca^{++} in cytosol } $\rightarrow$ Lysosome receptor irritation

Acid hydrolase are released

Phospholipases

Break membrane phospholipids

Proteases

Break enzymatic & cytoskeletal proteins

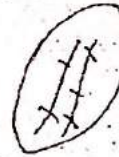
RNases

Break RNA

DNAases

Break the DNA in Nucleus

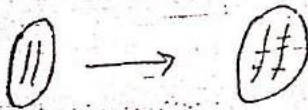
↓
Cause random
breaks in the DNA



↓
Extract this DNA and do an
agarose gel electrophoresis

↓
Smear pattern

Nuclear Changes



Pyknosis
(condensation
of chromatin)

↓
Karyorrhexis
(fragmentation
of nucleus)

↓
Karyolysis
(dissolution of
nucleus)

H&E
↓
Stains Nucleus
Stains cytoplasm & extracellular connective tissue

Necrosis

Def. cell death in living tissue

2. Processes that underlie necrosis are (Mech)

(a) Enzymatic digestion of cells by lysosomal enzymes.

(b) Denaturation of proteins

① Coagulative Necrosis

→ Due to denaturation of structural proteins of cells.

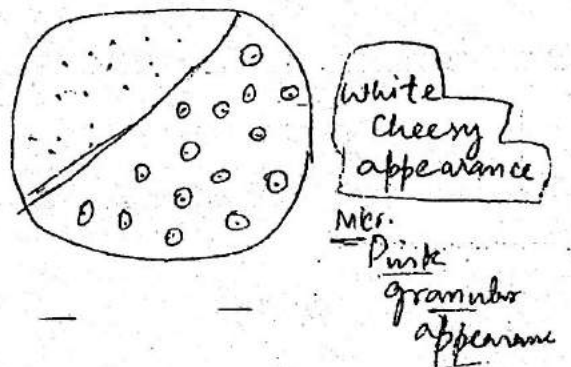
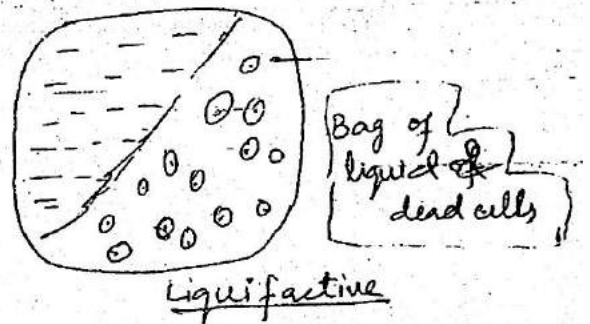
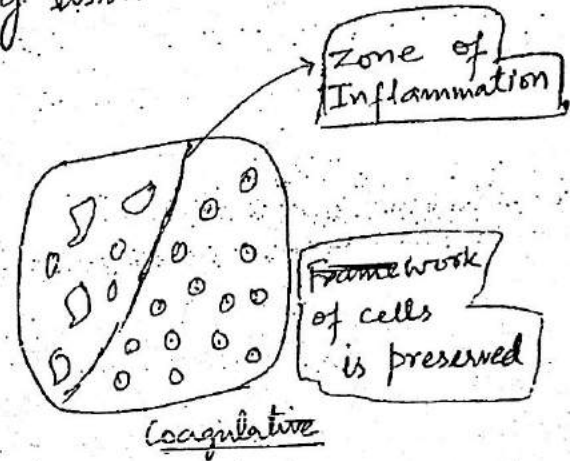
MC type of Necrosis

a) MC cause of Coagulative necrosis is Hypoxia except Brain

b) 2nd cause is Severe burns.

c) 3rd Dry gangrene.

d) Zenker's degeneration → Coagulative necrosis of muscle like rectus abdominis seen in pts with severe toxemia e.g typhoid



H/E staining

- Cell outline is preserved but cells do not have a nucleus
- ↑ cytoplasmic eosinophilia → due to denaturation of proteins
→ loss of blue nucleus
- Cytoplasm has a glassy appearance due to loss of glycogen
- Cytoplasm has a "moth eaten" appearance due to loss of organelles

M/c organ where coagulative necrosis is seen =

HEART (MI)

Others - Liver
Kidney
Spleen

Infarct

⇒ Area of necrosis, usually coagulative produced due to ischemia.

Infarcts are wedge or triangular shaped.

2 types

White Infarct
(also called as pale/anemic Infarct)

Seen in solid organs with single blood supply

e.g. In Heart, Kidney, Spleen
Liver (in hypovolumic shock)

Red Infarct
(also called Hemorrhagic Infarct)

Seen in spongy organs
Organs with dual blood supply

Lung
Liver
(Red)

More common

organs with collaterals
e.g. Intestines
Torsion of Testis/ovaries.

2) Liquifactive Necrosis (Colliquative Necrosis)

Due to enzymatic digestion of cells by lysosomal enzymes.

Dead tissue is converted into a bag of liquid.

e.g. brain hypoxia, always Liquifactive Necrosis

Abscess cavity $\left\{ \begin{array}{l} \text{Bacterial} \\ \text{Fungal} \end{array} \right.$

Wet gangrene.

3) Caseous Necrosis

Dead tissue has a white, cheesy appearance and it is friable.

Microscopically - Pink granular appearance

Causes

M. Tuberculosis (mycolic acid)

Syphilis

Fungal infections

Histoplasmosis

Coccidioidomycosis

4) Fat Necrosis

Enzymatic fat Necrosis

- Seen in pts with acute pancreatitis

- Abdominal cavity

↳ Mesentery

↳ Omentum

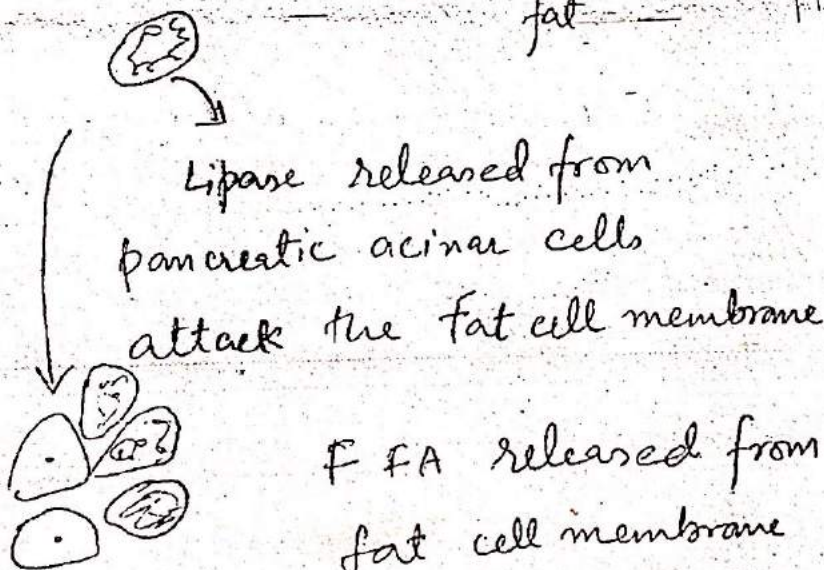
↳ Retroperitoneal fat

Traumatic fat Necrosis

⇒ Breast

⇒ Subcutaneous tissue

↳ Due to trauma



FFA released from fat cell membrane

↓
FFA + Ca

↓
Chalky white deposits of fat necrosis

↓
Saponification of fats

5) Fibrinoid Necrosis

Areas of fibrinoid necrosis has a homogenous pink appearance due to deposition of fibrin

[H & E staining]

Causes

- (a) Vasculitis e.g. PAN
- (b) Malignant HTN
- (c) Peptic ulcers
- (d) Aschoff nodules of RHD

Fibrinoid Necrosis in the centre
surrounded by Caterpillar cells, L, PC

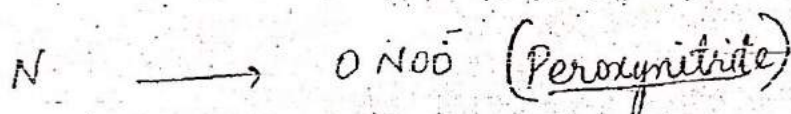
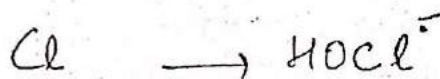
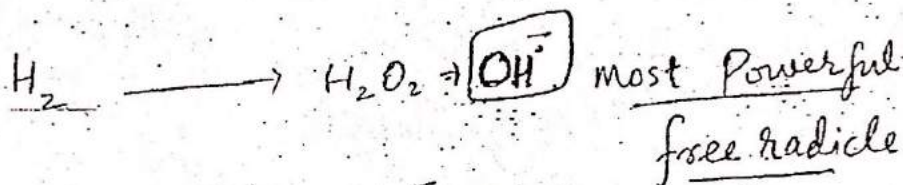
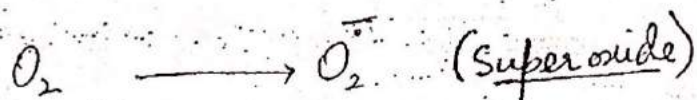
(e) AID → SLE, vasculitis
→ RA, Rheumatoid

nodules contain fibrinoid
necrosis



Free Radicals

Molecules with unpaired electrons in the outermost orbit.



Causes of free radical generation

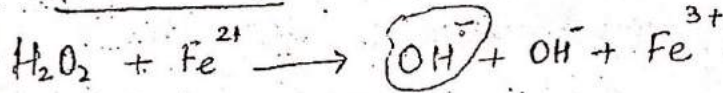
- ① Normal Oxidation & reduction reaction occurring in the cells
- ② Radiation $\rightarrow$ Hydrolysis $\rightarrow$ Free radicals
- ③ Oxygen toxicity.
- ④ Infections.
- ⑤ Drugs and chemicals.
- ⑥ Reperfusion injury $\begin{cases} \rightarrow \text{Heart} \\ \rightarrow \text{Brain} \end{cases}$

Free radicals damage cells in 3 ways.

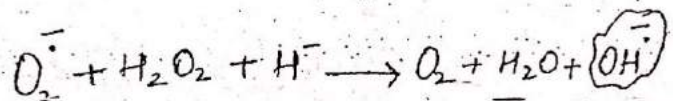
- ① Lipid Peroxidation of membranes (most imp. action)
- ② DNA Damage (oxidative)
- ③ Oxidative damage to proteins in cytosol.

Two reactions that generate ~~Peroxide~~ ^{Free Radicals}

Fenton's Rxn



Haber Weiss Rxn



Three enzymes that generate Free Radicals

- ① NADPH oxidases (phagocytic oxidase)
- ② Xanthine oxidase
- ③ Superoxide dismutase [Generates and also inactivates free Radicals]

Free Radical Removal Mechanisms

- ① Antioxidants → Vit A, C, E
Selenium
Cysteine & glutathione
Containing compounds.
- ② Enzymes

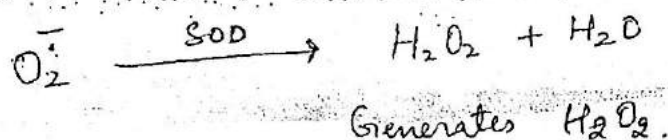
(a) Superoxide dismutase (SOD) - Inactivates Superoxides

Ca Zn SOD
(SOD I)

[Found in Cytosol]

Mn SOD
(SOD II)

[Found in Mitochondria]



(b) Catalase Found in peroxisomes
Inactivates H_2O_2

Peroxisomes are organelles where free radicals are generated and inactivated.

(c) Glutathione peroxidase → Cytoplasm
→ Mitochondria
Inactivates — H_2O_2
— OH^-

③ Serum Proteins

Albumin → binds Fe & Cu

Lactoferrin → Fe binding

Transferrin → Fe binding

~~Ceruloplasmin~~ Ceruloplasmin → Cu binding.

Free radicals can cause — cell death by

- Necrosis
- Apoptosis
- Necroptosis

Brain is protected from Free Radical injury
by CuZn SOD (SOD I)

↓
Mutation →

Amyotrophic Lateral
Sclerosis of Brain

Most important Ion involved in cell injury - Ca⁺⁺

First ion involved

- Na

Most susceptible to ischemic injury - Neurons
(3-4 min)

followed

by Cardiac tissues
(20-40 min)

Tissue least susceptible to ischemic

Injury

- Fibroblasts

- followed by

Skeletal muscle

First sign in all types of cell injury

except apoptosis

- Hydrophic
Change

Apoptosis

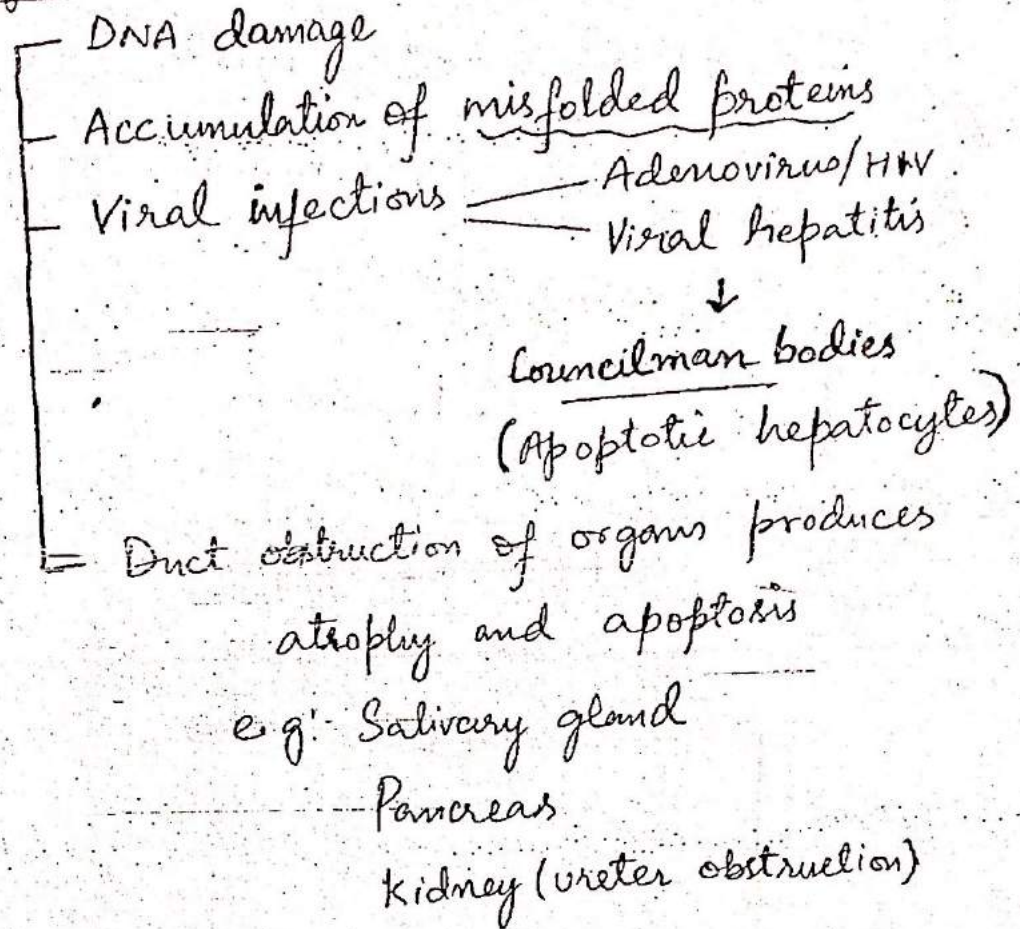
- (Programmed cell death)
- Active process.
- Death of single cell or small group of cells.
- No surrounding inflammation around apoptotic cells.

e.g.

Physiological

- Embryogenesis
- Involution of hormone dependent organs upon hormonal withdrawal
 - breakdown of endometrium during menstruation
 - ⇒ Ovarial follicular atresia following menopause
- Cell death in rapidly proliferating cells like cells in GIT, Skin, Respiratory tract
- Death of cells that have served their purpose e.g. death of neutrophils at the end of acute inflammation.
- Elimination of harmful self reactive lymphocytes.

Pathological

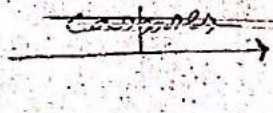
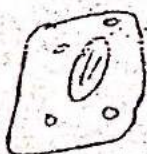


Morphology

2 enzymes that bring about apoptosis are

Caspases

Caspases break the framework
of the cell → cell will shrink
& tight packing of organelles



Chromatin
Condensation

Endonucleases

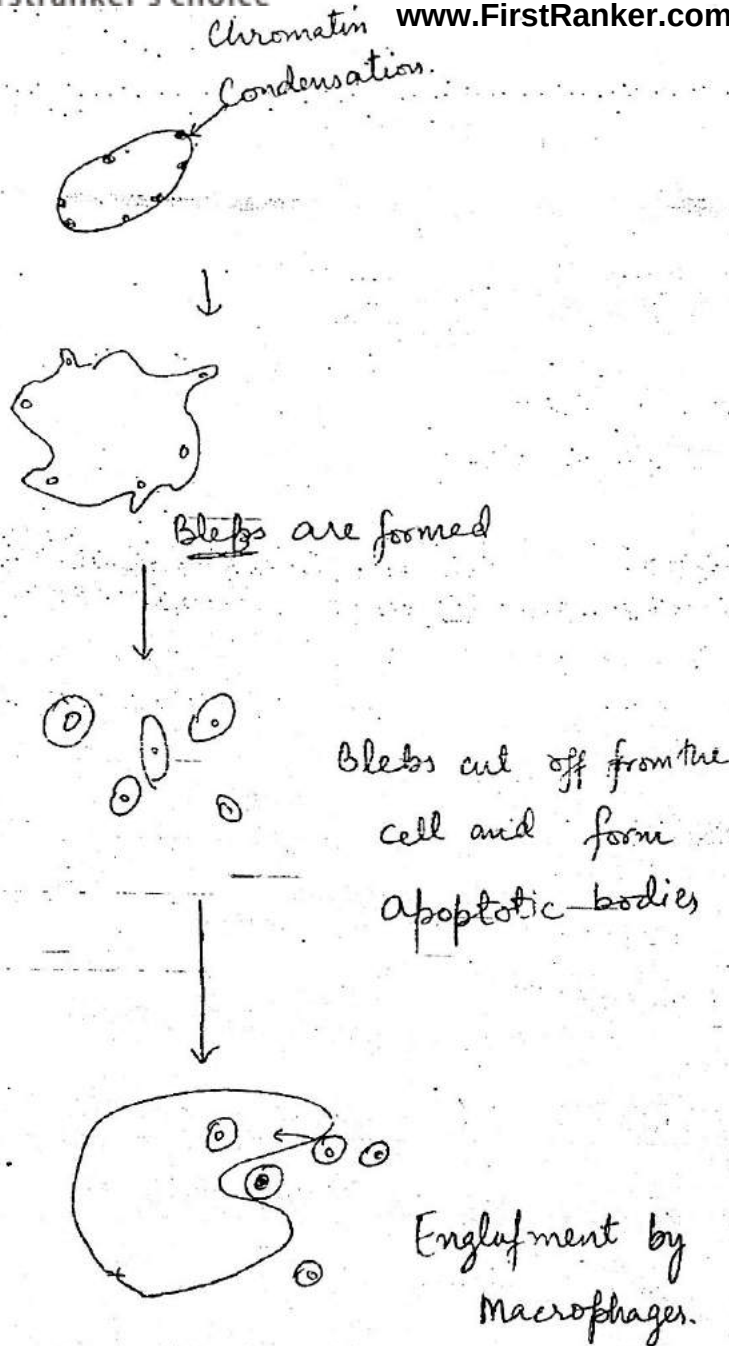
(Ca, Mg dependent
enzymes)

Endonucleases break
DNA at specific
sites (Internucleo-
-somal Regions)



180-200 bp DNA
fragments are produced

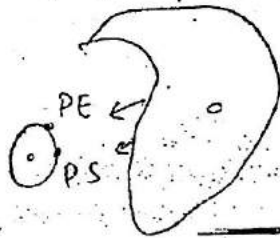
Agarose gel



Apoptotic bodies are removed by Macrophages because.

⇒ Apoptotic bodies express Thrombospondin I on their outer leaflet and macrophages have receptor for Thrombospondin II (absent in normal cells)

- Apoptotic bodies express phosphatidyl serine (PS) and phosphatidyl ethanolamine (PE) on their outer surface & Macrophages have receptors for PS & PE



Annexin V is a marker of cells undergoing apoptosis

It is an immunostain that stains PS & PE which are expressed on outer leaflet of apoptotic body.

Normal cells have PS & PE on Inner leaflet thus remain unstained by Annexin V

Microscopically

- Shrunken
- Hyper eosinophilic
- Chromatin condensation below the nuclear membrane / Pyknosis in nucleus.

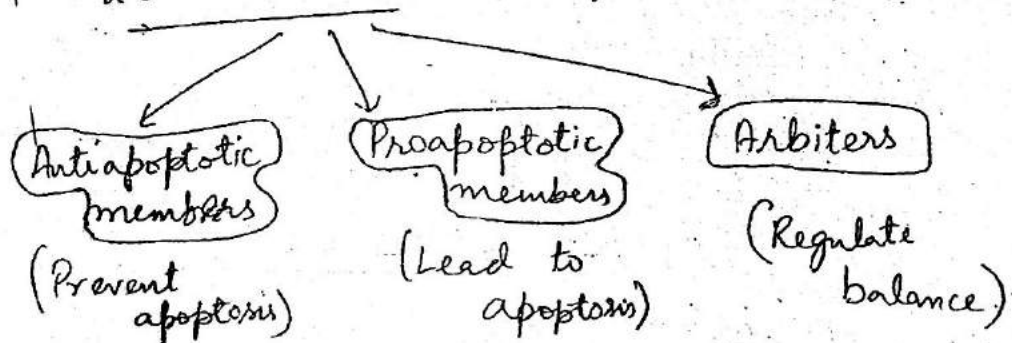
Pathways of Apoptosis

- 1) Intrinsic / Mitochondrial Pathway
- 2) Extrinsic / Death receptor initiated pathway
- 3) p53 Pathway
- 4) Perforin granzyme dependent killing

① Intrinsic / Mitochondrial Pathway

Brought about by BCL2 family of gene

20 members in the family



Antiapoptotic members

BCL2 BCL-XL, MCL-1

They reside in the outer mitochondrial membrane
↓
ER membrane & cytosol

↓
Keep the permeability of the membranes Intact

↓
Prevent leakage of Cytochrome C ⇒ No Apoptosis

Proapoptotic members

BAX BAK

They increase the permeability of outer mitochondrial membrane (drills holes in om m)

↓
Leakage of cytochrome C from mitochondria into cytosol

↓
which activates Apaf-1
(Apoptosis activating factor-1)

↓
Apoptosome is formed.

↓
binds and activates ^{Pro}Caspase 9.

⇓
Apoptosis

② Arbiters of apoptosis

BIM BID BAD PUMA NOXA

Also called as [sensors of cellular stress] &
[BH₃ only proteins]

Function is to regulate balance b/w above two groups

Inhibitors of intrinsic pathway

(IAP → Inhibitor of apoptotic pathway proteins)



Inhibits Procaspase 9

Smac/Diablo - Mitochondrial proteins

Proapoptotic

They Inactivate IAP



Thus promoting Apoptosis

Caspases



Initiator Caspases

Caspases 8, 9, 10

Intrinsic → Caspase 9

Extrinsic → Caspase 8, 10

Executioner Caspases

Caspases 3, 6, 7

Most important

Common for both the pathways

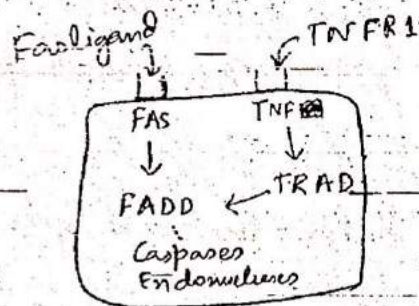
Extrinsic/Death receptor initiated pathway

Death receptors start this pathway

↳ Belong to TNF receptor family

FAS
(CD95)

TNFR1



FADD → FAS associated
Death domain

TRAD - TNF Receptor 1
Associated Death
domain.

Inhibitor of extrinsic pathway

FLIP

Produced by viruses
& normal cells.

→ Inhibits procaspase 8

p53 Pathway

Tumor suppressor gene

Chromosome 17p13.1

Called as - (Molecular Policeman)
(Guardian of Genome)
(Critical gate keeper)

It applies Emergency breaks and causes
~~genome an~~ G₁ arrest of cells

Cells with damaged DNA enter the cell cycle

↓
Sensors of DNA damage are activated.
(ATM and RAD family of proteins)

↓
Sensors activate transducers
(CHEK kinase family of proteins are transducers)

↓
p53 activated

↓
p53 recruits p21 (Inhibitor of cyclins & CDKs)

↓
p21 causes G₁ arrest of cells.

↓
Now p53 assesses DNA damage

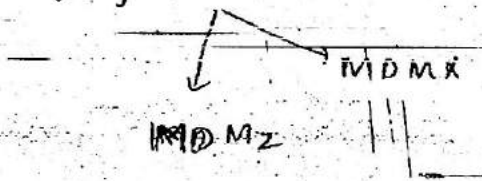
Too much DNA damage

↓
Induces Apoptosis
via mitochondrial pathway
by BAX.

Little DNA damage

↓
DNA repair gene
GADD45 is
recruited
& DNA repair done.

$t_{1/2}$ of p53 $\rightarrow$ 20 minutes



Loss of p53 (both copies) $\Rightarrow$ Li Fraumeni's syndrome

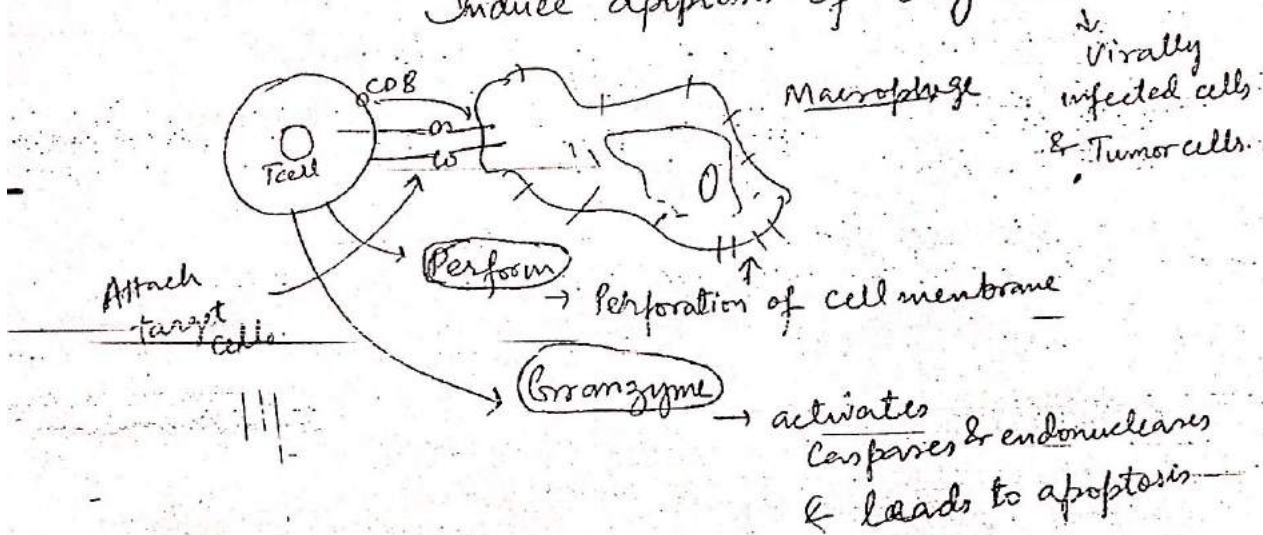
↓
↑ risk of developing carcinomas,
Sarcomas, lymphomas, etc.

gene most commonly mutated in human carcinoma
is p53.

Perforin Granzyme Dependent killing

Pathway used by NK cells and Cytotoxic T cells (CD8 cells)

Induce apoptosis of target cells.



Autophagy cell eats its own contents

Seen in nutrient deprivation.

Membrane of autophagic vacuole is derived from ER

Autophagic vacuole fuses with lysosome

Lysosomal enzymes degrade the contents → used as source of nutrient.

LC3 is a marker of cells undergoing autophagy

(Light chain)
microtubule
associated

Identifies targets of autophagy

Formation of autophagic vacuole

Necrosis

- Passive process
- Death of large no. of cells or large parts of the organ.
- Cells swell up
- Cell membrane permeability is increased
- Surrounding Inflammation is present
- DNA is broken by DNAases
 - ↓
 - Smear pattern
 - ↳ Pyknosis
 - ↳ Karyorrhexis
 - ↳ Karyolysis
- Pathological process

Apoptosis

Active process

- Death of single cell or small groups of cells.
- Cells shrink.
- Cell membrane permeability remains intact.
- No surrounding Inflammation is seen.
- DNA is broken by endonucleases
 - ↓
 - Step ladder pattern
 - ↳ Pyknosis
 - ↳ Chromatin condensation below the nuclear membrane.
- Both physiological & pathological.

Necroptosis

Programmed cell death

Active process.

Also called ~~program~~ Programmed Necrosis

Hybrid of Necrosis and apoptosis.

↳ Starts similar to extrinsic pathway

↓
TNF + TNFR1

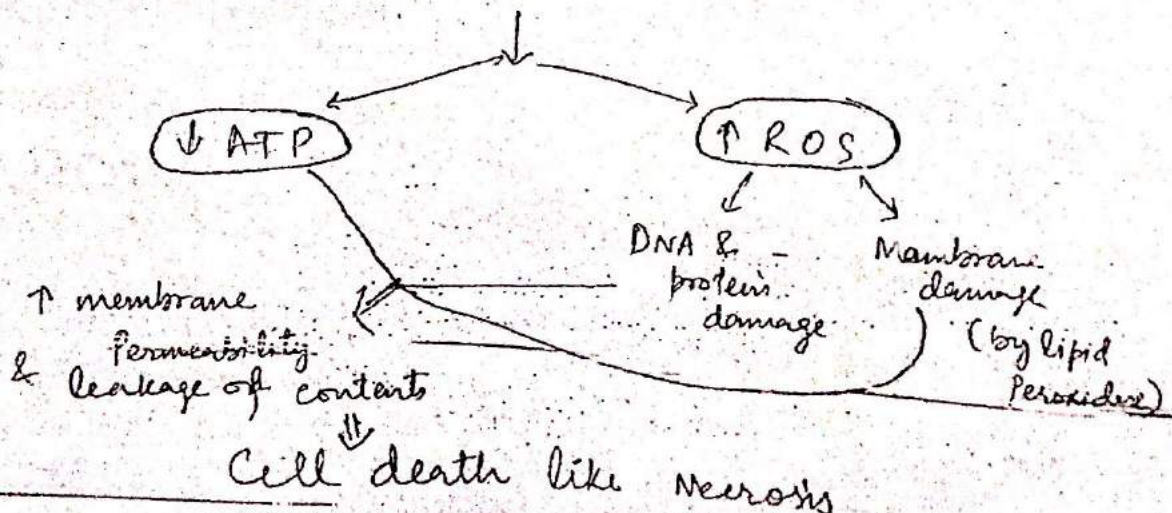
↓
Multiprotein complex called Necrosome
is formed.

[Necrosome → RIP1, RIP3 & Procaspace 8]

RIP
[Receptor Interacting Protein
~~Procaspace~~ Kinase]

↓
Necrosome (Procaspace 8 is
not activated)

↓
Metabolic alteration in cell



Examples of Necroptosis

Physiological Occurs during formation of bone growth plate.

Pathological Cell death in steatohepatitis, acute pancreatitis, reperfusion injury, & Neurodegenerative diseases e.g. Parkinson's disease.

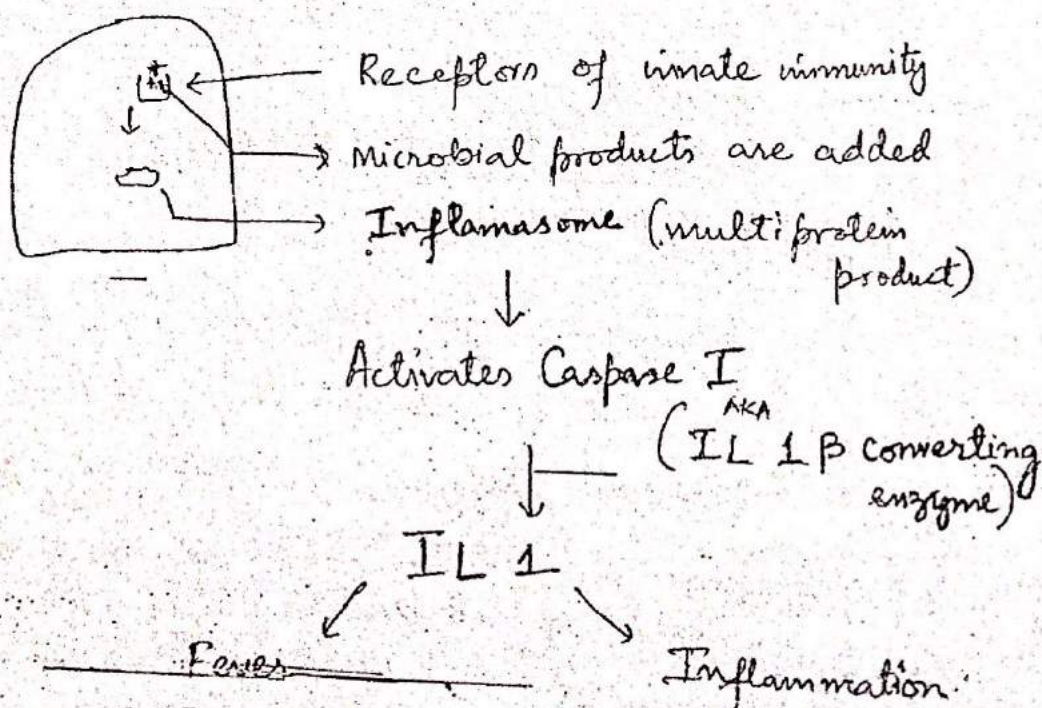
Pyroptosis

Active process

Programmed cell death

Also called as pyrogen induced apoptosis.

[accompanied by fever]



⇒ Caspase I & Caspase II induce cell death similar to necrosis

Cellular Adaptations

① Hypertrophy

↑ size of cells → ↑ size of organ
↓
↑ in functional capacity of the organ.

Size of cell increases due to increase in proteins and organelles in the cell.

Cause → ↑ Functional demand
→ ↑ Growth factor / Hormonal stimulation.

Physiological

→ Graavid uterus increases in size due to estrogens.
Hypertrophy >> Hyperplasia.

→ Skeletal muscles in weight lifters.

→ Lactating breast ↑ in size due to Hypertrophy.

Pathological

→ Cardiac hypertrophy / LVH due to HTN or aortic valve disease.

Different isoform of myosin in hypertrophic heart

α → β
myosin

Switch of contractile protein from adult (α myosin) to fetal form (β myosin) which produces slower and energetically economical contractions.

② Hyperplasia

↑ in no. of cells → ↑ in size of organ
↓
↑ in functional capacity.

Physiological

✓
Hormonal Hyperplasia

Seen in breast during

puberty & pregnancy

Compensatory Hyperplasia
seen in liver.

Pathological

Due to excessive hormone or GF stimulation.

↙
Endometrial Hyperplasia

due to excessive estrogen

↘
BHP

due to
androgen.

Pathological hyperplasia can lead to carcinoma.

Endometrial hyperplasia → Carcinoma

⇒ Endometrial adenoca can arise in background of endometrial hyperplasia

⇒ Endometrial adenoca can arise in background of endometrial atrophy also.

③ Atrophy

↓ in size of cells (due to loss of proteins & organelles)



↓ size of organs



↓ in functional capacity of organ.

Causes

↓ work load

↓ Loss of Nerve supply

↓ blood supply

Inadequate Nutrition

Loss of hormonal stimulations

Ageing (Senile atrophy)

Atrophic Cells

→ ↓ Protein Synthesis

→ ↑ protein degradation by

ubiquitin proteasome pathway

→ Show autophagy.

Example

Brown atrophy of heart.

[Atrophy + Lipofuscin accumulation]

(4) Metaplasia One type of adult cell is replaced by another type of adult cell because another one is better suited for the environmental condition.

- Due to stem cell reprogramming.

e.g. (a) Columnar to squamous metaplasia

Seen in smokers & Vitamin A deficient Patients (Respiratory Tract)

Protective function of epithelium is lost.

(b) Squamous to columnar metaplasia in Barrett's esophagus in pt of GERD.

(c) Mesenchymal metaplasia → Bone is formed in soft tissue in foci of injury e.g.; Myositis ossificans.

Stain used is Mucin

Intracellular accumulations and Pathological Calcification

Pathological Calcification

Dystrophic Calcification

- Seen in dead/damaged tissue.

- Serum Ca. $\uparrow$ (N)

- Ca metabolism (N)

e.g - dead parasites

- areas of necrosis

- damaged heart valves
(as in RHD)

- Blood vessels - Atherosclerotic plaques
Monckeberg's medial
Calcific sclerosis

Calcification in media of
medium sized arteries
in old ages

- Pseudomoma Bodies - Concentric
calcification on necrotic
tumor cells.

Metastatic Calcifications

- Seen in normal tissues
due to hypercalcaemia

- Serum Ca $\uparrow$

- Ca metabolism deranged

Sites

mc - Alveolar septae
① of lungs

② kidney

③ Gastric mucosa

④ Walls of systemic
arteries and
pulmonary veins

Causes

① CRF

② Hyperparathyroidism

③ Vit D intoxication

④ Milk alkali syndrome

⑤ Sarcoidosis

⑥ Paget's disease
Bone disease

⑦ Bone
tumor
(M.M.)

Calcification starts in mitochondria of all cells except kidney, where it starts in the basement membrane of tubules.

Stains for Calcium → Von Kossa (Black)
→ Alizarin Red S (Red)

Calcein is another stain for calcium.

Tetracycline labelling index is done to detect bone mineralization.

Intracellular accumulations

① Proteins

- Russel bodies in Plasma cells in M.M.
- Resorption droplets in PCT cells in nephrotic syndrome

 Intracytoplasmic accumulation of Ig in PC cytoplasm

② Fat

- Triglyceride accumulation → Fatty liver.
- Cholesterol accumulation → Xanthomas
→ Atherosclerotic plaques

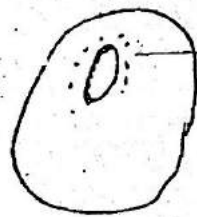


③ Glycogen → glycogen storage diseases
→ seen in PCT cells of kidney
in Pts w DM → **ARMANI EBSTEIN Lesions.**

④ Pigments

→ Lipofuscin

Lipochrome pigment
Brown in colour
→ Pigment of ageing
→ Wear and Tear pigment.
→ Sign of Free radical injury to cells.



→ accumulates in per nuclear
in the lysosomes in
the cytoplasm.

→ Hemosiderin

Iron containing pigment
→ Stain - Perl's prussian Blue reaction
H&E - golden brown in colour

Accumulation in conditions of Iron overload.

e.g. severe hemolytic anemia (Thal major)
Areas of infarction
Hemochromatosis

Cellular Ageing

Telomeres

Ends of chromosomes by which chromosomes are attached to nuclear membrane.

Also called as Biological clocks because with each cell division there is telomere shortening.

And when telomeres are shortened beyond a critical limit

→ Cellular Senescence

(terminal non dividing state of cell).

Telomerase

Maintains the length of telomeres.

Not found in somatic cells

Found in Stem cells

Germ cells

Embryonic cells

Cancer cells.

Telomere lengthening → Carcinogenesis

90% human cancers are +ve for telomerase enzyme

Werner's syndrome

→ Premature ageing

Def. of enzyme DNA helicase

Calorie restriction promotes longevity.

Needed for DNA unwinding & rejoin.

Calorie restriction promotes longevity

↑ Sirtulins
(SIR)

↓ Signaling through
IGF pathway

↓
↓ cell growth &
↓ cell metabolism
↓
↓ cell damage.

Sirtulins NAD dependent protein deacetylases.
Distributed in different components
of cell

7 different types known (SIR7)

⇒ Prevent free radical damage }
↓ Apoptosis } Promotes
Stimulate protein folding } Longevity
Inhibit cell metabolism }

Associated with

- Ageing
- DM
- Cancer.

Sirtulins
& Lipofucins

Tissue processing

[Paraffin Embedding] (10-12 hrs)

Steps

① Fixation

MC fixator used is 10 % Neutral buffer formalin

② Dehydration

Putting tissue in ↑ grades of ethyl alcohol.

(30% Ethanol → 50% → 70% → absolute alcohol)

③ Clearing

- Makes the tissue optically clear.

- Clearing agent is miscible with paraffin wax.

MC Xylene

④ Embedding

Molten paraffin wax enters the tissue and it hardens the tissue

⑤ Sectioning

Cut 4-6 microns ~~thick~~ sections and place them on slides → stain w/ H&E.

Fixatives

① M/C used fixative for HPE - 10% neutral buffered formaline.

② EM → fixative is 2.5% glutaraldehyde

↓
Followed by post fixation in Osmium Tetroxide

↓
Ultra thin sections are cut (1-2 micron)

Stain → Uranyl acetate
& observed in EM.

③ PAP smear fixed in 95% ethanol (Absolute alcohol)

④ IF examination → fixed in Normal Saline

↓
Frozen section is cut

↓
Section placed on slide
& stained by IF stains &

↓
Observed in UV light

⑤ Fixatives for Peripheral Smear and FNAC
↳ Methanol

Uses of Frozen Section

Also called as Cryo Section

or
Intraoperative biopsy

Tissue is frozen at -20° to -30°C in a cryostat.

Frozen section $\rightarrow$ can discriminate benign from malignant

② $\rightarrow$ Can analyse resection margins.

③ $\rightarrow$ Can detect metastatic deposits in
Sentinal nodes.

④ $\rightarrow$ Used for demonstration of fat
in tissue.

⑤ $\rightarrow$ Immuno fluorescence examination
- Tissue cut by frozen
section.

Special Stains

① MC stain used is H & E

② Fat $\begin{cases} \text{Oil Red O (Red)} \\ \text{Sudan Black} \\ \text{Orcein} \end{cases}$

③ Glycogen — PAS

— Colour — Pink/Rose Pink

→ glycogen is PAS +ve and diastase sensitive -

PAS +ve substances

Amyloid $\Rightarrow$ PAS +ve
diastase resistant.

Glycogen

Glycolipids

Glycoproteins

Mucins

Colloid

Amyloid

Basement membrane

All fungi

GGG CAMBRA

Used in

Russel bodies.

Diagnosis of

Glycogen storage disorder

Staining of macrophages in Whipple's disease

Demonstrating fungi

Mucins in adenocarcinoma of large intestines.

~~Seminoma, chondrosarcoma~~, Ewing's carcinoma

Lymphoblasts in AML (Block PAS +ve)
contains glycogen

④ Mucins (glycosylated proteins - plasma membrane, mucous membrane)

3 Stains → Alcian blue
PAS
Mucicarmine

- magenta
- Can stain Cryptococcus Capsule also
only not the whole fungi,
(Red coloured)

⑤ Basement membrane Stains

- PAS
- Silver Stain (Black colour)

⑥ Connective tissue Stains

→ Collagens - Massons Trichrome → blue colour
→ Reticulin fibre Silver Stain → Black
→ Elastic fibres Verhoff stain

⑦ Fibrin & Muscle

PTAH (Phospho Tungstic Acid Hematoxylin)

⑧ Fat/lipids

Oil Red O, Sudan black & Orcein

⑨ Calcium

Von Kossa (Black)

Alizarin Red S (Red)

Carlein

(10) Melanin pigment

Black
(Silver Stain)
Masson Fontana
Dopa reaction.

(11) Stain for Copper

Rubeanic acid
Rhodamine
Orcein

(12) Hemosiderin pigment

Pearl's Prussian Blue reaction
↓
Hemochromatosis

(13) Bile pigment

Fouchet's Technique (green)

(14) Mast cells

Toluidine Blue

Frozen section - Toluidine Blue

(15) Stains for Microorganism

(a) Mycobacteria Zeihl Neelsen Stain

(b) Lepra Bacilli Fite Stain

(c) Fungus PAS (Dead only) → Best
GMS (Gomori Methamine Silver) → Live & Dead

(d) Spirochetes Warthin Starry (Silver stain)
for H pylori

Inflammation

- It is Response of vascularized connective tissue to injury.

- Protective Injury

Acute

Chronic

Exudate is formed

Exudate

Transudate

- | | |
|---|---|
| - Inflammatory edema | - Non Inflammatory edema |
| - Formed due to increased vascular permeability | - Formed due to increased hydrostatic pressure. |
| - Rich in proteins & cells | - Poor in proteins & cells. |
| - Sp. gravity > 1.020 | - Sp. gravity < 1.012 |
| - LDH $\uparrow$ | - LDH $\downarrow$ |

Acute

- ① Sudden onset
- ② Lasts for a short duration
- ③ 2 characteristic features
 - extravasation of neutrophils
 - exudate formation
- ④ Local signs & symptoms are prominent
- ⑤ Usually self-limiting
- ⑥ Tissue injury is mild

Chronic

- ① Insidious onset
- ② Lasts for long duration (weeks - months - years)
- ③ 2 characteristic features
 - infiltration of tissue by mononuclear cells
 - Tissue destruction
- ④ Local signs & symptoms are not prominent
- ⑤ Progressive
- ⑥ Severe & may lead to fibrosis

Acute Inflammation

Events of acute inflammation

Mediators of acute inflammation

Events of acute inflammation

- Seen in post capillary venules
 - ↳ Vascular events
 - ↳ Cellular events

I Vascular events

www.FirstRanker.com

① Transient vasoconstriction



② Massive vasodilation



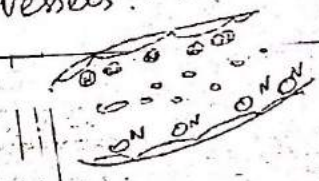
③ Increased vascular permeability → exudate formation Most imp



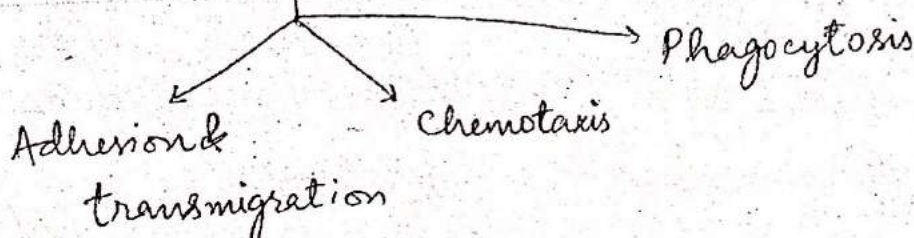
④ Stasis of cells in Blood vessels



⑤ Leucocyte margination to the periphery



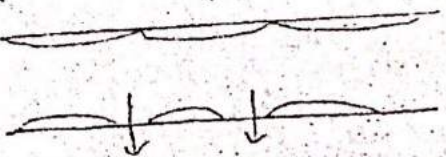
II Cellular events



Mechanisms of ↑ vascular permeability

① Endothelial contraction (M/c mech)
(occurs in post capillary venules)

Mediators →
→ Histamine
→ Bradykinin
→ Substance P
→ Leukotriene



⇒ Immediate Transient response

② Endothelial retraction / Junctional reorganisation
(venules & capillaries)
Delayed type of contraction

Mediators → IL-1
(cytokines) → TNF α

⇒ Delayed, sustained response

③ Direct Injury

(Seen in venules, arterioles, capillaries)

Severe Injury

e.g. Severe burns
Chemicals
Toxins

↓
Cells undergo necrosis
& detach.

↓
Fluid leakage
which starts immediately
↓
Leakage continues till
a new cell regenerates

⇒ Immediate sustained response

Mild Injury

e.g. mild sunburn.

↓
endothelial cells die
after a few hours due
to apoptosis.

↓
Fluid leakage starts
after few hours
↓
Leakage continues till
a new cell regenerates

⇒ Delayed sustained response

Transplant Rejection

For a transplant HLA matching is done b/w donor and recipient.

HLA antigens that should be matched are

HLA DR

HLA B

HLA A

HLA matching is not done for liver, heart, lungs, & cornea

because other factors like

- anatomical compatibility
- Severity of underlying disease
- Need to minimize the ^{time} of organ storage

Immunosuppressive therapy

- ① Steroid - Reduce Inflammation
- ② Mycophenolate mofetil - Inhibits lymphocyte proliferation
- ③ Tacrolimus (FK 506) - Inhibits Phosphatase
Calcineurin which is required for activation of NFAT
(Nuclear Factor of Activated

NFAT not activated



No IL 2



T cell inhibition

④ T & B cell depleting antibodies

⑤ Pooled IV immunoglobulins

Complication of organ transplant

① Infection (MC)

→ CMV most common infection

Cells show owl eye intranuclear inclusions.

⇒ Polyoma Bk viral infection

Deacy cells - PC T cells & intra-nuclear basophilic inclusion.

② Transplant rejection

③ GVHD

④ T risk of malignancies

→ HPV associated
SCE skin

→ EBV ass. lymphomas

→ HHV8 ass. Kaposi's
Sarcoma.

Transplant Rejection

Solid organ transplant

Recipient is immunocompetent.

3 types of Rejection.

① Hyperacute rejection occurs within minutes

(< 48 hours)

It is due to preformed antibodies in the recipient.

↳ Seen in

- [Multiparous women
- [Multitransfused individuals
- [Past H/o transplant rejection.

* ABO & RH incompatibility can also cause hyperacute rejection.

Gross

Slightly swollen + mottled + cyanosed

kidney — Anuric

Filters few drops of blood urine
or no urine at all.

M/E

① Neutrophilic infiltration in glomerular capillaries,
arterioles & peritubular capillaries

② Fibrinoid necrosis & thrombosis in the vessels

③ Thrombosis leads to cortical necrosis

TYPE II Hypersensitivity Reaction.

Acute Rejection

Occurs from weeks - months (< 6 months)

or
later when immunosuppressive therapy is withdrawn.

2 types

Acute cellular Rejection

Brought about by

- CD4 T cell
- CD8 T cell

Type IV HR.

Responds to increasing the dose of immunosuppressive therapy.

Acute Humoral Rejection

Brought about by antibodies that are produced after transplantation.

Type II > Type III HR.

Does not respond to increasing the dose of immunosuppressive therapy but responds to B cell depleting agents.

Biopsy

Microscopical Ex

Three types are seen.

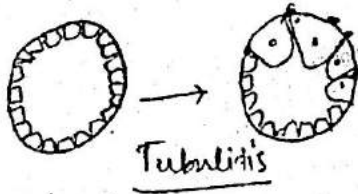
Type I / Tubulointerstitial pattern

Tubulitis
(T cell/macrophage) Interstitial mononuclear cells infiltration

M/C

vasculitis

↓
Damage to glomeruli & small vessels



Thrombi in small vessels

Fibrinoid Necrosis in vessels

Type II vascular pattern
Endothelitis

Type III vascular pattern
Endothelitis
+
Necrosis in the vessel wall.

IHC Cy4d deposited in vessels
glomerular capillaries Peritubular capillaries
(in immunoperoxidase stain)

Chronic Rejection (months - years)

Can be due to antibodies or T cells

More common - Type IV HR.

M/E - ① Obliterative intimal fibrosis of BV.

② Atherosclerosis of graft vessels

③ Glomerulosclerosis

④ Tubular atrophy

⑤ Interstitial fibrosis

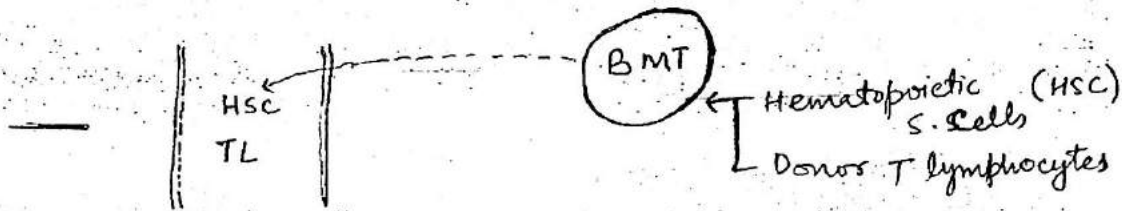
Transplant glomerulopathy

GVHD

Graft Versus host disease

It is a complication of Bone Marrow Transplant (BMT)

Type IV HR.



Recipient is immunocompromised

Due to primary disease for which Transplant is indicated

Due to Radiotherapy or chemotherapy that is given to form transplant bed.

GVHD

Acute (<100 days)

- ① Skin (mc)
Rashes & ulcers
- ② GIT Oesophageal & Intestinal ulcers
~~bloody diarrhoea~~
Malabsorption

Chronic (>100 days).

- ① Skin
Scleroderma like fibrosis
- ② Structures
malabsorption.

③ Liver

Cholestatic jaundice

Inflammation of
bile duct

Destruction of the ducts
cholestatic jaundice

④ Destruction of immune system of the recipient
e.g; LN, Thymus, spleen, etc.

T cell depleted B.M.T.

