CELL INJURY, CELLULAR ADAPTATION

Cellular Adaptation – Cells are neither (N), nor injured.

Types – 1) Atrophy → No. and size of cells are both reduced.

2) Hypertrophy – No. → same, size – ↑es

3) Hyperplasia → No. ↑ed, size → same

4) Metaplasia – One type of adult cell is replaced by another type of adult cell.

– Mechanism – Stem cell reprogramming.

→ M/c metaplasia → columnar to squamous (Smoker's resp. tract)

• Barrett's esophagus – squamous to columnar.

Mucin producing goblet cell (Greyish in colour)

Hallmark of Barrett's esophagus – Intestinal metaplas

Risk of – Adenoca. of esophagus.

– Vit A def. → is assoc with respiratory metaplasia from columnar to squamous.

Also seen in vit A. toxicity.

* Both hypertrophy and hyperplasia is seen in →

Pregnant uterus → Mainly hypertrophy, minor hyperplasia

Breast tissue

– Pregnant, – Pubertal → Both hyperplasia and hypertrophy

– Lactating → only hypertrophy, No hyperplasia.

DATE

* Endometrial adenocarcinoma – Type I – Hyperplasia
Type II – Atrophy

* Atrophy → premalignant condition
↳ Hyperplasia
↳ Metaplasia
↳ Regeneration (liver cirrhosis)
↳ Chronic inflammation (Ulcerative colitis, Crohn's)

* Hypertrophy – Not premalignant.
Pseudo-polyp →

CELL INJURY

DATE

Reversible ← Cell-Membrane → Irreversible

Intact ← Cell-Membrane → Damaged

Mitochondria

↓

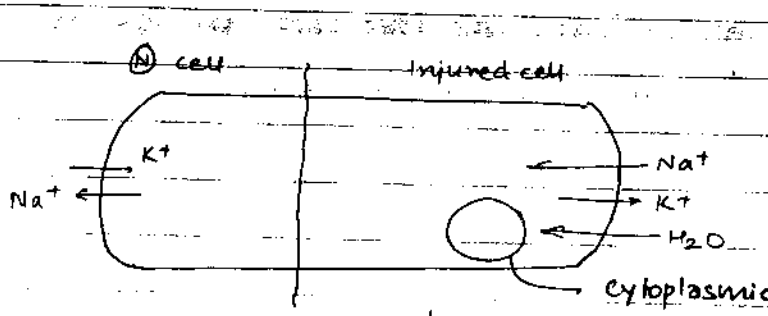
Most critical organelle for cell-injury

Reversible injury

↓ O_2 (Ischemia) → ↓ed oxidative-phosphorylation → ↓ed ATP production

(When ATP production is fed to 10% of normal, cell injury starts)

- Most susceptible tissue to ischemic damage → Neurons (3-4 mins-sur-time)
- Cardiac tissue - (30 mins)
- fibroblasts are most resistant to hypoxic/ischemic damage.



∴ Also k/a Hydropic degeneration)

Cell swells up - 1st sign of cell injury (Cloudy Swelling)

In Acute Tubular Necrosis

except for - Apoptosis

(In apoptosis - cell shrinkage)

* Ballooning degeneration of hepatocytes - is an example of cell swelling → seen in Acute hepatitis

DATE

- Mitochondrial swelling

+

Small Amorphous densities in mitochondria

- Endoplasmic reticulum swelling

+

Ribosomal detachment

* Most important ion for cell injury - Calcium

Initiator of cell injury - Na^+

Mildly elevated (Reversible)	severely elevated (Irreversible)
↓	↓
Activate phospholipase enzyme	Activates 3 enzymes • Phospholipase • Protease • Endonuclease
↓	
cell membrane damage	
↓	
Accumulation of phospholipids and calcium	
↓	
 - concentric lamellated coiled like structure (Myelin figure)	
↓	
Starts in reversible Max. in irreversible • can be visualised by electron microscopy	

DATE

- Phospholipase
  - Max. myelin figures
  - Large floculant amorphous densities in mitochondria
- protease
  - ↓
  - Damage cytoskeletal protein
  - ↓
  - cell architecture is lost
- Endonuclease.

Pyknosis
↓
Karyorrhexis
↓
Karyolysis

Irreversible damage - Pyknosis

* Pyknosis - Clumping of nuclear chromatin
* Karryorrhexis - Nuclear fragmentation
* Karyolysis → Chromatin lysis - led basophilia of nucleus.

* Pyknosis - occurs both in reversible, irreversible injury
  but, pyknosis + nuclear shrinkage - irreversible damage

* After cell death there are 4 changes.
  - Necrosis
  - Apoptosis
  - Necro-ptosis → Variant of necrosis
  - Pyro-ptosis → Neither apoptosis, nor necrosis
    ↳ Morphologically resemble necrosis

DATE

Reversible v/s Irreversible

[Sparsh Gupta]

Reversible	Irreversible.
• Cellular swelling	• Large flocculent, Amorphous density in mitochondria
• Loss of microvilli	• Swelling, disruption of lysosomes
• formation of cytoplasmic blebs	• Red basophilia
• ER swelling	• Severe damage to plasma memb.
• Detachment of Ribosomes	• Nuclear changes
• Myelin figures	↳ Pyknosis
• Clumping of nuclear chromatin	↳ Karyorrhexis
	↳ Karyolysis.

Coagulative Necrosis

CELL DEATH

Necrosis →

Denaturation of protein	Enzymatic
↓	↓
Tissue architecture (N)/intact	Tissue architecture lost
↓	↓
Coagulative Necrosis (most common)	liquifactive Necrosis
M/C organ → Heart	↓
→ Liver	Brain
→ Kidney	↳ • No stromal support
→ Spleen	• Brain tissue - rich in liquifacti enzymes.

Glial cells for repair

Coagulative Necrosis

TB → Coagulative Necrosis → liquifactive Necrosis → Caseous necrosis (variant of coagulative necrosis)

Accumulation of phospholipid

Gangrene → Dry gangrene → Coagulative necr

Wet gangrene - liquifaction necrosis.

* Zenker's degeneration necrosis - prototype of coagulative necrosis
  ↳ only coagulative necrosis.

* Mitochondria

Lysosomal permeability ↑ed

↓

Enzymes ↑ed

↓

cell membrane - damaged

↓

Inflammation

* Necrosis is pathological only.

Caseous Necrosis - Granulomatous conditions - TB

Histoplasmosis

Coccidioidomycosis

Syphilis

↓

Not in → crav

Wegner's Granulomatosis

leprosy

-fat necrosis - Common in breast

Apoptosis →

- Active process (Energy-dependent process) — ①
- Programmed cell death — ②

· Both physiological and pathological
physiological → more common.

* Anoikis → Apoptosis d/t loss of adhesion molecule

Physiological apoptosis

* Neovascularization.
* Organogenesis
* Morphogenesis
* ⊕ prevents auto-immunity

Pathological apoptosis

· Chemotherapy
· Radio therapy

· Severe stimulus - Apoptosis + Necrosis
mild stimuli → only apoptosis
· Glucocorticoids - induces apoptosis.

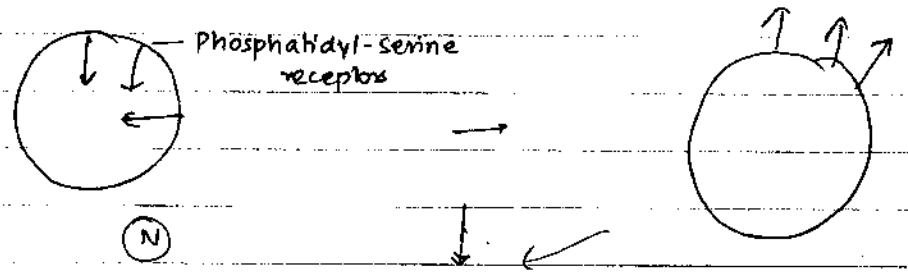
- e.g. - ∘ Salivary Gland destruction after obstruction
∘ Graft versus host dis.
∘ Tumor cell death
∘ Viral Hepatitis (Councilman bodies)

Morphology

- Cell shrink
- Most characeteristic feature → chromatin condensation
- Cell membrane intact

↓

- No inflammation → Receptor mediated phagocytosis.



Apoptosis.

Detected by "Annexin V" → Marker of Apoptosis.

↓

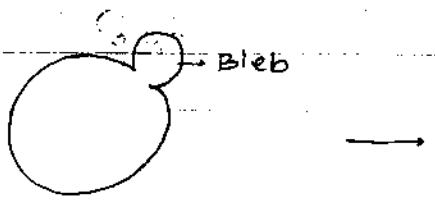
Acts on Lipid receptor

↓

Stained for Lipid

fat stain

* frozen section → Oil-Red O



Bleb → Apoptosis Body → • Cell memb. bound structure + • Tightly arranged organelles +/- Nuclear fragment

R +

Scavenger-Receptor

(Macrophages) ↓

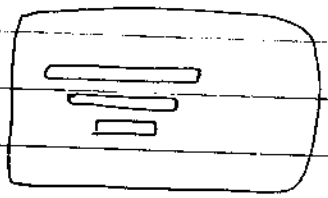
phagocytosis (end stage)

- Mechanism of Apoptosis →

pro-Caspase
↓
Caspase → Hallmark of Apoptosis
↓
Endonuclease → Removes Regular segments
↓
Chromatin condensation

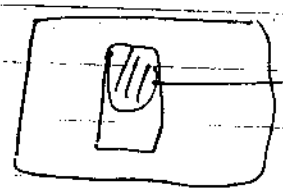
Inter-nucleosomal DNA damage.
↓
Can be seen on Agarose-gel electrophoresis

Agar Rose gel



Step ladder pattern
↓
Also seen in necrosis,
But mainly present in Apoptosis

* 180-200 base pair nuclear fragments



Diffused smearing pattern
↓
Seen in necrosis

Initiation → a) Intrinsic pathway → caspase-9
b) Extrinsic pathway → C-8
↓ Eight
C-10 (Human beings)

⊕ ↓

Execution
↳ C-3, 6, 7
M/I → C-3

⊕ ↓

End

Chromatin condensation

DATE

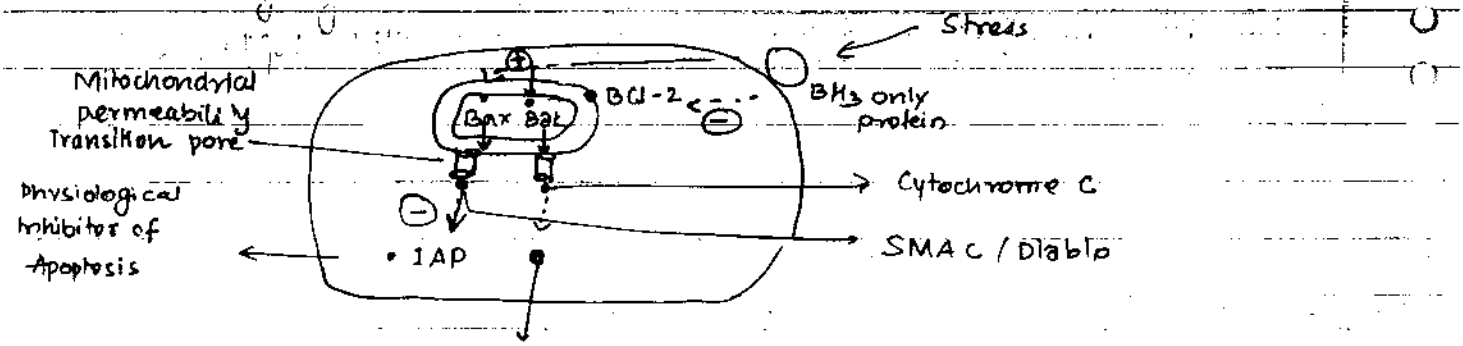
• Proto-oncogenes are both apoptotic → BCl-X_S - stimulate
BaX
BaK
and Anti-apoptotic
↓
BCl-2
BCl-X_L - lowers
MCl-1 - (over expressed in drug resistance)

BH_3 ~~protein~~ only protein → stress sensors of cell
↓
Pro-~~apoptotic~~ apoptotic.

Bim	PUMA
Bad	Nox-a
Bid	

(Bimla bad @ bidding)

Intrinsic pathway / Mitochondrial pathway (Major pathway)
Most commonly disabled pathway in tumorogenesis



Cytoplasmic Cyt. c. + Apaf-1 (Apoptosis Activating factor-1)

Apoptosome
↓
Activate pro-Caspase-9
↓
Caspase-9

Extrinsic Pathway / Death Receptor Mediated

↓

TNF-R-1

CD-95 (FAS)

Death Receptor ← D_R + Diligand

↓

Dimerisation of D_R and Ligand.

↓ ⊕ Adapter-protein

↓

pro-C-8 → C8

Extrinsic – CD-95 + FAS-Ligand

★ Intrinsic and extrinsic pathway can occur independently also.

$C_{8,9}$

↓⊕

Executioner

$C_{3,6,7}$

↓

Endonuclease

↓

Chromatin condensation

• Hallmark of neuronal apoptosis activation.

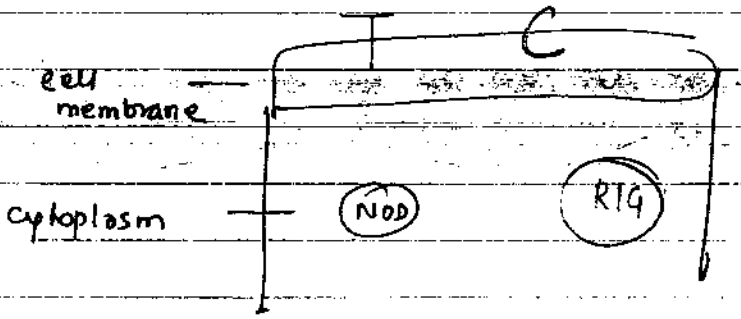
- Neurons do not have caspase
- Instead of caspase, they have Apoptosis Inducing factor (AIF)

DATE

Programmed cell death

Caspase (+)	Caspase (−)
↓	↓
Pyroptosis	Necroptosis.
→ Caspase - I, II	→ variant of necrosis
→ Inflammation (+)	→ Both physiological, pathological
→ lysozymes released	→ Physiological fn → Bone growth plate formation
→ lysosomes permeable	
→ Pyro → IL-1 involved.	

Pattern Recognition Receptors (Innate Immunity)



T - Toll like Receptor (TLR) → Best defined pattern recognition receptor

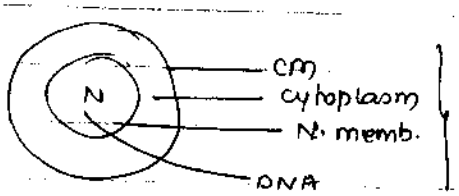
C - C-type Lectin Receptor (CLR) - fungus.

NOD - NOD-like receptor (NLR) → pyroptosis → Salmonella, toxic ~~substance~~ metabolites. (Gout-prevents)

RIG - RIG-like receptor (RLR) - virus.

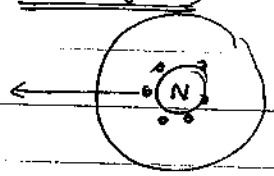
Free Radicles – oxidants / Reactive oxygen species

– Chemical species with unpaired electron in outer orbit



* M/C reason for ageing – free radical injury

(N) Ageing



↓

Lipofuschin – Tell-tale sign of free radical injury.

→ Also seen in Brown-atrophy of myocardium.

→ Also seen in brown color of carcinoid specimen.

– Lipofuschin seen in.

- Ageing
- Malnutrition
- Cancer cachexia
- free radicle injury.

Brown pigments in body

Lipofuscin

↓

Oil. Red O

Sudan IV / Black

Annexure V

Hemosiderin

– +ve for Pearl's prussian blue stain

DATE

Anti-oxidants

Vit → A/C/E

Enzyme - Catalase

Glutathione → Most potent Anti-oxidant } peroxisomal enzymes.

Superoxide dismutase (SOD)

↳ prevents brain from free radicle injury → SOD-1 → Mutation → ALS

* Vit A → not an anti-oxidant in vitreous of eye.

Peroxisome - can cause both production and degradation of H_2O_2

* Ageing - Cross-linking of collagen theory.

↓

When cross-linking ↑es, Ageing is more.

* Calories restriction - M/I to prolong life-span

↓ ← (+) Red wine

induces → SIRTUIN (NAD-DE-Acetylase family)

↓ PTH receptor protein

↓ free radical injury

↓ Apoptosis

↑ glucose metabolism

↑ Insulin sensitivity.

Telomers - Short stretches of DNA

↓

Prevent fusion and degradation of chromosome

↓

with every cell division - shortened

↓

When telomers are shortening occurs

↓

Telomerase

↓ Added

Telomer length ↑es

↓

Carcinogenesis

* Newborn Somatic cells are destined for - 60-70 times of division

↓

Hay flick limit / phenomenon

* Telomerase → DNA polymerase.

↳ seen in 1) Germ cells - max activity

2) Stem cells.

If telomerase ⊕ in somatic cells - carcinogeneosis.

* Cancer is more common in older age - because of ↑ed telomerase expression

Stress

↓

telomerase expression in ⊕ 90% of cancers.

10, 11, 15, 16, 19, 23, 24

DATE

Examples of Apoptosis

① Growth factor deprivation

② DNA damage → DNA damage d/t Radiation, chemotherapeutic agents

occurs via p53 protein

↓

Cell cycle arrests in G1 phase and repair may occur

but if the damage is too great

↓

Apoptosis via Bax, Bak

If p53 -absent → Apoptosis doesn't occur → Cancer

③ Accumulation of misfolded proteins.

May be caused by mutations, ageing,

Seen in — Alzeihmer's, Huntington, Parkinson.

Calcification

- Alkaline environment is required.
- Mitochondria - start of calcification

except in kidney - where it starts in Basement Membrane

2 types

1) Ca^{2+} (N), Tissue ab(N) → Dystrophic calcification - calcificatn in dead tissu
e.g. TB Lymph Node (Granulomatous inflammation
Psammoma bodies → Papillary ca. thyroid
Meningioma
Monkeberg medial calcific sclerosis
(Non-obstructive lesions)
Atheroma

2) Tissue - (N), Ca^{2+} → ↑ed → Metastatic calcification

1) M/C/C - 1° - Hyper - PTH
↓
M/C - ~~Renal cell ca~~ parathyroid adenoma

* M/C/C of hypercalcemic crisis → Ca. Breast
[PTHrP]
PTH - receptor protein

In lungs,
Hypercalcemia - m/c - squamous cell ca. lung
Also seen in small cell ca.

II) Renal failure
III) ↑ed Vit D. — In Sarcoidosis
↓
m/c reason for hypercalcemia in sarcoidosis - d/t production of vit D_3

- Vit A toxicity - causes metastatic calcification.
↓ (+)
Retinoic Acid
↓ (+)

DATE

Sites for metastatic calcification →

- lung (Alveoli) → most common site.
- Pulm. vessels
- Gastric mucosa
- Kidney

- Not seen in - Parathyroid

Special stains for Calcium →

- Von-Kossa Stain
- Alizarin Red
- Calcein
- Tetracycline labelling Index → Best method to detect Bone mineralisation.

Werner Syndrome ⟶ Premature ageing

Wer/MEr

MEN-I

↓

D/t defective DNA – Helicase.

* Triphenyl tetrazolium chloride (TTZC) – Enzyme substrate that colors viable myocardium magenta

Dead myocardium – doesn't stain.

Induces – SIRTUIN (NAD-De-Acetylase family)

↓

INTRACELLULAR ACCUMULATIONS

DATE

Main pathways for accumulation

- Substance produced @ high rate, or metabolised @ low rate
  E.g. fatty change in liver
- Defect in folding, packaging, transport of substances.
  E.g. α_1-Antitrypsin deficiency.
- Inherited defect in an enzyme may result in failure to degrade a metabolite. Disorders are called storage disorders.
- ABN exogenous substance is deposited and accumulates.
  E.g. → Carbon.

Fatty changes (steatosis)

M/C/C → fatty change → Alcohol abuse.
Diabetes assoc. with obesity

Cholesterol →

- Atherosclerosis
- foam cells
- Xanthomas - cluster of foamy macrophages.

Proteins →

Mallory body → ALD, HCC, Wilson's dis., Indian Childhood Cirrhosis, Biliary cirrhosis.
Neurofibrillary tangles - Alzeihmer's
Russell bodies - plasma cells. (Immunoglobulins accumulate)

Glycogen → Glycogen storage diseases.

★ Crooke's Hyaline body - Basophil ACTH producing cells in pituitary gland in Cushing's Synd.
↓
d/t Keratin filaments Accumulation.

Pigments →

- M/C exogenous pigment → Carbon
  Anthracosis
- Lipofuscin - not injurious to cell
- Melanin
- Hemosiderin

STAINS

Masson fontana → Melanin
Oil Red O → Lipids, fatty acids
PAs → Glycogen, Mucin, mucoprotein, Glycoprotein, fungi
Gomori methamine silver → fungi (Cryptococcus, Coccidioides, Pneumocystis carinii)
Alcian Blue → Mucopolysaccharide
Masson's Trichrome strain - Distinguish fibrous tissue from N., M
Prussian Blue → Hemosiderin
* Negative staining - Nigrosin (India Ink)
↳ To stain capsule of cryptococcus.

~~* Defect *~~ In Trichrome ~~strain~~ stain - collagen - Blue, smooth ms. appears red.

* Acridine orange → Both DNA, RNA
↳ Used with ethidium Bromide to differentiate b/w live and apoptotic cells.

* M/c fixative for Electron Mscopy - Glutaraldehyde (2.5%)
" Light Mscopy - 10% Buffered neutral formalin
* " for histopath. specimens - ~~formaldehyde~~ formalin 10%.
" Cytology → 95% Ethanol
" Hematopoeitic stem cells - $HgCl_2$ (mercuric chloride) (Zenker's fluid).
" Glycogen, lipid, Endocrinal tissue → Picric Acid (Bouin's fluid)

DATE

* components of Basement membrane
  - Laminin
  - fibronectin
  - Proteoglycans
  - Entactin (Nidogen)
  - Heparan SO_4 (perlecan)
  - Type IV collagen.

* Oncocytes - Epithelial cells stuffed with mitochondria.

* In CPVC spleen → Hemosiderin + calcium
  → Gamma Gandy bodies / Siderofibrotic Nodules.

* Esophagus - Non-keratinized, stratified, squamous epithelium for its entire length.

* BHP - Benign hyperplasia of prostate d/t action of dihydrotestosterone, not testosterone
  ↓
  2° obstruction to urinary flow → Bladder hypertrophy

* fenton Reaction - free radicals.
  ↳ $H_2O_2 + Fe^{2+} \longrightarrow Fe^{3+} + OH^+ + OH^-$

* mitochondrial vacuolization - Irreversible injury.

* In Liver hepatitis - ↑ in AST, ALT - d/t cell memb. rupture

* Fibrinoid necrosis - Malignant HTN
  PAN (polyarteritis Nodosa)
  Acute Rheumatic fever

INFLAMMATION

Acute Inflammation

a) Vascular events

Earliest

↓

Vasoconstriction (Transient, Involves arteriole)

↓

Vasodilation

↓

↑ed vascular permeability → Hallmark of Acute Inflammation

↑ed vascular permeability - mechanism

↓

1) Endothelial gap formation - most common mechanism
   - ↓
   - → mainly venules (except for lungs - @ capillaries)
   - •immediate and transient response

2) Direct endothelial injury
   - ↓
   - •Immediate and prolonged response

3) leukocyte mediated injury
   - ↓
   - • Delayed and prolonged.

• Endothelial gap formation

↓

Endothelial contraction
(immediate, transient response)
° Dominant response
↓
Because of chemical mediators
(e.g. Histamine, serotonin)
+
ER (Endothelial Receptor)

Endothelial retraction
(delayed, prolonged)
°Passive response
↓
Cytokine mediated
↓
Reorganization of cytoskeletal

DATE

↓ ↓

oxidative phosphorylation — delayed, prolonged response.

↓

↑ATP

↓

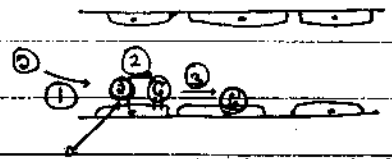
Polymerisation of cytoskeletal protein

↓

Contraction

Cellular events of Acute Inflammation

M-RAP



E-selectin → Transient attachment

P-selectin → Rolling only

↓ Mediate margination

① - margination

E-selectin - CD-62E

P-selectin - CD-62P

L-selectin - CD-62L

② - Rolling

③ Adhesion - Integrin + { ICAM-1 or VCAM-1

ICAM - Integrin- cell Adhesion molecule

VCAM - vessel cell adhesion molecule

④ Pavementing

cytokines → activates endothelium and neutrophil

↓

(CD-31) → PECAM-1 - platelet endothelial cell adhesion molecule.
↓ is expressed on activated cells.

M/I adhesion molecule of diapedesis

⑤ → Diapedesis – Trans-migration of leukocytes via endothelial gap.

⑥ → chemotaxis
↳ Unidirectional

Chemotactics - • Endotoxin of bacteria
• $C_{5a} > C_{3a} > C_{4a}$
↓↓ A/K/a - Anaphylotoxin.
Best

Aldosterone, not testosterone LTB-4 – 2° mediator of Anaphylaxis
• $C_{5a} > LTB-4$

⑦ phagocytosis – killing and degradation

Adhesion molecules
• Selectin → cell-to-cell interaction only
• Integrin → cell-to-cell
cell-to-matrix
• Immunoglobulin molecule → PECAM 1 (CD 31)
• Mucin like protein – Heparan SO_4 (ECM)

LAD (leukocyte Adhesion defect)

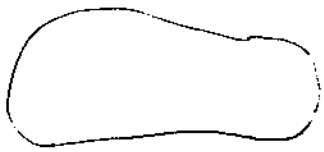
(Autosomal Recessive)

Type I	Type II
• M/c	• Selectin deficiency
↓	↓
• more aggressive.	Sialyl Lewis
• β_2 chain of β_2 integrin	ligand-def.
deficiency (CD-11/CD-18)	↓
* Delayed separation of	Bombay Bld group
umbilical cord stump	assoc. with LAD-II

Phagocytosis

- Neutrophils
- Macrophage
- Monocytes
- Eosinophils → parasites.
  - ↳ major basic protein.

Opsonization.



↓

Opsonin

↳ Best - IgG

IgM

C_{3b}

fibronectin.

↓

Opsonins

↓

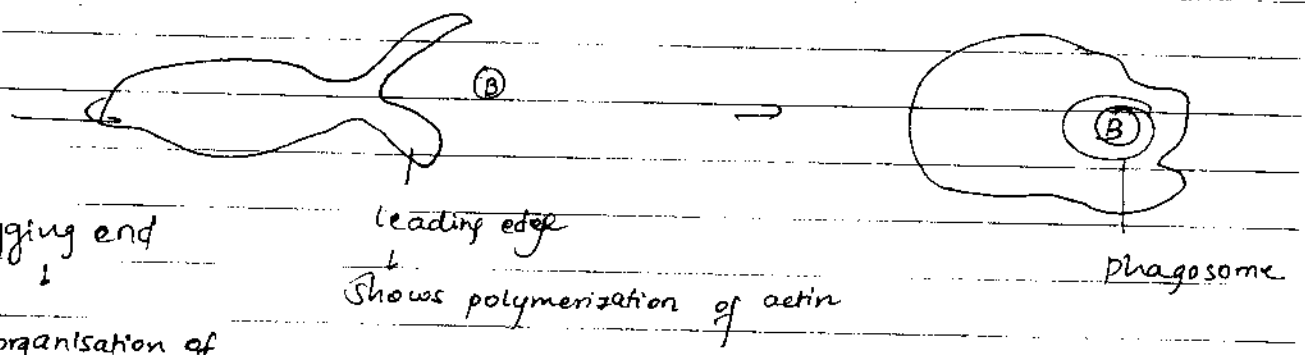
Carbohydrate binding protein

Phagocytosis

- Recognition and Attachment
- Engulfment
- Killing and degradation.

Recognition → Fc IgG
+ +
Attachment → FCγ-III-Receptor

↓

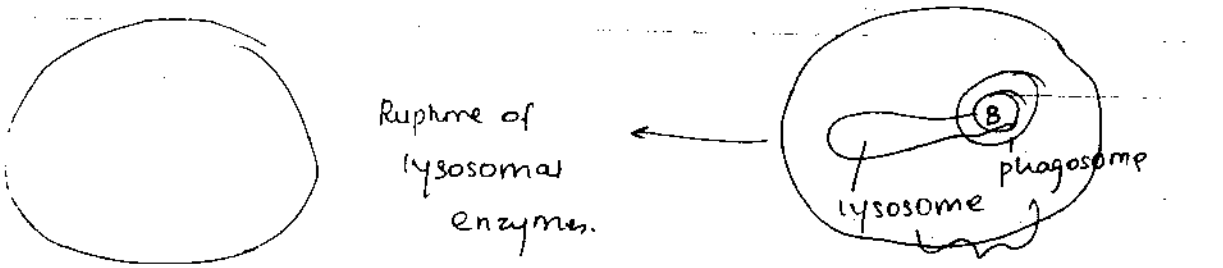


lagging end
↓
Reorganisation of actin.

leading edge
↓
Shows polymerization of actin

Phagosome

↓



Rupture of lysosomal enzymes.

phagolysosome.

↓

a/k/a Respiratory Burst

↓

Most effective bactericidal ----→ NADPH-oxidase (free radical) (O_2 dependent)

phagocytic oxidase (pH-9x gene)

mediators of neutrophil - Elastase
Cathepsin
Leukotrienes

DATE

NADPH oxidase

O_2 → $O^{2\cdot}$ (Superoxide free radicle.) —Superoxide Dismutase→ H_2O_2

Non-NADPH oxidase pathway

Staph Aureus → Catalase +ve → doesn't die

Strep → killed by non-NADPH oxidase pathway

In eosinophils

H_2O_2 —MPO (myeloperoxidase), Cl^-→ $HOCl^-$ (Hypochlorite ion)

↳ most effective bactericidal agent in neutrophil

H_2O_2 —E-PO (Eosinophil peroxidase), I^-→ HOI^- (Hypoiodide ion)

↳ most effective for parasite killing

In eosinophils.

Inflammation - Ted

Chronic Granulomatous Disease → NADPH oxidase deficiency

- Phagocytosis is (N)
- Respiratory burst is defective
  d/t mutation in pHOX-gene

2 types

(1) — membranous defect → m/c type → "gp 91 pHOX" gene mutation
↳ XLRecessive.

(2) — Cytoplasmic defect — Autosomal Recessive.
↳ p47 pHOX gene mutation
↳ p67 pHOX gene mutation.

Pediatrics Granulomatous lesions

- Abscesses / lymphadenitis

Chediak Higashi syndrome -
• Phagocytic disorder
• Gene mutation - (LYST) Transverse
lys-lysosomal
Transfer defect in
• Neutrophils - Infection
• platelet - Bleeding disorder.
• Schwann cells - peripheral neuropathy
• Melanin - Albinism.

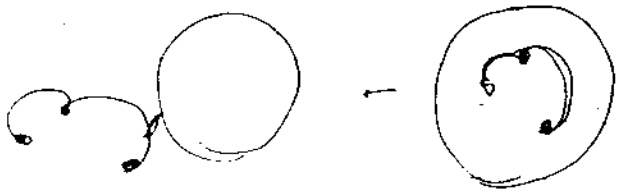
P/S → Giant granules inside the cell.

• Dohle bodies - Dark purple bodies
Mode of damaged neutrophil

• seen in - • Septicemia (mc)
• CHS (Chediak Higashi)
• Myelo-dysplastic Syndrome.

Attachment

* Neutrophilic extracellular Trap (NET)
Seen in septicemia.
Autoimmune disorders.



Bernard clod suicide
↓
Seen with neutrophil

Bruton's disease - Agammaglobulinemia - X linked disorder
↳ failure of B-cell precursors to mature into B cells
↳ Mutation of B-cell tyrosine kinase (B-tk)
↳ Plasma cells are not produced
Only in male

* ECM - Extracellular matrix

comprises of Basement Membrane and interstitial matrix

Degradation of BM occurs by - metalloproteinases (zinc containing

* Delayed prolonged bleeding caused by - Direct injury to endothelial cells.

* Earliest transient change following tissue injury - Neutrophilia.

* Defensins - Cationic arginine rich proteins having broad Antimicrobial activity - found in Azurophil granules of Neutrophils.

* Exudation → occurs in Acute inflammation - protein rich fluid.

* S/o inflammation - pain
Swelling
Redness
Loss of function

* Birbeck's granules - Langhan Cells.

* Eosinophils secrete → major basic protein
~~hydrolytic enzyme~~
ROS
Eosinophilic chemotactic factor

No - hydrolytic enzymes

Inflammatory Mediators

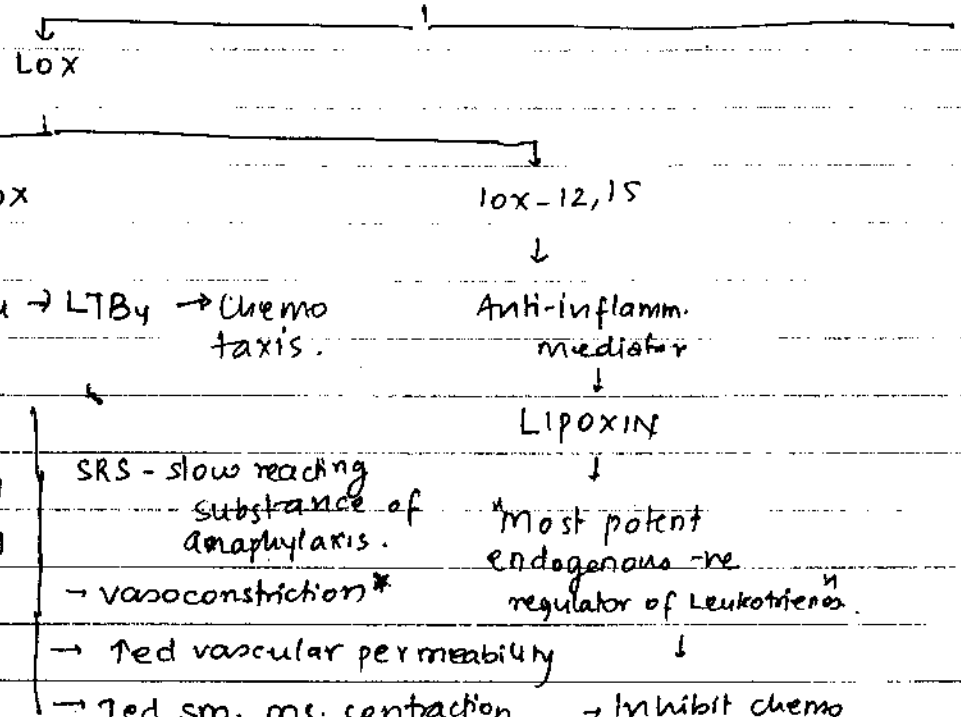
- Cellular
  - Preformed
    - Heparin
    - Histamine (Richest source - mast cell) — synthesised from - Histidine
    - Serotonin
    - Chondroitin sulfate.
  - Newly synthesized
    - Arginine → NO (Nitric oxide)
    - EFA - (linoleic Acid) → Arachidonic acid metabolite → Cox, Lox
    - PAF - platelet Activating factor
    - Cytokines
- Plasma (synthesized by liver)
  - Compliment, Bradykinin

Histamine	Serotonin	PAF	Bradykinin
• Vasodilation	for all 4.		• m/l function - Pain
• ↑ed vascular permeability			• m/l " in Acute Inflammation → ↑ed Vascular permeability
• ↑ed smooth ms: contraction (Bronchoconstriction)			

- * m/l mediator of pain in the body - substance-P
- * most potent inflammatory mediator - PAF
- * most potent pre-formed mediator - Histamine.

DATE

Arachidonic Acid



TNF-α

↑ Triple response (Lewis)

on giving I.D. histamine injection

- Red spot – capillary dilation
- Wheal – Due to exudation of fluid for capillaries, venules
- flare – Redness in surrounding area d/t arteriolar dilatation mediated by Axon Reflex

COX

PGG_2

↓

PGH_2

PGI_2	$PGE_{2\alpha}$	TXA_2
(Prostacyclin)	↳ • pain	(Thromboxane)
- Richest source - Endothelium	• fever	- Richest source of TXA_2 - Platel
- Platelet anti-Aggregators		- Platelet Aggregation
- Vasodilators		- Vasoconstriction

PGE_2, PGE_1

↓

Vasodilatation.

* Cadherin – calcium-dependent adherence protein
  - cell to cell binding
  - Help of catenins
  Important role in – cell motility
  proliferation
  Differentiation.
  and also l/t "contact inhibition"

↓ed E-cadherin in – Breast, Gastric ca.

* Mutation, altered expression of wnt/β-catenin pathway – G.I. and liver Cancer.

* following vessel injury – Immediate homeostasis by –
  vasoconstriction (via endothelin)

* PAF → ∘ platelet aggregation
  ∘ vasoconstriction
  ∘ Bronchoconstriction.
  ∘ At v. low conc, may cause – vasodilatation, ↑ed vascular permeability

CYTOKINES

- Soluble proteins
- synthesised by both hematopoeitic, non-hematopoeitic cells.
- Involved in inflammation, immunological reaxn and wound healing and repair
- Highly specific and have specific receptors

IL-2 → NK cells
IL-4 → Mast cells
IL-5 → Eosinophils (E-S)
IL-6 → plasma cells
IL-8 → Neutrophils.

Most important cytokine → Generalised systemic inflammatn → IL-1

1) fever → IL-1
2) Acute inflammation → TNF-α
3) SIRS (systemic Inflammation Response Syndrome) → TNF α
4) Septic shock → TNF-α
5) cancer cachexia → TNF-α
6) fibrogenic cytokine → TGF-β (tumor suppressor gene)
7) Angiogenesis → VEGF (Vascular endothelial Growth factor)
8) Acute phase Reactant → IL-6 > IL-1, TNF-α
9) Both morphogenic and mitogenic → TGF-β family
   (Embryogenesis) (Cell proliferatn)
   ↓
   One of the member
   BMP (Bone morphogenic protein)
   ↙
   Embryogenesis
   cellular proliferation

Anti-inflammatory cytokines. IL-4, 6 → Both pro, anti-inflammatn
IL-10, 13
TGF-β

- for granuloma formation → IFN-γ > TNF

DATE

Pyrogenic cytokines

IL-1

IL-6

TNF (Tumor Necrosis factor)

CNTF (Ciliary neurotopic factor)

IFN-α

IL-18 → Not pyrogenic

* PGE_2 - final mediator responsible for causing elevation of Thermoregulatory set point by ↑ing the conc. of cAmp

* exogenous pyrogens - Endotoxin of Gram Neg. Bacteria

* most Individuals with hypothalamic damage → sub(N) temp.

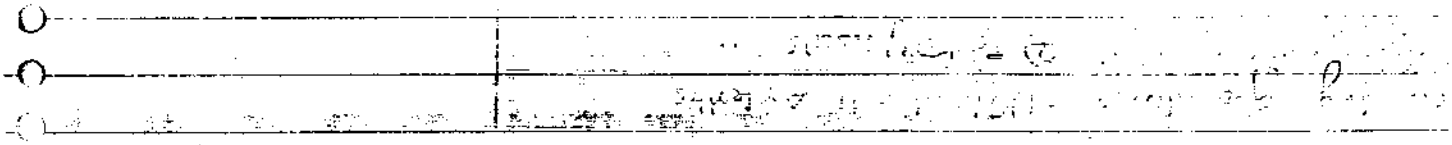
* C-C Beta chemokines includes → Eotaxin. — Eosinophils
↓ → MCP-1 (monocyte chemoattractant protein)
Attact all exept neutrophils → RANTES (Regulated and (N) T-cell expressed and secreted)

* CXC - α chemokines → Attract Neutrophils
E.g - IL-8
— induced by IL-1, TNF

* C - γ chemokines - lymphocytes.

- Mϕ release IL-1 → stimulates T-Helper cells
  Also IL-6 - Acts on late stages of B cell differentiation.

SIRS (≥2 of the following)
- fever (oral temp >38°C) / hypothermia (<36°C)
- Tachypnoea (>24/min)
- Tachycardia (>90/min)
- Leukocytosis (>12000) / Leukopenia (<4000) / >10% Bands.



CHRONIC INFLAMMATION

- Macrophage > ~~bpes~~ lymphocytes.
- Hallmark → tissue destruction (mediated by cytokines)

- Granuloma → pattern of chronic inflammation

Granuloma

● TB Ag → Macrophage

↓

IFN-γ

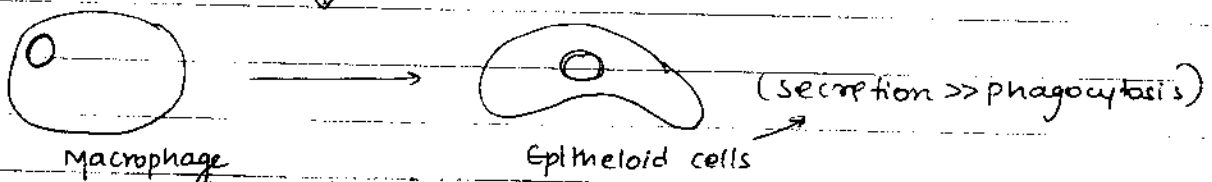
↓⊕

CD_4 TH_1

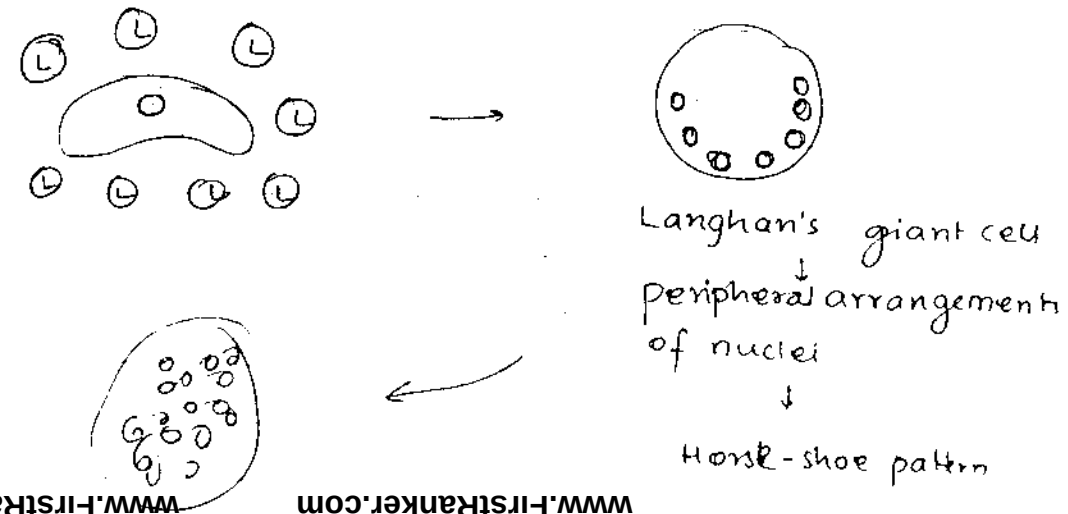
↓

IFN-γ

↓

I) 

II) IFN-γ → Also - lymphocyte proliferation and differentiation



DATE

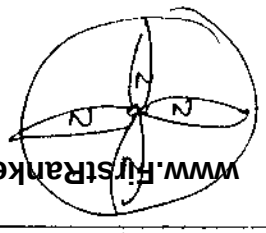
Epithelium	Epitheloid.
cells — BM	No BM (Basement memb.)
	→ E.g. – Islet cells of pancreas Theca leutein leydig cells.

Granuloma

- **Caseating**
  - Histoplasmosis
  - T.B.
- **Non-caseating**
  - Hodgkin's
  - Sarcoidosis
  - Leprosy (Non-necrotizing Non-caseating)

Durck's granuloma
seen in cerebral malaria (P. falciparum)

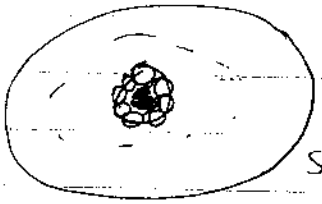
Neutrophilic granuloma/ Stellate granuloma.



→ Cat-scratch disease

Warthin-finkelday giant cells - seen in measles.

Amoeba like



— Touton giant cells
Seen in - Xanthoma

* Aschoff giant cells are diagnostic of Rheumatic fever.
  ↳ Not Anti-scho cells.

* for granuloma formation - Epithelioid cell more imp. than mϕ
  ↳ Macrophage - monocyte.

Systemic vasculitis causing granuloma :- 1) Giant cell Arteritis
2) Takayasu's "
3) Wegner's Granulomatosis
4) Churgg-Strauss

* systemic vasculitis with necrotizing inflammation
  ↳ PAN
  ↳ microscopic polyangitis
  ↳ Wegner's
  ↳ Churg-Strauss.

↳ ranulomatous d/s.
TB, Sarcoidosis, Crohn's
Catscratch d/s, Lymphogranuloma inguinale, leprosy, brucellosis, Syphilis, Beryliosis.

* TB - langhan's Giant cell
* Hodgkin's - RS cells
* Xanthoma - Touton giant cell

Toxoplasmosis
↳ Aced by - Sabin Feldman dye test

DATE

NBT Test (Nitro blue Tetrazolium)

- Most widely known test for chronic granulomatous dis.
- Test detects ROS in phagocytes.
- In chronic granulomatous dis. → This is Negative
- +ve - In (N) individuals

Inability of to form MAC - memb. Attack Complex

- Recurrent infn by Neisseria species.

Meningitis in child.

Pure T cell dysfn → Thymic Hypoplasia

DiGeorge Syndrome

Recurrent viral and fungal infections

* Young adults infected with Neiseria meningitidis - may be @ ted risk of disseminated infection if they produce too much serum IgA. As IgA - blocks attachment of IgM, IgG → prevents opsonization.

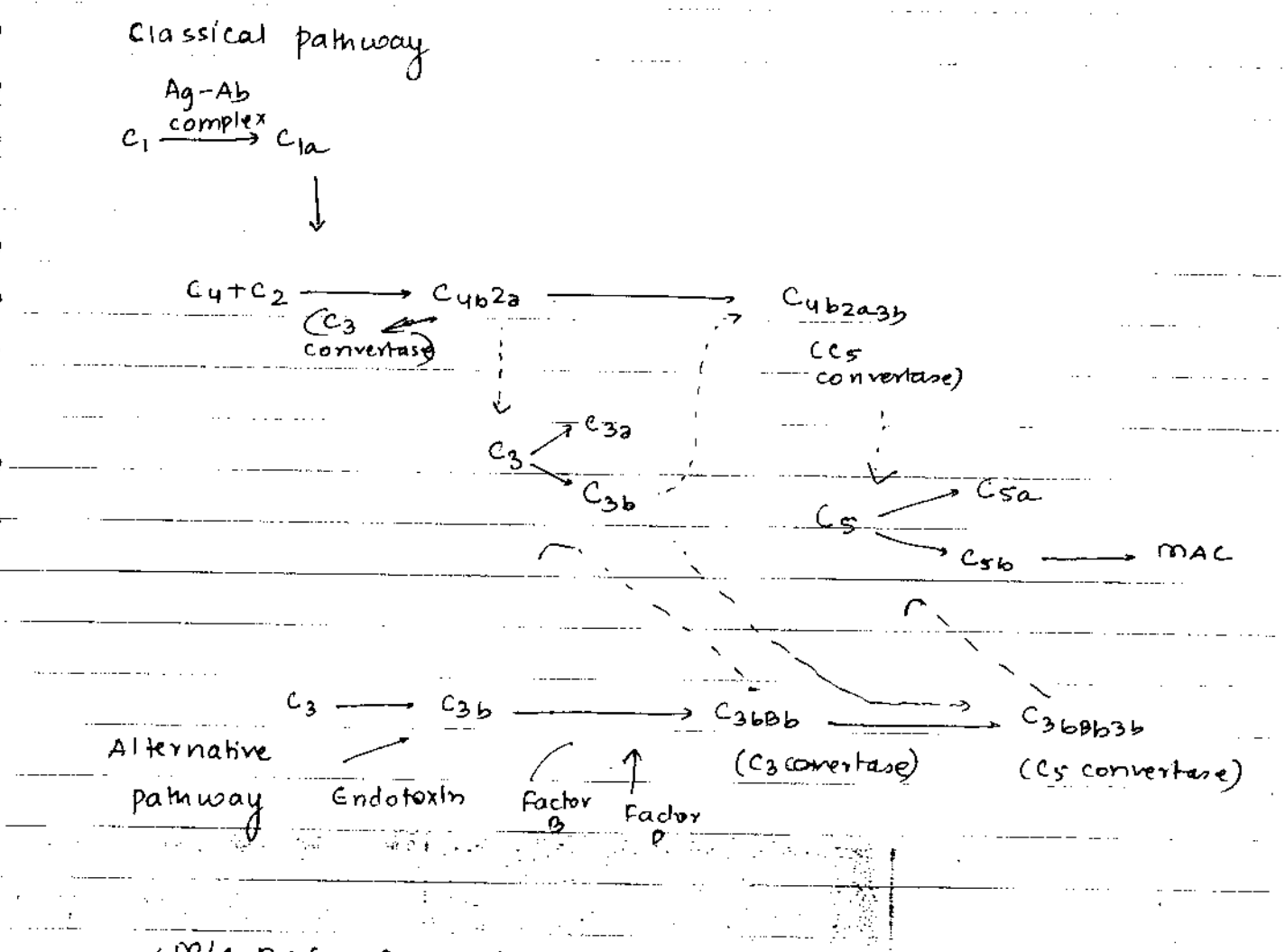
* Ultrastructurally endothelial cells contain - Weibel Palade Bodies.