- No GVHD

- Increased incidence of graft failure

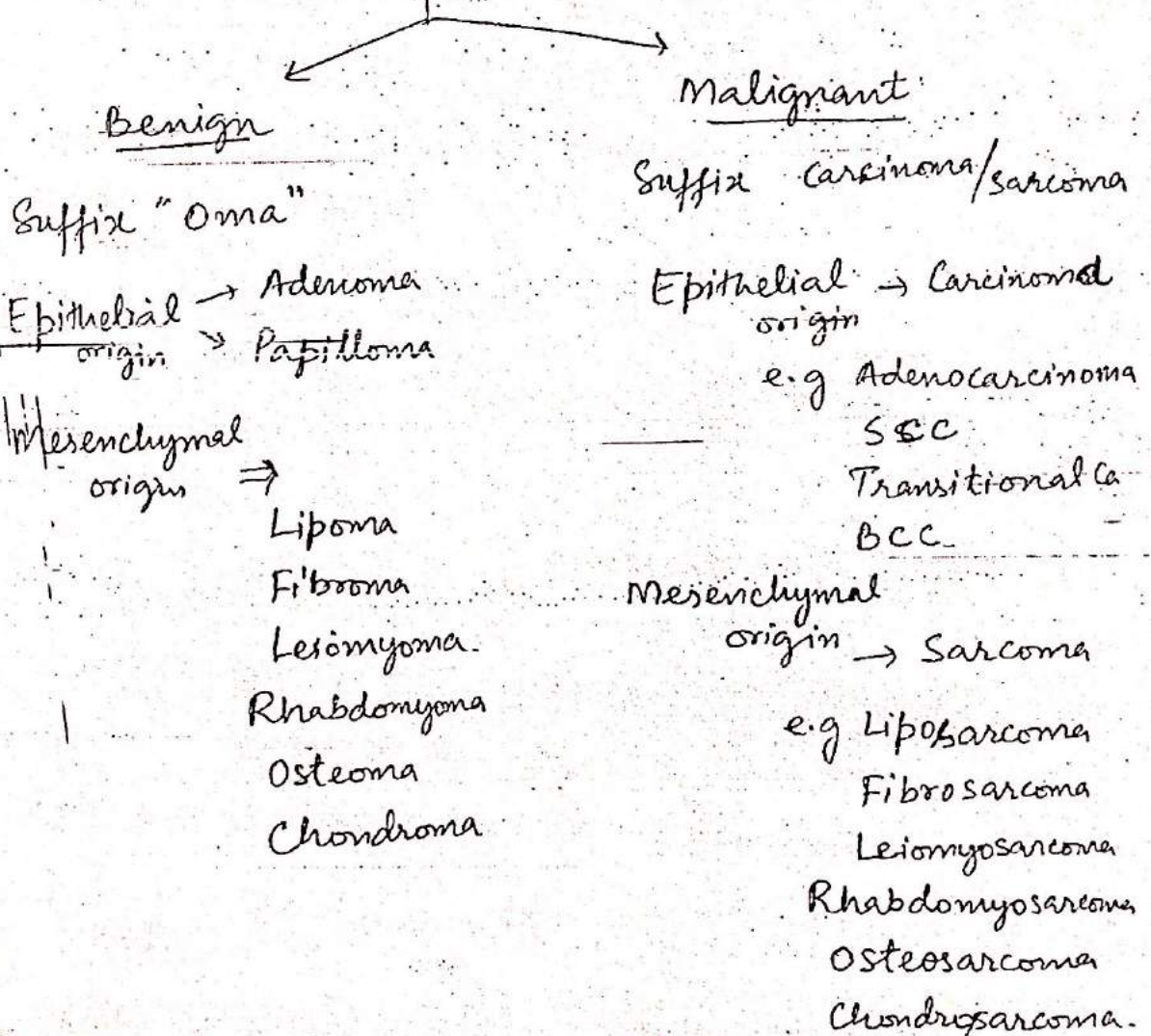
- Relapse of primary disease e.g. Acute leukemia

Also called as graft versus leukemia effect.

- ↑ incidence of EBV. related leukemias
& lymphomas.

Neoplasia

- New growth
- Neoplasm - Tumor



Malignant tumors - Suffix 'oma'

- ① Hepatoma (HCC)
- ② Seminoma
- ③ Melanoma (melanocytes)
- ④ Chordoma (notochord)

Teratoma

Tumor of Totipotent cells

(a) Mature cystic teratoma [Benign tumor]

→ Elements of all three germ layers
→ All components are mature

e.g.; Skin adnexal structures, bone, cartilage, blood vessels, tooth, fat, thyroid tissue

Ovary → Dermoid cyst

(b) Immature Teratoma [Malignant tumor]

Elements are immature or fetal type

e.g.; immature cartilage or bone
immature Neural tissue is important
↳ for grading.

(c) Teratoma with malignant transformation

Malignant tumor

One of the component has become malignant.

Pleomorphic adenoma

Benign tumor
[Salivary glands (MC)
(Parotid MC & Breast)

Epithelial component

glands
Sq. epithelium

Mesenchymal component

Cartilage
Fibrous tissue
Bone
Muscle

Cells of origin → Myo epithelial cell

Rx wide excision

As Tongues of tumor tissue are seen in the surrounding tissue.

NOT TRUE NEOPLASMS

Choristoma

- Ectopic rest of Normal tissue
- Normal tissue at abnormal location

e.g. glial tissue in nasopharynx
Adrenal rests in the kidney

Hamartoma

Normal tissue in normal location but in a disorganised arrangement

e.g. bronchial hamartoma.
Hemangioma
Lymphangioma.

Benign

Well differentiated
(Resemble the tissue
from which they rise)

Slow growing & may
regress on their own

Usually Encapsulated
un encapsulated are
as - Leiomyoma
Hemangioma
Lymphangioma

No local invasion

No metastasis

metastasis is most imp. feature that differentiate
that benign from malignant

Malignant

Poorly differentiated
or well - moderate
differentiated
or Anaplastic
↓
(Complete lack of
differentiation)

Rapidly growing, have
erratic growth.

Malignant tumors that
show spontaneous
Regression

- R C C
- Neuroblastoma
- Retinoblastoma
- Malignant Melanoma
- Chorio Carcinoma

Uncapsulated or
may show pseudo
capsule
(formed by compressed
normal tissue)

Local invasion +

Metastasis +

Malignant tumors that show local invasion but no metastasis $\Rightarrow$ BCC
Glioma

Features of Malignant cells

Large cells

High N:C ratio

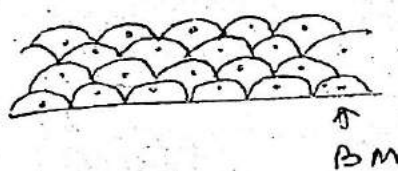
Pleomorphism - variation in shape & size

Hyperchromatic nucleus

Abnormal mitosis

Dysplasia

Premalignant condition e.g. cervical dysplasia



Loss of polarity

Pleomorphism

High N:C Ratio

Abnormal mitosis

Hyperchromatic Nucleus

Cervical dysplasia

CIN I - Abnormal cells
confined to $\frac{1}{3}$ rd of CX

CIN II - occupy $\frac{2}{3}$ rd CX
epithelium

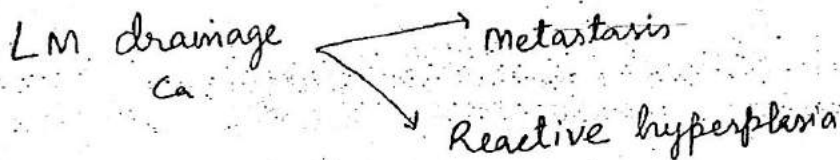
CIN III - occupy full thickness of
cervical epithelium | BM intact.

They are confined to the
basement membrane

Pathways for Spread

① Lymphatic Spread

Preferred mode of spread for a Carcinoma



② Hematogenous spread

Preferred mode of spread of a Sarcoma

3 carcinomas

first spread
by Hemato-
genous
route

RCC
HCC
Choriocarcinoma

M/C spread to - lungs > liver

Venous invasion is more common than
Arterial invasion

③ Direct spread

(a) Mesothelioma (MC) arises from mesothelial cells of pleura or peritoneum & spreads on the surface of pleura or peritoneum.

(b) Pseudo myxoma peritonei
Seen in

Mucinous adenocarcinoma Appendix

Mucinous adenocarcinoma ovary

Mucinous adenocarcinoma colon

Mucin produced
by tumor cells

↓
Causes adhesions b/w various
organs in the peritoneal cavity

Tumors that spread via CSF

Medulloblastoma

[Small round cell tumor]

[Childhood tumor]

Site - Posterior fossa
(cerebellum)

Extremely radiosensitive

Spreads via CSF &
produces

DROP METASTASIS

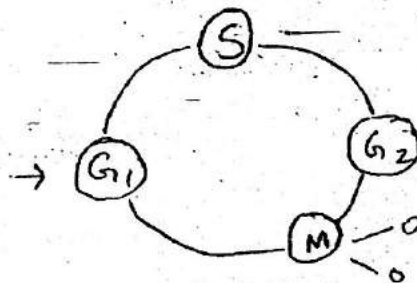
in Cauda equina

Ependymoma

Arises from
ependymal lining of
ventricles

- ① Neuroblastoma
- ② Retinoblastoma
- ③ Medulloblastoma
- ④ Embryonal rhabdomyosarcoma
- ⑤ Lymphoma (lymphoblastic)

Normal cell cycle regulation.

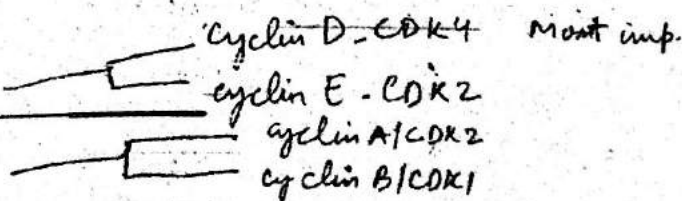


Orderly progression of cell through cell cycle is brought about by cyclins & cyclin dependent kinases (CDKs) [protooncogenes]

<u>Cyclins</u>	<u>CDKs</u>	
cyclin D	4, 6	} <u>G₁ to S transition</u>
cyclin E	2	
cyclin A	2	} <u>G₂ to M transition</u>
cyclin B	1	

G₁ S transition

G₂ M



Most imp.

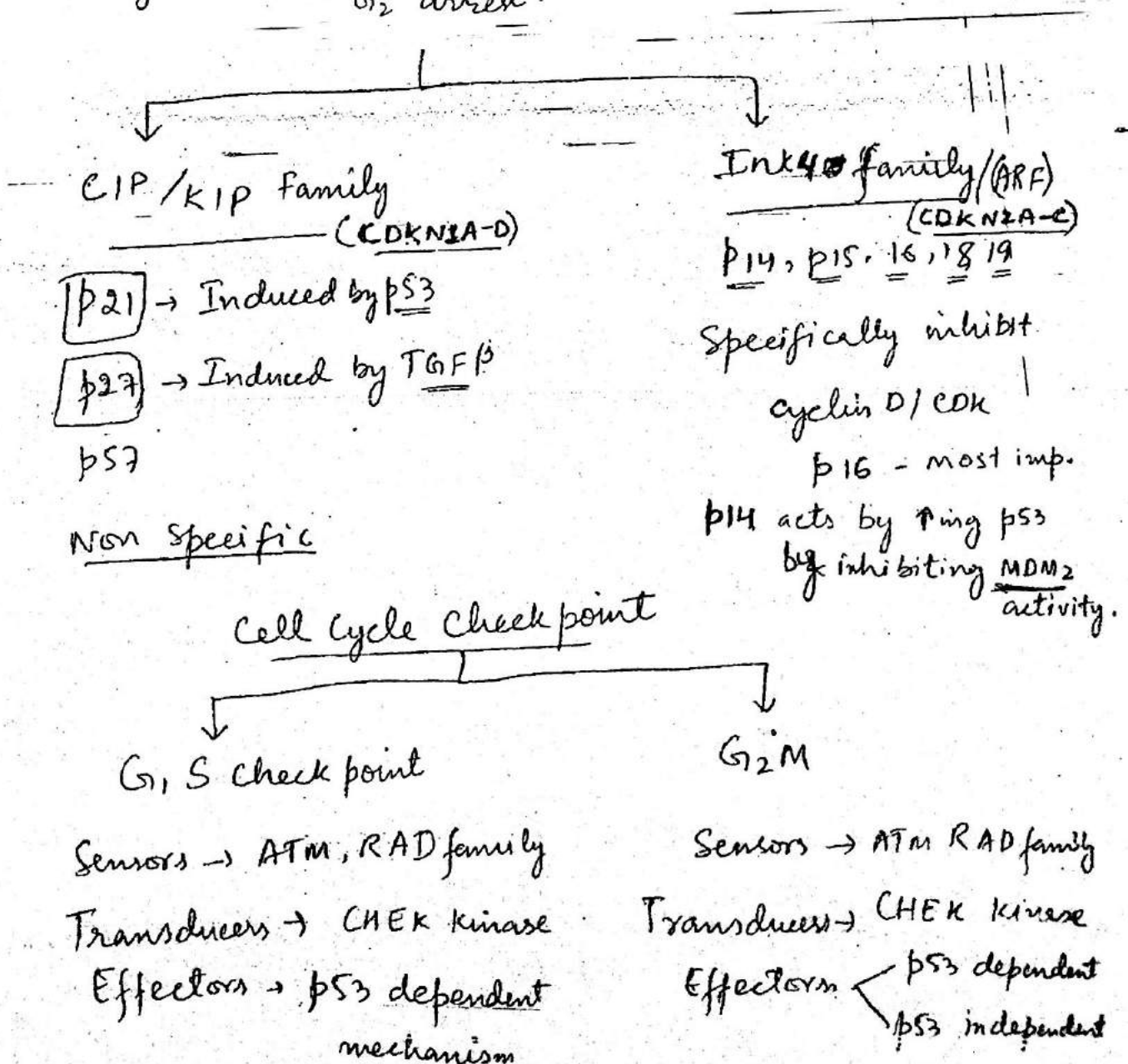
cyclin A/CDK₂ → Takes the cell through G₂ phase upto prophase of mitosis

cyclin B/CDK₁ → Regulates all initial events of mitosis beyond prophase.

Inhibitors of cyclins/CDKs

↳ Inactivate cyclins/CDKs and stop the cell in the cell cycle

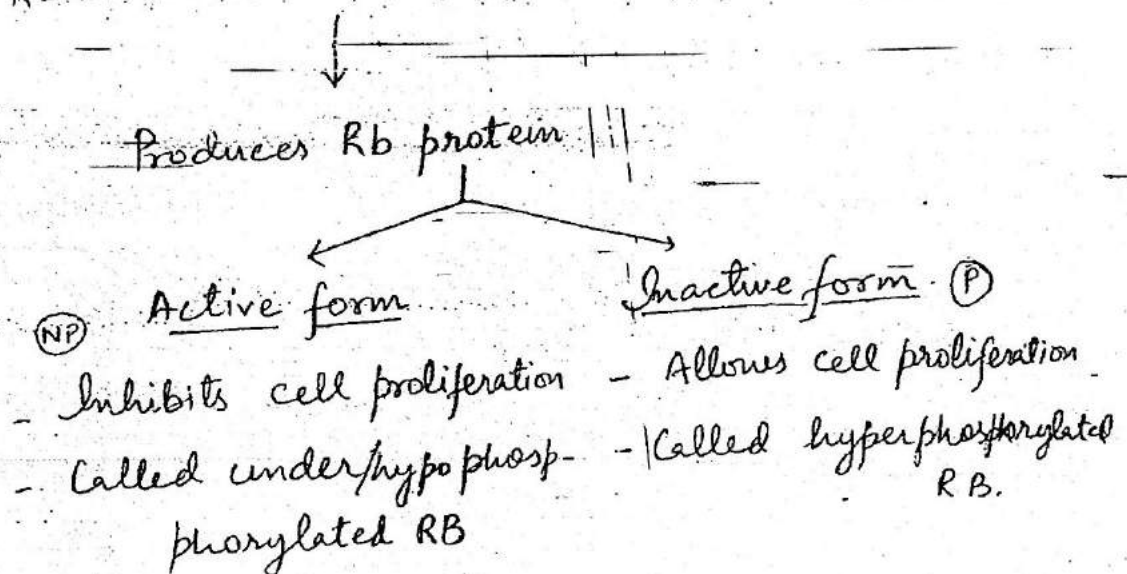
- G₁ arrest
- G₂ arrest



Rb gene

- Tumor suppressor gene - on chromosome 13q¹⁴
- Also called as Governor of cell cycle
or
Molecular on-off switch of cell cycle
- Rb causes G₁ arrest of cell cycle.

Rb is located on 13q¹⁴



⇒ Under phosphorylated RB has pockets in which it hides E2F/DP1 transcription factors - These factors are used in S phase for DNA synthesis.

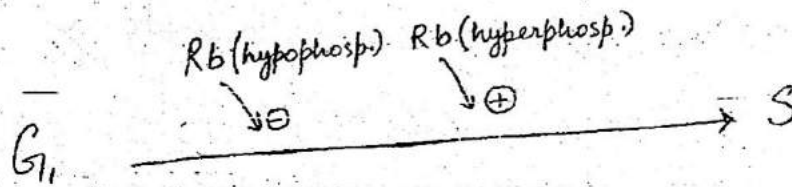
Thus causes G₁ arrest of cell

⇒ Under phosphorylated RB also recruits enzyme histone deacetylase causing compaction of nuclear chromatin thus G₁ arrest.

When the cell has to move from G_1 to S phase,
cyclin D/CDK4 phosphorylates the underphosphorylated Rb
to hyperphosphorylated Rb.

↓
releases E2F/GP1 TF from pockets

↓
Cell will proceed to S phase.



Loss of Rb gene produces — Retinoblastomas
— Osteogenic sarcomas.

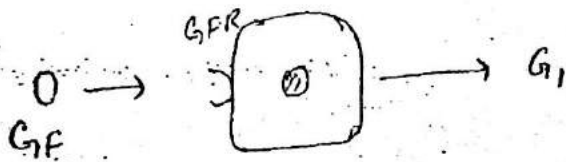
Regulatory genes

4 classes of regulatory genes

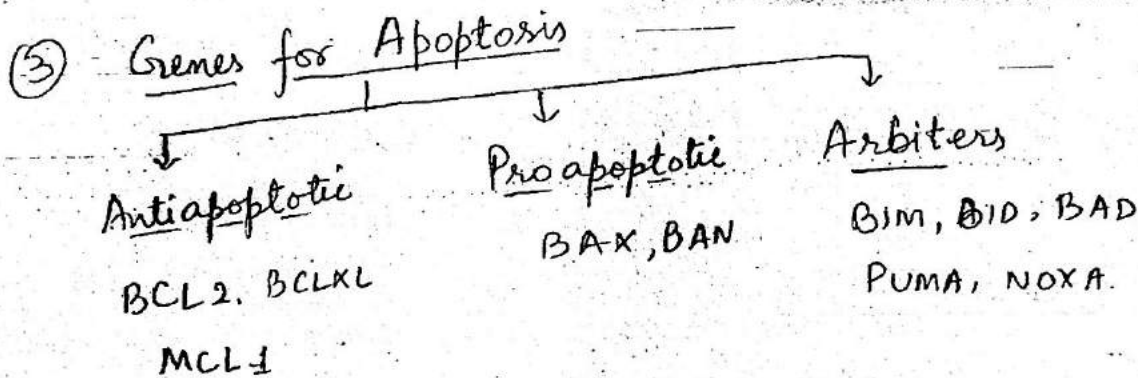
- ① Proto oncogenes
- ② Tumor suppressor genes/Anti oncogenes
- ③ Genes for apoptosis
- ④ Genes for DNA repair.

① Protooncogenes — Cause cell proliferation
Controlled cell proliferation

Protooncogenes can be G.P., GrR, STP (Signal Transduction),
NTP (Nuclear Transduction Proteins),
cyclins & CDKs

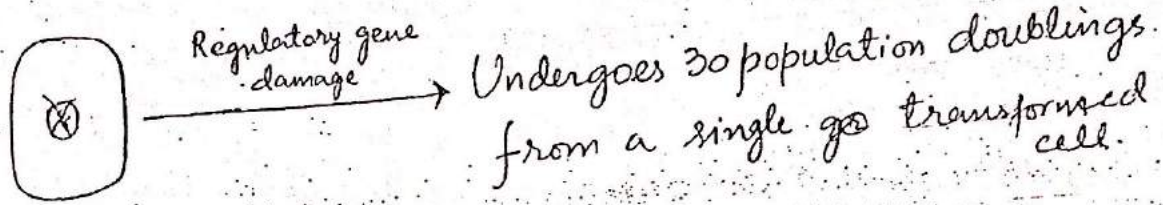


(2) Tumor suppressor gene / Antioncogene
Inhibit cell proliferation by inhibiting



(4) Gene for DNA repair

Molecular basis of Cancer



Kinetics of tumor cell growth

↓
1 gm cancer = 10^9 cells is formed
↓ 10 population doublings

1 kg cancer cells = 10^{12} cells is formed
(Largest mass compatible with life)

Genetic damage lies at the heart of carcinogenesis

Regulatory genes are damaged, transformed cell enters cell cycle & undergoes population doublings leading to cancer.

↓
Tumor cells establish their own blood supply by producing — VEGF, bFGF, PDGF
(Tumor angiogenesis)

↓
Local invasion & distant metastasis

[Phenotypic attributes of a cell & are acquired in step wise fashion]

Mechanism of Metastasis

- ① Metastatic sub clone is formed, which shows decreased expression of E cadherin → loosens up from the main tumor.
- ② Metastatic subclone produces enzymes that degrade BM & extracellular connective tissue
e.g. Type IV collagenase
Matrix metalloproteinases
Plasminogen activator
- ③ Metastatic subclone shows expression of laminin & fibronectin receptors by which they attach to laminin & fibronectin in the connective tissue.
- ④ Some cancers also produce autocrine motility factors which help in a metastasis.
- ⑤ Cancer cells enter the blood vessels where they attach to

Epithelial to mesenchymal transition (EMT)

Cancer cells acquire a mesenchymal phenotype (e.g; spindle shape) for metastasis

2 genes for EMT → $\left. \begin{array}{l} \text{SNAIL} \\ \text{TWIST} \end{array} \right\} \downarrow \text{Ecadherin.}$

Regulatory genes.

① Proto oncogene (Controlled cell proliferation)

Activated Protooncogene

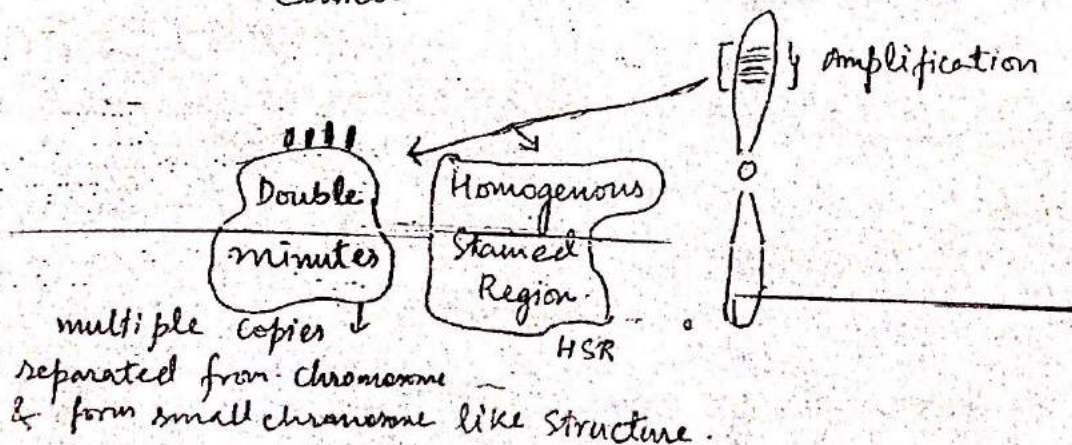
Oncogenes

Produce onco proteins

Cancer

- Translocation
- Point mutation
- Amplification
- Over expression.

POTA



I Growth factors

✓ SIS Overexpression → Astrocytoma
(PDGF-β)

HST 1 Overexpression → Osteosarcoma
(FGF)

INT-2 Amplification → Bladder Ca
(FGF3) Stomach Ca

HGF Overexpression → HCC
Thyroid Ca

II GFR (Growth Factor Receptor)

EGFR (Epidermal Growth Factor Receptor)
 ↳ ERB-B1 Overexpression → Adeno Ca Lung
 ↳ ERB-B2 Amplification → Breast Ca
 (Her-2-neu) | Ovarian Ca

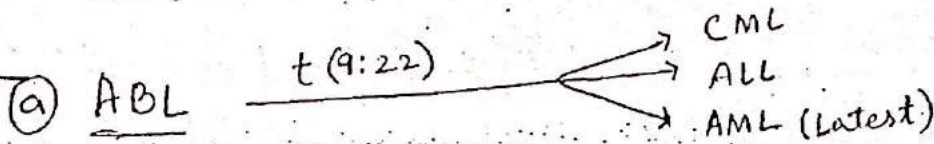
RET Point Mutation (Activation) → MEN 2A, MEN 2B
Medullary Ca Thyroid.

RET Point Mutation (Inactivation) → ~~Hirschsprung disease~~
HIRSCHSPRUNG Disease
(Congenital Megacolon)

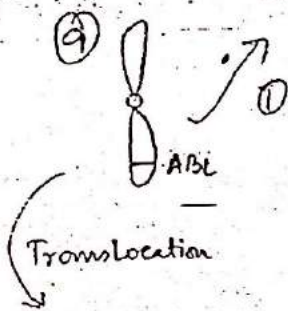
KIT Point Mutation → GIST
(CD117) Soft tissue tumors

Alk Translocation → Adeno Ca lung
Lymphoma

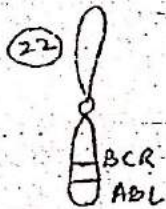
III Signal transduction proteins



ABL encodes for a protein with tyrosine kinase activity



Causes signal transduction through myeloid & lymphoid cells.



$\xrightarrow{(2)}$ BCR ABL Fusion gene

Fusion protein $\bar{c}$ very high tyrosine kinase activity.

Myeloid cells

$\downarrow$
210 KD size

$\downarrow$
CML

Lymphoid cells

$\downarrow$
190 KD size

$\downarrow$
ALL

⑥ RAS

→ Most common Oncogenic mutations in human Cancers → RAS Mutations.

KRAS $\xrightarrow{PM}$ Colon, lung, pancreatic ca
H RAS $\xrightarrow{PM}$ Urinary bladder & kidney tumor.
N RAS $\xrightarrow{PM}$ Melanomas & hematopoietic tumors.

2 forms of RAS protein

Active

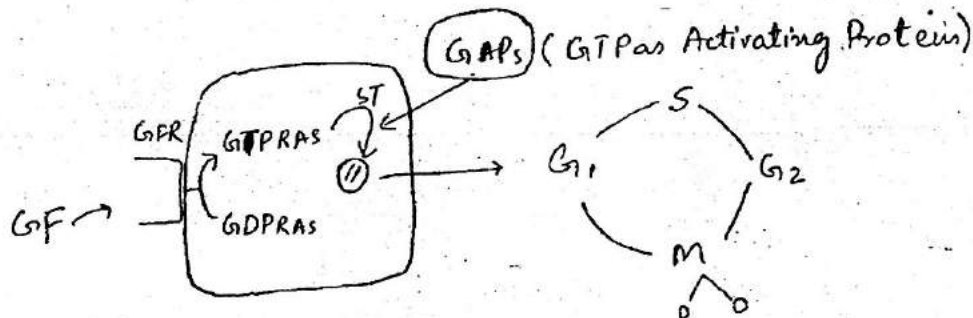
GTP RAS

Allows cell proliferation

Inactive

GDP RAS

Prevents cell proliferation



GF + GFR → GDP RAS is converted to GTP RAS

↓
Causes ST

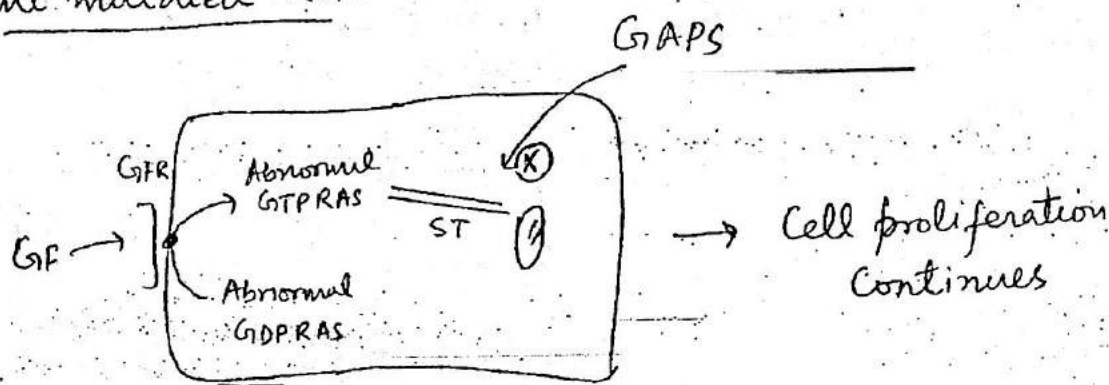
↓
Cell proliferation

After limited cycles

GAPs → Pull the Phosphate group from GTP RAS & converts it in GDP RAS

↓
Stops ST → Stops cell proliferation

Point mutated RAS

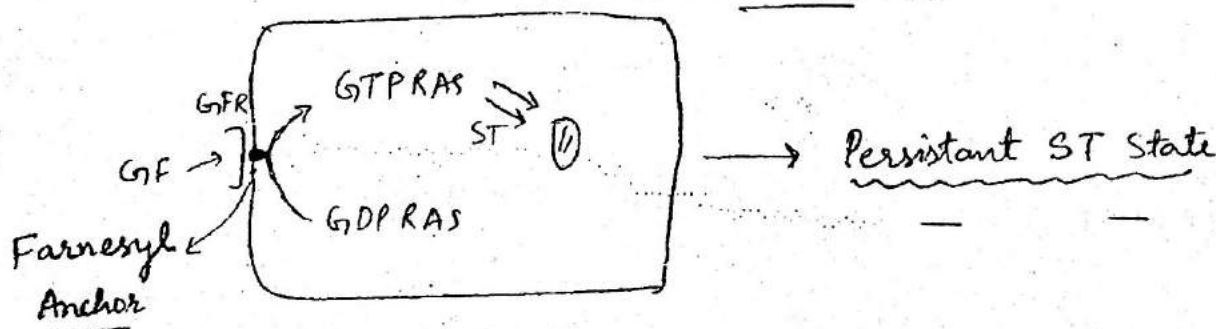


Due to point mutation in RAS, GAPs are unable to pull 'P' group from abnormal GTPRAS.

↓
RAS Remains in persistent Signal Transduction state & produces tumors.

NO GAPs

NO GAPs



GAPs are produced by NF1 gene

↓
loss of which leads to NF1 Syndrome Persistent ST state & produces Tumors.

③ BRAF

BRAF (V600) $\xrightarrow{PM}$
 - Hair cell Leukemia
 - LCH
 - Papillary Ca Thyroid
 - Astrocytoma
 - Colonie Ca.

HPLC A

Drug - Vemoraferib

④ β Catenin

β Catenin $\xrightarrow{PM}$ HCC
Hepatoblastoma

⑤ NOTCH

NOTCH $\xrightarrow{PM}$ Leukemias
 Lymphomas.

④ Nuclear Transcription Proteins

C MYC $\xrightarrow{t(8:14)}$ Burkits Lymphomas

N MYC $\xrightarrow{\text{Amplification}}$ Neuroblastoma

⑦ Cyclin / CDKs

Cyclin D₁ $\xrightarrow{t(11:14)}$ Mantle Cell Lymphoma

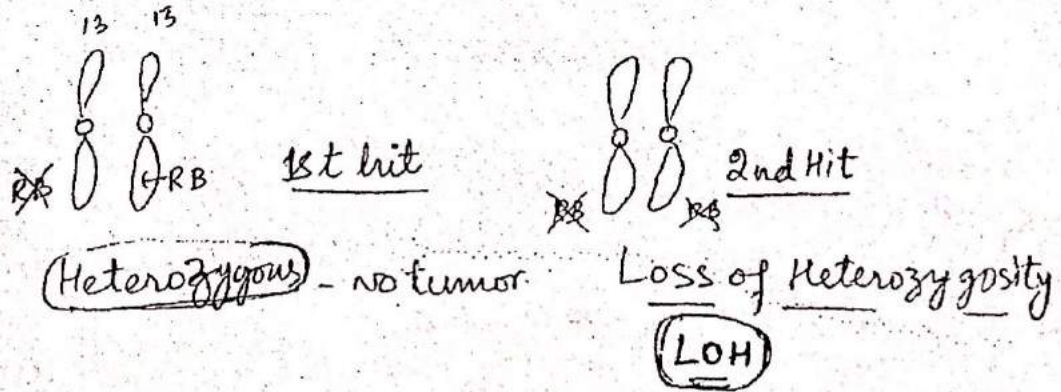
Cyclin E $\xrightarrow{\text{Overexpression}}$ Breast Ca

CDK 4 $\xrightarrow[\text{amplification}]{p16}$ Glioblastoma
Melanoma

② Tumor suppressor genes

Inhibits cell proliferation

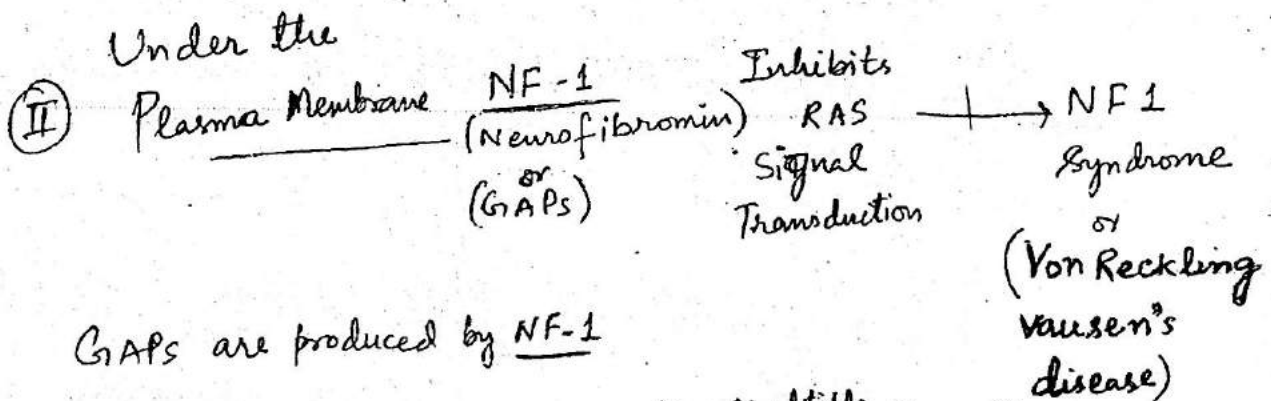
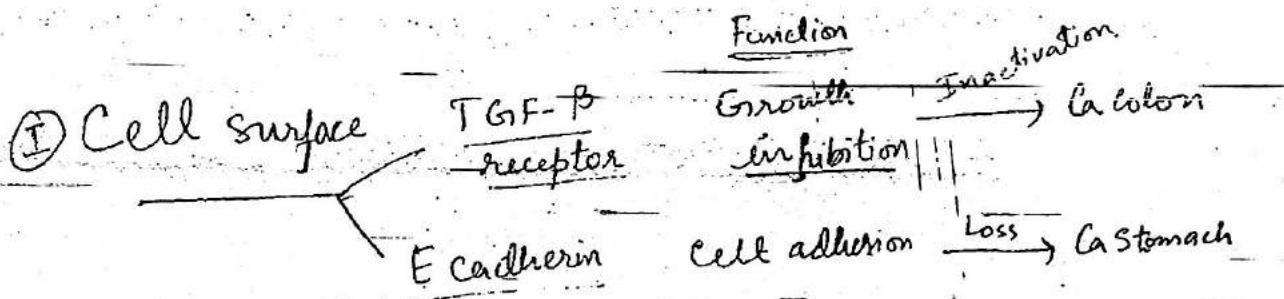
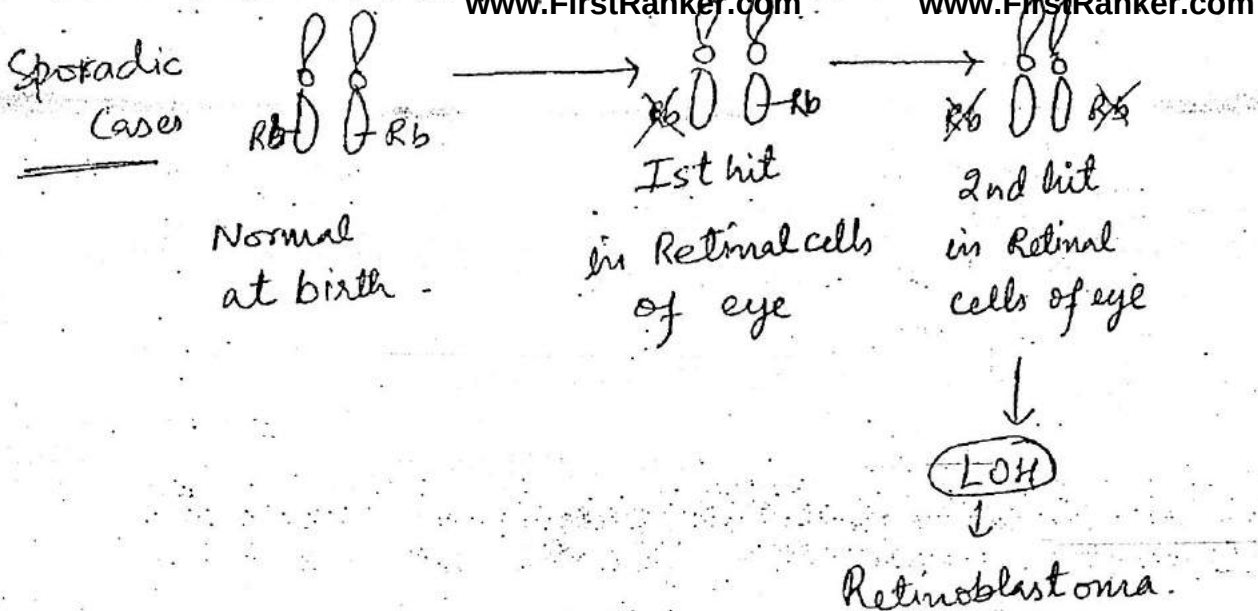
Loss of both copies (Inactivation) of TSG produces Ca.



1st tumor suppressor gene is RB

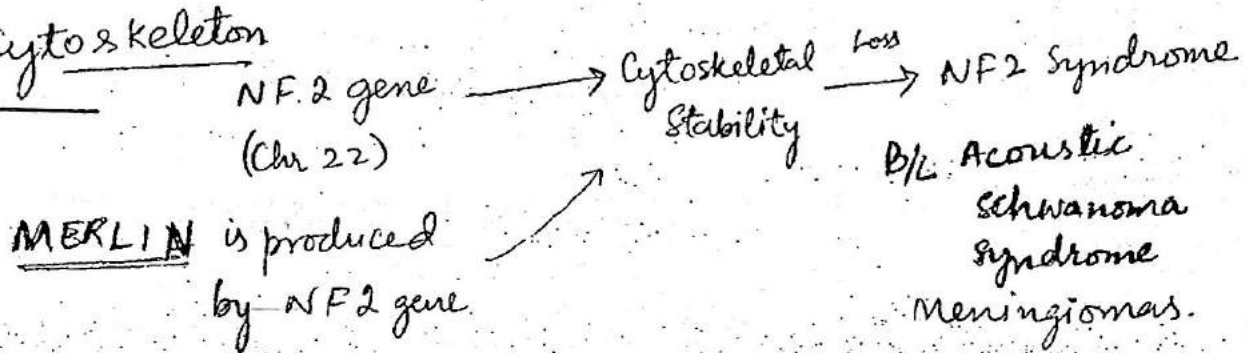
Loss $\rightarrow$ Retinoblastoma
Osteosarcoma

~~Knudson's Two HIT Hypothesis for Hereditary~~
Cases (Retinoblastoma) $\Rightarrow$ RB $\xrightarrow{\text{Time}}$ RB 2nd Hit

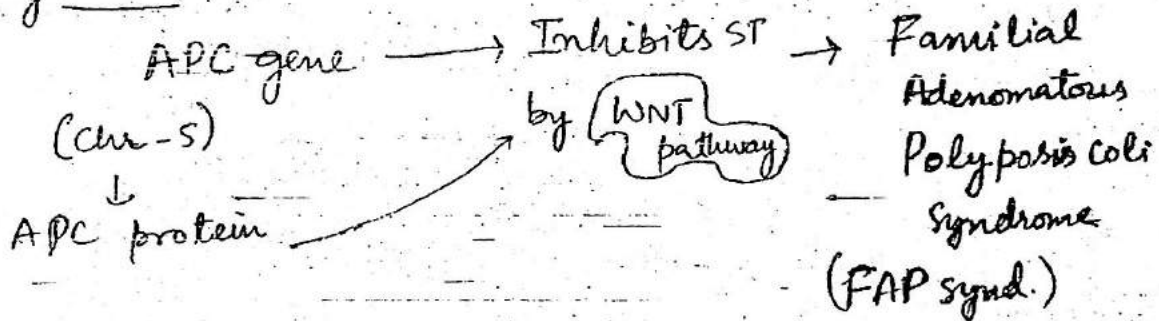


- ↳ Multiple Neurofibromas
- ↳ Cafe au lait spots
- ↳ Lisch nodules in Iris (hamartomas)
- ↳ ↑ risk of brain tumors (optic nerve glioma)
- ↳ Juvenile myelomonocytic Leukemia (JMML)

② Cytoskeleton



③ Cytosol



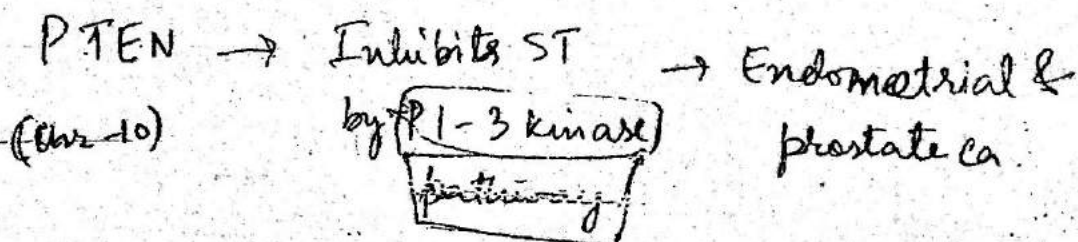
- Multiple adenomatous polyps in colon
- Minimum 100 polyps needed for diagnosis.

Polyps appear by teenage

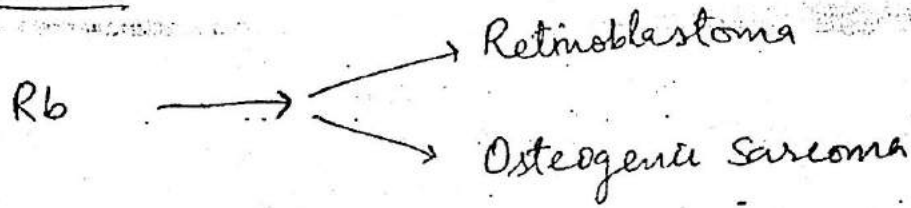
if untreated

↓
Risk of progression to Ca colon is 100%

④



⑤ Nucleus



p53 (chr. 17) → Li Fraumeni syndrome

M/C genes mutated in human Ca → p53 gene.

WT-1 }
WT-2 } Chr. 11 → Wilms Tumor

p16 → Malignant Melanoma
ARF/INK4A

BRCA-1 (chr. 17) → Hereditary breast & ovarian Ca (females)
Prostate Ca

BRCA-2 (chr. 13) → Hereditary breast & ovarian Ca (females)
Prostate Ca
Hereditary male breast Ca

③ Genes for Apoptosis

BCL2 $\xrightarrow{t(14;18)}$ Follicular lymphoma

Chr 14 - IgH gene

Chr 18 - BCL2 gene

④ Genes for DNA repair

DNA repair defect syndrome

Lynch / HNPCC syndrome } A Dominant

Xeroderma pigmentosa

Ataxia Telangiectasia

Bloom's syndrome

Fanconi's Anemia

} A Recessive

Genes for DNA repair are of 3 categories

① Mismatch repair genes

Act as spell checkers when a strand of DNA is replicating

Loss of mismatch repair genes $\rightarrow$ Spelling mistakes accumulate in new strand DNA

the cell which gets this DNA is said to have RER phenotype

Spelling mistakes also produce microsatellite instability.

Microsatellites → Tandem repeats of 1-6 nucleotides scattered throughout our genome.

Fixed for a person & fixed for life.

Also called as Molecular fingerprints.

Loss of mismatch repair gene is associated with Lynch Syndrome (↑ risk of developing colon Ca)

② Nucleotide Excision Repair Gene (NER)

NER genes remove UV light induced pyrimidine dimers from DNA.

Loss → Xeroderma pigmentosa

- Photosensitivity

- 200 times of risk of developing Cutaneous Ca

SCC

BCC &

M. Melanoma

T≡T
dimers

③ Genes for Repair by Homologous Recombination

Repair double stranded DNA breaks which can be produced by ionizing radiation.

① ATM gene - Sensor of DNA Damage
Loss produces Ataxia telangiectasia
Cerebellar Ataxia
Oculo cutaneous telangiectasia

Def. of Ig (Antibody)
↓
(Repeated infection)
cause of death

↑ed risk
of developing
Lymphoreticular Tumors

② Gene for enzyme BLM helicase

Loss → Bloom's Syndrome
growth retardation
mental retardation

↑ed risk of developing lympho reticular tumors

③ Fanconi Anemia gene

Loss → Fanconi Anemia

- Hereditary aplastic Anemia
- Aplasia of radius & thumb bone
- Hypoplastic kidney & spleen.

8 Hallmarks

- ① Self sufficiency of Growth signals.
- ② Insensitivity to growth inhibitory signals.
- ③ Altered cellular metabolism

Warburg effect

Also called as

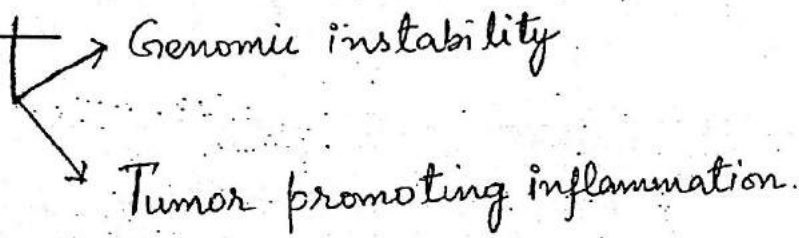
Aerobic glycolysis

It provides rapidly dividing cells with metabolic intermediates that are needed for synthesis of cellular components.

Mitochondria
manufactures
↓
other building
blocks of cells

- ④ Evasion of apoptosis
- ⑤ Limit less replication potential - due to reactivation of telomerase
- ⑥ Sustained angiogenesis
- ⑦ Ability to invade and metastasize
- ⑧ Ability to evade host immune response.

2 enabling factors



Carcinogens

Chemicals

Arsenic → Lung & Skin

2 Asbestos → Lung Ca, Mesothelioma
Oesoph., gastric, & colon Ca

1 Benzene → AML

Beryllium → Lung Ca

2 Cadmium & its compounds → Prostate Ca

Nickel & Chromium → Angiosarcoma, liver

Azo dyes → HCC

β Naphthylamine → Bladder Ca

Nitrosamine & nitrites → Oesophageal & gastric Ca

Aflatoxin

Carcinogens $\begin{cases} \rightarrow \text{Initiators} \rightarrow \text{causes DNA damage} \\ \rightarrow \text{Promoters} \rightarrow \text{stimulate genetically damaged cells to proliferate.} \end{cases}$

e.g. Promoters

Hormones like Estrogen, DES
(diethyl Stilboestrol)
Saccharin
Phenol
Phorbol esters

Complete Carcinogens

$\rightarrow$ Capable of both
Initiation
& promotion

Carcinogens

Direct acting

e.g. alkylating agents

They require no
metabolic conversion
to become active
carcinogens

Indirect acting

e.g. aromatic amines

benzo pyrines

They require metabolic
conversion to become
ultimate Carcinogens.

Radiation

UV light

UVB Associated with cutaneous Ca.

Xeroderma pigmentosa
are at ↑ risk of
developing cut. Ca
SCC
BCC
& M. Melanoma

Ionizing Radiation

All leukemia except
CLL
(MC)

Papillary Thyroid Ca

Ca breast, Ca lung

Ca Salivary gland

(Mucoepidermoid Ca)

Biological Carcinogens

Viruses

DNA

HPV
EBV
HBV
HHV8

RNA

HTLV-1
HCV

Bacteria

H. pylori

MALToma

gastric Ca

① HPV

70 serotypes are known

3 groups

Low risk serotypes — 6 & 11 ⇒ Condyloma
acuminatum Veneral warts

Intermediate serotypes — 31, 33

High risk serotypes — 16, 18 } → Cancer

Ca Cervix

Ca Vulva

Ca Vagina

Ca Anal

Cenal

Ca Penis

~~Ca Scrotum~~

Ca Larynx

Viral DNA encodes for 2 viral proteins

E6 — { Inactivates p53 protein
↑ TERT + ↑ telomerase expression

E7 — { Inactivates Rb protein
Inactivates p21 & p27.

② EBV

DNA virus

Infectious Mononucleosis

Oral Hairy Leukoplakia in HIV(+) } Benign Reactive.

Tumors

Nasopharyngeal Ca

Burkitt's lymphoma

Hodgkin's lymphoma

Bcell lymphomas in immunocompromised.

Extranodal NK T cell lymphoma.

Produces 2 ^{proteins} ~~produce~~ responsible for excessive cell proliferation

→ LMP-1
→ EBNA 2

③ HBV

→ HCC

Repeated cycles of injury and regeneration lead to accumulation of mutation

Some viruses have HBx gene

↓
Interferes with p53

↓
Ca

④ HHV8

[Kaposi's sarcoma Herpes virus 8]

Causes →

Kaposi's Sarcoma

→ Primary effusion lymphoma (variant of DLBCL)

RNA Virus

① HTLV-1

It Causes

Arthritis

Uveitis

• Tropical spastic Paraparesis

Tumor - Adult Tcell Leukemia/lymphoma

HTLV-1 codes to TAX protein

↓

Causes uncontrolled cell proliferation.

② HCV

HCC

[Splenic marginal Zone lymphoma]

Paraneoplastic syndrome

① Endocrinopathies

(a) Hypertension (MC)

Due to production of PTH related protein by tumor cells.

Tumors - SCC^{lung, skin}, Ca breast, RCC,
Adult T cell leukemia/lymphoma.

(b) Cushing syndrome

Due to ACTH production

Tumor - Small cell Ca lung.

(c) SIADH

Due to ADH production

Tumor - Small cell Ca lung.

(d) Hypoglycemia

Due to production of Insulin or Insulin like substances.

Tumor — { Ovarian Ca
Fibrosarcoma
HCC

(e) Carcinoid Syndrome

Due to production of Bradykinin & Serotonin

Tumors — { Bronchial carcinoids
HCC

(f) Polycythemia Due to erythropoietin

Tumors — E — RCC
 HCC
 Cerebra Hemangioma

(2) Nerve & muscle

Myasthenia gravis < — Ca lung
 Thymoma

Immunologic in origin

(3) Cerebral degeneration

[— Ca lung
 Hodgkins lymphoma

(4) Skin

Acanthosis Nigricans

Due to production of
epidermal growth factor.

Tumor — [— Gastric Ca
 Lung Ca

(5) Hypertrophic osteoarthropathy — Ca lung

⑤ Trousseau Syndrome
(Migratory Thrombophlebitis)

Tumor cells activate clotting

└─ Pancreatic Ca
└─ Lung Ca

⑥ Marantic endocarditis / Non bacterial Thrombotic endocarditis

In advanced malignancies

Tumor Markers

① Hormones

(a) Calcitonin — Medullary Ca Thyroid.

(b) Catecholamine — Pheochromocytoma

(c) β HCG — Trophoblastic tumor of Chorio Carcinoma

② Oncofetal antigens

(a) AFP (Alpha Feto Protein) — HCC, Hepatoblastoma
Yolk sac tumor

(b) CEA (Carcino Embryonic Antigen) — (no seminomatous germ cell tumor)
→ Ca colon, Pancreas, lung, Stomach

③ Specific Proteins

- (a) Immunoglobulins — Multiple Myeloma.
(b) PSA — Prostate Ca.

④ Iso-enzymes

- (a) PAP (Prostate Acid Phosphatase) — Prostate Ca
(b) Neuron specific Enolase — Neuroblastoma
Small cell Ca
Neuroendocrine Tumors.

⑤ Mucins

- CA 125 → Ovarian Ca
CA 19.9 — Colon & prostate Ca.
CA 15.3 — Breast Ca

⑥ Cell free DNA markers (LIQUID BIOPSY)

- TP53, APC, RAS in stool & serum — Colon Ca
TP53, RAS in stool & serum — Pancreatic Ca
TP53, RAS in sputum & serum — Lung Ca
TP53, in urine & serum — Bladder Ca

Tumor Markers detected in Tissue by IHC

① Carcinoma

Cytokeratin (m. imp)

EMA (Epithelial Membrane Antigen)

CEA (Carcinoembryonic Antigen)

② Lymphoma

LCA (Leucocyte Common Antigen)

③ Sarcoma — Vimentin

Ewing Sarcoma — CD99

Synovial Sarcoma — CD99
BCL2

Rhabdomyosarcoma — Desmin
MyoD1

Leiomyosarcoma — Smooth Muscle Actin
(SMA) +

Osteosarcoma — Osteopontin
Osteonectin
Osteocalcin

Chondrocytoma — S-100

④ Mesothelioma — Liposarcoma — S-100
Calretinin

Cytokeratin 5/6

Mesothelin

Calretinin

⑤ Malignant Melanoma
HMB45
Melan A
S100

⑥ LCH
CD1a
S-100
Langerin (CD 207)

⑦ Small cell Ca
Neuroblastoma
Neuroendocrine tumor
Synaptophysin
Chromogranin
Neuro specific enolase (NSE)
S-100

⑧ Schwann cells
Neurofibroma
Schwannoma
S-100

⑨ TTF-1
(Thyroid Transcription Factor)
Lung Ca
Thyroid Ca
Adeno Ca
Small cell Ca

⑩ HCC
Arginase 3
Hep Par 1

① Vascular events

① Transient vasoconstriction



② massive vasodilation



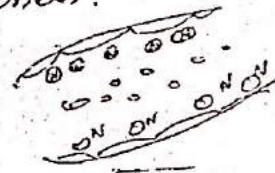
③ Increased vascular permeability → exudate formation ^{Most imp}



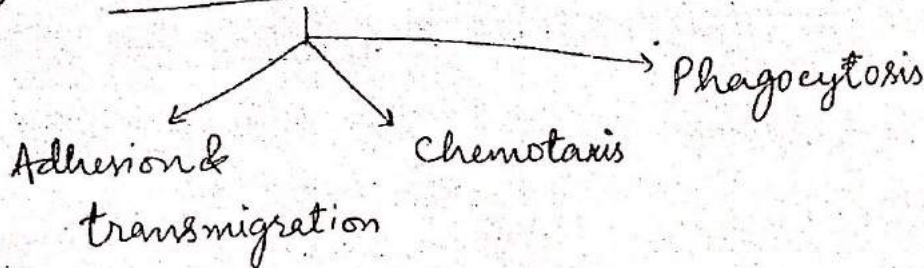
④ Stasis of cells in blood vessels.



⑤ Leucocyte margination to the periphery.



② Cellular events



Mechanisms of ↑ vascular permeability

① Endothelial contraction (M/c mech)

(occurs in post capillary venules)

Mediators

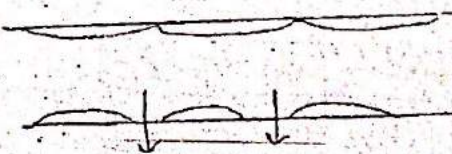
→ Histamine

→ Bradykinin

→ Substance P

→ Leukotriene

→ Immediate Transient response



(2) Endothelial retraction / functional reorganisation

Delayed type of contraction (venules & capillaries)

Mediators (cytokines) → IL-1
→ TNF α

⇒ Delayed, sustained response

(3) Direct Injury

(Seen in venules, arterioles, capillaries)

Severe Injury

e.g. Severe burns
Chemicals
Toxins

↓
Cells undergo necrosis & detach.