* Acute bronchial asthma → mast cell

Basophils → also show similar effect

* Monocytes - precursors of osteoclasts, Kupffer cells, Tissue mϕ, Alveolar mϕ
* platelets - Peripheral hyalomere, central granulomere
* Neutrophils - ~~Azophi~~ Azurophilic granules, multilobed nuclei
* Lymphocytes - Basophilic with dark stained nuclei

COMPLEMENT SYSTEM



- M/C def. of complement → C_2
- IgM, G → classical pathway
  IgA → Alternate pathway

- Classical pathway activation → ↓ed C_1, C_2, C_3, C_4, (N) factor B
- Alternate pathway activation → ↓ed factor B, C_3, (N) – C_1, C_2, C_4

★ C_{3a}, C_{5a} – Anaphylotoxins – cause release of histamine from mast cells ∴ causing vasodilatation and ↑ed vascular permeabl
★ C_{3b}, C_3 → opsonization
★ C_{5a} – chemotaxis.

DATE

Regulatory molecules of complement system

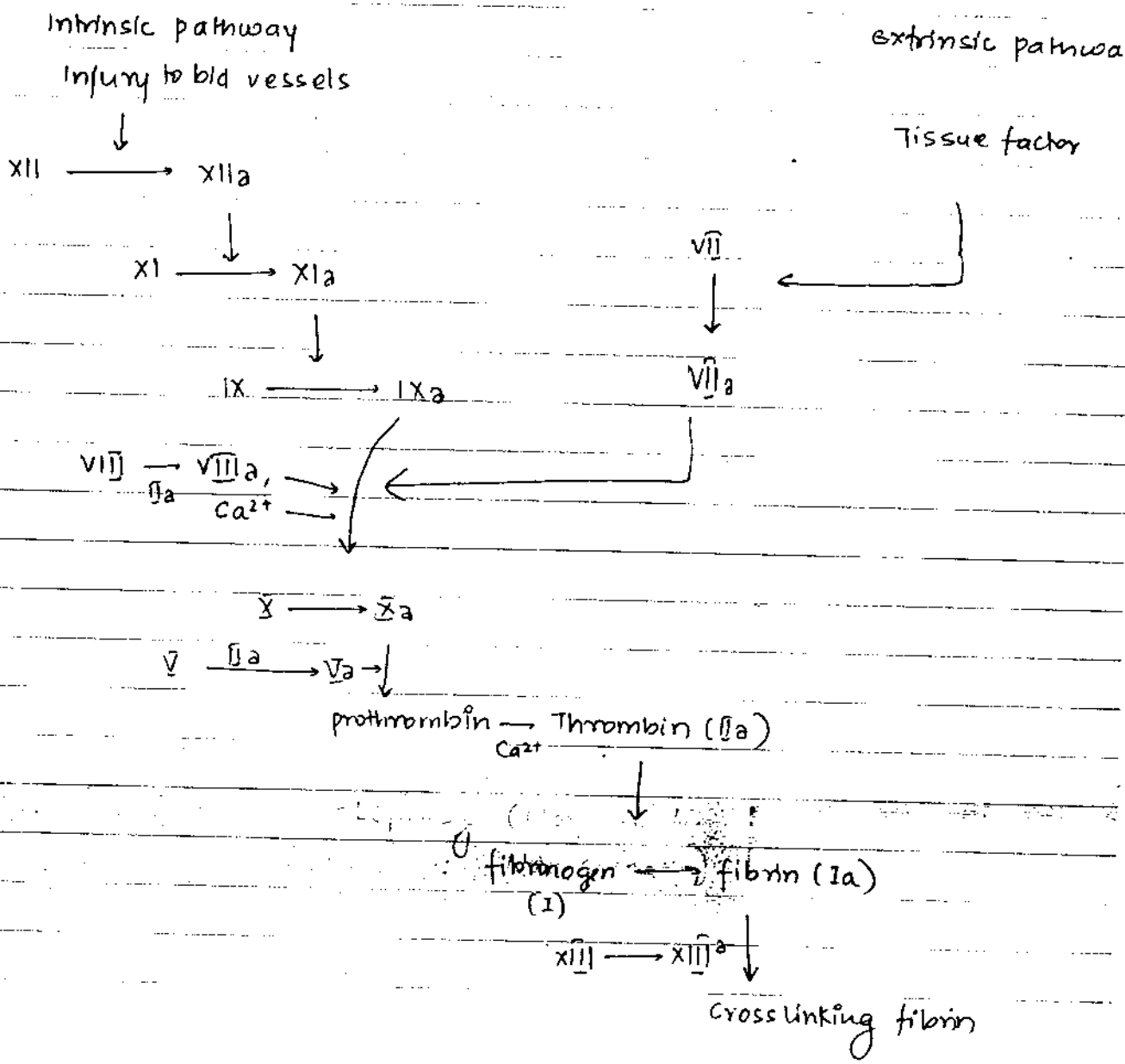
- DAF - decay Accelerating factor - Tes the dissociation of C_3 convertase
- Factor 1 - proteolytically cleaves C_{3b}
- CD-59 (membrane inhibitor of Reactive lysis) - inhibits formation of MAC
- factor H, 1, CD-46 - prevent excessive alternate pathway activation

Def. of	Di's.
C1 esterase inhibitor	Hereditary angioneurotic edema (Excessive complement activation)
Early complement proteins C_1, C_2, C_4	SLE, collagen vascular dis.
C_{3b}, C_{3b} inactivator	Recurrent pyogenic infns
$C_5 - C_8$	Neisseria, Toxoplasmosis
DAF, CD-59	PNH (complement mediated ↑ed intravascular lysis of RBCs, platelets, neutrophils)
CD-46, factor H and I	Atypical or 'Non-epidemic' Hemolytic uremic Syndrome (HUS)

Hereditary Angioneurotic edema

- Non-pitting edema
- AD
- Def of C_1 inhibitor
- ↑ed levels of bradykinin
- F >> M
- Asi's → lack of pruritus, urticarial lesions
  - → Prominent recurrent G.I. attacks of colic
  - → Episodes of laryngeal edema
  - → C1 - (N), but C_2, C_4 ↓ed.
- Dnse — Danazol

Clotting system



* Cryoprecipitate is rich in → factor VIII
* All are synthesised in liver except factor IV (Calcium), factor VIII carries protein called VWF (von Willebrand factor)
* Vit K dependent → factor II, VII, IX, X
* Intrinsic Pathway → APTT - Activated partial thromboplastin time
  Extrinsic → PT / International sensitivity Index (ISI)

P.T.E

↓

Prolonged in

* factor XII def. → NO bleeding

DATE

Kinin system

- Factor XII ⟶ XII_a (Hageman's factor)

↓

Pre-Kallikrein ⟶ Kallikrein

↓

Kininogen ⟶ Kinin
(Bradykinin)

Kallikrein - Also activate - plasminogen → plasmin
Also cause activation of complement protein C_{5a}

functions of Bradykinin

1) Contraction of smooth muscles
2) Pain
3) Dilatation of venules.

Morphological patterns of Inflammation

- Serous Inflammation - Effusion
- fibrinous - deposition of fibrin in extracellular space (meningitis, pericarditis)
- Catarrhal - Epithelial surface → ↑ed mucus secretion
- Purulent → pubulent exudate.

* Bleeding time - function of platelets

WOUND HEALING, REPAIR

* Hallmark of cutaneous wound healing → Granulation tissue

Granulation tissue - 3 essential components

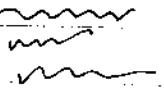
- Neovascularization (proliferation of new blood vessels)

 → Lumen + RBCs

Proliferating - Different shape, size of vessels.

- Proliferating collagen / fibroblasts.

Haphazard arrangement of wavy fibres.



- Type I, III collagen - will be found **
- Non-specific inflammation
  All type of inflammatory cells.

Liver cirrhosis
↓
Also - Type I, III Collagen see

Collagen

I → bONE, skin
II → cartwolage
III → threticular
e.g. Bld vs.
IV - under the floor (Basement membrane)

Max tensile strength → Type I collage
m/c collagen ↗
collagen vulgaris ↗

Scar → I

* Granulation tissue → to → scar formation is kia → Tissue remodelling

↓

Enzyme - most important

↓

MMP - Matrix metalloprotease

↓

Element most essential → Zn

Others - Ca^{2+}, Fe^{2+}, Cu

DATE

* EMT (Epithelial Mesenchymal Transition)

↳ Required for → Wound healing
metastases.

Cutaneous wound Healing

Primary

Day 1 → platelet > Neutrophil → life span
↓
Earliest to appear. In peripheral bld ↳ 6 hrs
In tissues → 1-4 days.

Day 3 → mϕ ↑↑↑
Early granulation tissue

Day 5 → max. granulation tissue
Total epidermal thickness
is recovered

End of 2nd week → max. collagen deposition
Edema, inflammation - disappears.

End of 28 days → scarring completed.

Secondary

• Most distinct feature which differentiates it from 1° → wound contraction.
↓
Done by → myofibroblasts.
↓
These are fibroblasts having special contractile activity like a smooth muscle.
↓
These are mesenchymal in origin

* fetal cutaneous wound healing → No scarring
d/t → osteopontin - gene
↓
Non-fibrogenic type of TGf-β.

* 100% wound strength → Never regained.

Wound-healing - strength

Starts @ day 5-7 → 10% of original

Max. @ 3 months (end) → 70-80%.

Complete regain → Never occurs

Masson's Trichrome Stain → collagen, connective tissue → Blue

CHAPTER-4

GENETICS

- Coding (Exons) → 1.5%
- Non-coding (Introns) → Rest 98.5%

- Non-coding RNA → Gene silencing (post-transcriptional)
  1) Micro-RNA (mi-RNA) (in-vivo - in the body)
     - "21-30" oligonucleotides
     - Gene silencing RNA (post-transcriptional)
     - Present Normally

     mi-RNA + Ca-gene ⇒ No cancer

     mi-RNA + tumor suppressor ⇒ cancer

  2) In vitro / exogenous mi-RNA (outside the body)
     ↳ K/a → small interfering RNA (siRNA)

  3) LINC-RNA (long intervening non-coding RNA)
     ↳
     Attach to XIST-gene (inactivate x chromosome)
     ↓
     formation of Barr-body

  4) pi-RNA (piwi-Interacting RNA)
     - M/C type of ~~RNA~~ non-coding RNA.

DATE

Genetic disorders

Single gene

Classical
(follow Mendelian inheritance)

AR → M/c type in inborn error of metabolism.

AD → M/c type of inheritance

XLR

XLD

Unclassic
↳ Variations of classical

1. Gonadal mosaicism
2. Genomic Imprinting
3. Mitochondrial inheritance
4. Trinucleotide Repeat mutation.

Multifactorial
(Complex polygenic inheritance)

- Environmental factors
+
- >2 mutant genes.

Eg. 1) DM
2) Congenital ♡ dis
3) cleft lip, cleft palate.
4) Coronary ♡ dis.
5) HTN
6) Gout
7) Pyloric stenosis.

AR → Horizontal inheritance

AD → vertical inheritance.

	AR	AD
Aa → Heterozygous	Carrier	Disease
AA → Homozygous	Disease	Dead-in-utero

DATE

AUTOSOMAL DOMINANT

Characteristics

1) Variable expressivity

Same gene showing different expression.

NF-1 → Eye
NF-1 → Cutaneous Nodules
NF-1 → Scoliosis

2) Reduced penetrance (Incomplete)

Mutant gene is present, but phenotypically normal.
(morphologically)

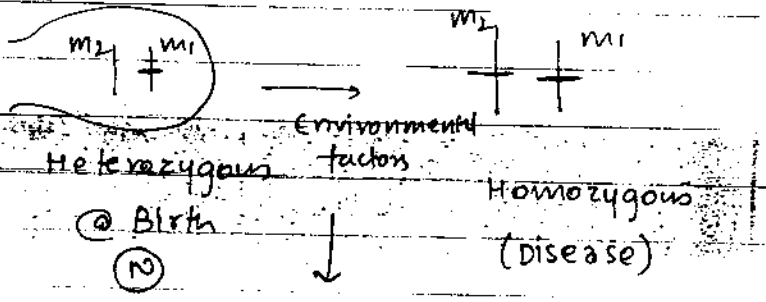
E.g. Retinoblastoma

Rb gene

Chr. 13q14

- p - petit (~~fact~~)
- q - (~~long~~) Next to p

Incomplete penetrance.



→ Loss of Heterozygosity → "LOH"

→ Knudson's two Hit hypothesis

Others showing this phenomenon → 1) Wilm's tumor
2) AD PCK (polycystic kidney)
3) Hirschprung's dis.

3) Dominant Negative effect

Mutant gene will effect (N) gene and their function (Eg. cricket)

- Protein affected → collagen
- Disorders of collagen
  - ↳ M/c hereditary collagen disorder → marfan's synd.
    - ↓
    - D/t - "fibrillin-1" gene Mutation
    - Chromosome - 15q (लंबी भुजा)
    - Hypermobility / Hyperextensibility of joint.
- M/c/c of death in marfan's synd → Aortic Dissection
- Revised Ghent's Criteria - used for Marfan synd. Asis

Ehler's Danlos Syndrome (Rubberman Syndrome)

- Hyperextensible joint + Skin (cigarette paper skin)
  Hypermobility — scarring

- M/c type - Type III EDS. (Hypermobility type
- M/c collagen affected → Type III collagen.
- spontaneous Rupture of colon and Arteries - ED syndrome.
  Type IV EDS
  ↓
  Alkla vascular type of EDS.
  ↓
  Worst prognosis.

- M/c pattern of inheritance → AD
- Cigarrette paper like thin scarring - seen in "EDS"

DATE

osteogenesis Imperfecta / Lobstein Syndrome

- # BONE → collagen one (Type 1) - m/c affected.

+

Blue sclera

AUTOSOMAL DOMINANT

- Von Willebrand Dis.
- familial Adenomatous polyp (Peutz-Jegher)
- familial Hypercholesterolemia
- Adult polycystic Kidney dis.
- Dystrophic myotonica, fascioscapulohumeral ms. dystrophies.
- Osteogenesis Imperfecta
- marfan Syndrome
- ~~Intermittent porphyria~~ not transmitted to
- NF-1+2
- Achondroplasia - ~~sickle cell disease~~
- Tuberous Sclerosis
- Huntington's
- Hereditary Spherocytosis.
- Von-Hippel Lindau

* Huntington's disease → can be transmitted by single AD genes
* Gardner's syndrome - subtype of FAP → Intestinal polyps + Epidermal cyst + fibromatosis + osteomas

DATE

PEDIGREE CHART

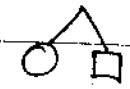
 → Male

 → female

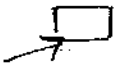
 → carrier

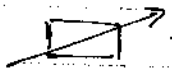
 → X-L-R carrier

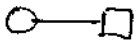
 → Unknown gender

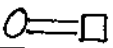
 → Dizygotic twins

 → miscarriage

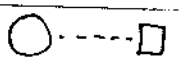
 → Index case / proband

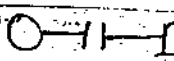
 → Deceased (dead)

 → Non-consanguinous marri

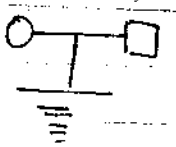
 → consanginuous marriage.

 → monozygotic twins

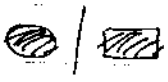
 → Extramarital affair / Emotional attachment

 → Divorced

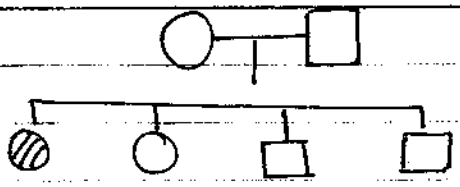
AD

 → Infertility

[6] / [5] / (3) → No. of same gender siblings

 → Diseased.

[○] / [□] → Adoption



→ Gonadal Mosaicism

↓

Parents are (N),

variable no. of Kids are affected

D/t germline mutation.

1/2/3/All 4 can ← be affected.

E.g. → 1) Osteogenesis Imperfecta
2) Achondroplasia
3) Tuberous sclerosis

Usually seen in AD type of disorders

1st step → Rule out gonadal mosaicism.

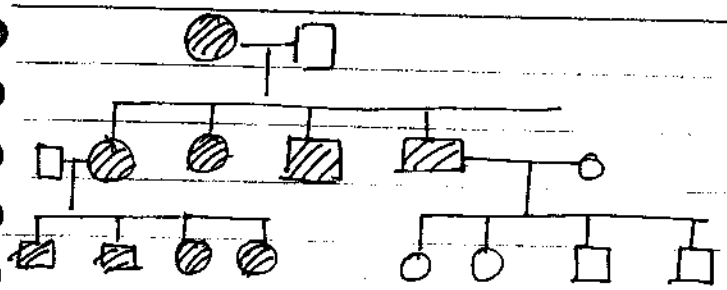
(maternal Inheritance)

Mitochondrial Inheritance

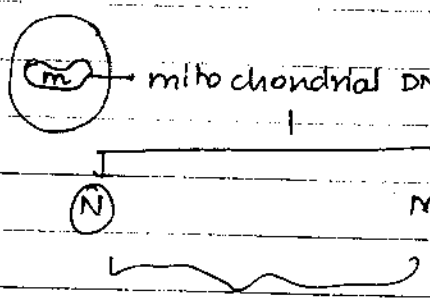
↓

mother is transmitting dis. to all her kids

Son – doesn't transmit the dis.

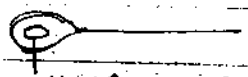


Orum



Heteroplasmy – same organelle has both mutant and (N) types of DNA

* Shows heteroplasmy



mtDNA → sperm mitochondrial DNA is not transmitted to next generation.

↓

d/t selective degradation by ubuiquitin proteasom pathway.

E.g. ① NARP – Neurogenic weakness
Ataxia
Retinitis pigmentosa

Retinitis pigmentosa
m/c-sporadic (60%)
Hereditary (40%)
↓
AR (60%)
m/c

② MELAS – m/c Mitochondrial Inheritance dis
↳ ~~mitochondrial disease~~
Mitochondrial encephalopathy, lactic acidosis, Stroke like episodes

* m/c clinical feature of mitochondrial

DATE

③ LHON'S

Leber's Hereditary Optic Neuropathy

↳ prototype of mitochondrial Inheritance

④ CPEO → Chronic progressive external ophthalmoplegia

⑤ Kearn's Sayre syndrome

⑥ Leigh's disease

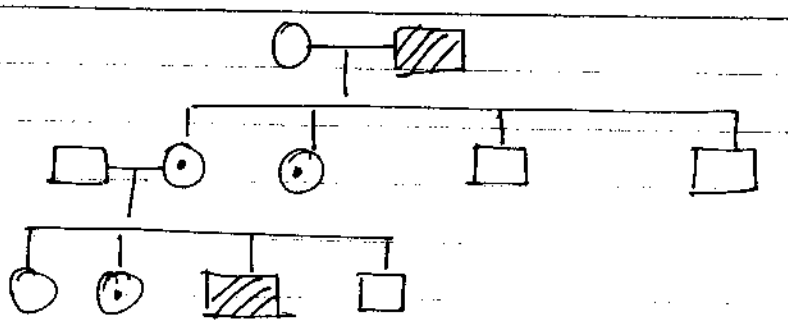
★ Intermittent muscle weakness → in all mitochondrial myopathie

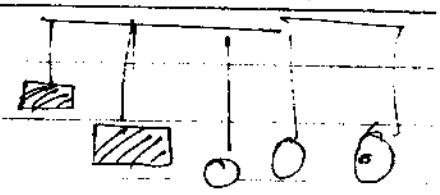
2nd step – R/o mitochondrial Inheritance

Nemaline myopathy

- Clinically heterogenous condition, not a mitochondrial disease
- → mutations of the nebulin gene

DATE





X-linked Recessiv Disorder

$X^a y$ → Disease

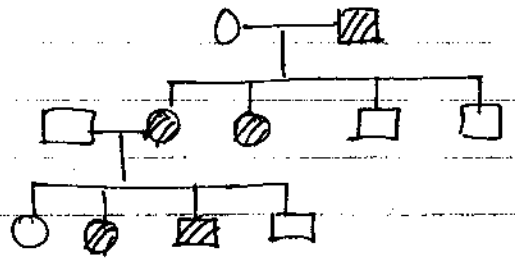
$X X^a$ → ~~Disease~~ carrier.

- Males are commonly affected.
- females may be ~~affected~~ affected.
  But, usually they are carriers.

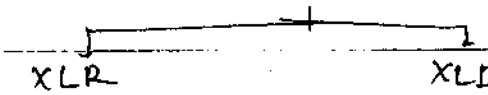
Eg. → G6PD Def.
Hemophilia A, B

(Hemophilia C – AR)

X-Linked Dominant- from affected males, all daughters are affected,
and none of the sons are affected.
from affected daughter, 50% of daughters and 50% of sons are affected.



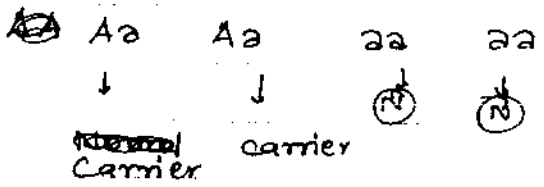
3rd step → Identify and R/o X-Linked disorder



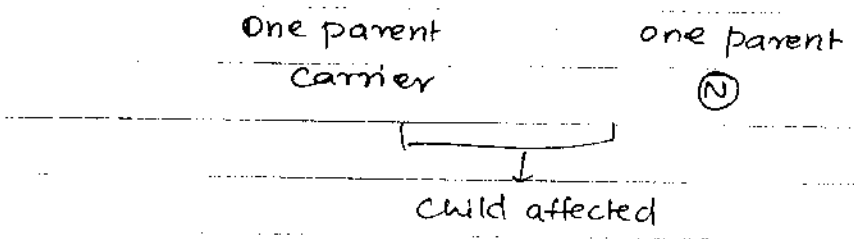
Alport Syndrome
m/c pattern → XLD
least common → AD

Autosomal Recessive.

Carrier	Normal
Aa	aa



Uniparental disomy → V.V. Rare pattern of inheritance.



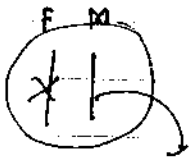
DATE

GENOMIC IMPRINTING.

(Inactivation)

- functional gene is inherited from one parent only
- Mechanism of genomic imprinting → Epigenetics → Hereditary chemical modification of DNA (Methylation) of DNA @ cytosin
  - ↓ led expression of gene.
  - ↓ Demethylation
  - ↓ Regain to (N) state.

Chromosome 15q



Imprinting

Papa → Paternal

↓

Prader-Willi Syndrome

Imprinting of maternal gene.

↓

Hypogonadism

Hypotonia

MR (mental Retardation)

Obesity [Ghrelin Hormone severely elevated]

Imprinting

↓

Mother's are Angel → Deletion of maternal gene

↓

Angelman Syndrome / Happy

- Imprinting of paternal gene
- A1K1a - Happy puppet syndrome
  - Bcz of Ataxia + Inappropriate laughter.
- Ghrelin (N)
  - MR
  - seizures
  - Ataxia
  - Inappropriate laughter

UBE 3A gene

↓

Ubiquitin gene.

- Uniparental disomy of paternal gene

★ Ghrelin Hormone

↳ Orexigenic Hormone (Appetite)

from Antrum cells of

- Uniparental disomy

- M/C/C of tumorogenicity → ~~Ras~~ Methylatn of tumor suppressor gene
  tumorigenesis
  ↓
  Epigenetics.

- Loss of Heterozygosity (LOH) → Also assoc. with epigenetics.

- Uniparental disomy is assoc with →
  - Angelman's
  - Prader-Willi
  - Russell-Silver syndrome
  - Bloom-Syndrome (very rare with unipaternal disomy)
  - Beckwith Widman syndrome
    - Uniparental disomy of Chr 11q involving WT-1 gene

Autosomal Recessive

- freidrich's Ataxia
- Phenylketonuria
- Galactosemia
- cystic fibrosis
- Hemochromatosis
- α_1-Anti-trypsin def.
- Wilson's dis.
- Alkaptonuria
- Lysosomal storage disorders
- Glycogen storage disorders
- Muscular atrophy
- congenital Adrenal hyperplasia
- ~~Sickle cell disease~~ Sickle cell dis.
- Thalassemia
- Homocystinuria.
- mps

Metabolic – Non-AR →

- Hunter syndrome – XLR
- Lesch Nyhan Syndrome – XLR
- Ocular Albinism – XLR
- familial hypercholesterolemia – AD
- fabry's disease (XLR)
- Acute Intermittent porphyria – AD

DATE _____

XLR

- Hemophilia
- Hunter's
- lysch Nyhan
- G-6PD def.
- Duschenne muscular Atrophy, Becker's, Emery-Dreifuss.
- Diabetes Insipidus
- Color blindness
- Bruton's Agammaglobulinemia
- fragile x synd.
- fabry's dis.
- Wiskott Aldrich Syndrome

XLD

- Hypophosphatemic Rickets
- Incontinentia pigmenti
- Alport syndrome
- Oro-facio-digital syndrome.

TRIPLE REPEAT MUTATIONS

Trinucleotide Repeat mutation.

- Codon - arranged in triplets → CGG, AGC
- N-Repeats - (N) - 6-35 times
  - 50-200 - premutation (Asymptomatic/carrier)
  - >200 Disease.
- A/K/a dynamic mutation
- No. of repeats is directly proportional to severity of disorder.
- The ↑ in no. of repeats occurs during gametogenesis

Oogenesis
- Involves Non-coding areas (Intron)
- "Loss of function" type mutat
- CGG Repeats
- e.g. fragile X syndrome → X-chromosome have fragile sites
  - (M/C → XLR)
  - when typical.
  - fragile sites more prominent when grown in folate def. medium)
- 2nd M/C/C of Hereditary Mental Retardatn
- Hallmark of fragile X synd - Macroorchidism (large testis).
- Also seen → MVP, AR
- large face, ear, mandible, maxillary bone
- Not seen - large nose : Nose-small (N)

Spermatogenesis
- coding areas (Exons)
- "Gain of function" type mutat
- e.g. Huntington's dis.

Other eg. → Freidrich's Ataxia
myotonic dystrophy

M/c Repeat - CCA.

Huntington's Disease.

- AD
- 20-40 yrs
- "CAG" repeats
- Chromosome-4

father (400 Rpts)
↓
Son (600 Rpts) → ↑ed severity

Anticipation { ↳ Affected @ early age (20s
(Early onset)

Anticipatn → ↑ed severity
+
onset @ earlier age.

* Sherman's paradox - Grandsons more affected than siblings.

DATE

KARYOTYPING.

- paired
- ↓ed order of length (Decreasing order of length)
- X, Y – last

- Samples –
  1. Amnion (shedding from skin, Resp. tract, GIT, Urogenital tract)
  2. Chorionic villi Biopsy
  3. Cordocentesis (fastest method to perform Karyotyping)
  4. In peripheral blood, only lymphocytes are used for Karyotyping (phytohemagglutinin)
  5. fetal tumor sample

     m/c fetal ~~tera~~ tumor → sacrococcygeal teratoma

     m/c ↳ malignant ↳ → ↳

fixatives of choice

1. Karyotyping → Methanol + Glacial Acetic Acid.
2. Histopathology → ~~formaldehyde~~ formalin 10%.
3. Electron Mscopy → 2.5% Glutaraldehyde > Osmium tetraoxide (~~formalin~~ - Never used)
4. Cytology (e.g pap smear) → 95% Ethanol
5. Hematopoeitic stem cells → Mercuric Chloride (Zenker's fluid) → maza
6. Glycogen, Lipid, Endocrinal tissue → Picric Acid (Bouin's fluid) → Bp
7. Hematology lab → methanol

DATE

* Routine Karyotyping arrest → Metaphase Arrest → 800 Bands / Haploid set

↓

Colchicine Alkaloid is used.

Resolution is enhanced in prophase arrest → 1500 Bands / Haploid set

* In Light Microscopy, conventional Karyotyping, chromosomal resolution

↓

5MB (mega-Base).

* Stain used → m/c-/Best → Giemsa stain

∴ k/a G-Banding.

4 types

1) Metacentric chromosome

q = p

2) Sub" MATA" centric Chromosome

p < q

Eg. → X chromosome.

3) Acrocentric chromosome

p << q

Eg. → Y

chr. 21, 22.

chr. 13, 14, 15

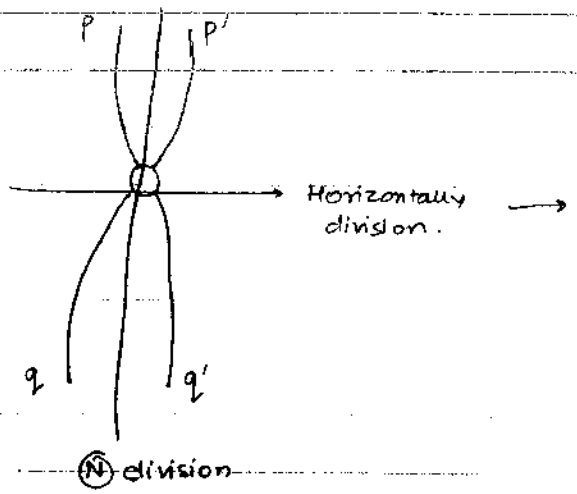
↓

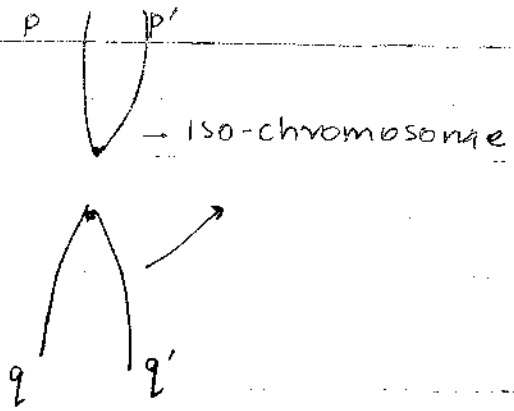
Usually assoc. with Robertsonian Translocation.

4) Telocentric

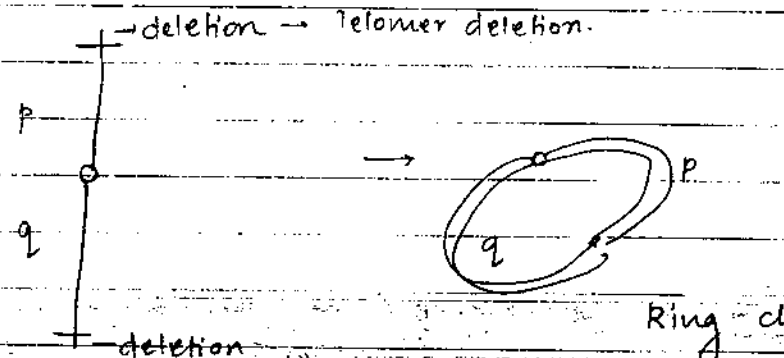
only q

Not seen in mammalian chromosomes.





i/2p - isochromosome 12 p is assoc. with
↳ Seminoma.
↳ other germ cell tumors of ovary/testis.



Ring - chromosome
↳ in Turner's Synd.
↳ Sarcoma.

Limitations of Karyotyping →

(1) ~~Complete~~ translocation can't be seen.
Complex
E.g. - t (9:22)

∴ Routine Karyotyping can't be used for complex translocation

(2) Amplification

(3) Microdeletion
m/c microdeletion syndr. → 22q− (Velocardiofacial) synd/ DiGeorge Synd.

FISH → Best method to detect Known gene loci
↳ Limitatn - Small gene can't be detected

PCR - Best method to detect point mutation.
↳ Limitatn - Large fragment can't be detected.

Best method

* To overcome limitations of both FISH, PCR → MLPA
(Multiplex ligation Assoc. Probe Amplification)

- Best method to detect both small, large ↑ pattern of gene

- In cystic fibrosis disorder, ⊛ CFTR genes are mutant,
27 EXONS → some large
↳ some small

↓

Best method → MLPA.

DATE

* Inversion → usually not assoc. with change in genetic material

* comparative genomic hybridizatn → Best method to differentiate b/w cancer and (N) cells.

* mosaicism →

Cells with more than one type of genetic constitution

seen in Down's

Chromosomal Disorders

M/C Chromosomal disorder → Trisomy-16 (most die-in-utero)

m/c " @ live birth → Trisomy-21

Trisomy-21

Down's Syndrome

3 pathogenetic mechanisms

mc → i) Meiotic Non-dysjunction during meosis-1 (95%)

In all trisomies, non-dysjn occurs during meosis-1, except trisomy 18 (Edward's Synd.) → occurs during meosis-

Non-dysjn
* Extrachromosome → Maternal
* Assoc. with advanced maternal age

ii) Robertsonian Translocation (4%)

* (21 → 13-15
22)

→ familial (90%)
→ Not assoc. with maternal age

iii) Mitotic non-dysjunction (mosaicism) - 1%

some cells → 46 chromosomes
some cells → 47 "

→ Not assoc. with maternal age.

DATE

Down's Synd.

1) m/c assoc leukemia → ALL

2) m/c assoc leukemia in < 3yrs → AML-M7
(Acute megakaryocytic leukemia)

* If Down's baby survives → >40 yrs - universally affected by Alzeihmer's Dis

* m/c cardiac defect - Endocardial cushion defect (ASD) > VSD

* ↓ed Immunity - I/t Recurrent episodes of resp. infections

* also a/w Autoimmune disorders.

TURNER'S SYNDROME (45XO)

- Webbed ht
- Widely spaced nipples
- Webbing of neck
- Short 4th metacarpal
- Assoc with paternal age., Not assoc. with maternal age.
- Streak ovaries (Atrophy)
- Breast tissue is (N) - Histologically
- m/c cardiac defect → BAV (Bicuspid Aortic Valve)
- Very rarely assoc. with tumor - Ca. colon

* A/w both maternal and paternal age → Klinefelter's Syndrome
  - m/c tumor in Klinefelter's Synd. → Breast ca. > Germ cell tumor
  - m/c Germ cell tumor in Klinefelter → Extragonadal >> Gonadal
    - ↓
    - M/c site → mediastinum.
  - m/c GCT in Klinefelter → Teratoma!

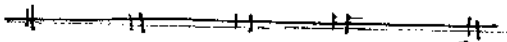
DATE

DATE

Recent advances In Genetics

- Genetic polymorphism →
  - Any 2 individuals are similar genetically by 99%
  - DNA variation b/w 2 individuals (1%)
    - ↓
    - 15 million base pairs

- Polymorphic genes – Marker loci to detect unknown mutant gene or for multifactorial inheritance.



Rules

① All polymorphic genes are closer to disease genes
(P) (D)

② linkage - disequilibrium

(P) – Stably transmitted from 1 gener → Next generatn

Types of polymorphism

- M/c type of polymorphic gene → SNP (Single nucleotide polymorphic) g
  DNA variation → 1 nucleotide / 1000 Base pairs.

- Repeat length polymorphism
  - a) Microsatellite → 2-6 base pairs repeat
  - b) Minisatellite → 15-70 base pairs repeat

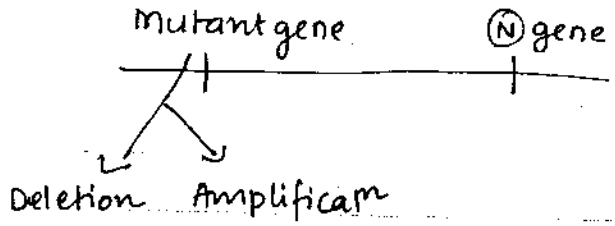
DATE

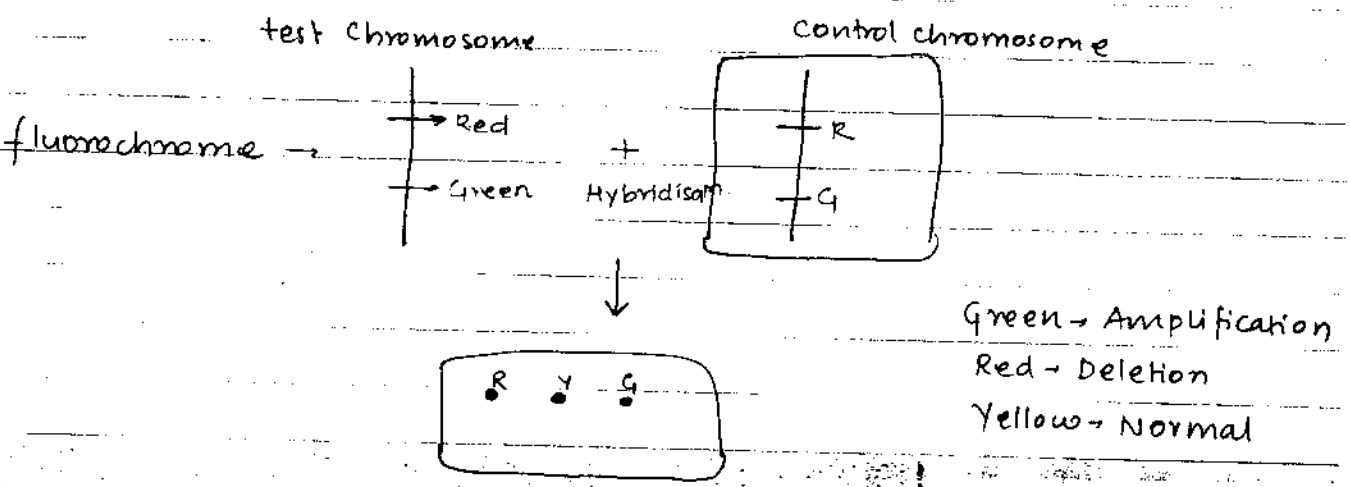
Genetic disorders

- Single gene disorder
  - Direct sequencing
    - PCR
    - FISH
- polygenic inheritance
  - Multifactorial
  - unknown mutation
  - Indirect sequencing
  - By using polymorphic gene.
    1) family → Linkage analysis
    2) large population → GWAS
       Genome wide
       Analytical study.

Solid cancers

• On same chromosome both (N) and mutant gene is best detected by →





Micro-array analysis → Study of multiple genes.
└ principle - Hydridisam.
alkla micro-array based comparitive genomic hybridisam (CGH)

Breast ca. classificam
ER+
PR+
Her2/New overexpression

Uses →
1) gene ~~expressing~~ expression profiling
2) Molecular classification of cancer

DATE

* On one chromosome, to detect "entire genome"

↓

Chromosomal painting

* To detect entire human genome on all chromosomes

↓

FISH

↓

Spectral Karyotyping / Spectacular Karyotyping → >5 types of fluorochromes + computer generated signals

* DNA fingerprinting → Banding patterns are analysed.

* Granulosa-cell tumor are → not germ cell tumor

* Cystic fibrosis → Gene located on → Chromosome no. 7.

* LOH (loss of heterozygosity) → Loss of (N) allele in mutant gene.

* Congenital syndrome → a/w Lymphoproliferative malignancy

↓

- Bloom syndrome
- fanconi's Anemia
- Chediak Higashi
- Ataxia telengiectasia.

* β-thalessemia → Splicing mutation
α-thalessemia → frame-shift mutation / Non-sense mutation

DATE

★ HOMEOBOX Gene (HOX) →

Implicated in patterning of limbs, vertebrae, craniofacial sutures.

- Possess Retinoic Acid response elements (RAREs)
  ↓
  required for mediating both physiologic, pathologic effects of retinoids during development
- mutation of HOXD-13 → Synpolydactyly (extra digits) in heterozygous individuals
- mutations of HOXA-13 → Hand foot genital syndrome (Distal limb, distal urinary tract malformatio

★ PAX

PAX 3 → Waardenburg synd. (congenital pigment abN, deafness)
PAX 6 → Aniridia (cong. absence of iris)
PAX 2 → Renal coloboma
PAX 3, PAX 7 → Alveolar rhabdomyosarcoma
PAX 5 → lymphoma
PAX 8 → Thyroid cancers

★ FMR gene → fragilex synd.
★ PTEN → 10q → Endometrial ca.
→ Glioblastoma
★ p16 → tumor suppressor gene

★ In lysosomal storage disorder → e.g → Nieman Pick

↓

Gaucher cells are seen

↓

Non- Glycogen → PAS ⊕, Diastase Resistant

Inclusion bodies (parallel rays of tubular structure) in lysosomes

DATE

Diastase test

If a cell is PAS +ve
↓
Indicates it can be d/t

- Glycogen
- Other substances (Glycolipid, Glycoprotein, Proteoglycans)

Rx with Diastase

- Glycogen → Digested → Become PAS -ve
- Not digested → Remain PAS +ve (Diastase resistant)

* Trans-differentiation → Ablity of stem cells to cross barrier of differentiation to transform into a cell of another lineage expressing the molecular characteristics of different cell type with the ability to perform the function of the new cell type.

BRCA-1 → 17q21
BRCA-2 → 13q12

* In-situ DNA nick end-labelling → Fraction of cells in apoptic pathways

TUNEL → method of detecting DNA fragmentation

* Gene therapy used →

① SCID (ADA def.)
② Wiskott-Aldrich synd.
③ Chronic granulomatous disease
④ Sickle cell disease
⑤ Thalassemia

* Folic acid → chromosome 21

IMMUNITY

Innate	Acquired
∘ Birth, 1st line of defence	
∘ No memory	∘ memory
∘ Non-specific	∘ Specific
↓ Dendritic cell, NT, mϕ	↓ Cell mediated → T cell
NK cells	Humoral → B cell
↓ Innate lymphoid cell (ILC)*	NK-T cell
Compliments	MHC
CRP	
Pattern Recognition Receptors	

*TLR - Toll-like Receptors
- ↳ 10 in number
- ↳ Can be present in hematopoeitic / Non-hematopoeitic cell

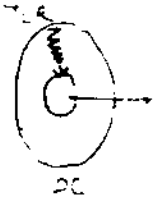
MoA -

Gram +ve → TLR-2 → Also fungus

Gram -ve → TLR-4 → Also against leptospira endotoxin (Endotoxin)

+2 - 4 = -2
- → fungus
- → leptospira endotoxin

MoA of TLR - Nuclear transcription



Nuclear transcription factor - (NFK/β) → cytokine synthesis

Attack is by virus - in place of nuclear transcription factor,
Interferon Response factor (IRF)
↓
IFN → cell surface receptor mediated interferons

DATE

viral nucleic acid synthesis is blocked

↓

prevent replication

STEM CELLS

↳ Immature cells

↳ CD-34

CD - Cluster of differentiation

↓

lymphoid progenitor cells

Study - Immuno-pheno-typing

PAX-5

↓

B-cell

Notch

↓

T-cell

NOTCH

BM (Immature) → IgM

Immature

MBBS

Mature - IgM/D (MD)

MD

Activated B cell - IgM/D/A (MDA)

MDA

DATE

B-cell →

CD-10 → CALLA → Good prognosis

Common Antigen

19-24

79

Involved in signal transduction ← Pan-B cell → CD-19

Macrophage- monocyte marker - CD-14 > 13, 15, 33.

T-cell - Notch

CD 1-8, 28

Involved in signal transductn ← Pan-T-cell - CD-3

* Glial cell tumor - CD-133
* Best marker for plasma cell - CD-138
* Best marker for myeloid cells → CD-117

↓

Myeloperoxidase (MPO) - most specific marker for myeloid cells

↓

Better than CD-117

* Memory cell - CD-45-RO
* Pan-leukocyte - CD-45
* Nk cell - CD16/56.

* In IgA nephropathy - mesangial cells - CD-71
* Transferrin Receptors → CD-71

Erythroblast "

Glycophorin A "

* EBV on B-cell → CD-21 / CR-2

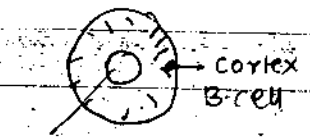
B-cells - Attain maturity in BM

precursor B cell ——(Tyrosine Kinase)——→ Mature Bcell

BRUTON'S AGAMMAGLOBULINEMIA → XLR → B-cells ↓.
→ B-cell tyrosine kinase def.
→ Absence of antibodies
→ Recurrent bacterial infn.

Sites - LN, spleen, GIT mucosa

LN → Cortex
spleen → White pulp.
GIT mucosa → Aggregates of lymphoid follicles - Peyer's patches.



WISKOTT ALDRICH SYNDROME

- XLR
- Mutatn in WASP gene → on ~~Xp~~ chr. X - short arm
- Becomes symptomatic in children
- Thrombocytopenia ——— Eczema
  — Recurrent Infn
- propensity of auto-immune disorder,
  malignancy (mainly lymphoma, leukemia)
- Small platelets

Rx – BM transplant

COMMON VARIABLE IMMUNODEF.

(N) no. of B-cells

Intrinsic B cell defect (defective cytokine receptor called BAFF)

Hypogammaglobulinimia

→ ADA def. - in severe cases

: α_1-antitrypsin def.

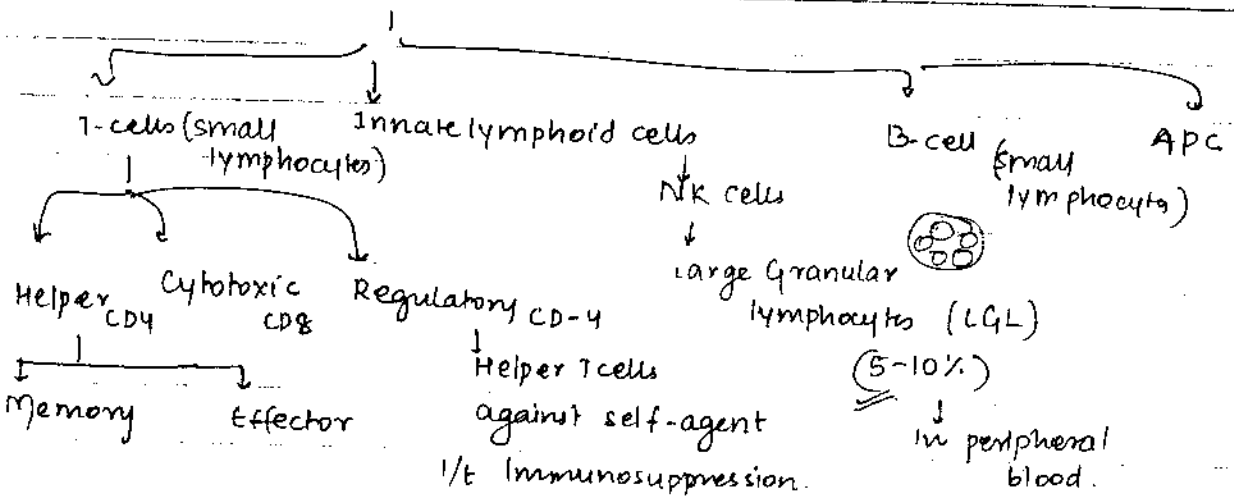
- AR
- panacinar
- pulm. ~~fibrosis~~ emphysema
- PAS+ve

  Diastase -ve.

HYPER IgE Syndrome, Job's Syndrome

- Coarse facial features
- Recurrent Staphylococcal Infn
- High serum IgE levels.

Immune cells

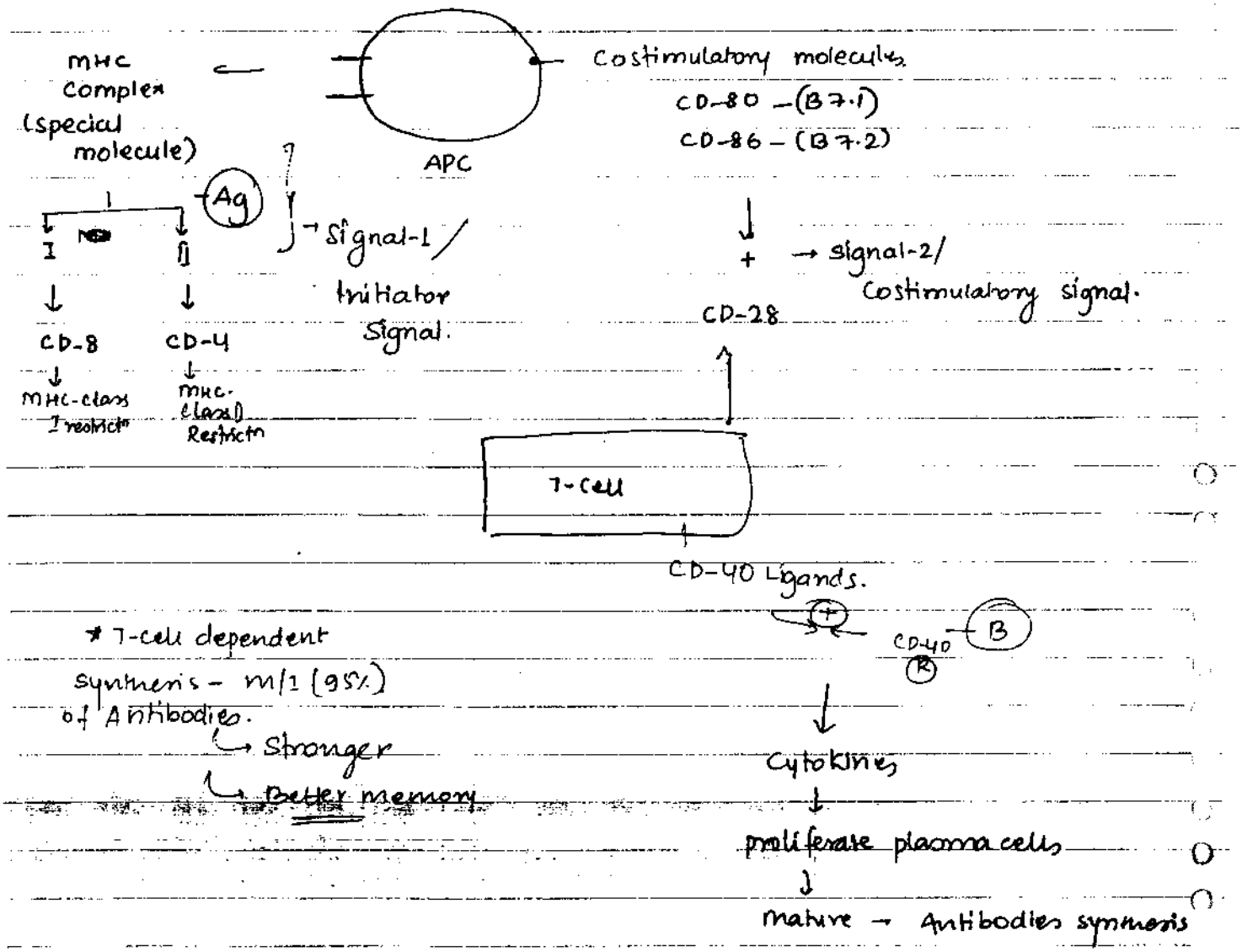


T-cell > B-cell
└ 70% of peripheral blood

origin - Bone marrow
maturation - Thymus.
Central organ

- Primary lymphoid organs - Thymus, Bone marrow
- Secondary lymphoid organs - LN, spleen
- Tertiary " → ① CALT (cutaneous Assoc. Lymph. tissue)
② Synovium (RA)

DATE



ANERGY → permanent inactivation of T cell d/t lack of costimulatory signal
↳ Also for B-cell.
↓
Mech. to prevent autoimmunity in peripheral blood.

• produced, maturation @ both places – Bone marrow, Thymus.

cytotoxic T cells. CD-8

function–

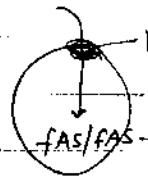
- Killing of viral infected cells
- Tumorcells – Killing
- killing of grafted cells.

NK-cell ↕ functionally similar to CD-8 T cells

More potent than NK-cells for all 3 functions.

• Perforin is secreted by CD-8 > NK cell

↳ Granzyme mediated action



→ Apoptosis (Extrinsic pathway)

Normal body cells – Have MHC-Class-1 cell ~ Non-MHC restricted.

∴ Inhibit – NK cell mediated killing

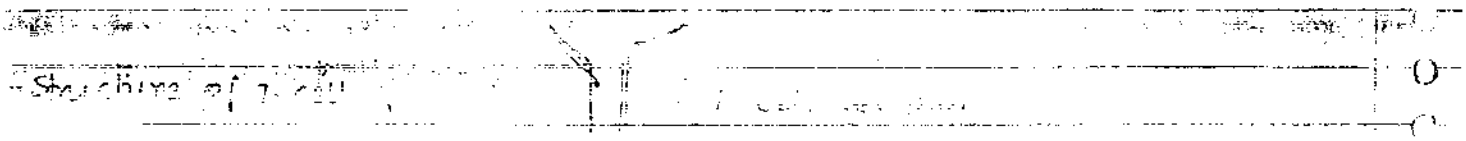
In c/o Viral infection/ Tumor cell

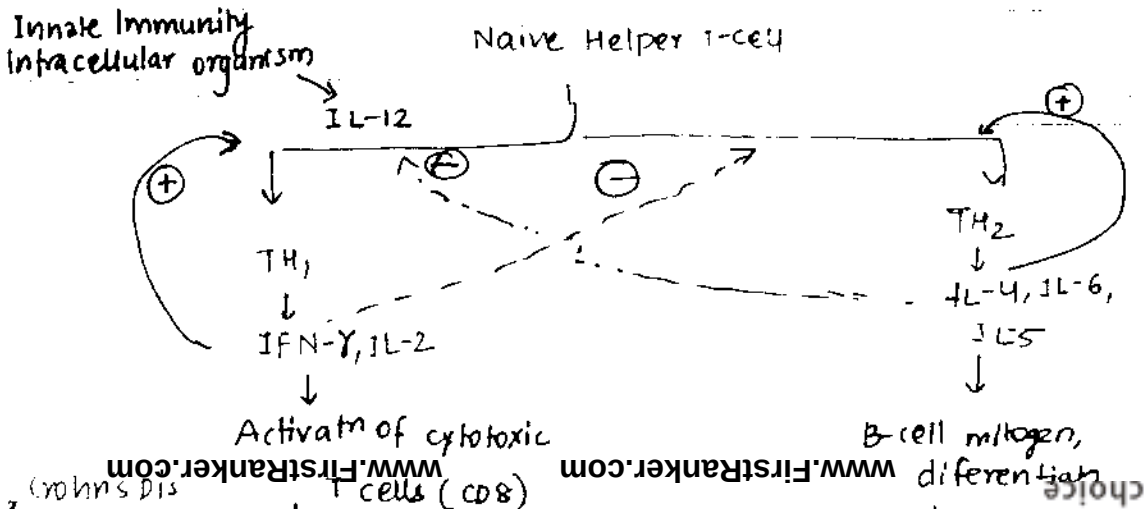
↳ MHC ↓ ved

Killing occurs.

• myeloid cells → CD-11

DATE





Helper T cells – T-CD-4.

Memory T-cell

Effector
TH_1 TH_2 TH_{12}

* Memory B-cell - more stable, long lasting effect- in comparision to memory T-c

TH_1 cell → IgM Ab

Activated by - IFN-γ

Release → IFN-γ, IL-2,12

IgM → MΦ

↓

Activate MΦ

↓

- Intra-cellular killing
- Granuloma
- Hypersensitivity Reaxn - Type IV

TH_2 cells. → IgG Ab

Activated by - IL-4

Release - IL-4 > 5 > 6, 13

↓ ↓

Mast cells Eosinophils.

4 - mast
1 2 3 4

5 → E (A-B-C-D-E)
1 2 3 4 5

- Type 1 Hypersensitivity Reaxn
- IgE antibody synthesis more
- Killing of parasites

DATE

TH-17 →

Activated by - IL-1, 6, TGF-β
Produces - IL-17

* Rheumatoid Arthritis
↳ Type IV Hypersensitivity

↳ severe inflammation
↳ consists of monocytes, NTs
Eg - Autoimmune disorders - Psoriasis,
RA,
Multiple sclerosis.
- fungal infection.

* CD_4TH_1 → memory
Ab synthesis → IgG, M
Opsonization
Activation of cytotoxic cells (Not full established)

DATE

* T-cell → maturation in Thymus → Nurse cells

↳ cells of thymus die → Thymic involution (puberty)

DiGeorge Syndrome.

↳ Absence of Thymus gland

↓

T-cell def.

C → Cardiac defects → m/c → TOF

A → Abnormal facies

T → Thymic aplasia

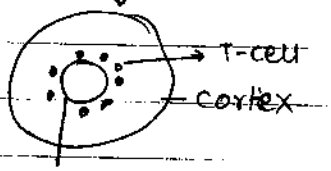
C → Cleft lip/palate

H → Hypocalcemia → d/t Absent PTH gland.

22 → Defect in chr. 22q

Site of T-cell →

① LN



② Spleen

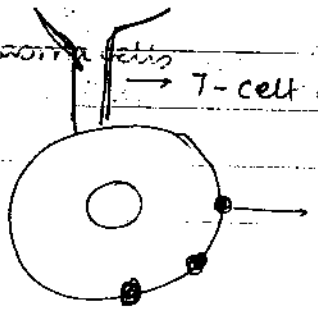
↳ (+) in white pulp

↳ peri-arteriolar area

③ G.I.T.

↳ Intra-epithelial lymphocytes.

Structure of T-cell



T-cell Receptors

↳ 95% → αβ T-cells (Blood, Tissue)

↳ 5% → γδ T-cells (skin, GIT)

CD molecule

↳ CD1-8, CD28

CD-3 → pan T-cell marker

↳ very near to base of T-cell receptor

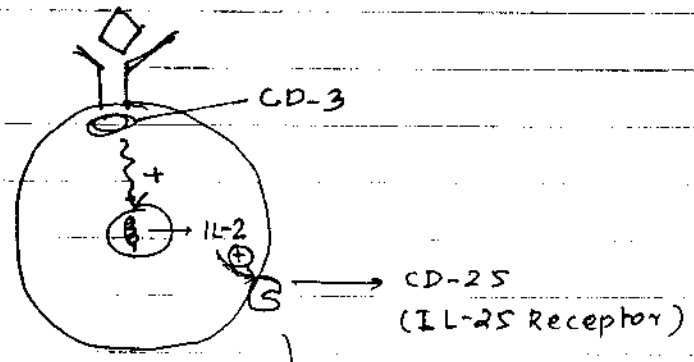
CD4 - Helper CD8 - Cytotoxic

$CD_4 : CD_8 = 2:1$

4 X 2 = 8

8 X 1 = 8

* Monocytes - In the tissues are called - mϕ
  - In kidney → Mesangial cell
  - In liver → Kupffer cell
  - In bone → osteoclast
  - In spleen → Littoral cell *
  - In placenta → Hoffbower cell *
  - In lungs → Alveolar mϕ (Dust cells)



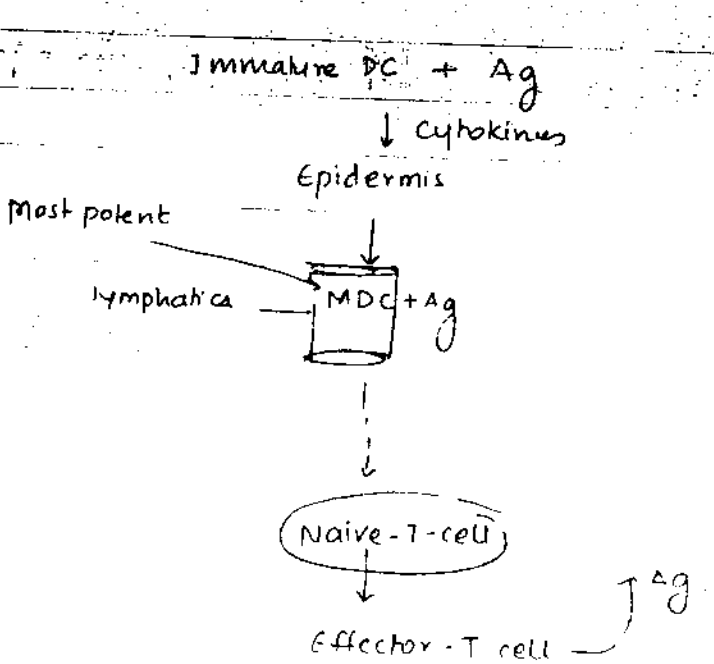
* To ↓ this clonal expansion
  - in organ transplant
    - ① Anti-CD-3 Ab
      - Muromonab
    - ② IL-2 Receptor Ab
      - Basiliximab
      - Daclizumab

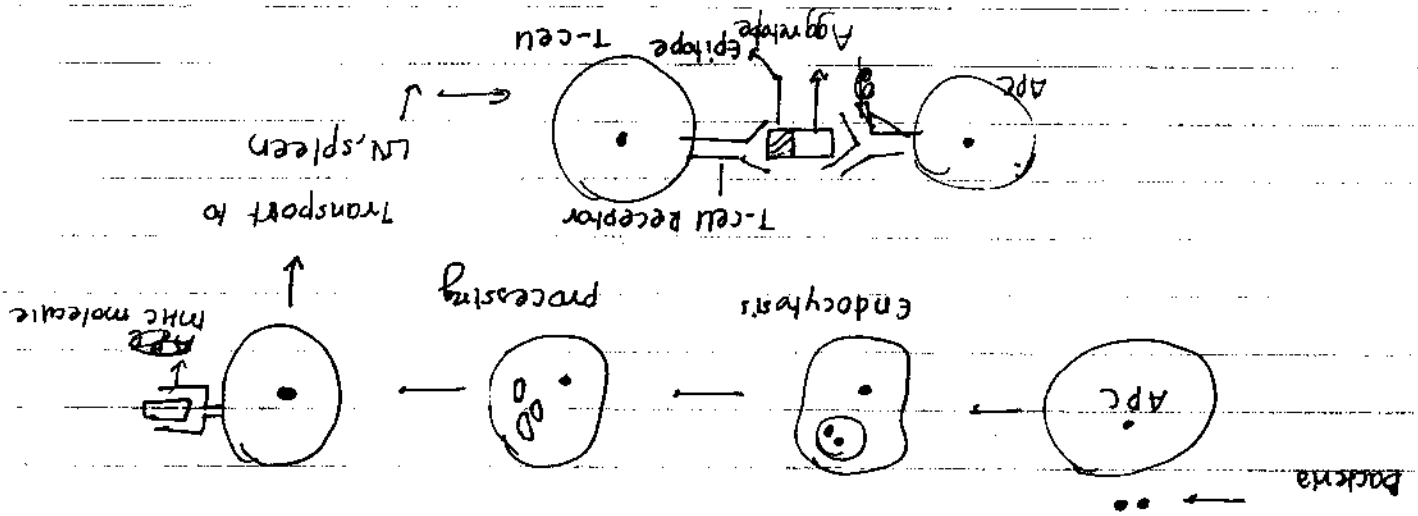
APC (Antigen Presenting cells)

Professional (Use MHC class)	Non-professional
↳ mϕ	↳ Glial cells (All)
↳ Dendritic cells	↳ oligodendrocytes / Astrocytes / Ependymal cells.
↳ Immature dendritic cells (Langhan's cell)	↳ Endothelial cells – All.
↳ B cell	↳ fibroblasts.

→ T-cell - not an APC
↳ certain epithelial cells
° Thymic epithelial cells

* most potent APC - Dendritic cells (mature)
* Site of maturatn of APC - Lymphatics.

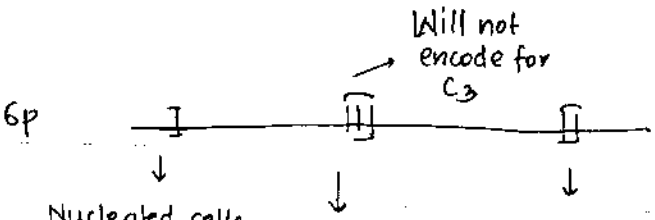




MHC (Major Histocompatibility Complex)

A/K/a HLA (Human leukocyte Antigen)

- Chromosome - 6p
- Adaptive Immunity
- Seen on APC



★ def. of C_1

m/c a/w Autoimmunity: C_2, C_4 → Autoimmune (SLE like in pediatric age group)

★ Mixed lymphocyte Reaxn – Used to detect MHC-type II

★ Graft Rejection, Graft Versus Host dis. → Both CD-4, CD-8 → Both are involved.

MHC class II + I

★ MHC-I → Indigenous Ag peptide

★ CD-4-Tcell → MHC-II → Exogenous Ag. peptide

CD4 : CD-8

2 : 1

MHC-II

MHC-I → CD-8

DATE

* Organ transplant tissue → HLA M/1 → for matching

HLA DR > B > A

↳ kidney transplant (M/C organ for transplant)

* for organ transplantation, size is not important in renal transplantation.

GRAFT REJECTIONS

1) Hyperacute → mins > hrs
→ d/t preformed Antibodies. ⌐ d/t blood transfusion, prev. transplant

2) Acute → Humoral → Type II Hypersensitivity Reaxn
↳ Cell-mediated

↓

Antibodies against fixed surface antigens

3) Chronic → Type IV

4) GVHD → Type IV

Acute Graft Rejection →

Humoral → m/c >> Cell mediated

↓ ↓

Type II Hypersensitivity Type IV Hypersensitivity

GVHD (Graft Versus Host dis.)

- K/a RUNT's disease in sheeps and cattles
- Donor - Immunocompetent
- Recepient - Immunodeficient

→ A/w solid organ transplantam like liver.

- m/c a/w stem cell transplantam

GVHD

- < 100 days → Acute → Skin → Scaly lesions.
- >100 days → chronic → D/D - scleroderma (d/t subcutaneous fibrosis and calcification)

m/c involved → Skin
liver
Small intesti
lungs (Rarel

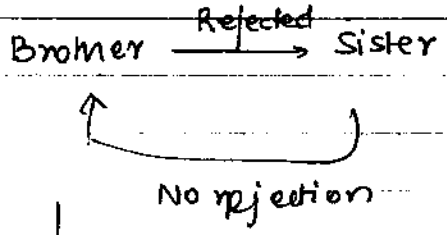
m/c c/c of Death → Bacterial pneumonia
↳ m/c - pseudomonas.

m/c cancer after GVHD → Squamous cell ca >>> Melanoma
(Intermittent sunrays expo

2nd m/c - NHL
3rd m/c - Kaposi's Sarcoma.

In HIV → m/c → Kaposi's Sarcoma
↓
intermediate grade Vascular tumor.
m/c site → lower limb
skin

DATE



XX

X Y → "H-Y Ag" → Alkla minor histocompatibility complex

- Ubiquitously transcribed Tetratricopeptide HY linked Graft Rejection (Eichwald Silmser effect)
- sex-linked Graft Rejection.

* Type V - Hypersensitivity Reaction

↓

Variant of Type II

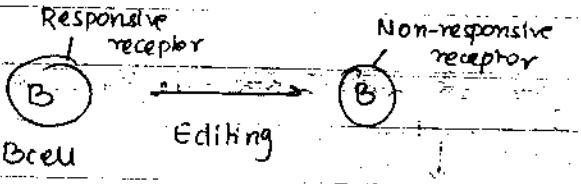
AUTO-IMMUNITY

- loss of "Immunological tolerance"
  - ↓
  - "Non-responsiveness to self-antigen"

Immunological tolerance

Central tolerance

- Negative selection (Central deletion)
  - ↓
  - By Apoptosis - Auto-reactive cells are killed.
  - ^ for both B-cell and T-cell
- Central editing (Receptor editing)



* for only B-cell.

Peripheral tolerance

- ANERGY → d/t lack of co-stimulate Signal (for both B, T cell), Permaner
- BIM / FASL → self-Ag → Apoptosis
- Hepler T cells → self Antigen → Regulaton T cell
  - CD-25 (α-chain of IL-2 receptor)
  - Fox-p gen
  - TGF-B, IL-10,13 ← Cytokines
    - ↓
    - Immunosuppressive Action
- Antigen sequestration (Discrete Ag mass away from
  - Immune previliged site → Brain
    - ← Eyes
    - Testis
    - Eg Sympathetic ophalmitis

* fox-p3 gene - mutation - IPEX syndrome

Immune dysregulation

Polyendocrinopath

DATE

* Other factors I/t autoimmunity.

ii) Susceptibility genes

e.g. MHC

HLA-B27 (93%) – Ankylosing Spondylitis

HLA-CW6 – Psoriasis

HLA-DR4 → RA

HLA-DQ2, DQ-8 → Celiac dis/
Dermatitis Herpetiformis.

• M/c assoc. with Autoimmunity – PTPN-22 (polymorphism)
  - RA
  - Bronchial Asthma
  - Psoriasis
  - multiple sclerosis
  - DM

• NOD-2 → Crohn's disease

• IL-2, IL-7 polymorphism is a/w → multiple sclerosis.

iii) Role of environment

Neuropsychiatric ← Infection → Endotoxin

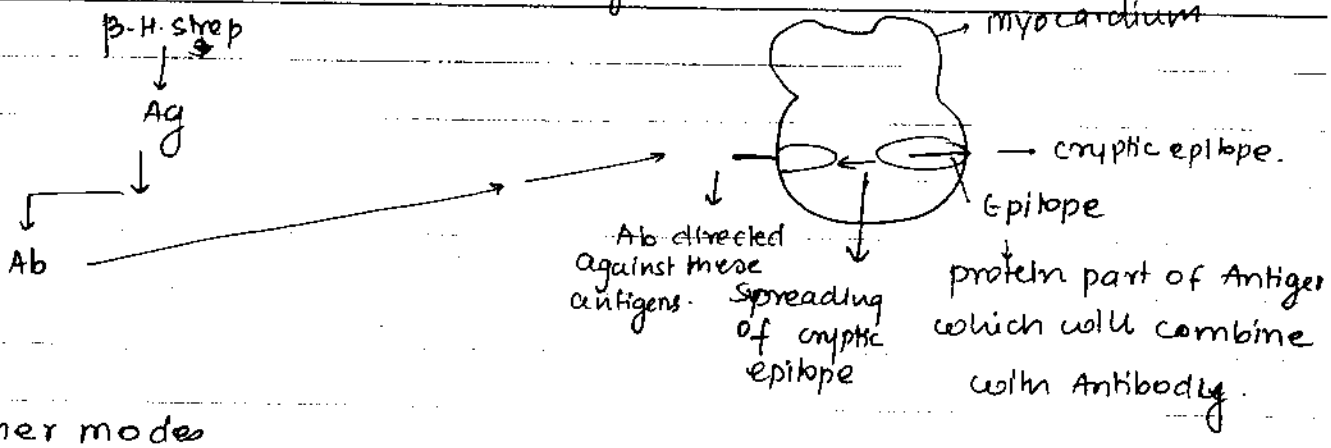
Raynaud's phenomenon → Anti-[illegible] DNA (DNA-[illegible])

↓ Immunosuppression.

- Molecular mimicry – DM
  (cross-reactivity) – RHD

RHD – Grp A β- Hemolytic streptococci
- M-1, 3, 5, 6, 18 strains
- Cross-reactivity / Molecular mimicry.

Molecular mimicry / Cross-reactivity



Other modes

* Upregulation of co-stimulatory molecules
* Polyclonal B cell activation → EBV, HIV.
* Alter the property of tissue Ag → to become antigenic.

DATE

DATE

AUTOIMMUNE DISORDERS.

- m/c - females
- m/c Age group (20-40 yrs)
  except - Sjogren's Syndrome 40-60 yrs.

SLE

- malar rash
- Polyserositis
- Photophobia → correlates to - RO (SSA-A) Ab.
- Pleuritis, shrinking lung syndrome - Ab - RO (SS-A)
- Neuropsychiatric symp → Anti-Ribosomal P- Antibody
- Reynaud's phenomenon → Anti-U1-RNP (RNP- Ribonucleoprotein)
- Heart - pericarditis - m/c >> LSE (Limbman-Sack's endocarditis)
- Renal - Lupus Nephritis (50%)
- Hematological - Auto Antibodies → RBC, WBC, platelets.
  (85% of pts.)
- Musculoskeletal (95% of pts.)

In lungs - m/c pleuritis
↳ Also seen
Shrinking lung syndrom

- m/c/c of Death - Cardiac failure
  ↳ Early death (< 10yrs) - Lupus nephritis

DATE

In SLE,

most sensitive Ab → ANA (Anti-nuclear Ab)

most specific Ab →

	Sm Ab	DSDNA
Sensitivity	30%	70%
Specificity	95-98%	90%

most important for prognosis correlation → dsDNA

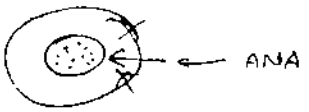
most specific and sensitive } → dsDNA
Best

- Mother - SLE
  ↓
  "Newborn" - CHB (cong. block) (Neonatal lupus) with CHB
  ↳ M/C - Ro > LA (SS-A) (SS-B)

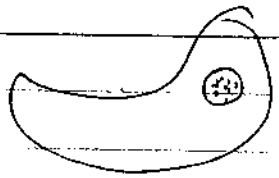
* Drugs procainamide / ~~Hydra~~ Hydralazine
  ↓
  drug induced Lupus → Anti-Histone Ab. (m/c)
  ↳ Renal } - involvement - Rare/Absent
  CNS }

  ↗ a/k/a - Hematoxylin Body

* LE cells → seen only in (1) Bone marrow (mC)
  (2) Peripheral blood



TART cell → Nucleus chromatin - (N)



* Wire loop lesion → seen in Type IV - lupus nephritis (Diffuse proliferative GN)
* ANA → Against Antigens in rat liver secretions.
* Onion-peel appearance of splenic capsule.

* APLA → Ab against β-2 glycoprotein I complex

* Kikuchi-fujimoto → Histocytic necrotizing lymphadenitis

SCLERODERMA

Systemic sclerosis

⇓

collagen deposition

- Subcutaneous fibrosis and calcification
- 20-30ys, female
- Hallmark of systemic sclerosis → vascular injury

↓

platelet - PDGF (fibrogenic cytokine)

↓

Induces fibrosis / collagen deposition

2 types of SS

① Diffused / Total

↓

- Anti-DNA Topoisomerase Ab (SCL-70)
- RNA-polymerase III Ab.

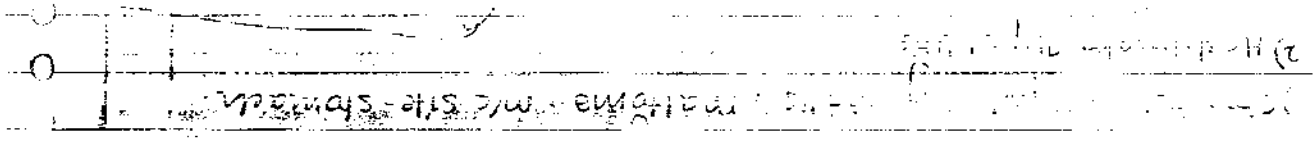
② localised.

- ← Anti-centromere Antibody

CREST → u

morphea → u

★ m/c Assoc with - Inflammatory myositis.



INFLAMMATORY MYOSITIS.

1) Polymyositis
2) Dermatomyositis → m/c - overall/ peds/ Adults
3) Inclusion-Body myositis → mc → >50yrs of age.

↳ m/c assoc. with paraneoplastic Syndrome.

i) Polymyositis - Endomysial inflammatn,
No perifascicular atrophy

ii) Dermatomyositis - perifascicular atrophy
+ Inflammatn
→ Vasculitis (Dermal capillary involvement)

- Heliotropic Rash
- Gottron's papule

→ Anti-"mi" Ab.

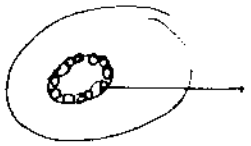
→ Mechanic hands/ Interstitial lung dis → Anti-Jo-1 Ab. (Jovan-Mechan)
(Anti-Histidyl t-RNA-synthase Ab)

- Juvenile Dermatomyositis
- paraneoplastic

→ Anti-p155/p-140 Ab.

iii) Inclusion-body myositis

"Rimmed vacuoles"



→ Basophilic material → Hyperphosphorylated Tau-protein

↓

Amyloid

↓

Congo Red +ve

→ Apple green Birefringence

SJOGREN'S SYNDROME

(40-60 yrs)

1° sjogren's
↓
No known etiology
↓
- Glandular: dry eye, dry mouth
- Extraglandular: m/c → Arthritis/Arthralgia
  - Splenomegaly
  - Hepatomegaly
  - Hepatitis
  - Lymphoma → marginal zone B cell lymphoma.

2° sjogren's
(Known Auto-immune dis)
m/c a/w RA (Rheumatoid Arthritis)
others - SLE, scleroderma
→ Chronic Active hepatitis (Autoimmune hepatitis)
→ 1° Biliary cirrhosis

* In chronic inflammation - m/c lymphoma → marginal zone B cell lymphoma
  1) Stomach → H. pylori gastritis → maltoma → m/c site - stomach
  2) Hashimoto Thyroiditis
  3) Sjogren's.

in stomach → m/c NHL - Diffused Large B-cell lymphoma

Dx is →

(1) Biopsy -
Site of choice - minor salivary gland of lips
Earliest finding - Around bld vessels → perivascular } Lymphocytic infiltration
Around ducts → periductal

(2) Serology - SS-A (Ro) - involvement correlation
↳ most sensitive
SS-B (La) → most specific

DATE

Anti-U1-RNP ab

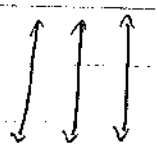
↑

* mixtures of symptoms → mixed connective tissue dis.

Eg. malar rash + erosive Arthritis + dry eye/mouth + subcut. fibrosis + inflammed muscle.

AMYLOIDOSIS.

Amyloid → Glycoprotein



Length - Infinite
Diameter - 7.5-10nm
Non-branching fibrils.
} Electron Myscopy.

β-pleated sheets (secondary structure) → I/t congo Red +ve
↓
Best seen by - ① X-ray Deffraction
② Infra-red spectroscopy

• Also seen in - prion's Dis (PrP^c)
↓
Prp^{sc} (dis.) (Kuru plagues)
↓
Congo Red +ve.*

Congo-Red staining
1
Light Mscopy (Ordinary staining)
↓
Red/pink
(Non-diagnostic)
↳ may be seen with
↳ Hyaline
↳ fibrin
↳ Collagen

2
Polarised Myscopy
↓
Apple green birefrengence.
(diagnostic)

DATE

C C

↳ Amyloid - Extracellular
Acellular
pink - Amyloid material

Other stains → 1) Thioflavin T
2) Methyl violet
3) Crystal violet
4) Toulidine Blue → Also used for mast cells.

* Silver stain → Never used for Amyloidosis.

Liver
↓
IL-6 > IL-1
↓
Amyloid

Primary (AL) - 1° (more common)
↳ L - light chain of Ig

m/c/c of Death - Cardiac failure
m/c/c - Morbidity - Renal

e.g. multiple myeloma → plasma cell disorder

Secondary
2° → AA
Usually chronic infl.

m/c/c of Death - Renal failure.

m/c/c of Death - Overall
↳ Cardiac failure.

Gingival Amyloidosis
↓
λ-chains (lambda)
(Amylambda chains)

m/c a/w
↓
Rheumatoid Arthritis

Also seen in chronic osteomyelitis

No amyloid deposition

Chronic Bronchitis → metaplasia → dysplasia → lung Ca.

Lung Abscess → Formed a/t Bronchiectasis → ∴ Amyloid will be seen.

Bronchiectasis → Amyloidosis
lung abscess → Brain abscess
→ Suppurative Arth
→ Renal abscess.
Not a premalignant condition

Renal Amyloidosis

a) RCC → AA type (paraneoplastic synd.)

b) Hemodialysis → A-β_2 microglobulin.

Paraneoplastic syn
1) Amyloidosis
2) fever
3) Nephrotic synd.

→ ~~Hodgkin's~~ Hodgkin's lymphoma → AA (Paraneoplastic synd.)

c) Familial Renal Amyloidosis
↳ A-α (α-fibrinogen)

* AIAPP → Islet cell Assoc Polypeptide → In DM - Diabetes mellitus

* ACal - Cal - Calcitonin - medullary Ca. thyroid.

* Aβ - Alzehmer's dis.

familial

1) familial Amyloidotic polyneuropathy
↓
Trans thyretin (prealbumin) - $T_{1/2}$ - 2 days
(TTR)
↓
Mutant type TTR in FAP

2) Senile systemic Amyloidosis
Wild type - TTR

DATE

Senile systemic Amyloidosis - AlK/a

Senile cardiac amyloidosis

Extracardiac findings - rare

↳ Benign condition (course)

↳ CHF - Rare.

* Best site for Biopsy for Δsis - Abdominal fat pad aspirate. > Rectal Biopsy

m/c site - Abd. fat pad aspirate.

Rectal biopsy - Sensitivity - 60%.

Abd fat pad - 80%

* Isolated organ amyloidosis - That particular organ will be site for biopsy

* Organ m/c affected by Amyloidosis - Kidney

most dangerous " - Kidney

Earliest site to be involved in Kidney — mesangial matrix > Capillary Basement Membrane

m/c presentation of Renal Amyloidosis → Nephrotic Synd (Massive proteinuria) > HTN

- Earliest site to be involved in liver amyloidosis - Space of disse

- Diffused amyloidosis of spleen → lardaceous

Spleen Amyloidosis
- ① follicles (localised) → Sago spleen.
- ② La"RED"aceous spleen - Red pulp - diffused type.

DATE

AIDS

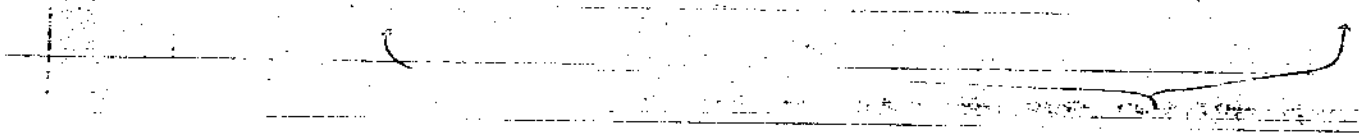
- HIV
- m/c mode of spread → Sexual contact
- Vertical transmission - m/c - Infected birth canal during (N) vaginal delivery
- M → to - f > f - to - M
- least efficacious - Sexual
- Risk of transmission → 0.3% - with needlestick injury
  whereas - Hep B - risk is max - 30%.
- M/c strain in India - HIV-1 group M subtype C.

- severe wt loss - Slim's dis.
- M/c Infn a/w HIV in India - Slim's dis
- Candidiasis - m/c fungal infn in India a/w HIV/AIDS.
- Pneumocystis Carini (PCP) pneumonia - m/c fungal infn in world
- m/c Cancer - Kaposi Sarcoma
  - ↳ vascular, sm. ms. cells.
  - B-cell lymphoproliferative disorder → Castleman's dis.
- In Non-HIV pt. - m/c site of lymphoma → Stomach
  (extranodal)
- In HIV pt. → m/c site - Brain / CNS.

- ADC Aids Dementia Complex - m/c Neurological manifestation of HIV infn.
- Inflammatory myopathy - m/c sk. ms. disorder in HIV.
  - ↳ vasculitis is always absent
- most specific change - CNS.

Aids. - most sensitive } ELISA
Best screening test }
most specific } - Western blot
Confirmatory }

During window period - 10C - PCR



* Not seen in the CNS lesions in ALDS- Inclusion bodies

Hypersensitivity Reaxns

DATE

Type 1 Hypersensitivity Reaxn/ Anaphylactic Reaxn.

- Rapidly developing immunologic Reaxn - occurring within minutes
- After combinatn with Ab of antigen, in an individual previously sensitized to the antigen.
- Commonly referred to as allergy.

1st step - Sensitizatn

↓

TH_2 cell activatn

↓

IL-4 → Basophil

IgE

IL-5 → Eosinophils

Subsequent exposure - 2 phases

Initial phase → within minutes → release of preformed mediators

↓ Degranulation

Late phase → 2-24 hrs → 2° mediators

↓

Cytokine release

*Anaphylactoid Reaxn — on 1st antigenic exposure

↳ short lived

Type II Hypersensitivity / Ab mediated.

Opsonizatn and complement, → Phagocytosis } → Transfusion Rxn, Erythroblastosis fetalis, AIHA, ITP

Complement, Fc Receptor mediated. → Inflammatn } → Goodpasteur Synd, Acute Rheumatic fever, vascular rejections, vasculitis

Ab mediated cellular dysfn } → Myasthenia Gravis, Pemphigus Vulgaris, Grave's Dis, Pernicious Anemia, Insulin resistant Diabetes.

Hemolytic Dis. of Newborn.

Type III

Hypersensitivity (Immune Complex Dis.)

Ag-Ab complex

Phase I → formation of Ab x 5 days

Phase II → Deposition of Immune complex

Phase III → Inflammation after 10 days of Ag administration

- Raji cell assays
  - To measure levels of immune complex

Deposited in Bld vessel - Vasculitis

Kidney - Glomerulonephritis

Joint - Arthritis.

localized Type III → Arthus Reaxn

farmer's lung

Hypersensitive pneumonitis

PAN

Systemic → SLE, Reactive Arthritis, HSP, PSGN, Serum Sickness, Type II lepra Reaxn.

Type IV Hypersensitive

1) Delayed type (CD4 T cells)

Organ m/c affected by Amyloidosis: Kidney

↳ TH1 cell

↳ TNF-α, IFN-γ, IL-2,12

↳ Granuloma formation

2) T-cell mediated toxicity (CD8)

- Perforin granzyme dependent killing
- fas-L

Examples

- Tuberculin Reax
- Lepromin
- multiple sclerosis
- Chronic graft Reject
- contact dermatitis
- Sarcoidosis
- Type 1 lepra Reaxn
- Crohn's Dis

Immunoglobulins.

IgG → Max. concentration in human body
Important for 2° immune response
Can cross placenta

IgA → present in physiological secretions of the body.
Present in monomer form in serum, dimer - in glandular secretions
Responsible to activate - Alternate pathway

IgM → Primary immune response
Max. molecular wt, max. molecular size
Present as pentamer
'Millionaire's Antibody'
B cell (R)
IgM, IgG → Responsible for classical pathway

IgD - B cell Receptor

IgE - Red in Allergic conditions
A/K/a - Homocytotropic antibody
Reaginic antibody

* Gaucher cells - In Gaucher's dis
↳ mφ containing lipids, glycogen, Fe

Pseudogaucher cells (ceroid histiocytes) - BM - in CML, ITP, leukemia
↳ mφ containing - only lipid

∘ Growth in the lack of stimuli

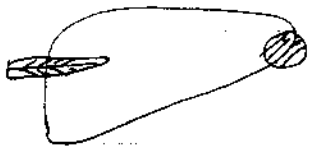
Characteristic features-

① Rate of growth - of tumor cell will be more than (N) surrounding tissue

"oma" - 1) Hematoma → Not a ~~tumor~~ neoplasm because rate of growth is equal to surrou
2) Choristoma →

Hamartoma - monoclonal growth - ∘∘ Tumor
polyclonality - s/o - inflammatn, infection
monclonality - s/o - tumor

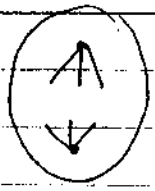
Choristoma
(N) tissue @ Ab(N) anatomical site
(Ectopic Rests of (N) tissue)



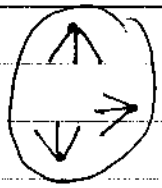
Hamartoma
Ab(N) tissue @ (N) Anatomic site

∘ In ~~clinically~~ palpable tumor mass - ~~brain~~ / CNS
1) Cell count - 1×10^9 cells
2) > 30 cell - doubling
3) > 1gm - tissue mass

② mitotic figures -
(N) mitotic figure - Endometrium
Bone marrow
Urinary bladder epithelium.
Atypical mitotic figure - Always s/o neoplasia



Typical mitotic figure (Bipolar mitotic figure)



Atypical mitotic figure (>2 poles) - Tri/Tetra/Pent

* max. proliferative index → Burkitt's Lymphoma.
↓
m/c assoc. with tumor lysis syndrome.

③ Metastasis → sure sign of malignancy
except - Glioma of brain
→ Basal cell ca. of skin

* m/c malignancy of skin → Basal cell ca. of skin

• Neuroendocrine tumors + mets ⇒ malignant, for

Without mets
↓
They are called benign

- ↳ pheochromocytoma
- ↳ PTH adenoma.
- ↳ Pituitary carcinoma

• follicular thyroid tumor → Invasiveness (vascular) > Capsular invasion ??

↳ Biopsy - Δstic
FNAC - Non-Δstic.

M/C route → lymphatics

↳ predominantly by carcinomas

except 2 ca., which spread by hematogenous

↓

RCC, HCC } m/c - venous.

Hematogenous Route → Sarcomas

1) Osteosarcoma
2) Embryonal Rhabdomyosarcoma
3) Pleomorphic "
4) Alveolar "
Synovial sarcoma } → Not hematogenous, Lymphatic route

(e.g. muscle tumor cells - Giant cells)

(4) Anaplasia - loss of differentiation

→ Hallmark of cancer.

* Tumor progression - Ting order of severity from benign to malignancy

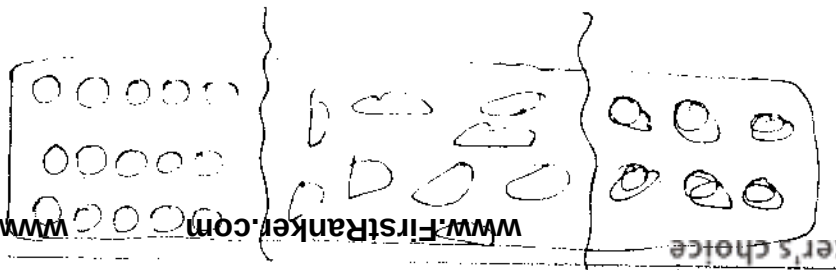
(N) tissue → metaplasia → Dysplasia → Anaplasia

↓ ↓ ↓

Reversible | partially reversible | Irreversible

Nuclear/Cytoplasm - (N) = 1/4-6 | N/C - altered | N/C ⇒ 1

(N) alignment anatomically ← Cell polarity (N) | Cell polarity - lost | Cell polarity - lost

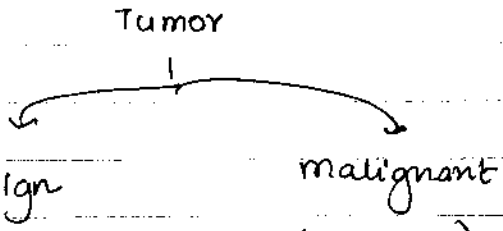


* CIN - Cardnoma in situ

DATE

* If BM is damaged → now called as Invasive carcinoma

* Differentiating b/w CIN, invasive ca → Basement memb



Tumorigenic

HPV – 6 + HPV – 16
11 18

Carcinogenic

only HPV – 16
18

* Mle mets to brain - Small cell Ca lung tissue

* Chemo-therapy drugs → mainly cause apoptosis,
Can cause necrosis

* Anoikis → Death of epithelial cells after removal from (N) milieu of substrate, particularly from cell-to-cell contact.

* No bony mets → Gastric carcinoma

* Desmoplasia - proliferation of non-neoplastic fibrous connective tissue

8 Hallmark changes in Ca cells →

1) Self sufficiency - Do not require external growth factors.

2) Resistant to growth inhibitory signal →
↓
"tumor supressor gene"

3) Evasion ~~for~~ from Apoptosis
- Intrinsic pathway is more important → disabled for tumorigenesis.

Bcl-2 / mcl } Anti-Apoptotic - get activated.

4) Limitless Replicative potential of ↑ed telomerase expression.

5) Angiogenesis

Tumor cells can't grow beyond "1-2 mm" limit →
without forming bld vessels.

→ Lymphatics → never formed by tumor

- m/c stimulus for angiogenesis → Hypoxia
↓
HIF-1α (Hypoxia Inducing factor)
↓
VEGF (Help in angiogenesis)

6) Metastasis →

most essential factor for metastasis - Angiogenesis.

↓

metastasis signature gene

1) Ezrin - Rhabdomyosarcoma, osteosarcoma
2) mi-RNA-10b
3) SNAIL
4) [illegible]

↓

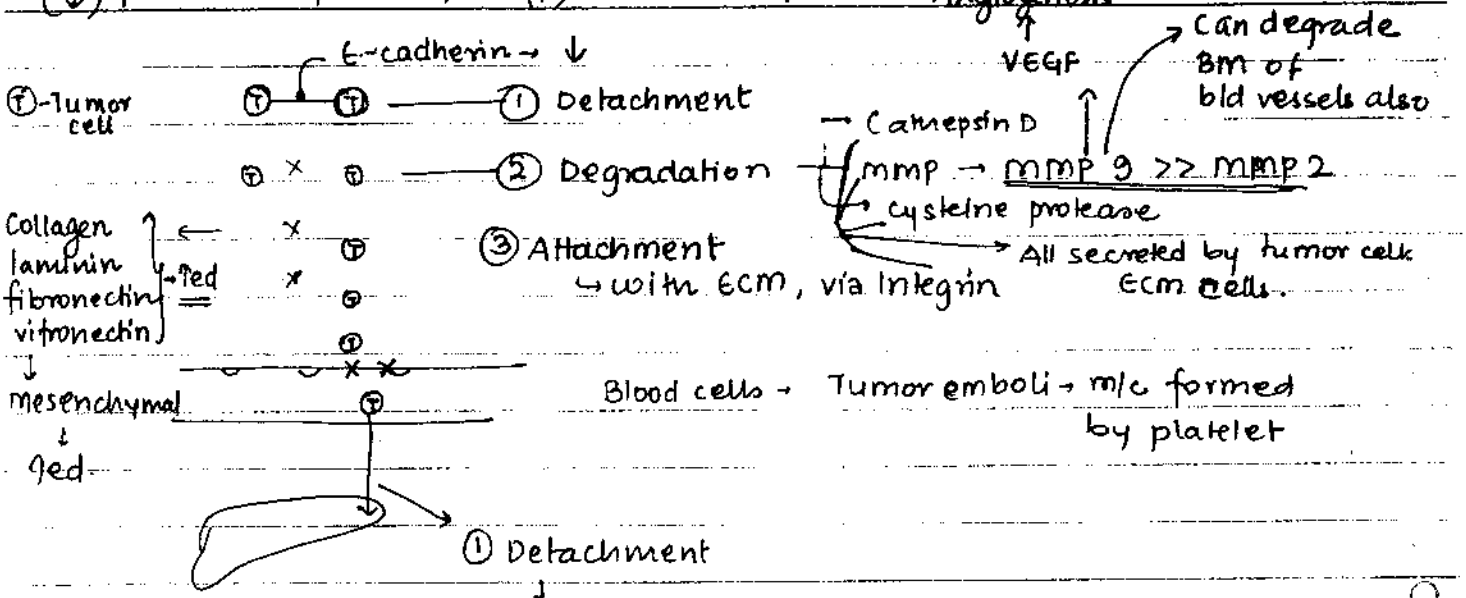
Anti-mets

1) mir 226
2) mir 335
3) NM 23
4) KAI-1
5) [illegible]

METASTATIC CASCADE

DATE

(↓) Epithelial mesenchymal (↑) transition → /EMT



Blood cells → Tumor emboli → m/c formed by platelet

① Detachment

↓

② Degradation

↓

③ Attachment

m/c mets
- ↳ Ca. colon → liver
- ↳ Ca. lungs → Adrenals

⑦ Evasion from immune system

i) By-pass → CD-8 T cell / MHC-Class 1

ii) Tumor cell ⊕→ co-stimulatory signal

↓

∴ Bypass anergy

iii) ~~⊗~~

CD_8 T cell > LAK > NK > mϕ } By pass

↓ (lymphokine Activated killer cell)

Most potent Anti-tumor cell

Tumor cells inhibit anti-inflammatory cytokines

IL-10, 13, TGF-β

⑧ Tumor metabolism

mainly by - Glycolysis (Aerobic)

↓

"Warburg effect" → bypass mitochondria,

↓

Nobel prize in 1931 — get O_2 from tissue O_2.

* "Gene - Repair" defect / Chromosomal Instability Syndrome -

AR
- B ig - Bloom Synd
- F - fanconi's Anemia
- A - Ataxia Telengiectasia
- X - Xeroderma pigmentosa → Nucleotide excision repair gene defect

AD
- Lync - Lynch syndrome (Hereditary Non-Polyposis colorectal ca.)
  - ↓ Mismatch Repair gene defect (Spell Checker)
    - Colon: Variable length of microsatellite
    - Endometrium
    - Ovary
    - Stomach ca

DATE

Chromothrypsis → Alk/a "chromosomal shattering"
or random/ haphazard chromosomal damage
↓
2 fn → Activate onco-gene
→ Inhibit tumor suppressor gene

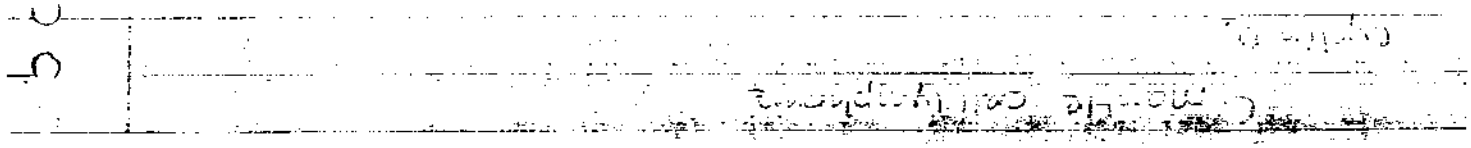
Seen in - Gliomas,
Osteosarcomas.

Oncogene - Addiction → Tumor is addicted to the oncogene
↓
"BCR-ABL" → CML ⟶ cured.
↑ Ph
Imatinib
↓
If oncogene is removed
↓
Tumor dies.

Differentiation therapy → By therapy, maturation of cells are done.
AML-M3 ⟶ Retinoic Acid
Promyelocytic (PML)
↓
Differentiated into Neutrophils.

* familial cancers -

- early age of onset
- Tumors arising in 2 or more close relatives to of the index case
- Sometimes multiple or B/L tumors
- familial cancers are not assoc. with specific marker phenotype



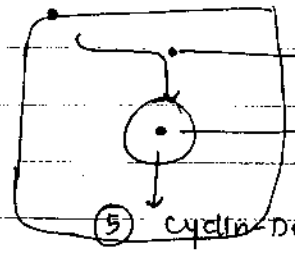
PROTO-ONCOGENE

- Normally present
- f^n - cell proliferation, differentiation

(1) GF (Growth factor)

↓

(2) GF-R - (Receptor for growth factor)



↓

cell-cycle

$G_0 - G_1 \longrightarrow S \rightarrow G_2 \rightarrow M$ (proliferatn/Differentn)

Proto-oncogene

- important for (N) growth
- may become - oncogenic

(A) Oncogene

- Viral origin
- Viral oncogenes do not have introns, ∴ differ from human oncogene

DATE

1) Growth factor → TGF-β - tumor suppression gene

- PDGF - α (SIS)
- FGF - fibroblast growth factor
- HGF - Hepatocyte growth factor
- TGF-α - Tissue growth factor

ii) Growth factor - Receptor -

ERBB-1 → Lung Adeno ca. (Non-small cell ca.)

ERBB-2/ → Breast ca.

Predicting ← (Her-2/New)

Therapeutic Response RET - proto-oncogene - medullary ca. of thyroid

↓

EGF(R) Steel factor → GIST

Epidermal growth factor (R) (C-KIT) → Also in seminoma, melanoma.

↓

CD-117

((R)-Tyrosine Kinase) myeloid cancers (AML, CML)

iii) Signal transduction protein →

(1) RAS (m/c oncogene mutation in human ca. - RAS)

↓

(20-30%)

Active in hyperphosphorylated form

• 53% of Human ca. → p53

* Ca-pancreas → K-RAS → 90% → oncogene

p-16 → 95% → Tumor suppressor gene

(2) ABL

BCR-ABL - CML → (+) of BCR-ABL - good prognosis

ALL → " → bad prognosis

(3) BRAF mutation (+) in >60% of melanoma

↓

④ JAK-2 → myeloproliferative disease

⑤ Notch → T-leukemia/ lymphoma
→ Breast Ca.

IV) Nuclear transcription factor

m/c → "C-myc"
"fos"
"Jun"

C-myc translocation - Burkitt's lymphoma
N-myc ~~trans~~ amplification - Neuroblastoma
Medulloblastoma
} Bad prognosis
L-myc - small cell lung ca.