↓
Fluid leakage which starts immediately

↓
Leakage continues till a new cell regenerates

⇒ Immediate sustained response

Mild Injury

e.g. mild sunburn.

↓
endothelial cells die after a few hours due to apoptosis.

↓
Fluid leakage starts after few hours

↓
Leakage continues till a new cell regenerates

⇒ Delayed sustained response

(4) Increased Transcytosis

⇒ Passage of liquid across the channels formed in the endothelial cell cytoplasm

⇒ Channels are formed close to the Junction

Mediator - VEGF

(II) Cellular events

(1) Adhesion and transmigration

Rolling → loose adhesions → firm adhesions
↓
Transmigration (Diapedesis)

Adhesion molecules ←

↓
Substances that coat the surface of neutrophils and surface of endothelial cells & help them to stick together.

4 Families of adhesion molecules

(I) Selectins

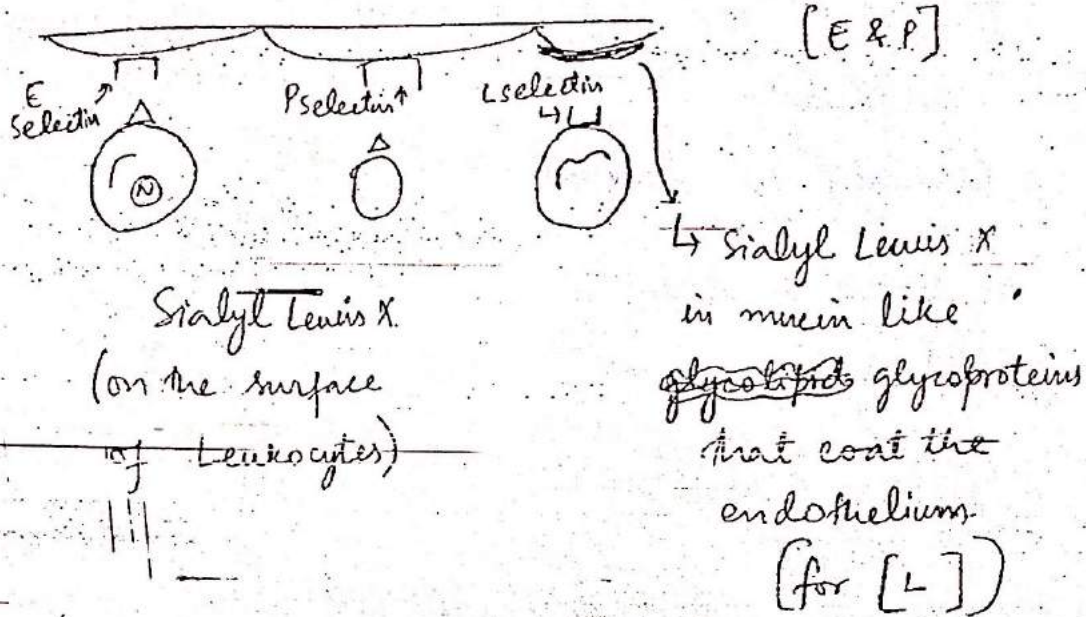
Bring about Rolling & loose adhesions

→ E selectin	CD 62E	Endothelium
→ P selectin	CD 62P	Platelets, endothelium
→ L selectin	CD 62L	Leukocytes

Complementary molecules

↳ Sialyl Lewis X

(Sugar formed by fucose metabolism)



Leukocyte Adhesion deficiency type II

↓ (LAD type II)

1 deficiency of Sialyl Lewis X due to defect in fucose metabolism.

② Immunoglobulin Superfamily

ICAM $\begin{matrix} \rightarrow ① \\ \rightarrow ② \end{matrix}$
(Intercellular Adhesion Molecule)
VCAM $\begin{matrix} \rightarrow ① \\ \rightarrow ② \end{matrix}$
(Vascular Cell Adhesion Molecule)

Both are found on endothelium

③ Integrins

β_2 integrins
e.g. LFA1 / MAC1
(CD11) (CD18)

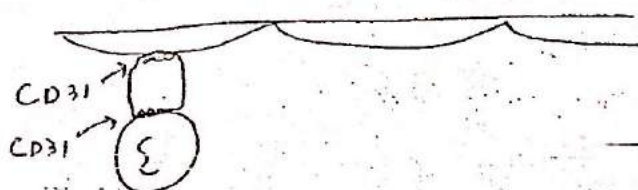
β_1 integrins $\rightarrow$ VLA4

Found on leukocytes

Responsible for FIRM ADHESIONS

(Platelet Endothelial Cell Adhesion)
Molecules

- Transmigration
- Homotypic adhesion molecule
- CD31 is found on leukocyte & endothelium.



Neutrophils produce
enzyme type IV collagenase
↓
breaks type IV collagen
(Basement Membrane)
& comes out of the vessel.

LAD type I

Autosomal recessive disorder

Deficiency of β_2 integrins LFA-1/MAC-1

There is mutation in MAC 1 (CD18) gene

C/F - Recurrent bacterial & fungal infection.

Impaired wound healing.

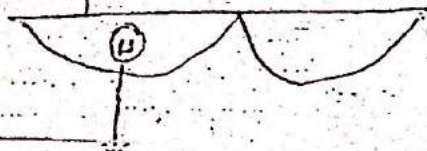
Delayed umbilical cord separation.

Leukocytosis ($\uparrow$ TLC)

Mechanism of appearance of Adhesion molecules.

① Redistribution → P Selectin

No inflammation



② Weibel Palade body in endothelial
cell cytoplasm
[contains P selectin]

During inflammation

Mediators → Histamine
→ Thrombin
→ BAF

redistribute P selectin
within few endothelial cell

① Induction

Fresh synthesis
during inflammation



www.FirstRanker.com

Mediators → IL 1

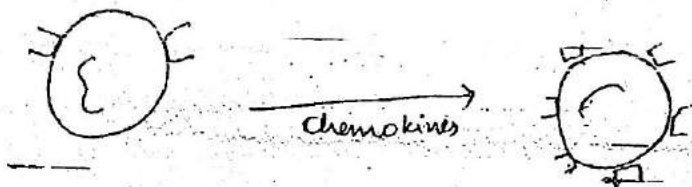
that induce

TNFα

Time taken is hours.

③ Increased avidity of binding
(Strength)

Integrins



↑ the no. of integrin molecules on leukocytes

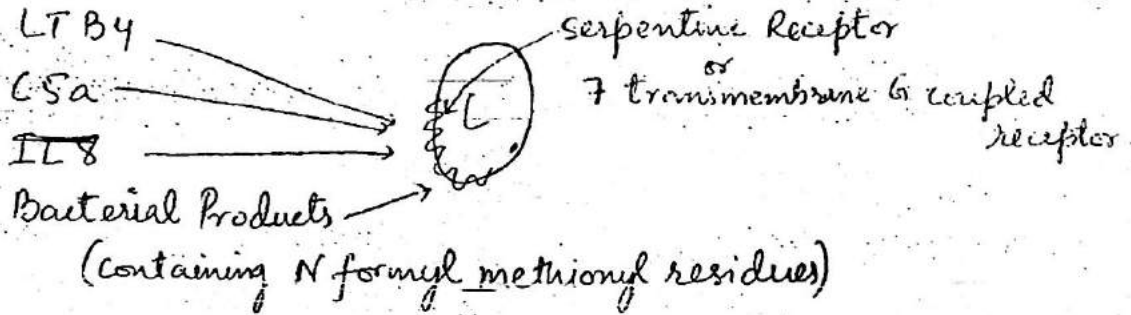
↑ the strength of binding of integrins many times.

⇒ Weibel Palade bodies are ultrastructural markers of endothelial cells (EM)

② Chemotaxis

Def. Locomotion orientend along a chemical gradient.

Chemotactic agents

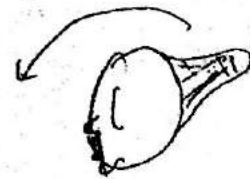


When these ligands bind to 7 transmembrane G coupled receptors

↓
↑↑ Ca²⁺ in the cytosol

↓
Polymerisation of actin filaments
at the leading edge

↓
Pseudopod formation

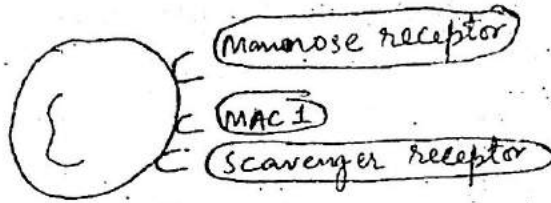


Defects In

DM, Malignancy, Severe burns, CRF

③ Phagocytosis

(a) Recognition & attachment.



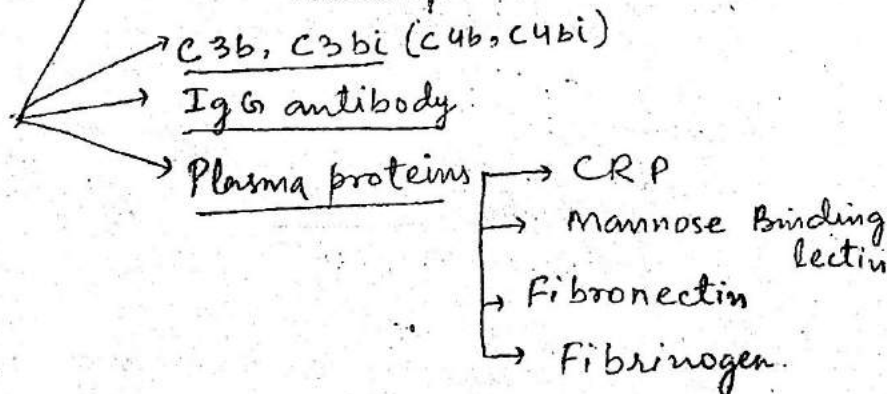
3 receptors that help the neutrophil to recognize & attach to the bacteria

- Mannose receptor
- MAC 1 integrin (CD18)
- Scavenger receptor

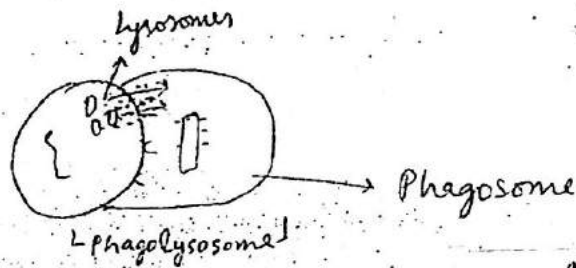
❖ Opsonization

↑ the efficiency of phagocytosis

⊕ Opsonins → Substances that coat the bacteria & make it tasty for neutrophil.



(b) Engulfment



Pseudopods flow around the bacteria & bacteria is enclosed in a phagosome

Phagosome fuses with lysosome to form phagolysosome

All enzymes are discharged in phagolysosome.

Chediak Higashi Syndrome - defect in engulfment

↳ Autosomal recessive disorder

Failure of fusion of phagosome & lysosome

C/F Repeated infections

- Oculocutaneous albinism & Silvery grey hair

- Nerve conduction defects

- Platelet function defects leading to bleeding

PBS Neutropenia with giant granules in leukocytes

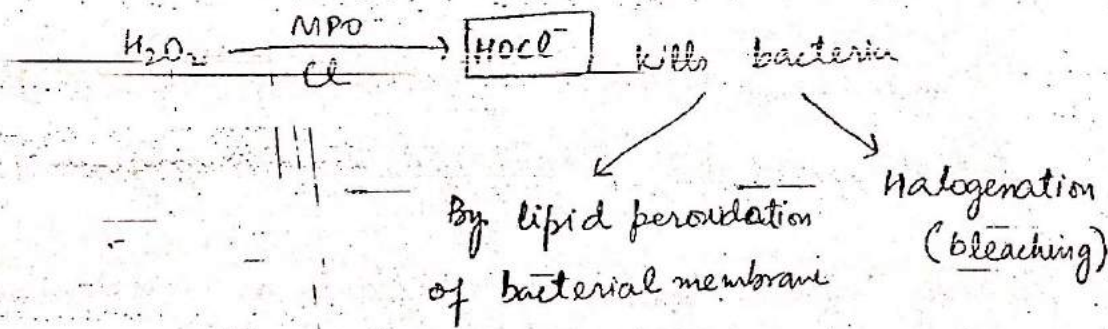
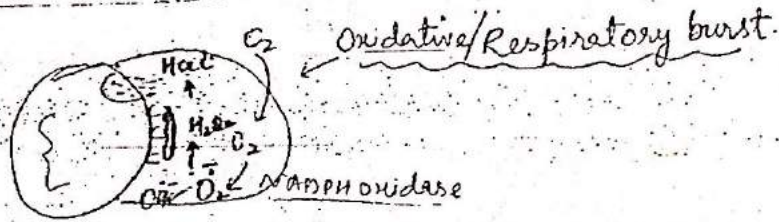
⇒ Lyst gene mutation are seen

~~Absence of Docking protein~~

needed for fusion of lysosomal membrane with phagosomal membrane.

(C) Killing $\begin{cases} \rightarrow O_2 \text{ dependent method (Main method)} \\ \rightarrow O_2 \text{ independent method} \end{cases}$

Oxygen dependent method



H_2O_2 MPO - Halide system kills bacteria, fungi, & parasites

MPO is a lysosomal enzymes.

Defect $\rightarrow$ Chronic granulomatous diseases

defect of enzymes NADPH oxidase

$\begin{cases} \text{X R (MC) (75\%)} \\ \text{AR (25\%)} \end{cases}$

Test for diagnosis Nitroblue tetra zolium Test. (NBT)

Oxygen independent killing

Lysosomal enzymes kill the bacteria

→ BPI Bacterial Permeability Increasing Protein

It is a phospholipase

↓
Breaks phospholipids & bacterial membrane

→ Lysozyme

It is a muramidase

↓
Breaks glycopeptide coat of bacteria

→ Lactoferrin

Binds Iron

↓
Iron is unavailable for bacterial growth

→ Major Basic Protein

Found in eosinophil granules

↓
Toxic to parasites

→ Defensins

→ Cationic proteins

} Found in Neutrophils

Mediators of acute inflammation

Cells

Preformed/Primary

Histamine

Serotonin

Lysosomal enzymes

Newly synthesised/Secondary

Arachidonic Acid mediators

PAF

Lipid mediators

Cytokines

ROS (Reactive Oxygen Sp.)

Chemokines

Nitric oxide

Substance P

Plasma

Kinin cascade

Complement cascade

Coagulation cascade

Fibrinolytic cascade

Preformed / Primary mediators

① Histamine First mediator to be produced

Source → Richest source is Mast cell

Others — Basophils, Platelets

Stimuli for release

⇒ IgE Ab binding to receptors on mast cells

Post
Cap. Venules

⇒ C3a
C5a } Anaphylatoxins

⇒ IL-1
IL-8 }

⇒ Histamine Releasing proteins.

⇒ Physical agents like heat, cold & trauma.

Actions

① Vasodilation

② ↑ vascular permeability → causing Immediate
Transient response.

③ Vasoconstriction (large vessels)

④ Bronchospasm. due to muscular layer presence)

② Serotonine (5HT)

Richest source → Platelets

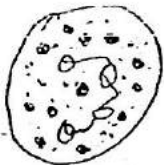
Others → Enterochromaffin cells

Actions Platelet aggregation

Other actions are same as histamine.

③ Lysosomal Enzymes

Found in granules of neutrophils



Primary/Azurophilic granules

- Large coarse granules

Secondary/specific granules

- Small fine granules

P ANCA →

C ANCA →

- MPO
- BPI
- Acid hydrolases
- Neutral proteases
- Lysozymes
- Phospholipase A₂
- Defensin
- Cationic Proteins

Lactoferrin

Alkaline phosphatase

Type IV collagenase

Gelatinase

Lysozyme

Phospholipase A₂

Vit B₁₂ binding protein

ANCA Antibodies against enzymes

found in - primary granules
of Neutrophils

P ANCA

↓
MPO

C ANCA

↓
Proteinases
(Neutral proteases)

Newly synthesised mediators.

① Platelet activating Factor (Lipid mediator)

Source - All leukocytes & mast cells.

Actions

— Vaso dilation —

— ↑ Vascular permeability —

— Vasospasm —

— Platelet aggregation —

— Bronchospasm —

— Chemotactic —

— Angiogenesis —

— Cell to cell signal transduction. —

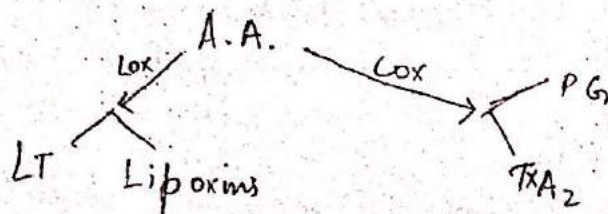
② A. acid mediators

20 Carbon polyunsaturated Fatty Acid

Found esterified in membrane phospholipids.

Membrane phospholipids

↓ Phospholipase



Eicosanides

Source - All leukocytes, mast cells, endothelial cells.

(steroids)

www bit phospholipase

AA

cyclooxygenase (COX)

COX 1 COX 2 inhibitors

PGG₂

↓

PGH₂

Platelets

Thromboxane Synthetase

Endothelium

Prostacyclin Synthetase

PGI₂

(Prostacyclin)

PGD₂

PGI₂ E₂

PGF₂

TXA₂

(no role in inflammation)

- plays role in hemostasis

- Inflammatory mediator

- Causes vasodilation

- Inhibits platelet aggregation

→ Platelet aggregation

→ Vasoconstriction

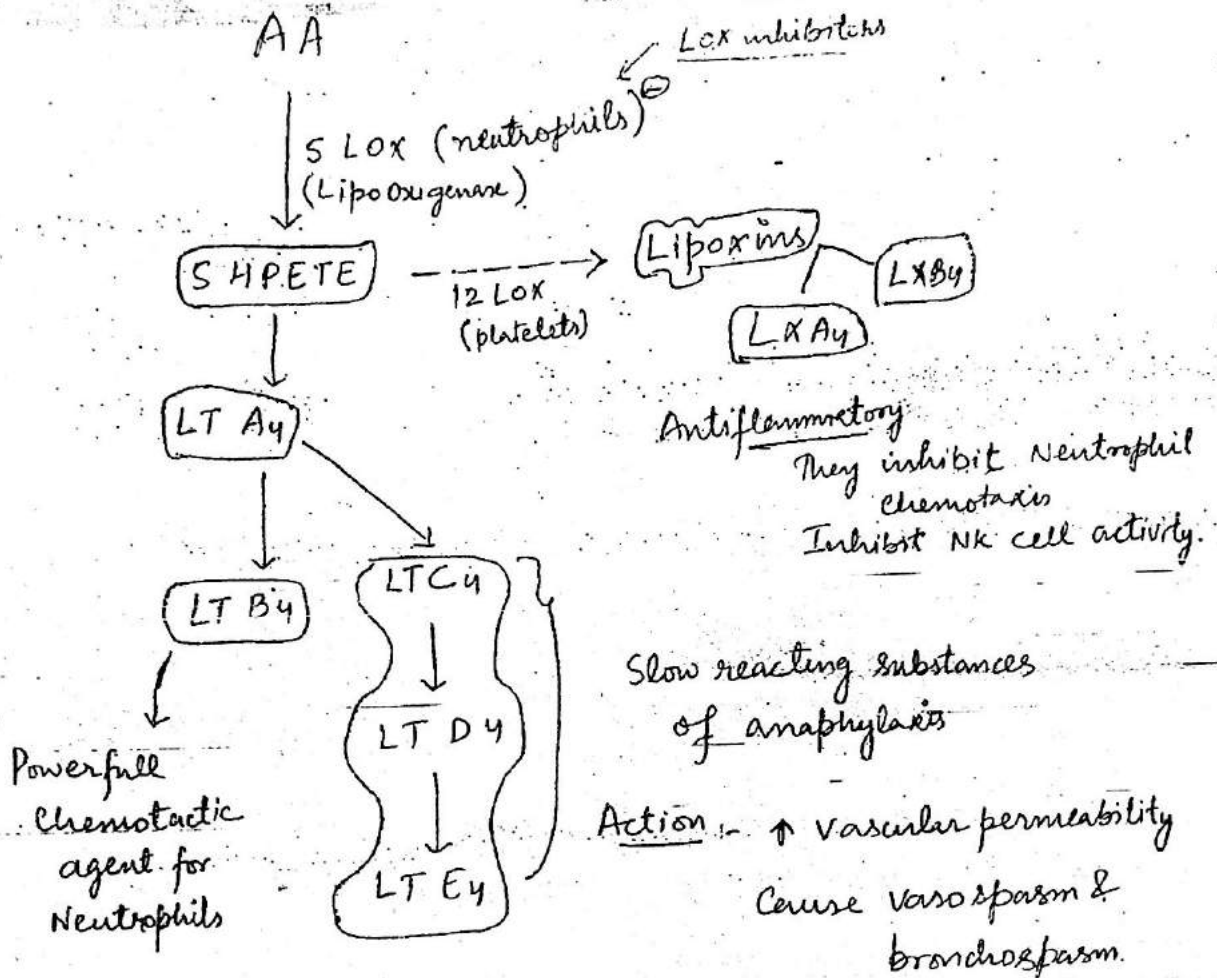
⇒ Increase vascular permeability

⇒ Cause vasospasm & Bronchospasm

⇒ Pain & Fever (PG E₂)

⇒ PG D₂ & PG F₂ ⇒ Chemotactic

⇒ PG F₂ α ⇒ Causes uterine smooth muscle contraction



Lipoxins are produced by transcellular biosynthesis
↓
2 Cells are cooperating for production.

- ③ Chemokines belong to family of cytokines
Short chain polypeptides that cause chemotaxis.

4 categories

① α chemokines / CXC chemokine
Chemotactic for Neutrophils

e.g., IL 8

② β chemokines / CC chemokines

Chemotactic for all except Neutrophils.

e.g., Eotaxin $\rightarrow$ only for eosinophils

Rantes $\rightarrow$ eosinophils + T lymphocytes.

MCP 1 $\rightarrow$ Monocytes

(Monocyte chemoattractant Protein 1)

MEP-1 α $\rightarrow$ Monocytes & Macrophages
(Macrophage Inflammatory Protein)

③ gamma chemokines / C-chemokines

e.g., lymphotactin $\rightarrow$ Lymphocytes.

④ CX₃C Chemokines

Only one member - Fractalkine - chemotactic
for monocytes

Chemokine receptors $\rightarrow$ CXCR4 } act as co receptors
 $\rightarrow$ CCR5 } for HIV

③ Cytokines

Macrophage & dendritic cells

Source →

IL-1

TNF α

TNF α in addition is also produced by T cells & mast cells.

Action -

① Systemic acute phase reaction

IL-1

TNF α

IL-6

→ Mc.

Fever, Increased sleep,

↓ appetite

↑ FLC

↑ ESR

↑ CRP

TNF α also regulates energy balance by causing lipid and protein mobilization & suppressing appetite

thus causing ↑ TNF levels

Cancer

cachexia → TNF α .

↓
Cachexia

④ Endothelial activation

↑ expression of endothelial adhesion molecules

↑ production of mediators - cytokines, chemokines & AA mediators

↑ procoagulant activity

(III) Leukocyte activation

TNF $\rightarrow$ Microbicidal activity of leukocytes

(IV) Fibroblast activation

IL 1 - Fibroblast proliferation & synthesis of collagen.

(5) Nitric Oxide

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

NO synthetase is found in $\rightarrow$ endothelial cells

Endothelial cells $\rightarrow$ eNO $\rightarrow$ Vasodilation

Macrophages $\rightarrow$ iNO $\rightarrow$ Produced during inflammation
(inducible) - Microbicidal gas.

Neurons in brain $\rightarrow$ nNO $\rightarrow$ Neurotransmitter in Brain.
(neuronal)

⑥ Substance P (Neuropeptide)

Source - Leukocytes

Sensory Nerves (CNS & PNS)

Actions

Pain

↑ vascular permeability

Regulation of BP

PAIN mediators.

PGI₂

Bradykinin

Substance P → M. Imp

Mediators coming from Plasma

① Kinin Cascades

[generate bradykinin]

Prekallikrein

K₁₁a

(Hageman factor)

Kallikrein



High M.W kininogen



Bradykinin

Action

1. Pain

- ↑ vascular permeability
↳ M. Imp

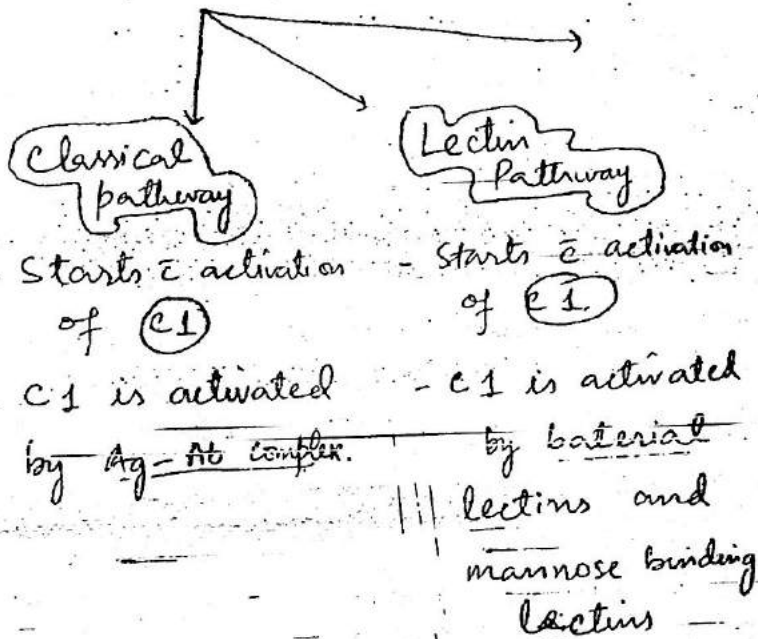
- Vasodilation

- Vasospasm

- Bronchospasm

② Complement Cascade [Set of 20 proteins found in plasma]

3 pathways for complement activation



Alternate Pathway

- Starts $\bar{c}$ activation of $C3$
- No participation of $C1, C2, C4$
- $C3$ is activated by LPS (Lipo P.s)
- Cobra venom
- Aggregates of IgA antibody.

Mediators produced

$C3a$ } opsonins
 $C3bi$

$C3a$ } Anaphylatoxins (cause release of histamine from mast cells)
 $C5a$

$C5a$ } Chemotactic for Neutrophils, eosinophils & monocytes

$C5-9$ } Membrane Attack Complex (MAC)

③ Coagulation Cascade

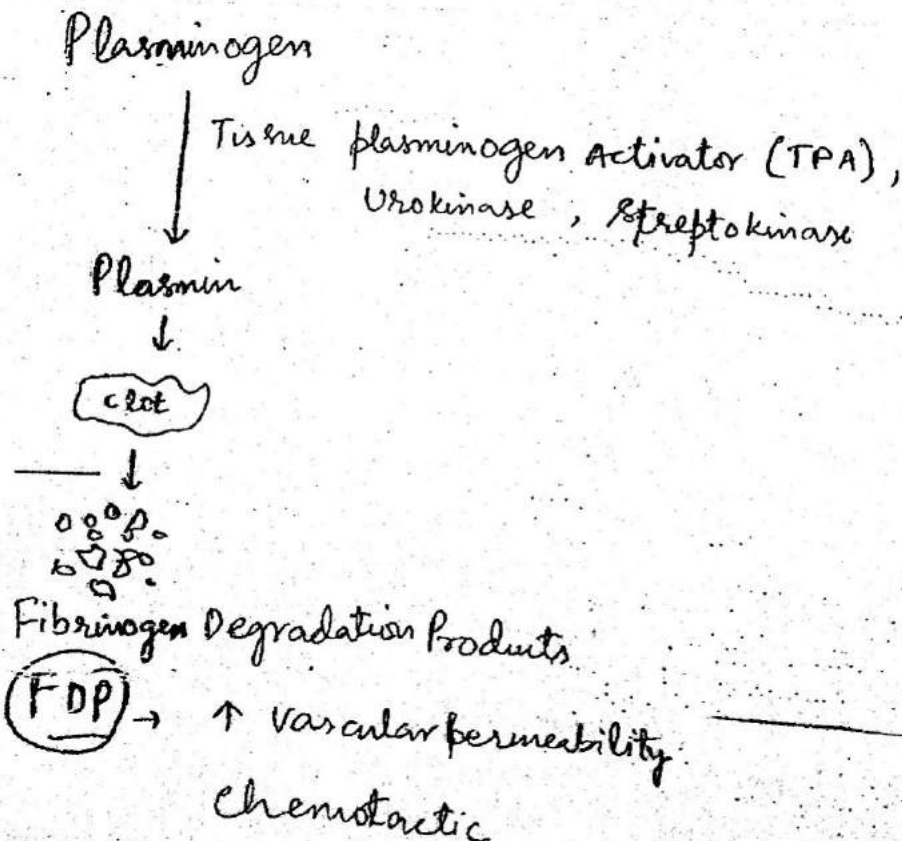
Mediators

(a) Fibrinogen $\rightarrow$ Opsonin

(b) Thrombin $\rightarrow$ Main link b/w inflammation & coagulation
Causes redistribution of Pselectin
Induces Cox enzymes in Endothelial cells
 $\uparrow$ expression of adhesion molecules on endothelial cells.

(c) Fibrinopeptides $\rightarrow$ Vascular permeability
 $\rightarrow$ Chemotactic

④ Fibrinolytic Cascade



NETs

Neutrophil Extracellular Traps.

Extracellular Fibrillar Network formed by Neutrophils to trap bacteria.

Formed from the nuclear chromatin of Neutrophils.

Lysosomal enzymes are discharged in the NETs & kill the bacteria.

At the end of NET formation, neutrophils die.

Chronic Inflammation

- ① Infiltration of tissue by mononuclear cells
(monocytes, lymphocytes, & plasma cells)
- ② Tissue destruction.

Macrophages

⇒ Main cells of chronic inflammation

⇒ Derived from blood monocytes which are produced in bone marrow.

* Resident macrophages - e.g. Kupfer cells in liver, microglial cells in brain are derived from stem cells in yolk sac & life span is in years.

⇒ Also called as Histocytes

Liver → Kupfer cells

Brain → Microglial cells

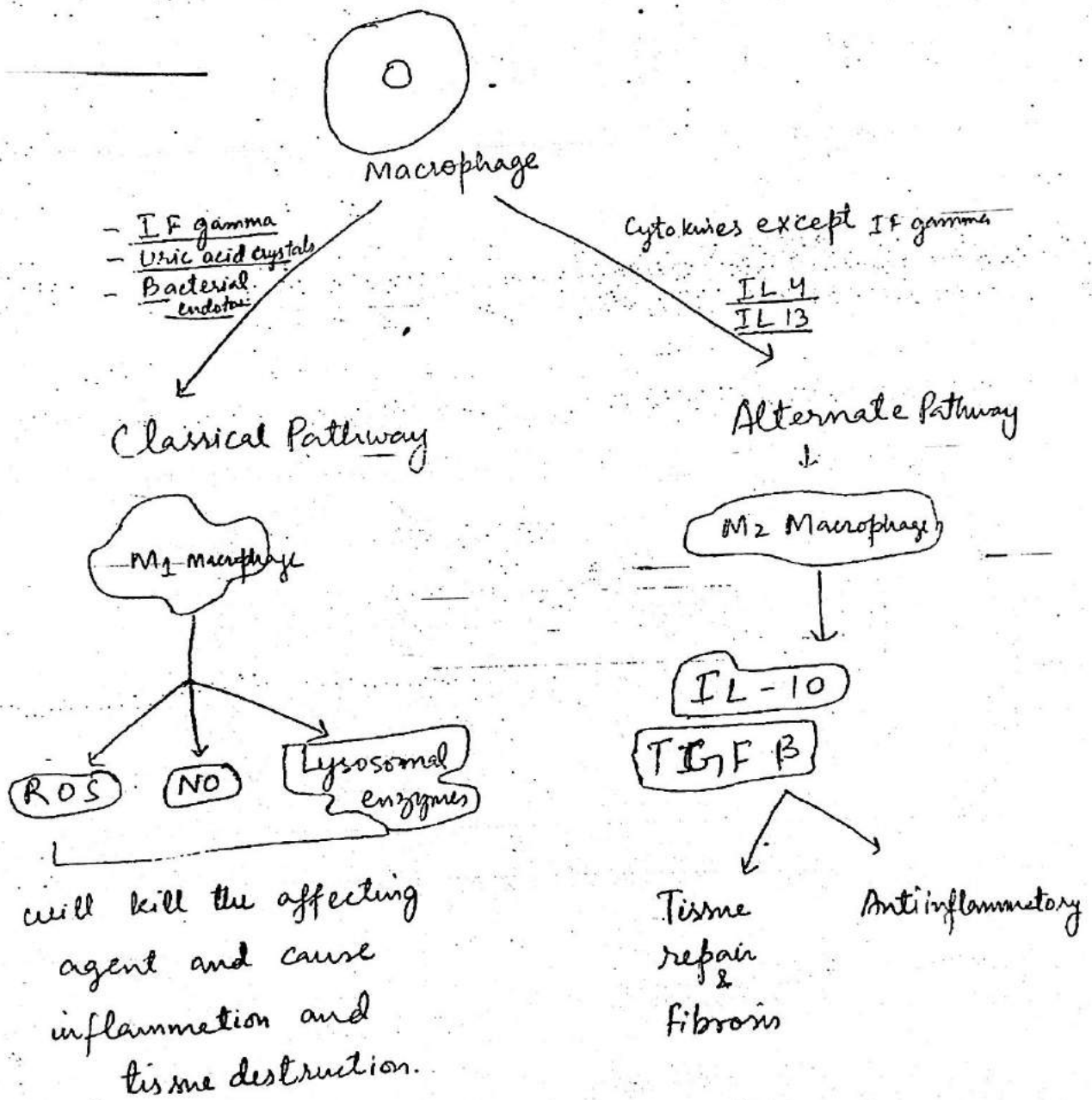
Bone → Osteoclasts

Spleen → { Littoral cells
Sinus histiocytes

LN → Sinus histiocytes

Lungs → Alveolar macrophages

In chronic inflammation macrophages are activated to kill the bacteria.



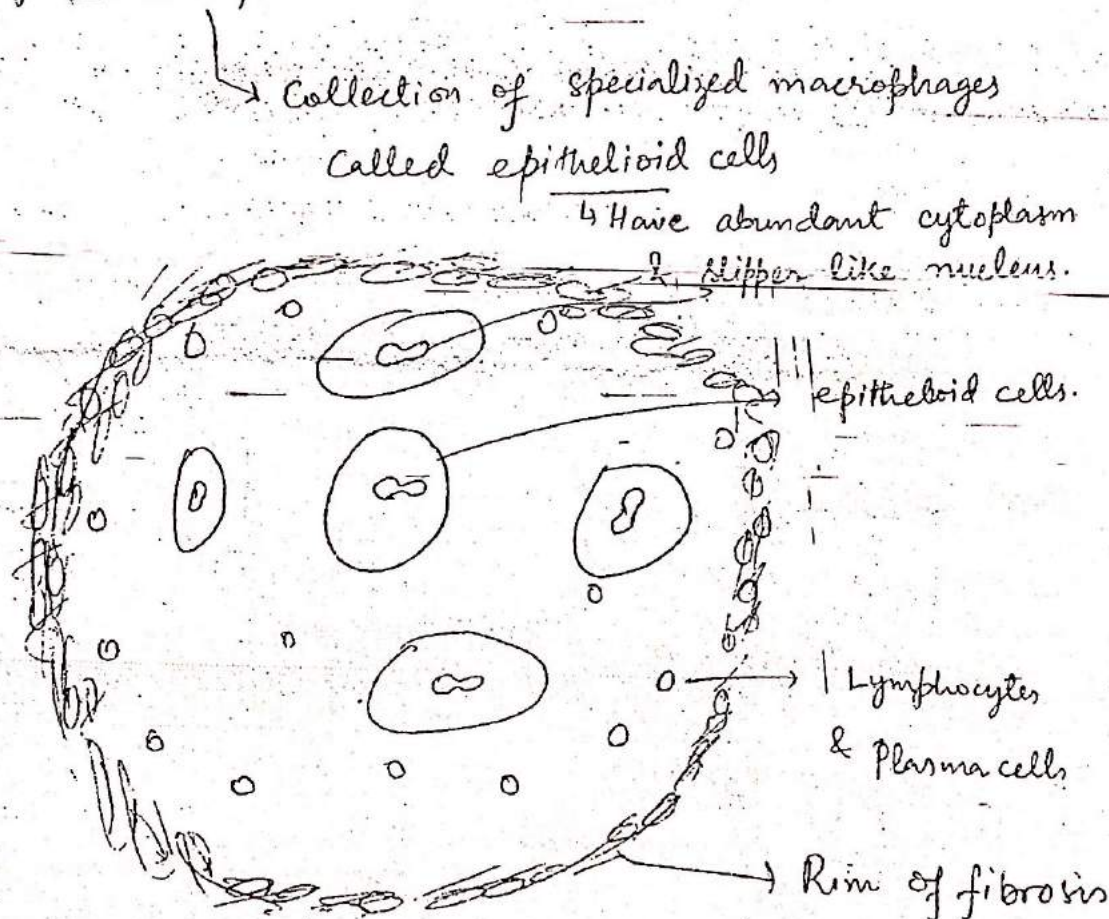
Fibrosis - TGF beta

Anti-inflammatory - IL 10
TGF beta
IL 6

✓ IL 6 is both
Pro inflammatory
& Anti-inflammatory

Chronic granulomatous inflammation

Special type of chronic inflammation characterised by granuloma formation.



2 types

- Immune granuloma
- Foreign body granuloma.

① Immune granuloma

Formed in type IV HR.

↳ IFN gamma & TNF α plays an important role.

Causes TB

Sarcoidosis

Leprosy

LGIV

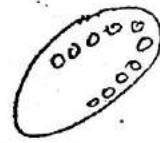
Cat scratch disease

Syphilis

Crohn's disease

Hodgkin lymphoma

Immune granulomas may show giant cells
e.g. Langhans giant cell.



Multiple nuclei arranged
in C or horseshoe shape.

→ Caseating Granuloma

Caseous necrosis in centre

TB

Syphilis

Fungal infection

Histoplasmosis

Coccidioidomycosis

→ Non Caseating

TB

Sarcoidosis (naked granulomas)

↳ NO lymphoid & PC surrounding.

Hodgkin's lymphoma

Leprosy (tuberculoid)

→ Stellate granulomas → Star shaped granuloma
Neutrophilic granuloma

LGV

Cat scratch disease

→ Necrotising granuloma

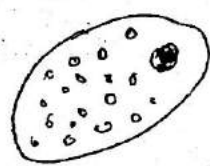
(Small vasculitis) Wegner's granulomatosis

- Eosinophilic granulomas
Churg Strauss
(small vessel vasculitis)
- Durck granulomas Cerebral malaria.

② Foreign body granuloma

Formed around
a foreign body e.g: talc, suture material, dead
parasites, uric acid crystals.

↳ Contains foreign body giant cell (numerous)



} Multiple nuclei arranged in
haphazard way
May contain foreign body

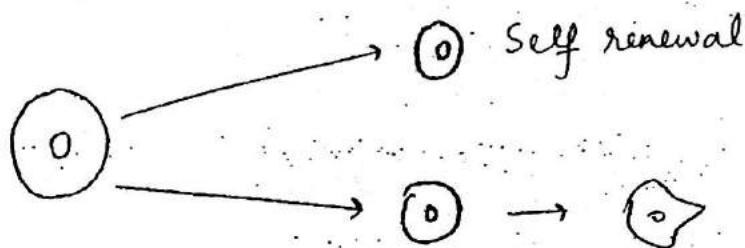
Cytokines for Fever

1. IL1 most imp.
2. IL6
3. TNF α
4. PGE₂
5. Ciliary Neurotrophic
factor

Cytokines for Septic Shock
- TNF α

Fibrosis - TGF β

Stem Cells



Self renewal
Capacity to generate differentiated cells by asymmetrical replication

2 types

① Embryonic stem cells Isolated from blastocyst
Totipotent - can generate all tissues of body.

② Adult or Somatic stem cells
Found in Adult/Normal tissues in special microenvironments called Niches
Can be Pluripotent/Multipotent/Bipotent.

(a) Bone marrow

Hematopoietic stem cells

- Pluripotent - give rise to all blood cell lineages.

- Can be obtained from

① Umbilical cord blood

② Bone marrow

③ Peripheral blood after injecting G-CSF

Marrow Stromal stem cells

Mesenchymal s.c.

Pluripotent

give rise to

adipocytes, endothelial cells, osteoblasts, chondrocytes

Mesenchymal stem cells are also found in abdominal fat.

b) Liver

Called "Oval cells"

Found in Canals of Hering

Bipotent $\begin{cases} \text{Hepatocytes} \\ \text{Biliary cells} \end{cases}$

c) Brain

Called Neuronal S.C.

Multipotent.

$\begin{matrix} & \swarrow & \searrow & \rightarrow \\ \text{Neurons} & & \text{Astrocytes} & \text{Oligodendrocytes} \end{matrix}$

Location $\begin{cases} \text{Subventricular zones} \\ \text{Dentate gyrus of hippocampus} \end{cases}$

d) Skin

Found in adnexa

$\begin{matrix} & \swarrow & \searrow \\ \text{Hair follicle bulge} & & \text{Sebaceous glands} \end{matrix}$

- e) Limbus of cornea
- f) Crypts of Intestine
- g) Satellite cells - sc. associated with Cardiac & skeletal muscles

Use of Stem cells

Used to repopulate the damaged tissue

Wound Healing

Regeneration
Dead cells are replaced by same cells

Repair
Dead cells are replaced by fibrous connective tissue

① Labile cells/ Actively dividing cells

They are in G₁ phase of cell cycle.

e.g. epithelia → Skin, GIT, Resp. tract
Stem cells
urogenital tract.

Hematopoietic cells
Cancer cells

② Stable cells In G₀ phase of cell cycle

They have low replicative potential.

e.g: i) Parenchymal cells of organ

Hepatocytes

PCT, DCT of kidney

Adrenocortical cells

(ii) Mesenchymal cells

Adipocytes

Osteoblasts

Chondrocytes

Smooth muscle cell

Endothelial cells

③ Permanent/Non dividing cells

They have left the cell cycle

They cannot divide at all.

e.g: - Neuronal

- Skeletal muscle

- Cardiac muscles

Repair occurs by formation of granulation tissue

Pink, moist & has granular appearance.

M/c → Chronic inflammatory cells/Macrophages

Lymphocytes, plasma cells

→ New blood vessels

→ Fibroblasts that synthesize collagen.

Wound healing by Primary intention

Seen in clean, surgical wounds where the edges can be approximated

0 hours → Incision is filled w/ blood clot.

in 24 hours →

- Neutrophils from margins infiltrates the clot.
- Mitosis begins in the basal layer of epidermis.

24 - 48 hours → Continuous thin layer of epithelium is formed below the scab/scab.

Day 3

- Neutrophils are replaced by macrophages
- Granulation tissue appears.
- Collagen fibers are evident at the margins of the incision.

Day 5

- Abundant granular tissue*
- Neovascularization is maximum.
- Collagen fibers bridge the incision (i.e. they lay down longitudinally)
- Epidermis regains full thickness - & surface keratinization.

2nd week → ↓ edema, ↓ inflammation
↓ vascularization
→ Proliferation of fibroblasts and
accumulation of collagen.
↳ Blanching begins due to ↑ collagen
deposition & regression of vascularity

3rd week → Scar is formed & maximum
fibrosis.

Wound Strength

1st week → 10% of normal unwounded
skin.

3rd month → Maximum wound strength
70-80% of unwounded skin.
(100% wound strength is never
regained).

↳ ~~Wound~~ Wound contraction is absent in primary intention
healing.

Healing by secondary intention

Seen in large wounds where wound edges cannot be approximated.

Large amount of granulation tissue is formed.

Large scar is formed.



Scar reduces in size - this is called as wound contraction

Brought about by Myofibroblasts.

⇒ Wound contraction is seen in healing by secondary intention.

Defects in wound healing.

Hypertrophic scar → Raised scar produced due to accumulation of excessive amount of collagen.

⇒ Seen in thermal / traumatic injury.

⇒ Grows rapidly & regresses over several months.

Keloids - Scar tissue grows beyond the boundaries of the original wound.

⇒ Do not regress

⇒ Genetic predisposition

Exuberant granulation tissue (Proud flesh)

Formation of excessive amount of granulation tissue which protrudes above the level of surrounding skin and blocks the re-epithelialization.

Removed by cautery or surgical excision.

Desmoid / Fibrosarcoma Fibromatosis

Excessive proliferation of fibroblasts and other connective elements on site of injury or surgical scar.

Contracture Exaggeration of wound contraction produces contracture

Common after severe burns

Site - Palm, sole, anterior thorax

Factors that impair wound healing.

- ① Infection
- ② DM
- ③ Poor nutritional status
 - ↳ Zn def.
 - ↳ vitc
 - ↳ PEM
- ④ ~~Mech factors~~
 - ↳ local
 - ↳ tension
- ⑤ Poor perfusion due to
 - ↳ atherosclerosis
 - ↳ DM
 - ↳ unpaired venous drainage
- ⑥ Foreign body
- ⑦ Type of injury & site of injury

Positive acute phase proteins

Also called as Acute Phase Reactants.

Production increases during inflammation.

CRP

Fibrinogen

Mannose binding Lectin

SAA [Serum Amyloid Associated]

Ceruloplasmin

Heptaglobin

} Opsonins

} Inhibits the growth of microbes.

~~Prothrombin~~ Thrombin

Factor VIII

vWF

} Bring about coagulation ~~cases~~

Negative acute phase proteins

Production by liver decreases during Inflammation.

Albumin

Transferrin

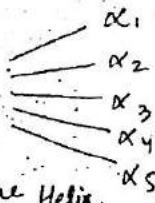
Trans thyretin

Trans cortin

Retinol binding proteins.

Collagen

⇒ Triple Helix



→ any three make the Helix.

Vitamin C is essential for crosslinking of collagen fibres.

Type I Collagen

Most abundant

Has high tensile strength

Found in skin, bones, tendons, internal organs & blood vessels.

Type II Collagen

Cartilage & Vitreous humor

Type III collagen

Granulation tissue

Embryonic tissue

Uterus

Keloid

Type IV Collagen

Basement membrane

Composition of basement membrane

Laminin

Type IV collagen

Fibronectin

Proteoglycans

Amyloidosis

Group of diseases that have in common -
deposition of abnormal proteinaceous substance
extracellularly.

H & E → Pink homogenous appearance

Physical Nature

1) Electron Microscopy



- Long non branching fibrils
- Indefinite length fibrils
- 7.5 - 10 nm diameter

2) X ray crystallography & infrared spectroscopy

⇒ β pleated sheet conformation



Chemical Nature

Fibrillar protein

Constitutes 95% of amyloid

15 different types of
Fibrillar proteins
discovered.

P-component Glycoprotein

Constitutes 5% of
amyloid.

⇒ PAS +ve & diastase
resistant.

Systemic / Generalized Amyloidosis

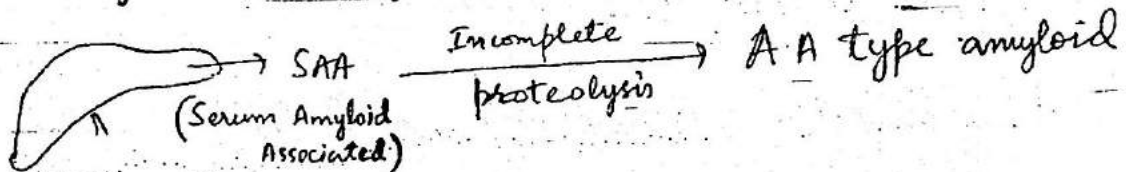
- ① Primary amyloidosis seen in patients of Multiple myeloma & other plasma cell tumors.

AL (Light chains) type of amyloidosis

(λ light chains) are more prone to settle down as amyloid

Site - Heart, kidney, GIT, etc.

- ② Secondary amyloidosis Also called Reactive systemic amyloidosis



Site - kidney, liver, spleen, lungs, etc

M/C organ involved in amyloidosis $\Rightarrow$ **KIDNEY**

Causes $\left\{ \begin{array}{l} \text{Older days - TB, DM, Lung abscess, Bronchi abscess.} \\ \text{Now} \end{array} \right.$

- Ankylosing spondylitis
- RA
- Ulcerative colitis
- RCC

③ Hemodialysis Associated Amyloidosis

Seen in patients who are on long term hemodialysis for chronic Renal Failure.

β_2 microglobulin $\rightarrow$ $(A\beta_2)$

Sites - Joints, tendons, synovium

$\rightarrow$ Carpal tunnel syndrome.

④ Senile Amyloidosis

Seen in old age

Site - Heart, liver, spleen, etc

Transferrin (TTR) is deposited as amyloid $\rightarrow$ $(ATTR)$

$\rightarrow$ (N) serum protein that transports thyroxine & retinol.

⑤ Familial Amyloidosis

Familial Amyloidotic
Polynuropathy

$\rightarrow$ ATTR derived from
TTR is deposited as
amyloid

Site $\leftarrow$ Sensory Nerves
Autonomic Nerves

$\rightarrow$ Mutated Transferrin
is deposited as amyloid
 $\rightarrow$ AD disorder

Familial Mediterranean
Fever

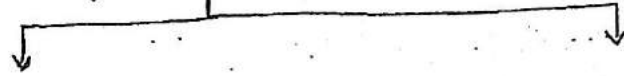
$\rightarrow$ AR disorder. (Recessive)

$\rightarrow$ AA derived from SAA
is deposited as amyloid
in many organs.

Fever, effusions seen.

* Pyrin gene mutations
are seen

Diagnosis



FNAC

Abdominal Fat
aspiration

Biopsy

Abdominal Fat
aspiration

Rectal biopsy

Gingival biopsy

— kidney biopsy is done only when kidney involvement is suspected.

Stains

- ① H&E → Pink homogenous appearance
- ② PAS → ~~PAS~~ PAS +ve: diastase resistant
- ③ CONGO RED → Most important stain*

light microscopy

(LM)

Polarized light

Brilliant Pink
— Colour of
Amyloid.

Apple green
bire fringence

↓
is due to β pleated
sheet conformation of
amyloid.

Metachromatic stains

Crystal violet & methyl violet

↓
Magenta coloured amyloid.

Thioflavin T AS

uv light

Secondary fluorescence.

Immunohistochemistry

ORGAN

Site

Liver

→ 1st site is space of Disse
& causes pressure atrophy
of hepatocytes.

ITO

↓
Storehouse
of vitA
& synthesis
collagen.

Kidney

→ 1st site is Mesangial matrix
Walls of capillaries of glomerulus,
arteries, peripheral capillaries.
Sub endothelial deposits.

Heart

→ Sub endocardium

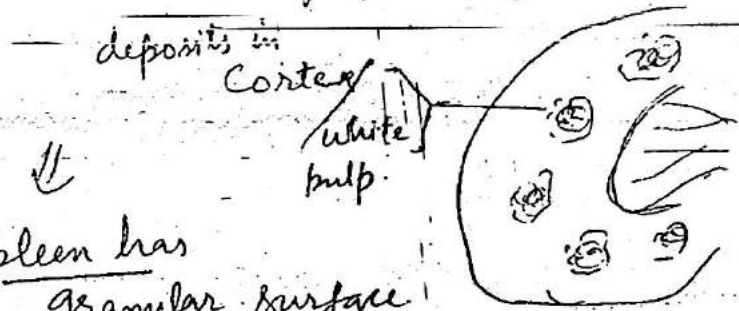
Between the Myocardial fibres
will cause Arrhythmias (bundle branch block)
Restrictive Cardiomyopathy
CCF

GIT → Any where from mouth to anus

Tongue — Macroglossia
 — Amyloid tumor of tongue

Spleen — Sago spleen
 — Lardaceous spleen

— SAGO SPLEEN Amyloid deposition in (white pulp)
in lymphoid follicles in cortex.



On cross section —
Gray Translucent
bodies
like grains of
Sago.

LARDACEOUS SPLEEN

Amyloid deposition in walls of splenic
sinusoids → produces large map like
(& Red Pulp) areas of amyloidosis

LARD → animal Fat

IMMUNITY

⇒ Self defence

Innate Immunity

- First line of defence
- Function - Prevention & eradication of infection.
- Innate immunity is non specific
- Innate immune response does not become better with each exposure
- NO memory cells

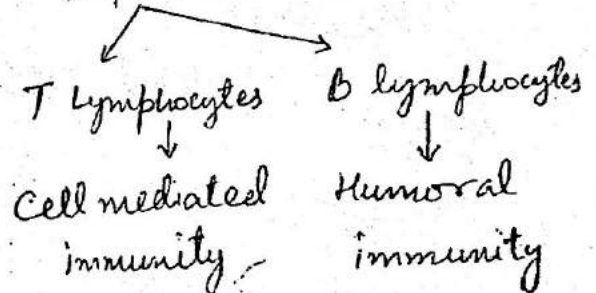
Components

- 1) Epithelia - Skin, GIT, Respiratory Tract.
 - Mech Barrier
 - Produce antimicrobial substances eg. defensins
 - Intraepithelial lymphocytes

Adaptive Immunity

- 2nd line of defence
- Function - eradication of infection
- Adaptive immunity is specific
- Adaptive immunity response becomes better with each response
- Memory cells present

Components



2) Cells -

- Neutrophils
 - Macrophages
- } Extra cellular bacteria & fungi

- NK cells - First line of defence against virally infected cells and tumor cells.

- Dendritic cells

- Mast cells.

3) Plasma proteins

- Mannose binding lectin
- CRP
- Complement { Lectin pathway
Alternate pathway
- Lung surfactant

Pattern Recognition receptors.

Cells that participate in innate immunity have receptors that recognize microbial components that are shared by microbes. These are called Pattern Recognition Receptors.