V) Cyclin D_1 (BCl-1)
↳ mantle cell lymphoma

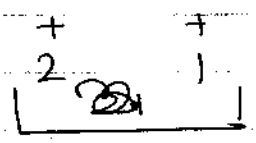
Cyclin D_2
↳ follicular cell lymphoma

CDK-4 (Cyclin-dependent kinase)
↳ Glioblastoma Multiforme
↳ melanoma

DATE

Cyclins → D ⟶ E ⟶ A ⟶ B

CDK → K4, 6 2



[Rb + EF.2] Inactive "Off"

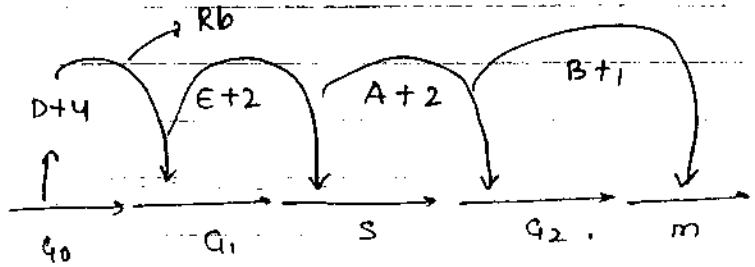
EF-2 → Cyclin E, A, B
DNA polymerase
Other proteins

Cyclin D + K4 → ↑↑ ATP

→ Hyperphosphorylated state of Retinoblastoma

Rb "On"

* Governor of cell cycle - "Rb-gene"



Cyclin-D - @ mid G0 phase.

Two check points

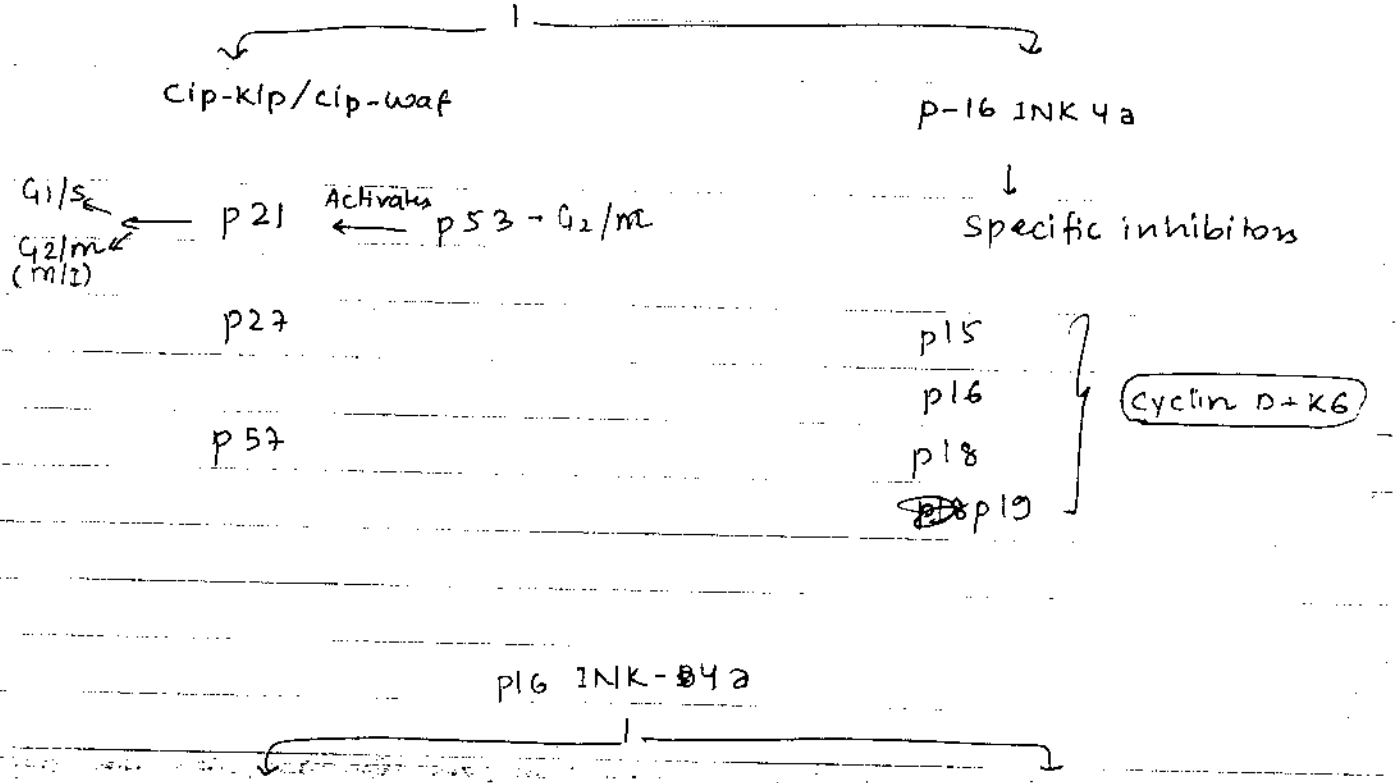
1) G1S
2) G2M

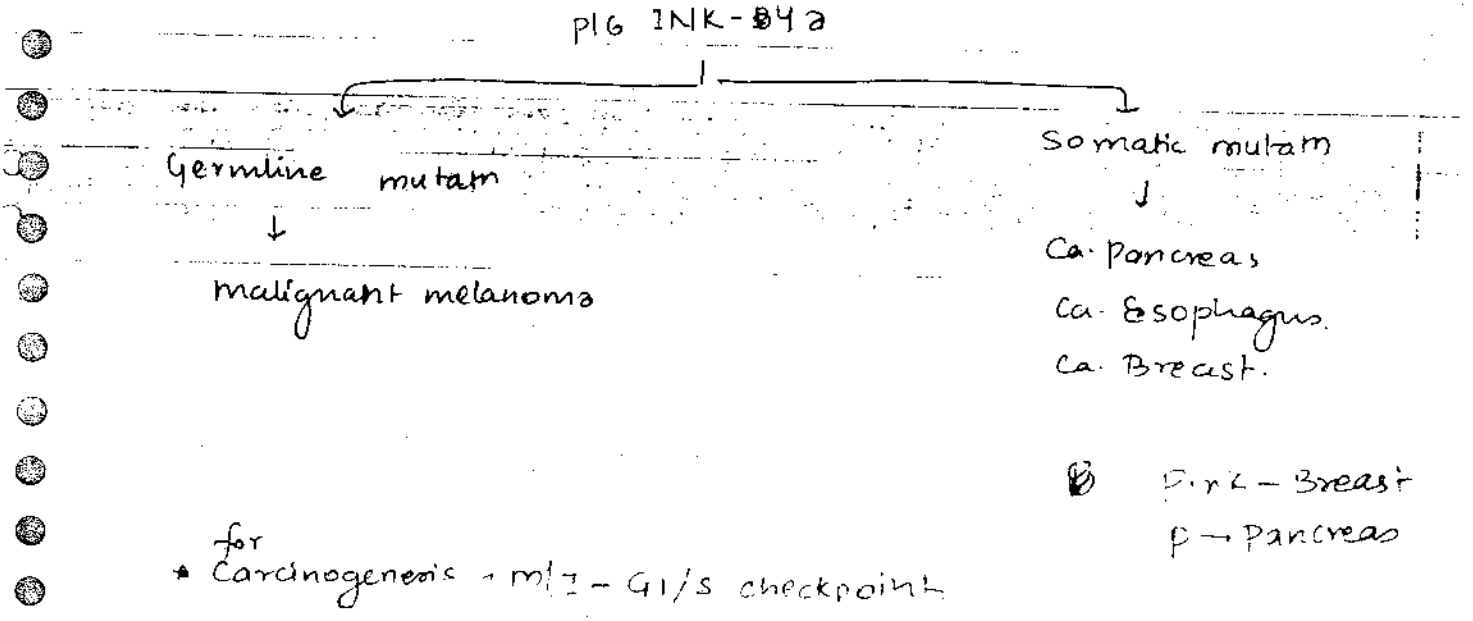
Any error before DNA replicat → G1S checkpoint

Any error after DNA replicat → G2M

G_2M checkpoint → cyclin B > cyclin A

Cell-cycle Inhibitors –





for
* Carcinogenesis → M/I – G1/S checkpoint

DATE

* most radiosensitive - G2M > M least - S.

* Doubling of DNA → S phase.

→ Duration

S - 6 hrs

G_2 - 4 hrs

M - 2 hrs

fixed.

Others - G_0, G_1 → variable.

* Topoisomerase I → nicks DNA

II → Break in strands.

* E-cadherin def → Breast
Gastric ca.

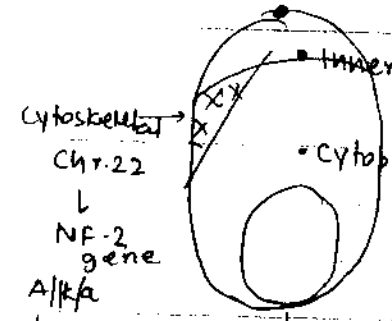
* wnt / β-catenin → GIT, liver Ca.

* m/c a/w Retinoblastoma - osteosarcoma

* [illegible] - No [illegible] Flexner-Rossettes are seen.

* APC - gene - Chromosome 5

TUMOR SUPPRESSOR GENE



on cell membrane → TGF-β
↳ E-cadherin → (m/c mutatn in familial gastric Adenoca.)

inner membrane
↳ NF-1 gene → somatic mutation → Neuroblastoma
↳ Germline mutation → Neurofibromatosis
↳ lobular ca. of breast.

Cytoplasm
PTEN → Endometrial adeno ca.
SMAD 2/4 → Ca. Pancreas/colon

p53
Rb
WT-1

17 X 1 = 17 - Breast
13 X 2 = 26 - Ovarian

BRCA 1 → Chr. 17q → Breast ca.
BRCA-2 → Chr. 13q → Ovarian ca.

Male Breast Ca → BRCA2 > BRCA1

• female → No Family h/o Breast ca. → most common mutation
↳ p53
(somatic m/c > Germline)

• If family h/o Breast ca. → m/c mutatn → Breast ca.

p53 → guardian of genome / Molecular policeman

- chromosome 17p
- mol. wt - 53 KDa
- A/w Li-fraumeni Syndrome (Multiple hereditary ca. syndrome)

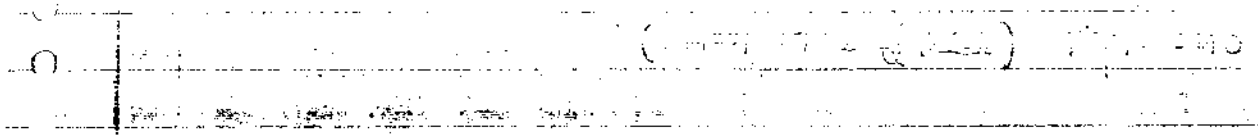
p73 → Big brother of p53

p53 → 53 KDa → 17p

Tissue Injury
↓
↑p53
⊖ ↓ | ↓
p21 | GADD-45 | Bax, Bam, PUMA
↓⊖ | Growth Arrest DNA damage-45 | ↓
G1S/G2M | ↓ | ↓
Block → Repair → Apoptosis

p53
↓
induce microRNA | LINC RNA
⊖ ↓ | ↓
Bcl-2 | Cell cycle blocked.
↓
Apoptotic

functions of proto-oncogene
↳ signal transduction
↳ Nuclear transcription
↳ Apoptosis inhibition/activation.



Chemical carcinogenesis

(1) Benzopyrene → p53 ↑
↓
liver
↓
Cyt P-450
↓
Benzopyrene → Epoxide (Unstable) → Carbonium ion (Nucleo-philic)
↓
DNA-damage → Cancer.

AMES test - used for chemical mutagenicity
↓
Salmonella Typhimurium (Histidine -ve)
↓
+ Chemical (To be tested)

His - → (N)

His (+) → mutagenic chemical.

DATE

Radiation

Ionizing

↓

m/c - Blood ca. → AML (m/c)
ALL
CML

Not assoc with - CLL
(CALL-AMLA)

m/c extrahematopoeitic ca. - papillary Ca. of thyroid.

Non-Ionizing

↓

UV light
A
B → Bad (m/c)
C

↓

Xeroderma Pigmentosa
- Intermittent ∞ exposure
↳ melanin

free radical

↓

MICROBIAL CARCINOGENESIS

1st organism → carcinogen

↓

H. pylori

↓ ↓

Gastric adenoca. ← NHL ← d/t chronic inflammatn

↓ (maltoma)

"Cag"-A" gene Marginal zone B cell lymphoma

mutation

- m/c NHL of stomach → DLBCL (Diffused large B-cell)
- m/c site for MALT tissue → Ileum.

Chronic H. pylori

↓

lymphocytes (polyclonal)

↓

free radical

↓

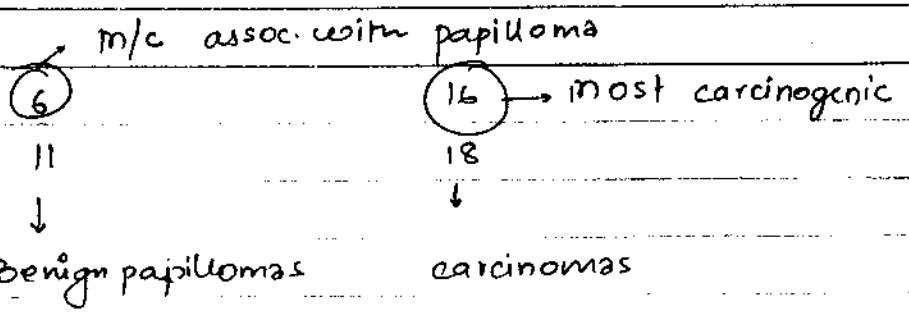
DNA damage

↓

Somatic mutation → "monoclonal"

DATE

HPV



* Integrated form → carcinogenic
* Episomal → Benign

E_6 → inactivate → p53 (3 half of 6).

E_7 → inactivate → Rb

* HPV → can be a risk for

Esophageal Sq. cell ca.

- Endemic Area → Risk (+)
- Non-Endemic → No Risk.

Hepatitis (B), C

└ most carcinogenic - as HBV → DNA virus → damage the DNA

↓

Incubation period of carcinogenesis

└ 10 yrs.

* HCV - cytoplasmic damage → incubation period of carcinogenesis → 21-30 yrs.

└ RNA virus

* Hep B - m/c for - 1) Hepatocellular ca.

2) Cirrhosis

3) Transfusion transmitted Hepatitis.

DATE

★ Post transplant lymphoma → EBV

★ LMP-1 gene – EBV

★ Most radiosensitive tumor – Testicular Seminoma.

★ ?°/c – Angiosarcomas of liver.

★ Non-neoplastic – CMV

★ Aflatoxin B1 → HCC

★ HTLV-1 → leukemia

★ PVC
Arsenic
Thorium
} → Angiosarcoma of liver.

★ Clonorchis sinensis – cholangioca.
opisthorchis viverrini →
Schistosoma hematobium → SCC of U. Bladder
Schistosoma japonicum → colorectal ca.

Δstics in Cancer

DATE

Tumor Markers

↳ Ald in Δsis

↳ Help in assessment of prognosis

↳ Help in assessing response to Rx

↳ Level of tumor marker correlates size of tumor.

Ca-125 → Ovarian tumor → Not used for screening nowadays.

Ca-15 → Ca. Breast

Ca-19.9 → Colon ca. / pancreatic ca.

NMP-22 → Urinary bladder ca.

★ Best / most specific, sensitive for HCC → Arginase-1

Others for HCC → α-Fetoprotein

↳ Tumor marker for all types of HCC except for fibrolamellar HCC

(50%) ↓ ↑ed AFP

↓

Tumor marker → α-Neurotensin

• α-Fetoprotein is raised in Hepatoblastoma → 95% → ↑ed AF

↳ Better Answer.

★ Seminoma → LDH

→ placental alkaline phosphatase

→ 15% cases → β-HCG +ve

→ CKIT +ve, CD30 -ve

DATE

Non-seminoma ⟶ ↑ed AFP

↓

→ Embryonal ca. → [CD 30 +ve, CKIT − ve]
→ Endodermal sinus tumor (↑ed AFP → max, α_1 − Antitrypsin ⊕]
(Yolk-sac tumor)
→ Teratoma
→ Choriocarcinoma

∘ Melanoma → i) Most specific → HMB-45
Most sensitive → S-100
2) Vimentin
3) Micro-ophthalmia transcription factor-1 (MITF-1)
↳ for choroid melanoma

* Sacro-coccygeal teratoma → AFP > β-HCG
* ~~CBAD~~ Ca. lung, Breast → CA-15-3.
* Tumor which follows Rule of 10 − Pheochromocytoma.
* migratory thrombophlebitis − m/c → adeno. ca. pancreas, lung, colon.
* EPO (erythropoeitin ↑ed) in → Renal ca.
* ↑ed Ca^{2+} levels in paraneoplastic syndrome in ca lung −
↳ PTH related peptides.

* prostate ca − PSA
colon ca − CEA
Ovarian ca − CA-125

* Spontaneous regression − Neuroblastoma.
* AFP may rise in ca. pancreas
↳ Not in ca. colon, kidney, Bladder Ca.
* CEA − elevated in → Alcoholic cirrhosis, Ca. colon, Emphysema
Not in Ulcerative colitis

DATE

* Polycythemia - seen in — cerebellar hemangioblastoma.
* Migratory Thrombophlebitis (Trosseau's sign)
  ↓
  Disseminated cancer.

* BCl-2 → marker of follicular lymphoma (B-cell-lymphoma).

* skeletal mets are usually multifocal, by Ca. Kidney, thyroid - solitary lesions.

* Tumor lysis syndrome → All hyper, except Calcium → Hypocalcemia

DATE

FNAC

- → only cells are visualised
- → only a preliminary test
- → Ideal needle size - 22-26G needle
- → Absolute contra-indicatn → 1) Pt refusal
  2) Bleeding diathesis
  3) H/o anaphylactic shock

- → Cannot differentiate b/w follicular ca. v/s adenoma

Imprint Cytology

m/c used for → Lymph Node biopsy

Exfoliative cytology - ∘ Sheddings are studied in body fluids, cavities.

∘ Cytology is used to descriminate b/w dysplasia and poorly-differentiated ca.

∘ Used for → any cancer. → e.g. → 1) Lung ca. → Bronchoalveolar lavag

2) Gastric ca. → Gastric lavage

m/c → 3) Renal, U.B. ca. → Urine

4) Cervical cancer → Pap smear

Cervical secretn

Immunophenotyping

CD markers

Immunohistochemistry –

[Ab → Tumor-tissue Antigen] → The reaxn will be Studied using microscopy.

m/c Antigen used → Intermediate filament

5 types of intermediate filaments

① Cytokeratin → Used for epithelial tumors (carcinomas)

for mesothelioma lung → cytokeratin 5, 6 → used.

in ALD (Alcoholic liver dis.) → mallory-Denk body.

↓

Cytokeratin 8, 18.

② Skeletal ms. intermediate filament → Desmin

for rhabdomyosarcoma → Desmin (Best marker)

↳ Another marker → myogenin

③ vimentin → for melanoma, seminoma,

Granulosa cell tumor of ovary → (Also +ve for (Inhibin) → CD99, Cytokeratin, Epithelial memb. Antigen)

④ Neurofilament → for – 1) Neuronal tumor of brain → Ganglioglioma, Gangliocytoma, Neurocytoma, Dysembryoplastic neuronal epithelial tumor

2) Neuroendocrine tumors

↓

Carcinoid
Neuroblastoma
Pheochromocytoma
paraganglioma

⑤ GFAP (Glial fibrillary Acidic protein)

for glial tumors → 1) Astrocytoma
2) Oligodendroglioma
3) Ependymoma.

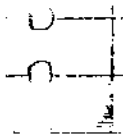
* Cytogenetic analysis of solid Ca. → m/c problem
↓
Bacterial contamination
2nd → Inappropriate sample

* Small cell Ca. lung - Chromogrenin
Synaptophysin
CD-57

* Malignant melanoma → CDKN2A gene

migratory [illegible] → c-myc fah [illegible], lung, colon.

[illegible] (embryonal tumors) = Rhabdomyosarcoma.



HEMATOLOGY

Bleeding and Coagulation disorder

- No clotting in (N) blood vessel → d/t → smooth endothelium, covered by Glycocalyx

- minor cut → spontaneous healing occurs d/t ↓ Endothelin mediated transient vasoconst

- m/potent vasoconstrictor → Urothelin > Endothelin > Angiotensin

- Anticoagulant properties in endothelium
  1) Heparin like molecule → + Anti-thrombin III → ~~Inactivates~~ inactivates ↓ factor II, 9-12
  2) Thrombomodulin
     - ↳ Seen in all bld vessels except cerebral microcirculation
     - Moderate thrombin (pro-coagulant) ↓ thrombin (Anti-coagulant) + Protein C, S ⊖ → Inactivate → factor 5-8.

DATE

Bleeding, coagulation disorder

↙ minor — major/massive ↘

minor

↓

petechiae, purpura (mucosa, skin)

↓

platelet disorder

↓

1st → Inv. - Platelet count (1.5-4.5 lacs)

Thrombocytopenia < 1 lac

Spont. bleeding - < 10,000

↓

2nd → Bleeding time

2-9 min - (N)

major/massive

↓

→ Bleeding into joint (Hemarthrosis)

→ Spontaneous hematoma

→ prolonged bleeding

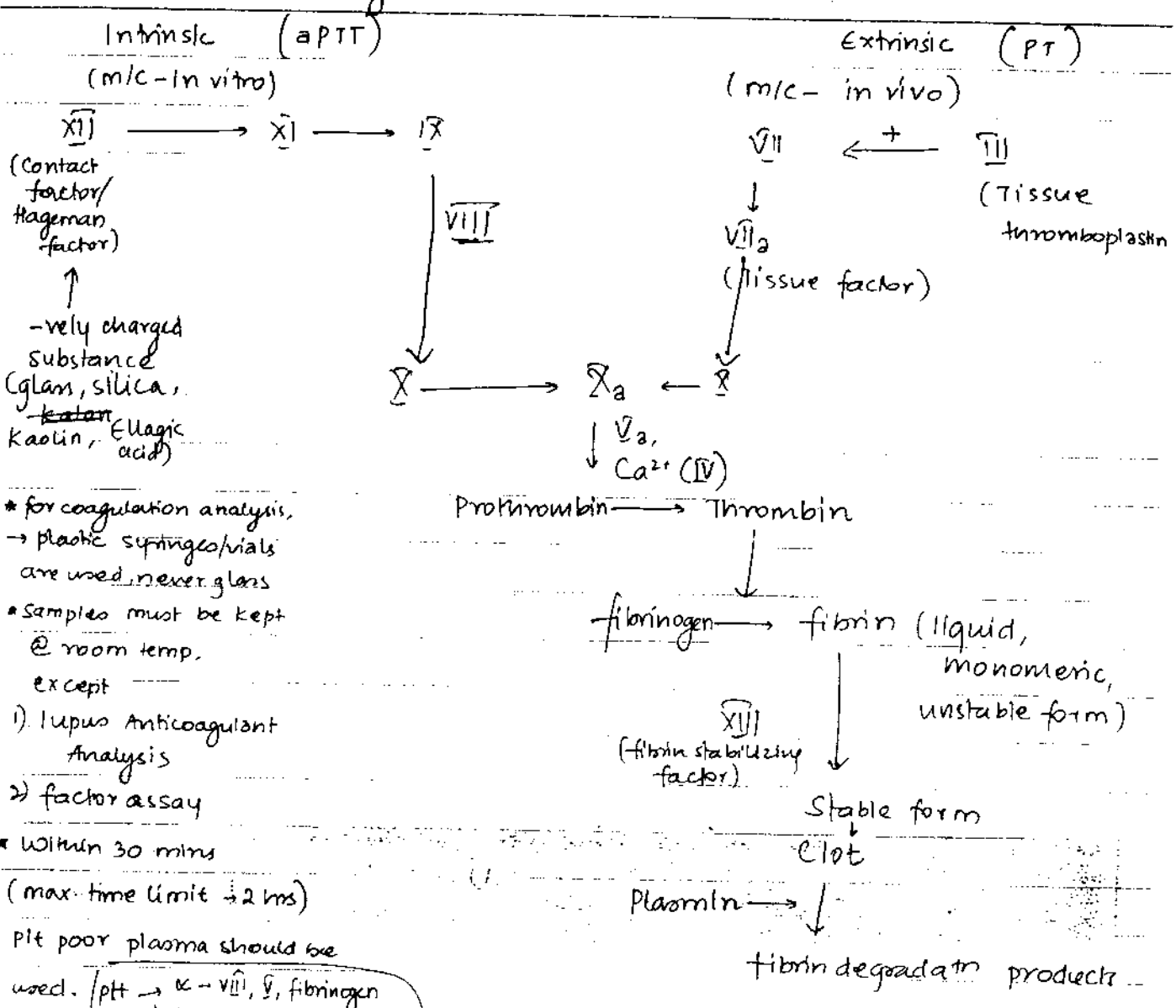
↓

clot factor def.

1st → 1) PT → 11-16 sec

2) aPTT → 30-40 sec (26-40 sec)

Coagulation

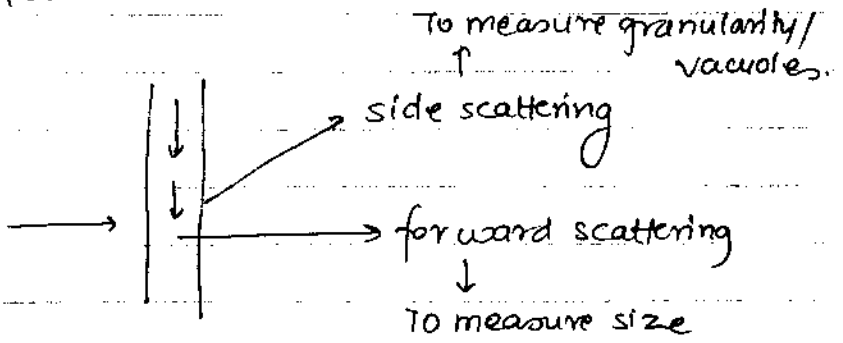


* for coagulation analysis,
→ plastic syringes/vials are used, never glass
* Samples must be kept @ room temp, except
1) lupus Anticoagulant Analysis
2) factor assay
* Within 30 mins
(max. time limit ± 2 hrs)
* Plt poor plasma should be used. (plt → α – VIII, V, fibrinogen; δ – ADP, Ca^{2+}, serotonin)
plt will cause coagulation
hence, factors can't be studied

* for platelet disorders, platelet rich plasma should be used.
* Anticoagulant of choice for coagulation studies → 3.2% Trisodium citrate
for ESR estimation - Westergren method → ——
Wintrobe ——→ oxalate (disodium/dipotassium)
* CBC — EDTA
* ABG → Heparin ← Leukocyte defect dis.
* flow cytometry → "Any" can be used. ← immunophenotyping

DATE

flow cytometry → * Best to detect lymphocytosis
↳ Also for immunophenotyping
↳ Inv. of choice for → CLL



Chronic liver disease → Vit K dependent factors - 2, 7, 9, 10

BT → ↑ed (D/t thrombopoetin def.)
PT → ↑ed } (Common pathway derranged)
aPTT → ↑ed } (factor 2, 10)

DIC → Consumptive coagulopathy
plt ↓ed, BT ↑
PT → ↑ed
aPTT → ↑ed
Se. fibrinogen ↓ed
Fibrin degradam product ↑ed

for DIC - 1) most sensitive - FDP
2) most specific - D-Dimer
3) Best → D-Dimer

Hemophilia A

factor VIII def.

XLR

Hemarthrosis

lab → BT - (N)

PT → N

aPTT → ↑ed

B

factor IX / Christmas factor

XLR

Hemarthrosis

lab → BT → (N)

PT - (N)

aPTT - ↑ed

Hemophilia C

factor XI

AR

mostly asymptomatic

BT - (N)

PT - (N)

aPTT → ↑ed.

→ Best Inv. to differentiate

↓

factor Assay Analysis

↓

Sample to be kept @2-6°C

* Acquired factor inhibitors

↳ Auto-antibodies

↳ m/c against - VIII

↳ commonly occurs in

1) Pregnant female, postpartum

2) Autoimmune dis.

3) Disseminated malignancies

DATE

Platelet disorders

Quantitative

↓ plt count ↑ed; BT- ↑ed

Megakaryocytic thrombocytopenia

↓

BM- (N),
In peripheral blood, plt destruction going on,
∴ BM (R), ↑ed megakaryocyte

↓

- Immunogenic
  - ↓
  - ITP
  - Auto immune
  - ↓
  - Coomb's +ve
- Non-immunogenic
  - ↓
  - DIC
  - HUS
  - TTP
  - ↓
  - Coomb's -ve

Amegakaryocytic thrombocytopenia

↓

BM- defect
(Aplastic Anemia)
- leukemia
- lymphoma
- Chemo Rx
- Radio Rx

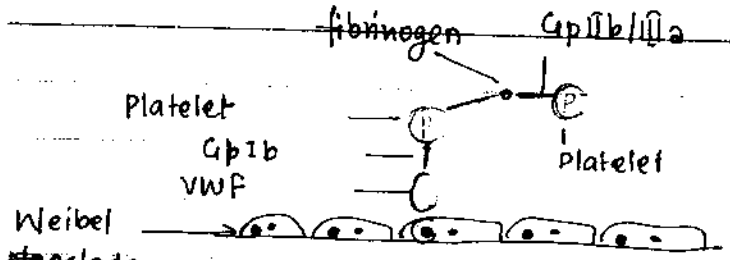
Qualitative

Platelet functional disorder

1) von-willebrand dis.
2) Bernard Soulier dis.
3) Glanzman's thrombasthenia

Lab- BT-↑ed, plt count - (N)

★ In Amyloidosis of skin → petechiae / purpura
↓
occurs d/t factor X def.



↓
containing
↓
VWF
↓
Synthesised by
1) Endothelium → (max)
2) megakaryocytes
3) Liver

• Platelet - fibrinogen - platelet → Aggre
• platelet - VWF - endothelium - Adhesion

→ Antibiotic which Tes interactn b/w VWF/GpIb
→ "Ristocetin" Adhesion test (RAT)
↓
Blood
↓
RAT +ve (N) [GpIb + VWF] → In def → RAT -ve / Ab (N)
↓
(N) Adhesion

→ Platelet Aggregation test →

collagen
↑
A / C / E
↓ ↓
ADP Epinephrine

Plt Aggregator
→ VWF
→ Thromboxane A_2
→ fibrinogen
→ Ig
Leukocytes → No aggregate

DATE

1) Bernard Soulier dis.

- def. Gp1b (plt. adhesion)
- mild plt ↓ed
- AR
- p/s - large platelets.
- lab - BT ↑ed
  PT (N)
  aPTT - (N)
  'Ristocetin' Adhesion test - (↓) Ab (N) / -ve
  platelet Aggregation test - (N)

II) vWD (von-willebrand dis.)

- m/c hereditary bleeding disorder
- ↓ VWF → Stabilise factor VIII
- m/c type - Type 1
- Total - 26 types
- m/severe → Type III
- m/c pattern of inheritance → AD.
- lab - BT ↑ed
  PT - (N)
  APTT - ↑ed.
  RAT - -ve / Ab (N)
  Platelet Aggregatn test - (N)

iii) Glanzman's Thrombosthenia

- Platelet Aggregatn dis.
- Gp 2b/3a def.
- AR
- platelets → small size
- Bleeding from umbilical cord stump - prolonged*, profused.
- lab - BT → ↑ed
  - PT → } (N)
  - aPTT } (N)
- RAT → +ve / (N).
- Plt aggregation test → Defective/Ab (N)

* m/c/c of umbilical cord bleeding - of factor origin - factor XIII

→ consumptive coagulopathy
↓ Cal, BT ↑

DATE

→ ITP (Idiopathic thrombocytopenic purpura)

- IgG → platelet
- Size of spleen → (N)
- BM biopsy - Not Δstic
  ↑ed megakaryocytes.

Spleen size-(N) in
1) ITP
2) Aplastic Anemia

DATE

TTP (Thrombotic Thrombocytopenic purpura)

q/t def. of ADAMTS-13 enzyme
(vWF – metalloproteases).

- If hereditary def. → ⊛ Upshaw-Schulman Syndrome.
  of ADAMTS-13

- omostly affects – arterioles, capillaries.

pentad of TTP → Lab – ↓ed plt count
Microangiopathic hemolytic anemia (MAHA)
Acute renal failure.
Stroke like syndrome
fever.

Hemolytic Uremic Syndrome

1) Typical HUS / Epidemic
- Diarrhoea +ve (D+ve)
- pediatric group
- m/c a/w E coli infn (O157:H7)
  - ↳ Shigella like toxin / verotoxin.
  - ↳ can be a/w → Strept. pneumonia (lung infn)
- picture similar to TTP
  - only triad ⊕, two features not seen → CNS, fever.
  - ↓
  - Renal failure
  - Thrombocytopenia
  - MAHA

2) Atypical HUS / Non-epidemic / HUS-TTP
- No Diarrhoea (D^{-ve})
- No infn
- 2° to compliment def → m/c → factor H def
- pentad of TTP.

To differentiate b/w HUS and TTP
- ↳ flow cytometry
- ↳ ADAMTS-13 enzyme levels
  - ↓ ted → TTP
  - (N) → HUS.

- Atypical HUS → like DIC.
  - ↓
  - To differentiate → DT, aPTT → ↑ed → DIC
    - ↳ (N) → Atypical HUS.

ANEMIA

Hematopoeisis → Starts on day-19

1st cell formed → Erythrocytes.

Stages of erythropoeisis

CFU-E ← (+) Erythropoeitin

↓

Pro-erythroblast (pro-normoblast)

↓

Early normoblast (Basophilic Normoblast)

↓

Intermediate normoblast (polychromatic ")

↓

Late Normoblast (orthochromatic ")

↓ ↳ (Nucleus removal)

Reticulocyte → Non-nucleated

↓ Peripheral Blood → Requires 1-2 days - maturation time

(N) RBCs.

Reduction in size.

- Hb → 1st appears @ pro-erythroblast → visualised by specialised staining
  - ↳ 1st identify in Intermediate Normoblast with Routine staining → Romanowsky stain fa
    1) Giemsa (may-Grunu
    2) Leischmann
    3) Jenner
    4) wright

DATE

Reticulocytes → Larger than RBCs

Non-nucleated.

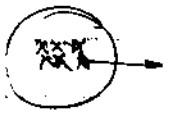
→ Can be stained with → Romanowsky stain

(But non-specific)

Specific stains → Supravital stain

Best stain for reticulocyte → 1) New methylene Blue

2) Brilliant cresyl Blue



- Criss-cross reticulum like structure which is Ribosomal RNA protein.

- Reticulocytes - seen in both peripheral blood, Bone marrow.

(N) - Retic. count → 1-1.5%.

In neonates - <2.5%

↑ed Retic count.	↓ed Retic count
Implies - BM ↑ed, P.B. destruction	1) Aplastic Anemia
↓	2) Nutritional An.
"Hemolytic An."	↳ Iron def. A.
↳ Hereditary Spherocytosis	↳ Megaloblastic A.
↳ PNH	3) congenital dyserythropoietic
↳ G-6PD def.	Anemia (CDA)
↳ AIHA	↳ (type I - III → Retic ↓)

→ Live dis.

* Linzenmeyer is used to measure ESR.

* Lymphocytes - longest living WBC
* Thrombosthenin → Contractile protein
* HSP - No ↓ in no. of platelets.
* freezing point of human plasma → −0.54°C.
→ 290 mosm/L

Megaloblastic Anemia

- B.M. → Hypercellular
- myeloid/erythroid ratio → ↓ed (N - 3:1)
  - ↳ Reversal
- M/C cell in B.M. → Erythroblast
- m/c cell amongst myeloid series - promyelocyte
- Retic. Count ↓ed (d/t Vit B12, f.A. → def. →∴ No nuclear maturation
  - ↓
  - ∴ Nuclear stage
  - ↳ Apoptosis
  - ∴ No reticulocytes for

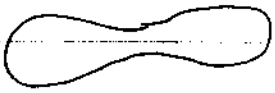
- Slight amt of hemolysis
  - ↳ Se. LDH ↑ed
  - ↳ Jaundice (+)
  - ↳ Nucleated RBC (+)
  - ↳ Extramedullary hematopoiesis → ∴ Splenomegaly.

- Bone Marrow Biopsy → Site of choice.
  - Infants - lateral part of Ant. Tibia (preferred site - medial part)
  - Children, Adults } - Post. sup. Iliac Crest
  - Obesity, Surgery, Radiotherapy } → Ant. sup. iliac crest.

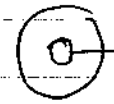
DATE

Normal RBC

diameter = 7.5 µm



– Biconcave shape → d/t - Spectrin via (spectrin-Actin interaction)



– central pallor (Ⓝ = 1/3 of RBC diameter)

Hypochromic Anemia → central pallor > 50% of RBC diameter,

- microcytic Anemia → when diameter of RBC → < 6 µm (MCV - < 80 fL)
- macrocytic " – " → > 9 µm (MCV - > 100 fL)

- for size estimatn → ~~Base~~ Best Index → MCV - 82-96 fL

for Anemia estimatn → Best Index → MCHC → Ⓝ - 34-37 mg/dL

↑ed in - Hereditary Spherocytosis

Ⓝ in - ~~AD~~ megaloblastic An.

MCH = 27-33 pg/dL

- Anisocytosis → size → RDW (Red cell Distributn width)

Starts @ → 11.5-14.5

↑ in → Fe def. Anemia

Ⓝ → Thalassemia.

- Poikilocytosis → Shape

Hemolytic Anemia

- Intravascular
  - lysis of RBCs
    - ↳ Raise LDH
    - ↳ Hb-nemia → Jaundice.
      - Renal excretion
        - As it is → Hb-uria
        - Tubule degradation → Hemosiderinuria
      - converted to non-toxic form → Meth-Hb-nemia → Meth-Hb-nuria.
      - Haptoglobin + Hb → Liver / Spleen / kidney
        - (Se. Haptoglobin → ↓ed)
        - ↳ It will be falsely (N) in c/o Bile duct obstructn
- Extravascular hemolysis
  - Spleen, Liver, Bone marrow
  - → Jaundice (unconj.)
  - → Haptoglobin (N)

Se. Haptoglobulin - ↓ed in → pregnancy
→ Liver dis.

Intravascular Hemolysis
↓
Acute G-6-PD def.
PNH.

Extravascular
↓
Sickle cell An.
Hereditary spherocytosis

DATE

Hereditary Spherocytosis

- AD > AR
- m/common protein on RBC memb. → Spectrin
- m/c mutation in Her. spherocytosis → Ankyrin
  2nd m/c → Band 3 (Anion transport protein)

other proteins on RBC memb
- ↳ protein 4.2 (Palladin)
- ↳ Glycophorin A

- Severity of ~~hemolysis & anemia~~ Hereditary spherocytosis is best correlated by → α-spectin
  - ↳ osmotic fragility —— ↓ ——→ ↓
  - ↳ Hemolysis —— ↓ ——→ ↓

- Not assoc with → HS → Glycophorin A
- Integral protein → Glycophorin A
  → Band 3.
- Rest all - peripheral protein

↳ ↓function of these memb proteins = ↓flexibility
↳ In HS ↓flexibility will be lost
↳ Bld flow - will remove RBC memb
↓
Cell become spherical (spherocytes)
- ↳ No central pallor
- ↳ smaller in size.

↓
Taken up by spleen
↓
mφ → damage the spherocyte
↓
Extravascular hemolysis.

Rx → Splenectomy.
After splenectomy spherocytes will be (+)

Spherocytes seen in
1) HS
2) G-6PD An.
3) PNH
4) AIHA (m/c/c of spherocytosis)
↓
Inv. of choice - Coomb's Test

DATE

- Triad of features - 1) Hemolytic Anemia (mild - mod.)
  2) Jaundice
  3) Pigment gallstones.
  4) Splenomegaly

D/D → Sickle cell Anemia → Anemia - much severe.
↳ Similar features - Hemolytic Anemia (severe)
- Jaundice
- pigment gallstones.

- c/o H.S. → with ↓ed Retic. count → d/t → Aplastic crisis (parvovirus B-19) → for 5-7 days.
- Hemolytic crisis (EBV)

- Screening - Pink's osmotic fragility test
↳ ↑ed osmotic fragility.
(N) RBCs - Isotonic - 0.9% NaCl
↳ Hemolysis - starts → 0.5%, complete - 0.3%.
Hereditary Spherocytosis → ~~complete~~ @ 0.5% NaCl.
Starts @

DATE

G-6-PD def.

- XLR
- m/c - Male
- Protects against falciparum malaria

Enzyme def.	Hb-pathies
1) G6-PD def.	1) Sickkecell an. carriers
2) Pyruvate Kinase def.	2) Thalassemia
	3) HbC (HbSC)

- Duffy -ve → Protective against plasmodium vivax malaria.

* Precipitator of G-6-PD def.
  - m/c - primaquine
  - Dapsone
  - fava beans
  - Sulfonamides

Heinz Bodies
- ↳ Denatured globin
- ↳ Not seen by Romanowsky Stain.
- method of choice
- Supravital staining
- Crystal voilet stain

Heinz bodies - Attacked by mϕ →

Bite cells.

→ • Not produce symptoms in neonates.

DATE

PNH – Paroxysmal Nocturnal Hb-uria

↝ 25% only – show (paroxysms, nocturnal)

↝ Acquired somatic defect in stem cell

↓

mutation in PIG-A gene (phosphatidyl inositol glycosyl A)

↓

PIGA ⟶ Synthesizes GPI anchor protein

↓

Anchors compliment Regulating proteins. ← ① CD 59

MIRL-Membrane Inhibition of Reactive lysis

② CD-55 – Decay Accelerating factor

③ C-8 Binding Protein

most Imp.

- mutation of C-regulating protein → CD-59
- m/l mutatn overall – GPI – Anchoring protein.

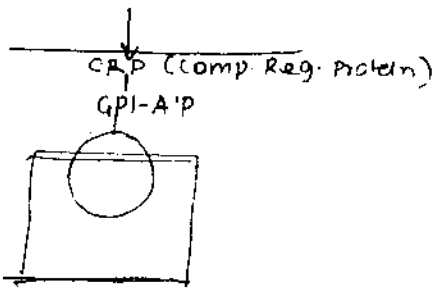
↳ Pancytopenia

↳ Hemolytic Anemia } First Triad of PNH

↳ Thrombosis (m/c – Hepatic Vein)

(m/c/COD → Hepatic v. thrombosis / Budd-chiari syndrome)

Acidic pH → Activated compliment pathway → C5-9 (MAC)



Intravascular hemolysis ←

• Screening → Best test

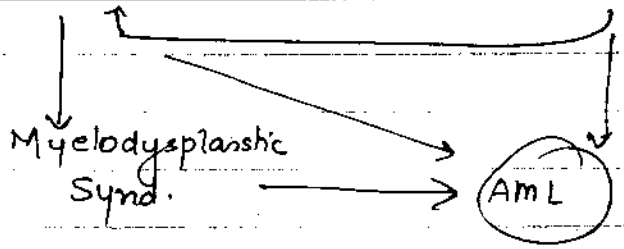
① Ham's test → Acidified Serum → lysis of RBCs

② Sucrose lysis test → complement system – fed by ⊕ of sucrose

Dx confirmed → flow cytometry

DATE

PNH → can transform into → Aplastic Anemia



pre-leukemic conditions – 1) PNH
2) Aplastic Anemia
3) Myelodysplastic Synd.

DATE

AIHA (Auto-Immune Hemolytic An.)

Now - Immune H.A.

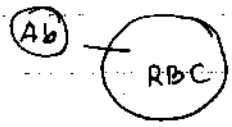
- Warm
  - ↓ 37°C
  - IgG
  - → m/c a/w CLL*
  - → AI disorder m/c a/w - SLE
  - Drugs →
    1) Penicillin
    2) α-methyldopa.
- Cold
  - 1) Hemagglutn
    - ↓
    - IgM
    - ↓
    - Mycoplasma
    - Syphilis
    - Viral inf
  - 2) Hemolysin
    - ↓
    - IgG
    - (Donath Landsteiner Ab)
    - ↓
    - IgG Ab against "P" antigen of RBC
    - ↓
    - Activation of C-pathway
    - ↓
    - C_{5-9} (MAC)
    - ↓
    - Hemolysis.
- Paroxysmal cold Hemoglobinuria.
  - m/c/c ↳ Viral Inf

Ig Garam

P/S - Spherocytosis (m/c)
→ fragmented RBCs (schistocytes)

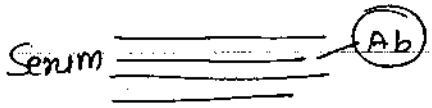
coomb's test

direct coomb's test



1) AIHA
2) ITP
3) HDN → fetal sample / NB baby
4) Mismatch transfusion reax.

Indirect Coomb's test



1) HDN - mother's sample
2) Unknown Ab
3) Compatibility testing
4) Rare bld groups.

Hemoglobinopathies

Embryonal Hb → upto 8 wks → then fetal Hb

↓

1) Gower-I → Zeta$_2$ Epsilon$_2$ ($\zeta_2 \varepsilon_2$)
2) Gower-II → α_2 ε_2
3) Portland → ζ_2 γ_2

(Hb-f) fetal Hb → $\alpha_2 - \gamma_2$ → Hb-Adult (Hb-A) → $\alpha_2 \beta_2$

$HbA_2 - \alpha_2 \delta_2$

fetal Hb ⟶ Hb-Adult

1) Switchover starts → 20 weeks of gestatn → β- starts.
2) Significant switchover →
   Starts → 30 wks → β > 50%
   Completed → Birth (38 wks) → γ-gene-silenced

(N) Adult → HbA - 96%
HbA_2 → < 3.5%
HbF - < 2%

1) At 6 months → Adult Hbf levels are attained.

Hemoglobinopathies.

- Quantitative
  - α → ↓ed → α-Thalasemia → Deletion
  - β → ↓ed → β-thalassemia
    - ↓
    - Non-sense point mutation.
- Qualitative.
  - ↓
  - Sickle cell Anemia
    - β-chain
      - 6 → Glutamine (polar) → Go
      - Valine (Non-p → welcome
    - mis-sense point mutation. ← Hbs
      - → only "Solubility" altered

m/c genetic change in SCA → point mutation.

DATE

SICKLE CELL ANEMIA (SCA)

- AR
- SS – SCA
- SA → carrier / trait → Heterozygous state
- * protection from Adult p. falciparum
- ★ sickle cells also kla Drepanocyte →

↓

Under hypoxia, sickle cell express adhesion molecules on their surface

↓

Adhere to each other and vessel wall

↓

obstructn, ↓ed bld supply to distant organ

↓ kla

1) Vaso-occlusive crisis
   - ↳ m/c clinical presentatn
   - a) Hand-foot synd. → involve hand, foot
   - b) Acute chest syndrome → involve lungs
   - c) fish mouth vertebra

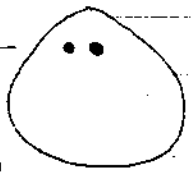
- m/c/c of osteomyelitis → Salmonella.

d) Autosplenectomy → repeated splenic infarction

↓

Replacement of spleen by fibrous tissue

Nuclear remanant (DNA) ←



Howell Jolly Bodies
- ↳ SCA (Autosplenectomy)
- ↳ post-splenectomy
- ↳ megaloblastic Anemia

RBC

Auto-Splenectomy

↓

↓ed maturatn of RBCs

↓

presence of nuclear material in PB. RBCs

↓

Howell-Jolly

2) Aplastic crisis

d/t parvo-virus B19 infn

Transient – 5-7 days

3) Sequesteration crisis

- most dangerous
- Large amt of RBC destruction in spleen

↓

Hypovolemic shock

(medical emergency)

Rx – Blood transfusion within 4 hrs.

* Congested splenic tissue

with fibrotic area with Ca, fe,

k/a – Gamna Gandy bodies.

Also seen in Congestive splenomegaly (SCA)

Liver cirrhosis

CML

factors affecting sickling

1) m/l factor – HbS conc. > Hypoxia → 2nd m/l.

2) SC Carrier/trait (HbSA)

HbS < 40%, HbA – 60%.

"No sickling" occurs – became. HbA inhibits polymerisation of HbS

3) HbF, HbA → ↓es sickling

HbC → ↑ed sickling → k/a HbSC

↳ ↑ed incidence of bone infarction

proliferative Retinopathy.

4) HbS + β-thalessemia → sickling less

β-chain ↓ed

↓

HbS ↓ed

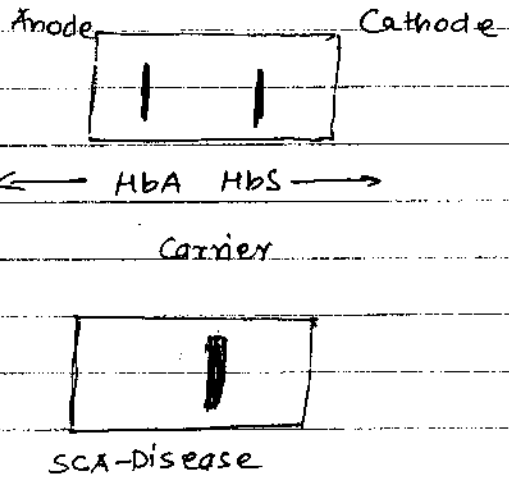
DATE

Screening

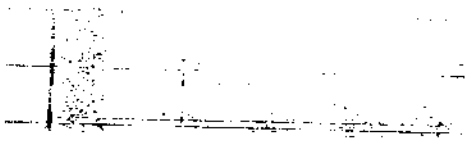
1) Sodium metabisulfite test
2) Sodium Dithionite test

Confirmation

1) Best → HPLC (High performace liquid Chromatography)
2) 2nd Best → Hb electrophoresis.



* In SCA, Renal ca. m/c → medullary ca. of kidney.



DATE

β-Thalessemia

1) Thal. major / Cooley's An. / mediteranean An.

→ Pediatric populatn

→ Hb < 3 gm%

→ Repeated Blood transfusion (transfusion dependent Anemia)

↓

Iron over-load.

↓

m/c cause of death.

↳ CHF 2° to iron-overload

usually @ Age of 10-20 yo.

Asis → HbE electrophoresis → ↑ HbF → 30-90%

* preferably saline washed packed cells should be given

↓

↓ the risk of urticaria.

2) Thalassemia Intermedia

* Pediatric populatn
* Hb > 7 gm%
* Occasional Bld transfusion in pediatric

↓

Adult/Adolescence

↓

Transfusion dependent Anemia.

- Δsis - Hb Electrophoresis - ↑HbF (10-30%).

3) Thalassemia minor

- Hb - 9-12 gm%
- No h/o blood transfusion.
- mild ↑ of HbF ↑ed, HbA2 ↑ed Imp.

↓

Δstic - HbA2 ↑ed → 4-8%

Microcytic Hypochromic An.

hal minor	Iron Def. An.
1) RDW - (N)	↑ed (>16)
(N) - 115-145	
2) Mentzer's Index < 13	≥ 13
mcv / RBC count	

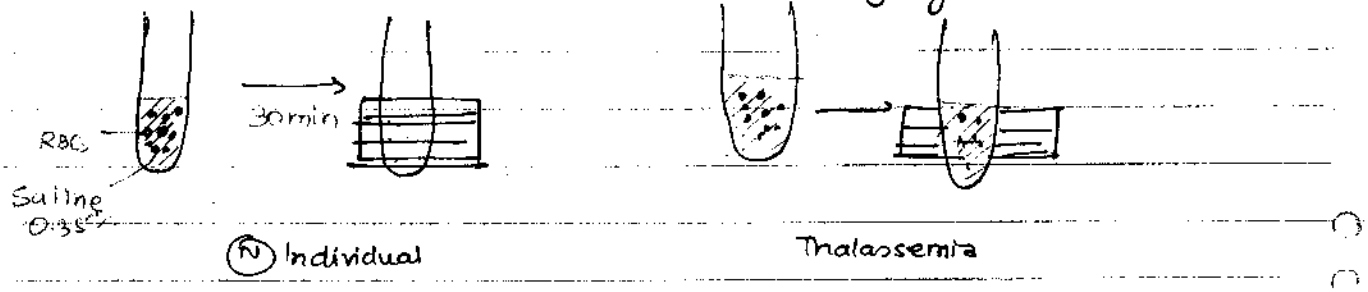
(thirteen less semi)

DATE

NESTROF Test

→ Naked Eye Single Tube Red cell osmotic fragility
→ Most widely used Screening test → World wide
→ In India.

* RBC memb. of thalassemia → more stable. against osmotic fragility



α- Thalessemia

Deletion of α-chains

αα / αα

1) 1α- deletion → carrier
2) 2 α- deletion → Trait
3) 3 α- deletion → HbH → tetramer of β- chain
4) All 4 α-chain deleted → Bart's Hb (seen in Hydrops fetalis)
↳ tetramer of γ- chain

• Target cells are seen in
1) Thalassemia (most characteristic)
2) Megaloblastic An.
3) Iron def. anemia.
4) Sickle cell an.

Cabot's ring → visualised on Romanowsky
→ most char. → megaloblastic Anemia.

(8)

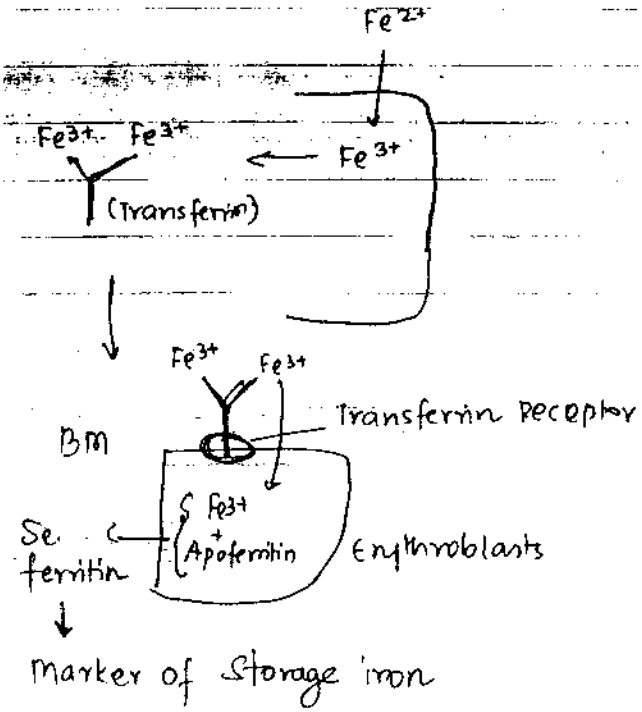
fine basophilic stippling - megaloblastic An.
Course " " → Pb poisoning
Sideroblastic anemia.

DATE

Iron deficiency Anemia (IDA)

- m/c presentation → fatiguability, irritability.
- Latent Iron def. Anemia – m/c presentation in India/ world.
  - ↓ → fatiguability, irritability
  - Iron def. without Anemia
    - ↓ → Se Fe^{3+} ↓ed
    - ↓ → Hb (N)

- Fe^{2+} → form → absorbed
  - → site → proximal duodenum
- Fe^{3+} → form → Stored in BM, Spleen, Liver.
- Master regulator of Iron metabolism → Hepcidin
  - ↓
  - ↓es iron absorption
  - ↓es iron mobilisation from storage site.



Marker of Storage Iron

↓

mech. of Anemia of chronic disease (Only 2nd)

Isolated IDA

↑

Lab (IDA)

((N) – 150–200 ng/dL)

↑

1) Earliest / m sensitive → ↓ed se. ferritin
2) Transferrin levels ↑ed
3) TIBC → ↑ed.
   (Total iron binding Capacity)
   ↳ (N) – 300–400 mg/dL
   (>400 → IDA, <300 – Anemia of chronic dis.)
4) ↓ed se. Iron
5) ⊗ ↓ed % saturation of transferrin
   (N) – 30–50%
   <16% → Diagnostic of IDA

DATE

IDA + Infection/ Inflammation.

↳ Se. ferritin → is an acute phase reactant → which will be ↑ed.

∴ IOC ⇒

Best → 1) B.M. biopsy + Prussian Blue stain

2) most sensitive, specific → "sTR" free serum transferrin Receptors. (↑ed) in IDA

2nd Best →

Also, the best inv. to differentiate b/w Anemia of chronic dis and IDA

* STR ratio with log Index of serum ferritin → Better than STR alone.

STR / log(se ferritin)

< 1·5 → Anemia of chronic disease.

> 1·5 → IDA

* IDA → Responding to Rx

1) Earliest finding → symptoms ↓ed

↑ed intracellular enzymes (within 12-14 hrs)

2) Retic-Hb → ↑ed (4-7 days)

3) Retic-count (7-10 days) → ↑ed.

* Anemia of chronic disease

Chronic Inflammatn

↓

IL-1, TNF-α (cytokines)

⊖ (minor mech) — ⊕

CFU-E → ↓ed RBC mass

Liver (major mechanism) → ↑ed Hepcidin → ↓ed Fe absorption

1) Se. ferritin ↑

2) Transferrin ↓ed

3) TIBC ↓ed

4) % saturation ↓ed.

5) Se. Iron ↓ed

6) Hepcidin ↑ed.

p/s – Normacytic normochromic (n/c)

→ Hypochromia occurs before microcytosis.

* Whenever a question is given, about IDA and Thal.
always calculate → Mentzner Index
$\frac{MCV}{RBC}$
< 13 – Thalessemia
> 13 → IDA.

* Hemochromatosis – doesn't involve salivary glands
may involve → liver, pancreas, heart
Skin pigmentation d/t – melanin deposition
Hereditary hemochromatosis → Ted se. Iron,
TIBC ↓ed.

* Rate of Iron uptake is regulated by → mucosal cell iron stores.

Echinocytes/Burr cells - Burns / Hemolytic an.

Acanthocytes /Spur → Abetalipoproteinemia

Stomatocytes → slit-like (mouth like) area of pallor

Schistocytes → fragmented RBCs

leptocytes → Thin flat cells

Codocytes → mexican hat cells

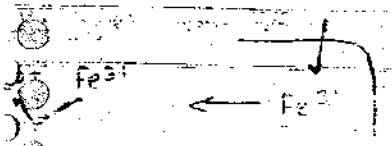
Dacrocytes → Tear drop cells (myelophthisic)

Drepanocytes → sickle cells

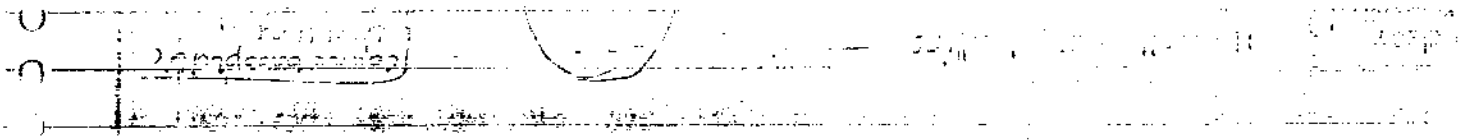
Elliptocytes → Pencil cells

Keratocytes → Helmet cells

Knizocytes → Cells with >1 concavity.



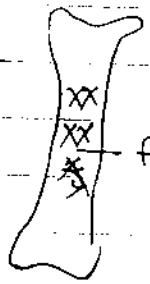
Isolated IDA



Myelophisic Anemia

- Anemia d/t space occupying lesion of BM.
- m/c/c → ① mets (m/c - ♂ Ca. Breast)

② leukemia-lymphoma involving B.m.
③ Granulomatous inflammation involving BM
④ myeloproliferative disorder involving BM.
⑤ Hairy cell leukemia



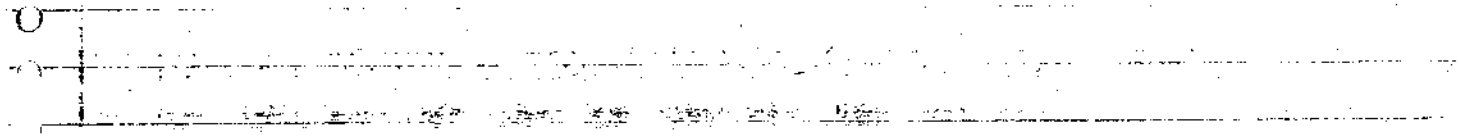
fibrosis → maturation defect

P/S

→ ① ↓ed WBC
↓ed RBC
↓ed plt
} pancytopenia

② Immature precursors of leucocytes, erythrocytes
* (leuco-erythroblastic Reaxn)

③ Tear-drop RBC
a/k/a Dacrocytes.
↳ Dacrocytitis (rare)



MEGALOBLASTIC ANEMIA

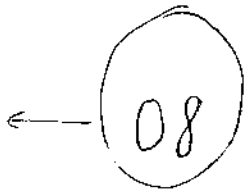
- Vit B12 def → Peripheral Neuropathy
- folic acid def → No peripheral "
- Pernicious Anemia → Auto-antibodies → def. of Intrinsic factor (Cubilin Receptors)
  - ↓ Atrophic Gastritis → Premalignant condition
  - ↓ Stomach (parietal cells @ funclus)

- BM - Hypercellular
  - Erythroblastic Hyperplasia
  - Reversed M:E ratio → leukopenia, thrombocytopenia → may be (+)
- Lab Δsis → Retic count ↓ed
- P/S → Earliest → macro-ovalocytosis (3 months earlier than 2nd finding)
  - 2nd → Hypersegmented neutrophil (>6 loops - in one neutrophil / >5 loops in >5% of neutrophil)

(Nuclear Remanant) DNA
- Howell Jolly bodies
- fine basophilic stippling

Coarse basophilic stippling → 1) Lead poisoning 2) Sideroblastic An.

"figure of 8" or "loop" ↓ CABOT RING



Cabot Ring m/c → Megaloblastic Anemia > Her Ane

In treated pt → Vit B-12 and folate supplementation ↓ Retic count → ↑ed

DATE

causes of megaloblastic anemia

→ Cobalamin deficiency
→ folic acid def.
→ Purine and pyrimidine antagonists
→ Procarbazine, Zidovudine, Hydroxyurea, Acyclovir
→ Hereditary orotic aciduria
→ Lesch-Nyhan syndrome
→ Cong. dyserythropoeitic anemia

* Copper def → Hypochromic normocytic anemia.

→ Causes of vit B_{12} def. → fish tapeworm infestatn (D. latum)
→ Gastrectomy
→ Ileal resection

→ Aplastic Anemia → can progress to
↳ AML
↳ PNH
↳ Myelodysplastic Anemia

* Se. Vit B_{12} levels → ↑ed in → Hepatitis
→ cirrhosis of liver
→ Hepatocellular ca.

* Macrocytic Anemia → Hypothyroidism.
* pure red cell aplasia → Thymoma
* maturation failure in poor absorption of vit B_{12} → is a/w →
Anemia occurs after 3-4 months of poor absorption.
* FIGLU → folic acid def.

Schilling Test

Radiolabelled oral Vit B_{12}

f/b

i.m. inj. of unlabelled vit B_{12}

↓

Urinary excretion of radioactive B_{12} – measured

↓

(N) urinary excretion → Vit B_{12} – (N) absorption

(probably dietary def.)

↓ed urinary excretion → vit B_{12} → ↓ed absorption.

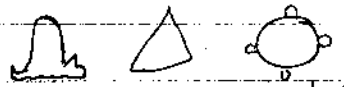
DATE

fragmented RBC syndrome

1) large Bld vessels - Heart
↓
d/t Prosthetic ♡ valves.

2) small bld vessels
a/k/a - microangiopathic hemolytic anemia
↳ AIHA
↳ vasculitis (PAN)
↳ DIC
↳ HUS
↳ TTP
↳ APLA syndrome (Anti-phospholipid Antibody synd.).
• malignant HTN

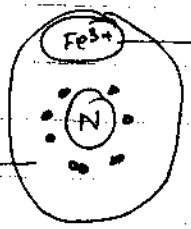
Both have similar picture on P/S
↳ fragmented RBCs (Schistocytes)
↓
Sign of hemolysis on P/s.

↳

↓ Helmet
↓ Triangular cell
↳ Burr cells/ Echinocytes.
↓
equidistant projections (all over)

Acanthocyte/Spur cell

← Abetalipoproteinemia
← Liver disorder
← Uremia

SIDEROBLASTIC ANEMIA.



Ring sideroblasts

Fe^{3+} + protoporphyrin ⇒ Heme

↓

This reaxn doesn't occur

∴ Iron accumulates in the cell around nucleus

In peripheral blood →

→ Siderocytes.

↳ pappenheimer bodies (contain iron)

↳ ∴ Prussian Blue stain.

Pathogenesis

1) Hereditary (XLR) (d/t ↓ed ALA synthase activity)

2) Acquired → AKT drugs (INH)

- Penicillamine
- → Alcoholism
- → Auto-immune disorders.
- → myelodysplastic syndrome

→ Erythropoetic porphyria

→ lead poisoning

(Not in cutaneous porphyria)

Lab Δsis → .Ser ferritin ↑ed

- Transferrin ↓ed
- TIBC ↓ed.
- P/S - Dimorphic Anemia

Microcytic Hypochromatic

Macrocytic

* pathogenesis of Anemia in lead poisoning → ALA dehydratase inhibitor

* Sideroblastic An →

↑ed se. ferritin
↓ed TIBC
↑ed se. Iron
↑ed % saturatn

Causes of microcytosis
→ IDA
→ Thalessemia
→ Sideroblastic An.
→ Anemia of chronic dis.

* Anemia in CRf occurs d/t -
→ ↓ed EPO
→ ↓ed RBC survival
→ ↓ed folate
→ B.M. hypoplasia
→ Iron def

* Iron def. Anemia seen in →
→ CRF
→ Bilroth II operatn
→ Hookworm Infn
→ Celiac sprue
→ Ca. colon

* BM Iron ↑ed in →
→ Thalassemia
→ An. of Chronic dis.
→ megaloblastic anemia.

* Hb leprae - β, δ fusion
A₂ (N) & Hb
No B chain.
Type of Thal. minor

* c/o persistently raised HBP

→ ⊕ of HBP in adult life

→ Pt - symptoms.

LEUKEMIA / LYMPHOMA

Malignancies of hematopoietic precursor cells → often spill into circulation

↓ Tumor → Peripheral blood → Bone marrow

↓ Tumor → LN → Organ

↓ → Solid, cohesive tumors of immune system

- Leukemia may have lymphoma and vice versa.
  - ↳ m/c Affected → Cervical LN
- WHO classification is followed.

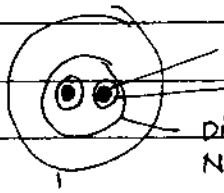
Hodgkin's Lymphoma	Lymphocytic ~~leukemias~~ NHL	Plasma cell dyscrasia
Nodal.	Extranodal	
Orderly involvement of LN in stepwise manner	Commonly affected LN ↳ Waldeyer Ring ↳ Mesenteric LN	
Rarely affect - Waldeyer Ring, Mesenteric LN	Spread is unpredictable	
Less common, less aggressive	m/c, more agressive	
* Clasically from easily accessible LNs. ↳ Axial LN	Peripheral LN	
Origin - Lymph nodes	⅓rd - extralymphoid tissue.	
fever, unexplained wt loss, Night sweats, Pruritus	d/t Inflammatory cytokines	

* → for prognosis, Bx - most important → B-cell or T-cell.

Dt.:
Pg.:

Delta

Classical RS cells



15-45%

CD30+

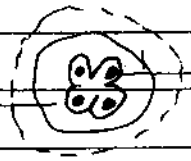
CD15+

↓

- somatic hypermutation
- class switch.

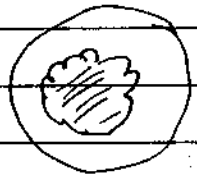
Variant

① Lacunar



CD30+

② Pop-corn cell



→ CD20+ve.

Delta

HODGKIN'S LYMPHOMA

- Assoc with EBV ⟶ B-cell

(Receptor - B-cell receptor - CD-21, CR-2)

↓

EBV ⟶ B-cell (R)

↓

⟶ Nuclear transcription factor "Rel" proto-oncogene

↓

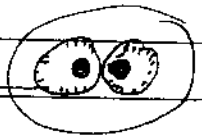
B-cell ⟶ ~~Red~~ Reed Steenberg cells.

Binucleated with prominent nucleoli

"Owl eye" appearance

(Aneuploid cell).

* central nucleoli + peripheral chromatin



*RS cells - ⊗ If found alone, non-Astic,

as it can be seen in other tumors also,

m/c - Diffused large B-cell lymphoma.

↳ m/c - 1) Immunoblastic NHL (+ in 60% of HIV pt)

2) 1° CNS - Lymphoma (+ in 20% of HIV pt)

3) ⊗ 1° effusion lymphoma

⟶ m/c lymphoma of CNS in HIV - primary CNS lymphoma

⟶ Sarcoma

⟶ Carcinoma

⟶ Infectious mononucleosis

↓

Atypical lymphocyte (Downey cells)

↓

EBV affected B-cell → CD_8 T cells - Activated

↓

Atypical lymphocytes

Defn of HL

* RS cells + mixed Inflammation →
(Nodular, lymphocyte, eosinophils)

Histological Asis of HL → combination of neoplastic
+
Non-neoplastic cells.

Types of HL

1) classical
CD30> CD15
1) Nodular Sclerosis → mc in world
CD15-ve
CD30 -ve
2 mixed cellularity → mc in India
a) lymphocyte rich
germinal centre of LN
CD20+ve
b) lymphocyte depleted.
Bcl-6 +ve.

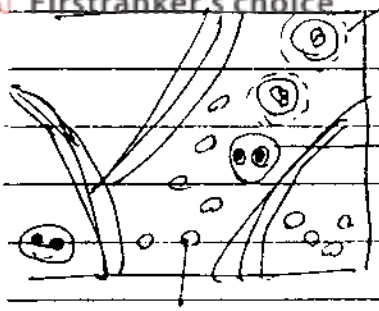
2) lymphocyte predominant
immunophenotyping
↓
CD15-ve
proliferating transformed
of germinal centre.
CD45+ve,
→ pop corn cells/Polypoid
(Multilobulated/polytypoidal
Nuclei)

* Nodular Sclerosis
→ Best prognosis.
→ lymphocytic - Histiocyte (LH)
Rich vonKauf of RS.

- lacunar
Reed Sternberg cells.

inflammation

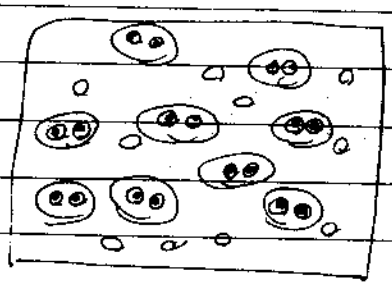
- HIV
- EBV → m/c a/w mixed cellularity
- Not a/w EBV
* Nodular sclerosis.
* Lymphocyte depleted.



→ CD20+

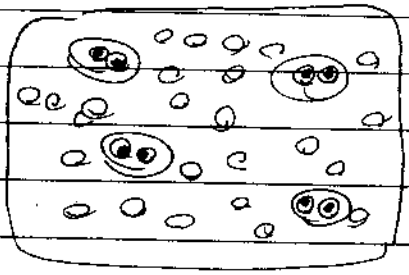
Lymphocyte predominant

* NHL are HIV defining lymphomas (immunoblastic NHL)
HL - Non-HIV defining.

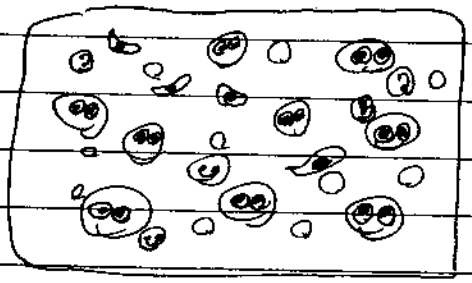


• Worst prognosis-
↳ Hodgkin's cells
↳ Histiocyte.
↳ pleomorphic, mummified cells

• Lymphocyte depleted.



• Lymphocyte rich
• mono-nuclear cells.



* Mixed cellularity-
• mono-nuclear cells
• Poor prognosis
• Used @ advanced age
• more severe systemic symp.

(117)

Prognosis of HL -

- RS cells of worse prognosis
- lymphocyte of good prognosis

- B- symptoms
- fever (Pel-Ebstein fever)
- Unexplained wt loss
- Night sweats.

Dr. Neha

NHL (Non-Hodgkin's leukemia)

Acute leukemia

Acute leukemia

↓

BM Aspirate / Biopsy

↓

Blast cells > 20%

(Astic of leukemia).

*Δsis of leukemia/lymphoma now is a multi-dimensional

Δsis. BM biopsy / Aspirate + Immunohistochemistry

↓ ↓

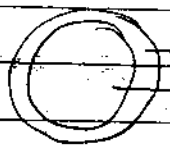
Lymphoblast | Myeloblast

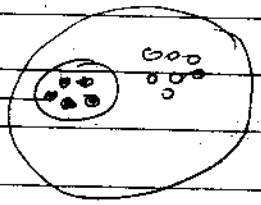
↳ cytoplasm scanty, Agranular

↳ Nucleus large, No-nucleoli

↳ cytoplasm abundant, granular

↳ ~~small nuclei~~, with prominent nucleoli





PAS +ve ← Stains → MPO +ve → most characteristic

Sudan Black B

If monocytes (M_3, (M_4, M_5))

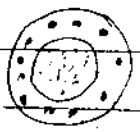
↓ mainly

Non-specific Esterase +ve.

(NSE +ve)

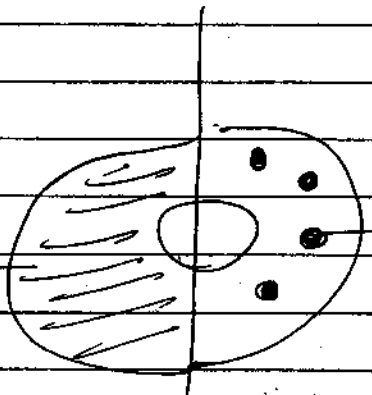
Erythroblast +ve. (M_6)

PAS



Differentiate B/w
enthmoblast and lymphoblast
Both PAS +ve

lymphoblast



enthmoblast
↓
ant-mb

Delia

ALL (acute lymphoblastic leukemia)

- m/c ca. in childhood → leukemia
- m/c ca. in infancy → Neuroblastoma
- m/c solid tumor child → Brain tumor
- m/c extracranial solid tumor in childhood → Neuroblastoma.

- ALL is common in ALL → 1) CNS involvement
  V/s AML 2) Mediastinal
  3) Testicular
  - These involvement → carry bad prognosis.

ALL

pre-B	pre-T
↳ 85%	↳ 15%
↳ common in pediatric age group (2-5 yrs)	↳ common in 13-17 yrs.
↳ Common presentation - Anemia, BM involvement	↳ m/c presentation - Mediastinal/ Thymic mass
↳ Immunophyting → CALLA +ve, CD10+ve → CD19-24, 79 → Good prognosis. → PAX-5	↳ Immunophyting ↳ NOTCH +ve ↳ CD1-8 +ve ↳ CD-28.

* Undifferentiated leukemia
  ↳ CD 34+, ↳ HLA-DR+ve,
  TdT +ve → Terminal deoxy Nucleotidase

Dt.:
Pg.:

ALL

Good	Bad
→ 1-8 yrs	→ < 1yr, > 8 yr
→ White	→ Black (Race)
→ female	→ Male (Gender)
→ -/-/-	→ CNS/ Mediastinum/ Testicular involvement
→ Hyperdiploidy	→ Hypodiploidy
→ Trisomy - 4,7,10	
→ Translocation t(9:12), t(12:21)	→ Translocation t(9:22) → Philadelphia t(8:14) → (Burkitt's lymphoma) t(1:19)
→ B-type (B-ALL)	→ T-ALL
→ CALLA +ve/CD10 +ve	→ pre-B-ALL
→ Early pre-B-ALL	→ ~~B~~ mature B-ALL
→ Peripheral Blast count < 25,000	→ >1,00,000

MYELODYSPLASTIC SYNDROMES. (MDS)

↓

Maturation defect

of myeloid stem cells

↓ — ↓ — ↓

Erythrocytes WBCs (Neutrophils) Megakaryocytes

* Primary MDS → 750 yrs (older)
* Secondary MDS → ✗ - related MDS → worse prognosis.
  ↓ Incubation period - 2-8 yrs.
  gets transformed to AML

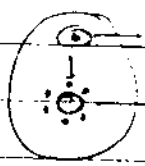
Cytogenetics -

monosomy 5
" 7 ⇒ m/c in children
Deletion 5 ⇒ m/c in Adults / Overall.
" 7
Trisomy 8

Whenever the above changes are seen in AML → carries bad prognosis.

Effect of MDS

1) Erythroid



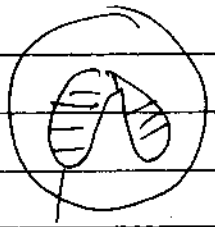
Fe ✗ protoporphyrin

Ring sideroblast.
↳ lead poisoning
↳ sideroblastic Anemia
↳ MDS

Bm biopsy → sideroblasts are (N) → (20-40%)

But Ring side[illegible]

(i) Neutrophilic



Bilobed

Bilobed neutrophil

↓

(1) pseudo-pelger-Huet cells.

Pelger-Huet cells

↓

Pelger-Huet Anomaly

↓

AD disorder

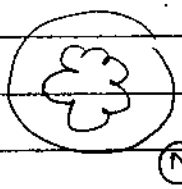
(2) DOHLE bodies (damaged Rough endoplasmic Reticulum)

↓

Purple colored.

purple colored.

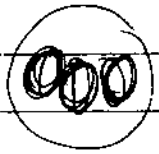
(ii) Megakaryocytes.



→ largest cell in BM aspirate/Biopsy

↓

In MDS →



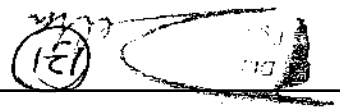
→ Nuclear fusion doesn't occur

↓

separate lobes of nucleus

↓

Pawn ball megakaryocytes.



AML (Acute myeloid leukemia)

Type 1 - AML assoc. with Genetic Abnormalities

a) t(8:21) ⟶ Good prognosis → M2

b) t(15:17) ⟶ Intermediate prognosis > Good → M3

c) t(16:16) → Inversion ⟶ Good prognosis - M4Eo (Hyper-eosinophilia)

d) t(v:11) → v → variable (Any chromosome) → Bad.

e) Mutant nucleophosmin gene (NPM)

↓

Good prognosis.

* Even if blast count is < 20%, if the cytogenetics are seen, i.e., t(8:21), t(15:17), t(16:16) → They are classified as AML.

↓

Best prognosis
↳ t(8:21)

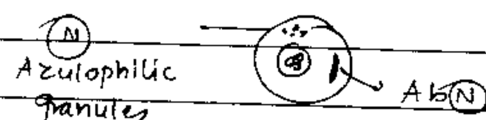
→ AML + MDS → Bad prognosis.

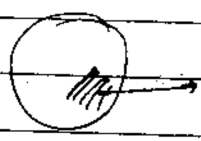
→ AML Rx related
↳ Alkaloid &
↳ Topo-isomerase II inhibitors
→ "Worst prognosis"
m/c translocation - t(9,11)

* Not otherwise specified AML → All have intermediate prognosis.

M0 → Undifferentiated
M1 → AML without maturatn
M2 → AML with maturatn ——→ MPO +ve → Chloroma.
M3 → Acute promyelocytic leukemia → max. Auer rods, faggot cells, DI
M4 → Acute myelomonocytic " → NSE +ve, Tissue infiltratn
M5 → Acute monocytic " → m/c a/w Tissue infiltratn.
M6 → Acute erythroleukemia → CD-71
M7 → Acute megakaryocytic leukemia.

* most definitive marker of myeloid differentiatn → Auer Rods





Grouped Auer rods → faggot cells.

* Monocytes - NSE +ve → M4
M5
→ A/w tissue infiltratn → Gum Hypertrophy
Leukemia cutis.
↓
m/c: M5

Best marker ← Lysozyme
MPO → may be +ve

* Chloroma → Myeloblastoma / Granulocytic sarcomas
↳ Hematopoeitic stem cell tumor
↳ BM biopsy, P/S → (N)
↳ Infiltratn of skin → tissue infiltratn
m/c site → orbital tissue
M/c [illegible] tumors.
m/c - A/w - M2 AML / t-8;21
can be assoc with - MDS

• CD34, CD43. CD-117
Chloroma
↓ 2nd be
Bad prognosis
although its also

chloroma → V. Rare → CD-45
↳ m/c symp → proptosis.

M6 → CD-71 → marker for → Glycophorin A
Mesangial cell (IgA)
Erythrocytes.
Transferin Receptor.

M7 → ~~fibrosis~~ BM → fibrotic stroma
p/s → pancytopenia.
megakaryocytes, Release PDGF → ~~TGF~~
fibrogenic cytokine
↓
Cause BM fibrosis

m/c leukemia in Down's in < 3yrs → AML M7
Overall → ALL.

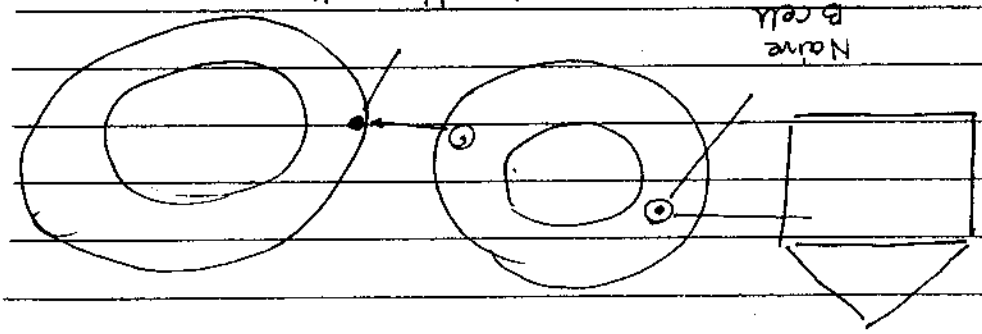
Somatic hypermutations

Do not have

CLL/SLL

Naive B cell

Mantle cell



CLL

Chronic lymphocytic leukemia (CLL)
Small lymphocytic lymphoma (SLL)

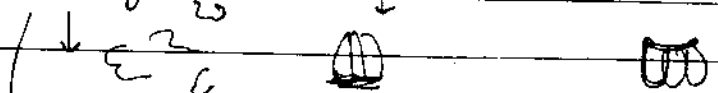
- Age - >60 yrs
- LN enlargement, Splenomegaly
- B-cell > T-cell type
- peripheral blood

Absolute lymphocyte count > 5000/dL.
>50% Mature lymphocytes
↓
Best method → flow cytometry.

* flow-cytometry - Best - lymphocytosis
  ↳ Also immunophenotyping
  ↓
  CD5+
  CD23+

Mantle cell lympho
→ CD 5+ (Mantle zone Marker)
→ CD 23-ve

* Anemia → AIHA (warm antibody)
* Smudge cells / parachute cells / Basket cells.



- Cells rupture, as they are fragile
  ↓
  Smudge cells

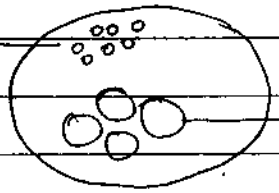
Characteristic of CLL, but also seen in septicemias, other leukemias also.

d/t vimentin defect

* Smudge cells - Also an indicator of prognosis.

Pg.: Delta

* Diffused pattern



→ large

LN Biopsy → mitotic Activity Ted.

↳ form proliferative centres.

↓

V/E diffused expansion of LN architecture.

↓

m/c pattern in LN biopsy, BM Biopsy. ← 1) Diffuse expansion of LN architecture

2) Pseudofollicular pattern → V. rare pattern

3) Mixed pattern

poor prognostic factors-	Good factors prognosis
1) Expression of Zap-70	1) No expression
2) No somatic Hypermutation	2) somatic hypermutation
3) loss of Ch. 11, 17, Trisomy-12	3) 13q deletion
4) Transformation	
a) Prolymphocytic leukemia (Splenomegaly, massive cytopenias, prolymphocytes in peripheral bld)	
b) Richter's transformation → SLL → DLBL → m/c NHL in India/world)	
↓ Richter's Syndrome	↳ worse prognosis. ↳ m/c gastric NHL

* m/c cytogenetic change in CLL → 13q deletion → Good prognosis

MM → → Bad prognosis

- Hypogammaglobulinemia

- If there is deposition of tumor cells in LN → lymphoma

Cytogenetics → Trisomy-12

Deletion - 11, 13

* only diffused lymphomas → CLL,

DLBCL

Burkitt's lymphoma

CHRONIC MYELOPROLIFERATIVE DISEASES

(Ab(N) myeloid stem cell proliferation)

↳ * Tyrosine kinase Ab(N)

1) CML
2) Polycythemia Vera
3) Essential thrombocytosis → mild/ No splenomegaly
4) Primary (Idiopathic) Myelofibrosis → Early - Hypercellular
   ↳ Late → Hypocellular
5) Chronic Neutrophilic leukemia
6) Chronic Eosinophilic leukemia
7) Systemic Mastocytosis
8) Stem-cell leukemia

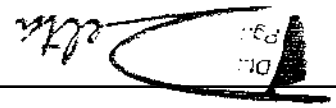
* Essential thrombocytosis

plt count > 4.5 lacs.

* JAK-2 mutation → PV
  Essential thrombocytosis
  Primary myelofibrosis.

∴ • PV → Hematocrit >65%
• Essential Thrombocytosis } → MPL-mutatn.
  primary MF

m/c → JAK-2



CML

- Peak Age - 50-70yrs
- m/c presentation → Massive splenomegaly
  LN enlargement → Absent
  ↓
  Sudden painful LN enlargement → Blast crisis.

- peripheral blood -
  WBC ↑ed, neutrophils - Max
  ↓
  Immature cells > Mature
  ↓
  Myelocytes
  Metamyelocytes
  Promyelocytes
  Band form → 1st to reach peripheral blood.

Plt count ↑ed
Basophils ↑ed
Eosinophils ↑ed.

Leukemoid Reactions	N/s	CML
• Sepsis • Burns		
• Severe infn		
• TB • Boun's synd.		
→ TLC → 50,000 - 1 lac		
mostly neutrophils		
c/F → • No splenomegaly / Hepatomegaly		• Splenomegaly ⊕
P/S → • NT ↑ed, mature > immature		• NT ↑ed, immature > mature
• Other WBCs (N)		• Other WBCs ↑ed.
LAP-score → ↑ed (leukocyte Alk. phosphatase) ↳ (13-130)		↓ed, except blast crisis,

Delta

Inv. of choice → Cytogenetics

Bm biopsy - only for prognosis.

Cytogenetic method of choice → "FISH" > PCR

↓

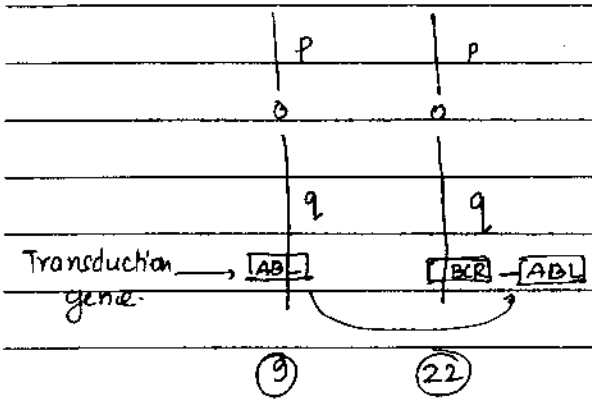
t (9:22) - (P)hiladelphia Chromosome → 22q

→ BCR-ABL fusion gene.

P-never involved

Ph'

Erythroblasts | Mega Karyocyte | Myeloid cells.



Phases of CML -

i) Chronic CML → without Rx - can survive upto 3yrs

↓

Triphasic leukemia

↳ Blasts - <10%

After 3yrs → Accelerated phase → BM Biopsy

↓ 3 months

① Blasts - 10-19%

② Basophils - >20%

③ splenomegaly,

④ plt count ↑ed

→ >20% Blasts ← Blast crisis

→ Extramedullary Blast cells (organs)

Eg. chloroma ← Survival <6 months

Not responding to Rx

→ New cytogenetic ⑤ changes

→ B.M. biopsy

↳ large group of blast cells on BM biopsy

→ Duplicate of ph' chromosome

→ Trisomy 8

If ≥1 satisfied

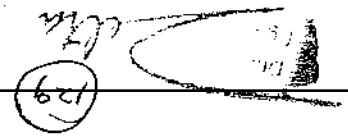
↳ Blast crisis - myeloid > lymphoid

Delta

* Pseudo-Gaucher cells/
  Ceroid histiocytosis/
  ↓ Sea-Blue histiocytosis.

BM Aspiratn

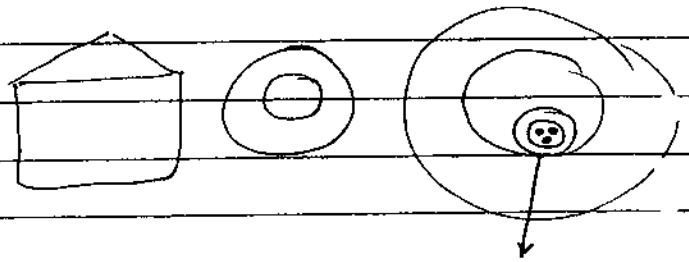
Best seen in - Blast crisis.



Dt.:
Pg.:

Diffuse Large B-cell lymphoma.

- m/c NHL in adults.
- cytogenetics ♀ F > M



↓

Only 30% of cases

↳ t(14:18) → ∴ probably follicular cell lymphoma which became more aggressive.

DLBL → Somatic hypermutation (+)

Another → 30% of cases

↳ Bcl-6 mutation → over expression (on chr. 3)

- 3 sub-categories

1) EBV ⟶ AIDS
   ↳ Transplant pt
   } Risk factors.

↓

Polyclonal proliferam

↓

Oncogenesis

(MOA)

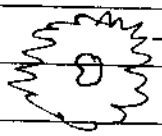
2) HHV-8 → Human Herpes Virus-8 → produces a protein which is homologous with Cyclin-D

↳ Spreads into cavities, produces effusion

3) Mediastinal mass.

HAIRY CELL LEUKEMIA

- B-cell lymphoma (NHL)
- m/c presentation → splenomegaly
- Rare disorder



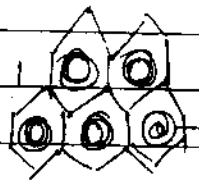
→ cytoplasmic projections

↓

Best seen by → Phase contrast Mscopy

Δstic → Electron Mscopy → Ribosomal - lamellar complexes.

- >90% of Hairy cell leukemia → BRAF mutation.
- +ve for TRAP (Tartarate Resistant Acid phosphatase)
- BM Aspirate → Dry tap.
  - ↳ fibrotic
- BM Biopsy → (1) Honey comb appearance - Tumor pattern
  (2) fried egg appearance

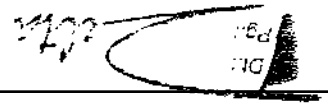


peri cytoplasmic halo

- Immunophenotyping → CD-11c
  CD-25 +ve
  most specific CD marker → CD-103 +ve
  CD-123 +ve

Most-specific /Δstic - Annexin-A-1.

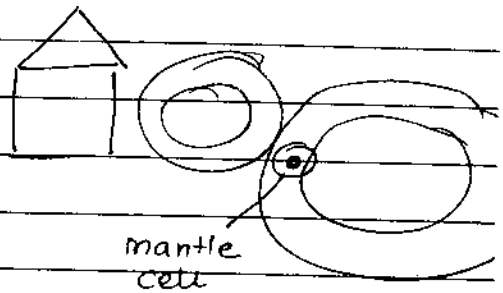
- Monocytopenia → I/t → ↑ed risk of Atypical mycobacterial infn.



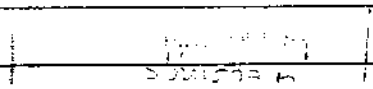
Delta

MANTLE CELL LYMPHOMA

- B-cell lymphoma
- 60/m
- m/c → painless cervical LNAP
- Immunophenotyping (CD5+)
  CD23 −
- Cytogenetics →
  - t(11:14)
  - Cyclin D_1 +
    (BCL-1) +).



- Aggressive tumors.



Delta

FOLLICULAR LYMPHOMA → B-cell

→ 20-30 yrs – ?

→ LN Biopsy –

1) Centrocytes → Nucleus - shows clearage.

↳ Predominant

Buttock cells →

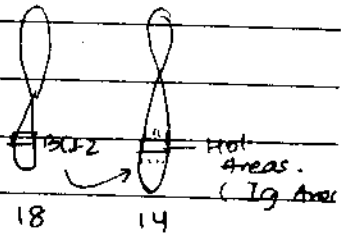
2) Centroblasts

→ Immunophenotyping

CD10+, 19-24+

→ Cytogenetics

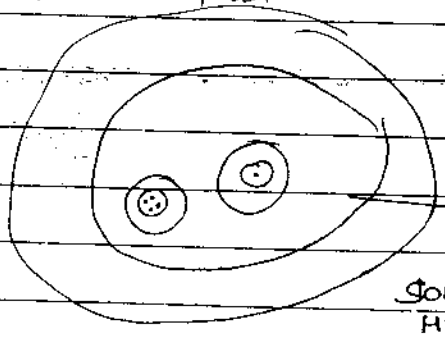
t(14:18)



Overexpression of Cyclin D_1 +ve

Bcl-2 +ve.

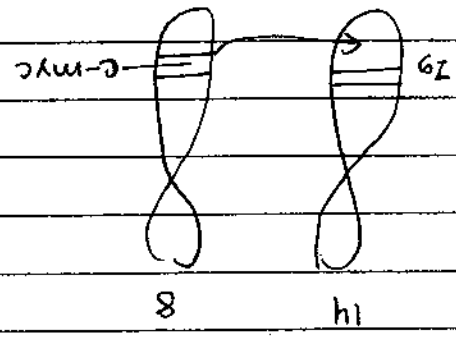
→ Aggregates of centroblasts, centrocytes.



★ V. slow growing tumors.

★ Rx → Not effective

follicular lymphoma	Reactive follicles (2° to infn)
→ No mitotic bodies	→ mitotic bodies +
→ No apoptotic figures	→ Apoptotic figures +



Delta

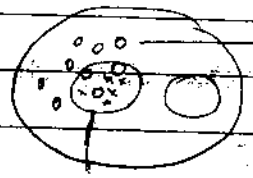
BURKITT'S LYMPHOMA

- Mature B-cell
- CD34-ve, Ig+
- max proliferative Index
- most commonly assoc. with tumor lysis syndrome.
- CNS involvement
- BURAKITT → BAD prognosis

2 types →

Endemic	Sporadic
EBV +ve	Rarely
m/c site → mandible/face	m/c site → Abdomen (mesentry LN)
Pediatric	Adult

- BCl-2 -ve
  BCl-6 +ve
- somatic hypermutatn (+)



small, round, blue cell tumor
↓
(Starry)

Starry - Sky Appearance

~~Starry-Star Ap~~

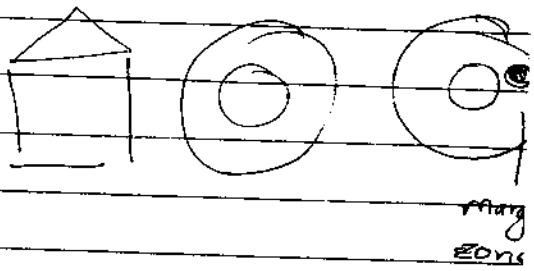
→ D/D of small, round
- Ewing's
- Burkitt
- Neuroblastoma
- Wilm's.
- Small cell ca. lung

Cytogenetics → t(8:14) → m/c
t(8:22)
t(2:8)

Burkitts
↳ 8 → chr. 8 → "c-myc" translocatn.

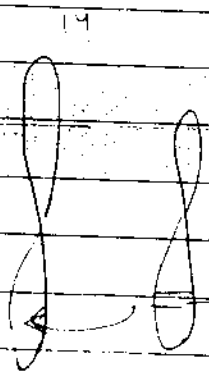
Marginal zone lymphoma (Extra Nodal)

- Slow growing, well differentiated.
- Grows in MALT tissue → Parotid
  - → GIT
  - → RS.
- → Other site - Orbits
  Breasts

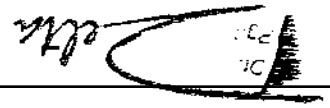


- → A/w sjogren's synd.
- → A/w H.pylori → MALTOMA → in stomach.

- → If antibiotics are given against H-pylori infection



→ t(1;14)
→ Bcl-10 mutam.



Plasma Cell dyscrasias (Paraproteinemia - ted monoclo- 7g)

1) MGUS - monoclonal Gammopathy of unknown significance → m/c
2) Smoldering MM
3) MM
4) Waldenstorm's macroglobulinemia.
5) Heavy chain dis. → ~~α → Franklin dis.~~ ~~γ → Seligman's dis.~~
   α - Seligman
   γ → Franklin

MGUS

- Plasma cells < 10%.
- Monoclonal Immunoglobulins → < 3g%

Smoldering Multiple myeloma.

- PC > 10%.
- m.Ig. > 3g%.

10-15 yrs ↓

Multiple Myeloma

↳ Plasma cell tumor (terminally differentiated plasma cells)
m/c site - vertebral columns
m/c presentation → Bone lytic lesion (50%)
Normocytic normochromic Anemia (80%)

least common → Bleeding/ coagulation disorder
(Platelet surface coated by m-protein)

Dt.:
Pg.:

Delta

Ⓝ plasma cells → ⓃⒹ

↓ IL-6

Ab Ⓝ plasma blast → Perinuclear clearing (Hoff)

↓ ↳ No perinuclear clearing

IgG → M/C

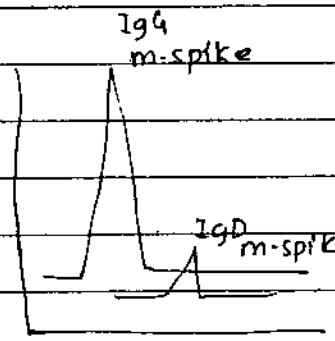
IgA → 2nd M/C

M

D → Rare.

E → least common

Electrophoresis.



IgD → Bad prognosis

↳ light chain → excreted in urine

↓

Bence-Jones proteinuria

↓

50°C → clot

↓

100°C → liquid

↳ M/C/C of Renal failure → light chain deposition

↳ M/C/C of Death → Recurrent infections. (Bacterial)

2nd M/C → Renal failure.

Ab Ⓝ plasmablasts → Activate → MIP-1α

(Mϕ Inhibitory Protein 1α)

Delta

MIP-1α

(+) ——— (−)

Osteoclasts → Hypercalcemia

Osteoblasts → Se. Alk. Poyase → (N)

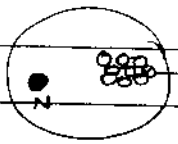
★ Ab (N) Immunoglobulin deposition

1) In ER → Endoplasmic Reticulum → Russell bodies.

(N) → Russell bodies.

2) Nuclear Ig → Dutcher bodies

3)



Cluster of grape like bluish deposition → MOTT cells.

fiery-red cytoplasm → flame cells

★ IOC → BM Biopsy

KIHO Δstic criteria

1) BM biopsy → plasma cells → >10%

2) ↑ed M-protein (in urine / serum) → (Except 1% cases of Nonsecretory MM.)

3) Evidence of end-organ damage (ROTI)

(CRAB) → Related organ damage

Hypercalcemia Renal failure

Delta

Plasma cell leukemia →

- P.B. → >20% plasma cells
- Absolute plasma cell count > 2×10^9/L

★ Best prognostic marker → β_2 → microglobulin

↓

Marker of tumor load.

★ BM → plasmablasts → poor prognosis

★ cyclin D1 → good prognosis

↳ Best IHC marker for MM.

★ m/c cytogenetic change → 13q deletions.

↳ Bad prognosis.

Bone lesions

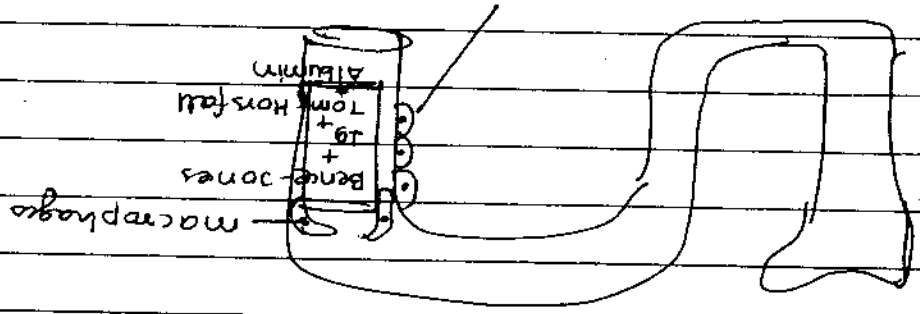
- m/c → vertebra > ~~Ribs > Skull~~ Ribs > Skull
- m/c presentatn → Backache

- Bones + Stones — Stones (d/t Hypercalcemia)

Abdominal groans.

psychic moans.