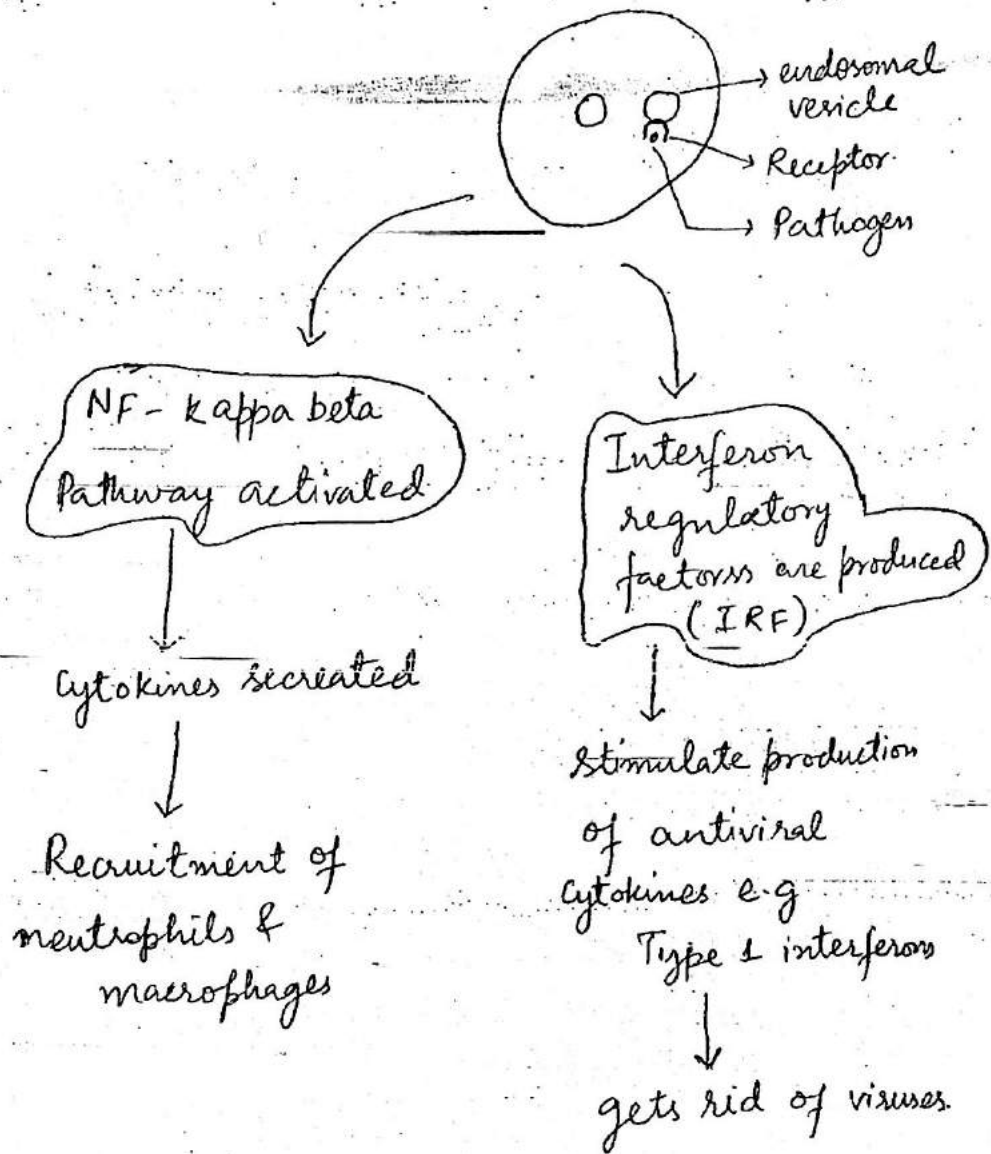
Location

Plasma membrane

Endosomal vesicles

Cytosol





Pattern Recognition receptors

① Toll like receptors - (TLRs)

Found on —
{

 Plasma membrane
Endosomal vesicles

11 TLRs are recognized Till date

e.g. TLR-2 —
{

 gram +ve bacteria
Fungus
Leptospira

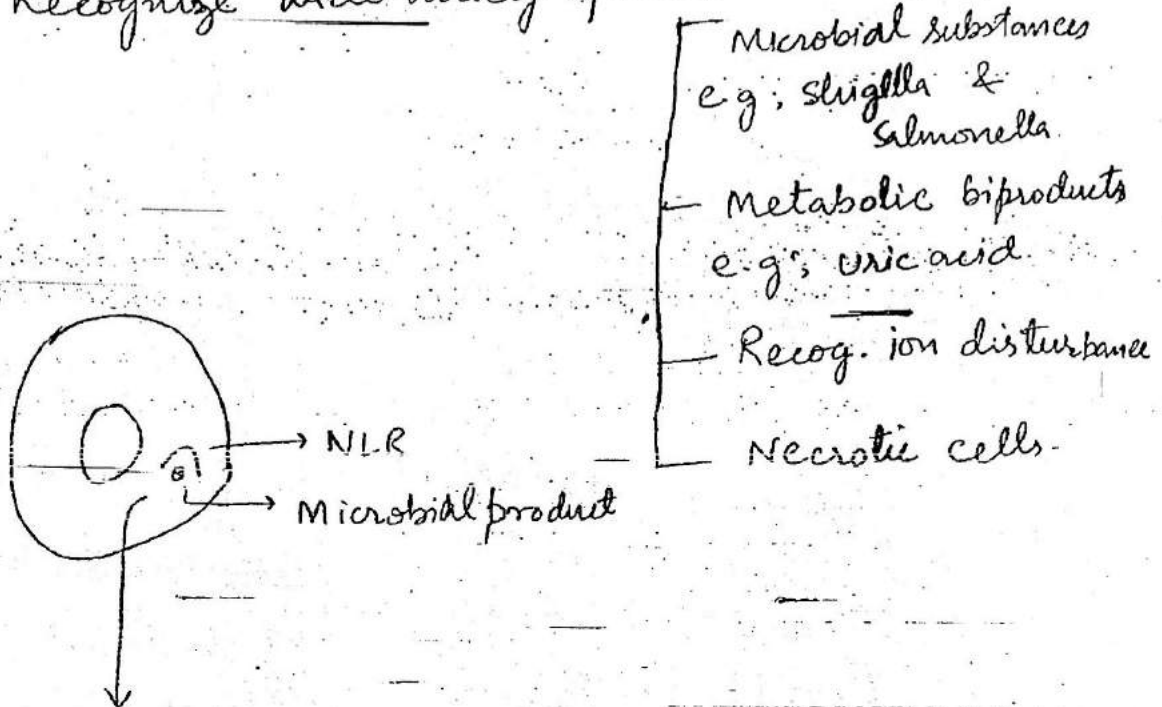
TLR-4 — gram + -ve bacteria

Founder member "Toll" discovered in *Drosophilla*

2) NOD like receptors (NLR)

Location-cytosol

Recognize wide variety of substances



Inflammasome
(multi protein
complex)

→ activates Caspase I (IL-1 β
converting
enzyme)

IL-1

Fever

Inflammation

⇒ Gain of function mutation in NLR gene leads fever periodic fever syndrome called auto inflammatory syndrome which responds to treatment with IL 1 antagonist.

③ C-type Lectin receptors

Found on plasma membrane

Detects Fungal glycans and leads
to inflammation → gets rid of fungi.

④ Rig like receptors

Found in cytosol

Detects viral nucleic acid

↓
IRF are produced

↓
Type I interferons.

⑤ 7 transmembrane G protein coupled receptors

Recognize bacterial products $\pm$ N-formyl
methionyl residues → stimulates chemotaxis.

⑥ Mannose Receptors

Recognize mannose sugar in bacterial wall

↓
stimulate phagocytosis.

Adaptive Immunity

T cells
(CMI)

B cells
(HMI)

Lymphocytes are antigen specific.
Mature lymphocytes that have not encountered antigen
or immunologically inexperienced are called

Naive Lymphocytes

Effector cells

Function- eliminate
microbe

memory cells —

Live in a state of
heightened awareness
Rapidly combat the
microbe if it returns.

Lymphocytes are antigen specific - Lymphocytes
of same specificity form a clone.

When an antigen enters, it selectively
recruits antigen specific clone, this is
called clonal selection.

Non B & Non T cells

Do not have TCR/BCR.

→ Also called large granular lymphocytes.

Function

① Innate Immunity

First line of defence against virally infected cells and tumor cells.

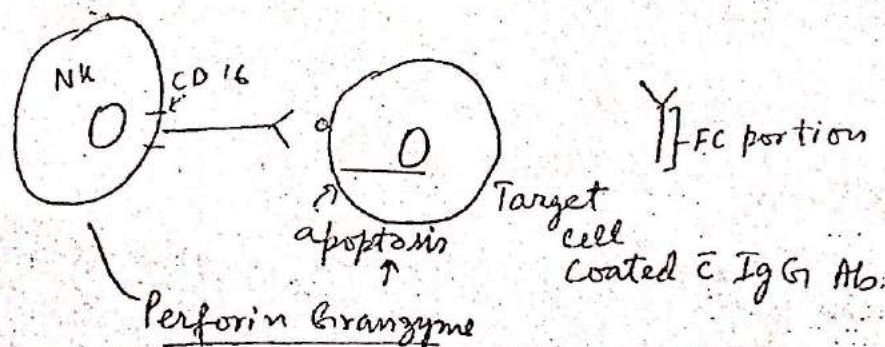
② Adaptive immunity

Play a role in ADCC (antibody dependent cellular cytotoxicity).

③ Location → Constitute 5-10% of P. B Lymphocytes.

Markers → CD 16 → FC receptor for IgG Ab.

CD 56 → Function Not known.



FC portion of IgG Ab fits into CD16 on NK cells.

NK cells release perforins & granzyme & kill the target cell.

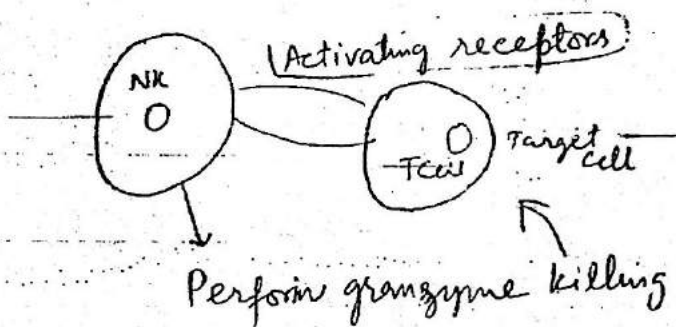
Role in Innate Immunity

- - Kills virally infected cells & tumor cells.
- - NK cells are not MHC restricted.
- - NK cells have 2 types of receptors.

① Activating receptors

Activate NK cells to kill the target cells.

- Belong to NKG2D family.



- NK cells attach to target cells by activating receptors & kill the target cells by Perforin granzyme dependent killing.

② Inhibitory receptors

Prevents NK cells from killing normal cells.

Inhibitory receptors belong to

CD 94

family of Lectins

KIRs (CD 96)

(killer cells Ig like receptors)

Cytokines produced by NK cells - IFN gamma

↓
activates macrophages
by classical pathway

Cytokines that regulate NK cell activity

IL12

Activates killing &

secretion of IFN gamma
by NK cells

[IL2
IL15]

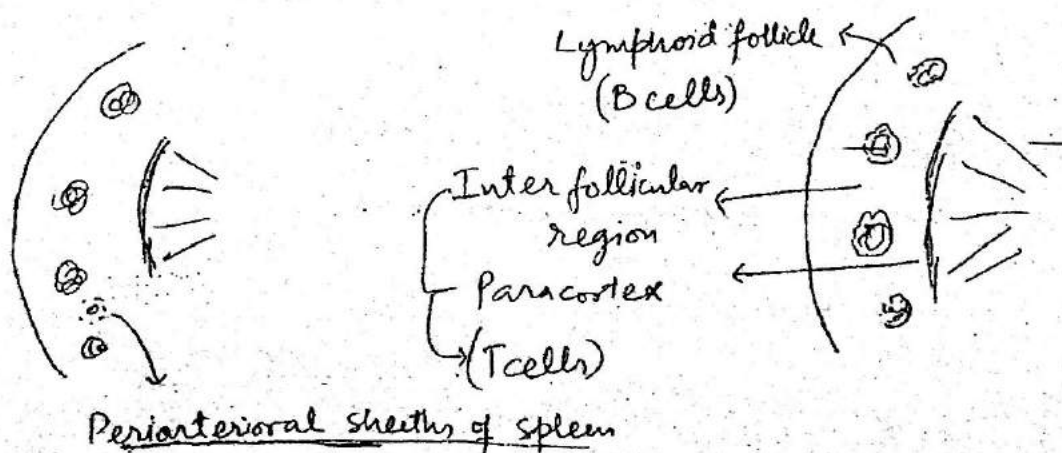
Stimulates NK cell
proliferation

T cells

Play a role in cell mediated immunity.

Location - Peripheral blood

60-70% of P.B. lymphocytes.



→ Found in ~~Paracortex~~ Interfollicular region of LN

→ Found in Paracortical region & periarteriolar sheaths
of spleen

T cell Markers

TCR (T cell Receptor)

CD1, CD2, CD3, CD4, CD5, CD7, CD8, CD28.

TCR

- Antigen specific

- 2 types

αβ TCR

- Found on 95% T cells

- MHC Restricted.

γδ TCR

- Found on 5% T cells.

- Not MHC Restricted.

- Found in the epithelia

like skin, GIT,

urogenital etc → provide

protection against microbes

that try to enter through

the epithelia.

- Do not have CD4 & CD8

on their surface. (γδ)

CD3

⇒ Signal transduction is function

⇒ Lineage specific T cell marker

⇒ Pan T cell marker

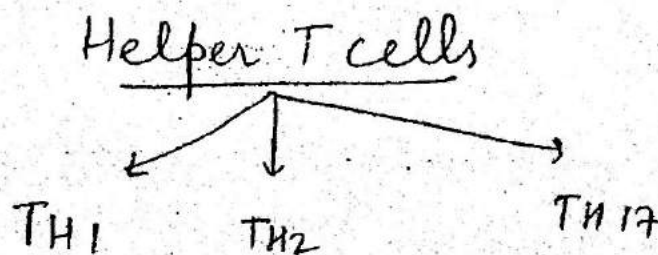
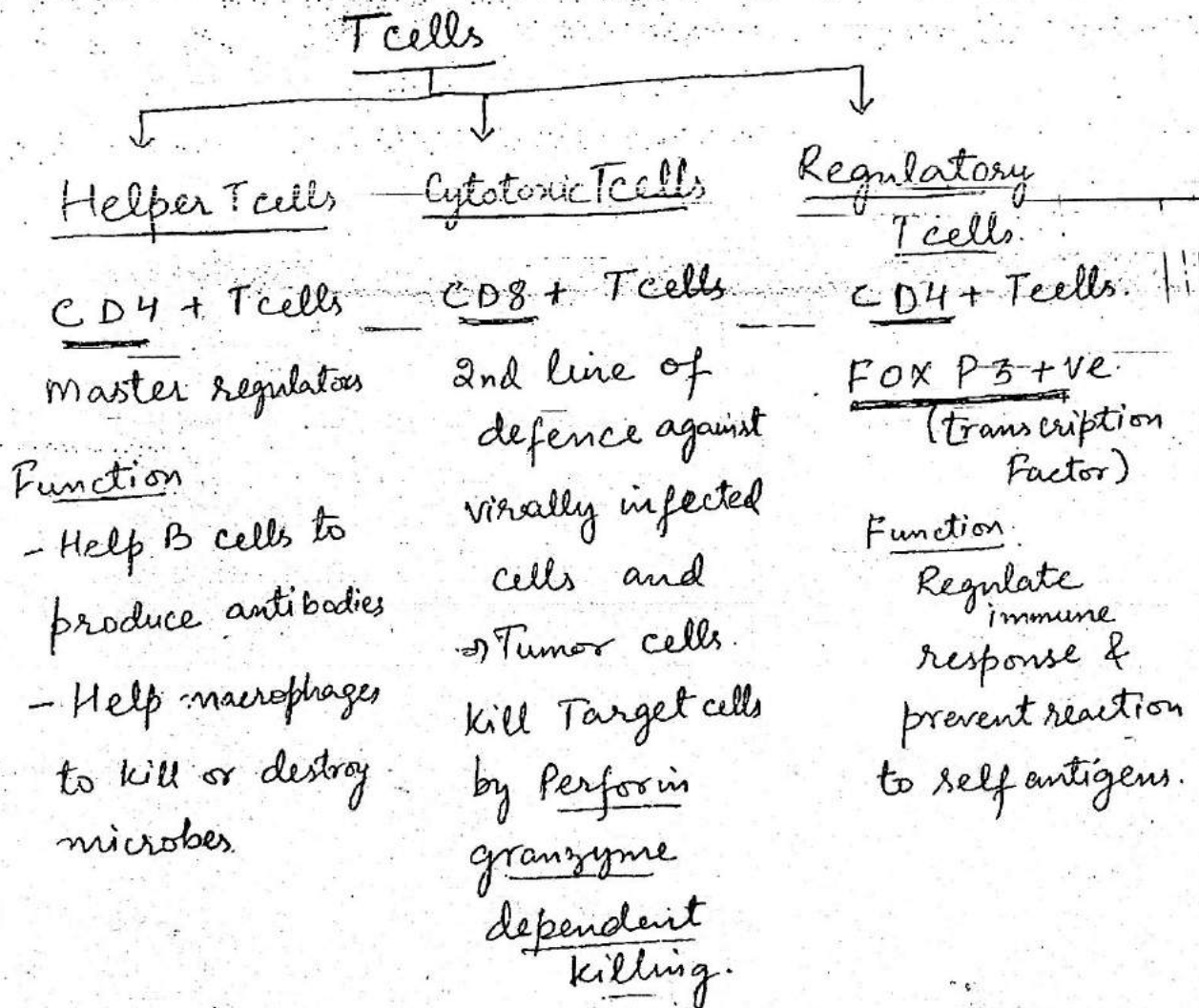
CD7

Pan T cell marker

Not lineage specific.

CD4 } Found on two mutually exclusive
CD8 } subsets of T cells.
(CD4:CD8 :: 2:1)

CD1a Thymocytes & Langerhan cells



TH1

Cytokine produced - IFN gamma

[Biggest producer
Signature cytokine]

Function

IFN gamma [Activates macrophages by
classical pathway
Stimulate B cells to produce
IgG antibody.

Host defense
against - Intracellular microbes

Role in disease - Chronic Auto immune disease
e.g. IBD, Psoriasis

TH2

Cytokines produced

- IL4 (signature cytokine)
- IL5
- IL13

Function

IL4 stimulates B cells to produce
IgE antibody

Activates Macrophages by Alternate
pathway

IL5 - Stimulates B cells to produce IgA Abs.

Activates mast cells & eosinophils.

IL 13 → Activates macrophages by alternate pathway
→ Activates epithelial cells to produce mucus

Host defense against - Helminthic parasites

Role in disease - Allergies

TH 17

Cytokines produced

IL 17

IL 22

Chemokines

Function

Recruitment of neutrophils and monocytes/macrophages

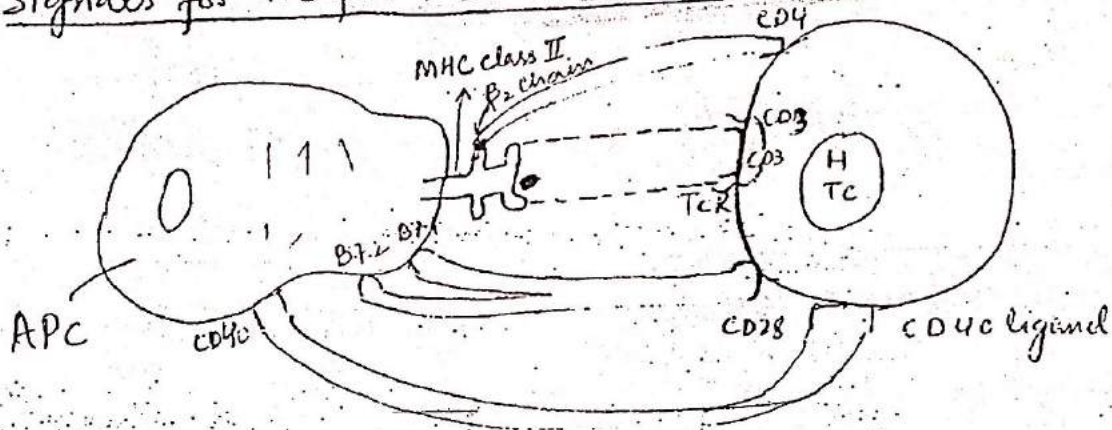
Host defense against Extracellular bacteria & fungi.

Role in diseases

Chronic AID like IBD,

Psoriasis & multiple Sclerosis.

Signals for Helper T cell activation.



Signal 1

- (a) TCR (Tcell) binds to antigen which is presented by APC in context of MHC class II
- (b) CD4 of T cells attaches to β_2 chain of MHC class II

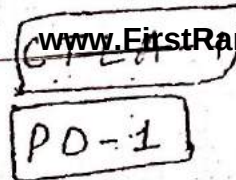
Signal 2 (also called - Co-stimulatory signal)

CD28 (Tcells) attaches to $\left[\begin{array}{l} B7.1 (CD80) \\ B7.2 (CD86) \end{array} \right]$ of APC

Signal 3

CD40 ligand (Tcells) attaches to CD40 on APC.

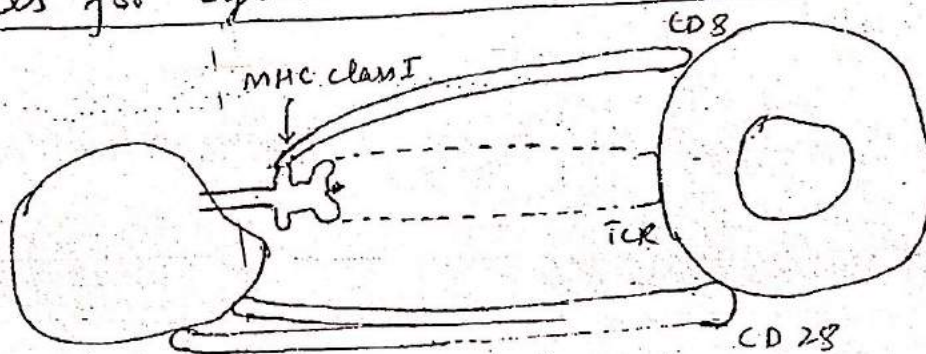
by ~~stop~~ T cell (helper) ~~cell~~ activation
by co-inhibitory receptors



Stops helper T cell activation

Belongs to CD28 family, blocks
signals from TCR and CD28
& terminates T cell response.

Signals for Cytotoxic T cell activation.



Signal 1

(a) TCR (T cells) attaches to antigen
that is presented by APC in context of
~~CD8~~ class I MHC

(b) CD8 (T cells) attaches to α_3 chain of
MHC class I.

Signal 2

~~co-stimulatory signal~~

CD28 (T cells) attaches to B7.1 CD80

CD8 T cell kills Target cells by Perforin granzyme killing.

B7.2 CD86 of APC

Humoral immunity

Sites [PB → Constitute 15-20% of PB lymphocytes
Found in lymphoid follicles in LN, spleen,
Peyer's patches, BM, tonsils, etc.

B cell Markers → BCR (B cell Receptor)

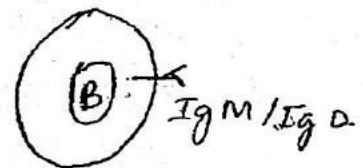
CD 19, CD 20, CD 21, CD 22, CD 23, CD 10 (CALLA)

Ig α (CD 79a)

Ig β (CD 79b)

BCR IgM/IgD antibody (Intramembranous)

- Antigen Specific.



Ig α (CD 79a)
Ig β (CD 79b) } Signal transduction
(like CD 3 of T cells)

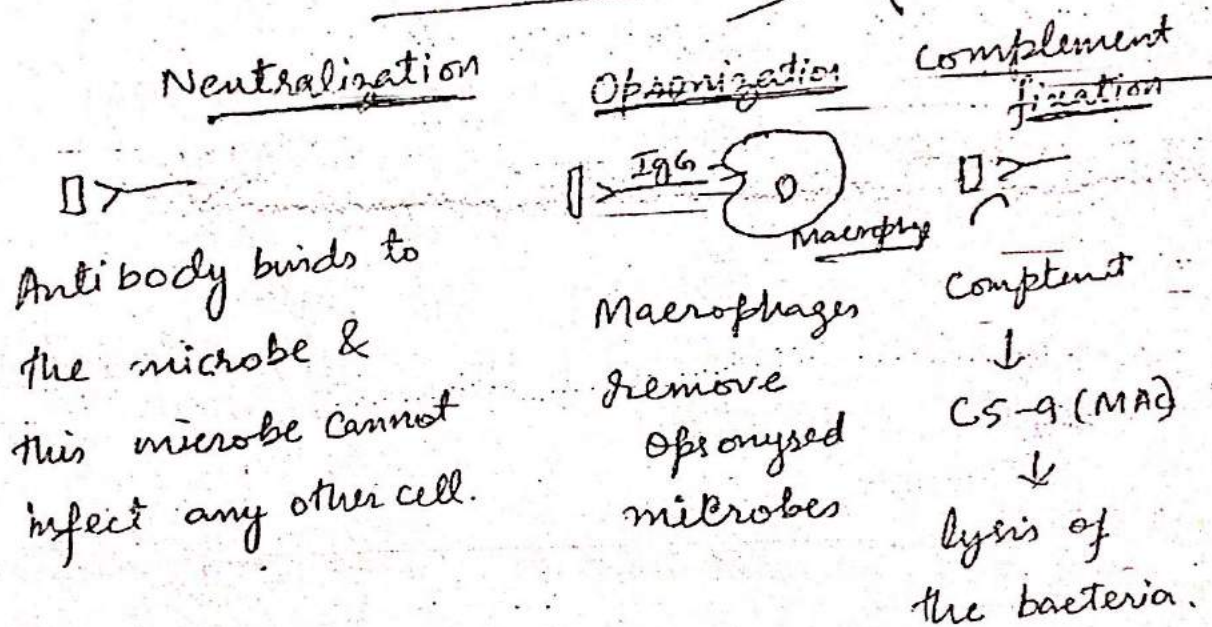
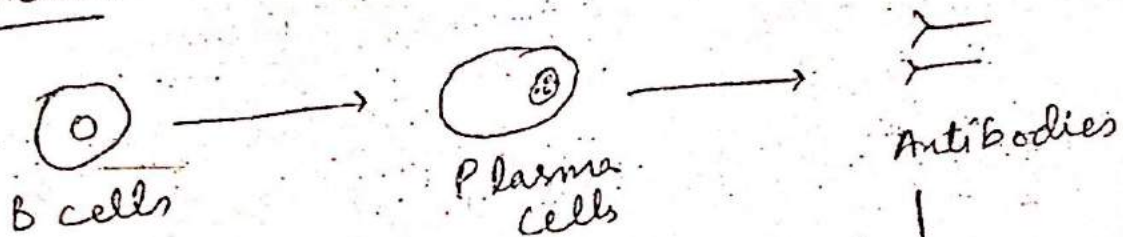
CD 19 Pan B cell marker
Lineage specific

CD 20 Lineage specific IHC

CD 21 [Complement Receptor (CR₂)
EBV receptor

CD40 site where B cells receive signals from Helper T cells.

Function



↳ IgG antibodies cross placenta and provide passive immunity to new born.

↳ IgE antibodies → Parasitic infection

↳ IgA antibodies are produced in the mucosal surface → provide protection on mucosal surface.

2 pathways for Ab production by B cells

T Independent Pathway

Polysaccharide & lipid antigen occupy a number of antigenic determinants (i.e BCR) on

B-cells



B cells → PC → IgM

No help of T cells (HelperT) is taken.

T Dependent Pathway

Protein antigens stimulate B cells which bind to HelperT cells and then B cells

produce

IgG

IgA

IgE

class of Ab

Help. from Helper T cells is taken.

This is called isotype or class switching.

Helper T cells also stimulate B cells to produce antibodies with high affinities for antigen. This is called as affinity maturation.

Dendritic cells

- Antigen presenting cells - Best APC.

Best APC because

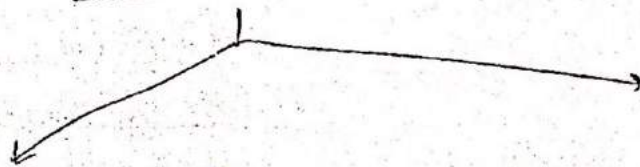
① Located at the right place where antigens are encountered.

② They have fine hair like processes that trap antigens.

③ Each Rich in MHC class I & II & can present antigen to $\begin{cases} \text{CD4 T cell} \\ \text{CD8 T cell} \end{cases}$

④ They are also rich in co molecule B7.1 & B7.2

Dendritic cells



Interdigitating DC

Present Ags to T cells

Location -

Skin Langerhan cells.

Interstitialia of organs

e.g. lungs, GIT, heart liver etc.

Langerhans cells
CD1a

S 100

Langerin (CD207)

Follicular DC

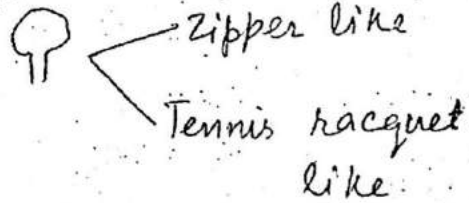
Present Ags to B cells

Location -

In centre of lymphoid follicles

E/m

Birbeck granules in their cytoplasm



MHC antigens

RBC do not have MHC Ag.

MHC class I

HLA A

HLA B

HLA C

⇒ Found on all cells except RBCs

CD 8 T cells mount an immune response in context of class I MHC.

MHC class II

HLA DP

HLA DQ

HLA DR

Found on APC i.e;

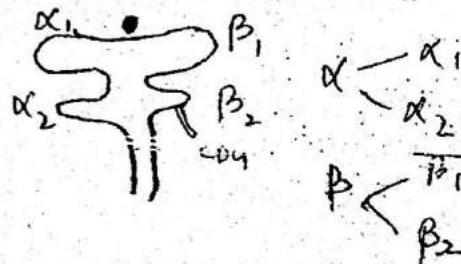
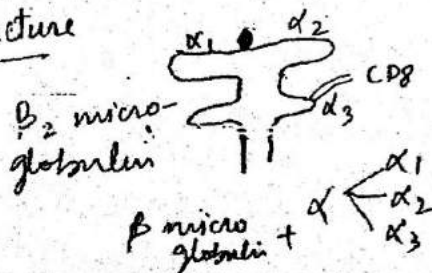
dendritic cells

B lymphocytes

Monocytes/macrophages

CD 4 T cells mount an response in context of class II MHC.

Structure



Antigen binds in the cleft
b/w α_1 & α_2

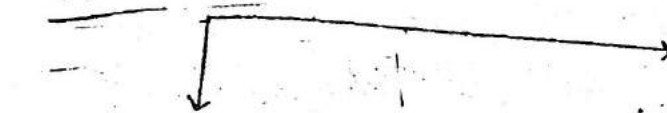
α_3 is the site of CD8
attachment

Antigen binding cleft
is b/w α_1 & β_1

β_2 is the site of
CD4 attachment

Genes for MHC antigen are found on the short
arm of chromosome no. 6.

APC



Professional APC

- Dendritic cells
- Monocytes
+ Macrophages
- B cells

Non Professional APC

- Thyroid follicular cells
- Thymic epithelial cells
- Fibroblasts
- Glial cells
- Endothelial cells

Hypersensitivity Reactions

Injurious immune reactions are called Hypersensitivity Reactions.

Type I

Rapidly occurring reaction which occurs within minutes of binding of antigen to IgE antibody on the mast cells in a previously sensitized individual.

→ Localized (ATOPY)

[Genetic predisposition]

Bronchial Asthma, Hay Fever

Allergic conjunctivitis, dermatitis
& allergic rhinitis

Food allergies

→ Systemic

Anaphylactic Shock

Drugs

e.g. Penicillin

Hormones

Antisera

Bronchial Asthma

Pollen Antigen binds to APC (dendritic cells)



APC presents Ag to Naive T cells



TH2 Subset



TH2 binds to B cells



B cells → PC → IgE Ab

IgE antibodies attach to the Fc receptor on mast cells.



Pollen Ag causes cross linking of IgE antibody on mast cells



Mast cells degranulate & release Mediators

Preformed/Primary

Brings about initial phase of Bronchial Asthma

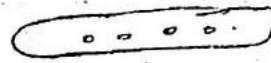
CF → Vasodilation
→ ↑ vascular permeability
→ bronchospasm.
⇒ Histamine, lysosomal enzymes
Serotonin (Proteases)

Newly synthesised
Secondary mediators

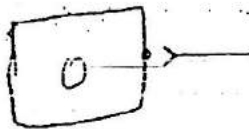
- Bronchoospasm
- Leukocytic infiltration
- Epithelial damage
⇒ PAF, AA mediators (C1b, LTB₄, LD₅, PGD₂)
Cytokine, Chemokine

Type II

- Antibody mediated (IgG/IgM)
- Brought about by antibodies which are directed against fixed antigens



Antigen can be fixed on cell membrane or connective tissue



- (a) - Antibody attaches to fixed antigen on cell membrane & causes destruction of Target cell.

(or)

- (b) - Antibody attaches to fixed antigen & causes disregulation of function of target cell.

e.g. Grave's Disease
Myasthenia gravis

Type I (in Micro)

& Type II here

Destruction by
 ← Opsonisation
 ← Complement fixation

Antibody attaches to Basement membrane
↓
Activate Complement
C3a C5a

↓
Enzymes released
↓

Breakdown of Basement membrane
↓

Good Pasture Syndrome

eg. AIH Anemia.
AI granulocytopenia
AI Erythroblastosis
fetalis.
Mismatched blood Transfusion
reaction.

Pemphigus vulgaris

Pernicious anemia
(antibodies against
Parietal cells)
Acute Rheumatic Heart disease

↓
No IF
↓
Meg. Anemia.

Type III

[Called Immune complex disease.]

Antigen is not fixed.

3 stages

① Formation of immune complexes (IC)

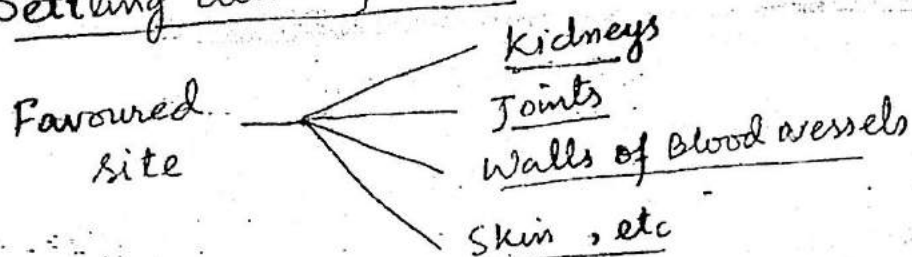
Antigen $\xrightarrow{\text{5 days/week}}$ IC

Most pathogenic complexes are

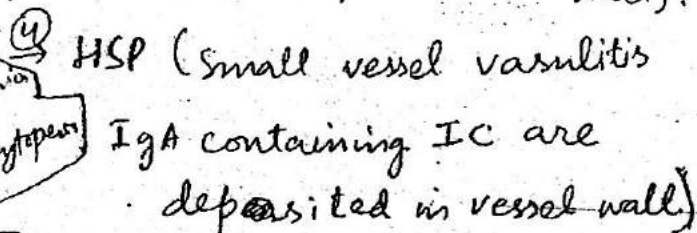
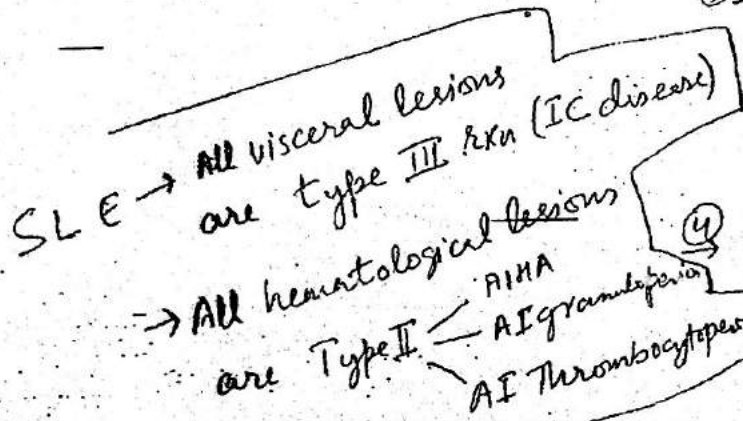
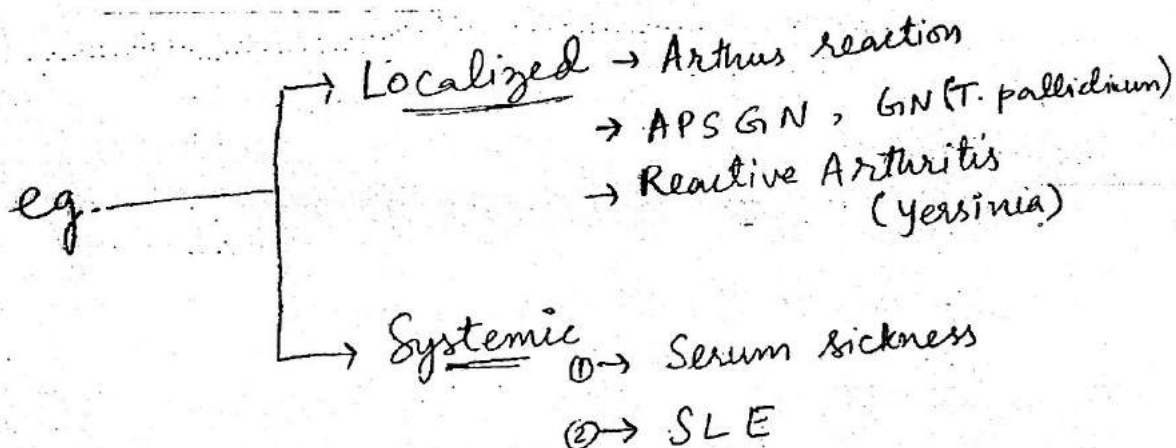
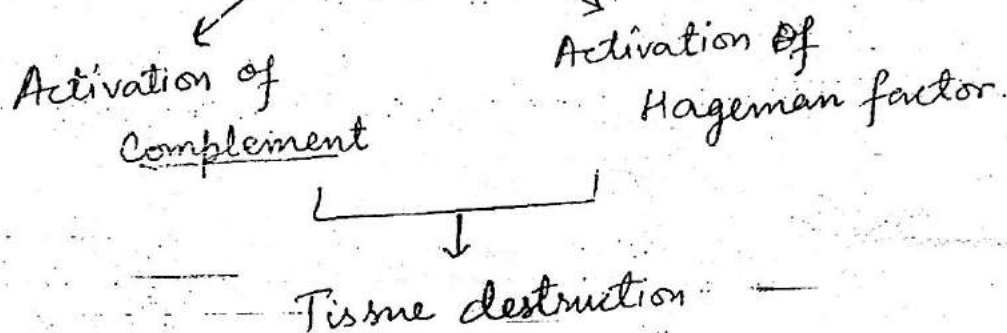
Small/medium
size

Found in
Antigen excess

② Settling down of IC



③ Tissue destruction by IC



Type IV

- Brought about by T cells (Cytokine mediated)

↓
CD4 T cells

Delayed HR

e.g; Tuberculin Reaction

Immune granulomas

Contact dermatitis

↓
CD8 T cells

Destruction of virally
infected cells & tumor
cells.

Both
CD4 $\Rightarrow$
& CD8

① Rheumatoid Arthritis

② IBD

③ Type I DM

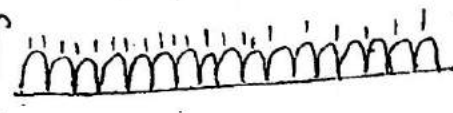
④ Psoriasis

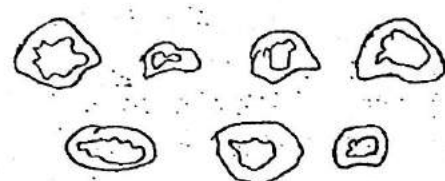
⑤ Multiple sclerosis

Acute cellular graft Rejection

Graft versus Host disease.

Respiratory System

A {  epithelium

B {  Mucus gland layer

C {  cartilage

$$\text{Reid's Index} = \frac{B}{A+B+C} \quad \left[\begin{array}{l} N = 0.4 \\ \uparrow \text{sed} = \text{Mucus gland layer} \end{array} \right]$$

Asthma - Airway Remodelling

1. Sub basement membrane fibrosis [Type III and Type I collagen]
2. Mucus gland hyperplasia
3. ~~Goblet cell metaplasia~~
4. Goblet cell metaplasia
5. Smooth muscle hypertrophy + hyperplasia

ARDS

M/c/c — Sepsis > Pneumonia

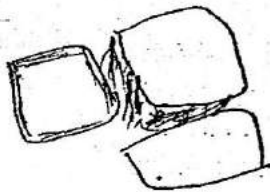
IL-8, IL-1 and TNF α is involved.

Respiratory failure occurring in
1wk of a known clinical insult & 4%
opacities on chest imaging,
not fully explained by effusion,
atelectasia,
cardiac F.
or F. overload

(Chemokine for neutrophils) $\rightarrow$ So, neutrophils are M/I culprit responsible for ARDS.

$\rightarrow$ IL-8 rises in 30 minutes of injury

$\rightarrow$ Cells damaged — endo & epithelial cells
— leakage of fluid + cellular debris
+ leaked plasma proteins



Hyaline

Along the alveoli

making membrane

$\rightarrow$ Diffused alveolar damage — Histological Hallmark (DAD)

Coal workers Pneumoconiosis

$\rightarrow$ Pneumoconiosis $\rightarrow$ To describe non-neoplastic lung reaction to inhalational of mineral dust mainly at workplace; also includes organic as well as inorganic particulates, chemical fumes & vapours

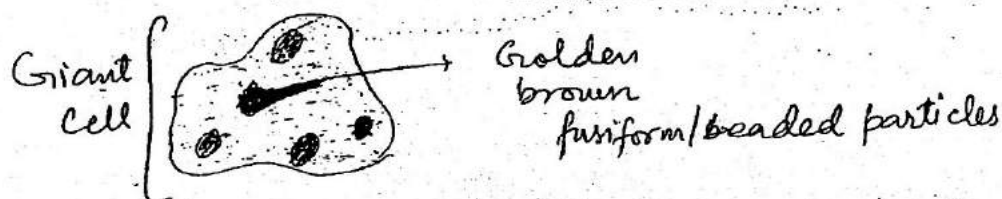
M/C — Silicosis (quartz)

Collagenous nodule in lung

egg shell
Calcification
(lymph nodes classically)

Asbestos Related Disease

- ① Pleural Plaque (mc manifestation)
 - ② Pleural effusion
 - ③ Diffuse Pul. fibrosis [Asbestosis]
 - ④ Lung Ca - [mc Ca in asbestos exposure]
 - ⑤ Mesothelioma → (most specific Ca) (25-40 yrs)
 - ⑥ Laryngeal Ca
 - ⑦ Ovarian Ca
 - ⑧ Colon Ca
- } Latent period
(10-15 yrs)



ASBESTOS BODY [Coated $\bar{c}$ Iron & Proteinaceous material
↓
Perls' Stain +ve

Any other particle coated $\bar{c}$ Iron & proteinaceous material
↳ FERRUGINOUS BODY

In Anthracosis → Pigment laden macrophages are seen

Coal Macule → Aggregated Macrophages (1-2mm)
↓
Coalesce to form nodule

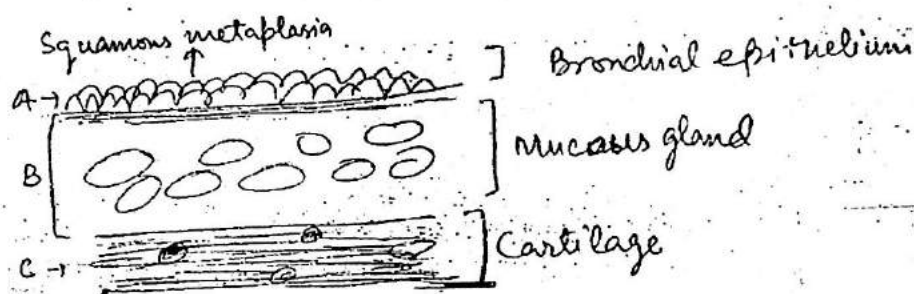
Progressive ~~massive~~ massive Fibrosis of lung parenchyma

↳ Risk of Cancer is more in domestic use of coal
i.e; Bituminous coal.

Chronic Bronchitis

M.C. Cause - Smoking

Earliest change - MUCUS HYPERSECRETION



$$\text{REID'S Index} = \frac{B}{A+B+C}$$

done in autopsy (N) = 0.4

↑ in → ↑ Mucous gland.

Manifestations in Pneumoconiosis

- ① Localised fibrous plaques, or rarely diffuse pleural fibrosis (M.C. manifestation)
- ② Recurrent Pleural effusion
- ③ Parenchymal interstitial Lung fibrosis (Asbestosis)
- ④ Lung Ca (M.C.)
- ⑤ Mesothelioma (most specific)
- ⑥ Laryngeal, ovarian, colon Ca.
- ⑦ ↑ risk of autoimmune disease
- ⑧ CVS disease.

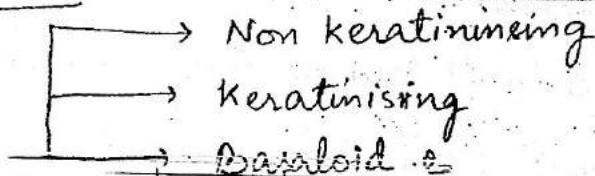
LUNG Ca

Histological classification (WHO 2015)

① AdenoCa

- Acinar, papillary, Micropapillary, Solid, lepidic, predominant, mucinous subtypes

② Sq cell Ca



③ Large cell Ca

④ Neuroendocrine Ca

- Small cell Ca
- Large cell neuroendocrine Ca
- Carcinoid Tumor

AdenoCa

- Pre invasive lesions
 - Atypical Adenomatous Hyperplasia
 - AdenoCa insitu
- Minimally invasive AdenoCa
- Invasive AdenoCa

AdenoCa In situ (AIS)

Previously known as Bronchoalveolar Ca.

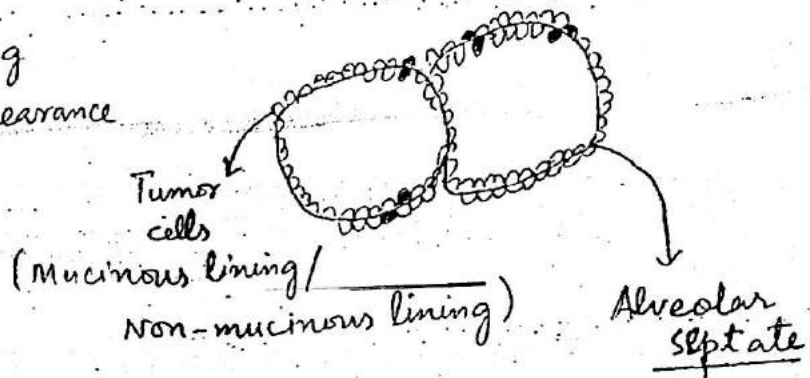
→ < 3cm

No stromal invasion

No Pleural invasion

No Lymphovascular invasion

⇒ Butterfly sitting
on Fence Appearance



(No desmoplastic stroma)

LEPIDIC PATTERN OF GROWTH

Minimally Invasive

< 5 mm stromal invasion & < 3 mm in size

No pleural invasion

No lymphovascular invasion.

Squamous cell Ca

- Keratinising (new)
- Non keratinising
- Basaloid (new)



Basophilic
psamoma
bodies

Eosinophilic

Neuroendocrine Origin

Histology

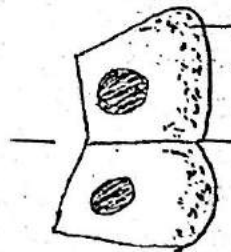
IHC

E. Microscopy

Salt & Pepper
Chromatin
Stippled
Chromatin

Synaptophysin
Chromogranin
& CD56
CD57

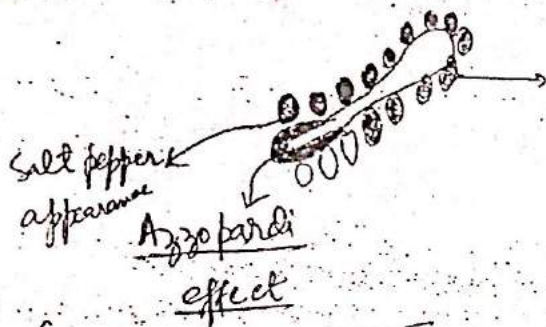
+ve



Dense
Core
Neurosecretory
granules

In High Gr.
Hyperchromatic

[Oat cell carcinoma]



Small cells
↑ N/C ratio
Round to oval nuclei

Stippled chromatin

(DNA encrustation on vessel wall)

Tumor cells have a high turnover & are fragile → disrupt easily

Purplish Blue
Powdery discoloration
of vessel walls

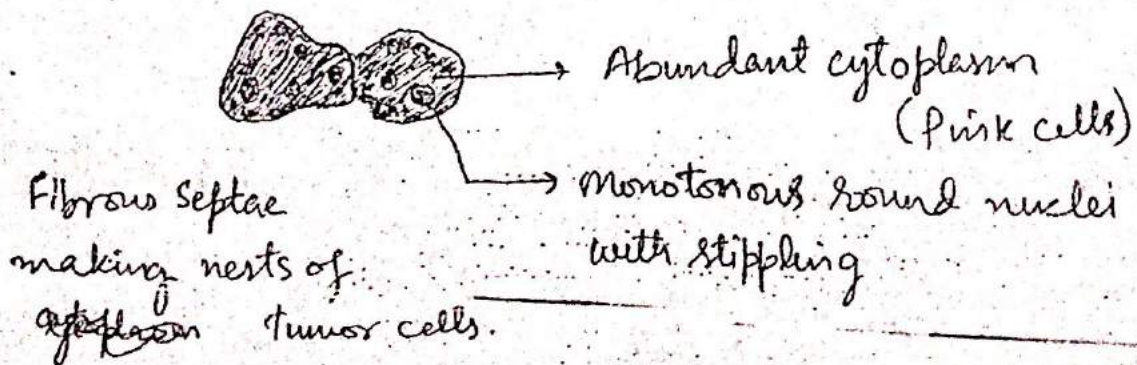
Their DNA gets encrusted
upon vessel wall
[BLUE]

↓
Azzopardi effect

Carcinoid [Carcinoma like epithelioid tumor]

	Grade	Mitotic count
Typical	I	< 2/10 HPF
Atypical	II	2-10/10 HPF

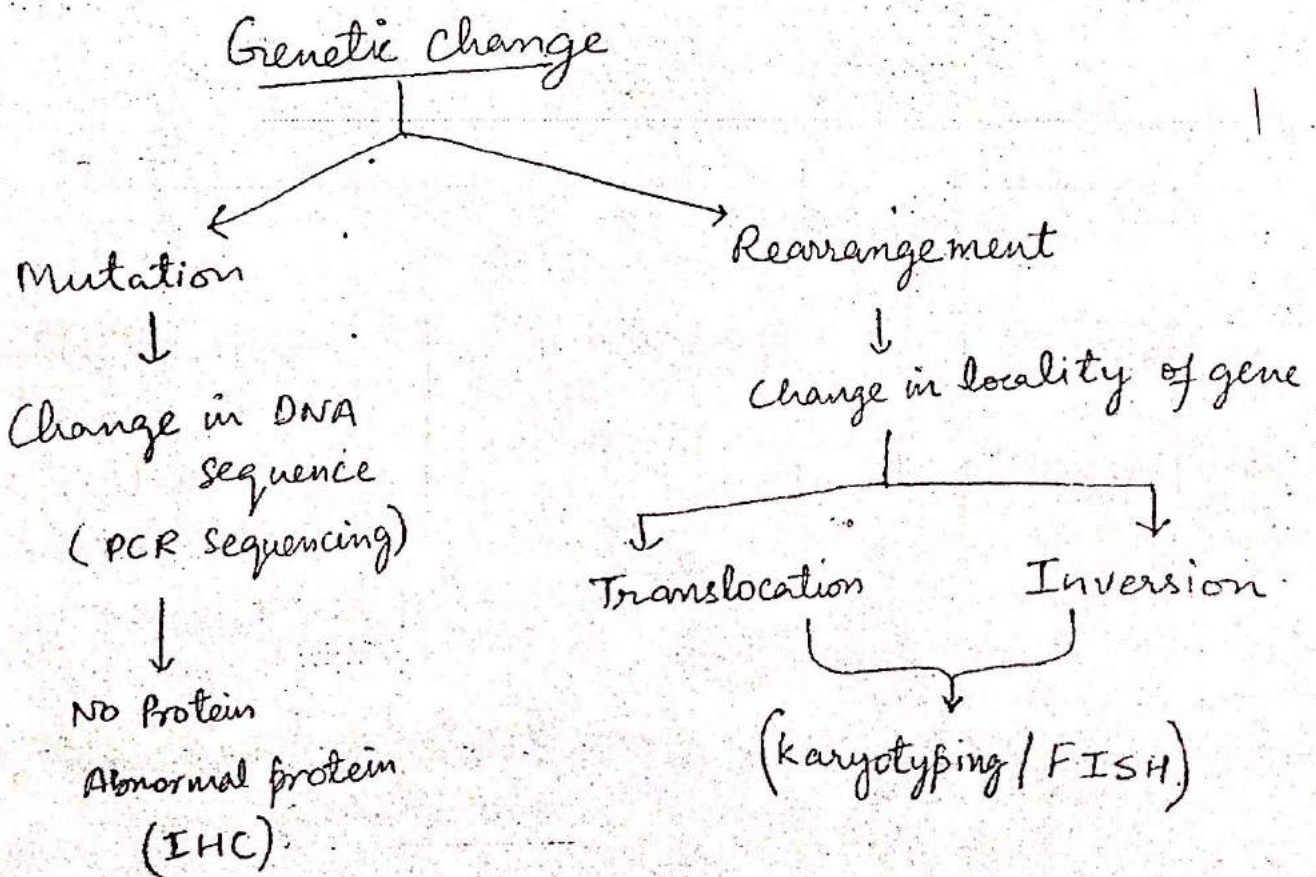
HPF = High Power Field
~ 40x

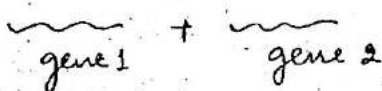


Small cell	Squamous cell	Adeno
Rb mutation	P53 mutation	EGFR mutation & amplification
P53 mutation	EGFR mutation amplification (more than mutation)	KRAS mutation
myc amplification	FGFR ₂ amplification	ALK rearrangement

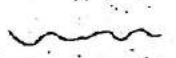
Amplification is checked by FISH

↓
Overexpression is checked by IHC



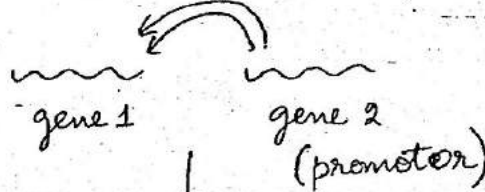
①  gene 1 + gene 2

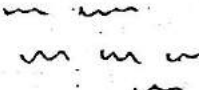
↓ Transcription

 (Fusion Transcript)
(Fused mRNA) (RT PCR)

↓

 (ONCOPROTEIN)
(IHC) [↑ed function than before] e.g. BCR ABL
or
[↓ed function than before]

②  gene 1 gene 2 (promoter)

 gene 1 ↑↑↑ed (FISH)
(overexpressed)

↓

FISH Overexpression (IHC)

FISH INTERPRETATION

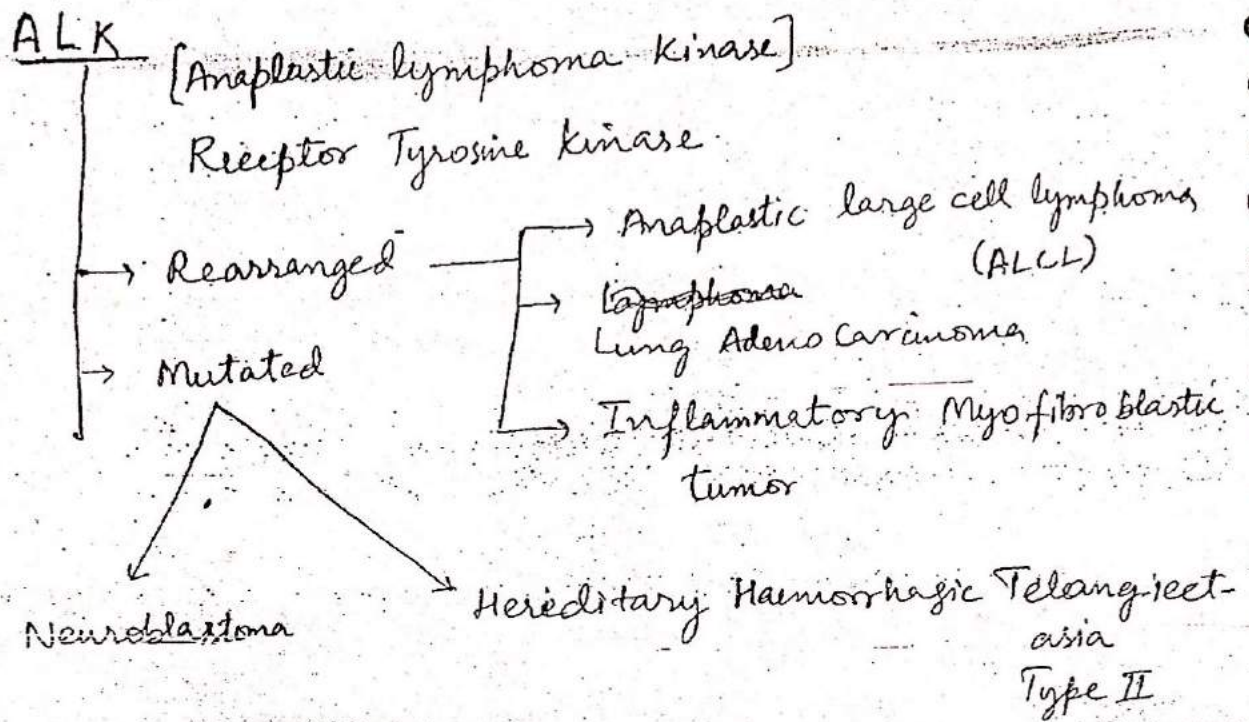
 A } Normal
B }

 → Deletion or Monosomy

 → Trisomy

 → Amplification

 → Fusion



In lung Adenocarcinoma

EGFR & ALK can be targetted

[EGFR & KRAS are mutually exclusive]

In non smokers & women → EGFR mutation.