In renal pathology



↓

Complete Renal failure

↓

- Janeway's Syndrome.
- Nephrocalcinosis.
- Interstitial myeloma cells.

Delhi

LANGERHAN'S CELL HISTIOCYTOSIS

(HISTIOCYTOSIS X)

* Dendritic cell neoplasm
* Common in pediatric age group (5-10 yrs)
* common presentatn - Bone lytic lesions involving all bones simultaneously
* Gonadal involvement - Rare/Absent

Disorders

1) LeHerer- Sewe → Seborrhoeic dermatitis - m/c presentatn in Infants
2) Eosinophilic Granuloma
3) Hand-Schuller Christian dis.

Letterer- Sewe -

Multifocal, Multisystem

Eosinophilic Granuloma

Unisystem, Multi-focal

Hand- Schuller - Triad

DI

Proptosis (Exophthalmos) — Calvarial bone defects.

* Best marker - CD_1a

CD_{207} (langerin)

HLA-DR

S100

* On biopsy - langerhans cells + Eosinophilia

X-bodies

Birbeck granules → On Electron Mscopy

Coffee-bean nucleus

Tennis Racket cell/ Tadpole cell/ Strap cells

↓

Rhabdomyoblasts

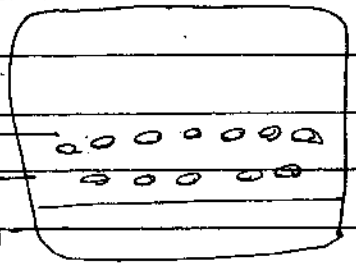
↓

Sarcoma Botryoides (Embryonal Rhabdomyosarcoma of vagina (<5yrs))

Tennis Racket appearance

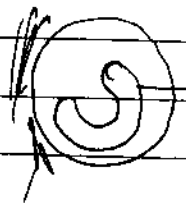
Pentalaminar rod like structure with dilated terminal en

Embryonal Rhabdomyosarcoma.



Delta

★ HALLMARK cells →



Horse-shoe or
Embryoniform Nucleus

↓

Angiocentricity → Anaplastic large T-cell lymphoma
m/characteristic

★ Post-transplant lymphoproliferative disorders → B-cell type
↳ A/w EBV

★ M/c cutaneous lymphoma - Mycosis fungoides (skin)

CD4-T-cell → ↓ peripheral blood

Seizary leukemia

(Generalised erythroderma)

Skin biopsy

Epi-dermis

Band like lymphocytic infiltrate

Dermis

Epidermotropism

Pautrier microabsecess

(Neoplastic T-cell)

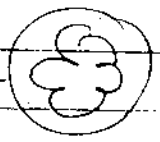
Munro's micro abscess

↓

Psoriasis

(Neutrophil

Inflamma



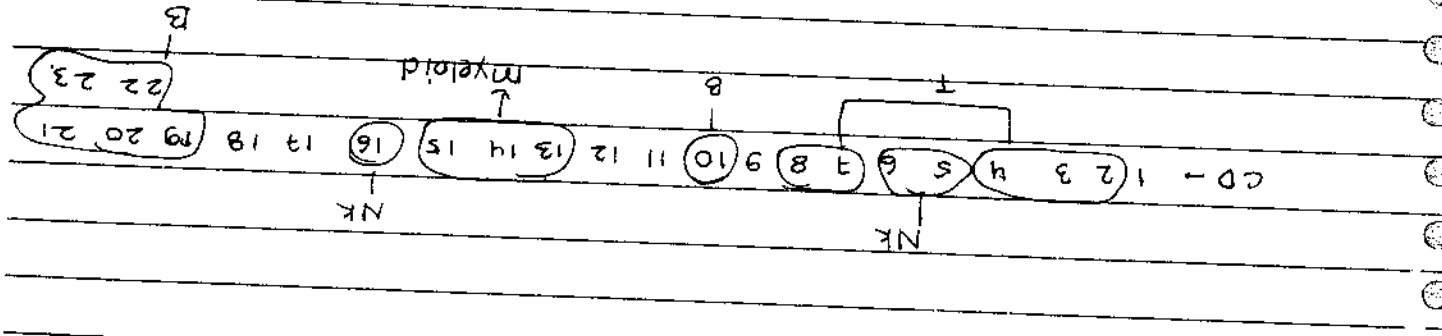
Hyper-

Convulated nucleus

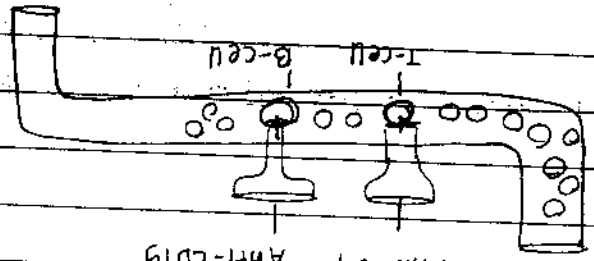
(cerebriform nucleus)

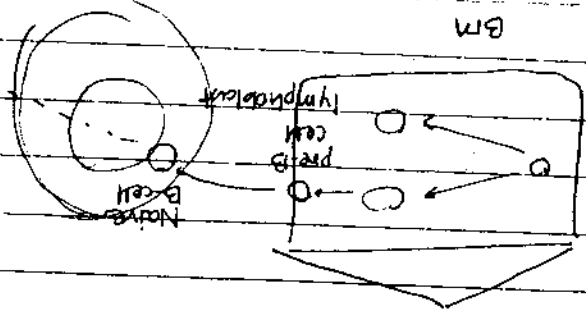
Non-Hodgkin's lymphomas

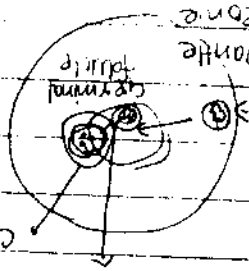
4 main characteristics
- cytogenetics
- Phenotype → Origin of cell - whether B/T-cell
- morphological feature → Arrangement of cells in tissue
- Clinical feature



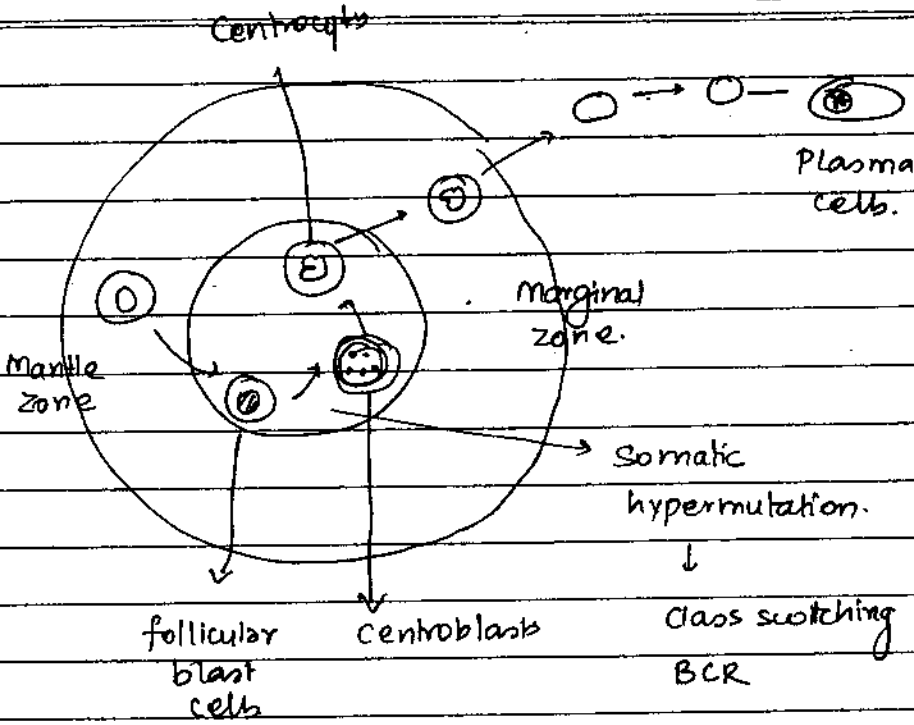
flow cytometry







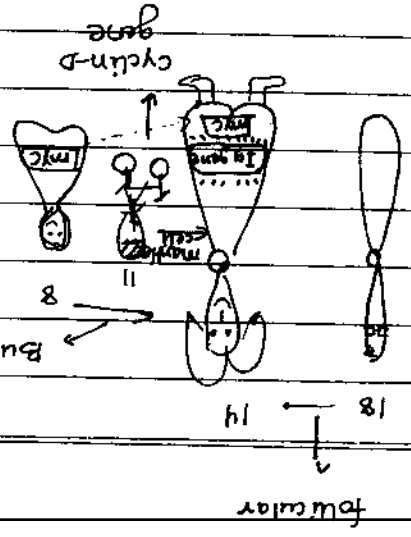
Dt.:
Pg.:



Monoclonal	≠	Polyclonal
↓		↓
Identical BCR/TCR		Different BCR/TCR

Types of

1. Precursor B or T cell
2. SLL/CLL
3. follicular lymphoma
4. mantle cell lymphoma
5. Diffused large B cell lymphoma (DLBL)
6. Burkitt Lymphoma



SLL / CLL

↓ chronic lymphocytic leukemia.

Small lymphocytic lymphoma

- Indolent disease
- m/c- Elderly
- 30% of leukemias in west

↓

Refer to class notes

KIDNEY

RENAL PATHOLOGY

- Glomerular pathology
  - Proteinuria
    - Nephritic
    - Nephrotic
- Tubular pathology
  - Salt and water loss
    - (salt loosing nephritis)
    - (Interstitial nephritis)

Nephritic

- HTN
- Hematuria (>3 RBCs/HPF × 3 times) (Twice apart)
- RBC casts
- Proteinuria (< 3.5 gm/day)
  - ↳ Sub-nephrotic Range.
- Hematuria → Extraglomerular
  - Glomerular
    - ↓
    - Dysmorphic RBC
  - Isomorphic RBC
    - ↓
    - m/c c/c of extraglomerular hematuria
    - ↓
    - Idiopathic hypercalciuria
- Edema → mild
  - ↳ d/t - Na^+, H_2O retention
- causes of Nephritic Syndrome.
- m/c/c in pediatric age → PSGN
- m/c/c in Adult age → IgA nephropathy
- m/c/c overall → IgA nephropathy

Nephrotic

- Rare → HTN, Hematuria, RBC casts
- → Massive proteinuria (>3.5 gm/day)
- → Protein C, S, Anti-thrombin III } loss
- → Increased fibrinogen (from liver)
  - ↳ (Acute phase reactant)
- → Hypercoagulable state.
- → Hyperlipidemia
- → Lipiduria.
- → lipid casts (waxy casts)
- → Edema → Severe
  - ↳ d/t → Hypoproteinemia
  - m/c cause - Na^+, H_2O retention
  - (Hydrostatic pressure)

Dt.:
Pg.:

Delta

Causes of Nephrotic Synd.

m/c/c in ped → Minimal Change dis. (MCD)

m/c/c in Adults → FSGS (DM)

m/c/c in Elderly → Membranous GN

m/c/c overall → FSGS.

Genes of Nephrotic Syndrome

Chr. 19q ← 1) NPHS-1 gene → Congenital Nephrotic Synd. (finnish type)

Slit diaphragm component ↓

Nephrin

Chr. 1q ← 2) NPHS-2 gene → Steroid resistant N.S.

↓ → AR → FSGS

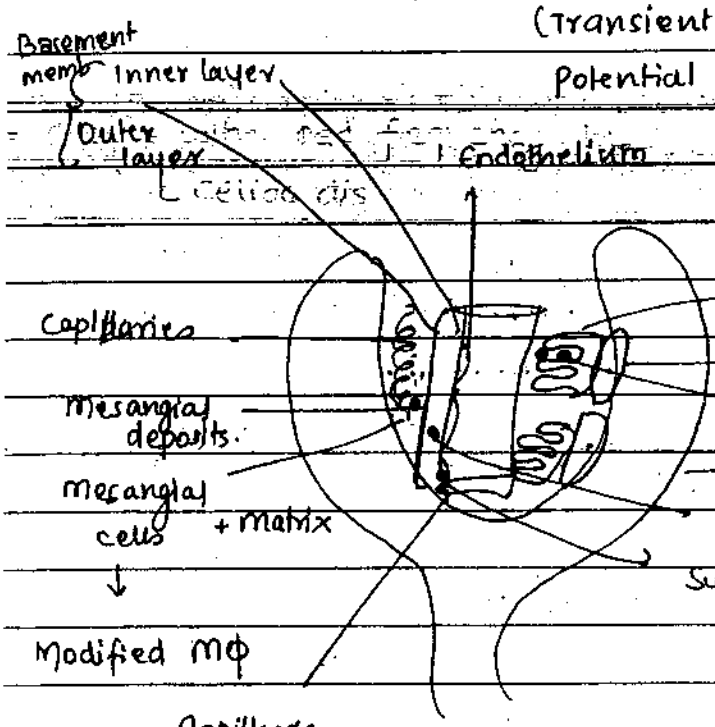
Podocin

3) α-Actinin-4 gene → AD type of FSGS.

mutation

Ca influx ← 4) TRPC-6 gene → Adult onset of FSGS.

(Transient Receptor Potential Calcium channel-6)



Delta

Intramembranous deposits → mpGN (Type II)

Mesangial deposits - IgA nephropathy
fibrinonectin nepropathy

PSGN (Acute proliferative GN)

- 6-10 yrs
- Can be seen in adults
- Grp. A β-hemolytic streptococci → 1, 4, 12
- Can occur → 2° → pharyngitis (streptococcal) → m/c
  skin infn (Impetigo)
- Immune complex mediated

→ Pharyngitis

Incubatn period → 1-4 wks → PSGN → C_3 led (transient) → for 6-8 weeks - C_3 led

Hematuria (cola-colored smoky urine)

Incubatn period → 1-4 day → IgA Nephropathy (Berger dis.)

- → Viral pharyngitis
- → Hepatitis/G.I. infn
- → Recurrent hematuria (IgA nephropathy - m/c c/c of hematuria)
- → C_3 → (N) levels
- → only IgA_1 → pathogenic
  └ mesangial deposit

- m/c Antigen → Streptococcal pyogenic exotoxin B

Delta

on Light microscopy

PSGN

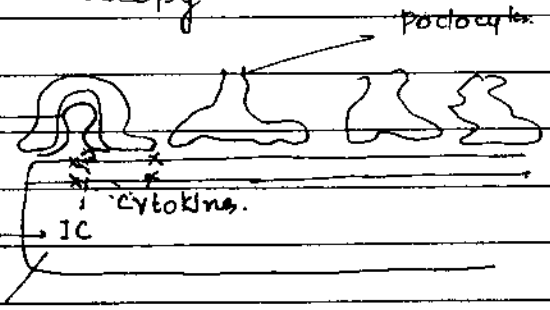
↓

- Hypercellular glomeruli
  - Endocapillary ↑ (max) → Endothelial cells, Inflammatory cells ↑ed
  - Exocapillary → mesangial matrix
    - ↑ed Inflammatory cells
    - ↳ mesangial cells.

Seen in other GN also, but maximally ↑ed in PSGN.

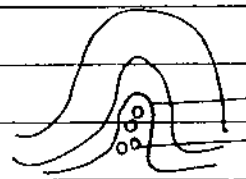
- Electron microscopy

(IC) Hump sign/ Subepithelial deposit (m/c).



* All types of deposits are ↑, max → sub-epithelial deposit

- Immunofluorescence Mscopy
  - Granular ~~Ige~~ IgG, C_3 in GBM and mesangium



→ lumpy-Bumpy appearance

↓

Also seen in RPGN

~~especific~~ especially when - PSGN → RPGN

"Starry-Sky" appearance

PSGN - Usually resolves in acute phase

↓

V. less chronicity (least).

Most chronicity → RPGN

Serology - Anti-DNAase Ab → 70%.

ASO (30%)

IgA nephropathy (Proliferative changes) (+)

- m/c/c of GN worldwide
- m/c/c of Recurrent hematuria
- D/t ↑ed mucosal IgA secretion (only IgA_1 - Nephritogenic)
- Occurs with ↑ed frequency in
  - Celiac dis
  - GI. Infection (↑ed IgA_1 production)
  - Liver pathology (d/t ↓ed IgA clearance)
  - HSP
- C/F → • After 1-4 days of infecth
  - Gross hematuria following RS, GIT, UTI infecth.
  - Recurrence common in 15% cases who are transplanted
  - Slow progression to CRF occurs in 15-40% cases over a period of 20 yrs.

L/m - mesangial proliferath

E/m - mesangial deposits (IgA, IgG or IgM) with C_3

C_3 levels (N)

Delta

RPGN (Rapid progressive GN)

- Crescentic GN

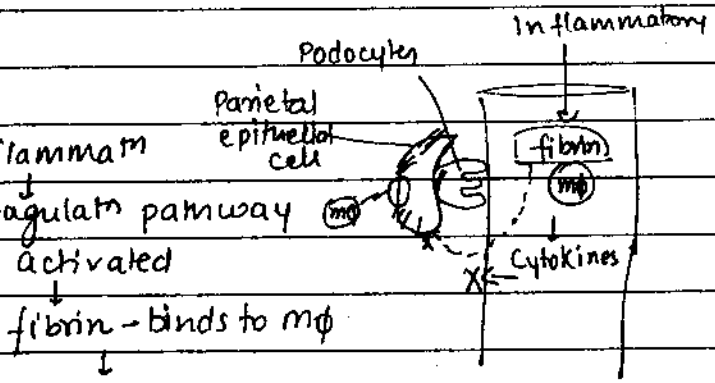
↓

Crescents ∝ prognosis

↓

No. of crescents ∝ prognosis

(If >50%) → Bad prognosis



↓

Cytokines → Rupture of BM. (wrinkling, rupturing of B.M.)

↓

fibrin - mononuclear cell escape . ↳ most characteristic

↳ Attach on parietal epithelial cell RPGN

Crescent → Parietal epithelial cell

+

fibrin

+

mononuclear cells.

→ M/I factor for crescent → fibrin.

RPGN → Overall → m/c → Subepithelial deposit.
↳ Overall → Worse prognosis amongst GN

I (20%)	II (25%)	III (>50%)
Anti-GBM Ab	Immune complex	Pauci Immune (m/c-50% of all cb RPGN)
• Auto-Ab against Glomerular B.M.	↳ SLE, HSP	Best prognosis ← ANCA assoc.
◦ Auto-ab against α_3-chain → Type IV Collagen	↳ IF - Granular deposits of Immune complex	P-ANCA → ① microscopic polyangiitis • IF - No deposit ② Churgg-strauss Synd.
• E.g. → Goodpasteur Syndrome	• Idiopathic • SLE • IgA Nephropathy • HSP • MPGN	C-ANCA → ① Granulomatosis polyangiitis (Wegener Granulomatosis) ② Idiopathic Crescentic GN.
◦ Type II Hypersensitivity		
◦ Lung affected before kidney		
◦ m/c/COD → Renal failure	• Cryoglobulinemia	• IF - No deposit
◦ IF → Linear GBM deposit of IgG and C_3	◦ PSGN	

Lupus Nephritis → WHO classificatn → Ting severity of prognosis.

I) → Minimal change
II) → Mesangial GN
III) → Focal GN → Wire-loop lesions. (sub-endothelial deposits)
IV) → Diffuse proliferative GN → m/c ↓ S/O Active disease. Bad prognosis
V) → Membranous GN
VI) → Lupus sclerosing GN

* Renal vein thrombosis → m/c a/w → membranous GN.
↳ Type V > IV > III > II > I (No thrombosis)

* PAN → No ANCA is (+)

• Correlating with severity
↳ level of proteinuria
↳ Hypo complimentemia
↳ ds-DNA titres

Dt.:
Pg.: Delta

ALPORT SYNDROME

- 5-20 yrs , CRF @ 20-30 yrs.
- Triad – Hematuria
  - Eyes → Ant. lenticonus, corneal dystrophy
  - sensori-neural deafness (Ear)
- m/c → Ab against α_5 → Type IV collagen
- m/c → XLD → α_5 - chain Type IV collagen.
  V. rare → AD

In Autosomal type - α_3, α_4
In X-Linked - α_5

- m/c presenting symp → Hematuria
- Light Mscopy } Non-Astic
  Immunoflorescence }

- EM → only Astic
  → earliest finding - irregular thinning of Basement memb.
  ↓
  lamina densa tries to heal
  ↓
  "Basket-weave" appearance.

Delta

Urinary casts.

- Main material - "Tomm-Horsefall" proteins

↓

Thick ascending loop of Henle (TALH)

PAS +ve

(N) Mucoprotein

Most common site - DCT

for urinary cast formation

M/C Urinary cast - Hyaline Cast.

Broad cast - CRF

(Upld) Waxy cast → Nephrotic Synd.

Muddy cast → ATN

RBC cast → Nephrotic Synd.

- Rifampicin
- NSAIDs
- IFN
- HIV

→ Interstitial Nephritis

Dt.:
Pg.:

Delta

Minimal change dis. (*HBV doesn't cause)

(lipoid Nephrosis)

↳ Deposition of lipids in proximal tubule

→ Immunological

→ Idiopathic

→ characteristically a/w Hodgkin's lymphoma

→ Any leukemia / lymphoma

→ Age - 2-6 yrs.

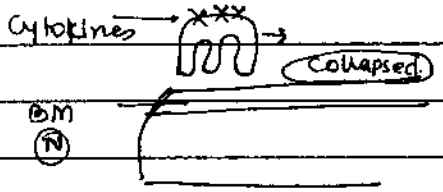
→ 2° to resp. infn, immunizatn, Atopic disorder

m/c for malignancies → membranous GN

- fever may be (+)

EM

- Effacement of ~~podocytes~~ foot process of podocyte
- fusion of foot processes of VEC.



Effacement of foot process of podocytes

↓

MCN

BM - N ← MCD

MPGN

FSGS

DM - Nephropathy

Pathogenesis → Immune dysfn, elaboratn of cytokines

→ loss of glomerular Negative charge.

- may progress to fSGS.

• m/c presentation - massive proteinuria
↳ Non-selective, do not respond to steroids
- occurs in 40% of transplanted cases

Membranous GN

M/C/C of Nephrotic Synd. → Elderly patient

→ Heyman Nephritis

Antigen used - Megalin in rats.

• Ab to PLA-2 (R)

→ In autoimmune dis. m/c also - memb. GN

→ Membranous GN

↓

1° memb GN (75%)

↓

(75%) Idiopathic

↓

Autoimmune 1° memb GN

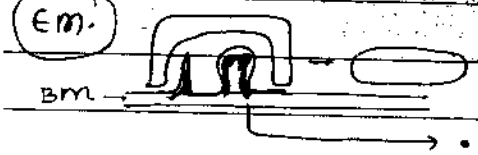
↓

HLA-DQA-1

IF - Diffuse granular staining of BM

LM - Capillary B.M. thickening
• No rupture of B.M.

Em.



• Epimembranous deposit/ Sub-epithelial deposits.
• Spike-n-dome appearance

↓

Best visualised by

↓

LM + special stain (Silver stain, ~~Rex-30~~ PAS)

★ Phospholipase A_2 - Receptor - correlates with diagnosis of

• Drugs - Penicillamine, captopril, Gold, NSAIDs

2° memb GN (25%)

↓

→ Malignancy → m/c Ca. colon, breast, lung, melanoma

→ Autoimmune disorder like SLE, thyroiditis

→ Infn - Syphilis
Schistosomiasis
Hep B (in children)
Malaria

Hep B (in adult) ↓ MPGN-I

Hep C - m/c - Essential mixed cryoglobulinemia
2nd → MPGN-1 > ∅
3rd → memb GN

leprosy - ① Systemic / secondary Amyloidosis
② mesangiocapillary
③ MPGN-I
④ memb. GN (least)

• Visceral leishmaniasis - MPGN > memb GN

• It is m/c also Renal V. Thrombosis

↓

m/c sensitive test

Idiopamic
~~SLE~~
Hep C, Hep B
EMC

Dt.:
Pg.:

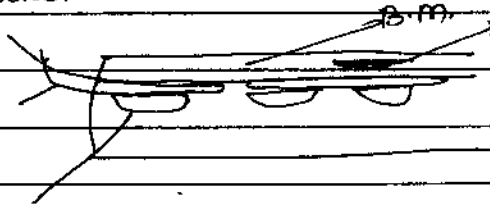
(Mesangio-capillary)

MPGN (Membrano-proliferative GN)

Immune-mediated injury

I	II	III
→ m/c	→ Alternate	→ Compliment – receptor
→ Activatn of	Pathway	def.
compliment	→ IgG – Absent – C_{1q}, C_4	• Sub-endomelial
↓	→ C_1, C_2, C_4 – (N)	+
Both Alternate,	• Intra-membranous	Intra-membranous
Classical	deposits.	deposit.
• All compliment	↓	↓
proteins – ↓ed.	Idiopamic	Idiopamic
→ Sub-endothelial	C_3 Nef Assoc.	Complement factor def.
deposits	partial lipodystrophy	
	* High recurrence rates.	

Sub endomelial deposits.



mesangial cell

endothelial cells.

Sub-endomelial deposits
↓
① splitting of B.M.
Double contour of BM.
Tram-track appearance.

↓
Thick, dense deposit
↓
∴ Type II – A/k/a – Dense deposit dis.

* C_3 Nef (C_3 Nephritic factor) → Type II
↓
Stabilize
↓
C_3 – convertase

* Partial lipo-dystrophy – Type I

HCV

↓

f/60

↓ HCV-titre

MPGN

↓ HCV-titre + synovitis + vasculitis

Essential mixed cryoglobinemia.

★ Toxoplasmosis - m/c a/w - MPGN

Dt.:
Pg.:

FSGS

Primary - Idiopathic

Secondary
- → HIV (HIV-Assoc. Nephropathy)
- → Heroin-Abuse
- → Scarring (IgA Nephropathy)
- → loss of tissue (Renal Ablat° - Sx of cancer) or any Cx
  - ↳ only one kidney (+) (U/L Renal agenesis)
- → Reflux nephropathy
- → HTN nephropathy → NSAIDs
- → Sickle cell dis → Palmidronate
- → massive obesity → Alport synd.
- → IgA nephropathy → Sjogren Synd.
- → HBV

Histologic Variants
- ① Collapsing gs (Worse prognosis)
- ② Glomerular tip type (best)

C/F - HTN, Hematuria, ↓ed GFR
- Non-selective proteinuria

factors a/w rapid progression -
- Proteinuria level
- Renal failure level
- Collapsing variant

Genetic Basis -
- NPHS-1
- NPHS-2
- α-Actinin-4
- TRPC-6.
- APO-L1 gene on Chr. 22 → ↑ed risk of FSGS, Renal failure

Hallmark → ◦ Visceral epithelial cell damage
- ◦ focal degeneratn, disruptn of podocytes.

EM → ◦ Effacement of foot process of podocytes.

LM - sclerosis of some glomeruli (focal), in affected glomeruli only a portion of capillary show sclerosis, collapse (segmental).

IF - IgM, C_3

Delta

fibronectin Nephropathy (FN)

- AD
- D/t accumulat of plasma fibrinogen
- FN-1 gene mutatn (chromosom-1)
- m/c presentatn - massive proteinuria (Nephrotic Synd.)
- fibronectin - ECM protein
  - ↳ synthesized by
    - liver → plaoma fN → "pathogenic"
    - mesangial cell → cellular-FN.

1) LM - Hypercellular Glomeruli
   - ↳ PAS+ve
   - masson's trichrome deposits. (deposits - fibronectin).
2) IF - ~~Fibrosis~~ No Ig, compliment deposits.
3) EM - large (Giant) - mesangial / sub-endothelial deposits.

HIV-Nephropathy

- Severe collapsing type FSGS
- Retraction and collapse of entire glomerular tuft, cystic dilatatn of tubular segments, inflammatn, fibrosis.
- Em - proliferatn, hypertrophy of visceral epithelium
- - Tubulo-reticular inclusions (modified ER) within endothelium are Astic

Delta

Diabetic Nephropathy -

- Type 1 DM - 30-40% chances
- Type 2 DM - 15-20% chances.

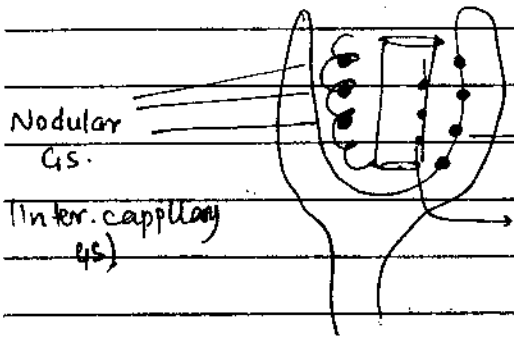
M/C factor - Duration of dis.

Earliest Lab finding → ↑ed GFR
↑ 1st yr (↑ed size, ↑ed vascularity)

5-10 yrs → micro-albuminuria
↓
30-300 mg/day

Histology

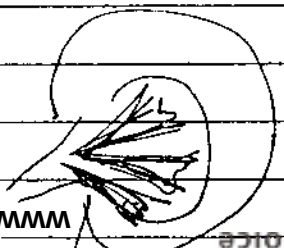
- Earliest Histological finding → Capillary B.M. thickening *
- M/C → Diffused Glomerulosclerosis. *
- Most specific - Nodular glomerulosclerosis (Kimmelstein-Wilson lesion)
↓
Inter-capillary glomerulosclerosis



features of Nodular GS.

* Armani Ebstein cells - in untreated / uncontrolled DM
↓
Proximal tubule epithelium
↓
with cytoplasmic vacuoles, having glycogen - PAS +ve.

- M/C/C of papillary Necrosis / Necrotizing papillitis
↓
DM

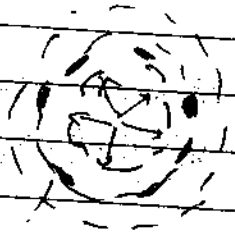


1) Benign HTN- (Benign nephrosclerosis)
   ↳ Gross - B/L symmetrical contracted kidneys
   ↳ M/E - Arteriolar - 1) Hyaline Arteriolosclerosis (Narrowed Lumen d/t accumulation of hyalin material)
   2) cystic medial necrosis

★ Malignant HTN (Malignant Nephrosclerosis)
   ↳ Variable size
   ↳ petechial Hemorrhages (d/t rupture of arterioles, capillaries)
   ↳ flea-bitten appearance.

   ↳ Also seen in - HUS
   TTP
   SABE (IBE)
   Pyelonephritis
   UTI (Obstruct°)

Microscopy -



→ Tunica media - hypertrophy
↓
Hyperplastic Arteriosclerosis
- Onion peel appearance
- fibrinoid necrosis

fibrin material →
↓
d/t fibrin deposition

Delta

Tubular

- Interstitial nephritis (salt losing nephropathy)
- Aristolochic Nephropathy →

d/t consumption of herbal medicine

Aristolochic

↓

Risk → RCC

U.Bladder Ca.

- M/c/c of Acute Renal failure → Acute Tubular Necrosis (ATN)

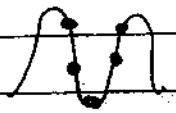
ATN → m/c site → PCT

↓ ↓

ischemic — Toxin-Induced

↓

(m/c)



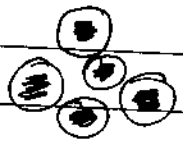
- Patchy necrosis

- Uniform / continuous
- Mercury
- Arsenic
- CCl_4 → In urine - Neutral lipid
- Ethylene Glycol → Ca. oxalate Crystals

envelope shaped

Delhi

Microscopy



→ Thyroidisam of tubule - chronic pyelonephritis

↓

scarring is irregular, symmetrical scarring

Chronic glomerulonephritis → Regular, symmetrical scarring

Pathogenesis. → Ist chronic inflammam

↓

plasma proteins come out of tubules

↓

Thyroidisatn.

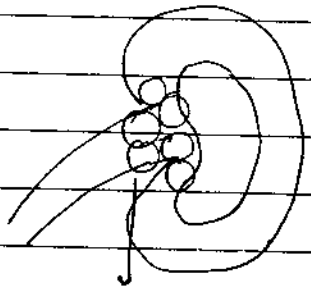
Dt.: Pg.: Delta

cystic Diseases

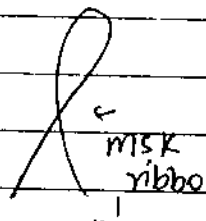
~~ADKD~~

Autosomal Dominant PCKD	ARPCKD
Adults	Children
Polycystin-1 (PKD-1 gene) → m/c protein ↳ Chr 16	PKHD gene - Chr. 6 (fibrocystin protein)
Polycystin-2 (PKD-2 gene) protein ↳ Chr 4	
→ loss of heterozygosity	→ Hepatic cyst fibrosis
→ B/L symmetrical	→ Cylindrical dilatation of tubules.
→ CRF starts after 40 yrs.	
→ Extra-renal manifestations	
→ m/c → Hepatic cysts	
Other cysts — Spleen	
↳ liver	
↳ Pancreas	
↳ ovary	
↳ lung (Rare).	
↳ Brain (V. Rare).	
• Brain - Berry Aneurysm	
→ • m/c/COD → HTN/Cardiovascular complications.	
→ Rx - Renal transplant	

Medullary sponge dis.

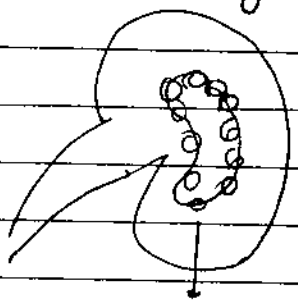


Hilar cysts
↓
Obstructn
↓
Infectn
↓
Calcificatn
(Nephrocalcinosis)
↳ m/c - sporadic
- AD may be seen.
→ M = F
- 9/K/D - Cachi-Richi dis
. Age - >50yrs.



MSK ribbon
↓
Purple, Teal, Green.
· ~~Bilateral~~ symmetrical cysts
- Asymmetrical
- on IVU
↓
"Paint-brush" appearance

medullary cystic dis.



cysts @ cortico-medullary jn
↓
Tubular damage
↓
Salt losing Nephritis
(Interstitial nephritis)
· AD

* Dialysis assoc. cystic kidney dis. - m/c - RCC (papillary RCC)
Sickle cell an. - Medullary RCC.

Two types

MCKD - 1
↓
mutatn - MUC-1 gene
↓
glycoprotein - mucin-1
- AD
- frame shift mutatn

MCKD - 2
↓
mutatn - UMOD gene
Tomm Horsefall protein
Uro-modulin protein
↓
Chr. 16
- AD

Dt.: Pg.: Delta

Cancers

RCC

Hypernephroma

GRAWITZ TUMOR

→ 60 yrs

→ most characteristics → Smoking

→ Incidence → m > F.

→ R/F → • DM
• Obesity
• Sickle cell An.
• Tecl estrogen
• HTN
• Asbestosis

→ m/c - Upper pole

→ proximal convulated tubule

→ m/c pattern - Sporadic, U/L

→ Hereditary → B/L

① VHL (von-Hippel Lindau Synd.)
↳ Chr. 3p.
↳ Risk of clear cell type RCC

Triad of VHL -
cerebellar hemagioblastoma
Pheochromocytoma
B/L RCC
Retinal Angioma

② Hereditary leiomyomatosis + RCC
→ AD
→ Cutaneous leiomyoma / Uterine leiomyoma
→ Papillary RCC
→ Aggressive, Bad prognosis
→ fumarate - Hydratase gene mutation → "FH" gene

③ Birt-Hogg Dube Syndrome
↳ AD
↳ a/w BHD mutatn.
↳ m/c a/w Chromophobe RCC

④ $X_p 11$ → AD
↓ → TEF-3 gene mutation
Has → papillary RCC (d/d)
papillary appearance

C/P of RCC

Triad
→ Hematuria (m/c)
→ Abd mass
→ pain

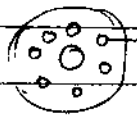
Wilm's
↳ m/c - Abd mass
pain +
fever +
↳ L/C - Hematuria

* RCC - most characteristically angio-invasive.
RCC > HCC
• % of RCC involving venous system - 10%.
• m/c site for mets - lungs.

peri-neural invasion
↳ Salivary gland ca
↳ Ca. pancreas
↳ Ca. Prostate.

Types

1) Clear RCC cell → m/c Type.
→ PCT
→ U/L



Clear-vacuole
↓
Contain both
glycogen, lipid

→ mostly sporadic
→ When hereditary - a/w VHL - VHL gene mutation (3p-deletion) - m/c
→ Hypermethylation of chr. 3p
→ t(3;6), t(8;?)

Dt.:
Pg.:

↳ fibrovascular stalk = papilla.

i) Papillary (Chromophilic) RCC
- ↳ most angio-invasive.
- ↳ DCT
- ↳ Cystic (dialysis assoc.)
- ↳ Trisomy - 7, 16, 17.
- ↳ Hereditary papillary RCC - a/w - Trisomy - 7
  - a/w - 'MET' - proto-oncogene mutation
- ↳ Pediatric papillary RCC → t(X:1)

ii) Chromophobe - Best prognosis
- CD (Intercalated cells) (Collecting duct)
- Birt-Hogg-Dube
- Cytoplasm distinct
  - Plant cell like tumor cell
  - perinuclear Halo

(Worst → Sarcomatoid RCC)

↑ Chromophobe RCC
- a/w loss of multiple Chromosomes (extreme hypodiploidy)

iv) Bellini Duct RCC
- ↳ Collecting Duct
- ↳ Desmoplastic Reaxn (extensive fibrosis)
- ↳ Desmoplasia - ↑ed collagen synthesis in tumor cell vicinity
  - ↳ max/m/c → a/w - Ca. pancreas.
  - Also in ~~chong~~ cholangioca, Benign mesothelioma

- m/c RCC in Infancy, Childhood } → Wilm's Tumor (Nephroblastoma)

★ Congenital mesoblastic Nephroma
- ↳ seen in Infancy only
- ↳ But is not m/c.

Wilm's Tumor

Peak age group - 2-5 yrs

U/L - 80%

B/L - 20%.

Also

1) WAGR synd.

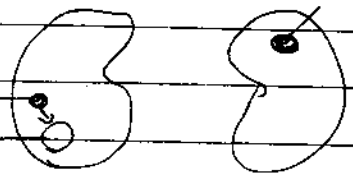
2) Denys-Drash synd. (>90% - m/c)

↳ max. risk of WT.

3) Beckwith- Widdmon synd.

• Nephrogenic rests - precursors of Wilm's tumor

B/L



Nephrogenic rests (fibrous tissue with immature glomeruli)

↓

precursor of tumor in the opposite kidney

• Histology - Triphasic

↳ Blastemal cells - Blue colored, small cluster of cells

↳ Epithelial cells & immature glomeruli, tubules.

↳ Stromal cells - Adipose tissue, cartilage, bones.

• Histology - m/c for prognosis

• m/c site mets - Lung

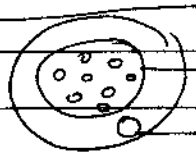
• Clear cell variant of Wilm's Tumor → Bone mets.

Dt.:
Pg.:

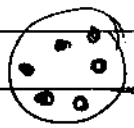
Neuroblastoma → o m/c tumor of infancy

→ m/c extracranial solid tumor of childhood.

- o m/c site - Adrenal medulla
- o Derived from sympathetic ganglia
- o Sporadic → m/c (98%)
- familial - Rare (2%) → a/w - germline mutation of anaplastic lymphoma Kinase gene.
- o peak age group - 18 months
- o At the time of presentation, 760% of pts. will have had metastasis.
- • All neuro-endocrine tumors - have poor prognosis
- o Other sites - parasympathetic ganglia of abdomen, mediastinum
  - * m/c site of mets - Bone, Liver, LN
  - Lungs (least common)
- * Also a/w sporadic mutation of NF-1 gene.
- * 2 types - Clinically - ① Pepper type → sHUborn, young infants, mets to liver
  - ② Hutchinson → older age. Bony mets to orbit, skull → exophthalmos
- * Histo - Small round Blue cell tumor



In EM -



Chromogranin
synaptophysin
Neuron specific enolase
Leucine-7
Neurofilaments.
→ used as tumor markers

- Histology - "Rosettes"
  - True → flower-petal → Clear space
  - pseudo-rosettes → Bld vessels, Tumor cells.

① Neuroblastoma
② medulloblastoma
③ PNET

- In neuroblastoma - pseudo-rosettes,
  Kla Homer - wright pseudo-rosettes.

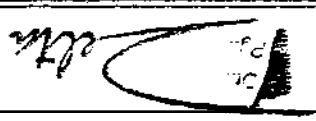
- In retinoblastoma → true rosettes
  → Kla - flexner wintersteiner

- Ependymoma → (pseudo > True)

	Good prognosis	Bad prognosis.
Histology	Mitotic/Karyorhexis Index - < 200/5000	> 200/5000
	(1) Gangliocytic differentiam*	-
	(2) Schwannonian stroma*	-
	(3) Intra-tumoral calcificam*	-
Cytogenetic	Hyperdiploid	Hypodiploid, 17q gai
	- No loss - * CD-44	* MRP loss of Chromosome 1, 11
	- No amplificam -	*Telomerase n-myc amplificam overexpression.
	- TrK-A (Accha)	- TrK-B (Bura)
Biochemical	- Se. LDH (N)	- Se. LDH - ↑ed
	- Se. ferritin (N)	- Se ferritin - ↑ed.
Age	< 18 months	> 18 months.

* most sensitive - chromogranin
most specific - ~~synaptoph~~ synaphophysin

* Malacoplakia - U.Bladder / Skin / Bone / Small intestine
  ↳ Phagolysosome defect
  ↳ Ca deposits (Michelis Guttman bodies) - Intracellular
  ↳ Alw Chronic infectn + Extracellular
  Immunosuppressive &
  Alw HIV.



LUNGS

(156)

- M/c congenital malformatn
  - cong. Adenomatoid cystic malformatn
- Pulmonary sequestratn
  - M/c site → Carina
  - Blood supply → Brach of Aorta
  - Site of infection.
  - ✓ M/c → post. Basal segment of (L) lower lobe.

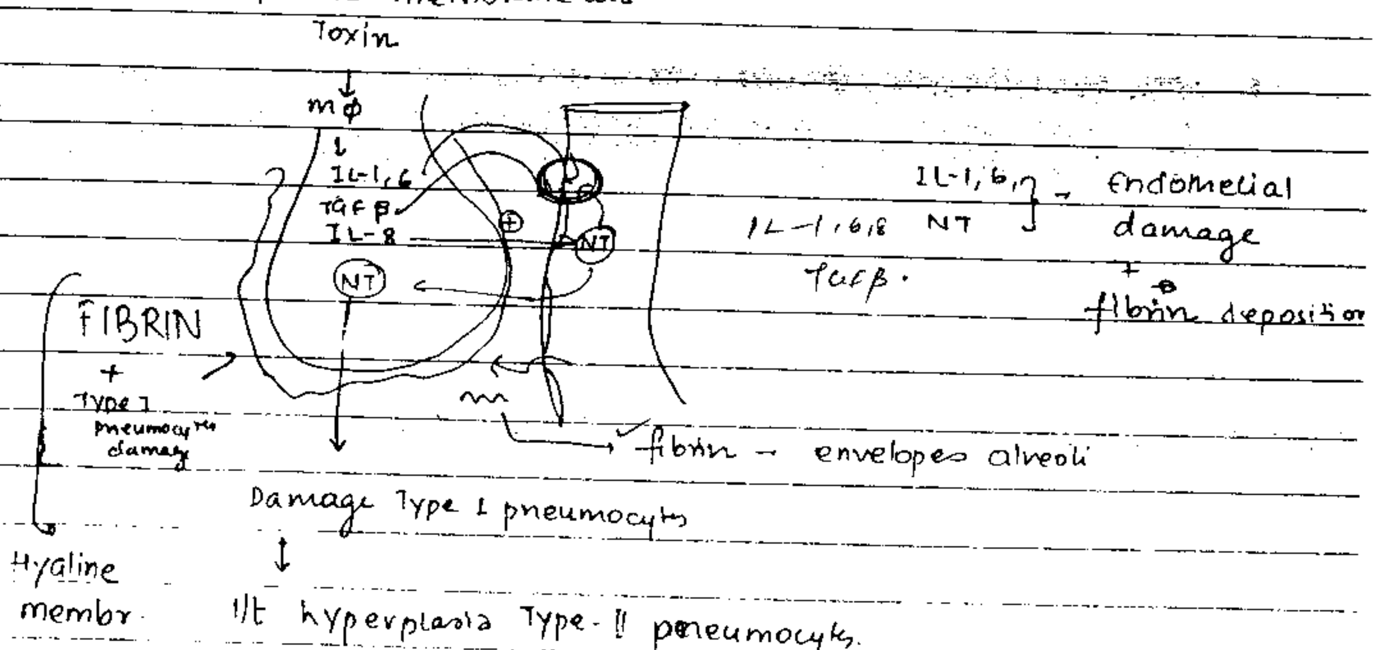
post Basal (L) Lower Lobe

- Acute Interstitial pneumonia (ARDS with unknown etiology)

↓ Diffuse Alveolar Damage / Shock lung. AIP = ARDS c out known etiol.

Histologically finding → same as → ARDS   Hyaline memb D/S.

- M/c presentatn → Hypoxia (Dyspnoea) ✓
- a/k/a → Diffused Alveolar damage
  - → Shock lung
  - → Hyaline membrane dis.



★ Even if 100% O_2 is given, pt is persistently hypoxic

∴ K/a - Shock lung

Dt.:
Pg.: Delta

* central role in ARDS - endothelial damage
↓
m/s in pathogenesis. Endothelial Damage.

* All alveoli - show same finding - ~~Alveoli~~ Diffused Alveolar damage.

* TGF-β ⇒ fibrosis

* Poor prognosis
(mortality Rate - 40%.) 40/.

Delta

PNEUMONIA

- Infn of lung parenchyma

Typical	Atypical (no consolidation)
C/F → more aggressive	less aggressive
fever, cough, cxr - consolidatn →	–
leukocytosis →	–
Pathological	
Congestion + Consolidatn	congestion without consolidatn.
d/t alveolar exudate	(No alveolar exudate)
	↳ Interstitial mononuclear inflammatory cells. (lymphocytes/ mϕ / plasmace
∘ m/c - strep. pneumoniae. (Pneumococci)	↳ m/c a/w ↳ Viral infn. ↳ m/c a/w - mycoplasma infn
	∘ Giant cells may be seen ↓ Warthin-finkeldey giant cells of measles.

Typical pneumonia

- **Bronchopneumonia**
  - Good immunity
  - Patchy consolidation
- **lobar pneumonia.**
  - Bad immunity
  - Entire lobe / continuous.
  - → Laennec Staging
    - ↳ congestion – Bld vs. congestn, ↑ red Bc (1-2)
    - ↳ Red hepatisatn → RBC + WBC + Bacteria (3-4)
    - ↳ Grey hepatisatn → fragmented RBC + WBC (5-7)
    - ↳ m/c outcome – Resolution (8-10)

(10 days)

Dr. Pg. Ekta

OBSTRUCTIVE DISEASE

1. Bronchial Asthma (Reversible Bronchospasm)
2. Bronchiectasis
3. Chronic Bronchitis (Blue bloaters)
4. Emphysema (pink puffers)

Bronchial Asthma

- Reversible
- Inflammatory.
- Autoimmune - Gene - PTPN-22
  ADAM-33 (smooth muscle hyperplasia)
  IL-4 polymorphism
- Alw chromosome 5 ✓
- YKL-40 protein in lung tissue / sputum → correlates severity of Bronchial Asthma.
  (Chitinase like protein)

Bronchial Asthma

Atopic (Extrinsic)	Non-Atopic (Intrinsic)
- Pediatric	- Adults
- H/o family	
- h/o allergy	
→ IgE Ab ↑ed.	- E.g., Exercise Induced
→ E.g., ABPA (Allergic Broncho-pulmonary Aspergillosis)	
• Drug-Induced (Aspirin)	

Sputum examn

1) Curschmann spirals
2) Charcot Leyden crystals
   " galectin - 10^4
3) CREOLA - bodies
   (individual epithelial cells)

Microscopy -

- a/w airway remodelling ↓
  - Epithelial thickening
  - Inflammation
  - Smoom ms. hyperplasia

} - 1/t narrowing of lumen

(ADAM 33)

816
520
696
816
816
816

4k

Delta

BRONCHIECTASIS.

- Irreversible dilatatn / destructn of Bronchi
- Initiating events – • Obstructn
  • Infection
- Necrotising infn
- A/w kartagener Syndr. (primary ciliary dyskinesia)
  d/t mutatn of (dy-nein) Dynein-mutation
  a/w- 1) Situs inversus
  2) Recurrent sinusitis
  3) Infertility.
- Bronchiectasis – Lung Abscess ← Cerebral Abscess
  Renal abscess
  Synovial / supp arthritis
- Not a precanc. condition
- 2° amyloidosis (AA type)

EMPHYSEMA

- Irreversible damage of acinus
  - ↳ Resp. bronchiole + Alveolar duct + Alveolus

- Centri-acinar → Resp. bronchiole involved. (other parts not involved)
  - → upper lobe - m/c site
  - ↳ m/c type of emphysema
- Pan-acinar - Involves full acinus
  - ↳ m/c site - L/L

→ Pathogenesis - Imbalance b/w protease, anti-protease

↓ ↓

NT/mϕ → Elastase α_1-Antitrypsin

Centriacinar	Panacinar
- Cigarrete	- α_1 AT def. (congenital)
- Coal worker pneumoconiosis	↓
↓ (+)	(NT) → elastase
Mϕ	
↓	
Elastase → MMP → digests - α_1-AT	

★ m/c cancer in lung scarring → a/w - Adenoca.

↓

T.B.

Infarct

Radian.

Dt.:
Pg.:

CHRONIC BRONCHITIS.