IHC of lung Cancer

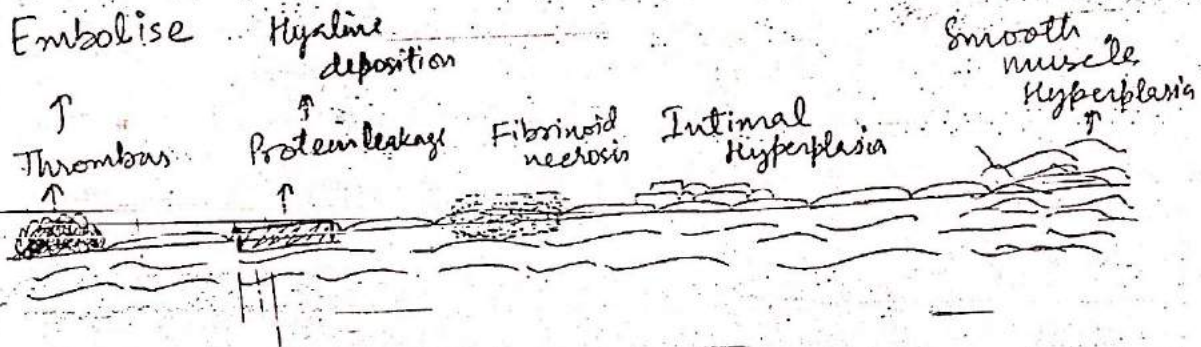
	Small cell	Squamous	Adeno
Thyroid Transcription Factor (TTF-1)	+	-	+
NAPSIN-A	-	-	⊕
Other markers	Synaptophysin Chromogranin CD56/CD57	p63	CK7 + CK20 -

	Mesothelioma	Adenocarcinoma
PAS	-	+
embryo- Carcinogenic genic antigen	-	+
TFE1	-	+
NAPSIN	-	+
CK7	(+)	(+)
CK5/6	+	-
Calretinin	+	-
WT1	+	-
Electron microscopy	Long slender microvilli	Short Stubby villi

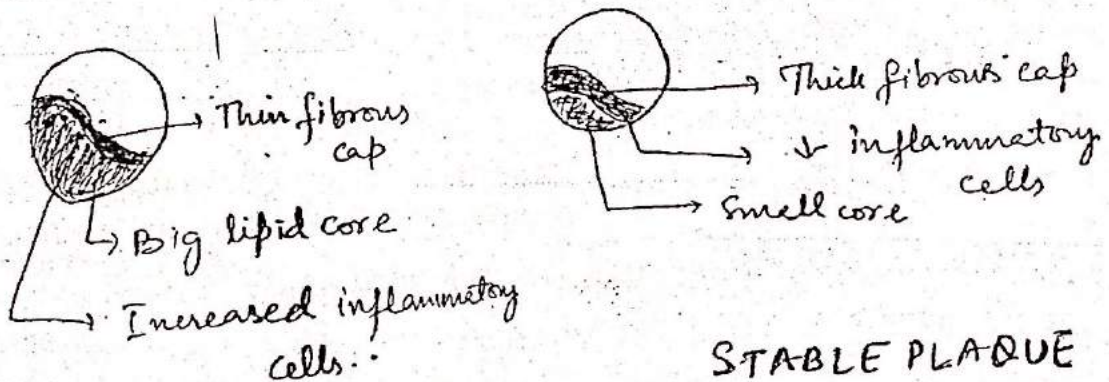
Adenocarcinoma	Squamous cell Carcinoma	Small cell Carcinoma
- Most common lung cancer world wide In women In non smokers	- Most common lung cancer in India in smokers	- Strongest association with smoking.
- Peripheral location	- Central location	- Central location
- Most common gene mutated is KRAS	- Most common para- neoplastic syndrome is - <u>Hypercalcemia</u>	Most common Para- neoplastic syndrome is SIADH.
⇒ Most common Para- neoplastic syndrome is <u>Hematological</u>	⇒ Cavitation (also in large cell ca)	⇒ SVC obstruction <u>LAMBERT EATON</u> Synd.
⇒ Clubbing is seen	⇒ Pan coast tumor ↓ <u>HORNER'S</u> Syndrome	⇒ Worst Prognosis ⇒ Max Risk of Metastasis ⇒ Clubbing is rare.

Lung cancer most commonly metastasises to BRAIN &
most specifically to Adrenals.

VASCULAR PATHOLOGY



① Atherosclerosis : Atheroma/Atheromatous plaque



VULNERABLE PLAQUE

STABLE PLAQUE

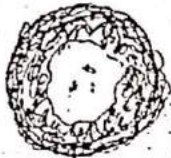
② Mönckeberg medial calcific sclerosis

- No luminal obstruction
- Clinically insignificant

Q 3. Arteriosclerosis → Hypertensive changes

Site → arterioles

Benign

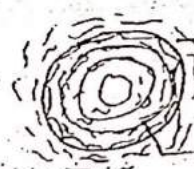


Hyaline Arteriosclerosis

- Wall thickening
- Narrowing of lumen
- Kidney → Benign Nephrosclerosis
- Granular kidney: Leather Grain Appearance

~~Kidney~~

Malignant



Fibrinoid necrosis

New basement membrane formation

Smooth muscle hyperplasia

Hyperplastic Arteriosclerosis

- PAS stain → Onion skin appearance
- New basement membrane

Kidney → malignant Nephrosclerosis

Pin point Hemorrhages

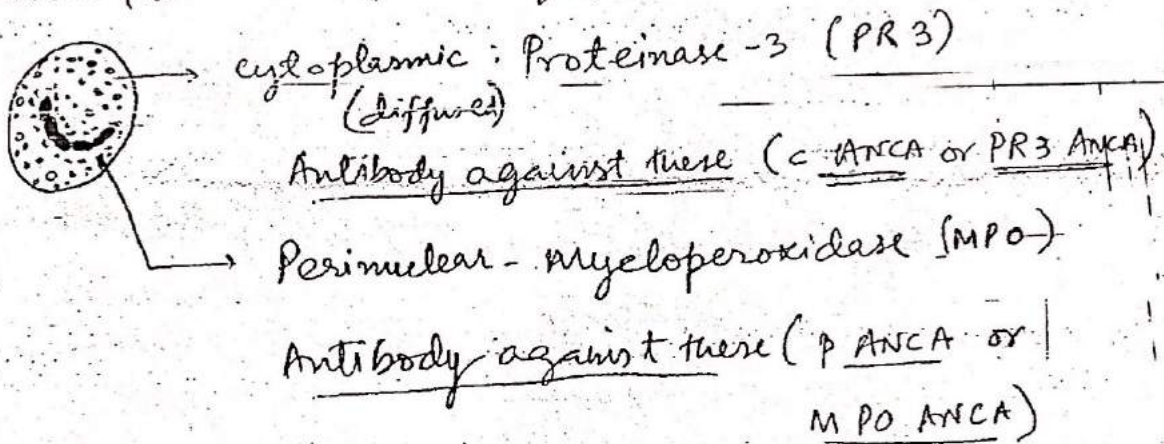
↓
Flea bitten Appearance

Vasculitis

→ Infections
→ Non Infections (Immune)

Mechanisms

1. Anti endothelial or smooth muscle antibody
2. Immune complex deposition
3. T-cell mediated Response (granulomatous)
4. ANCA (Anti neutrophilic cytoplasmic Antibody)



Leucocyte Activation → surface exposed to these granules

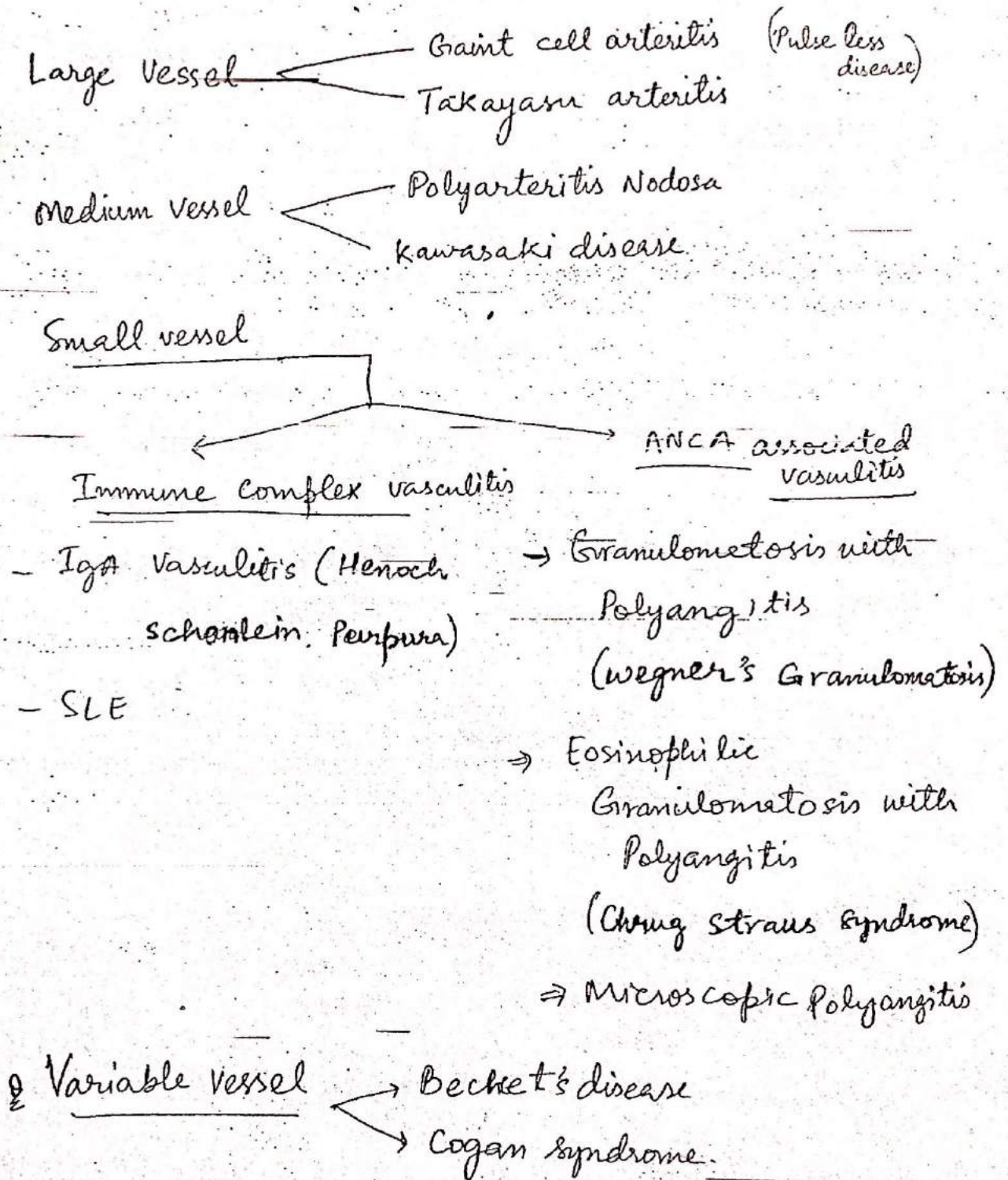
↓
If ANCA Present (Susceptible individuals)

↓
Binds to the surface granules

← Degranulation of Neutrophils

↓
Enzyme Leakage → Tissue damage

CHAPEL HILL CONSENSUS CLASSIFICATION



Giant cell Arteritis

> 50yrs

Head & Neck arteries

Temporal - Headache (MC)

Facial → Jaw claudication

Ophthalmic → Blindness

[most specific]

Diagnosis

Biopsy

segmental involvement

↓
3-5cm → adequate biopsy Required.
or
at least 1cm

Etiology

Anti endothelial &

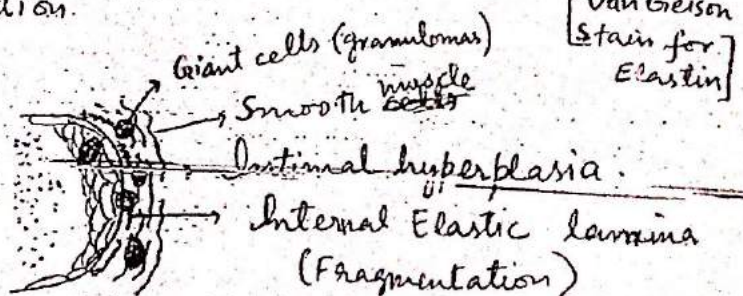
Smooth cell antibodies (?)

Cytokine mediated Response

Granulomatous

Inflammation

Histopathology



Takayasu's Arteritis

< 50yrs

Aorta & branches
↳ (Aortic arch)

Most commonly: Subclavian

② Common carotid

③ Abdominal aorta

④ Renal

⑤ Aortic arch or root

⑥ Coeliac axis

⑦ Coronary

↳ (least common)

Diagnosis

Arteriography

CT Angio

Polyarteritis Nodosa (PAN) [MC - Kidney involved]

(PAN PATCHY) → (entire circumference ^{of vessel wall} is not involved).

(PULMONARY ARTERY SPARED

[Bronchial vessels may be involved]

Features

Transmural : Aneurysms, Fibrosis
(Through out wall)

Necrotising : Fibrinoid Necrosis

Inflammation : $\left\{ \begin{array}{l} \text{Acute} \\ \text{Chronic} \end{array} \right\}$ ~~are~~ stages of activity
can be seen at the same time.
(ongoing Injury)

Associated c Hep-B → Immune complex deposition.

⇒ The pathology in the kidney in classic polyarteritis nodosa is that of arteritis (without glomerulonephritis)

⇒ May involve bronchial vessels but not pulmonary vessels.

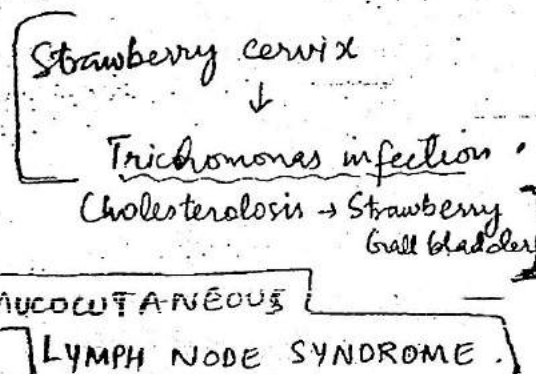
⇒ Renal & visceral arteries are very commonly involved.
(Musculoskeletal)

⇒ No granulomas. No eosinophilia

Granulocyte Aortitis → Aortoarteritis

Kawasaki Disease

- < 5 years
- Anti endothelial cell antibodies
- Acute Necrotising Vasculitis (Transmural)
- Febrile illness
- Strawberry Tongue
- Cervical lymphadenopathy
- Mucocutaneous ulcers



- Most common artery involved → Coronary
↓
Thrombosis, M I, Aneurysms
- MC cause of cardiac mortality in children.

ANCA associated

Wegener's

- c ANCA > p ANCA
- URT + LRT involvement
- Renal involvement
- Necrotising &/or granulomatous vasculitis

Churg Strauss

- p-ANCA
- Asthma
- Allergic Rhinitis
- Nasal polyps
- Peripheral eosinophilia
- Necrotising &/or granulomatous vasculitis

MPA (Microscopic Polyangiitis)

Hypersensitivity or p ANCA

LEUCOCYTOCLASTIC VASULITIS

- ↓
(WBC - Breakdown)
↳ Apoptotic Neutrophils
- NO granulomas
- Fibrinoid Necrosis

URT - upper Respiratory Tract involvement

Vascular Tumors



Endothelial cell origin

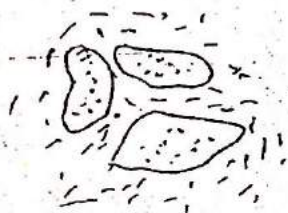
IHC → PEACAM / CD31

Benign

Hemangioma



Capillary Hemangioma



Cavernous Hemangioma

Borderline

Kaposi sarcoma

[HHV-8]

- ① Classical
- ② Endemic (Africa)
- ③ Transplant associated
- ④ Immundeficiency associated

Malignant

Angiosarcoma

① Hepatic

Exposure to
Polyvinyl chloride &
Thorium contrast
dyes

② Cardiac

most common
cardiac
primary malignancy
in adults.

Microabscesses (Misc)

- Neutrophil microabscesses in TAO
- Neutrophil crypt abscess in IBD
- Pautrier's Microabscess (Tumor lymphocytes in mycosis fungoides)
- Munroe microabscess of neutrophils in Psoriasis

Thyroid Cancers

Follicular origin

Papillary: most common

Parafollicular origin
(c-cells)

↓
CALCITONIN

↓
Medullary

Amyloid (Acal)

CEA

MEN2 syndrome

Papillary Ca Thyroid

Most common subtype

overall
Children

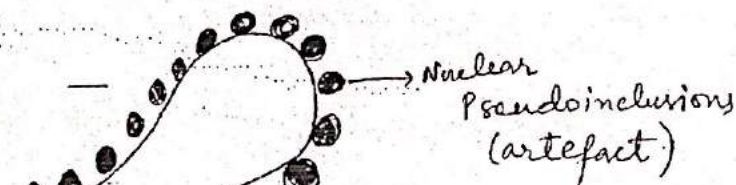
Thyroglossal cyst

Post Radiation

Hashimoto Thyroiditis

→ Lymphatic Spread

⇒ Best prognosis



Longitudinal grooves

Coffee Bean Nuclei

[Granulosa cell Tumor]

also found in

Breuer Tumor

Chondroblastoma

Langerhan cell histiocytoma

- Chromatin margination

- Optical clearing of nucleus

ORPHAN ANNIE - EYE NUCLEI

Follicular Ca

most common subtype to arise in multinodular goiter

⇒ Capsular or vascular invasion

⇒ Cytology (FNAC) will not help

⇒ Histopathological examination (No biopsy is done)

↳ also in Testicular mass.

↓
[Hemithyroidectomy to be done]

⇒ Hematogenous spread (Bones & lungs)

Anaplastic Ca

Bizarre cells

Fibrosis ↑↑

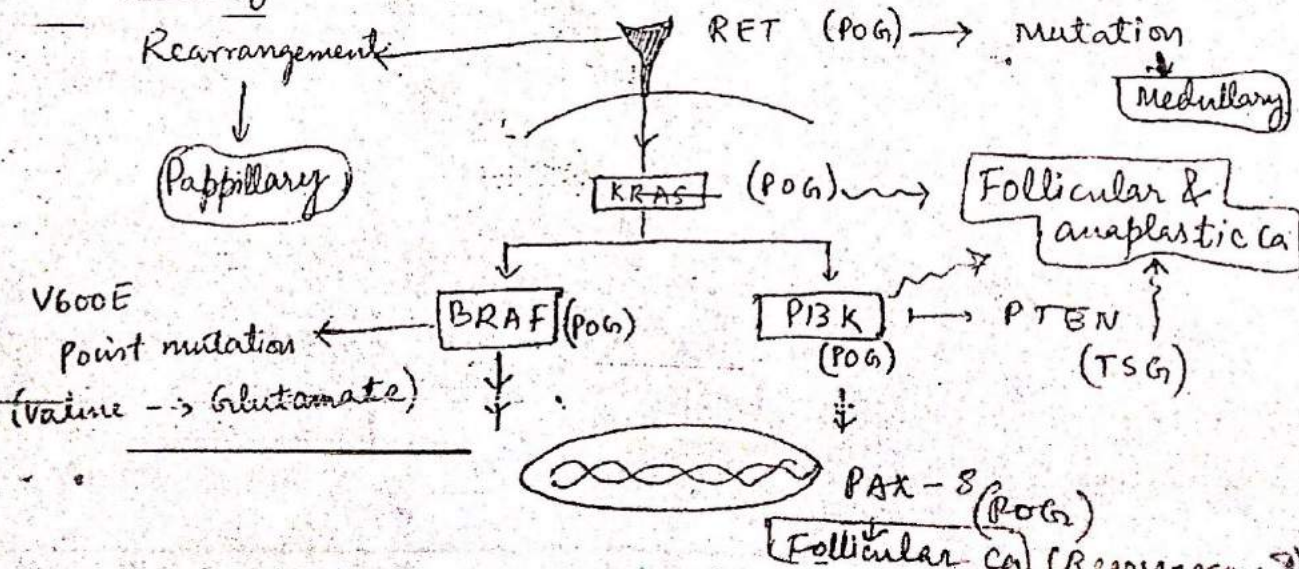
Least common subtype

Most aggressive (rapid onset)

Worst prognosis

Tumor genetics

POG → Proto onco gene
TSG → Tumor suppressor gene



Q. Most common genes

Papillary : BRAF

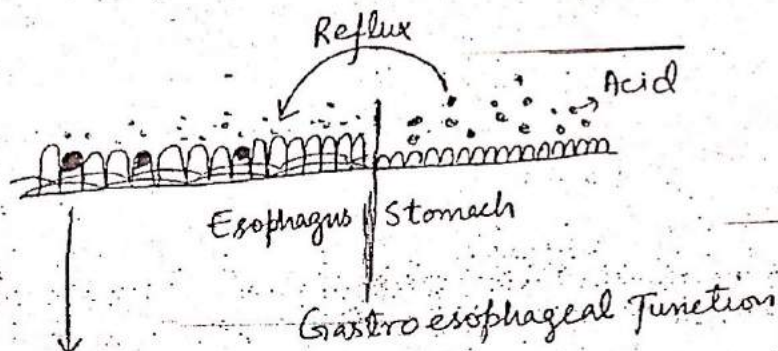
Follicular : KRAS

Anaplastic : p53

Medullary : RET

GIT

Esophagus



Columnar cells

+ Gland cells

→ Acid mucin

Alcian blue stain

Intestinal metaplasia → BARRETS Esophagus

Gross → Red velvety patches in esophagus.

Metaplasia → Displasia → Anaplasia (Irreversible)

[Some serotypes of H pylori are associated
→ decreased risk of esophageal adeno.ca.
because they cause gastric atrophy → ↓ acid → ↓ Barrett's esophagus]

[Adeno-Carcinoma]

Gastro Intestinal Stromal Tumor (GIST)

Origin Intestinal cells of cajal —
(Pacemaker cells in muscularis propria)

Gross Nodular capsulated tumor

Arising from the wall

mass effects

Cut section → Grey Tan, fleshy tumor with hemorrhage & necrosis

Strong & Vimentin mesenchymal marker

Microscopy → { Spindle cell (most common)
Epithelioid
Mixed

Genetics

85% **c kit** mutation

→ AML
→ seminoma
→ Mastocytosis

Imatinib

→ Inhibitor

→ Receptor Tyrosine Kinase (RTK)

→ 8% **PDGFRA** mutations

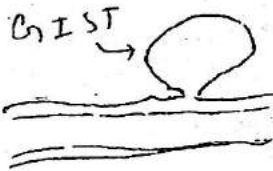
[c kit & PDGFRA mutations are mutually exclusive]

In a small proportion of non c kit & non-PDGFRA mutated GIST → **SDH mutation**

↓
SDH Deficient (Succinate & Dehydrogenase)

Exclusively seen in

- ↳ Gastric In Location
- ↳ Indolent Course (slow growing)
- ↳ Younger Population
- ↳ Imatinib Resistant
- ↳ Part of Casney Stratakis Syndrome [Parangangliomas]



Carney Triad { GIST
Pulmonary Condroma (Hamartoma)
Paranganglioma

IHC → CD117 (c kit) : +ve (most sensitive)

DOG 1 : +ve (most specific)

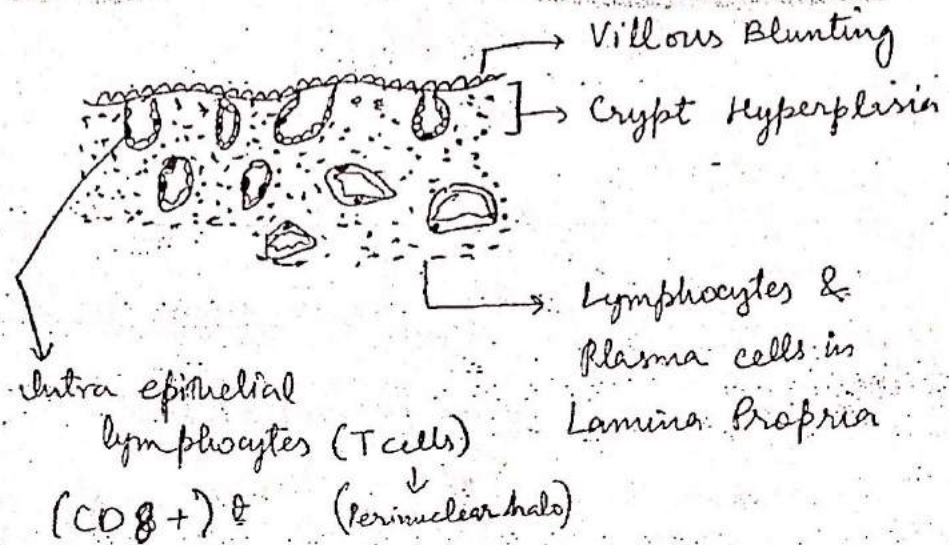
Myxomas
Skin Lesions
Multiple endocrine involvement

Prognosis

- Location (stomach : better)
- Size (< 5 cm : better)
- Mitotic count (counted per 50 HPF)

Different cut offs for different sizes at different locations.

Celiac Disease



Risk of enteropathy associated

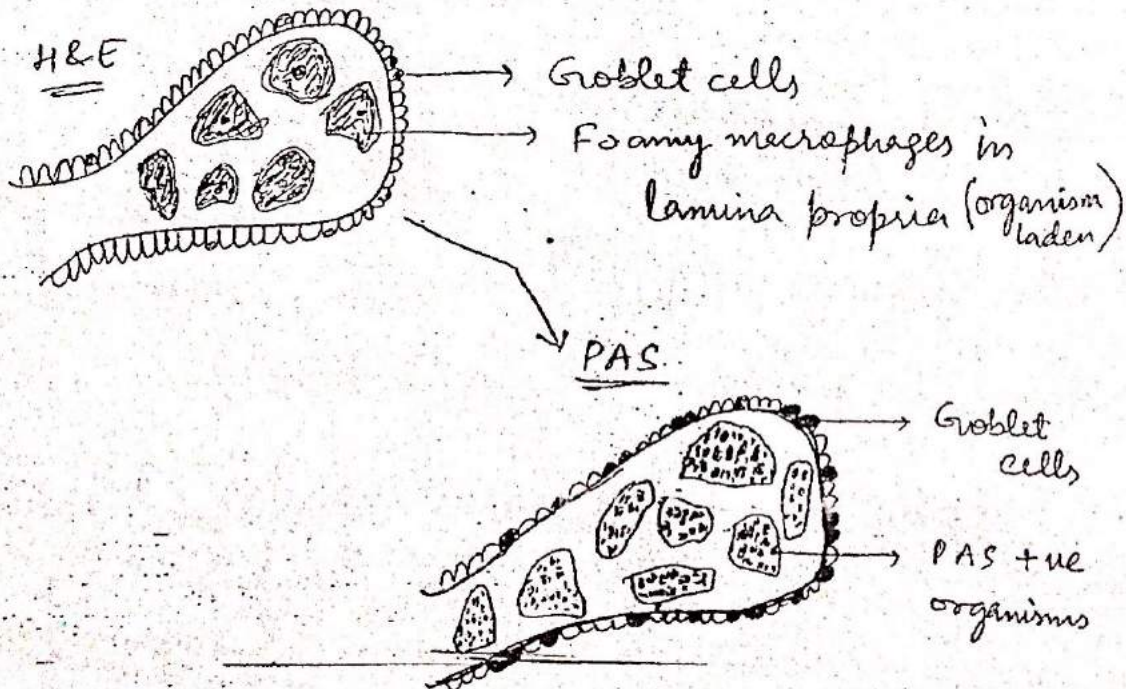
T cell lymphoma is high
(EATL)^o

- Adenocarcinoma Risk also increased because of Crypt Hyperplasia
- Associated $\bar{c}$ HLA DQ2 > DQ8

- IgA Nephropathy
- Dermatitis Herpetiformis

Whipple's Disease

(Malabsorptive syndrome)



Intestinal polyps

Non Neoplastic

- Hyperplastic

- Inflammatory (MC)

- Hamartomatous

① Disorganised mass

→ Indigenous to that organ

↳ now considered Neoplastic

② (Choriostoma)

Normal tissue
Abnormal site

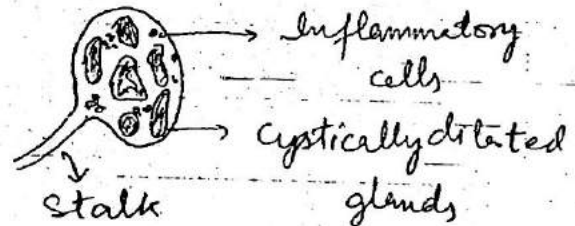
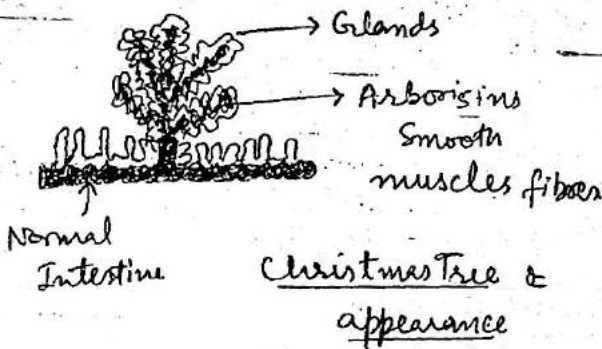
Peutz Jegher Polyp

Neoplastic polyps

Adenomatous/Adenomas

DYSPLASIA

Juvenile Polyp



Multiple PJPs + Mucocutaneous melanosis

Peutz Jegher Polyp

(STK11 gene)

aka - LKB1

Solitary → No risk of cancer

Multiple → Juvenile polyposis
↳ Syndrome
Slight risk of cancer

BMPR1A - (Primary Pulmonary hypertension)

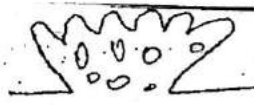
SMAD4 - (Pancreatic Cancer)

Lymphoma

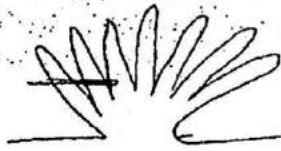
MC primary →
↳ H. Pylori associated

MALToma (extranodal Marginal zone ly)
CD5- , CD10-
CD23- , CD43+

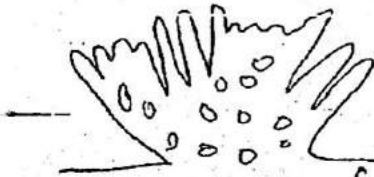
Adenomas/Adenomatous polyps



(Tubular) (mc)



(Villous)



(Tubulovillous)

Familial Adenomatous Polyposis (FAP)

• APC gene mutation

Most commonly: Tubular Adenomas

Diagnosis > 100 polyps

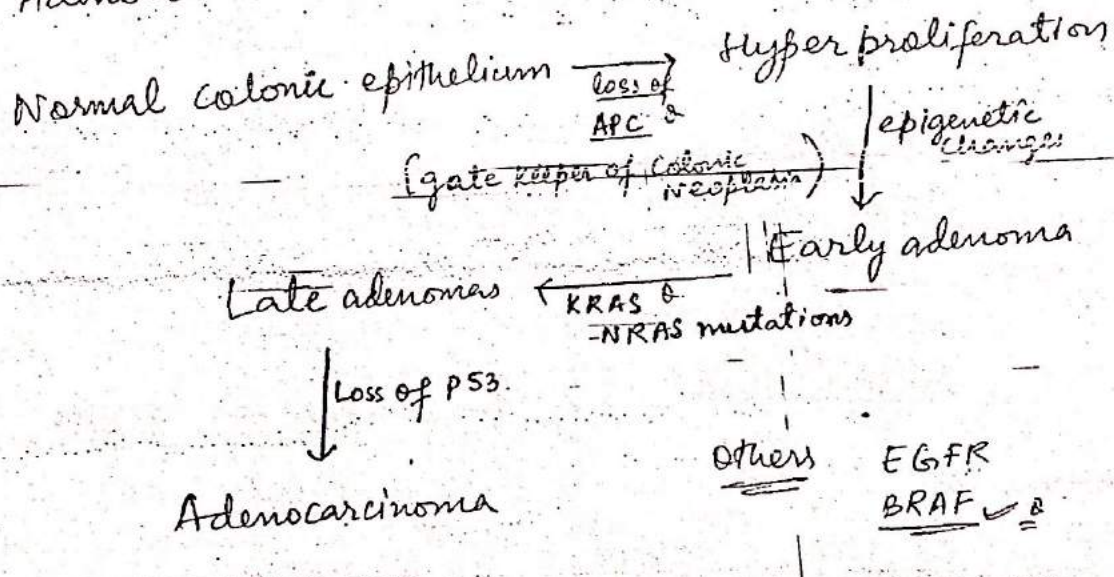
Attenuated FAP < 100 polyps (variant)

<u>FAP</u> + Skull osteomas	}	<u>GARDNER SYNDROME</u>
+ Epidermoid cysts		
+ <u>Desmoid tumor</u> (Fibromatosis)		

FAP + Medulloblastoma & Cilioblastoma } Turcot syndrome & ^{& more common}

Colo Rectal Ca

Adenoma - Carcinoma Sequence



Right sided colon

Diameter is more $\rightarrow$ space for tumor to grow $\rightarrow$ cauliflower fungating / Polypoid

$\downarrow$
Loose consistency stools $\rightarrow$ easily pass through

$\downarrow$
(Fecal occult blood test) Causes erosion of tumor $\rightarrow$ Bleeding

$\downarrow$
Iron deficiency Anemia

Left sided colon

Diameter is less $\rightarrow$ No space to grow $\rightarrow$ Constriction (Napkin Ring constriction)

Bulky stool $\rightarrow$ Cannot pass easily

$\downarrow$
features of Intestinal obstruction

Hereditary Non Polyposis colon Cancer (HNPCC)

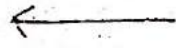
or LYNCH SYNDROME

Defect in DNA mismatch Repair gene
(MSH2, MLH1)



DNA mistakes accumulate → genomic
Instability

MSI



[Especially microsatellites
(Tandem sequences)]

[Microsatellite Instability]

Colon Cancers

- Mean age ~ 40yrs
- Proximal to splenic flexure
- Mucinous/signet ring cell morphology
- Used lymphocytes in tumor
- Better prognosis

Extracolonic Cancers

Endometrial (MC)

Gastric

Ovarian

Transitional

Small intestinal

Pancreatic Carcinoma

MC subtype → Ductal Adenocarcinoma

Very aggressive

~~Procoagulant Tumor mass~~ + cellular debris

→ DIC risk is increased

→ Non bacterial Thrombotic endocarditis

→ Migratory thrombophlebitis
↓
(TROSSEAU SYNDROME)

→ also seen in Breast Ca
Gastric Ca
Lung Ca

Normal Pancreatic epithelium

KRAS ~90% (onc)
CDKN2A/P16 ~95% (TSG)
(Protein)

Pancreatic epithelial
Neoplasia (PanIN)

SMAD4
BRCA2
P53 TSG
↓
Adenocarcinoma

Most common gene mutated - CDKN2A

Most common Protooncogene mutated - KRAS.

Most common TSG mutated → CDKN2A/P16

[KRAS changes occur earlier in the progression]

Chromosome locations (Misc)

BRCA1 - 17q

P53 - 17p

APC - 5q

HFE - 6p

SERPINA1 - 14q

13q - BRCA2, RB, ATP7B

MET (Hepatocyte Growth Factor) - 7chr. → Papillary RCC
Receptor

Mallory Dark Bodies

Mallory Dark Bodies/ Mallory Bodies

↓
Remnants of intermediate filaments
following hepatocyte damage
↓
cytokeratin
↓
CK 8/18



→ Eosinophilic Inclusions

Prognostic Markers For tumors

<u>Stage</u>	<u>Lymph Nodes</u>	<u>Others</u>
Esophagus	Breast (Axillary)	Metastatic Breast
Stomach	Colon	- ER/PR status
Gall bladder	Penile (Inguinal)	Renal
Pancreatic	Head & neck	- Pathological Stage
Prostate		Wilms
Testis		- Histology (Anaplasia)
		Soft tissue Sarcoma
		- Grade
		Melanoma

Barrett's Esophagus → AdenoCa

Early genetic changes

PS3 (TSG)
CDKN2A/p16 (TSG)

Late genetic changes

EGFR (erb b1)
Her 2 Neu (erb b2)
MET
cyclin D1

Proto oncogenes
[Pog]

Cardiac Pathology

Myocardial infarction

Coronary Artery Spasm

Hypoxic damage

in 30 minutes
Reversible
(20-40 min)

Beyond -
Irreversible

Myocardial response
(Ischemic Injury)
↓ ATP

Infarction

TTC (Triphenyl Tetrazolium chloride)

→ +LDH → BRICK RED : Normal viable myocardium

→ -LDH → PALE YELLOW : Recent infarct

Features	Onset
Onset of ATP Depletion	Seconds
Loss of contractility	< 2 min
ATP Reduced to 50% of Normal	10 min
to 10% of Normal	40 min
Irreversible injury	20-40 min
Microvascular injury	> 1 hr.

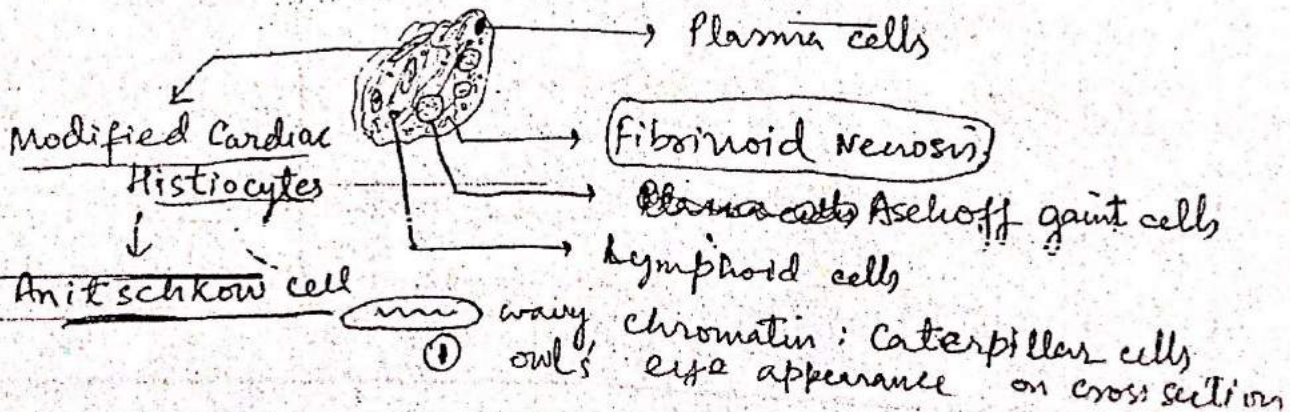
Mitral valve Prolapse	<u>Morphologically</u> Gross ballooning of valve Myxomatous degeneration	<u>Special points</u> a/w Marfan's syndrome mid systolic click
Rheumatic H.D	Verrucous vegetations along lines of closure [MAC cullum Plaques]	Pathognomic Aschoff nodule
IE (Infective Endocarditis)	Friable vegetations along lines of closure, invading Chordae Tendinae	Risk of Septic embolisation
NBTE (Non Bacterial Thrombotic endocarditis)	Large Fibrin clots along lines of closure; NO Invasion	Seen in Cancer malnourished (Marantic Endocarditis)
LSE (Libman Sack Endocarditis)	Vegetations on both sides of Cusp	SLE

Rheumatic Heart Disease

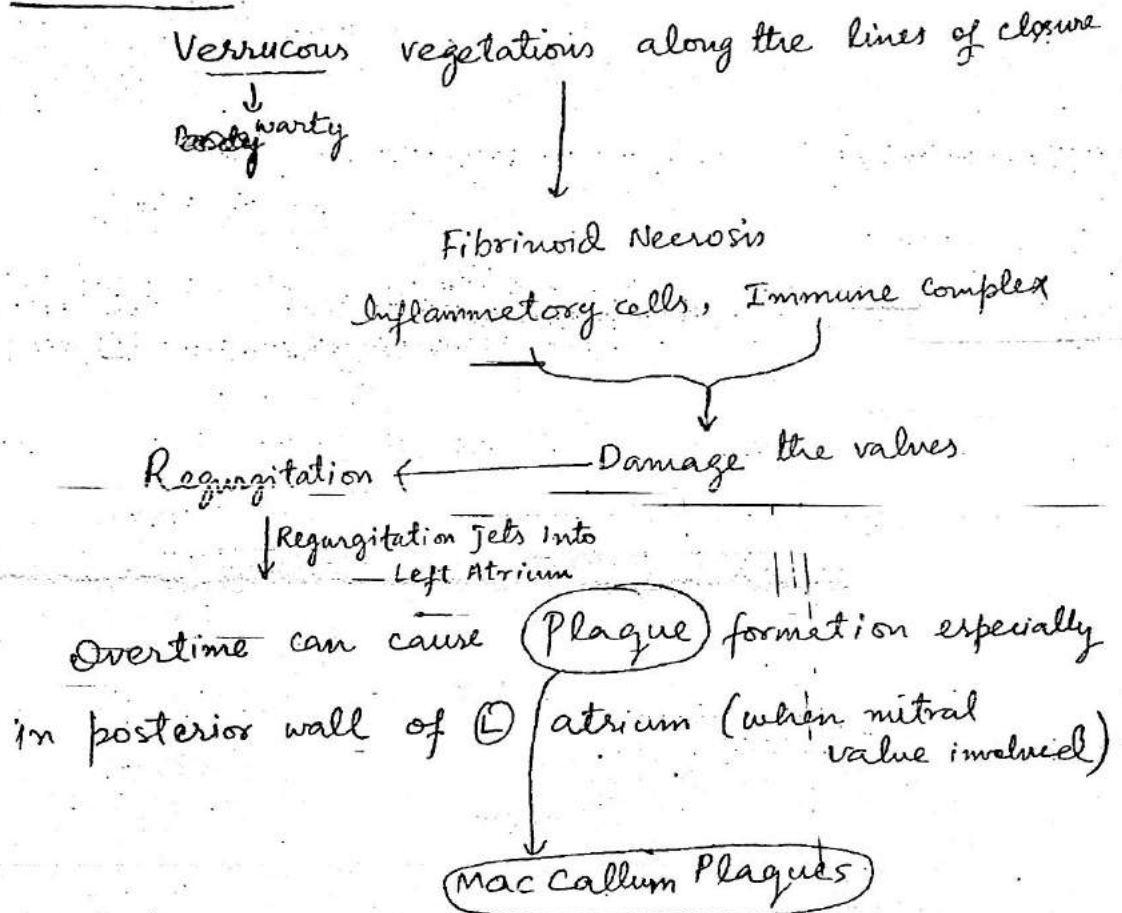
Molecular Mimicry

Acute Pancarditis $\left\{ \begin{array}{l} \text{Myo} \\ \text{Endo} \\ \text{Peri} \end{array} \right.$

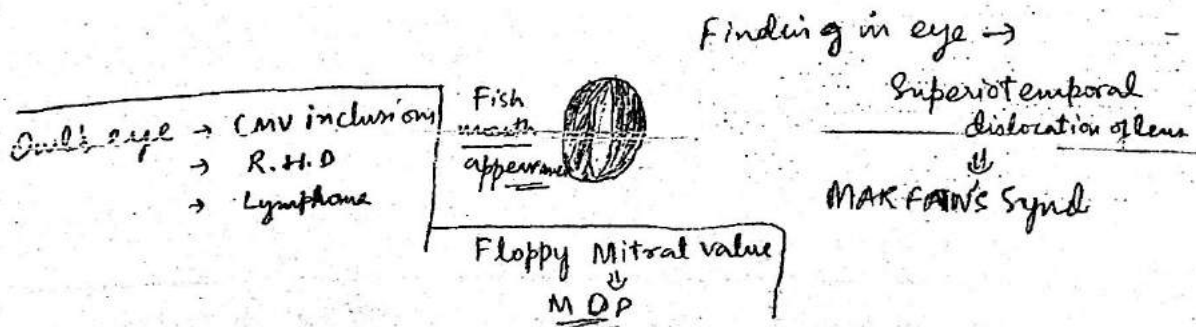
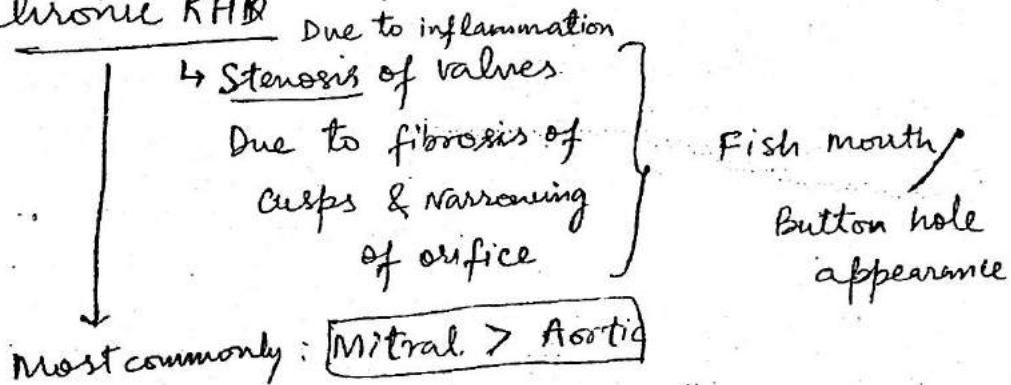
Pathognomic feature is Aschoff Nodule which
[can be seen in myo, endo, pericardium]²



Endocarditis



Chronic RHD



CNS & PNS Pathology

Schwannoma

Benign peripheral nerve sheath tumor

↓
Most commonly - Cerebellopontine Angle ♂

NF₂ associated

Variably cellular tumor

↓
Hypercellular
compact
areas

Antoni-A

↓
Hypercellular
loose
areas

Antoni-B

↓
 → Tumor nuclei are arranged in parallel to each other ⇒ TRUE ♂
PALISADING

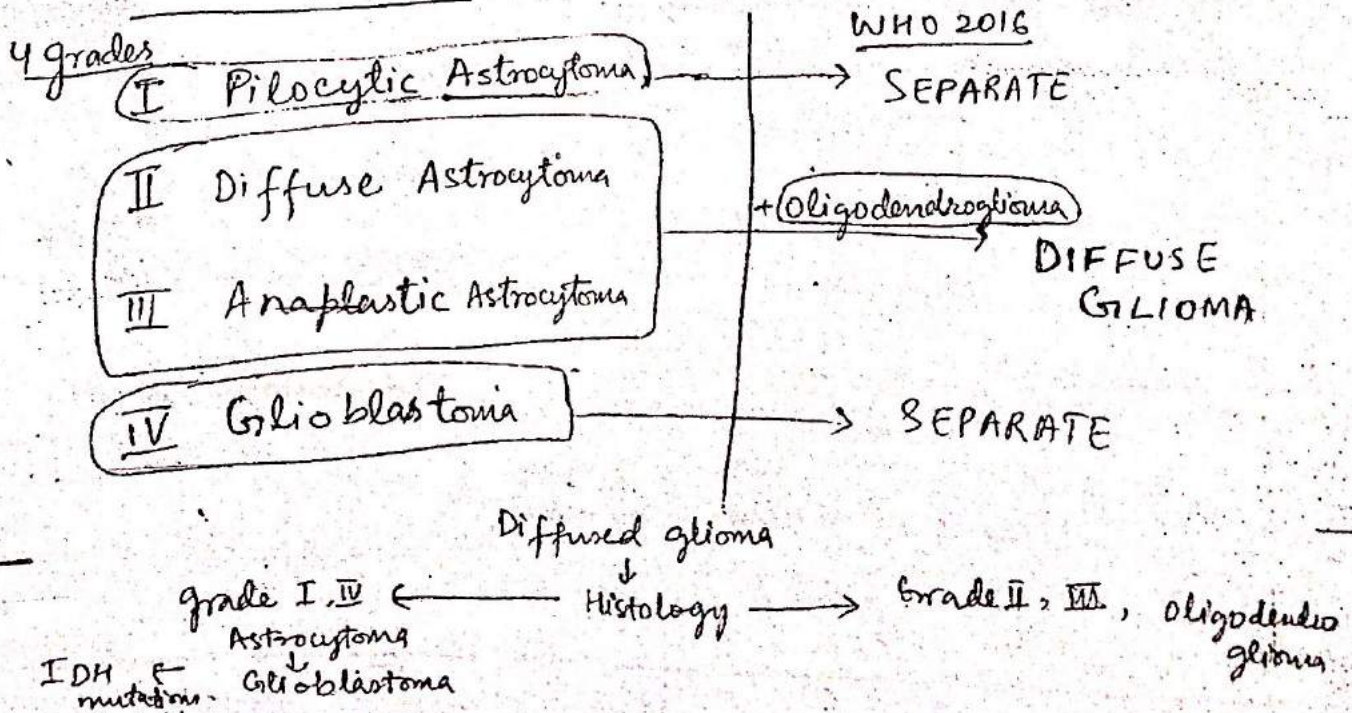
↓
VERROCY BODY

CNS TUMORS

1. Glioma (m.c 1^o tumor)
 - Astrocytoma (m.c) glioma
 - Oligodendroglioma
 - Ependymoma
2. Meningiomas (2nd m.c 1^o tumor)
3. Embryonal Tumors
 - Medulloblastoma (m.c 1^o CNS malignancy in children)
 - Atypical Teratoid / Rhabdoid Tumor (ATRT)

PNET is not included under this anymore WHO 2016
4. Neuronal Tumors (neurofilament +ve)
5. Lymphomas
6. Secondary Tumors (m.c CNS Tumors)
 - ↳ (1^o is Lung Ca. m.c)

ASTROCYTOMAS



Pilocytic Astrocytoma

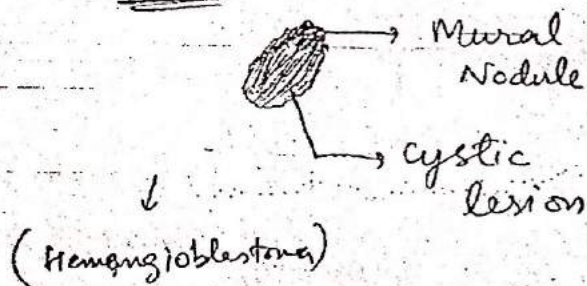
Most common 1° CNS

Tumor in children

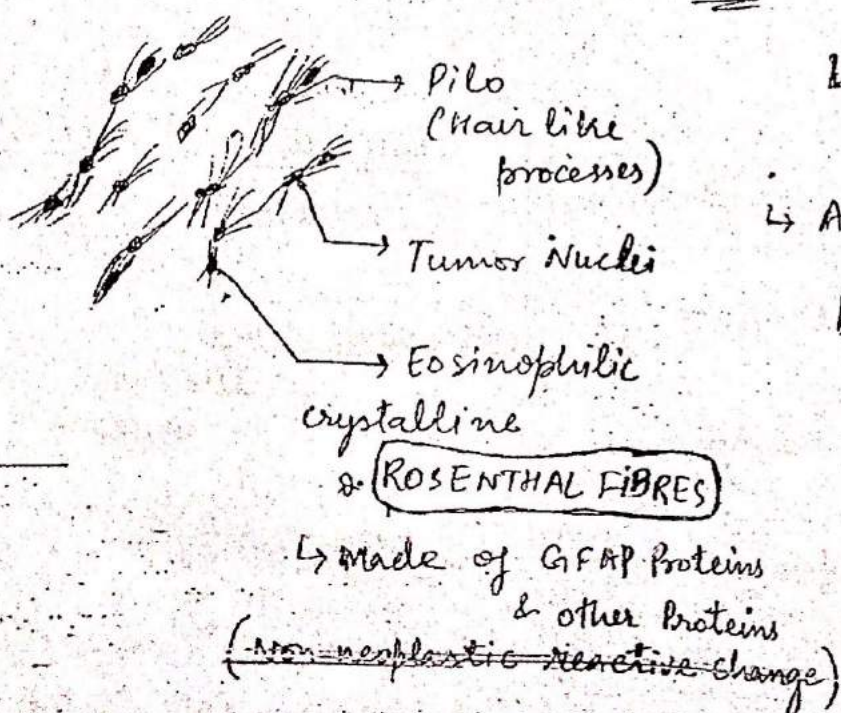
Seen in
Cerebellum

BRAF ← mutated (V600E)
Rearranged

Gross



Micro



Glioblastoma

Most common 1° CNS

malignant in Adults

Seen in
Frontal & Parietal Lobes

EGFR

PS3

CDKN2A / p16

PDGFRA

Gross

Tumor infiltrating
normal brain

↓
crosses midline (**Butterfly glioma**)

- Areas of Hge & necrosis

Micro

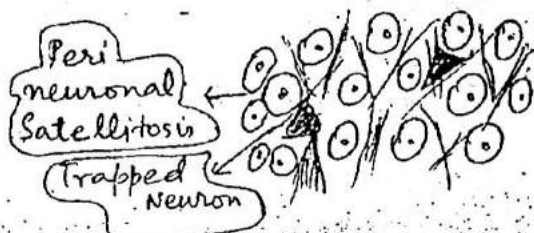
↓
Leaky vessels → **Contrast enhancing**

↳ Areas of necrosis (Pink)

bordered by viable
Tumor cells (blue dots)

↓
**PSEUDOPALISADING
NECROSIS**

OLIGODENDROGLIOMA



Monotonous uniform tumor cells with Perinuclear Halo

[Fried egg appearance
(also in hairy cell leukemia - mycoplasma)]

Delicate anastomosing vasculature
[chicken wire vasculature]

chicken wire

→ Fibrosis - Alcoholic liver disease

→ Calcification - Chondroblastoma

Microcalcification: Imaging
→ (Basophilic on H&E)

Genetics

[IDH1, IDH2 mutation
1p/19q codeleted
Favourable Prognosis]

MEDULLOBLASTOMA [grade IV]

Mc site - cerebellum (posterior fossa)

CSF dissemination → Dropt metastasis

Small round blue cell tumor

→ Neurophil (cytoplasmic feature)
HOMER WRIGHT
ROSETTE

→ (Pseudorosette

[True Rosette has Nucleus]

→ Ependymal Rosette

MENINGIOMA (I-III)

1. Arises from Arachnoid cap cells / Meningothelial cells

Dura based tumor (DURAL TAIL)

Easily Detachable

→ Causes reactive hyperostotic change in overlying bone.