- Productive cough
- > 3 months — 3 months
- > 2 yrs (consecutive) — 2 yrs.
- Unknown etiology

- Strongly assoc. with smoking - chronic bronchitis
- Earliest finding - ~~none~~ mucus hypersecretn
  d/t hypertrophy of mucin-filled goblet cells

- Reid Index = $\frac{\text{Mucus gland thickness}}{\text{Bronchial epithelial thickness}}$
  (N) - 0.4
  Chronic Bronchitis > 0.5

- ~~Complicatn~~
- Complicatn - Infl → metaplasia - dysplasia → Ca. ✓ Q

Pneumoconiosis

Silicosis - Corundum DIS.

- Coal worker pneumoconiosis
- Silicosis - m/c - occupational → a/k/a - Grinder's disease } Upper lobe.
- Asbestosis → starts at L/Lobe of lung

- Dangerous - size - 1-5 μ → Escape phagocytosis 1-5 μ

pathogenic properties ~~minimize~~ >5 μ - get phagocytosed.

- Shape
- Size
- Physico-chemical properties

- ferruginous bodies - seen in all above
  - ↓ → m/c Asbestosis
  - ferrous + glycoprotein + organic/inorganic dust fibres.

- Asbestos → lung } ↑ k/a Asbestos bodies.
  - ↳ Sputum }
  - ↓
  - Beaded/ Dumb-bell shaped

6.00 - 8.00 - 2
9.00 - 11.00 - 3
12.00 - 4

Dt.:
Pg.:

Delta

ASBESTOSIS

1) Straight fibres - ~~Cor~~ Crocidolite → Banned
(Amphosite) (carcinogenic) / most pathogenic

2) serpentine - ~~Chrysotile~~ Chrysolite → m/c S.C

- Once exposed - Risk of asbestosis - remains same
↓
Thru'out life

- Incubation period - 5-10 yrs.
- most characteristic finding - Diffused calcific pleural plaque
Diffuse calcified pleural plaque
- Asbestosis - m/c - Bronchogenic ca. lung
(~~A~~)~~regular ca.~~ ~~SCC~~ (Adenoca. > SCC)
↳ m/specific - mesothelioma.

- mesothelioma - I.P. - 25 - 40 yrs
↓
Hence incidence loco.

- Other ca. mat can be caused by Asbestosis.
1) laryngeal ca.
2) pharyngeal ca.
3) Stomach ca.
4) Colon ca.
5) RCC.

Adenoca.

Both glandular

IHC - Napsin-A ✓

Thyroid Transcription factor-1 (TTF-1) ✓

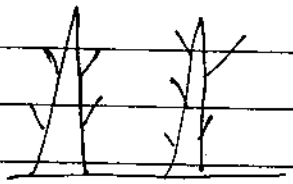
Gm. → Best method

small-non-branching microvilli

Epitheloid mesothelioma.

Glandular

- Calretinin (Best)
- Cytokeratin (5/6 ❌/7)



long branching microvilli

mesothelioma

- generally malignant
- CD 34 -ve
- Cytokeratin (+)
- Biphasic pattern (Epitheloid, sarcomatoid)
- usually U/L (R > L)

Because of greater size of (R) pleural cavity.

- intense fibrosis

solitary fibrous tumor of pleura / Pleural fibroma / Benign mesothelioma

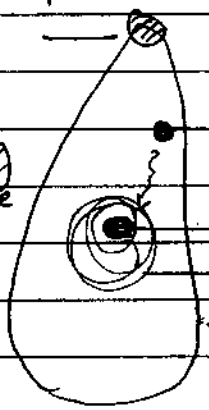
No alw Asbestosis

- CD 34 +ve
- Cytokeratin -ve
- Desmoplakin (+)

Dt.:
Pg.:

TUBERCULOSIS

1° TB	2° TB / Reactivation TB
- pediatric	- Adult
- exogenous	- Endogenous
- U/L Hilar LN	- pulm. fibrosis
- fibrocaseous consolidation	
- pleural effusion	
- phlyctenular conjunctivitis.	
- Simon focus	



Ghon's focus + LN + fibrosis + calcification → Ghon's complex → Ranke's complex

Supraclavicular focus - PUHL's lesion

Infra " - Assman focus

- Hematogenous -

1) Simmond's focus - Isolated granuloma in liver

2) Rich focus → (F) in cerebral cortex

→ T.B. meningitis (m/c)

↓

m/c presentation - Diffuse meningoencephalitis

m/c characteristic - Basal exudate

m/c/ Complication - Cerebral Infarction.

3) Wielgert's focus - Subintimal space of pulm vein

Congenital TB

CANTWELL

1) mother - source

2) TB in NB (within 7 days of birth)

3) No other nearby person should have TB info

4) liver granuloma - should be (+)
(1° complex)

m/c site - overall
primary complex } - liver

Dt.:
Pg.:

LUNG CANCER

- m/c lung ca. → mets

ped → m/c 1° - osteosarcoma > Wilm's

Adults → m/c 1° - Breast ca.

In peds, 1° - malignancy.

m/c → Cardnoid

m/c site - Bronchus > ileum

GIT > RS

APUD cells (Amine precursor uptake, decarboxylation)

m/c site - ileum.

m/c 1° malignancy

World - Adenoca.

India - SCC.

m/c Benign tumor

In peds, m/c Benign tumor → Hamartoma

Inflammatory myofibroblastic tumor

In Infants, m/c benign tumor → pleuropulmonary blastoma.

- m/c lung ca. a/w Pancoast syndrome → SCC > Adenoca.
- m/c u Sup. vena cava u → Small cell ca.
- m/c u Golden pneumonia (lipoid pneumonia) → SCC > Adenoca.
- m/c u Trousseau's syndrome → Adenoca.
  - Thrombophlebitis ← Mucin from glands

- m/c mets of lung → Adrenal > liver > Brain

Delta

SCC (Sq. cell ca.)

- central
- Strongly a/w smoking (strongest)
- m/c a/w - cavitatn
  → paraneoplastic syndrome → Hypercalcemia (SCC > small cell ca
- microscopy
  ↳ epithelial pearls (Intercellular bridging)
  or
  Keratin pears
- m/c type in males.

Dil:
Pg:

Adenocarcinoma

- Peripheral
- Slow growing ✓
- more mets ⊕
- poorer prognosis
- Lung → lung mets
- m/c cancer in scarring ✓

(Aerogenous mets)

↓

1) mucinous (m/c → Aerogenous spread)
2) Non-mucinous.

- ↑ed surfactant production

- Bronchiolo alveolar ca. ✓

(Adenoca. in situ)

No mets

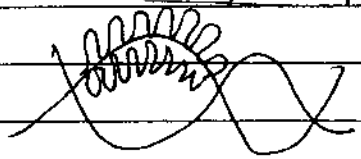
Good prognosis

↳ Tumor cells grow along pre-existing alveolar septa.

↓

Butterfly sitting on fence

(lepidic) pattern



* Lepidic cells
↓
Cardiac myxoma

Small cell ca. of lung / OAT cell

- Neuroendocrine tumor

- Nuclear molding
- salt-paper chromatin

Neurosecretory granules → ① Bombesin ✓ ② Leu-7 ✓ ③ Synaptophysin ✓ ④ Chromogranin

- Nuclear chromatin
  - ↳ leak outside → get deposited on vessel wall
    - ↓
    - Basophilic staining of vessel wall (Azzopardi effect)

- m/c paraneoplastic syndrome → Overall → Hypercalcemia
  m/c endocrinological syndrome → ACTH → Cushing's

- m/c in paraneoplastic syndrome in small cell ca
  - ↓
  - SIADH >> Cushing's
- → lambert eaton
- → Hypercalcemia

★ SVC syndrome → obstruction of venous return from HFN

Delta

Neuroendocrine tumors of lung →
- → collar button lesion
- → mc presentation - Hemoptysis
- → Not a/w smoking
- → v. rarely a/w carcinoid synd.

1) Carcinoid → Typical
   → Atypical (↑ed mitotic figures, Necrosis)

2) Tumorlets →
   precursors of carcinoid
   Seen in scarring (chronic inflammation)
   Size < 5mm.

3) Small cell ca.

4) Large cell NET.

* Asteroid bodies of Sarcoidosis → Lipid bilayer.
* Shauman bodies →
  → Iron - concentric
  Calcium - on H&E - Homogenous basophilic.

* Only 10% of pulm. A. emboli → cause infarctn

* Red infarctn on Gross → lung, liver, Intestine

White Infarctn → Brain, spleen, kidney, heart

* Lung - pulm thromboembolism → wedge shaped mass.

pulm. HTN

Arterioles - medial hypertrophy ✓

Thickening, duplicam of elastic lamina ✓

plexiform pulmonary arteriopathy ✓

Large arteries → Atheromatous plaques.

← Thrombi in pulm. vasculature

← Vasoocclusive dis.

* Sudden cardio-pulmonary collapse in pulm. embolism occurs d/t →

60% pulmonary O^n is obstructed by emboli

* Pulm. emboli

- Only 10% - cause infarction
- uncommon in young
- About 3/4th of all infarcts in lower lobes
- Wedge shaped Infarct → Apex towards the hilus.

Delta

CNS

Glial cells

Neuro-ectodermal	Mesodermal
① Astrocytes.	modified mϕ in brain
→ (Wound healing, repair)	↓
→ Blood-brain barrier formation	Microglial cell
	↓
② Oligodendroglial cells.	Lipophage (fat eating) → ~~Gitter cell~~ Gitter
→ myelin synthesis in CNS	→ complex granula corpuscles
eg. → demyelinatn	→ Hortega cells.
ⓘ PML (JC-polyoma virus)	Rods → in Neurosyphilis → modified microglial cells
↳ affect → oligodendrocytes.	
↓	
Ground glass nuclei	
ⓘⓘ SSPE (measles)	
↳ ed apoptosis of oligodendrocytes.	
③ Ependymal cells	
→ for ventricle lining	
↓	
damage	
↓	
ependymal cells lost	
↓	
sub-ependymal granulatn tissue	
↓	

which is derived from → Astrocytes.

Dt.:
Pg.: Delta

CNS Responses →

i) Ischemic / Hypoxia – Survival time of neurons → 3-4 mins.

→ Red neurons (Hypoxic Ischemic Encephalopathy) eg.

↓

d/t both apoptosis and necrosis

ii) Alzeihmer Type I cells →

Ammonia → damage (N) cells → Alzeihmer Type II cells.

Eg. → Liver cell failure

Wilson's dis.

→ Inborn error of metabolism - in Urea cycle.

iii) Rosenthal fibres → Astrocytic response

→ seen in astrocytes in response to injury

Seen In → Juvenille pilocytic Astrocytoma.

→ Inflammatn (gliosis)

Rosenthal fibres are formed by - α & β-crystallin and heat-shock protein

↓

cytoplasmic inclusions.

★ Brain-lipid binding protein / fatty acid binding protein-7 [FABP-7]

↓

(+) on Mature astrocytes

fn → involved in cortical layer development

↓

forms - Radial glial system of brain

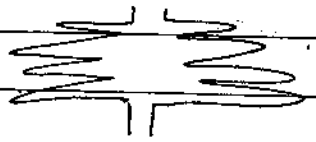
Delhi

Congenital anomalies of Brain

Neuronal migration Disorder

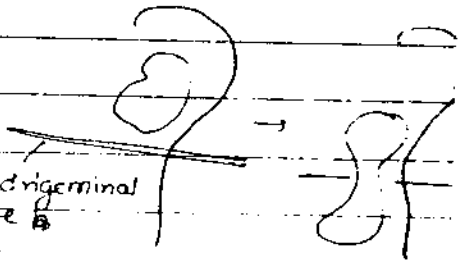
- Neuronal migration - 12-16 weeks in intra-uterine life
- If >12-16 weeks → Neuronal migration disorder
- Genes -
  - DCX-1 (Double cortin gene)
  - Filamin-A gene
  - LIS-1 gene

1) Lissencephaly or Agyria
2) Schizencephaly
3) Neuronal heterotropia
4) Agenesis of corpus callosum ⟶ Pressure on ventricles by cortex
5) Poly-microgyria ↓
6) Holoprosencephaly (Trisomy-13) Bat wing defect on Radiology



★ Dandy Walker Syndrome
- Cystic dilatation of IVth ventricle.
- Hydrocephalus
- Chiari II malformation → Cerebellum herniation

★ Arnold-Chiari malformation → d/t tectum breaking → Radiological - Banana-like

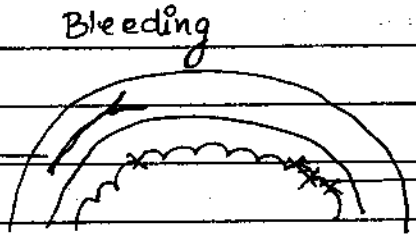


↓

Chiari I malformation → descent, no herniation of cerebellar tonsils
↳ Quadrigeminal plate intact
Tectum intact

Dt.:
Pg.:

Delta



Epidural

Middle meningeal A.

Subdural

→ cortical bridging veins.

Intracranial bleeding –

I-C bleeding	SAH
↓	↓
m/c d/t HTN	m/c d/t 1) Trauma
m/c Artery → MCA	2) Berry Aneurysm Rupture
↳ Lenticulostriate Branch.	↓
↘	Congenital defect
→ Lipid ← Hyaline	Tunica media defect (internal elastic lamina fragmented)
→ Lipo-hyalinosis	↓
↓	
CHARCOT-BOUCHARD ANEURYSm	↓
↓	
Rupture	m/c affected site of Berry's Aneurysm
↓	↓
m/c site → putamen	Jn of Anterior cerebral A. with Ant. communicating branches.
	l/c site - Vertebral A.

- m/c affected artery - by atherosclerosis - Abdominal aorta.

l/c affected " → Berry's Aneurysm Circle of Willis (Berry's Aneurysm)

Delta

Infections.

→ T.B. Meningitis

↳ m/c presentation → Diffuse meningoencephalitis

↳ m/c complication → Infarction

↳ m/characteristic → Basal exudate

* Periventricular calcification, Necrosis → CMV

* Robin's - Virchow space → Soap bubble appearance → Cryptococcal inf.

→ Viral Meningitis -

1) Microglial nodules

2) White matter necrosis.

3) perivascular Inflammation

4) Vasculitis

5) ~~Viral infection~~ Viral Inclusions → Intranuclear, CMV

Warthein-Finkeldey → Measles

COWDRY A → Herpes virus

* HIV-meningitis = ADC (Aids Dementia complex)

↓

Sub-cortical damage

cortex - not affected

→ Most characteristic finding - microglial nodules

Never seen → 1) Vasculitis

2) Viral Inclusions.

* m/c ICSOL of HIV pt → Toxoplasmosis

* m/c Space occupying tumor of HIV pt → CNS lymphoma

* In HIV pt → Spinal cord → vacuolar ~~myelopathy~~ myelopathy

↓

SACD (sub-acute combined Degeneration) → Dorsolateral Tract affected

similar to vit B12 def

Poliovirus.

- spinal cord → Ant. horn cells
  ↓
  LMN type.
  m/c/COD → Resp ms. paralysis
- 35 yr/M → (R) leg paralysis → progresses to → pain
  weakness
  loss of muscle
  ↓
  I.P. → 25-30 yrs. ← post-polio syndrome

CSF Analysis	(N)	Bacterial (Pyogenic (M))	TBM	Viral
Gross	Clear, watery	Turbid, Yellowish	Cob-web (Clot-fibrin)	Clear
Pressure	60-150 mm H_2O	↑ed.	Med (max.)	↑
Inflammatory cells	0-5 lymphocytes/mm^3	Neutrophils	Lymphocytes (↑↑ed)	Lymphocytes (↑ed)
Proteins	15-40 mg/dL	↑ed	↑ed	↑ed
Sugar	60-70 mg/dL (2/3 of BSL)	↓↓↓ed	↓ed (mild)	(N)
Chloride	116-122 ug/dL	↓ed (mild)	↓↓↓↓ (severe) (< 50 µg)	(N)

fungal
Clear
Pres → ↑ed
Inflammatory → mixed inflammam
Protein - ↑ed
Sugar - ↑ed
Chloride - ↓ed

Delta

* Albumino-cytological dissoc.
  - ↳ Ted albumin, Ⓝ-cell count
  - ↳ GB Synd.

* oligoclonal IgG Band - multiple sclerosis

PRION DISEASE

* Alkla - Transmissible spongiform Encephalopathy
* Infectious protein, Neither DNA nor RNA

Prp^c → Ⓝ-protein → α-Helix → protease-sensitive

conformational change → β-helical → Prp^{sc} (S → Scrapi) → protease-resistan → Congo-Red +ve.

* M/c/c - Iatrogenic → NSG
  - → Corneal transplant Sx
* Incubation period - months to years.

Codon 129

- Genetic polymorphism → ↑es Risk
- Heterozygosity → protective

Histopath

→ Cluster of grape like Spongiotic vacuole

Ⓝ

↓

Neurons - Spongiform necrosis

Dt.:
Pg.: Delta

E.g.

1) Creutzfeld's Jacob dis.
2) Gerstmann Scheinker dis
3) fatal familial Insomnia → No spongiform neurons
4) Kuru, scrapie
5) Mad-cow dis.
(Bovine spongiform encephalopathy)

Cortical dementia disorder

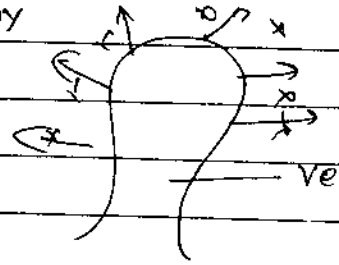
Alzeihmer's dis.

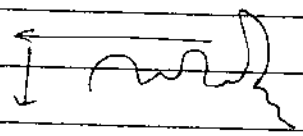
- 60 yrs
- m/c/c of senile dementia
- Earliest site → Medial temporal lobe
- m/c/cod - ~~previous~~ Recurrent infn (Pneumonias)
- 'Centaurin-A' gene
  ↓
  controls a protein - Amyloid precursor protein (APP)
  on Chromosome 21
  mutatn - Defective App
  ↓
  A-β - amyloid plaques
  ↓
  Damages synapses
  ↓
  Nucleus Basalis of meynert

* As Chr. 21 → affected
↓
Alzeihmer's dis. - universally seen in all c/o Down's.

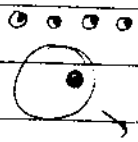
* Gross -

- Cortical Atrophy
↓
Vacuum
↓
Hydrocephalus ex-vacuo
↓
Also seen in pick's dis.





Knife-edge gyri
(Thin-wafer like gyri)

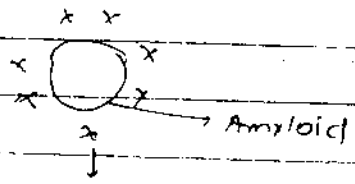


Ballooned neurons.

* microscopic Examn →

1) Amyloid → A-β amyloid
- Cerebral amyloid angiopathy

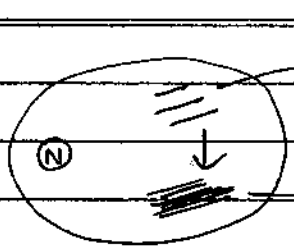
2) Neuritic plaques - senile plaques
↓
correlate to severity of dementia.



• Non-specific finding,
Can be seen in other dementias also

3) Neurofibrillary tangles.

Dt.:
Pg.:



→ Tau-proteins
↓ Hyper-phosphonylam
Condensed
Tau-proteins
↓
Neuro-fibrillary tangles.
← Initially intracellular
↓
Neuronal damage → Extracellular.

∴ No. of Neurofibrillary tangles ∝ Severity of dementia
↓
NFT ⇒ better indicator of
severity than Neuritic plaques

← Stain to Ase → NFT - Bielschwosky stain (silver-stain)

4) Inside the neurons → Hirano-bodies
↓
α-Actin
α-Synnclein → Lewy bodies
↓
Parkinsonism → Nigro-striatal system.

Delia

BRAIN TUMOR

- m/c Brain tumor → Mets
  - ↓
  - m/c primary → Lung ca.
- m/c 1° tumor → Glioma > Meningioma > Astrocytoma

~~3rd m/c - Astrocytoma~~

- m/c 1° malignant tumor in adults → Glioblastoma multiforme
- m/c 1° benign tumor in children → Juvenile pilocytic astrocyto
  (m/c site → cerebellum)
  (Cerebellar astrocytoma)
- mk 1° malignant " → Medulloblastoma.

Classificatn

Glial	Neuronal → m/c site		Undifferentiated	Miscella
		Temporal lobe	↓	↓
• Astrocytoma	m/c • Ganglioglioma		• medulloblastoma	• Mets
• Oligodendroglioma	• Gangliocytoma		• Atypical ~~er~~ teratoid or rhabdoid Tumor	• 1° CNS lym
• Ependymoma	• Neurocytoma			• Extra-gonc
	• (Dysembryoplastic neuroepithelial tu.)			Germ cell tun
GFAP ⊕	↓			↓
	Neurofilament ⊕			m/c site → pines in brain/spi
				Overall → Medias

* floating neurons in mucopolysaccharide matrix ⇒ Dysembryoplastic Neuroepithelial tumo

Origin- foramen of Monro

Dt.: Pg.:

ASTROCYTOMA (SEGA) A/w-Tuberous sclerosis

Low grade { I → Juvenile pilocytic Astrocytoma, Sup-ependymal Giant cell Astrocytoma (Best prognosis)
II → Diffuse

High grade { III → Anaplastic
IV → Glioblastoma (multiforme)
↳ Worst prognosis

* CSF-mets are seen in → medulloblastoma
Also in → High grade meningioma.
→ High grade astrocytoma.
→ Ependymoma.
→ 1° CNS lymphoma
→ Extragonadal Germ cell tumor (EGGCT)

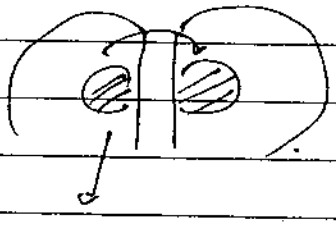
- Prophylactic radiotherapy is given to prevent CSF mets

- Gliomatosis cerebri → Neoplastic astrocytes are scattered throughout brain → considered high grade
Individual tumor — Diffusive disease.
Bad prognosis.

* Juvenile pilocytic Astrocytoma
↳ Peds
↳ Rosenthal fibres ⊕
↳ Sx → will cure nearly 100% of pts.
↳ carry good prognosis

Glioblastoma.

- m/c 1° malignant tumor in adults
- m/c site → frontal lobe
- Butterfly tumor.
  - ↳ follows Bid vs. → spread to the other side



Butterfly tumor

Histopath -

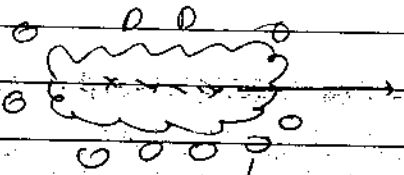
1) Vascular proliferation / Endothelial proliferation.

↓

Glomeruloid bodies

Glomeruli → Also seen in → Endodermal sinus tumor.

2) Pseudopalisading ~~tumor~~ Necrosis



Serpentine central necrotic area

Tumor cells @ edges.

★ Oligodendroglioma → Brain tumor which is m/c calcified.

peri-nuclear halo (fried egg cell).

tumor

In suprasellar tumor, Calci Craniopharyng

Patchy tumor cells

↓ Neuro

↓ Peri-neuronal satellitosis

Dt.:
Pg.:

Delta

Medulloblastoma

- PNET (primitive neuro-ectodermal tumor)
- Undifferentiated
- m/c 1° malignancy in childhood
- CSF mets → 'Drop metastasis'
- n-myc amplificatn → bad prognosis
- TrK-C → Good prognosis
- Rx - Radiotherapy / Sx
- Name of staging - "Chang"

Meningioma

- A/w ~~deletion of~~
  ~~chr. 22~~
  chr. 22 deletion (NF-2)
- Origin - from - meningothelial cells (Arachnoid cap cells)

Types -

1) fibroblastic - fibrosis
2) Psammomatous - Psammoma bodies
3) meningothelial - meningothelial cells
4) Anaplastic - worst prognosis

- Tumor cells - PR+ve (Progesterone (R) +ve)
  ↳ ∴ Grow during pregnancy

Delta

1° CNS lymphoma

- A/w immunosuppression
- A/w HIV infⁿ → 3 months survival (worst prognosis)
- A/w EBV infⁿ
- B-cell lymphoma (DLBCL) - Diffused large B-cell lymphoma
- m/c site - frontal lobe
- Sx → Not for Dx

↓

for histopath. Δsis

↓

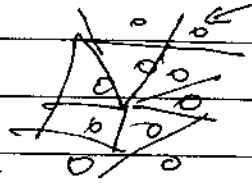
Hooping sign

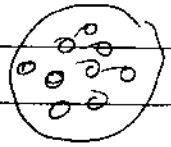
1° lymphoma v/s 2° lymphoma

Reticulin stain

↓

fibre → stained black





↓

Individual tumor cells separated from each other by reticulin fibres - K/a - Hooping sign.

↓

Hooping sign -ve.

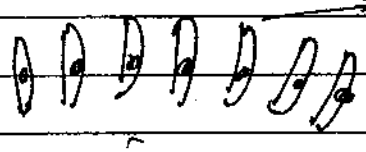
Dt.:
Pg.:

Delta

Schwannoma

- 8th C.N.
- Histology →

Certain areas where tumor cells are more in no. and arranged parallely



→ Hypercellular area → Antony A

↓

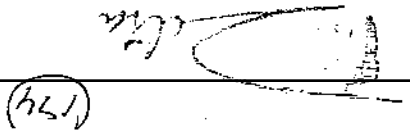
palisading arrangement

↓

Nuclear palisading - Verocay bodies

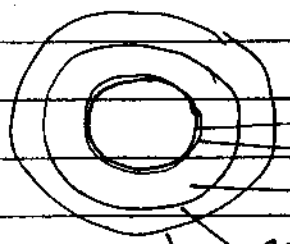
↳ ⊕ in Antony A areas

↳ Hypocellular area → Antony B.

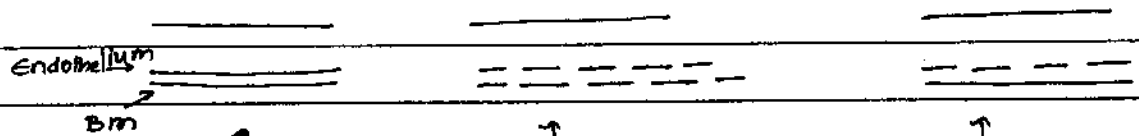


Dt.:
Pg.:

BLOOD VESSELS AND CVS



Types of capillaries



Arteriosclerosis → Arterial wall thickening and loss of elasticity

3 patterns – ① Arteriosclerosis → Affects small, medium sized arteries
↳ seen in DM, HTN
↳ Benign → Hyaline
Malignant → Hyperplastic

② Monckeberg medial sclerosis
↳ medial calcification in muscular arteries.
↳ commonly seen after 50 yrs of age.
↳ Non-obstructive, no clinical significance.

③ Atherosclerosis → mc clinically significant
↳ Occurs d/t Intimal damage.

mature atherosclerotic plaque.

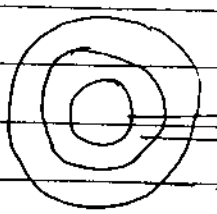
i) fibrous cap → sm. ms., mϕ, foam cells, lymphocytes, collagen, elastin
ii) Necrotic core → Dead cells, lipid, cholesterol, foam cells, plasma proteins

Complications of plaque → • Rupture, ulceration, erosion
• Hemorrhage

CARDIOVASCULAR system

Delta

- Neo-infima → seen in vascular injuries



↓

In vascular injury → T. Intima contains added smooth muscle

↓

Neo-intima

- Atherosclerosis → Elevated intimal based plaques

Best hypothesis

↓

Inflammatory Response to endothelial injury → Intima damage

↓

foam cell { mϕ, smooth ms ← Sub-endothelial space
+ oxidized LDL

↓

fatty dot

↓

fatty streak. (Earliest histological feature seen)

* m/c site for atherosclerosis - Abdominal Aorta (Below renal A.) > Coronary A. > Popliteal A > Descending Aorta > ICA > Ci of wi

~~Atherosclerosis~~ ANEURYSM

Aneurysm → True - Intima, media, Adventia - All 3 layer will be (+) ↓ after atherosclerosis

localised abn dilatation of bld vs.

Pseudo - Not all 3 layers

post MI - ventricular aneurysm

↓ Extravascular hematoma - that communicates with

m/c/c of pseudo-aneurysm - post M.I. Rupture.

↓

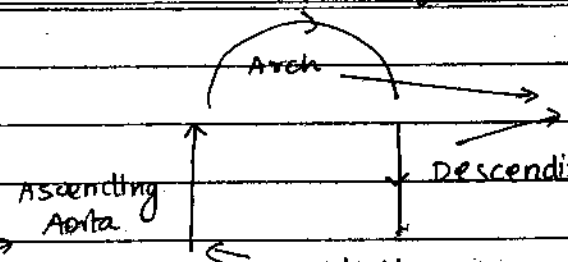
intravascular space d/t loss of vessel wall portion

• m/c/c of Aortic aneurysm overall → Atherosclerosis

• Ascending aorta aneurysm >> Descending

Dt.: Pg.: Delta

M/c/c of ~~Abdom~~ Aneurysms by site



Syphilitic Aneurysm (Luetic Aneurysm)
↳ Tertiary syphilis
↳ m/c site - Ascending Aorta (linear calcification)
↳ Tree barking appearance
↳ d/t intimal wrinkling by fibrous scar contraction of Aorta
↳ cor bovinum / cow's heart
↓
d/t AR → l/t cause of hypertension

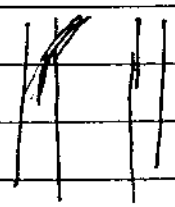
• Mycotic Aneurysm → Infective
→ Staphylococci → m/c
→ m/c site → femoral A.

• c/o salmonella gastroenteritis, m/c a/w → Abdominal Aneurysm

• m/c peripheral A. a/w aneurysm → Popliteal A.

• m/c visceral A. a/w aneurysm → splenic A. > Hepatic A.

• Dissecting Aneurysm
↓
Runs thru' tunica media
males - 40-60 yrs.
A/w connective disorders → marfan's, ED.
m/c/c of Aortic dissectn - HTN
m/c pre-existing histological change - Cystic medial degeneratn
m/c site → 1st 10 cm above Aortic valve annulus.
↳ Dissecting hematoma - spreads along the laminar planes of aorta b/w middle and outer third.
↳ ocassionaly -
↓
Double barelled Aorta
↓
Saves pt from fatal hge.



classifan of Aortic dissectn
↓ Type A → proximal part of ascending Aorta
↓ Type B → Distal to Subclavian A.

ANCA - Anti-neutrophil cytoplasmic Ab

① Churg Strauss ← (perinuclear)
② microscopic polyangiitis
③ Goodpasture
④ Idiopathic crescentic GN
⑤ IBD

③ C-ANCA (cytoplasmic) → Proteinase-3 (PR-3) → Wegener's

Large vasculitis — medium — Immune cx mediated → SLE, HSP, Goodpasture's dis — Small

Large:
- Giant cell (Temporal) Arteritis (Granulomatous)
- Takayasu's (Granulomatous)

medium:
- Immune complex mediated → PAN, Thrombo-angiitis obliterans (Burger's dis)
- Anti-endothelial Ab → Kawasaki

Small:
↓ paucl-Immune (ANCA)
① Wegener's
↓
70% → C-ANCA
25% → P-ANCA
5% → No ANCA
② microscopic Polyan (No asthma/granulom
③ Churg-Strauss. (Asthma, Granulo Eosinophilia)

* Idiopathic crescentic GN → pANCA >> c-ANCA

* m/c vasculitis in adults → Giant cell Arteritis.
* " in pediatrics → HSP (Henoch-Schonlein Purpura)
* m/c/cop in a vasculitis in pediatrics → Kawasaki
↓
myocardial infarctn
(d/t coronary arteritis)

* Takayasu → m/c site → Subclavian A.

Dt.:
Pg.:

Myocardial Infarction.

- Earliest gross finding → in 12-24 hrs → occasional dark mottling.
- " LM " in ~~4-12 hrs~~ < 4 hrs → waviness of ms. fibre.
- " EM " in < 30 mins → large flocculant amorphous densities in mitochondria

- Early granulatn tissue → d 7-10
- max " " → d 10-14
- Scarring completed by → 2 months.

- on Gross examn → Hyperemic border → on d (3-7).
- ~~Necrosis~~ Cell death → Necrosis → Enzyme released.

		Rise	Ends
Earliest marker →	myoglobin	(2 hrs	→ 24 hrs)
	CK-MB	(2-3 hrs	→ 3 days)
Best marker/Gold std →	Troponin-I > T	(2-4 hrs	→ 10 days)
	LDH	(	→ > 10 days)

Best marker for re-infarctn → CK-MB

↓

As reinfarctn is common on Day-5

and Troponin-I/T → continues to be raised.

- flipping of LDH → seen in MI

(N) → LDH-1 < LDH-2

In MI → LDH-1 >> LDH-2

Delta

Rheumatic fever / RHD

- Auto-immune Inflammatory
- grp A B hemolytic strep 1, 3, 5, 6, 18
- mech - molecular mimicry, Cross reactivity
- 2° to only pharyngitis → (3% of pt) Not alw skin Infn
- m/c valve - mitral valve
  l/c valve - pulmonary valve.
- Histologically, Asis is confirmed by
  - Aschoff Giant cells
    ↓
    Swollen collagen surrounded by histiocytes, lymphocy plasma cells, some atypical large histiocyte
    ↓
    (caterpillar like nuclear chromatin)
    ↓
    Anti-schkow cells. (Non Astic, ⊕ in ⊖ myocardi also)
  - m/c site of Aschoff Giant cells - myocardium
    ↓
    ~~(⊖ ⊕ in endocardium~~
    ⊕ In all layers → (myo > peri > Endo)
  - No Langhans giant cells are seen
  - No epithelioid cells are seen.

in

- m/c/cod of ~~Rheumatic~~ Acute Rheumatic fever → Endocarditis (l/t valvular dame
- Overall m/c/cod in Rheumatic fever → myocarditis.
- In Acute rheumatic fever - m/c finding - mitral regurgitam (MR)
  ↓
  Sub-endocardial collection of Aschoff bodies in Left Atrium post cavy
  ↓

Delta

Chronic RHD → fibrosis → calcification → mitral stenosis
(fish mouth / Button hole deformity)

Rheumatic fever	Marantic Endocarditis (NBTE)	Libman Sack Endocarditis	Infective Endocarditis
	Non-bacterial Thrombotic endocarditis ↓ Seen in cancers (Hypercoagulable states)		• Large • friable • Sterile / Non-ste. • Upper surface > lower surface
• small, sterile vegetation • Along the line of closure of valves. • Non-friable • Non-destructive	• small sterile vegetation • Along the line of closure of valves. • friable • prone for embolisation	• medium sized • verrucae (papillae) • flat vegetations. • Sterile • Both upper and lower surface of valve ↓ m/c → lower surface of valve (Inside pocket of valve). • Destructive - mild destruct of myocardium, valve	• max destruction • m/c a/w embolisation • max. destructive ↓ myocardium ulceration valve.

- m/c Tumor of heart → mets (most common 1° → lung ca.)

- m/c Benign tumor in peds → Rhabdomyoma
- " Malignant " " → Rhabdomyosarcoma
- m/c Benign tumor in Adults - myxoma
- m/c 1° malignancy In Adults → Angiosarcoma.

- m/c vascular tumor → capillary hemangioma.
- m/c spleen tumor → Cavernous hemangioma
- m/c 1° malignancy of spleen → marginal zone B cell lymphoma.
- m/c mets to spleen → melanoma.
- m/c 1° for isolated Splenic mets - Ovarian tumors (Gynecological tumors)

- Kaposi Sarcoma → Intermediate grade vascular tumor

↓

m/c site - L/L skin.
m/c extracutaneous site → Lymph node.
m/c site in GIT → duodenum (small intestine)
m/c/ cancer in HIV infn - Kaposi

Delta

Giant cell Arteritis → • m/c vasculitis in adults

- focal granulomatous inflammatn of arteries, mainly cranial vs.
- m/c - superficial temporal A.
- may involve, vertebral A., ophthalmic A.
- Arteries show - segmental nodular thickening with narrowing of lumen
- microscopy - vs. wall - granulomatous inflammatn of vs. wall with langhan / foreign body giant cell

GIT

- Mallory-Weiss Tear → longitudinal, mucosal tear
  - ↳ ~~M/C site~~ lower 1/3rd of esophagus (involves)
  - M/C site → Cardia (Below squamo-columnar jn)
- Strongest layer of esophagus → Sub-mucosa

Boerhaav-syndrome - All 4 layers involved
- M/C site → (L) posterolateral of esophagus

- M/C Cancer of esophagus → Squamous cell ca. (in India, World)
  - M/C site → Middle 1/3rd of esophagus.
- M/C Benign tumor of esophagus → leiomyoma
- M/C Benign tumor of stomach → Adenoma (Epithelial polyp)
- M/C malignant " → Adenocarcinoma
- M/C Benign tumor of SI → Adenoma
- M/C symptomatic benign tumor of SI → leiomyoma
- M/C malignant tumor of SI → Adenocarcinoma
- M/C site for GIST → Stomach
  (Gastro-Intestinal Stromal Tumor)
  - GIST → S/I → more aggressive
    - → more ~~risk~~ risk of malignancy
- M/C neoplasm of appendix → Carcinoid
- M/C malignancy of appendix → mucinous adenoca.

SCC of esophagus → Risk - Celiac dis. — Celiac dis.
- factors → Human papilloma virus — Risk → Adenoca. in Intestine
  - In endemic areas.
  - → Ca Chronic Chagas dis.

Gastric Adenoca. → Early → mucosa + Sub-mucosa ± LN
- Advanced → more than ~~M~~ Sub-mucosa.

Delta

Histological → 2 types

Intestine	Diffused
Glandular pattern	Sheets / Nests
↓	mucin → signet ring
"TGF-β" mutation.	↓
	"E-cadherin" mutation
	↓
	Also seen in familial gastric adenocarcinoma.

If >50% → signet ring (+)

↓

signet ring adenoca.

If <50% → mucinous adenoca.

(worse prognosis)

GIST

- mc mesenchymal tumor of stomach
- origin → Interstitial cells of Cajal

2 types

Epithelioid	Spindle
↓	
Exclusively seen in Stomach	

- Pathogenesis →

70% → CKIT mutation

10% → PDGF (R) eceptor - α gene mutation

Delta

- IHC → CKIT +ve.
- monoclonal Antibody → DOG-1 → Best, most specific. (Designed only for GIST-1)
  - CKIT ⊕ detect°
  - PDGF-R-α mutam.
- DOG-1 → Best marker for metastatic GIST also
- m/c site of mets of GIST → Liver
- → malignant GIST
  - ↳ • Lobulated tumor mass with areas of necrosis
    - ↑ed mitotic figures (>10 mitotic figure/HPF)
    - ~~Invasion~~
    - Mets found in liver/SI.
    - size ⊕ >10 cm (<5 cm → Benign)

Delta

SI → malabsorption syndrome

Hallmark → fatty stool

1) Coeliac dis.
2) Tropical sprue
3) Whipple's dis.
4) Abetalipoproteinemia → No vili damage (defect is d/t epithelial transport of lipid)
5) Giardiasis

* Coronary Artery dis → Best predictive marker

↓

① Highly sensitive-CRP
② TG: Cholesterol ratio
③ LDL
④ HDL

Celiac dis.

M/c site - proximal duodenum.

(∵ more prone for Iron def. Anemia)

• Gluten - sensitive enteropathy

B - Barley
R - Rye
O - Oat
W - Wheat

→ Gliadin → Dermo-epidermal jn

↓

Dermatitis Herpetiformis

↓

• Most sensitive test → Se. Antigliadin Ab

HLA-DQ2, DQ-8.

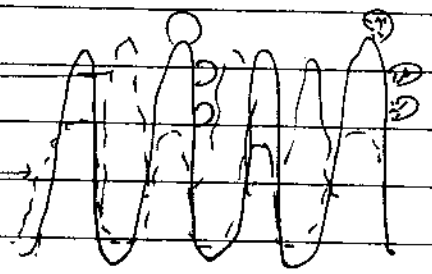
Se. Trans-glutaminase Ab.

Most specific → Anti endomysial Ab.

• Biopsy → Non-Caseating

Delta

Asis → CLF
↳ Biopsy
↳ Endoscopy
↳ serology



Biopsy
- Villous atrophy
- Cryptic hyperplasia
- Overall mucosal thickness → remains same
- lymphoepithelial lesion
  ↓
  R/f for Lymphoma
  m/c - Enteropathy assoc. T-cell lymphoma
- lamina propria - Chronic inflammatn
- Cryptitis / Crypt abscess → Never seen

- S.I. - epithelial T-cell
  ↓
  CD8 - T-cell
  (N) → < 3 / epithelial cell
  > 3 → lymphoepitheli lesion

Tropical sprue
- Villous Atrophy
- Blood culture < PCR
- Alw E. coli infn

Whipple's dis
- Biopsy - Astic - Lamina propria
  ↓
  mϕ → PAS +ve
  Diastase Resistant
  ↳ Tropheryma whipellei
  (Gram +ve)

Delta

Giardiasis

Biopsy → Organism is seen

↓

Pear shaped

* Gastric Adenoca → Incidence → ~~[illegible]~~ ↓ing

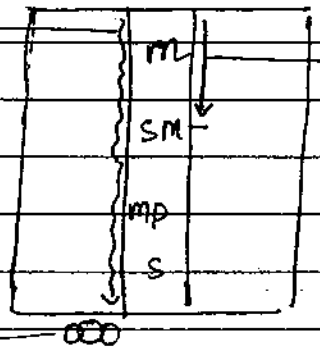
Inflammatory Bowel disease

- Hygiene hypothesis

↓

Immune Response ↓ed.

Crohn's	UC
• HLA-DR1, CD4-TH1	• HLA-DR-2, CD4-TH2
• mΦ	• Eosinophils, Mast cells, plasma cells.
• Non-caseating granuloma	• m/c site - Rectum
• m/c site - Terminal ileum	
(Rectum- Spared)	
Transmural ulceration	ulceration Submucosa • Toxic megacolon
• Perforation	
• Adhesion	
• peritonitis	
Mesentric creeping fat	• pseudopolyps (diffused distribution)
• Inflammation fibrosis → Cobblestone Appearance	• continuous / diffused



- Lesions are patchy

↓

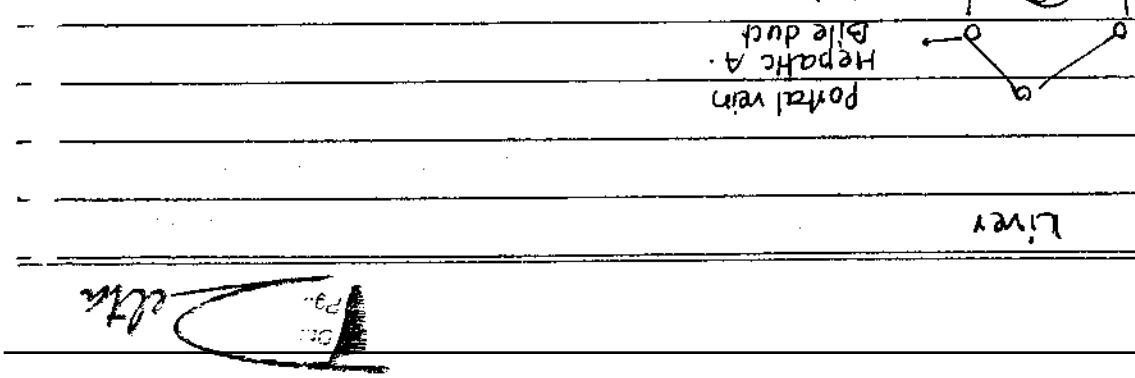
Skip lesions are seen

- Patchy distribution of pseudopolyp

- Granuloma
  - ↳ may be ⊕ in Ⓝ/skip areas also
  - ↳ may be ⊕ in all layers

- Both UC and Crohn's dis. → pre-malignant
- more premalignant → UC
- NOD-2 gene → Crohn's
  - ↳ Nucleotide oligo
- ASCA (Anti-Saccharomyces cerevisae Ab) → Crohn's Ab
- lead-pipe deformity → chronic UC
- IBD → Crypt abscess → UC, Crohn's

Liver



↓

max. blood supply

↓

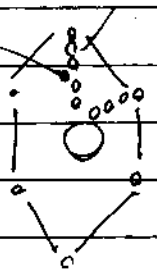
Hypoxic ithration → zone-3, 1st to be affected - CHF, CCl_4, chloroform
e.g.

Toxins → zone-1 -1st to be affected (old supply max)

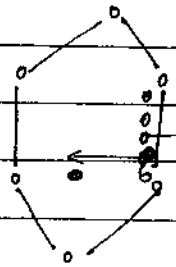
↓

e.g. → eclampsia,
phosphorus poisoning

• midzonal necrosis → Yellow fever



Stellate cells (Ito cells)
↳ Vit A metabolism
↳ Collagen 1,III synthesis
Seen in liver cirrhosis



single layer of hepatocytes in periportal area → Limiting Plate

Chronic Active Hepatitis
↓
limiting plate damage.

Chronic persistent hepatitis.
↓
When inflammatn is restricted to limiting plate and limiting plate is intact

Se. Bil - (N) → < 1 gm%
Direct - 0.3
Indirect - 0.3-0.7
Jaundice - > 2.5 gm%.

Alkaline Pohase
↓
origin → GB ducts

Conjugated
Direct > 15% of total

Unconjugated
< 15%

ALP > ALT / AST → Obstructive

ALP < ALT / AST → Hepatocellular

ALT/AST = 1 → Ischemia / Hypoxia
< 1 → NAFLD (Non Alcoholic fatty liv Dis.)
> 2.5 → ALD

Delta

Hereditary Hyperbilirubinemia

Conjugated	Unconjugated
→ Dubin-Johnson (Only one with ab(N))	→ Gilbert → AD > AR
Biopsy of liver, Hepatocytes - Black d/t epinephrine metabolite)	Biopsy (N) → Crigler-Najjar 1 & 2 → AR

Acute hepatitis	Chronic hepatitis
• Ballooning degeneratn	• Ground-glass hepatocytes (HbSAg) → HYDZYANNIS cell
• focal / spotty necrosis	(Tubules + spheres) → Shikata cells.
• Councilman bodies.	• Bridging fibrosis
	• piecemeal necrosis (Chronic Active hepatitis)

Non-cirrhotic portal fibrosis

Steatosis

Microvesicular	macrovesicular.
Central nucleus	Peripheral nucleus
Small vacuoles	Large vacuoles
→ Reye synd.	→ Late ALD
→ Acute fatty liver of pregnancy	→ Obesity
→ lysosomal acid lipase def.	→ Diabetes
→ Drugs - Tetracycline, Valproic Acid	→ Severe malnutrition
→ Early ALD	→ Total parenteral nutrition
→ Chronic viral hepatitis.	→ Jejuno-ileostomy

Delta

Cirrhosis

< 3mm → Nodules	> 3mm →
↓	↓
Micronodular	Macronodular
→ Hemochromatosis	→ Wilson's
→ Indian Childhood Cirrhosis	→ Late Alcoholic
→ Budd-Chiari Syndrome	→ Chronic hepatitis
→ Primary biliary cirrhosis	

• m/c metabolic liver dis - causing cirrhosis - Hemochromatosis
↓
In 30% cases - Hepatocellular ca.

Reye Syndrome
- Jamshedpur fever
- Pediatric
- Viral illness + (Aspirin) → Not compulsory
- Cerebral edema
- Coma
- Liver Biopsy → microvesicular steatosis
→ Glycogen ~~deposition~~ depletion

• Pathogenesis - Mitochondrial dysfunction
CM - Branching and budding of mitochondria
↳ Astic finding for Reye
↓
Hyperammonemia

Dt.:
Pg.:

Alcoholic liver disease

1) Steatosis → fatty change

↓

m/c → Triglycerides.

Starts @ centri-lobular area

2) Hepatitis → Neutrophilic infiltrate

→ central hyaline sclerosis

→ Mallory-Denk bodies. → Cytokeratin 8/18

(Eosinophilic)

↓

Keratin → better answer

→ Mega-mitochondria (visible even on LM)

↳ 4X larger.

3) Cirrhosis → HCC

Delta

NAFLD/NASH

- m/c accumulation → TG
- Steatosis → NAFLD → No jaundice
  ↓
  NASH → Non-Alcoholic steatohepatitis (with jaundice)

- NAFLD → cryptogenic cirrhosis
  ↓
  HCC

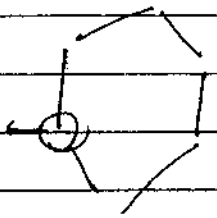
- m/c/c of cryptogenic cirrhosis → Hep B.

NCPF

Non-cirrhotic portal fibrosis

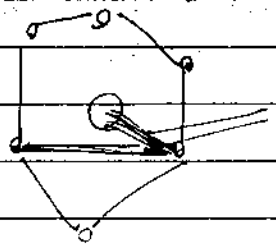
- Young (20-30 yrs)
- Splenomegaly
- Liver - (N)
- Ascites - minimal
- m/c presentatn → G.I. bleeding d/t rupture of esophageal varices.
  - Rectal varies. may be (+)

Etiology → (1) Arsenic
(2) Steroid Rx
(3) E. coli infn
→ Vascular disorder



↓
obstruction
↓
Sinusoidal space-large
↓
*mega-sinusoids-
(periportal angiomatosis)

- inflammation - ⊕ in portal and peri-portal areas only.
- fibrosis - in portal, peri-portal.



↓
seen in ALD, viral hepatitis
Not seen in NCPF

Delhi

Autoimmune Disorders of Liver

- m/c → Autoimmune hepatitis
  - ↓
  - A/w HLA-DR3
  - female
  - IgG ↑ed
  - Respond to immunosuppressant drugs.

Type 1 AIH → ANA → most sensitive

SMA (smooth muscle Actin) → most specific

Type II AIH → LKM-1

Liver kidney microsome

- Liver Biopsy → Characteristic → periportal plasma cells.

(Chronic Active hepatitis)

Delta

Mets Tumor

m/c liver tumor → mets → 1° → Ca. colon

M/c Benign tumor → Cavernous hemangioma

M/c 1° malignant tumor → HCC (Hepatoma)

m/c 1° malignant tumor in peds → Hepatoblastoma.