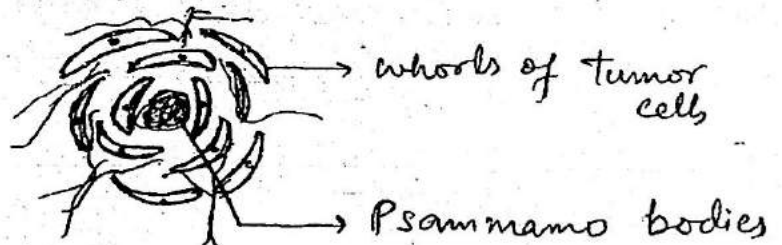
↓

X Ray

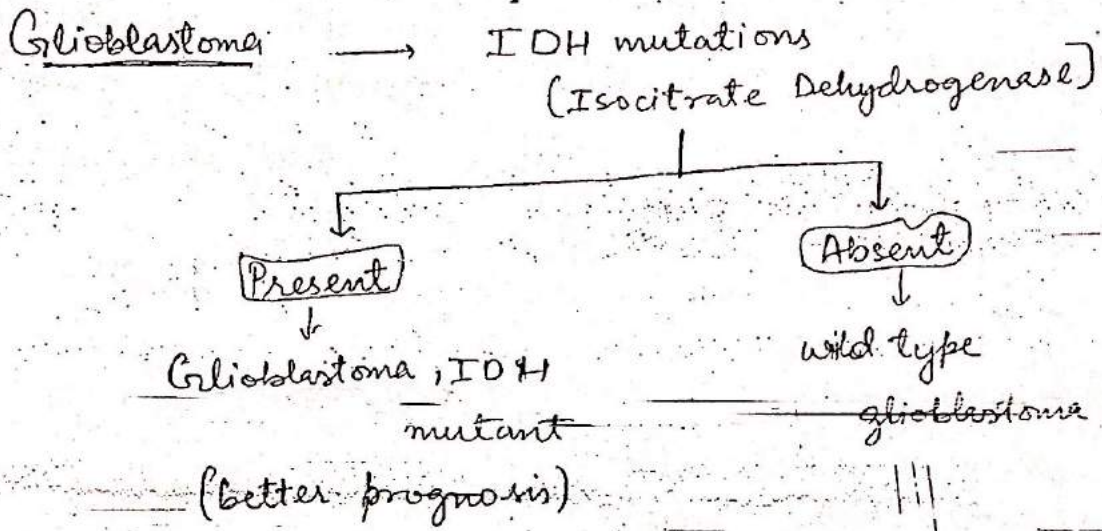
Express PR ⇒ ↑ size during pregnancy.

Associated ± NF₂

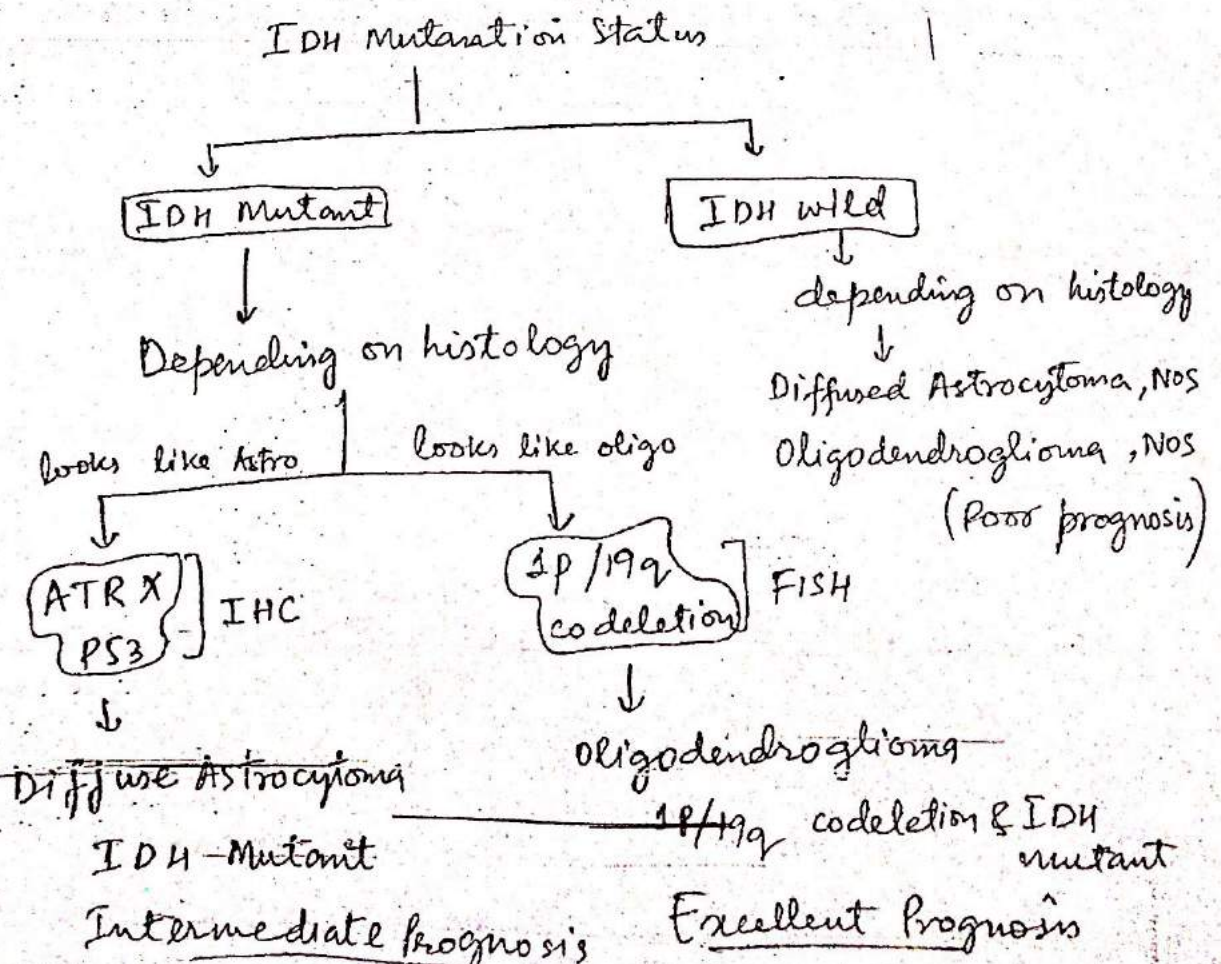
Most common Histology is - Meningothelial



WHO 2016 → genetic incorporation into histology



Diffused gliomas



Schwannoma

Neoplastic Schwannoma cell

Cerebellopontine angle = Most
Commonly

S100 +ve

NF2 associated.

Variable cellular areas

Antoni A

Antoni B

Neurofibroma

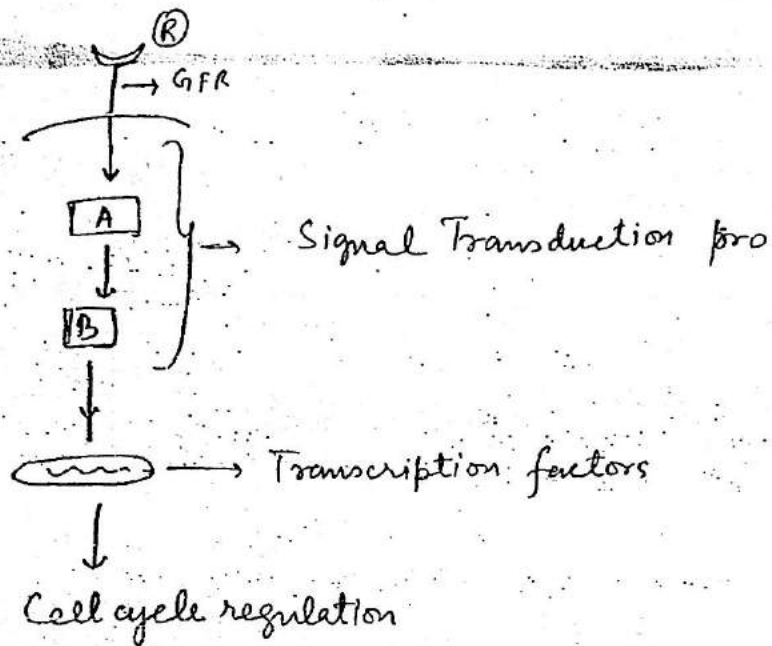
Neoplastic Schwann cells
+ Fibroblasts + Perineural
like cells + Fibroblasts +
Spindle cells (CD34 +ve)
+ Mast cells

S100 +ve

Heterogenous

NF1 associated

Wavy collagen &
wavy buckled
nuclei.



GPCR

EGFR (erbB1)

PDGFRA

RET

MET

Her2neu

STDPs

KRAS

BRAF

PI3K

Tyrosine kinase Receptor TK

ALK

Kit

Transcription of

Par 3

myc

Cell cycle inhibitors

CDK 4/6/p16

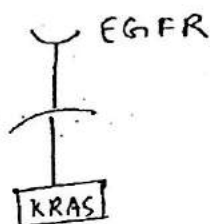
Repair genes: BRCA1 & 2

p53

Rb

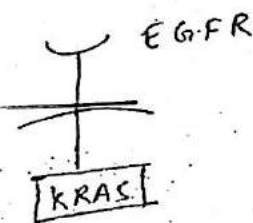
217

Lung



↓
Mutually exclusive

Colon



KRAS/NRAS mutation analysis
is mandatory now before
starting anti EGFR Therapy.

Q. Mutation analysis of which of the following genes
will not help in prognostication of colon cancer?

(A) EGFR

(B) KRAS

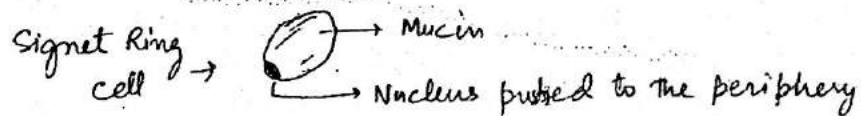
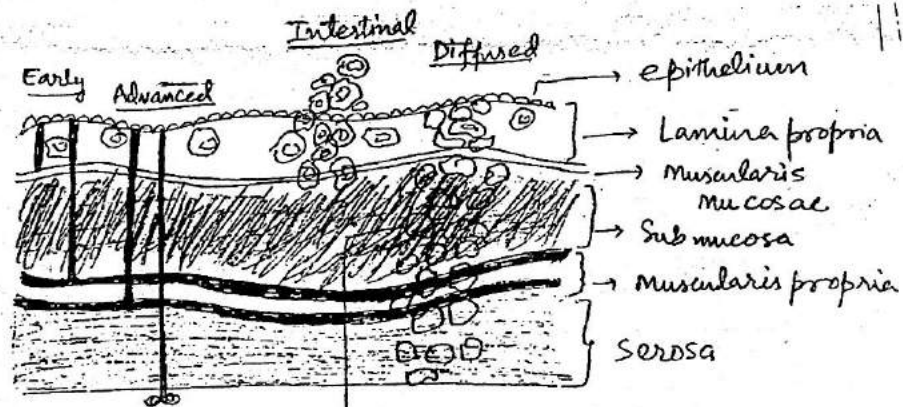
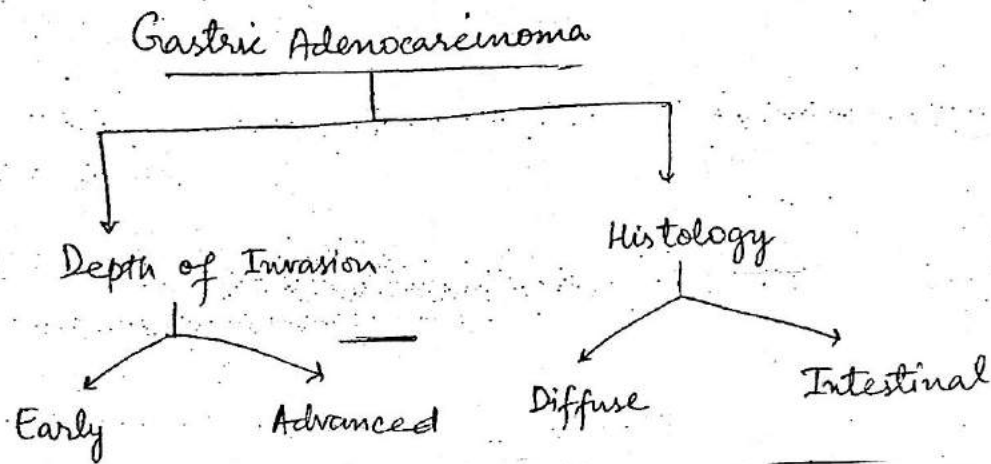
(C) P53

(D) MSH2

↓ DNA mismatch

↓

Ly Syndrome



- No mucosal mass
- Loss of Rugal folds
- Transmural thickening - Infiltration → wall thickening
↓
Leather bottle appearance
→ **LYMPHITIS PLASTICA**

Disease

Effect www.FirstRanker.com

www.FirstRanker.com

Intraluminal
digestion

Terminal
digestion
(+)

Trans epithelial
Transport (+)

Lymphatic
Transport

Celiac disease

Lactase

(+)

Whipples

(+)

Abeta

(+)

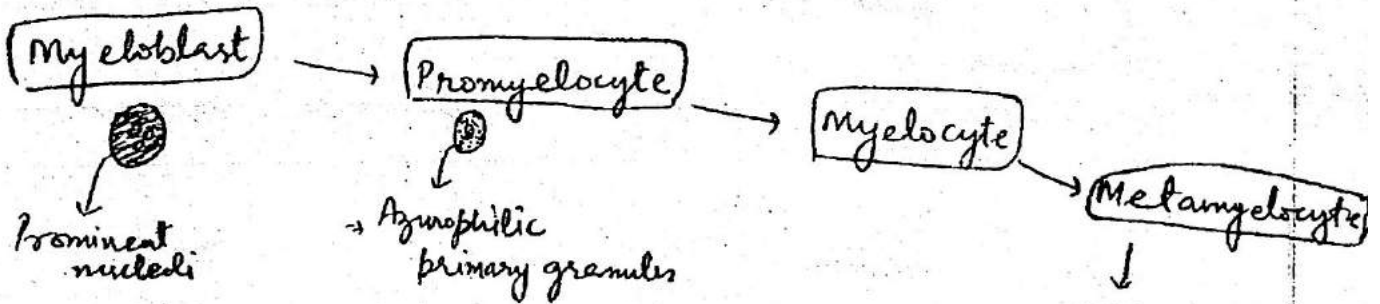
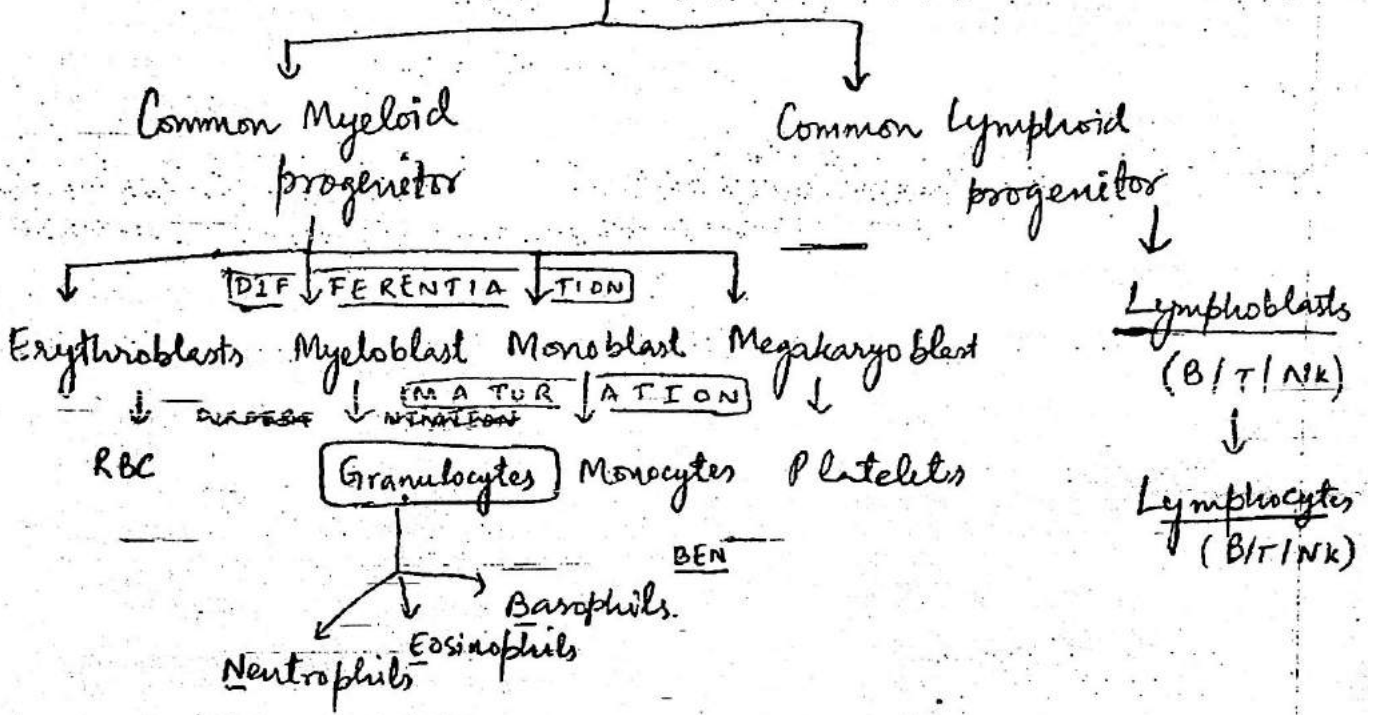
Chronic
Pancreatitis

(+)

Hematology 23/04/18

Hematology

Hematopoietic Stem cells

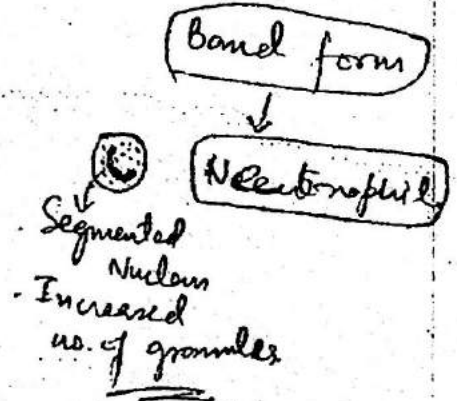


- While maturation
- Increased segmentation
 - Increased functional granules
 - Decreased size

Right Shift (Immature cells)
(Infection)

Left Shift (Hypoplastic marrow)
(↑ Immature cells)
(Few lobes of Neutrophils)
Mileus

⇒ **ARNEITH Index**
OR
ARNEITH COUNT



Leukemia

White in blood.

Liquid tumor

Origin - Bone Marrow

Malignant

Inv.

Flow cytometry of peripheral blood or B.M. aspirate

Lymphoma

Lymphocytes
↓
Tumor

Solid tumor

Origin - Lymphoid organs
→ L.N., thymus, spleen, tonsils, any where in body.

Benign/malignant

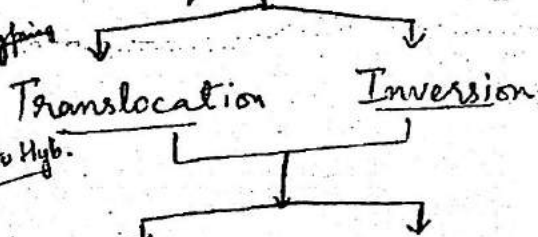
Inv.

Immunohistochemistry on Histopath sample.
(IHC)

Gene Rearrangement

Change in location

Karyotyping
FISH
F. In Situ Hyb.



gene 1 + gene 2

gene 1 → gene 2

mRNA (fused)

[FUSION TRANSCRIPT]

Inv.
RT-PCR



New protein (oncoprotein)

IHC
Flow cytometry

Cancer

(↑ Leukemias)

Mutation

Change in sequence
(PCR + Screening)

→ Commonly seen in solid tumors.

→ Increased expression
or
Decreased expression

↓
New protein (IHC)

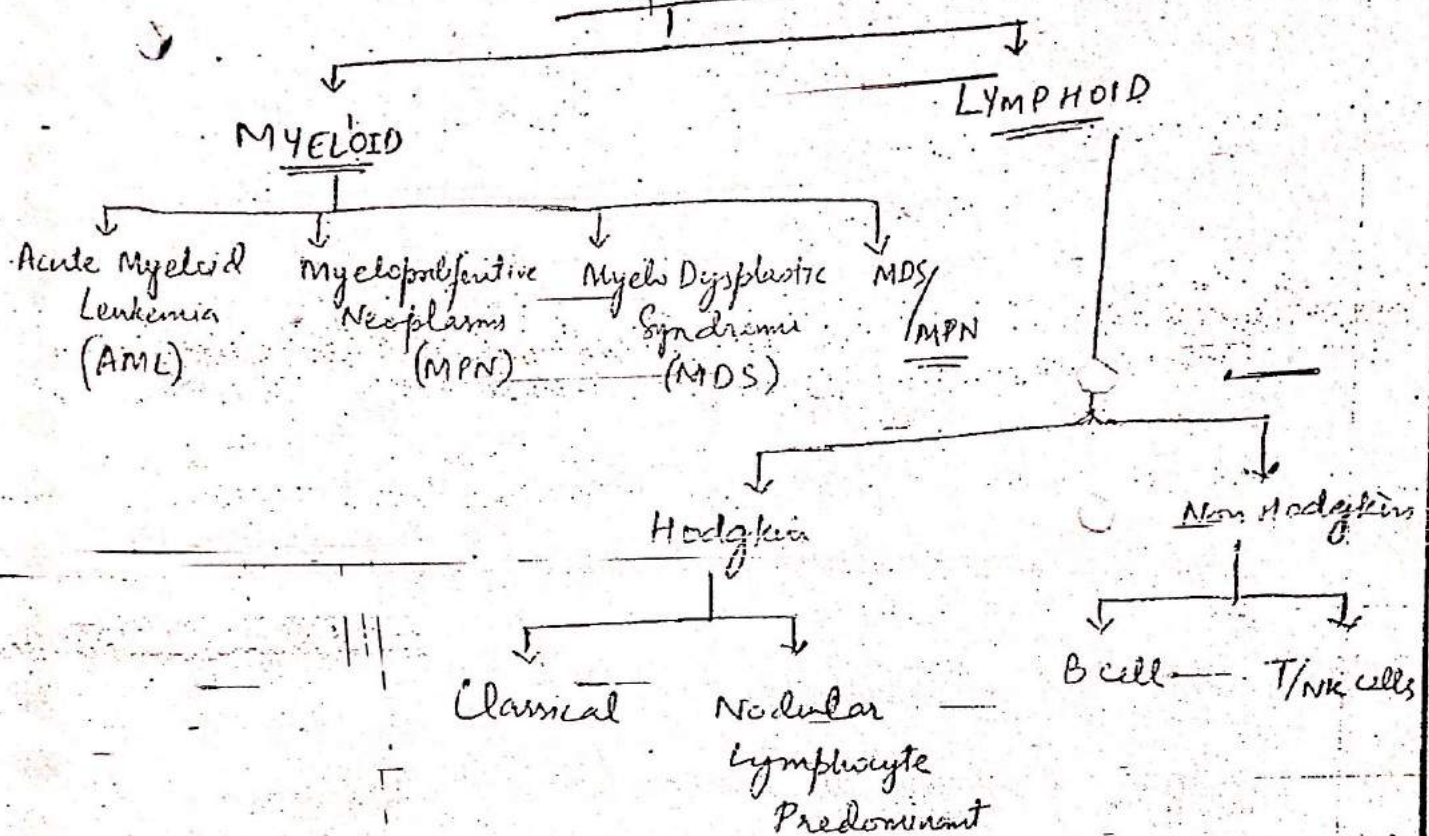
↑ sed copies
↓ [Amplification]
↓ [FISH]
Increased protein
↓ [IHC]
↓ [Overexpression]

Increased unregulated proliferation

Cancer

(↑ Lymphomas)

Hematology Neoplasms

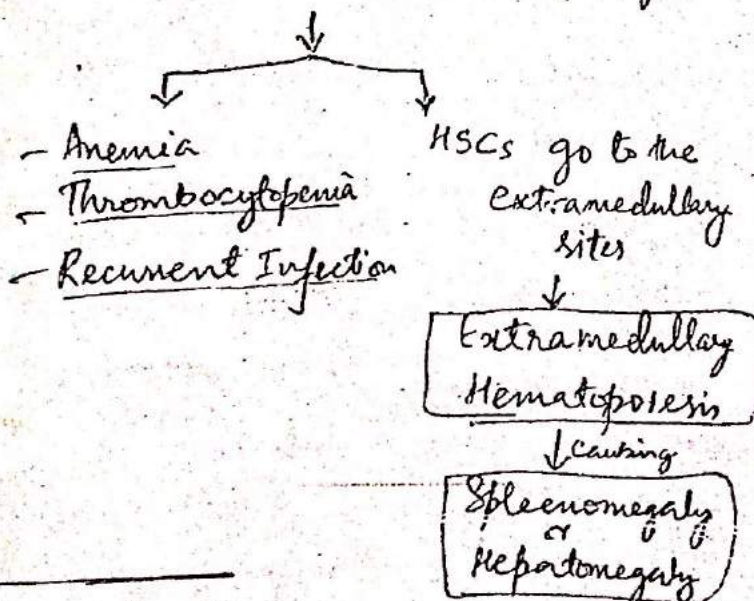


Acute Myeloid Leukemia (AML)

→ Inc in Immature cells in marrow.

Origin :→ Haematopoietic stem cells/progenitor

Marrow is taken over by bad cells → thus - no place for good cells.



→ Combination of Maturation arrest + Clonal proliferation
↓
Increased T...

- AML - with minimal differentiation (M0)
- AML - without maturation (M1)
- AML - with maturation (M2)
- AML - with promyelocytic maturation (M3)
- AML - with myelomonocytic differentiation (M4)
- AML - with monocytic differentiation (M5)
- AML - with erythroid differentiation (M6)
- AML - with megakaryocytic differentiation (M7)

↳ (↑ risk of myelofibrosis)

Indented nuclei ⇒ Monocyte

2017 WHO AML Classification

≥ 20% Blast cells in Marrow (< 20% - MDS) -

1. AML with recurrent genetic abnormalities.

do not require ≥ 20% Blast counts for diagnosis (exceptions)

AML with t(8;21)	} Favourable Prognosis
AML with t(15;17) [M3]	
AML with t(16;16) or inv(16)	

AML with t(6;9)

AML with 11q23 rearrangements (MLL gene) } unfavourable Prognosis

AML with t(9;22) (WHO 2017)

AML with normal karyotype

- (i) Biallelic [CEBPA] mutation
- (ii) [NPM] mutation

{ Phil. chromosome, 22nd chr. formed after translocation }
(2017) } Favourable prognosis

2. AML; therapy related

~~Alkylating Agents~~
Epipodophyllotoxins

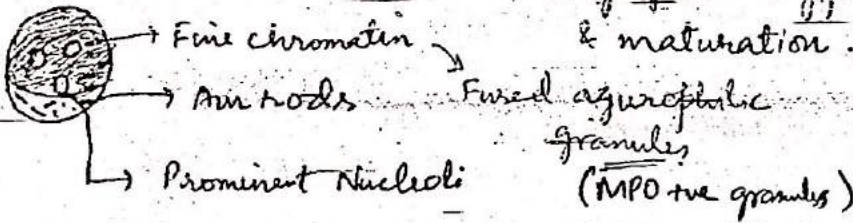
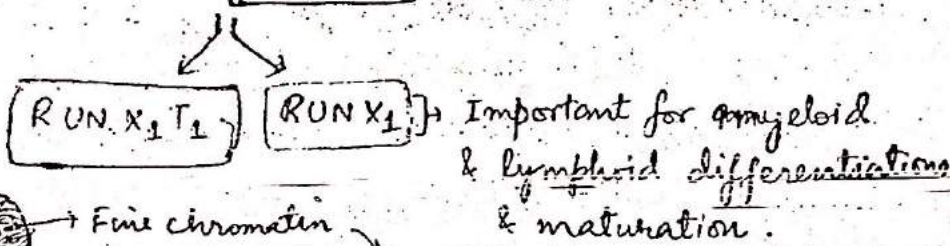
3. AML, with dysplasia related changes.

With prior MDS
Without prior MDS

4. AML, Not otherwise Specified (NOS)

Previous FAB M0 - M2, M4 - M7. (30-40%) more common in adults.

AML with **t(8;21)**



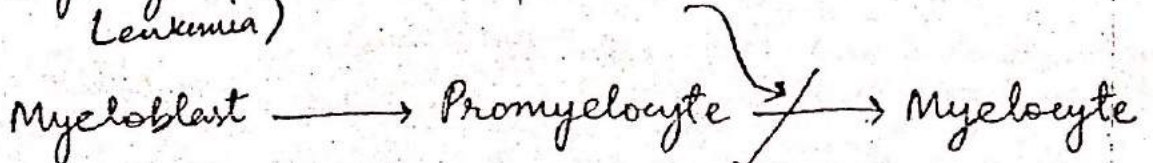
- with M2 Morphology.

AML with **t(15;17)**

PML (Promyelocytic Leukemia)

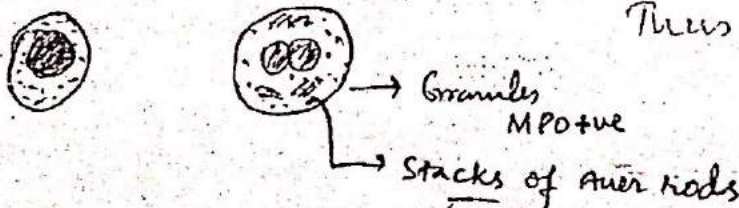
RARA (Retinoic acid receptor α)

PML-RARA Fusion



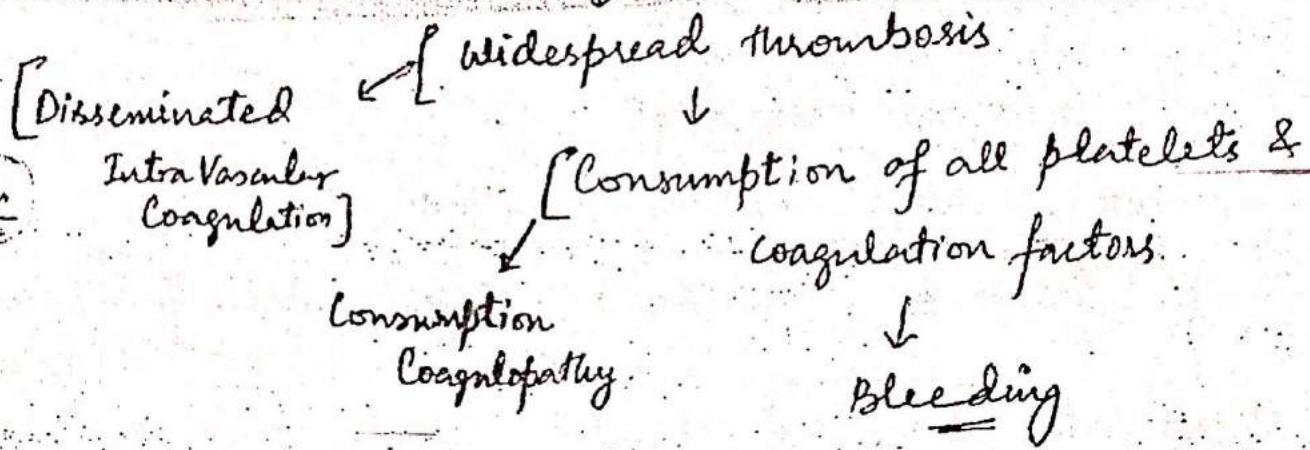
PML-RARA fusion blocks the maturation

Thus ↑ Promyelocyte



Atypical promyelocyte + Stacks of Auer rods ⇒ **FAGGOT cells**

DIC



All Trans Retinoic Acid (ATRA) Remove the Arsenic block!

AML E - DIC = M3
 AML E best prognosis = M3

AML with t(16; 16) or Inv(16)

Gene - Core binding factor β (CBF β)

Usually shows M_4 & M_5 morphology.

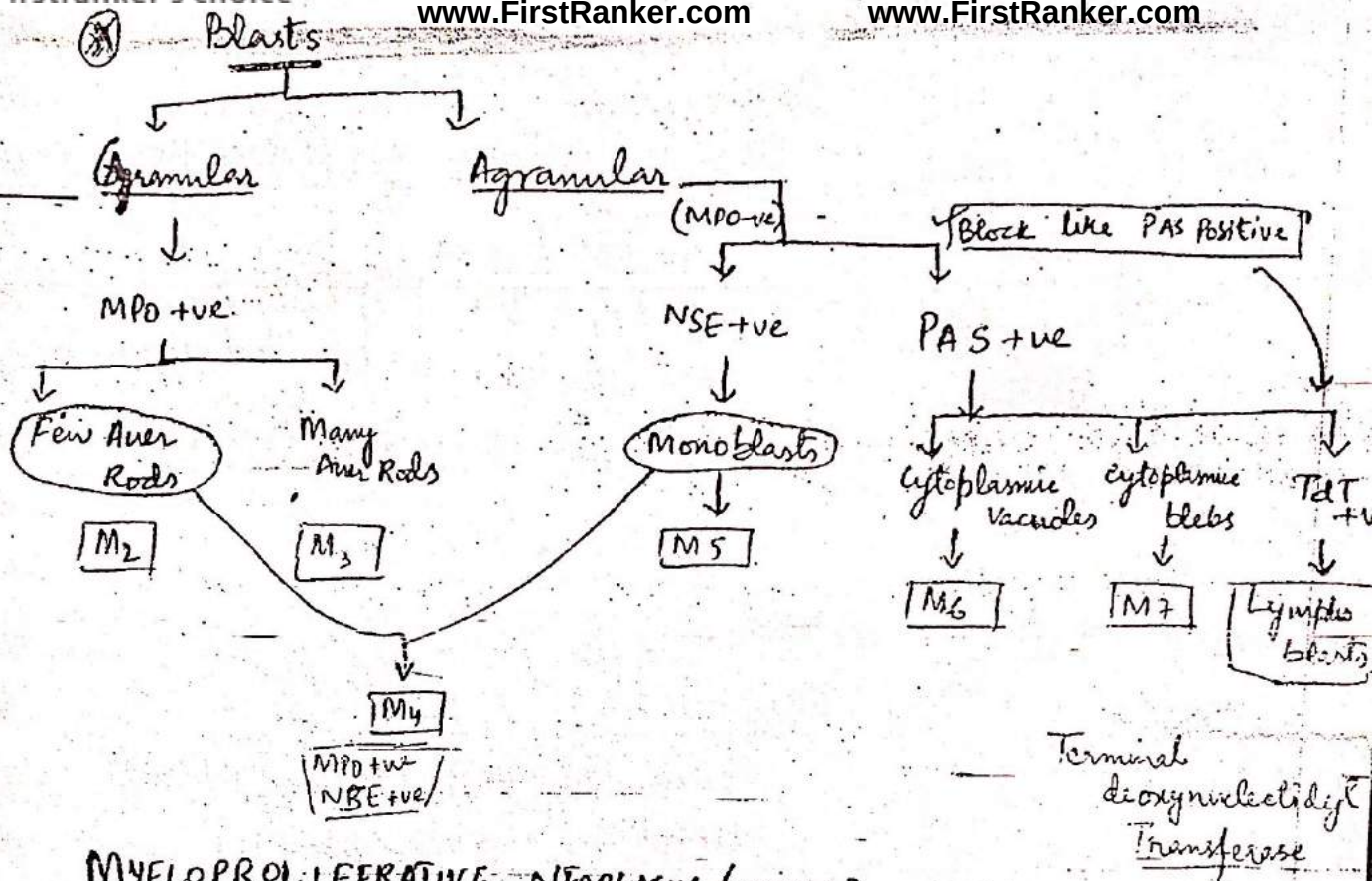
→ Nuclear creases/folds/Indentation.

Monoblast (NSE +ve)

✓ M_4 = MPO + NSE +ve.

✓ M_5 = NSE +ve

Myeloblast → Auer Rods



MYELOPROLIFERATIVE NEOPLASMS (MPNs)

Origin - Hematopoietic cells (stem cells)/progenitor cells

PAN MYELOSIS

↓ ALL ↓ Myeloid cells

with **GRANULOCYTE DOMINANCE**

Chronic Myeloid Leukemia (CML)

$t(9;22)$ = Fusion of BCR - ABL1 on Chr 22

Tyrosine kinase

Philadelphia Chr.

→ Variable excess of BCR may fuse with a fixed sequence of

(i) Major BCR (M-BCR) + ABL1 = 210 KD = **P210^{BCR/ABL}**

(ii) Minor BCR (m-BCR) + ABL1 = 190 KD = **P190^{BCR/ABL}**

② ~~one can have both (p210 & p190)~~ WHO 2017

Unregulated Tyrosine kinase

Chronic phase
 TLC ↑ → Differential c. → Marrow preferable over blood
 Myelocyte peak
 Neutrophil peak
 Blasts < 2%
 Basophilia
 Eosinophilia +/-
 Additional cytogenetic changes
 Garden Party Appearance
 College Girl Appearance

↓
 Progression to Accelerated Phase

↑ TLC → Differential c.

Blasts 10-19% (marrow > blood)
 Basophilia > 20% (blood)

Thrombocytosis / Thrombocytopenia
 ↑↑ Spleenomegaly

Unresponsiveness to Tyrosine Kinase Inhibitors (WHO 2017)

↓
 Additional Genetic Changes

↓
 Blast Crisis

Blasts ≥ 20%
 (marrow > blood)

OR Extra medullary
 Blast Proliferation
 (skin, CNS)

75% (Myeloid)
 Blasts

25% (Lymphoid)
 Blasts

RT PCR → To monitor response to treatment & to followup

Neutrophil Alkaline Phosphatase (NAP)
(Leukocyte ALP)

www.FirstRanker.com

NAP → Number - ↑ (Leukemoid reaction)
→ Function - ↓ (CMV)

2. Erythrocyte Dominance

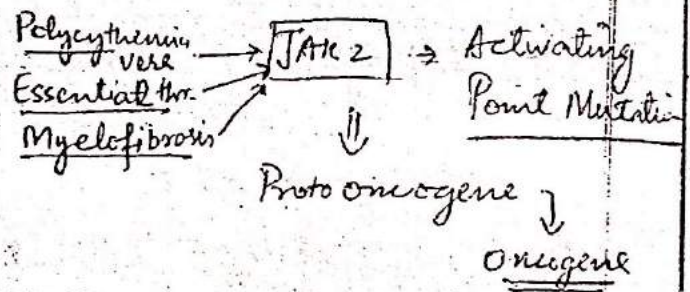
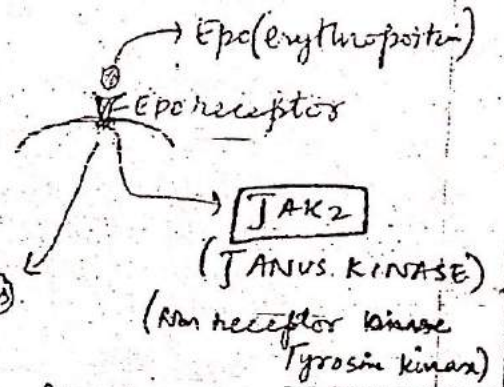
Polycythemia vera

Unregulated & unregulated Erythropoiesis

- RBC mass ↑
- Hb > 16.5 g/dl (M)
> 16.0 g/dl (F)
- Hematocrit > 49% (M)
> 48% (F)

Biopsy - Erythroid hyperplasia

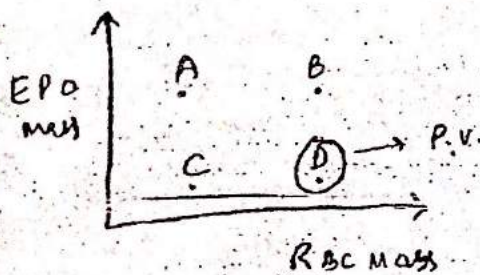
- EPO Level = Normal / Subnormal



At 617th position Valine → Phenylalanine

Unregulated & unregulated Erythropoiesis

POLYCYTHEMIA VERA



↑ Risk of thrombosis → Budd Chiari Syndrome

Platelet function defects may be present → Bleeding manifestation

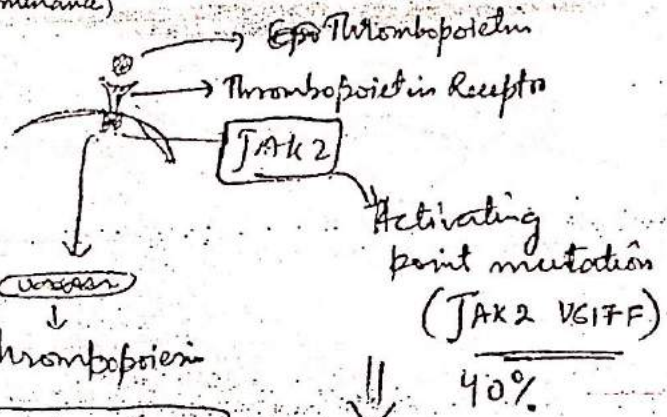
③ Essential Thrombocythosis / Thrombocythemia (Megakaryocyte dominance)

Platelet count $> 450 \times 10^9/L$

Biopsy $\Rightarrow$ Mature enlarged
Megakaryocytes

Genes - JAK2 (40%)
MPL } WHO 2017
CALR }

$\uparrow$ Thrombosis (+)



Bone Marrow Aspirate
& Biopsy indicated $\Rightarrow$ Essential Thrombocythosis

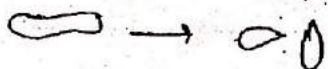
④ Primary Myelofibrosis

De novo Marrow collagen deposition

Panmyelosis $\rightarrow$ Atypical Megakaryocytes
(JAK2, MPL, CALR)

TGF β }
PDGF } $\Rightarrow$ Fibrosis

- Tear Drop cells/cells/
Dacryocytes (distorted RBCs)



$\downarrow$ Cellularity is increased

$\Rightarrow$ Extra Medullary Hematopoiesis (EMH)

- Precursors of RBCs & Granulocytes.

Erythroblasts } LeukoErythroBlastic Reaction } Myelofibrosis
Leucoblasts } (LEBR)

Biopsy is diagnostic

$\Rightarrow$ Aspirate is Dry tap

Demonstrate fibrosis (stains)

$\rightarrow$ Reticulin Stain (Silver $\rightarrow$ Black)

AML $\neq$ Myelofibrosis

[Biopsy indicated]

Visualize Reticulate fibers
(Fibrosis of liver)

Myelophthritic Anemia.

- Metastatic Carcinoma
- Storage disorders
- Granulomatous Inflammation
- Radiotherapy/Chemotherapy

MYELODYSPLASTIC SYNDROME

Disordered growth in marrow → Cytopenia in blood.

At least 10% of the cells of a series should have dysplasia to call it significant.

MDS can occur in a single lineage ⇒ Single Lineage Dysplasia (MDS-SL)
or Multi lineage ⇒ (MDS-ML)

[MDS with ring sideroblasts
MDS with excess blasts.]

	Blood cytopenia	Bone marrow dysplasia	Ringed sideroblasts	Blasts in marrow
MDS-SL	One or B1 cytopenia	One cell line	≤ 15%	≤ 5% (No Auer Rod cells)
MDS-ML	One to Pan cytopenia	More than one cell line	≤ 15%	≤ 5% (No A.R. cells)
MDS-RS Ring Sideroblasts	One cytopenia	One or two cell lines	> 15%	≤ 5% (No A.R. cells)
MDS-RC MLD	One to Pan cytopenia	More than one cell line	> 15%	≤ 5% (No A.R. cells)
MDS-EB1 Excess blasts	One to Pan cytopenia	One to three cell lines	None or any	5-9% (No A.R. cells)
✓ MDS-EB2	One to Pan cytopenia	One to three cell lines	None or any	10-19% Auer Rods



Normal



Budding



Lobulation

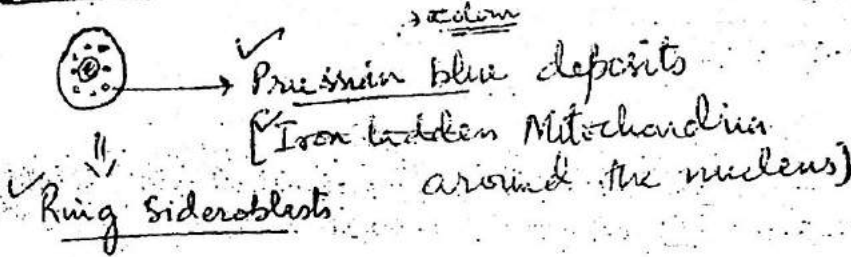


Multi-nucleation



Megaloblastic change

Perle stain



Granulocyte Dysplasia



Normal neutrophil



Hypersegmented (>5)



Hyposegmented & hypogranulated neutrophil

Pelger Huët Anomaly

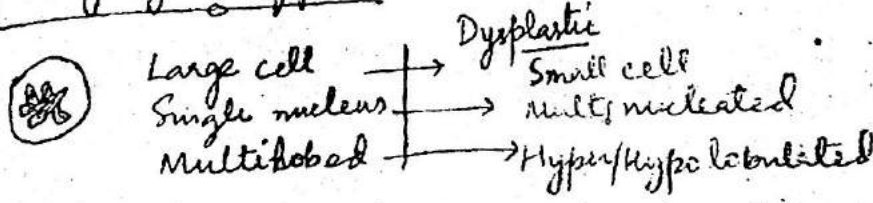
- Inherited condition
- Neutrophils are morphologically abnormal but functionally normal

Pseudo Pelger Huët anomaly



PINCE NEZ Appearance

Megakaryocyte Dysplasia



⇒ Most significant Dysplasia for diagnosis of MDS.

Pavlov ball megakaryocytes - small megakaryocytes & multinucleation & Hypolobation

Most common cytogenetic abnormality

In Adults
In Children
Overall

Monosomy 7 (also 2012)

MDS/MPN

$>10^9/L$

$\bar{c}$ monocytosis $\approx 10\%$ of cells

Leucocytes

Chronic Myelomonocytic Leukemia (CMML)

Juvenile Myelomonocytic Leukemia (JMML)

Atypical Chronic Myeloid Leukemia (ACML)
(Philadelphia Chr. -ve)

New confirmed addition by WHO.

→ MDS/MPN with ring sideroblasts and thrombocytosis

Lymphoid Neoplasms

HODGKIN LYMPHOMA

NON HODGKIN LYMPHOMA

Involves contiguous group of lymph nodes.
Contiguous (sharing common border)
- Almost always Nodal (Axial L.N.)
- Bimodal age distribution (young adults & old)

Non Contiguous group of lymph nodes.

Can be Nodal/Extranodal
Waldenstrom's, Ring, Mesenteric (CN) commonly affected
No specific age group.

Neoplastic cells $\lll$ Non neoplastic cells
(1:10 - 1:100)

Almost all cells are neoplastic.

HL → Classical R.S cells
Lacunar cells
Mononuclear cell
L&H cell

NHL

B cell (more common)

T/NK cell

Precursor

Peripheral/mature

Precursor

Peripheral/mature

B-acute Lymphoblastic Leukemia/Lymphoma

T/NK-Acute Lymphoblastic Leukemia/Lymphoma

Acute lymphoblastic Leukemia/Lymphoma

Most common Cancer in children

B-ALL

- Children
- Leukemia (↑ Tendency)

T-ALL

- Adults
- Lymphoma (↑ Tendency)
- Thyroid mass ↓

SVC obstruction

Also seen with

- small cell CA.
- Hodgkin Lymphoma



Large cell

↑ N:C ratio

Less/no prominent Nucleoli

Scanty cytoplasm

Agranular

Block like PAS +ivity

Prognosis of ALL

Unfavourable

<1yr, >10yrs

CNS involvement

Testicular involvement

Male

T. phenotype

t (9;22) (P190)

11q23 MLL gene

Hypoploidy
(<45 chr.)

Favourable

2-9 years

Absent

Female

B phenotype

t 12;21

Runx1

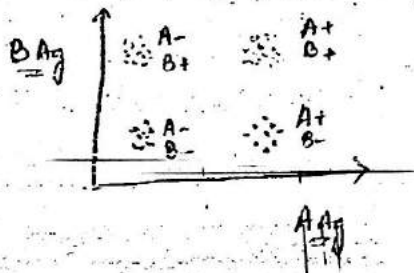
Hyperploidy

(>47 chr.)

Priority for All prognosis

- ① - Response to treatment (steroids)
- ② - Cytogenetics $\begin{cases} \text{Polidy} \\ \text{Translocations} \end{cases}$
- ③ - Clinical features.

⊗ Flow cytometry :-



Myeloid Markers :-

Myeloperoxidase (MPO) :- Lineage Specific marker for granulocytes

$\left[\begin{array}{l} \text{CD 13} \\ \text{CD 33} \end{array} \right] \Rightarrow$ Seen in granulocytes + Monocytes
(Myeloid Lineage marker)

$\left[\begin{array}{l} \text{CD 11c} \\ \text{CD 14} \\ \text{CD 64} \end{array} \right] \Rightarrow$ Monocytic markers.

$\left[\begin{array}{l} \text{CD 71} \\ \text{CD 235} \end{array} \right] \Rightarrow$ Erythrocytic markers.

$\left[\begin{array}{l} \text{CD 41} \\ \text{CD 61} \end{array} \right] \Rightarrow$ Megakaryocytic markers.

Lymphoid Markers :-

T cell

- CD 1a $\rightarrow$ Thymocytes, Langerhan cells
- ✓ CD 2 $\rightarrow$ Almost all T cells
- ✓ CD 3 $\rightarrow$ Part of T receptor (more diagnostic)
- ✓ CD 4 $\rightarrow$ Helper T cell

Pan T cells
2, 3, 7

B-cell markers

✓ CD19 → Lineage specific and consistently expressed.

CD20 → Marker of choice for B cell lymphomas (Mature)

✓ CD21 → EBV receptor

CD23 → Activated B cells

CD79A → Almost all B cells

✓ PAX 5 → B cell transcription factor (P65)

(new marker)

[✓] → First line of B cell; PAX 5

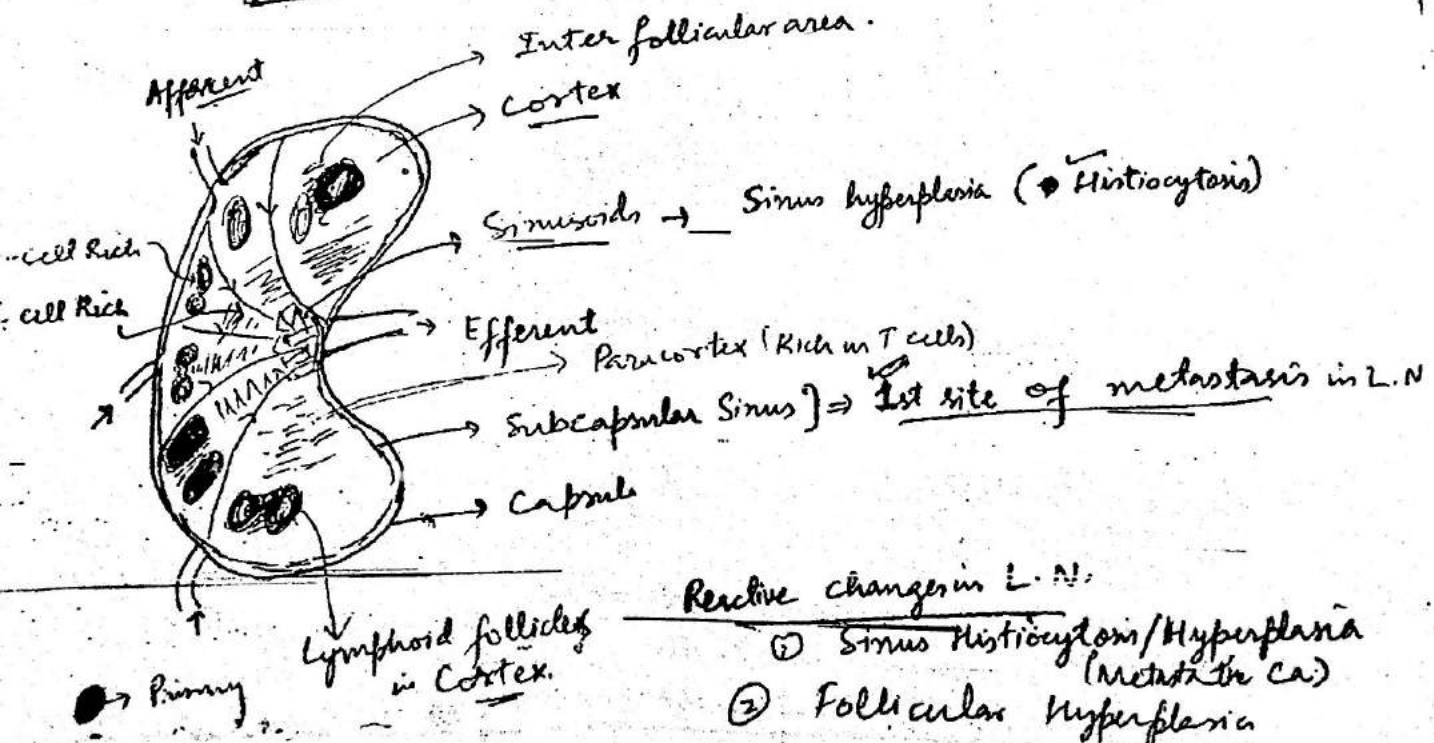
Miscellaneous markers

✓ CD34 → Hematopoietic stem cells + Progenitors

HLA DR → Blasts (immaturity)

CD10 → Precursor B cell + T cells
Germinal centre - B cells

CD15 → Mature granulocytes



Reactive changes in L.N.

- ① Sinus Histiocytosis/Hyperplasia (Metastatic Ca)
- ② Follicular Hyperplasia

✓ Follicular hyperplasia -

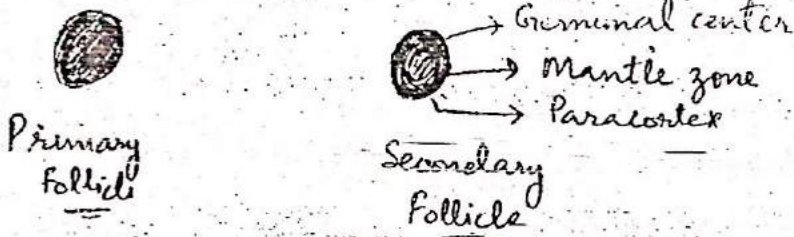
Humoral immunity requirement ↑↑

✓ Paracortical hyperplasia -

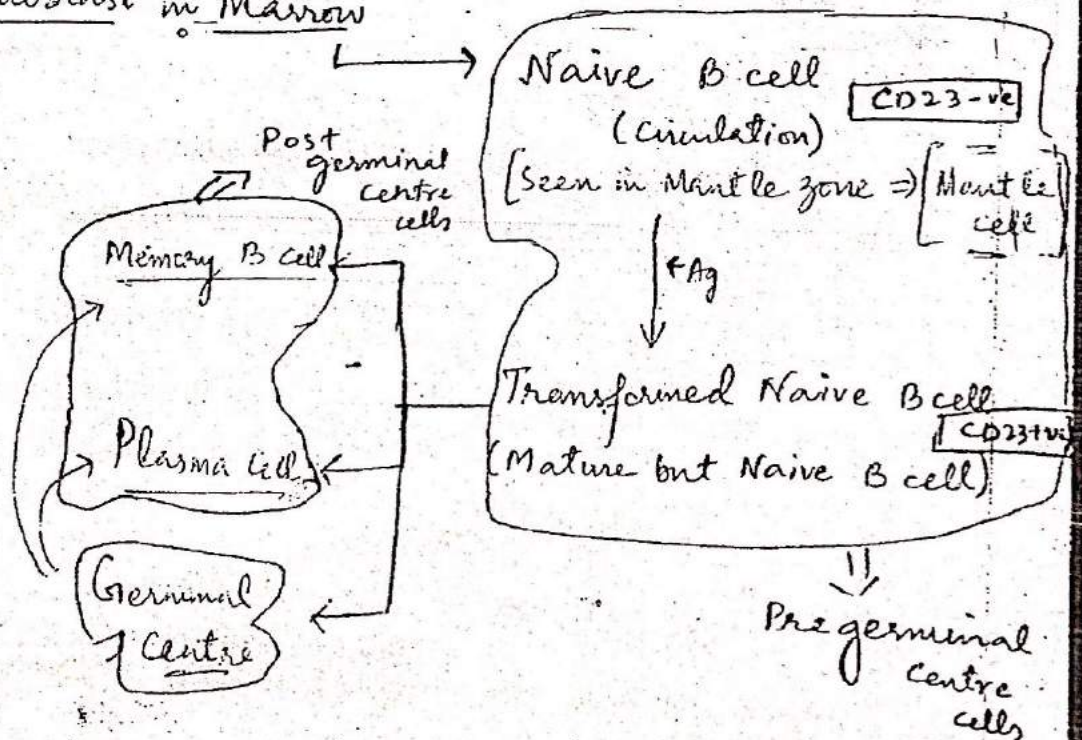
↑ T cell mediated immunity

↳ infected B cells but increases T cells.

⇒ Plasmal cells and Histiocytes are found in Medulla.



B Lymphoblast in Marrow



- 1 Mantle cell lymphoma CD23 -ve
- 2 Chronic Lymphocytic lymphoma/leukemia CD23 +ve

Burkitt lymphoma
Follicular lymphoma
Diffused large B cell lymphoma (DLBCL)

Marginal zone lymphoma
Plasma cell neoplasm
Lymphoplasmacytic Lymphomas (LPL)
CLL
DLBCL

CD5 +ve
CD10 -ve

CD10 +ve
CD5 -ve

CD5 -ve
CD10 -ve

① Mantle cell lymphoma

Elderly

Nodal & Extranodal

↓
GIT - Polypoidal appearance

May be high grade. (small cells & cleaved Nucleus)

✓ t(11;14)

→ IgH (Heavy chain Ig) (Promoter)

→ Cyclin D1 (cell cycle regulator which

↓ pushes the cell cycle forward)
✓ Overexpressed (IHC)

New marker for cyclin D1 negative MCL

↓ [REDACTED] May AMMS17
SOX 11

IHC

CD20 +ve

CD79a +ve

CD5 +ve

~~CD23~~ -ve

CD10 -ve

✓ Cyclin D1 +ve

2) Chronic Lymphocytic Leukemia (CLL/SLL)

Small cell
Non cleaved
Low grade

Resembling small lymphocyte

Coarse/clumped chromatin
Scanty cytoplasm.

Soccer ball appearance

- CLL is most common Leukemia in adults
- Almost exclusively in the elderly

Peripheral blood: uniform monotonous population

[Convent School Girl appearance]

Tumor cells have very less Vimentin

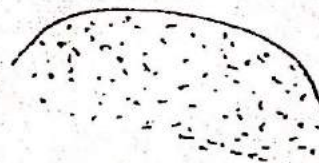
Intermediate filament of cytoplasm

Become fragile

Making a smear ~~will~~ disrupt easily.

Smudge cells / Basket cells

Lymph Node Histology



Diffused effacement of LN architecture (no demarcation between cortex & medulla seen) Most common Pattern

Pro lymphocyte (another type of tumor cell)

(Rapidly multiplying cell)
enough cytoplasm.
thus lighter staining.

Proliferation centres
(Pseudo follicular pattern)

Most Pathognomonic pattern of CLL
More the proliferation centres more the prognosis

Most common cytogenetic change
50% - Deletion 13q⁺
20% - Trisomy 12⁺ (47 x4 +12)
New marker for CLL - **LEF1**

Best marker to differentiate b/w MCL & CLL

	MCL	CLL
Nucleus	+	+
CD5	+	+
CD23	-	+
CD20	+	-
Cyclin	+	-

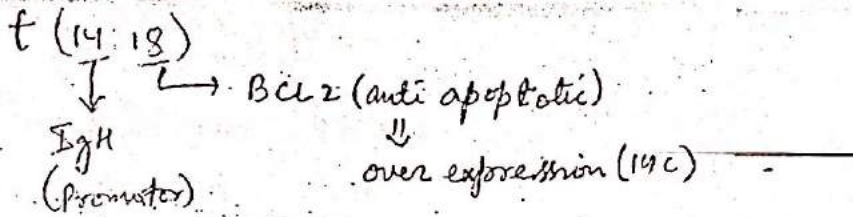
③ Follicular Lymphoma
nodal >> Extranodal
Most common NHL in western hemisphere
Dual population.

 multiple peripheral nuclei
Centroblast

 cleared nuclei
Centrocyte

WHO grading of FL = No. of centroblasts per high power field.

gr I < 5
gr II 6-15
gr III > 15



$\Rightarrow$ Back to back closely packed follicles with very little interfollicular space.

To differentiate from follicular hyperplasia

$\checkmark \rightarrow$ BCL2 is the marker of choice

$\downarrow$
+ve in germinal centres of follicles

lymphoma & -ve in germinal centre of follicular hyperplasia

BCL2 is normally expressed in mantle zone.

ZNC
 CD20+
 CD79a+
 CD5-
 CD10+
 BCL6 (germinal center)+
 BCL2+

④ Burkitt Lymphoma

$\checkmark$ Extranodal $\gg$ Nodal

$\checkmark$ EBV +ve

Types $\rightarrow$

- Endemic (African continent) most common site is Jaw
- Sporadic most common site Ileocecum
- Immunodeficiency associated (HIV) most common site - CNS
GIT

$\checkmark$ $8 = B$

$\downarrow$
 Chr. No 8.
 "c-myc" Transcription factor $\Rightarrow t(8;14)$
 $\rightarrow$ IgH $\rightarrow$

- Kappa (K) Chr 2 $t(2;8)$
- Lambda (L) Chr 22 $t(8;22)$

To assess proliferation of tumor cells -

Ki-67 (Mib-1)
(% of cells express)

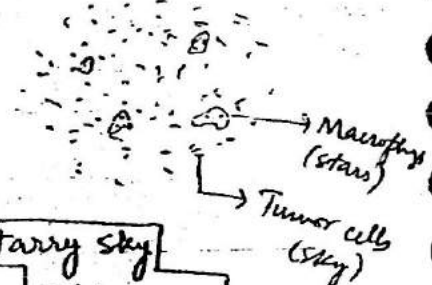
Lymphomas
 $< 40\%$ - low grade
 $> 40\%$ - high grade

[different cut offs for different tumors]

Ki67 in Burkitt lymphoma $\approx 100\%$

i.e. rapidly proliferating & rapidly dying cells

High mitotic Index $\Rightarrow$



Starry sky appearance

Also seen in

- ALL
- DLBCL
- Variants of MCL
- Reactive lymph nodes.

IHC

CD20 - +ve

CD79a +ve

CD5 -ve

CD100 +ve

BCL6 +ve

BCL2 -ve

Translocation C-myc +ve

New marker is CD100 who 2017

⑥

DLBCL (Diffused Large B Cell Lymphoma)

Diffused Effacement of architecture

Nuclei of tumor cell is 3x - 5x that of normal lymphocyte nuclei

Most common NHL worldwide

Most common CA arising in HIV patients

$\rightarrow$ Molecularly heterogeneous

BCL6 rearrangement
 BCL2 rearrangement
 C-myc rearrangement

Frequency

DLBCL is high grade lymphoma.

Large cell

Histological variants

Centroblastic

Immunoblastic

Plasmoblastic

Most common in
Immunodeficiency

IHC

CD20 +ve

CD79a +ve

CD5 -ve

CD10 +ve

ConyC +/-

BCL2 +/-

BCL6 +ve

Ki 67 740% (not as high as Burkitt)

Low grade

Small cell

Lymphoma

Can transform

High grade

Large cell

Lymphoma

Richter
Transformation

⑥ Marginal Zone Lymphoma

⇒ Diagnosis of exclusion

(CD5-, CD10-) (CD43 +ve)

NODAL & Extranodal

⇒ MALToma

Chronic inflammatory states

- Sjogren's Syndrome

- Hashimoto Thyroiditis

- H. Pylori Gastritis

(regression of MALToma
on treating H. Pylori)

New marker for Marginal
Zone Lymphoma

IRTA1

MNDA

⑦ Lymphoplasmacytic Lymphomas

Commonly associated with HepC.

Lymphocytes

Plasmacells

IgM → forming pentamers

↑ Viscosity in blood

Waldenström's
Macroglobulinemia
(WM)

LPL in CNS & WM
↓
Bing Neel Syndrome

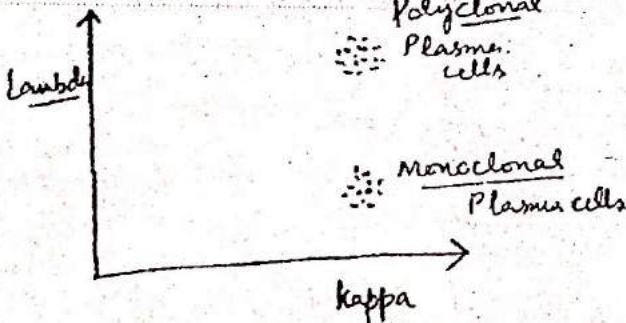
⑧ Plasma Cell Neoplasms

Clonal plasma cells

Abnormal Immunoglobulins
+
Excess of Light chains

Monoclonal Proteins
(M-Proteins)

JIPMER 2017



Deletion 13q

Monoclonal Gammopathy
of Uncertain Significance
(MGUS)

Heavy chain disease

↓
Rare monoclonal gammopathy
occurs in malnourished
population

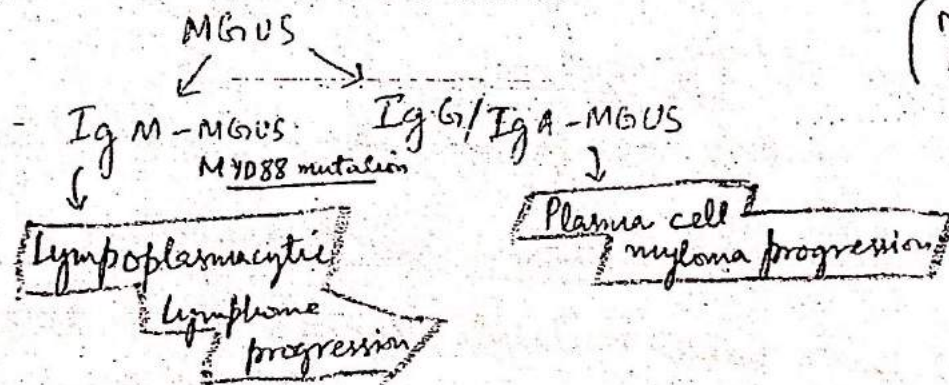
↓
Mediterranean
Lymphoma

Smoldering Myeloma

Plasma cell Myeloma

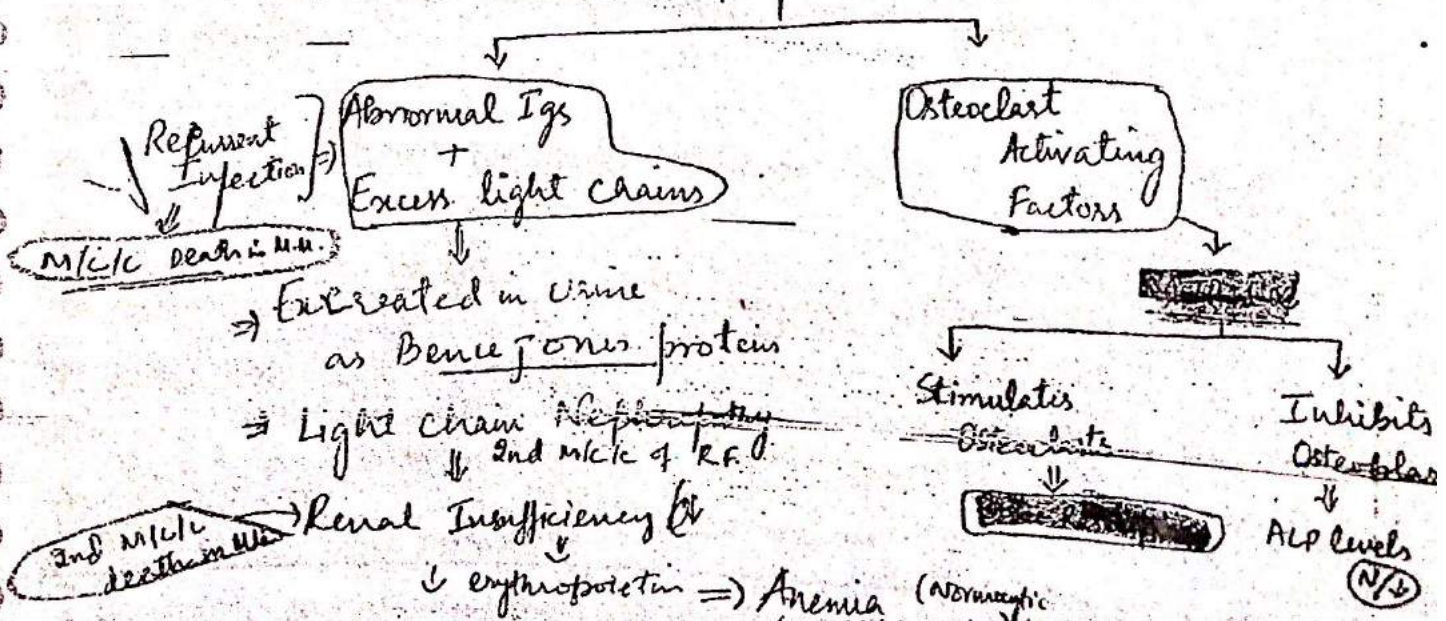
	Monoclonal Gammopathy of Uncertain Significance	Smoldering Myeloma	Plasma cell Myeloma
M protein (g/dl)	< 3	> 3	> 3
Bone marrow clonal plasma cell (%)	< 10%	> 10%	> 10%
Symptoms	Absent	Absent	Present

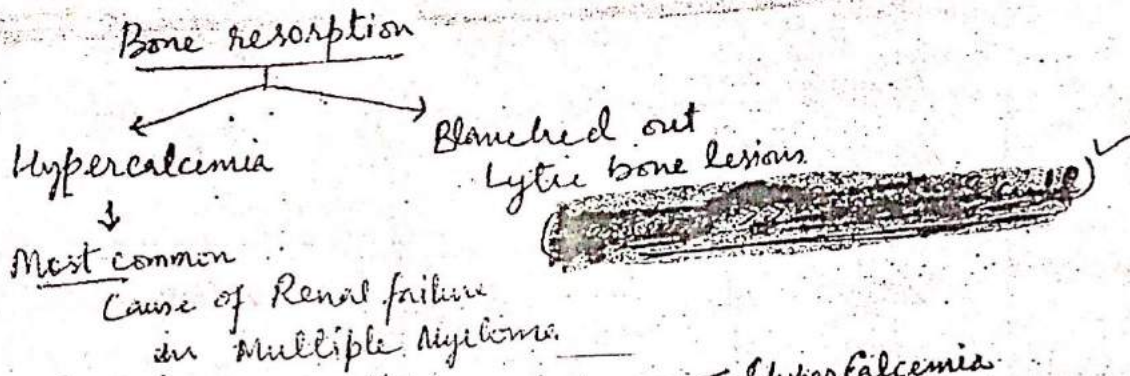
MGUS → Pre malignant condition.



Plasma cell Myeloma

Tumor plasma cells





CRAB Symptoms of M.M.

- Hypercalcemia
- Renal insufficiency
- Anemia
- Bone Resorption/lesions

Tumor plasma cells
IL-6 → Survival, proliferation & level correlate with disease activity.

Symptoms of P.C. Myeloma

> 20% of Plasma cells in peripheral blood
↓
Plasma cell leukemia

How to Diagnose Multiple Myeloma As per 2014 IMWG Criteria

1st → Look for >10% clonal plasma cells in bone marrow or biopsy proven plasmacytoma (either bony or extramedullary)

2nd → Any of the myeloma defining events.

End Organ Damage (CRAB)

Hypercalcemia
Renal Insufficiency
Anemia
Bone lesions

Any one or more of malignancy biomarkers

- > 60% of plasma cells in bone marrow.
- Involved/Uninvolved Serum free light chain ratio > 100
- > 1 focal lesion on MRI

In Multiple myeloma order of frequency of Ig secreted

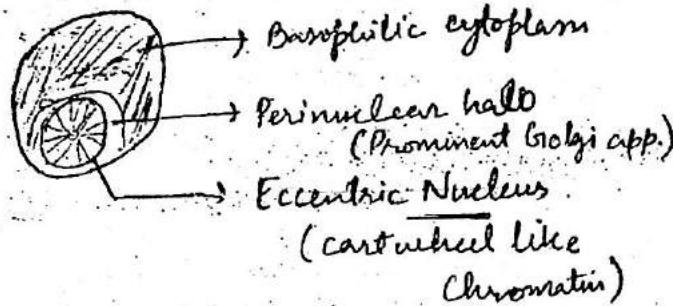
⇒ Ig G (50%)

Ig A (20%)

Ig D

Ig E

Ig M



Globular inclusion
↓
Mott cell/Grapel cell

Intra Nucleus inclusion
↓
Dutcher Body common

Intra cytoplasmic
↓
Russell Body

Malignant plasma cells are ⇒ Binucleate / Multinucleate
⇒ Have Inclusions

Most common cytogenetic abnormality associated is

Rearrangements of 14q (IGH)

Most common gene involved is cyclin D1

Drugs used ⇒ Ibrutinib
Rituximab

9) Mature T cell lymphomas

1. Mycoses Fungoides

(Most common cutaneous T cell Lymphoma)

Leukemia when developed is called

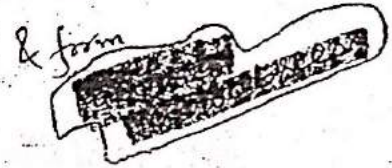


→ Cerebriform Nuclei

(Tumefaction of Skin Lesions)

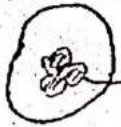
SEZARY LUTZNER cell

→ Invade epidermis



10) Adult T cell Lymphoma/Leukemia

Caused by HIV-1



→ Flower shaped/cloverleaf shaped Nuclei

11) Anaplastic Large Cell Lymphoma

ALK positive

→ Anaplastic Lymphoma Kinase

(Receptor tyrosine kinase)

↓ Rearranged in

↓ Mutated in

- ALCL
- Lung Adenocarcinoma
- Inflammatory Myofibroblastic Tumor

- Neuroblastoma
- Hereditary hemorrhagic telangiectasia (HHT)

"Hallmark cells"



Embryoid Nuclei

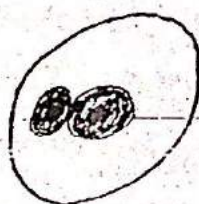
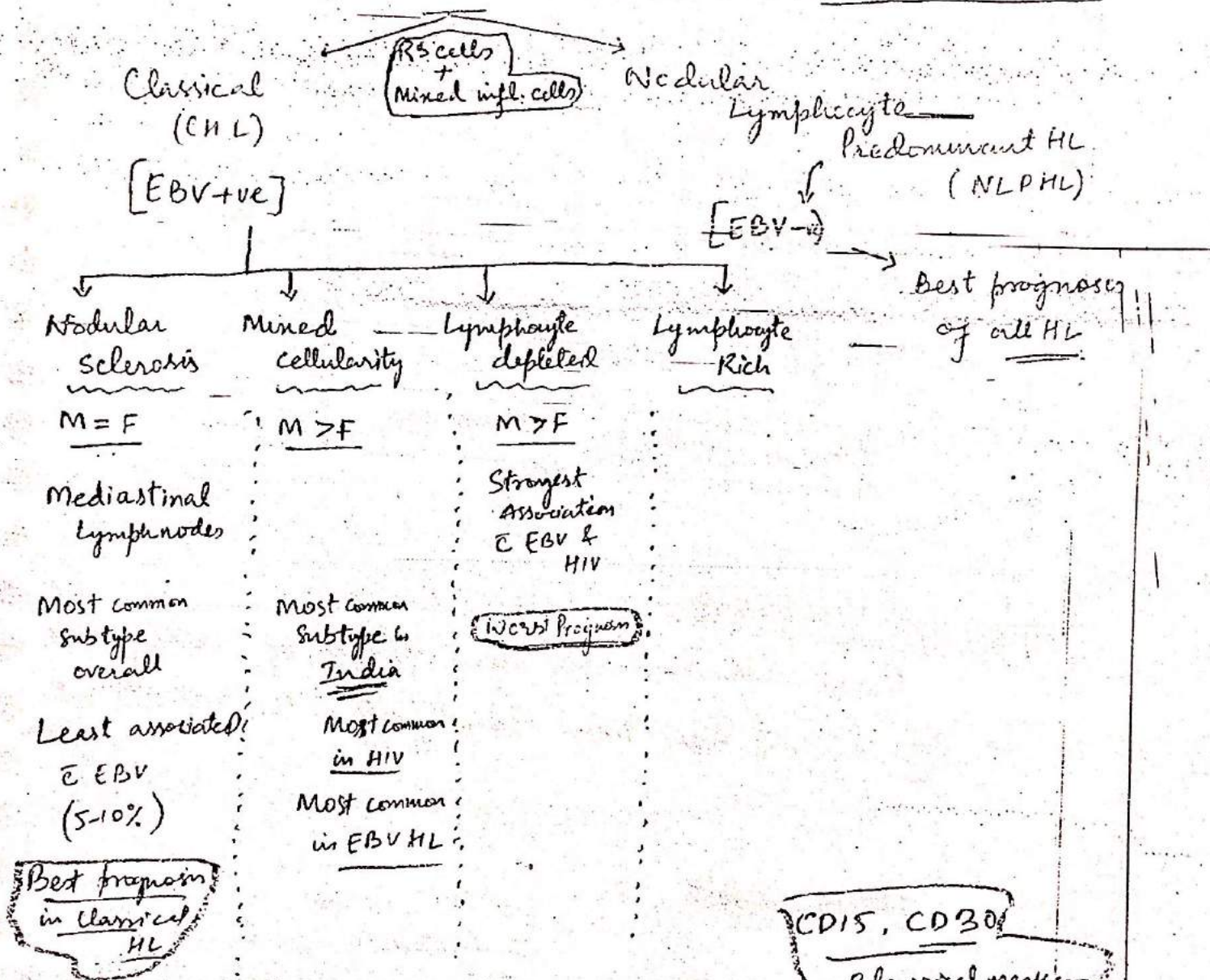
Horseshoe shaped

R-S like cells

HODGKIN Lymphoma

- Involves Contiguous group of LN.
- Almost always Nodal ——— Most common is Cervical group (Neck/Axial)
- Bimodal age
- Neoplastic cells && Nonneoplastic cells

ASSOCIATED WITH EBV



Owl's eye appearance

→ Large/giant cell
Binucleate

Prominent macronucleoli

origin - germinal centre
B cells
Size - 45 um

Variants - Mononuclear cell / Hodgkin cell

{ } - Lacunar cell
Nodular Sclerosis

Popcorn cell / LP cell / L & H cell
NLPHL

	RS cell	LP cell
CD45 (Leukocyte common Ag)	-	+
CD20	-	+
CD10 BCL6	-	+
CD30	+ 100%	-
CD15	+ 75-85%	-
PAX 5	Weakly +ve 75%	Strongly +ve

Hairy cell Leukemia

- Tumor cells resemble the features of memory B cells
- Mutation has been identified in the hematopoietic stem cells.



Signal transduction protein
Glu to Val substitution

Also seen in - Langerhan cell histiocytosis

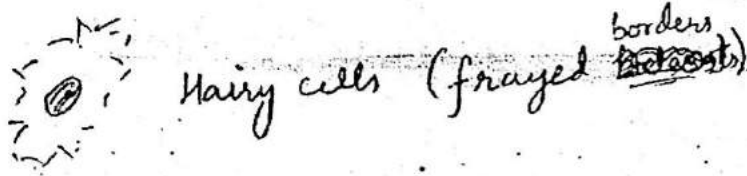
BRAF inhibitor

→ Vemurafenib

- Pilocytic Astrocytoma

- Papillary Carcinoma Thyroid

- Malignant Melanoma



Im marrow → Individual cell fibrosis



→ fried egg appearance

→ also seen in Oligodendroma Mycoplasma c.

Aspirate - Dry Tap

Biopsy - Diagnostic

- Also infiltrates Spleen → Splenomegaly (involves Red pulp)
- Pancytopenia
- Tumor cells stain positive for acid phosphatase

Tartrate

Resistant

Acid
Phosphatase

(TRAP) +ve

↓ wash them with tartrate

↓ Stain is retained

Associations

Monocytopenia → ↑ Risk of Infection with atypical Mycobacterium

Erythema nodosum

Polyarthralgia Nodosa

IHC

Annexin A1

most specific marker

CD 11c

CD 103

CD 25

- Tumor of Immature Dendritic cells (Langerhan's cells)
- ~~RET proto-oncogene~~ mutation
- Clinically

Unisystem

Multisystem

Unifocal

- Eosinophilic granuloma

Multifocal

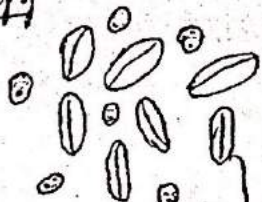
- Calvarial bone defects
- Exophthalmos
- Diabetes Insipidus

Hand Schüller
Christian Triad

- Cutaneous
- Hepatic
- Splenic
- Pulmonary

Letterer Siwe Disease

Histology



Coffee Bean Nuclei
(Longitudinal groove)

Also found in

- Granulosa cell tumor
- Brenner tumor
- Papillary Ca. Thyroid
- Chondroblastoma

Langerhan cells

Eosinophil

Electron Microscopy



Peritubular

crystalline structures

with fusiform dilatation

(Tennis Racquet appearance)

⇒ most specific

marker ⇒ LANGERIN (CD 207)

⇒ Birbeck Granules

Pulmonary LCH

Neoplastic

BR AF V606E

Reactive

Smoking

Cessation of smoking causes regression of disease

IH

CD 1a

5-100 → Neuroectodermal marker

~~HbA-OR~~ - Malignant Melanoma

- Schwannoma

- Lipoma / Liposarcoma

- Sustentacular cells of pheochromocytoma.

Scanned with CamScanner

Routine - Polychromatophilic

Supravital: Reticulocyte

- ↳ New methylene blue
- Brilliant crystal blue
- Crystal violet

Reticulocytosis → marrow is normally functioning
→ marrow is in hurry.

Normal Retic count = 0.5 - 1.5% ✓

Hemolytic Anemia

↑ red RBC destruction

~~Extrinsic~~

Intrinsically wrong c RBC



or There is Intracorpuscular defect.



Extravascular Hemolysis

↳ Splenomegaly.

Extrinsically wrong c RBC



or There is Extracorpuscular defect.



Intravascular Hemolysis

Lab findings



✓ Sign of red defect/destruction

- Hemoglobinemia/uria
- ↑ red Indirect Bilirubin
- ↑ red LDH
- ↓ red Haptoglobin

Signs of compensatory production

- Reticulocytosis
- Bone marrow hyperplasia

Hereditary Spherocytosis

Defect in membrane proteins

Integral

Glycophorin (CD235)
Band 3 (most abundant
Integral glycoprotein)

Peripheral

⇒ Ankyrin - Most common def.
⇒ Spectrin - most severe def.
⇒ Responsible for biconcave shape of RBC

⇒ Protein 4.1

⇒ Protein 4.2
(Palladin)

Most common inheritance is Autosomal Dominant

Loss of Surface area

Spherical shape

Splenic macrophagic

destruction of RBC
formed

↓ Mean corpuscular Hb conc.
(MCHC)

Less deformable

⇒ Osmotically ~~more~~ ^{more} fragile

⇒ RBCs without any central pallor

↳ Characteristic feature of Spherocytes

Paroxysmal Nocturnal Hemoglobinuria (PNH)

↓
Episodic

↓
Intravascular hemolysis

↓
Decreased pH in body
during night activates complement.

⇓
Acquired genetic defect

PIGA gene

GPI anchored proteins

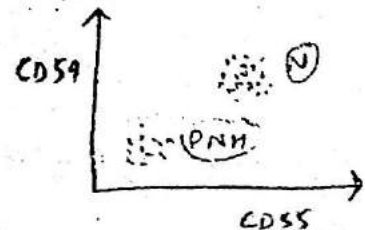
⇓
(Protect cells from complement mediated damage)

GPI anchored Proteins

↓
Membrane
Inhibitor of
Reactive lysis
most common & important (MIRL)
(CD59)

↓
Reactive
Decay
Accelerating
Factor
(DAF)
(CD55)

↓
C8 binding
protein



Triad of Hemolytic anemia

→ Pancytopenia

→ Thrombosis (50%) - common cause of death
(Multifactorial)

5-10% → Progress to AML/MDS

Stem cell
Transplant

Diagnosis

Ham's test

incubate lysate

Flow cytometry → Best technique

⇓
Treated

HMP Shunt → Detoxify H_2O_2

In G6PD deficiency → when there is oxidative damage ↓

H_2O_2 is not detoxified ↓

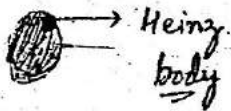
Free radical damage to Sulfhydryl groups of Hb

Denaturation of Hb

↓
HEINZ Body

Can be visualized on Supravital Stain

→ Denatured Hb doesn't take other stains.



When stained Routinely

Heinz body → capable of damaging the membrane ↓

EV Hemolysis

without membrane damage - IV Hemolysis

G6PD deficiency

→ X linked recessive

Males full expression

Females - Carriers.

Oxidant damage

— Infections

Drugs —

Fava beans

- Antimalarials
- Dapsone
- Co-trimoxazole
- Nitrofurantoin

[C DNA]

Adult Hb

HbA $\alpha_2\beta_2$ - 96%

HbA₂ $\alpha_2\gamma_2$ - 3%

HbF $\alpha_2\gamma_2$ - 1%

- α is coded by a pair of genes on chr. 16
- β is coded by a single gene on chr. 11

Sickle cell Anemia

Glutamate changes to valine at 6th position of β globin chain

Hb becomes sticky

In reduced state $\rightarrow$ the stickiness of Hb causes polymerization

 Sick cell
Drepanocyte

HbS polymers distort the shape of RBC

Fragile
 $\downarrow$
Hemolysis

Can cause microvascular occlusion

$\downarrow$
Hypoxia $\rightarrow$ Ischemia

$\downarrow$
Tissue damage

If there is repeated occlusion in splenic tissue,

$\downarrow$
repeated cycles of damage & fibrosis

Autosomal Recessive

BB - (N)

$\beta^S\beta \rightarrow \alpha_2\beta_2 = \text{HbA}$

$\alpha_2\beta^S$ Heterozygous

$\Rightarrow$ Sickle cell trait

Autosplenectomy $\rightarrow$ Red risk of infection by encapsulated organisms

Interferes w polymerization of HbS.

$$\beta^S \beta^S \Rightarrow \alpha_2 \beta_2^S - \text{HbS}$$

Homozygous condition

www.FirstRanker.com

Diagnosis

Hb Electrophoresis] - Qualitative

High performance liquid chromatography [HPLC]

↳ Quantitative & Qualitative

Sickling test

Na meta bisulphite is used.

or Na dithionite

THALASSEMIA

α or β thalassemia ($\alpha \downarrow$ or $\beta \downarrow$)

↓ globin production → Microcytic cells

If $\alpha \downarrow \Rightarrow \beta \uparrow, \gamma \uparrow$

$\beta \downarrow \Rightarrow \alpha \uparrow$

Thus getting Excess unpaired chains

↓ form tetramers

↓

Precipitate $\Rightarrow$ Hemolysis

$\beta \uparrow \Rightarrow \beta_4 - \text{HbH}$

Golf ball Inclusions

$\gamma \uparrow \Rightarrow \gamma_4 - \text{Hb Bart's}$

α thalassemia

Most common Genetic Change $\Rightarrow$ Deletions

$\alpha\alpha / \alpha\alpha \rightarrow (N)$

$\alpha\alpha / \alpha - \rightarrow 1/4 \text{ deletion} / \text{Silent carriers}$

$\alpha\alpha / - - \rightarrow 2/4 \text{ deletion}$

or $\alpha - / \alpha - \rightarrow \alpha \text{ Thal. Trait}$

$\alpha - / - - \rightarrow 3/4 \text{ HbH disease}$

$- - / - - \rightarrow 4/4 \text{ deletion} \rightarrow \text{Hydrops fetalis}$

β Thalassemia

Clinically — { Major
 Intermediate
 Minor

β - Genetic changes

β - (N)

β^+ - Reduced production of β] $\Rightarrow$ Splicing mutations

β^0 - Absent production of β] $\Rightarrow$ Chain Termination mutation

When both alleles are mutated

$\hookrightarrow$ Homozygous (Major)

When only one allele is mutated

$\hookrightarrow$ Heterozygous (Minor)

Major	Minor
- Severe anemia	- Mild to moderate anemia
- Dependence on blood transfusion	- No history of blood transfusion
- Target cell +ve	- Target cell +ve
- Microcytic cell	- Microcytic cell
$\Rightarrow$ Considerable amount of anisocytosis & reticulocytosis	$\Rightarrow$ Uniformly microcytic so no anisocytosis



Target cell
OR CODOCYTE



Microcytic cell

Anisocytosis $\Rightarrow$ Variation of
↓
Size

Poikilocytosis $\Rightarrow$ Variation of
Shape

RDW - Red cell Distribution width

Range over which RBCs are distributed.

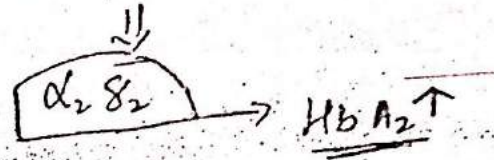
$\hookrightarrow$ Anisocytosis Confirmation by RDW.

β Thal. Minor

At least one allele is functional (β)

Mild reduction in β

↓
Mild excess of α → binds ϵ & γ



β Thal major

Both alleles are affected

Severe reduction in β

Severe excess of α → binds more ϵ & γ → $\text{Hb } \alpha_2 \gamma_2 \uparrow$
& γ also → $\text{Hb } \alpha_2 \gamma_2 \uparrow$

HPLC - Quick Interaction

	HbA	HbA ₂	HbF	Additional.
Normal	~96%	<3.5%	<1%	—
β Thal. Trait	<96%	3.5-9%	Normal or ↑ sed	—
β Thal. Major	~3%	Variable	>85%	—
Sickle cell Trait	40-60%	~3.5%	Normal or slightly ↑ sed	HbS-30-40%
Sickle cell Homozygous	Markedly reduced	slightly ↑ or normal	5-25%	HbS-70-90%

Autoimmune Hemolytic Anemia (AIHA)

↓
Auto antibodies targetted against RBC Ags

Warm Antibody type (IgG Antibodies Active at 37°C)

Primary

Secondary

- Autoimmune disorder ⇒ SLE
- Drugs
- Lymphoid Neoplasms ⇒ CLL

(No clumping in PBS smear)

Cold Agglutinin Type (IgM antibodies active below 37°C)

Acute (mycoplasma Infection) (Infection mononucleosis)

Chronic

Idiopathic

- Lymphoid neoplasms.

(Clumping is found in PBS)

Cold Hemolysin Type (IgG antibody active below 37°C)

→ Donath Landsteiner Ab.

Rare; Occurs mainly in children following viral inf.

As RBC is covered with antibodies

Complement mediated membrane damage

IVH

Spherocytes

Most common cause is AIHA

Splenic macrophages destroy them

EVH

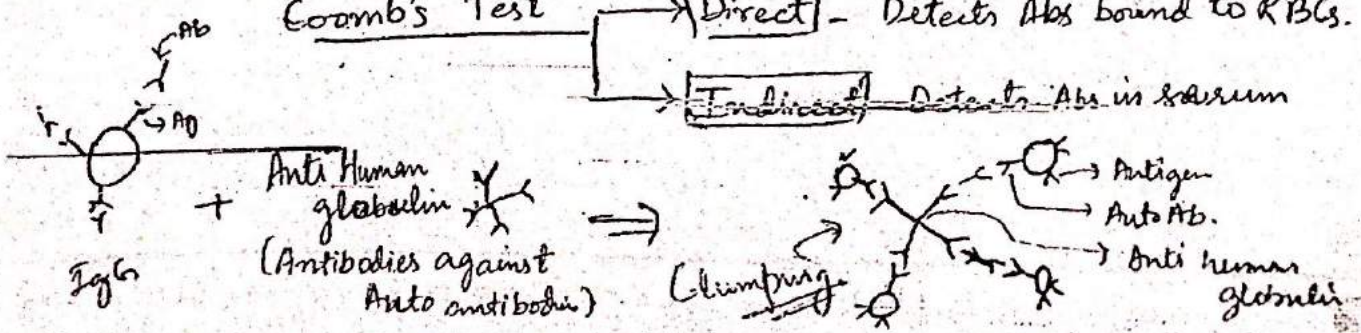
Coomb's Test

Direct

- Detects Abs bound to RBCs.

Indirect

- Detects Abs in serum



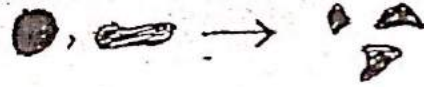
Microangiopathic Hemolytic Anemia (MAHA)

↓
Small Vessel pathology

- In Vasculitis (SLE)

- DIC
- TTP/HUS

Thrombi
formation



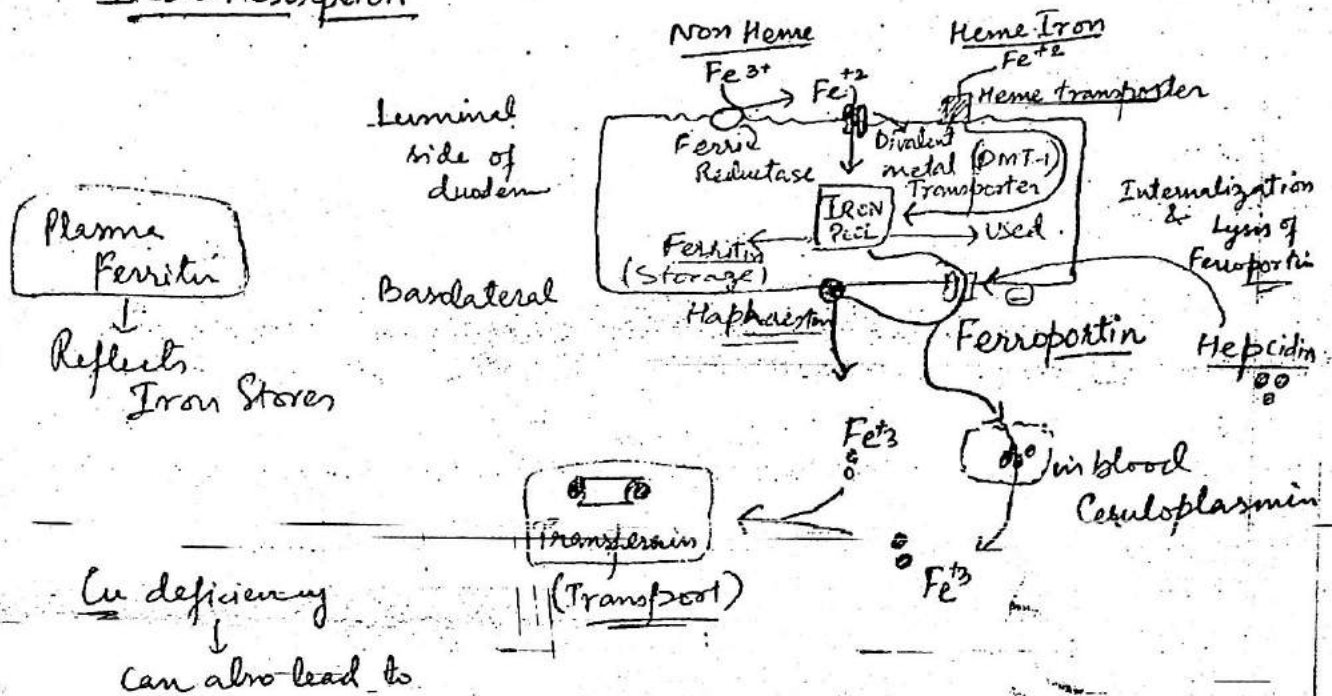
- Schistocytes
or
Schizocytes
Fragmented RBCs
Helmet Shaped

Macroangiopathic Hemolytic Anemia



Prosthetic valves
Coarctation of Aorta

Iron Absorption



Hepcidin → using the exit of Iron from cell to blood.

TIBC ⇒ Reflection of Transferrin Production in body.

Transferrin % Saturation

Iron deficiency Anemia

- Earliest smear finding is : **Anisocytosis (RDWT)**
- After treatment first response: **Improvement of Mood**
Sign is **Reticulocytosis**
(rise in Reticulocyte %)
- Pencil Shape cells +ve → characteristic of Iron def. anemia

Megaloblastic Anemia is

- It is a macrocytic anemia, but every macrocytic anemia is not a megaloblastic anemia

- Macrocytic anemia $\Rightarrow$ $MCV > 100$

Folic acid/Vit B₁₂ ↓ $\longrightarrow$ Retarded DNA Synthesis

Other cells are also affected

↓
Giant metamyelocytes

+
Hypersegmented neutrophils

↓
most characteristic

Megakoblasts in marrow

↓
Macroovalocytes in blood

↓
Earliest finding

Immature Nuclei
+
Mature cytoplasm
+
Big cells

Ineffective erythropoiesis $\longrightarrow$ Improperly formed cells
↓
Destroyed in marrow itself
↓
Hemolytic phase
↓
Jaunder

Platelets

Injury to vessel



Vasoconstriction

Primary Platelet Plug
(unstable)Primary Hemostasis

- Disorders will present c Superficial hemorrhages.
- Not associated with family history

Thrombocytopenia

Immune Thrombocytopenic
Purpura (ITP)Thrombotic Thrombocytopenic
Purpura (TTP)Fibrin clot

Coagulation Cascade

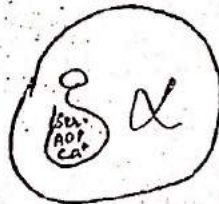
Secondary Hemostasis

Deep hemorrhages

Family history +ve

Hemophilia (A/B/C)

Clotting factor inhibitors

Von Willebrand
DiseaseDisseminated
Intravascular Coagulation

Platelets release ② granules

 α

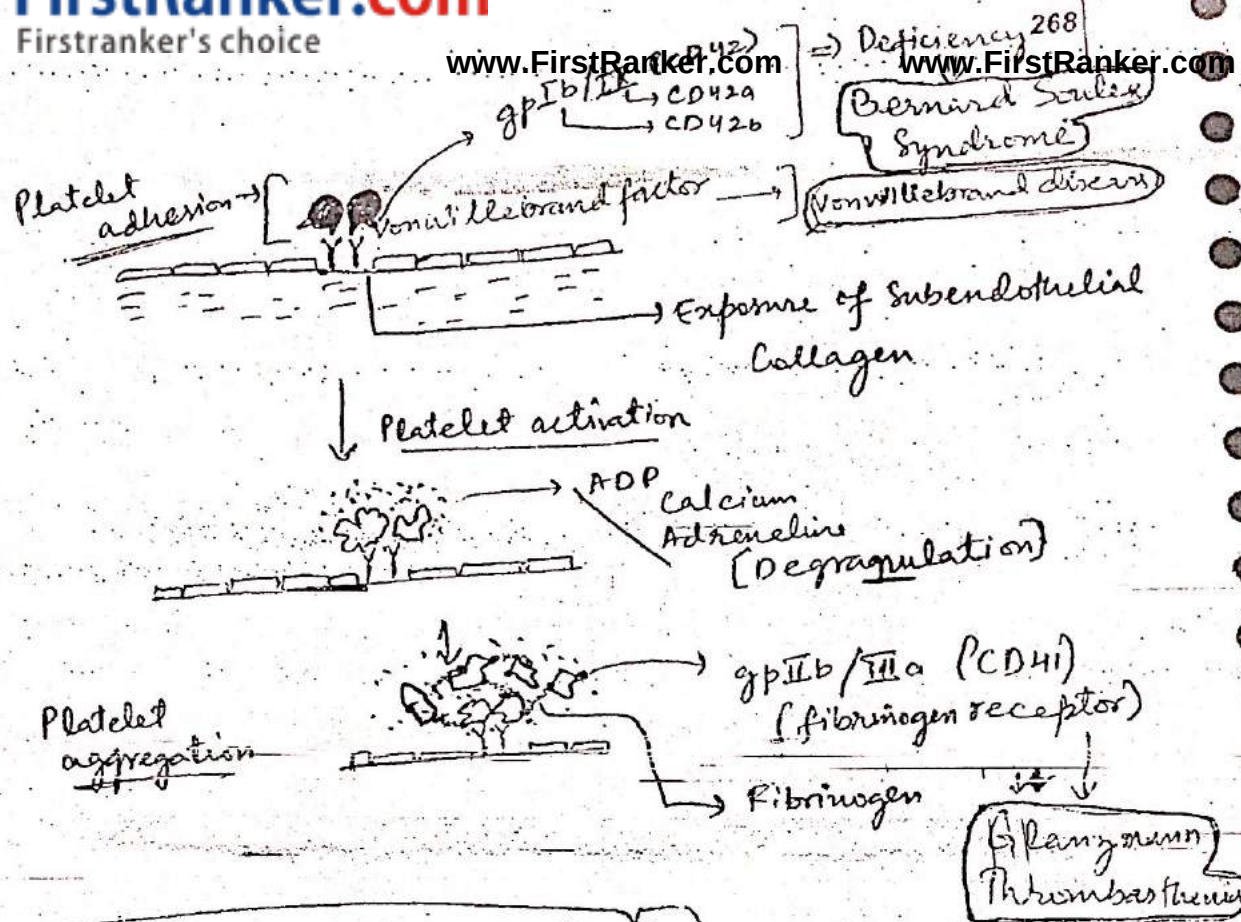
② Thromboxin A₂

Fibrinogen

Coagulation

→ Fibrin

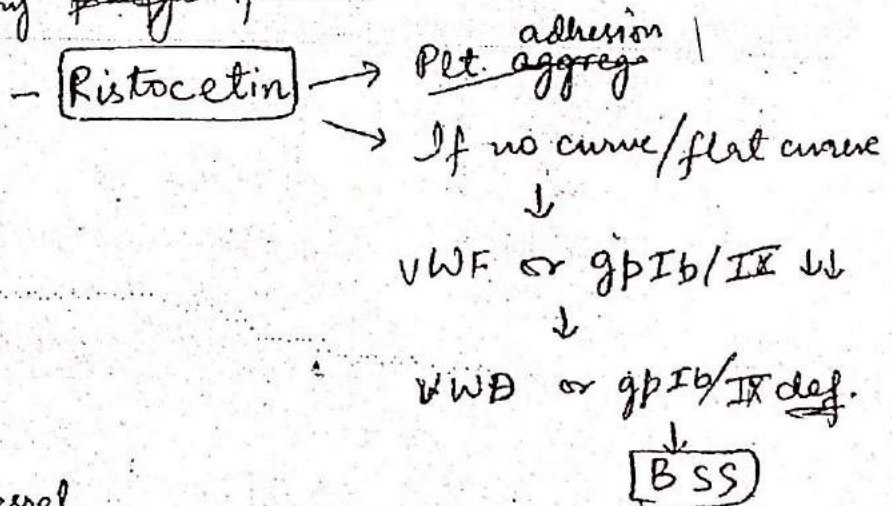
(on the surface of
primary platelet plug)



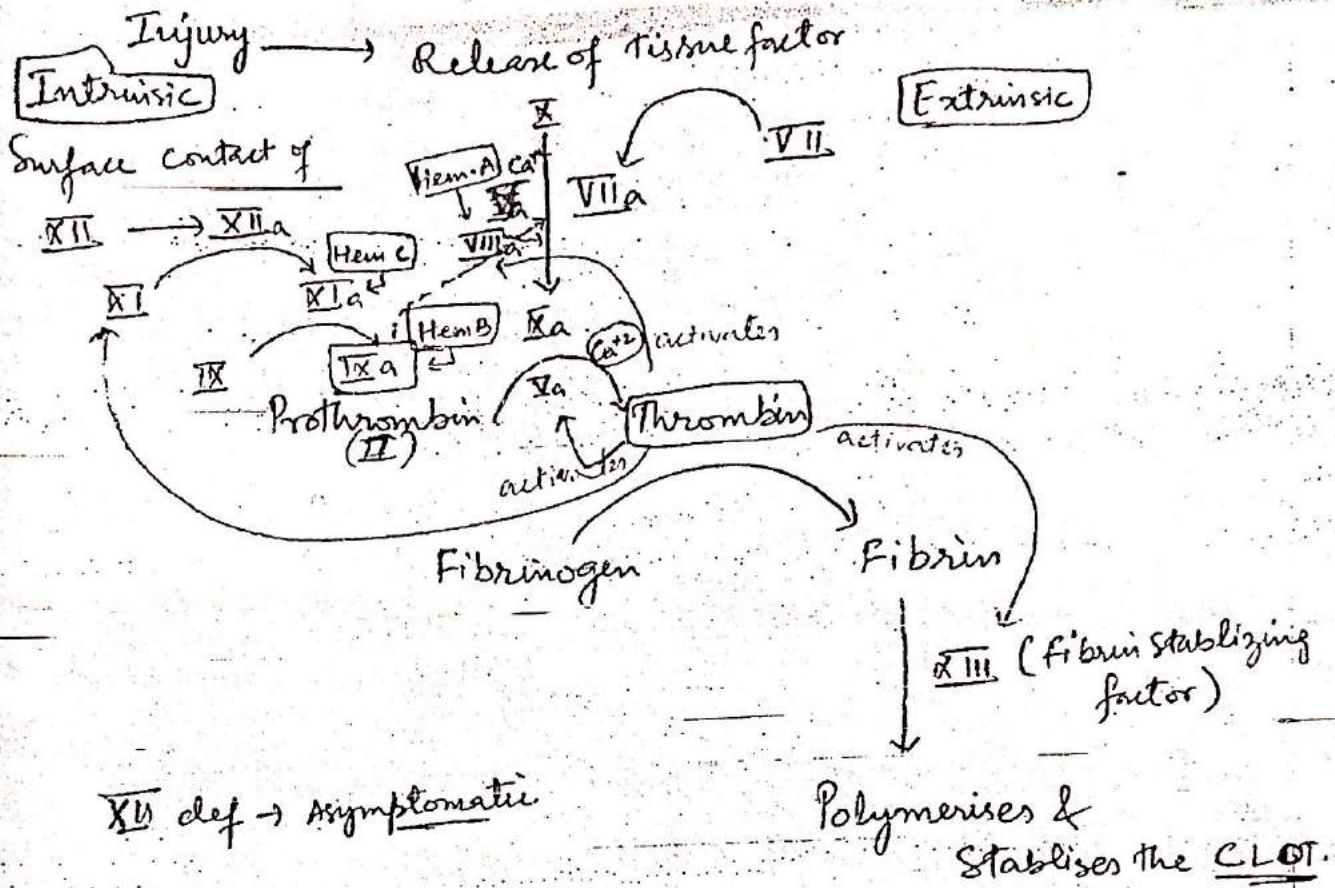
Platelet function Aggregometry (PFA)

Umbilical Stump bleeding

Agonists are given to stimulate Primary ~~platelet~~ Plug formation



Injury to vessel
↓
Release of Tissue factor



Intrinsic pathway
Measured by
APTT (Activated Partial
Thromboplastin Time)
(25-40 sec (N))

Extrinsic Pathway
Measured by PT.
[11-14 sec (N)]
• Factor VII - K dependent factor

Prothrombin time is measured as
Platelet Poor Plasma + Tissue factor
[Thromboplastin]
↓
Phospholipids (Platelets are missing)
↓
Calcium (monitor stopwatch)

APTT

Platelet poor plasma + Surface Activator
(glass, silica, kaolin)
↓
Phospholipids (platelets are missing)
↓
Calcium → (start stopwatch)

Immune Thrombocytopenic Purpura

Auto antibodies against Plt. Ags.

Most common - gp IIb/IIIa

Destruction of plts.
by splenic macrophages
[Toc - Splenectomy]

Children (Acute) - Following Infection

Adults (chronic) - NO H/o Infection

Auto immune disorders.

Marrow → ~~hyp~~ Megakaryocyte hyperplasia
(not required of D_2) ✓
as it is non specific

VWF (von Willebrand Factor)

Produced as large multimers $\xrightarrow{\text{ADAM TS 13 enzyme}}$ broken in small molecules

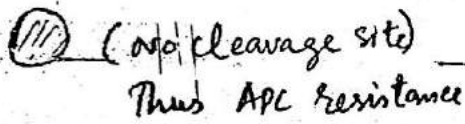
Deficiency of ADAM TS 13 enzyme

↓
Large multimers of VWF will
cause widespread platelet aggr
adhesion followed by aggregation.

↓
Act as carrier for
factor VIIIa

⇓
Thrombotic Thrombocytopenic Purpura

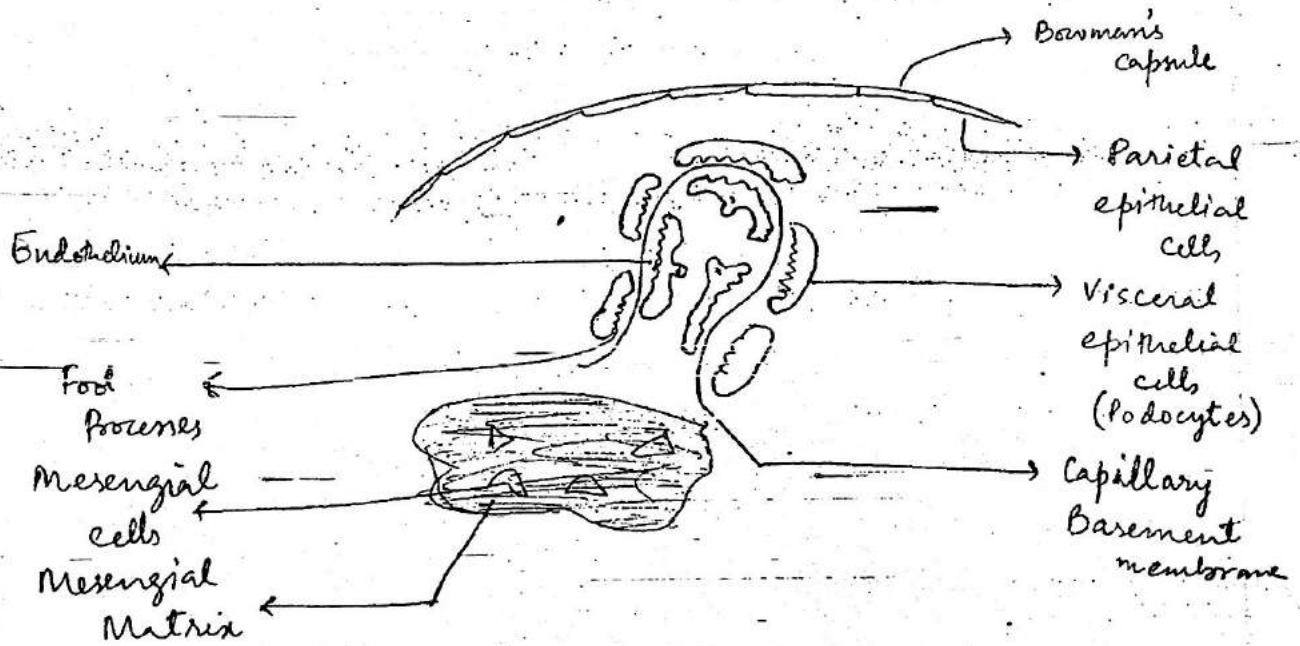
Clearance site:
for APC



Extrinsic

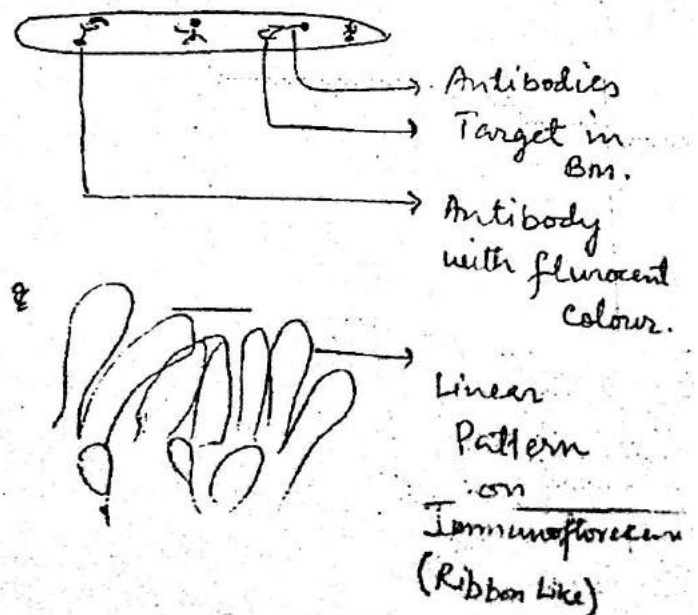
Renal Pathology

Ultrastructure of Glomerulus

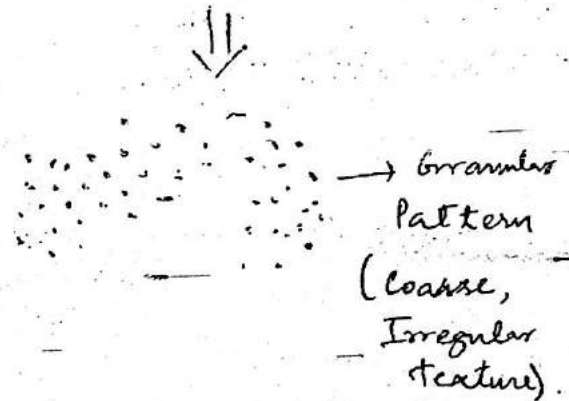
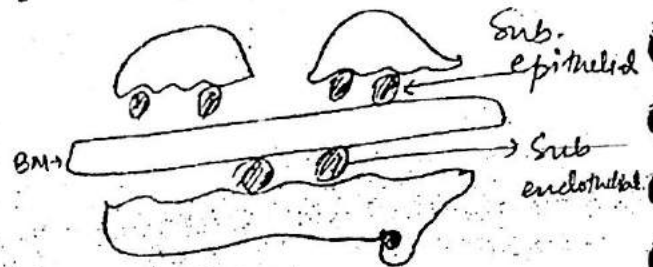
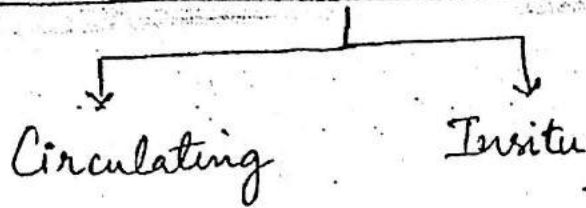


Mechanisms of Glomerular Injury

① Antibodies to components of Basement membrane



2) Immune Complex deposition



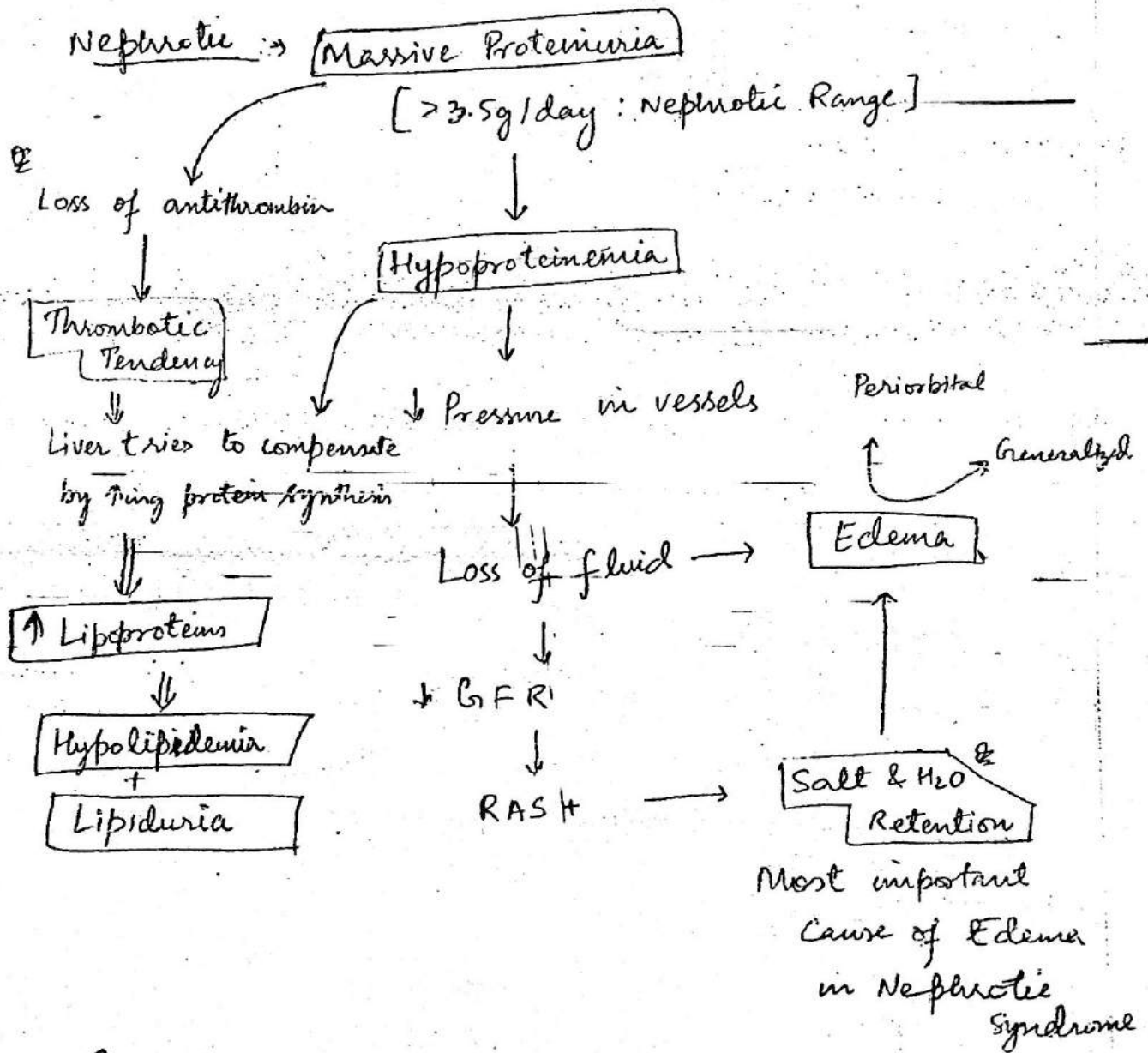
3) ANCA mediated

(Anti Neutrophil cytoplasmic Antibody)

↓
No pattern on immunofluorescence

Clinically

- Hematuria — Damage to glomerular basement membrane (most often due to inflammation)
↓
Nephritic
- Proteinuria — Derangement of capillary wall
+
Podocytes.



Classic
Proteinuria
Lipiduria
Hypolipidemia
Hypo proteinemia

Clinicopathological features

1. Minimal change disease (Nephrotic)
2. Focal segmental glomerulosclerosis (Nephrotic + Nephritic)
3. Membranous Nephropathy (Nephrotic)
4. Membranoproliferative glomerulonephritis (Nephrotic + Nephritic)
5. IgA Nephropathy (Nephritic)
↳ (BERGER'S Disease)
(BUERGER X → Thrombocytopenic Purpura)
6. Post infectious glomerulonephritis (Nephritic)
7. Rapidly progressive glomerulonephritis (RPGN) (Nephritic)

Pathological Assessments

① Light Microscopy

- H & E

- Special stains

- PAS (magenta)
- Jones's Methanamine Silver (Black)

② Immunofluorescence

→ No pattern.
→ Linear
→ Granular
→ Any other

③ Electron microscopy

→ Size of deposition
→ Associated changes

Minimal Change Disease

(NIL LESION or LIPID NEPHROSIS)

? Cytokine mediated podocyte Injury.

↳ Dramatic Response to steroids.

↳ This condition is associated with Hodgkin lymphoma & T-cell lymphomas.

LM ⇒ None

IF ⇒ None

EM ⇒



Effacement/loss of foot processes

Focal Segmental glomerulosclerosis

Only some of the glomeruli are involved

Only a part of glomerulus is involved

Thickening/Hardening

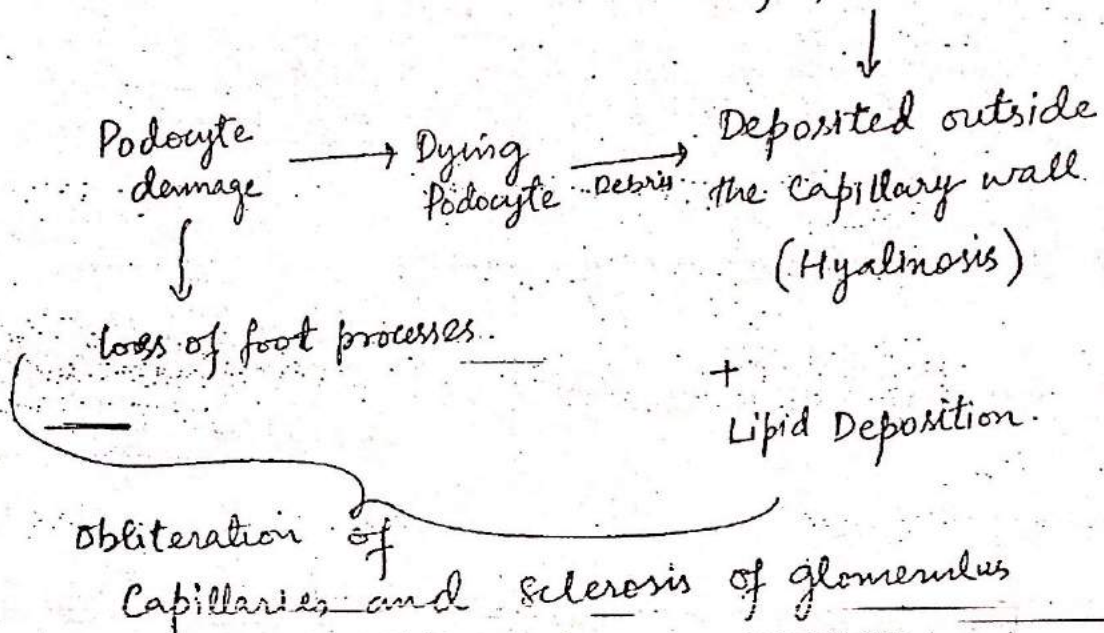
Hyaline deposition

~~Eosinophilic Amorphous~~ Acellular

Homogenous glom.

[Intracellular/Extracellular]

Tiny Tiny damage to BM → Tiny Tiny leakage of plasma proteins



⇒ Idiopathic (Primary)

⇒ Secondary focal segmental glomerulosclerosis

→ Virus: HIV/HepB/Parvovirus

→ Hypersensitivity Nephropathy

⇒ Reflux Nephropathy

cholesterol emboli

⇒ Drugs: Heroin/analgesic/Pamidronate

⇒ Oligomeganephronia

⇒ Renal dysgenesis

⇒ Alport's syndrome

⇒ Sickle cell disease

⇒ Lymphoma

⇒ ~~Radiation nephritis~~

⇒ Familial podocytopathies

Gene Protein

→ NPHS1 mutation/nephrin

→ NPHS2 mutation/

LM:

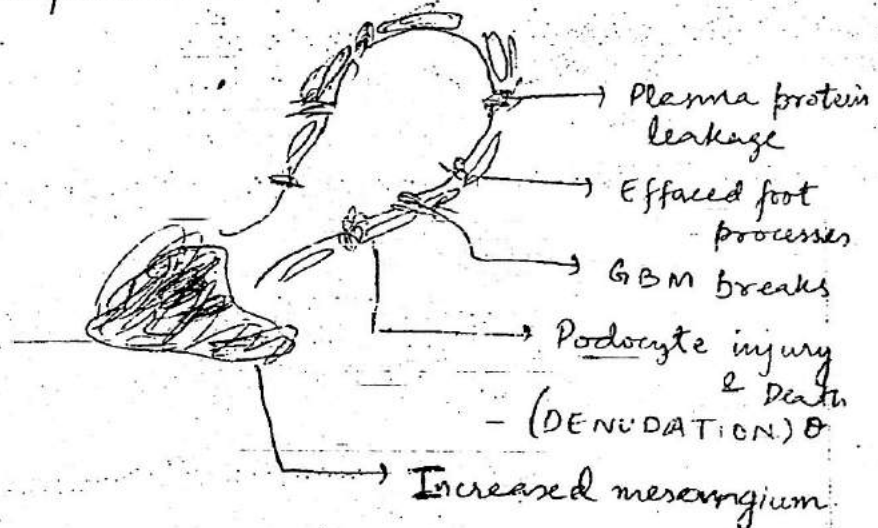
Mesangial widening by sclerosis

↓
obliterate capillaries

↳ hyaline nodules.

IF:

Usually no pattern > Granular.



Membranous Glomerulopathy

Primary

Antibodies against

Phospholipase A₂ Receptors on podocytes

Secondary

① Drugs - Gold
NSAIDs
Penicillamine

② Infections - Hep B
- Hep C
- HIV
- Leprosy, Syphilis

③ Cancers - Lung
- Colon
- Melanoma

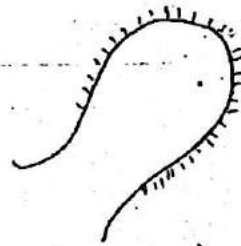
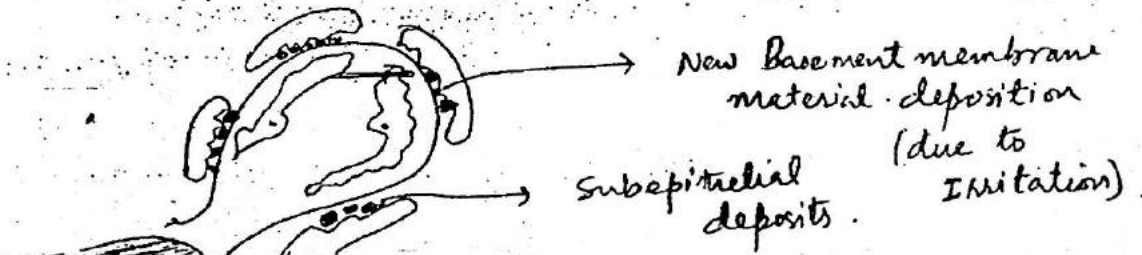
④ Autoimmune
Hashimoto
& SLE



LM :- Thickened basement membrane H & E

IF
Granular IF

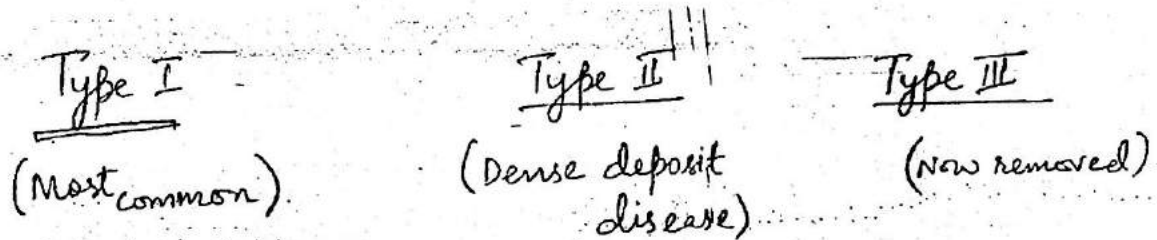
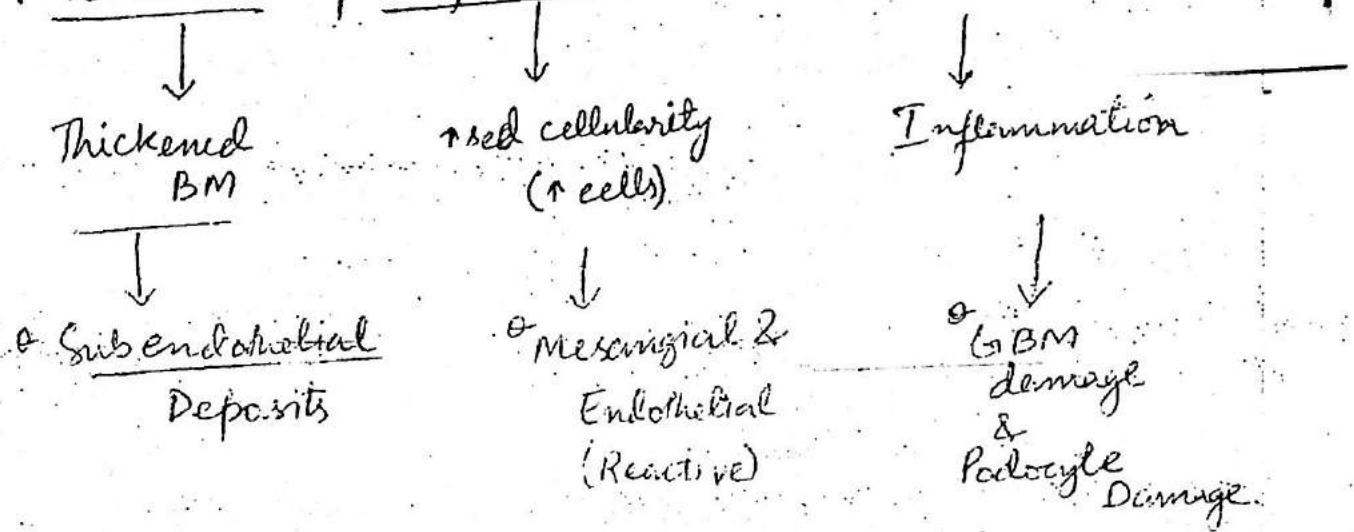
EM



Spike and Dome
Appearance

EM
Silver stain (best viewed)
PAS

Membrano proliferative Glomerulonephritis



Type I

Subacute bacterial endocarditis
Systemic Lupus erythematosus
Hepatitis C ± cryoglobulinemia
Mixed cryoglobulinemia
Hepatitis B
Cancer: Lung, breast & Ovary (germinal)

Type II

C₃ nephritic factor-associated

Type III

Complement Receptor deficiency

LM
Hypercellular glomerulus

- Mesangial cells red (more)
- Endothelial cells red

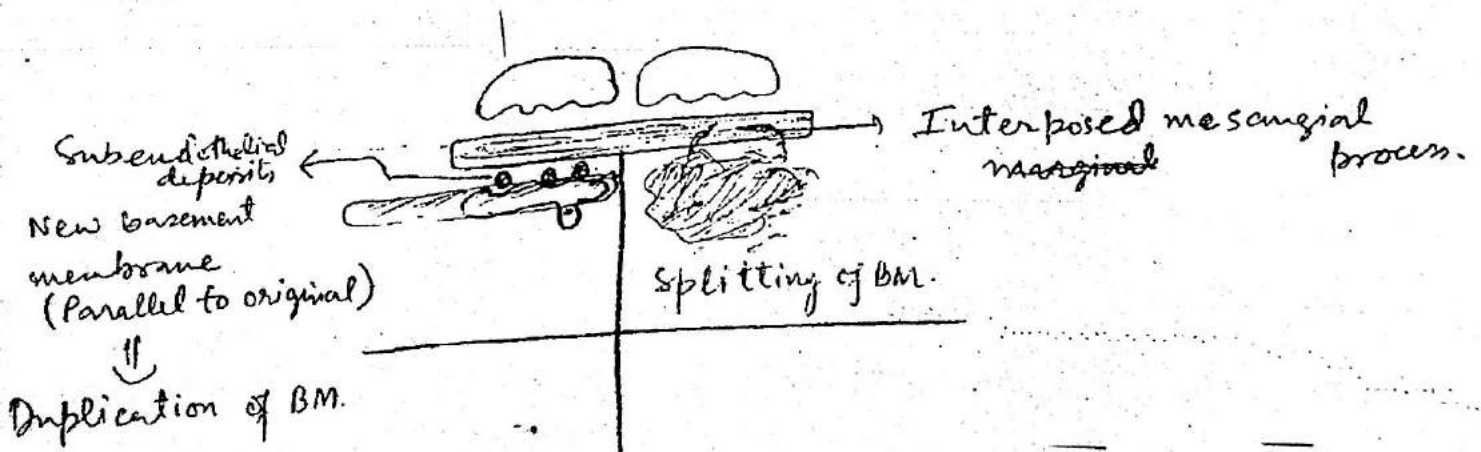
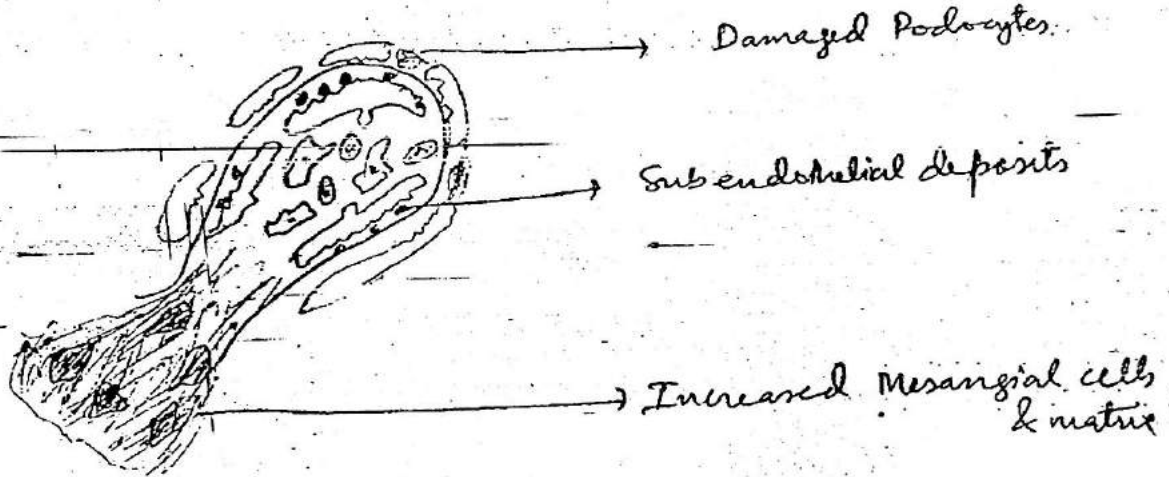
AKA
Mesangial Capillary
glomerulonephritis

Inflammatory cells (+)

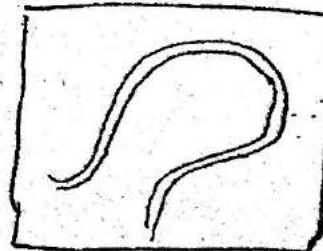
Silver

IF - Granular

EM



⇓
TRAM TRACK APPEARANCE
or
DOUBLE CONTOURING



IgA Nephropathy (BERGER'S Disease)

↑sed IgA: Following Respiratory/GIT infections.
< 1 week

↓sed IgA clearance Liver diseases
 - (↓ed hepatobiliary clearance)

Abnormal IgA: Celiac disease

Also attacks anchoring filaments in hemidesmosomes
 of dermal papillae thus leading to



Dermatitis herpetiformis.

LM

Mesangial widening.
 (even on PAS)

IF

Mesangial pattern.

EM



Mesangial deposits

↑↑ mesangial matrix & cells.

↓
 Mesangio proliferative

(mesangial widening)

POST INFECTIONOUS

After 1-3 wks of
of throat infection
or 3-5 weeks of
skin infection

POST INFECTIONOUS

Streptococcal
Staphylococcal
Viruses
Parasites

or

Acute Proliferative

Onset is quick;
transient
Rarely leads to
chronic renal
failure

Glomerulonephritis

Increase in number
of cells.

Hypercellular glomeruli

Inflammation &
↳ Damages GBM

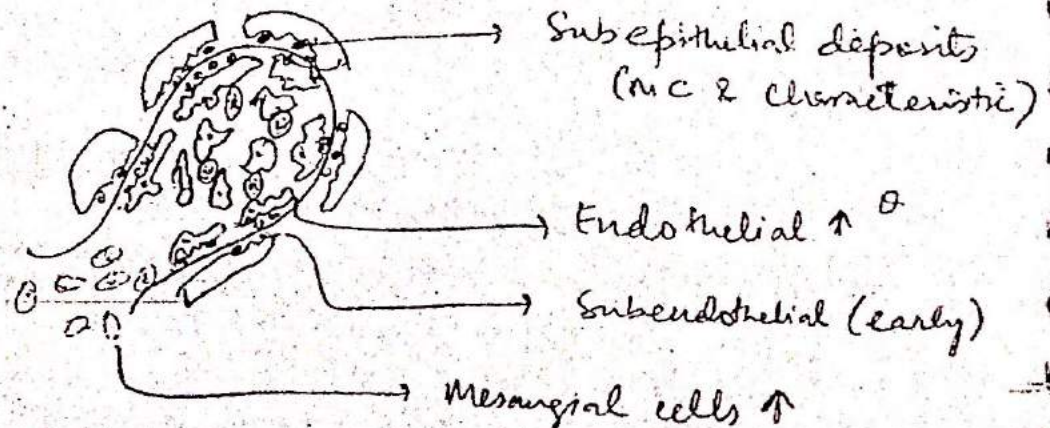
LM:-

Hypercellular glomerulus

increased Endothelial cells — More ↑ (max & seen)
Mesangial cells
Inflammatory cells

IF : Granular

EM
=



Most common cause of Nephrotic Syndrome.

In adults - Focal segmental Glomerulosclerosis

In Children - Minimal change Disease

In Elderly - Membranous nephropathy.

Most common cause of Glomerulonephritis.

Primary GN in world : IgA Nephropathy

Primary GN in India : Post Streptococcal glomerulonephritis

Secondary GN : Diabetes Mellitus.

Most common type of Glomerular Disorder in.

⇒ Leprosy - MPGN

⇒ Syphilis : Membranous Nephropathy.

⇒ Malaria : Mesangioproliferative.

⇒ Hepatitis C : Cryoglobulinemic glomerulonephritis > membranous glomerulopathy > type 1 MPGN.

⇒ Hepatitis B : Membranous Nephropathy (Component of Hep B virus Responsible - HbsAg).

⇒ SLE - Diffuse glomerulonephritis (class IV) - Lupus Nephritis

⇒ Colon cancer / Lung cancer - Membranous glomerulopathy.

Rapidly Progressive Glomerulonephritis

Onset

Has progressed from something.

Type I

Anti GBM antibody

- Renal Limited
- Good Pasture's Syndrome

Type II

Immune Complex mediated

- IgA Nephropathy
- PSGN
- SLE

Type III

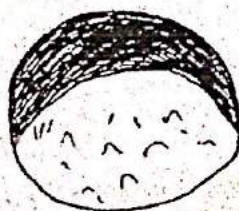
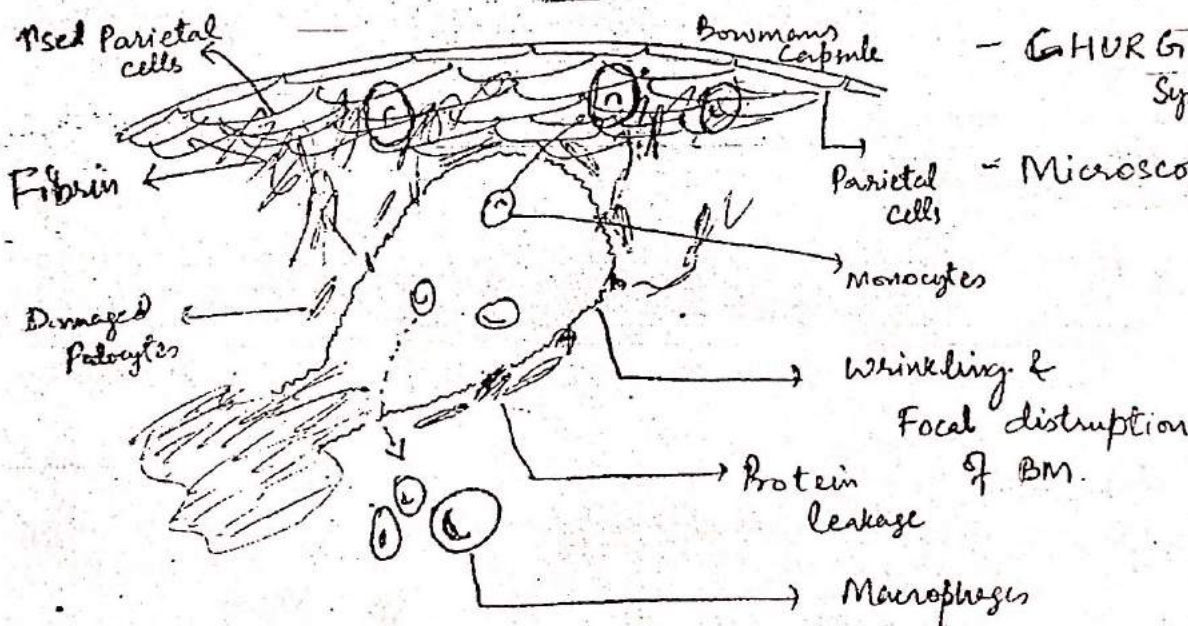
ANCA mediated.

(Pauci Immune)

- Wegener's granulomatosis

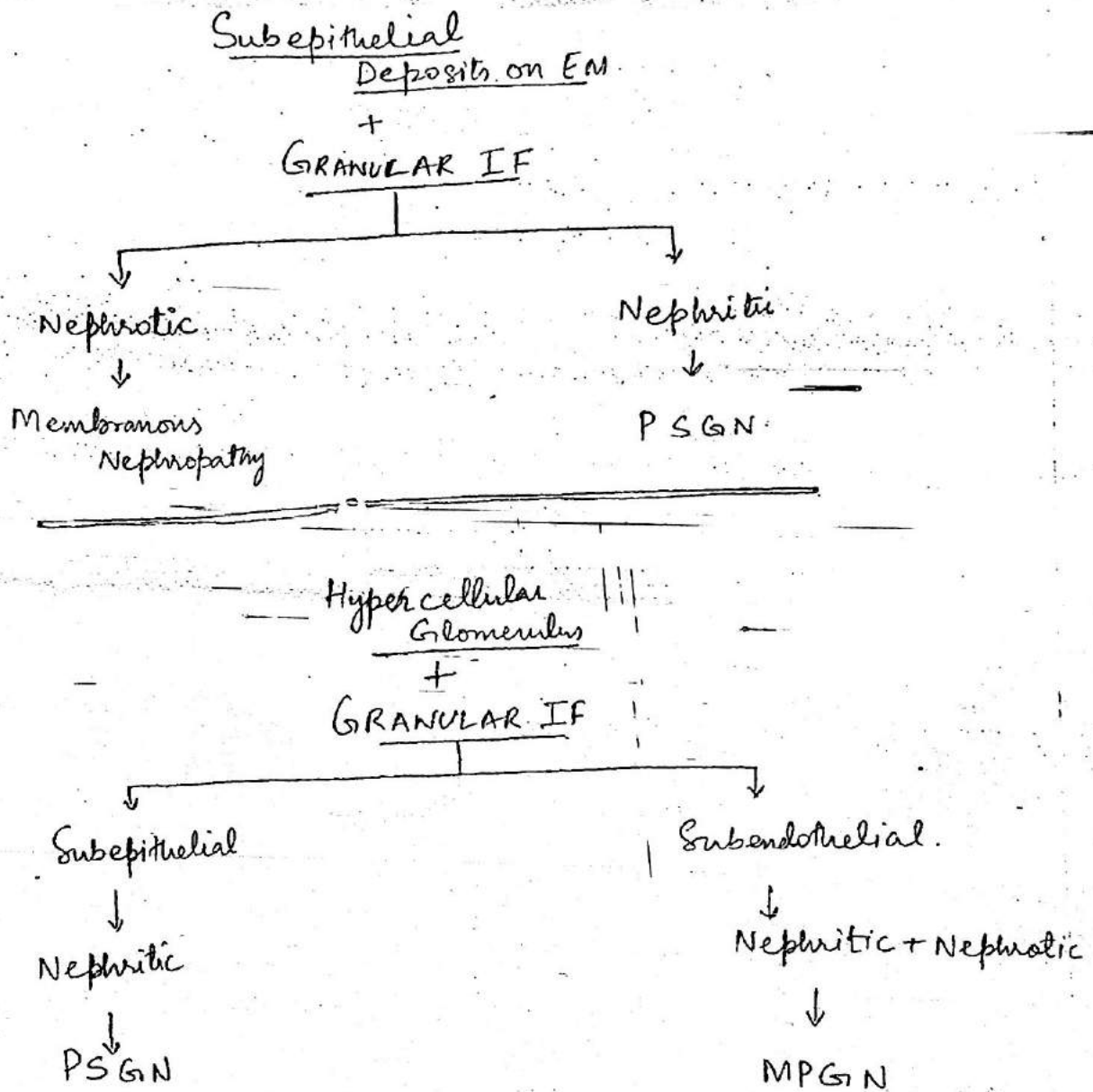
- GARG STRAUSS Syndrome

- Microscopic polyangitis



⇒ CRECENT

⇒ [↑ Parietal cells
Fibrin
Macrophages]



Renal Cell Carcinoma

Clear cell

Papillary

Chromophobe

ORIGIN ← Proximal tubule →

Genetics 3p deletions
→ VHL gene

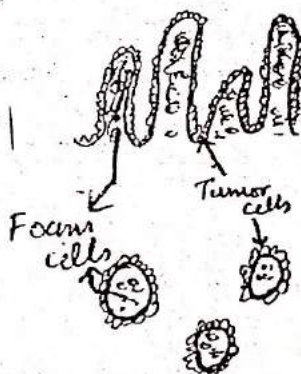
Trisomy 7 12
Loss of 9
Metproto-oncogene

Intercalated cells of CD.

Extreme Hypodiploidy.

Histology

Nest of cells
Fibrous Septate
Pleomorphism with
Clear cytoplasm
(because of glycogen/lipid)



Distinct cell outlines
Nuclear Pleomorphism
Perinuclear halo
Eosinophilic granular cytoplasm

- CK7 +ve
- Her2/neu +ve

Pseudomoma Bodies



- Papillary Ca thyroid
- Prolactinoma
- Serous CAO
- Somatostatinoma
- Meningioma
- Mesothelioma

(Dystrophic Calcification)

- Papillary Ca thyroid
- Serous cystadenocarcinoma ovary
- Meningioma
- Mesothelioma

ARISE FROM THE INFARCT and CALCIFICATION OF PAPILLAE TIPS.

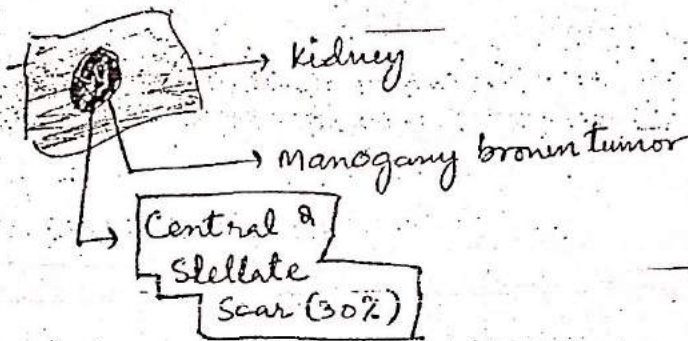
Intercalated cells of collecting duct

↓ gives rise to

Benign Tumor

Oncocytoma

Angiomyolipoma
Phecoma



Phecoma
↓
Central scar

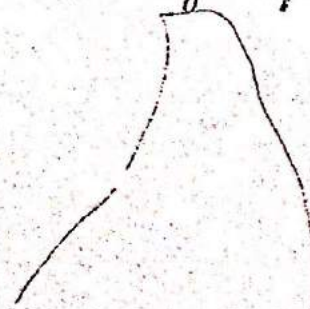
Histology Same as chromophobe except

- No perinuclear halo
- No nuclear pleomorphism

(cells are eosinophilic & granular because of increased number of mitochondria)

Renal cell Carcinoma

- Most common subtype: clear cell carcinoma
- Most common subtype in sickle cell anemia: Medullary Ca
- Most favourable prognosis: Chromophobe
- Least favourable prognosis: Sarcomatoid > Medullary > Collecting duct > Clear cell



BREAST PATHOLOGY

www.FirstRanker.com

www.FirstRanker.com

- Epithelial hyperplasia
- Atypical hyperplasia
- In situ carcinoma
- Invasive Carcinoma
- Adenosis
- Small duct papilla

Paget's disease of nipple

Nipple areola
larger duct

Duct ectasia
Duct papilloma

Terminal ductal lobular unit

Pectoralis

Intra lobular stroma

Fibroadenoma
Phyllodes Tumor



Duct ectasia
(Dilation)

greenish nipple discharge



Superficial erosion

Bloody nipple discharge

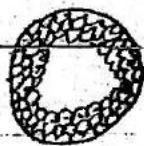
Duct papilloma

(Benign papillary tumor of lining Epithelium)



Myoepithelial cells (Basal cells)

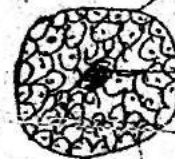
Epithelial cells (Luminal cells)



Epithelial hyperplasia
(No pleomorphism of nuclei)



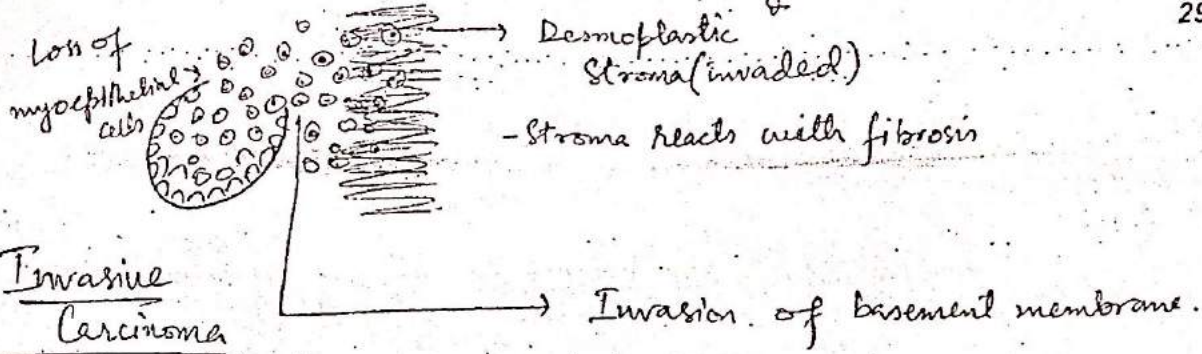
Atypical ductal Hyperplasia



Myoepithelial cell

Central necrosis (comedo type)

Ductal carcinoma in situ (DCIS)



Benign epithelial Lesions

Non Proliferative^o
(No relative Risk)

- Duct ectasia
- Fibrocytic change
- Apocrine Metaplasia

Proliferative^o

Without Atypia
(Slight Risk)

Duct Papilloma
Epithelial Hyperplasia
Sclerosing Adenosis

With Atypia
(Moderate Risk)

Atypical ductal hyperplasia
Atypical lobular hyperplasia

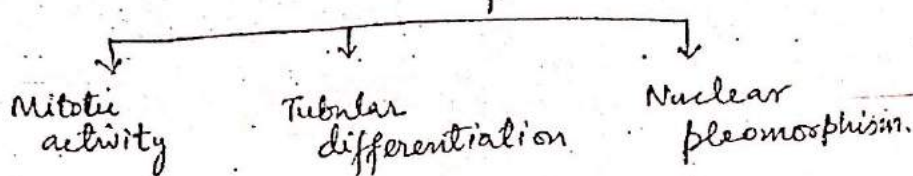
High Risk

- DCIS
- LCIS

Histological Subtypes of Invasive Carcinoma

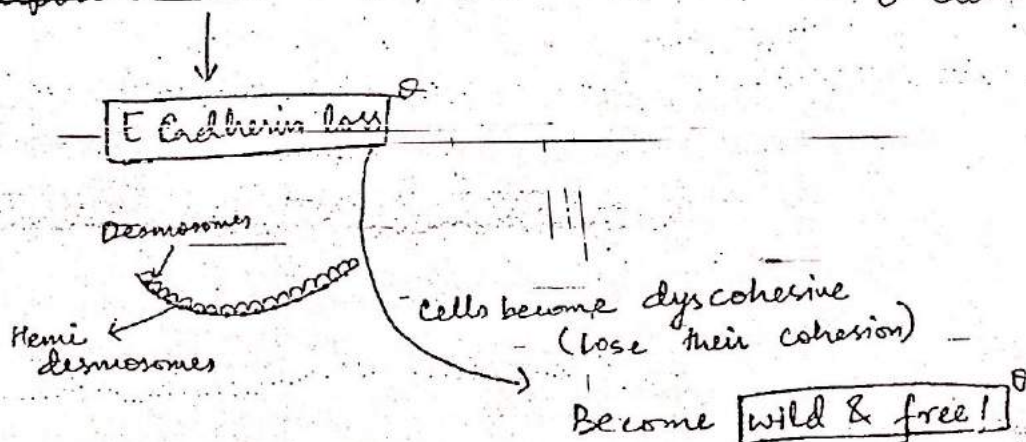
- Invasive Ductal Carcinoma, Not otherwise specified (IDC, NOS)
Most common histological subtype
~~Poorly circumscribed, Irregular~~

- Grading based on NOTTINGHAM CRITERIA



② Invasive Lobular Carcinoma (ILC)

CDH1 gene mutation (loss of function for making protein E-Cadherin)



⇒ Fail to elicit a desmoplastic response
[difficult to detect as a well defined mass on imaging][⊕]

Single File / Indian File Pattern

⇒ Involve contralateral side commonly.

Metastasis to - Leptomeninges (arach. + pia)
- Peritoneum
- Ovaries

③. Medullary Carcinoma

Sheets of tumor cells interspersed with lymphocytes.

↓
Poorly differentiated tumor

↓
Improves
treatment
response

Usually associated with

BRCA 1 gene mutation.

- Triple Negative

(ER-, PR-, Her2 Neu-)

↓
Thus better prognosis
as compared to
other poorly
differentiated
tumors.

④. Tubular Carcinoma

Best prognosis

⑤. Inflammatory Carcinoma

± Dermal lymphatics

are involved by tumor cells

↓
Peau d'orange
appearance.

Tumor genetics

Sporadic
(more common)²

most common: **PS3**

Familial

BRCA1
(most common)²
↓
Ovarian Cancer

Triple Negative
(ER-, PR-, Her2^{-ve})

- Male breast Cancer
- Pancreatic Cancer
- Prostate Cancer

ER+ (Her2^{-ve})
- ~~Her2⁺~~
- ~~Her2⁺~~

PS3

Li Fraumeni Syndrome

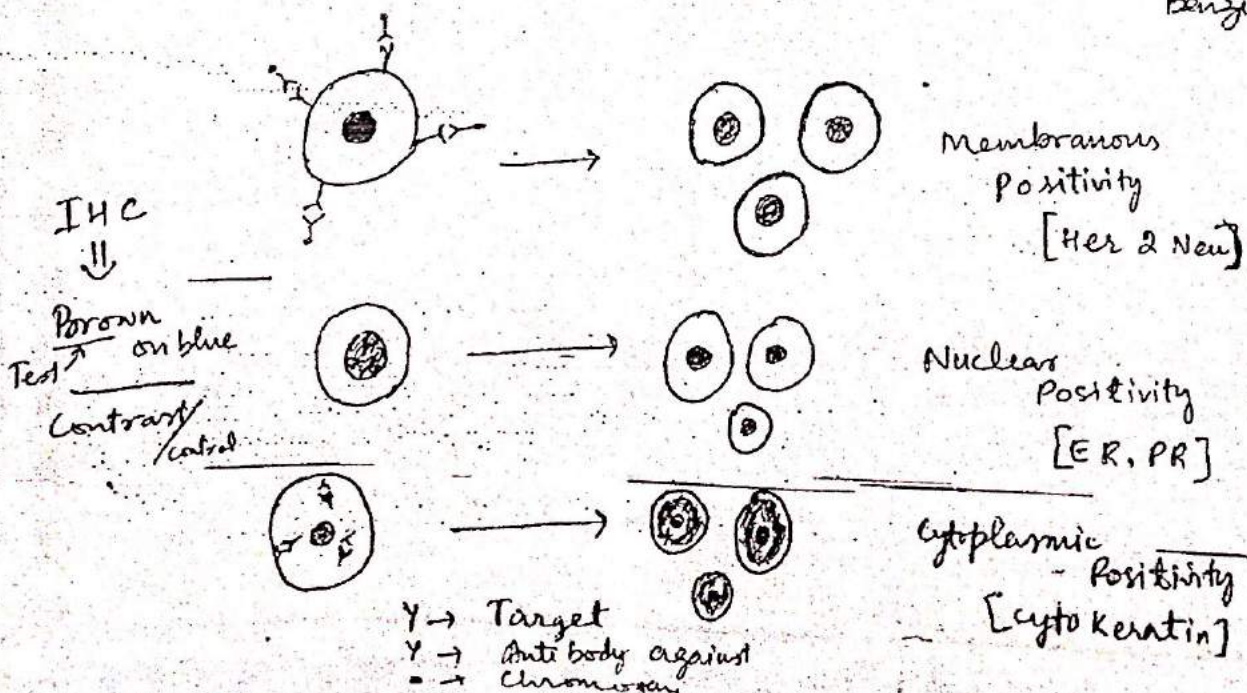
Her2⁺ Neu⁺
- ER+
- ER-

IHC

Chromogen: Di Amino Benzidine (DAB)

BROWN

di amino
Benzidine



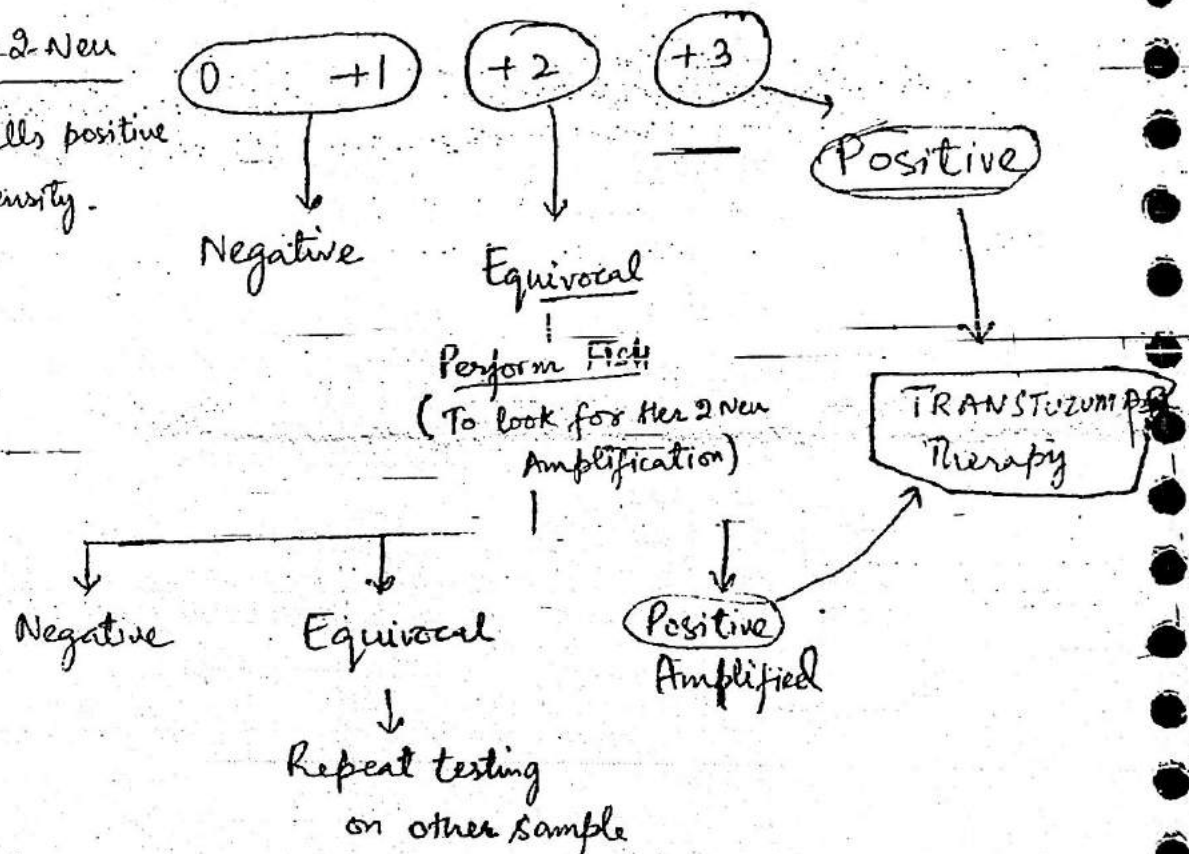
IHC in Breast Cancer

① ER/PR: Allred Score = [0-8]

Intensity + % of positive cells

② Her-2-Neu

% of cells positive
& intensity.



Breast Carcinoma

Most common histological subtype - IDC, NOS

Most common molecular subtype - Luminal A

Histological subtype with best prognosis - Tubular > Mucinous

Molecular subtype with best prognosis - Luminal A

Most common genetic mutation - p53

Most common familial genetic mutation - BRCA1

Highest susceptibility seen with which mutation - BRCA1

Association of male breast cancer, prostate cancer, pancreatic melanoma and gastric cancer - BRCA2

Association of ovarian cancer (serous) - BRCA1 > BRCA2

Most common molecular group associated with BRCA1 - BA1

Most common molecular group associated with BRCA2 - Luminal

Most important prognostic marker - Lymph node status

Most important marker (prognostic) for metastatic Cancers - ER/PR status

Least desmoplastic tumor - Lobular Carcinoma