Liver Biopsy

↓

Tumor cells

↓

Arranged in adenoca. pattern

↓

Bile stained.	Not bile stained
↓	↓
HCC	Cholangiocarcinoma.

Wilson's Dis. WI → 13

- Chromosome 13
  - ↳ ATP-7B mutatn
    - ↓
    - ↳ ecl ceruloplasmin
      - ↓
      - ↳ ed Copper excretion in bile.
        - ↓
        - Copper accumulatn → Hemolytic Anemia
          - ↳ liver damage → All spectrum → Acute → Chron
            - ↓
            - fulminant

In brain → putamen → cavitatory lesions

∴ Wilson's dis. a/k/a → Hepatolenticular degeneratn

Symptoms - start after 6 yrs.

Sensory involvement → late/Absent

Diagnosis - Se. Cu → Non-Astic (variable)

Best method → liver biopsy → Cu^{2+} levels

most sensitive, precise ↗ ↓

> 250 µg/gm dry wt of liver tissue

Most specific screening test → Urinary copper excretion

↳ Keyser-fischer Ring - helps in Asis

in Corneal descement memb.

Dt.:
Pg.:

Delta

Hemochromatosis

- Chr. 6
- HFE gene
- ↑ed iron
- All damage directly
  except → Infertility → indirect → d/t hypothalamo-hypophyseal circulatn damage.
- Earliest m/c effected } Liver
  - cirrhosis → Characteristic feature

- In pancreas → DM
- In skin → Bronze colored skin (∴ Known as Bronze DM)
  ↓
  d/t Melanin → fe - Bom

- m/c metabolic disorder a/w ~~Liver dis~~ Cirrhosis, HCC

Delta

Blood Transfusion

Chromosome-19 → H gene

↓

fucosyl transferase

↓

Galactosyl / fucosyl

↓

Glycoprotein

↓

A/B/AB

fucosyl + N-Acetyl galactosamine

↓

'A' antigen

• In 'O' blood grp - 'H' antigen only

No A, B antigen

fucosyl + Galactose

↓

'B' Antigen.

in serum - opp. Antibodies are ⊕

* Clinically ABO - most imp. - because - Antibodies ⊕ in serum are not present corresponding to Antigen on RBCs.

A B H

↓

can be ⊕ in RBC, serum, saliva, semen, urine, tears, except saliva

↓

Secretors

ABO bld group → A, B, H Ag.

• Pattern of Inheritance - Co-dominance

Ditta

Bombay Bld group

- AR
- No H gene → No A, B, H ag
- Chr 19 ab(N)
- (h,h) - Homozygous → Anti-A, B, H - Ab

H - HAb - Interaction
↓
Very severe

- Non-secretory Bld group.
- symbol → (Oh)

Whole Blood
↓ } 2-6°C Shelf life - 42 days
Packed RBC
↓
Platelet → Room temp. with continuous agitation Shelf life - 5 days
↓
Contains all clotting factors ← FFP → >-18°C × 1 yr
↓
Cryoprecipitate −18°C × 1 yr.

Cryoprecipitate → used for
↓ ↳ Afibrinogenemia
↳ vWD (von-willebrand dis)
Components - fibrinogen
→ vWF
→ factor VIII
→ factor XIII

* Malaria - transmitted thru' all blood components
* Red risk of infection - platelets

* Routine proto-col →

Whole blood / Packed cells
- Start transfusion - within 30 minutes
- completed - within 4 hrs.

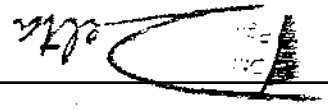
- m/c - Transfusion Reaxn
  ↓
  febrile non-hemolytic transfusion Reaxn
  ↳ d/t → leukocyte cytokines.

- m/c/cod - TRALI (Transfusion-Related Acute lung Injury)
  ↓ ↳ < 6 hrs of transfusion
  m/c alw → FFP

- massive bleed transfusion
  ↳ > 1 blood volume is transfused within 24 hrs
  (5L) = 10 pints.
  ↳ > 50% bld volume is transfused within 4 hrs
  (2.5L) = 5 pints.

- M/c/cod - in Massive bld transfusion - Dilutional coagulopathy
  DIC
  ↳ Metabolic Alkalosis
  ↳ Citrate → HCO_3^-
  ↳ Hyperkalemia
  ↳ Hypothermia
  ↳ Dilutional thrombocytopenia.

* Metabolic acidosis → only in rapid bld transfusion.



Delta

Germ cell tumors (Testicular)

Seminoma (15-34 yrs)	Non-seminoma
↓	↳ Embryonal ca.
Spermatocytic seminoma	↳ Yolk sac tumor (Endodermal sinus tumor)
>60 yrs	↳ Teratoma
→ Benign	↳ Choriocarcinoma
→ mets - Never seen	

→ mets may be seen

Ovarian counterpart of seminoma → Dysgerminoma

Intra-tubular germ cell neoplasia (Ca in-situ) (ITGCN) → All except

↓

Yolk sac tumor

Spermatocytic seminoma.

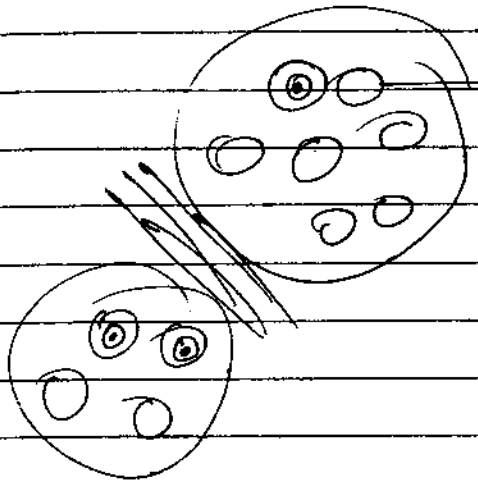
- Gene - OCT 3/4, NanoG → i12p, CKIT

* m/c GCT of testis - Seminoma
m/c GCT of testis in < 3yrs old → Yolk sac tumor
m/c u pubertal age grp → Teratoma
m/c u childhood → Teratoma

Dt.:
Pg.: Delta

Seminoma

Sheets / Nests



cell memb. prominent

Nucleus large, prominent nucleoli

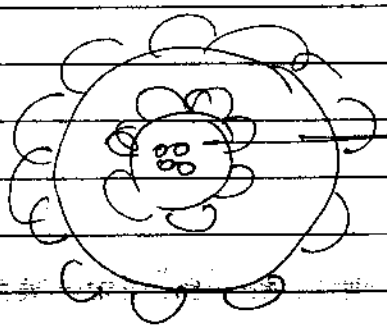
separated by fibrous band

↓

lymphocytic infiltrate.

↳ No glandular pattern

* Schiller-Duval body → Yolk sac tumor



Central blood vessel → covered by tumor cells

↓

Glomeruloid bodies.

↓

in a cystic cavity

↓

which is again covered by tumor cells.

* Benign cystic teratoma → Rokitansky protuberance

↓

Clinical significance

↓

s/o malignant transformation

↓

SCC (sq. cell ca.) >> melanoma > carcinoid

Delta

* Rinke - crystalloid → Hilus cell tumor

* Urinary Bladder Transitional epithelium - Brenner's Tumor.

* Nemaloid Rod myopathy - floppy Infant Synd
↓
Z band formed by → α-actinin

* mitochondrial myopathy → on EM →
parking lot Inclusion
↓
in cristae
↓
in mitochondria

* CIDP
Charcot Mary Tooth dis } Onion-bulb neuropathy

Dt.: Pg.: Delta

MALE GENITAL SYSTEM.

Condyloma Acuminatum

- HPV-6,11
- Recurs after excision, rarely transforms to malignancy
- Gross - 1-5 mm size, single or multiple sessile or pedunculated red papillary excrescences on coronal sulcus or inner prepuce
- M/E - Branching papillae covered by hyperplastic stratified squamous epithelium with hyperkeratosis and epithelial cell vacuolation (Koilocytosis)

Malignant tumors of the penis

I) CIS - Carcinoma-in-situ.

- HPV-16 infn
- a. Bowen dis. - Both male, females affected.
  - Typically present with solitary or multiple thickened, gray-white or red-shiny plaques over penile shaft.
  - → Histology → marked epithelial Atypia with lack of maturation but no invasion
  - → 10% → ~~invasive~~ transform into Invasive Ca.
- b. Bowenoid papulosis
  - Multiple, pigmented, papular lesions on external genitalia
  - Histology - same as Bowen dis.
  - Regress spontaneously

II) Invasive Carcinoma →

- Age - 40-70 yrs
- A/w - • Carcinogens within smegma accumulating under the foreskin
- HPV - type 16, 18
- Gross - Epithelial thickening to ulcero-proliferative to exophytic growth
- Histology - similar to SCC

Delhi

- Verrucous ca. - uncommon well-differentiated SCC variant with low malignant potential.

Cryptorchidism - • Arrested germ cell development
- Marked hyalinizatn thickening of BM of Spermatic tubules.
- Ley dig cell prominence

TESTICULAR tumors

I. Germ cell tumors →
- 95% of cases are germ cell tumor
- Generally malignant
- further - seminomas
  Non-seminomas

II. Sex chord - stromal tumors → usually benign.

Germ cell tumors -
- M/c malignancy b/w 15-34 yrs in men
- R/f - • Cryptorchidism (m/c a/w abdominal testis)
  • Testicular dysgenesis Syndrome (TDS)
  ↳ cryptorchidism, hypospadias, poor sperm quality
  ↳ a/w - pesticide, Non-steroidal estrogen exposure in-utero
- Genetic factors - • familial clustering
  • A/w genes encoding ligand for the receptor Tyrosine kinase KIT and BAK.
- most germ cell tumors - ITGCN (Intra-tubular germ cell neoplasia)
- Occurs in utero, remains dormant till puberty
- These cells have expression of totipotential transcription factor OCT3/4 and NANOG.
- Others - isochromosome 12p (i12p) formation
  - C-KIT mutations

Dt.:
Pg.:

C|F of GCT

- most cases - painless enlargement of testis
- lymphatic mets - 1st involve retroperitoneal para-aortic nodes.
- Hematogenous mets - lung (m/c) → > liver, brain, bone.
- Mets may be different from their primary, as they are histologic mixtures.
- NS-GCT (non-seminomas) → more agressive than seminomas.
- Seminoma - Radiosensitive - 70% present with ~~advanced disease~~ localized dis.
- NSGCTs → Radioresistant - 60% present with → Advanced dis
- pure choriocarcinomas → Aggresive
  - Poor prognosis
  - ↳ Extensive hematogenous spread
- max. α-FP → yolk sac tumor
  max. β-HCG → choriocarcinoma.

SEMINOMA

- m/c type
- 30-40 yrs.
- ovarian counterpart - Dysgerminoma
- i12p, OCT 3/4, NANOG, CKIT

Gross - • Homogenous, lobulated, grey-white mass
- No areas of H'ge, necrosis
- Tunica albuginea - m'act

M/E - • Sheets of uniform cells divided into lobules by fibrous septa containing lymphocytic infiltrate
- Tumor cells - large, polyhedral, containing abundant clear cytoplasm (d't glycogen), large nuclei, prominent nucleoli
- Tumor cells also +ve for PLAP, β-HCG.

Delta

Spermatocytic seminoma
- Uncommon
- GS +
- Not a/w ITGCN
- Slow-growing tumor
- No mets seen
- Excellent prognosis

Gross - Soft, gray cut surface with mucoid cyst

M/E - mixture of 3 types of tumor cells
a) Small sized
b) medium sized
c) Giant cells.

EMBRYONAL CARCINOMA

- Mostly affects 20-30 yrs of age.
- Greyish white mass with areas of H'ge and necrosis and crossing beyo the tunica albuginea

Histology - • Tumor cells are primitive epithelial cells with indistinct cell borde forming irregular sheets, tubules, alveoli, papillary structures.
• Cytokeratin +ve, CD-30 +ve
C-KIT -ve

YOLK SAC TUMOR (ENDODERMAL SINUS TUMOR)

- M/c testicular tumor in infants and children upto 3 yrs.
- most adult cases occur - as a component of embryonal ca.
- Good prognosis

Histology - • Tumor shows cuboidal neoplastic ~~cells ar~~ cells arrange in a lacelike (reticular) or papillary pattern
• 50% of cases will show primitive glomeruli-like structure (Schiller-Duval bodies) - which have a central bld vs. surroun by tumor cells enclosed inside a cystic space which is again covered by tumor cells
• Tumor cells are a/w eosinophilic hyaline globules

Delta

CHORIOCARCINOMA

- Higuly malignant, arises from both cytotrophoblastic, syncytiotrophoblastic cells.
- Incidence - < 1%
- Gross - Hgic mass
  - No testicular mass, presents with small palpable nodule.
- Microscopy - Tumor consists of polyhedral cytotrophoblastic cells growing in sheets and cords admixed with Multi-nucleated syncytiotrophoblastic cells.
- β-HCG +ve.

TERATOMA

- These tumors show differentiation along endodermal, mesodermal, ectodermal lines.
- pure teratomas — rare in adults, common in children.
- In children, mature teratomas are benign tumors with excellent prognosis.
- In post-pubertal men → All teratomas are malignant, regardless of mature or immature components.

Gross -
- Commonly large (5-10cm) with heterogenous appearance
- Hemorrhagic and necrotic mass will be suggestive of admixture with embryonal and/or choriocarcinoma

Histology - Composed of haphazard arrangement of following elements
- a) Mesodermal - ms., cartilage, Adipose tissue
- b) Ectodermal - Neural tissue, skin
- c) Endodermal - Gut, Bronchial epimelium

- Teratoma with malignant transformation means - Non-germ cell malignancy developing within a teratoma and most common
  - ↳ SCC
- These non-germ cell malignancies retain -12p.
- Non-germ cell component spreads outside the testis, will not respond to chemotherapy.

TUMORS OF SEX CORD - GONADAL STROMA

Leydig cell tumor -

- Only 2% of all testicular tumors
- Age - 20-60 yrs.
- Tumor can produce androgens, estrogens, and/or corticosteroids
- mostly present with testicular mass but can show changes d/t hormonal elaboration like gynaecomastia or sexual precocity.
- Most are benign - only 10% malignant

Gross - tumors are circumscribed nodules with homogenous, golden brown cut surface.

Hyscopy - • Tumor cells are polygonal with abundant granular, eosinophilic cytoplasm and indistinct cell borders.
• Lipid droplets, lipochrome pigments and eosinophilic Reinke crystalloids are common within tumor cells.

Sertoli cell tumor - Hormonally silent testicular mass

Gonadoblastoma — Rare neoplasms containing mixture of germ cells and gonadal stromal elements
- Almost always arise in gonads with some form of testicular dysgenesis

Testicular lymphoma

- 5% of all neoplasms of testis
- m/c testicular neoplasm in pts older than 60 years
- m/c - DLBL > Burkitt > EBV-tve lymphoma
- Widespread mets at the time of presentation
- High affinity for CNS involvement
- Worse prognosis

MUSCLE DISEASES.

- Benign tumors outnumber malignant tumors
- Soft tissue tumor and their pattern
  - → smooth muscle tumors - intersecting fascicles of spindle cells at right angles
  - → fibro-histiocytic tumors - storiform pattern ie., short fascicle of spindle cells radiating from a central point (spokes on a wheel)
  - → Schwann cell tumors → Nuclear pallisading, i.e., nuclei arranged in columns
  - → fibrosarcoma → Herringbone pattern

- M/c site of sarcomas - Extremities
- m/c site of Rhabdomyosarcomas → Head and Neck (Orbits)
- m/c soft tissue tumor of childhood, adolescence - Rhabdomyosarcoma
- m/c " adults → lipoma
- m/c malignant " adults → liposarcoma

RHABDOMYOSARCOMAS.

- sarcomas arise from sk. ms. progenitors
- m/c site - Orbit
- 3 main types -
  1) Embryonal rhabdomyosarcoma → Overall m/c
     - common in younger children
     - Botryoid variant arises in mucosal cavities
     - m/c site - orbit
  2) Alveolar rhabdomyosarcomas
     - m/c in older children
     - m/c site - extremities
     - A/w t(2;13), t(2;1;13)

L/M - Rhabdomyoblast - which appear round strap-shaped, tennis racquet and spider forms.

- Rhabdomyoblasts show ms. striations.
- Botryoid variant - linear aggregates of tumor mat lightly abut an epithelial surface.
  "Cambium layer"
- IHC → +ve for intermediate filaments - Desmin, vimentin, myo-D, myogenin.

★ All sarcomas follow hematogenous route,
except Alveolar Rhabdomyosarcoma - Lymphatic route

SYNOVIAL SARCOMA

- Name is misnomer as tumor can be ⊕ @ sites lacking synovium
- Age - 20-50 yrs
- m/c site - deep soft tissues of lower extremity
- Genetics - t(x:18)
  producing SS-18 - SSX1 / SSX2 / SSX4 fusion genes.
- Histology may be monophasic or biphasic
- Biphasic synovial sarcoma will have dual lining of differentiam consisting of epithelial and spindle tumor cells
- IHC - Vimentin +ve → spindle cells
  - CytoKeratin +ve → epithelial cells.
- m/c site of mets - lungs.

MUSCULAR DYSTROPHIES

- Heterogenous group of inherited disorders
  - start in childhood
  - progressive weakness and ms. wasting.
- Histologically - degenerated ms. fibres - replaced by fibrofatty tissue and collagen.

Delta

DUCHENNE'S MS. DYSTROPHY / BECKER'S MS. DYSTROPHY

- DMD - • m/severe
  - • m/c
  - • Clinically manifest by the age - 5 yrs
  - • L/t wheel chair dependence by 10-12 yrs, Death @ 20
- BMD - • L/c, less severe
  - • Later onset, slower rate of progression

Pathogenesis

mutation in DMD gene @ Xp21

encodes - 427-KD dystrophin protein (sarcolemmal protein)

• ~~Mutation~~ ms. from -

- • DMD - No dystrophin
- • BMD - Red dystrophin

Histology → DMD - large, rounded, hyaline fibers lacking (N) cross striation

Both DMD, BMD -

- • variation in fiber size
- • ↑ed nu. of internalized nuclei (>5%)
- • Degeneration, necrosis, phagocytosis of ms. fibres.
- • Regeneration of ms. fibres (basophilic hue)
- • Proliferation of endomyseal connective tissue
  - At advanced stage, ms. totally replaced by fat and connective tissue.

C/P - Weakness starts in pelvic girdle ms., extending to shoulder girdle.

- lower leg - hypertrophied (pseudohypertrophy)
- COD - Resp. depression

Dt.:
Pg.:

MYOTONIC DYSTROPHY

- AD
- ↑↓ in severity and appear @ younger age in suceeding generations (Anticipatn)
- Cardinal symptom – myotonia – sustained involuntary ms. contracn
- CTG trinucleotide repeat, Chr. 19q13.

Histology –
- pathological changes in ms. spindle (fiber splitting, necrosis, regeneratn)

– They will show – • fiber size heterogeneity
• ↑ed no. of internal nuclei
• Ring fibers

C/F – Ab(N) in gait 2° to foot dorsiflexor weakness
- weakness of intrinsic hand, wrist ms.
- facial ms. atrophy, ptosis.
- ↓ed plasma IgG, Ab(N) GTT.

MITOCHONDRIAL MYOPATHIES
(oxidative phosphorylatn dis.)

- Mutations in bom nuclear and mitochondrial genes.
- extraocular eye ms. involvement → common
  - can be clue to Dsis

L/M – Aggregates of ab(N) mitochondria causing irregular ms. fiber contour (Ragged red fibres) on trichrome stains)

E/M – ↑ in no. of and ab(N) in shape and size of mitochondria
– Ab(N) mitochondria with concentric membranous rings (phonograph records) and rhomboid paracrystalline inclusion or parking lot inclusion

C/F → young adulthood.
→ proximal ms. weakness
→ external ophthalmoplegia
→

- Disorders d/t point mutations in mt DNA -
  - Myoclonic epilepsy with ragged red fibers
  - LHON
  - MELAS
- Disorders d/t deletion or duplication of mtDNA
  - CPEO
  - Kearns- Sayre syndrome.

ION CHANNEL MYOPATHY

- AD
- C/P - myotonia or hypotonic paralysis
- Hypotonia variants → A/w - hyperkalemia, hypokalemia (N)-kalemia.
- Examples of mutated gene product -
  a) KCN-J2 - mutation -
     - ↳ Affects K^+ channel, results in Anderson Twail synd
     - ↳ AD - with periodic paralysis, heart arrhythmias and skeletal abN
  b) SCN-4A mutations
     - ↳ sodium channel
     - ↳ presentations ranging from myotonia to periodic paralysis
  c) CACNA-1S mutation -
     - ↳ mis-sense mutation in ms calcium channel
     - ↳ m/c/c of hypokalemic paralysis
  d) CLC-1 mutation
     - ↳ Affecting chloride channel
     - ↳ CLC-1 expression - ↓ed in myotonic dystrophy
  e) RYR-1 mutation
     - ↳ Ryanodine receptor - which regulate the calcium release from the sarcoplasmic reticulum
     - ↳ RYR-1 mutation seen in - congenital myopathy (central core dis) and malignant hyperthermia

Pg.: Delta

DIS OF NMJ

MYASTHENIA GRAVIS

- D/t auto-Ab directed against skeletal ms. Ach receptors
- f > m • 40 yr.
  in older populam - m > F
- Also thymic ab (N) → Thymic hyperplasia - 30%.
  Thymoma - 10%.
  ms. biopsy - type 2 fibre atrophy
- m/ sensitive test - single fibre EMG
- m/ specific - Ab to ~~ace~~ acetylcholine (R)
- Nerve conductn test - (N)
- Symptom worsen with repeated stimulam.

LAMBERT - EATON

- Autoimmune disorder caused by Ab - that block Ach release by inhibiting presynaptic calcium channel
- most cases - paraneoplastic
  - m/c - small cell ca. lung.
- may be also other auto-immune dis. - vitiligo.
- In contrast to MG, Rapid repititive stimulatn ↑es ms. response.

ENDOCRINOLOGY

Pituatary gland → weighs 0.5 grams

→ 2 lobes

a) Ant lobe - 2 type of cells

1. Acidophilic → somatotrophes

(ASL) → Lactotrophes

2. Basobhilic - corticotrophs (ACTH, POMC, MS,

→ Thyrotrophs

→ Gonadotrophs

b) Post lobe - Neurohypophysis

- Secrete oxytocin, ADH

- ADH, oxytocin - both stored in Herring bodi

(Neurosecretory ~~granules~~ bodies)

Hypopituatarism

- loss of more than 75% of pituatary parenchyma → Hypopituarism
- m/commonest cause → pituatary adenoma *
- Earliest hormone lost → GH > Gonadotropins.
- Causes - Sx, Radiation, Ischemia,

Sheehan syndrome (postpartum pituatary necrosis d/t hge or shock)

- ~~Empty~~ Empty sella syndrome (d/t pituatary destruct
- C/F - Growth failure, hypogonadism, hypothyroidism

Hyperpituatarism

m/c/c - Ant. pituatary adenoma

(microadenoma > macroadenoma)

↓ ↓ ↓

<1 cm >1cm Usually non functional

- m/c adenoma - prolactinoma
- Aggressive pituatary adenoma → P53 mutatn

→ Ted mitotic activity

Date

1. prolactinoma
   - m/c pituatary adenoma
   - microadenoma - functional, macro - Non-functional
   - Prolactin secreted → causes - Amenorrhoea, Galactorrhoea, Infertility
   - Stalk effect → Suprasellar mass deranging inhibitory function of hypothalamus on prolactin secretn - causing hyperprolactinemia

2. GH adenoma - • Hypersecretn of IGF-1 or somatomedin-C
   a) Gigantism (in children)
   b) Acromegaly (in Adults)
   - Also DM, ms. weakness, ~~hypersecretn~~ hypertension, CHF

3. ACTH - adenoma →
   - Ted ACTH - Cushing's dis.
   - Nelson's synd. → large destructive ACTH-adenoma caused by excess of pituatary corticotrophs d/t surgical removal of adrenal gland.

Info → • Pituatary tumors - 10% of all Intracranial neoplasm
- Ca can be differentiated from adenoma - If mets are ⊕
- pituatary adenoma expands and damages sella turcica, Ant. clinoid proc

Histology - ① Cellular monomorphism - only one type of cells.
② Absence of reticulin - network
~~③ Poly~~

Post pituatary Syndrome -
① ADH-def (DI) → Hypernatremia, → polydypsia, polyuria.
causes - Head injury, Tumors, Inflammations, pituatary ⊕ or Hypothalamic Sx
② SIADH → Hyponatremia, oliguria, cerebral edema, Neurological manifestations.
- m/c/c → Ectopic ADH → m/c → malignancy → m/c small cell ca. lung
- others - pulm. TB, pneumonia.

- m/c hypothalamic Suprasellar lesions - Gliomas > craniopharyngioma

CRANIOPHARYNGIOMA → • From Rathke's pouch
• Bimodal age of presentation
• Slow growing, rarely malignant, good prognosis.
c/p – • Growth retardation in children
• Visual disturbances in adults.
2 types – ① Adamantinomatous type → m/c in children
→ calcification – common
→ cyst contain – thick cholesterol rich brownish – yellow fluid (Machinery oil like)
→ Spongy reticulum with peripheral palisading of epithelium and compact lamellar Keratin (wet keratin)
② Papillary type – m/c in adults
– calcification – rare
– Sheets, papillae of well-differentiated squamous epithelium with no keratins or cysts.

THYROID GLAND

• (N) wt → 15–25 gms
• follicular cells – T_3, T_4
• parafollicular " → Calcitonin

Hypothyroidism

• m/c c/c of Hypothyroidism → • Iodine def.
In iodine sufficient areas, i.e. developed countries – Hashimoto's thyroiditis
• m/sensitive screening test for thyroid dysfn → serum TSH
• Hypothyroidism can be
① m/c – Primary type.
② Secondary – TSH deficiency

• Genes – SLC-26A4 gene → pendrin anion transporter on thyroid and inner-ear epithelium → causing sensori-neural deafness, hypothyroidism → Pendred syndrome

Delta

C/F → ① wt gain, poor apetite
② ↑ed DBP, brady cardia
③ Cold intolerance, cold peripheral extremities
④ Constipation
⑤ Arteriosclerosis – ↑ed cholesterol, phospholipids, TGs
⑥ mennorhagia, Amenorhea, oligoamenorrhea
m/c
⑦ Cretinism – Children
– Short stature, MR
– Coarse facial features
– Enlarged protruding tongue
– Umbilical hernia.
⑧ myxedema (Gull disease) → Adults
→ Atherogenic lipid profile.
→ Hair loss
→ Solid edema – caused by mps accumulation within dermis and other tissues

Hashimoto's Thyroiditis → • Autoimmune disorder
• m/c/c in developed countries
• Age – 45-65 yrs • f > m • HLA-DR-3, HLA-DR-5
• Also Down's synd., Turner synd.
• Genetic polymorphism in CTLA-4 (cytotoxic T-lymphocyte Assoc. Antigen-4) and PTPN-22 (Protein-tyrosine phosphatase-22)
• C/F - painless enlargement of thyroid gland
• Hypothyroidism (initially transient hyperthyroidism)
• Assoc. with other autoimmune diseases – Type 1 DM, myasthenia gravis, SLE, Sjogren's.
• High Risk of marginal zone B cell lymphoma*
pathogenesis – IgG Ab ~~against~~ – Antithyroglobulin,
– Anti-microsomal
– Anti-TSH-Receptor

Thyroid

- Gross - Diffuse symmetrical enlarged thyroid with intact capsule
- M/E - • Atrophic thyroid follicle
  - • follicle destructn by lympho-plasmacytic infiltrate.
  - • oncocytic metaplasia (Hurthle cell metaplasia / oxyphilic change - ~~each~~ eosinophilic granular cytoplasm) → Hallmark
  - • fibrosis, squamous metaplasia may occur

Subacute thyroiditis - Granulomatous thyroiditis / De Quervain thyroiditis
- ↳ f > m 40-50 yo.
- ↳ post viral inflammatn eg. measles, mumps, Adenovirus, coxsackievi and causing follicular destructn by CD8 - T cells
- ↳ HLA B35
- ↳ It is the m/c/c of thyroid pain
- ↳ No LN enlargement
- ↳ Transient hyperthyroidism, (R) after 6-8 weeks
- ↳ Histology - Thyroid follicle destructn with neutrophilic infiltrate, later replaced by lymphoplasmacytic, MNG cells (multi-nucleated giar

Subacute lymphocytic thyroiditis (Subacute painless thyroiditis)
- ↳ self-limiting, painless
- ↳ f > m (5% postpartum females)
- ↳ A/w - Auto-Immune etiology with antithyroid Ab
- ↳ HLA - DR-3, DR-5
- ↳ follicular destructn by lymphocytic infiltrate with germinal centre, no fibrosis, no hurthle cell metaplasia.
- ↳ ↑ed T_3, T_4, ↓ed TSH (transient)

Reidel Thyroiditis → • Rare, fibrosing disorder, with invasive nature
- • Unknown etiology • ♀ middle age females

→ fibrous tissue replaces thyroid and its capsule and enroaches into contiguous surrounding structure like trachea, eshophagus

→ A/w - Retroperitoneal, mediastinal fibrosis

Hyperthyroidism

causes – ① Grave's dis – m/c c/c (85%)
② Toxic Multinodular goitre
③ Toxic adenoma
④ Others – Iatrogenic, thyrotoxicosis factitia, Struma ovarii, Acute subacute thyroiditis

C/F – • CVS – Earliest and most consistent
- ↑ed BP
- wide PP., sinus tachy
- Hyperdynamic precordium, mid-systolic murmur, Atrial fibrillation
• Distal ms. weakness

• Apathetic hyperthyroidism – seen in elderly
- Blunting of thyrotoxicosis by various co-morbidities

* Any functional thyroid dis. – Best test → Se. TSH.

GRAVE'S DISEASE → m/c/c of hyperthyroidism
↳ Triad – Hyperthyroidism — infiltrative opthalmopathy
— infiltrative dermopathy (pretibial myxedema)

females, Age – 20 – 40
Genetics – HLA DR-3, HLA-B-8, CTL-A-4, PTPN-22
• Autoimmune dis. – Ab against → TSH-receptors.
↳ TSI (Thyroid stimulating immunoglobulins)
↳ LATS (Long acting Thyroid stimulators)

* Thyroid acropachy → Digits with clubbing, swelling in Grave's Dis.
* Black thyroid → seen in pt on minocycline
↳ pigment deposition in apical surface of follicular cells.

Goiters – m/c manifestation of thyroid dis
2 types – ① Simple (diffuse non-toxic) → Diffused involvement
- No nodularity
- Enlarged follicles filled with colloid (colloid goiter)
a) Endemic goitre → low iodine areas, goitrogenic food
b) Sporadic Goitre – mostly ~~young~~ young females

Delta

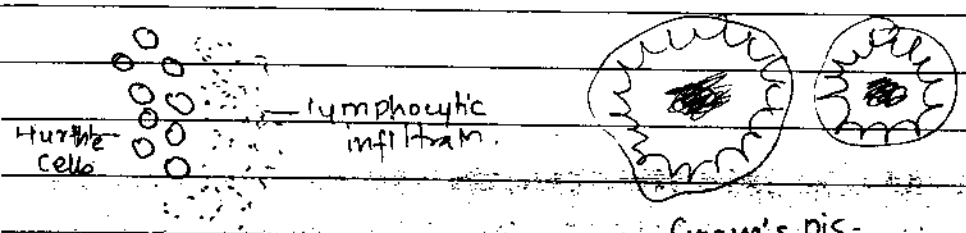
Morphology - 2 stages - ① Hyperplastic - diffused, symmetrical enlargement, with follicular epithelium hypertrophy, hyperplasia

② colloid involution stage (as thyroid demand is met) - glossy brown surface showing involution of follicular epithelium to large colloid filled gland. → l/t scalloped appearance of edges of colloid

note → Euthyroid pts., with TSH ↑ed.

MULTINODULAR GOITRE

- ↳ Recurrent episodes of stimulation and involution of diffuse goiters.
- ↳ can be d/t variation in follicular cell response
- ↳ Nodular growth
- ↳ Gross - Asymmetrical, enlarged multifocal, multilobulated, may compress trachea, esophagus.



THYROID NEOPLASMS

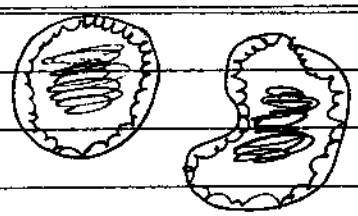
- 1% of solitary nodule of thyroid is malignant
- Risk of malignancy ↑es with
  - ↳ solitary nodules
  - ↳ Nodules in younger pts.
  - ↳ Nodules in men
  - ↳ H/o Radiation exposure
  - ↳ Cold nodules (Nodules which do not take up iodine in Radio-scans
  - ↳ Solid

* Radiation - usually - l/t - benign thyroid lesions
Also, an ↑ed incidence of papillary ca.

Delta

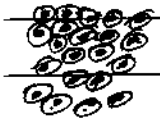
Benign tumors

1) Thyroid adenoma (follicular adenoma) →



- Solitary mass
- Asymptomatic cold nodules
- Intact capsule (Capsular invasion → s/o follicular ca.)
- Histological types-
  - ↳ Normofollicular (simple)
  - ↳ macrofollicular (colloid)
  - ↳ Microfollicular (fetal)
  - ↳ Trabecular/Solid (embryonal)
  - ↳ Pseudopapillary structures.

Variants - 1) Hurthle cell adenoma → >50% Hurthle cells (oncocytic cells = oxyphilic cells)



- Oncocytic/Hurthle cells - have granular eosinophilic cytoplasm d/t ↑ed no. of mitochondria.

2) Atypical adenoma → pleomorphic cellular proliferation but no capsular or vascular invasion

3) Hyalinizing trabecular adenoma → well defined, organoid trabeculle simulating paraganglioma.

4) Adenoma with bizarre nuclei - Huge, hyperchromatic nuclei usually in clusters.

Malignant Neoplasms

1. Papillary Ca. (m/c - 75%)
2. follicular Ca. (10-20%)
3. Medullary Ca. (5%)
4. Anaplastic Ca. (<5%)

Papillary Ca. - • m/c • f > m • Age - 20-40 yrs
- • A/w radiation exposure
- • Excellent prognosis, least malignant
- • Spread by lymphatic route.

Dr. Divita

- Genetic factors –
  1) Rearrangement of RET or NTRK-1 (Neurotrophic tyrosine kinase receptor-1), e.g. RET/PTC (papillary thyroid ca.) fusion gene with t(10:17)
  2) BRAF, RAS – oncogene mutation.
- Histology – ◦ Nuclear features are ΔStic ★
  ◦ consits of fibrovascular core coith tumor cells and psammoma bodies
  ◦ Tumor cells will have –
    1) optically clear nuclei (orphan annie eye = ground glass appearance) ★
    2) Nuclear grooves
    3) Intranuclear pseudo-Inclusions (cytoplasmic invagination into nuclei)

Variants – ① follicular variant –
- ◦ Almost entirely follicles but with ΔStic nuclear featu
- ◦ Psammoma bodies

② Papillary microcarcinoma
- ◦ size < 1 cm
- ◦ Incidental cervical LN mets.
- ◦ Distant mets – rare ∴ Good prognosis.

③ Encapsulated variant
- ◦ well encapsulated.
- ◦ may have LN mets – but no distant mets.

④ Diffuse sclerosing type – Diffused involvement of one or both lo dense sclerosis, Numerous psammoma bodies, Squamous metaplasia, heavy inflammation
- ◦ widespread LN mets, lung mets.
- ◦ worse prognosis
- ◦ D/D – Hashimoto's thyroiditis

⑤ Tall cell variant – Abundant eosinophilic cytoplasm, often lymphocytic infiltrate.
- ◦ worse prognosis

Delta

⑥ columnar variant

↳ like tall cell, but with nuclear stratification

⑦ oxyphilic variant

↳ like Hurthle cell ca.

Poor prognosis	No effect on ~~good~~ prognosis.
> 40 yrs old	↓
male	• Relative amts of papillae v/s follicles
Extra-thyroid extension	• H/o irradiation
large size tumor	• fibrosis, squamous metaplasia,
Non-capsulated	+ve cervical LN.
multicentricity, distant mets	
Aneuploidy	

follicular ca.

• F > M • 40-50 yrs • A/w → Iodine deficiency (long standing MNG)

• Histology – • scanty colloid with small sized follicles

• Psammoma bodies absent

• Hurthle cells – occasionally seen.

• Δsis – confirmed by – Tissue biopsy and FNAC – inconclusive.

• Vascular invasion – confirm Δsis

• m/c route of spread – Hematogenous – Bone, lung, liver

• prognosis overall – good.

Hurthle cell tumor

• > 50% Hurthle cells

• Variant of follicular ca.

• Aggressive ca.

medullary ca. (C-cell ca., Parafollicular ca.)

• Origin – C-cells (parafollicular cells)

• 80% cases – sporadic, adults (45 yrs),

U/L, solitary cold thyroid mass

Ultra

- familial type - AD
  - Younger age (35 yrs)
  - multiple, bilateral
  - C-cell hyperplasia in residual gland.
  - A/w - MEN-Ⅰ-B, Ⅱ-A
  - VHL synd.
  - NF
- Histology - • Round to polygonal tumor cells with amyloid in strom
- Only thyroid ca. - a/w amyloidosis
- Most produce - calcitonin, some also produce - PG, histaminase, ACTH, VIP, serotonin, CEA.
- Spread via lymphatics and blood both, mets to LN, lung, liver, bon
- Sporadic, MEN-Ⅱ-B → more prone to mets, than MEN-Ⅱ-A
- Good prognosis - Young age, female gender
  - familial cases
  - confined to gland
  - Extensive amyloid.

Anaplastic Carcinoma

- a/k/a - undifferentiated / sarcomatoid ca.
- m/c - elderly females
- Rapidly growing mass with dyspnoea or dysphagia.
- Highly necrotic or hemorrhagic mass
- 3 major patterns - 1) Squamoid - may even keratinize
  2) Spindle cell - storiform, may even form bone/cartilage.
  3) Giant cell - scattered.
- Mostly arise within pre-existing tumor (m/c - papillary ca.)
- 100% - mortality. mean survival - 6 months.
- m/c/c/o ☠ - extension into neck structures

Delta

MALIGNANT LYMPHOMA

- m/c - elderly females
- commonly arise in setting of lymphocytic or Hashimoto's thyroiditis.
- Often - Rapid enlargement
- Euthyroid, one or more cold nodules
- Grossly, solid white fish-fleah.
- Example — MALT lymphoma
- m/c — Diffuse large cell,
  follicular center cell origin.
  immunoblastic, lymphoplasmacytic are also seen.
- Packing of follicles with lymphocytes - Astic,
- Better prognosis if restricted to thyroid, may recur in GIT.

PARATHYROID GLAND

- (N) anatomy — 4 glands
  - Avg. wt - total - 120 mg
- Two types of cells - (1) Chief cells — contain parathormone granules
  (2) Oxyphil cells - contain glycogen
- Have colloid filled follicles, can be distinguished from thyroid by -
  a) presence of glycogen in cell *
  b) Absence of oxalate crystals *
- parathyroid gland function is controlled by serum free calcium.
- Ted PTH activity will cause - Ted se. Ca levels
  - Ted urinary phosphate excretions
  - Ted Vit D → Vit D_3
  - → Augmenting G.I. calcium absorptn
  - → Teo bone resorptn
    Teo RANK-L expression osteoblast which combines
    RANK (Receptor activator of Nuclear factor-Kb) on osteoclast,
    and activate them
- → hypercalcemia
  - ↳ Asymptomatic hypercalcemia — PTH adenoma

Delta

• Hypercalcemia in cancer → ① Osteolytic mets
② PTH rp
③ Vit D_3 producth.

primary Hyper-PTH.

• m/c/c- pituatary adenoma
• 2 types - ① Sporadic - m/c type
- D/t - Cyclin-D-1 overexpression
- MEN-1 mutatn (Chr. 11) - 20-30% ca
② familial - MEN-1 d/t germline mutatn (chr. 11q) → MEN-1 ge
- MEN-2 → d/t RET tyrosine kinase Receptor (Chr. 10q mutatn.
- familial hypocalciuric - hypercalcemia (FHH)
↳ AD
↳ mutatn of CASR gene (Calcium sensing recep gene) - resulting in red sensitivity to extracellul calcium.

C/F - • A/w Neck radiatn, sarcoidosis
• Hypercalcemia, hypophosphatemia, Duodenal peptic ulcer.
• Osteitis fibrosa cystica - A/Kla Brown's tumor or Recklinghausen's dis
↳ Expansile multilocular cyst
↳ m/c site - jaw
↳ Alternating solid, cystic areas with hemosiden deposition, occasional giant cells, reversible with removal of hyper-funct ing gland
• kidney - Renal Stones, nephrocalcinosis

Secondary Hyper-PTH
• m/c/c - Chronic Renal dis.
• Intestinal malabsorptn
• Vit D - dietary def.
→ morphology - Cheif cell hyperplasia.

↳ lab - red serum phosphorus, red se. calcium
* Calciphylaxis → Organ ischemia caused by

Delta

Tertiary hypoparathyroidism -
- m/c/c - Accidental surgical ablation
- ~~Hypokalemia~~, Hypocalcemia,
- 2° hyper-PTH, in whom one or more gland has become autonomous → 2° Hyper-PTH + chief cell adenoma

Hypoparathyroidism -
- m/c/c - Accidental surgical ablation
- Hypocalcemia, mental changes, calcificatn of lens, calcificatn of basal ganglia (parkinson's), cardiac conductn defects.
- Astic of parathyroid ca. → mets

ADRENAL GLAND
- (N) wt - 4-5 gm
- 2 parts - cortex, medulla
- cortex - ① zona glomerulosa - outermost - (m)ineralocorticoid
  ② zona fasciculata - middle - Glucocorticoid.
  ③ zona Reticularis - innermost - Androgen (sex steroid)

Hypo-adrenalism →
① Addison's dis. (1° Chronic Adrenocortical insufficiency)
↳ Destructn in >90% of cortex
↳ causes - m/c/c in world - Autoimmune adrenalitis (idiopathic/ Atrophy)
m/c/c in India - TB
↳ other causes - Amyloidosis, Hemochromatosis, mets.
Morphology - cortex is atrophic, with chronic ~~atrophic~~ inflammatory cells
C/F - Weakness, fatiguability, Anorexia, Nausea, Vomiting, wt loss, hypotension, hyperpigmentatn* (from elevated propio-melanocortin peptides)
Autoimmune - Type I - Hypoparathyroidism, mucocutaneous candidiasis
↳ Depressor in T cell function
Type II (Schmidt's Syndrome) → HLA-A1, B8

2. Primary acute Adrenocortical Insufficiency

- Causes → Rapid withdrawal of steroid Rx (m/c/c)
  - → Crisis in pt with Addisons
  - → Stress
  - → Massive H'ge
  - → Neonates - massive H'ge
  - → Waterhouse - friderechsen Syndr.
    - ↳ H'gic destruct of adrenals d/t bacterial Infn
    - ↳ Starts in medulla, involves cortex
    - ↳ Rapidly progressive shock and hypotension
    - ↳ m/c/c - meningococcemia
    - ↳ others - pneumococci, staphylococci, H. Influenzae
    - ↳ Widespread petechiae, purpura, H'ges throughout bod. particularly skin, mucosal surfaces
  - → Grossly - adrenals are h'gic and necrotic with sacs of blood clots.

3. Secondary Adrenocortical Insufficiency

↳ D/t hypothalamus, pituitary problems.

↳ No hyperpigmentation.

Hyperaldorenalism

3 patterns → Glucocorticoid excess - Cushing Syndrome

m/c - Hyperaldosteronism

Androgen excess - Adrenogenital Syndrome

Cushing's → m/c/c - exogenous CS Rx

- → C/F → Impaired glucose tolerance (overt diabetes)
- → moon facies, buffalo hump,
- → Abd. striae, loss of libido,
- → Vascular fragility, skin H'ges.

Crooke's hyaline change - in pituitary gland

↳ Granular basophilic cytoplasm is replaced by

(60-70%) → can be suppressed by high dose dexamethasone

Pituatary cushing's syndrome → B/L Adrenal hyperplasia
d/t elevation of ACTH levels, m/c/c - pituatary adenoma
Cushing's dis-
↳ Hyperplasia is usually diffuse, sometimes nodular
(20-25%) Adrenal cushing's → Neoplasm (adenoma)
ectopic Cushing's Synd (10-15%) → ACTH or similar compound.
↳ Not suppressed by high dose Dexamethasone
↳ Bronchogenic ca. → m/c/c.
other - malignant thymoma.
Iatrogenic cushing's → On Rx

B PRIMARY HYPERALDOSTERONISM (CONN'S SYNID)

- HTN, Neuromuscular symptoms, Renal potassium wasting
- Elevated aldosterone levels, in the absence of elevated renin levels.
- No edema
- most common - Adrenocortical adenoma
- Aldosterone secreting adenomas - usually < 2 cm, bright yellow, non-encapsulated, mixed cell type

ADRENAL CORTEX TUMORS

- Adenoma/ carcinoma -
  - Bright yellow
  - Adenoma - 40-60 gm, < 5 cm
  - carcinoma - > 100 gm, > 5 cm.
- Adenoma - difficult to distinguish from hyperplastic nodule, if residual cortex is (N) or atrophic → Adenoma
- ca. - more likely to show necrosis, other features
- most of adenomas, ca. are functional.
- myelolipoma - Asymptomatic, benign
  - Sharply circumscribed, uncapsulated,
  - fat cells mixed with myeloid cells and lymphoid cells.

MUSCULOSKELETAL SYSTEM

Bone → connective tissue which is composed of cells and ECM

Type I collagen

* Cleido cranial dysplasia → Run X2 mutation.
(CBFA-1 - core binding factor A-1)

Mesenchymal origin cell

↓

Osteoblast

↓

get mineralised

↓

osteocyte

ADRENAL MEDULLA

- Derived from neural crest
- Sympathetic paraganglia
- Body's major source of epinephrine
- Epi: Norep → 5:1

Neuroblastoma - In Kidney chapter

PARAGANGLIOMA (PHEOCHROMOCYTOMA)

- Neuroendocrine neoplasm
- Originates from adrenal medulla; paraganglia in chromaffin--ve glomus cells derived from embryonic neural crest, functioning as part of the sympathetic nervous system.
- "Rule of 10" → • B/L - 10%
  - Extra-adrenal - 10%
  - Malignant - 10%
  - Seen in children - 10%
  - No HTN - 10%

25% - Hereditary (chances of being multiple, developing @ an early age)

- Mutations of genes for Succinate DH → SDHD (PGL-1)

• Carotid body tumor - parasympathetic paraganglioma.
↓ Glomus cells are seen

Dt.: Delta
Pg.:

★ Definitive evidence of malignancy → Mets.

• familial syndromes asso. - ① Sturge webber
② vHL • NF-1 • Men-IIa, IIb

• Highly vascular tumors ★

• microscopy → ① Individual cells - oval / polygonal - arranged in distinctive cell balls - Zellballen

② Chief cells → • In the cell balls, +ve for chromogranin, synaptophysin, NSE, serotonin, Neurofilaments, Neural cell adhesion molecule.

• S-100 → Negative.

③ Sustentacular cells - S-100 +ve, GFAP +ve (Only focally)

★ Histochemistry - • Argyrophilic, PAS -ve,
Mucicarmine -ve, Argentaffin -ve.
↳ CD10, CD56, CD57, CD-68 → +ve.

Inv → Norepi > epi - secreted
Ped plasma, urinary catecholamines and their metabolites, e.g. VMA (vanillyl mandelic acid), metanephrines.

MEN

• Autosomal Dominant, high degree of penetrance

A/w • Younger age • Arise in multiple organs
• Often multifocal • Usually preceded by asymptomatic hyperplasi-
• Usually more aggressive.
• Recur in higher proportion of cases.

MEN Type I (Wermer Syndrome)

• Germline mutation in MEN-1 tumor suppressor gene encoding protein "Men in" on Chr. 11.

• Consists of → ① Pituitary - m/c type of Ant. pituitary tumor - Adenoma
② PTH gland → 1° Hyper-PTH → most common, initial manifestation
③ Pancreas → Hyperplasia, Adenomas, Carcinomas

• Others - Adrenal cx, Nodular hyperplasia thyroid, carcinoid tumor of lung

Delhi

* m/c site of gastrinoma in MEN-1 → duodenum

MEN I A → Sipple's syndrome

- Chr. 10
- C-cell hyperplasia / medullary ca. thyroid
- Pheochromocytoma
- Parathyroid chief cells hyperplasia,
- Occassionally - Adrenal Cx tumors.

MEN I-B → Gorlin's syndrome

- Medullary ca. thyroid
- Pheochromocytoma
- Ganglioneuromas of corneal nerves, lips, G.I. tract
- Skeletal abN, marfanoid habitus
- Occasionally - Adrenal Cx tumors, PTH tumors.

In MEN-1 → m/c tumor - PTH adenoma
m/c pancreatic tumor - insulinoma
m/c enteropancreatic tumor - Gastrinoma
m/c endocrine abN - 1° Hyper-PTH.

Dt.:
Pg.:

DIABETES MELLITUS

- Euglycemic person - FB - <110
  PP - <140

Asis of DM - ① RBSL ≥200 with S/S of DM
② FB ≥126 on more than one occasion
③ OGTT - PP - ≥200 after 2hrs of 75 gm glucose
④ HbA1C - ≥6.5 gm%.

IGT - (Impaired glucose tolerance)
FB - 110-126
PP - 140-200
HbA1C - 5.7-6.4.
Risk of 5-10%/year.

HbA1C - formed by non-enzymatic combinatn of glucose with globin of Hb. Helps in estimating glycemic control in the past 3 months.
→ HbA1C < 5.6%. - (N)
5.7-6.4 → IGT
≥6.5 → DM.
Target in DM → <7%.
Alternative of HbA1C - Glycated Albumin

HbA1C unreliable in
- Hb-pathies
- Hemolytic anemia
- Uremia

INSULIN → • Synthesized by β-cells of pancreas in ER in inactive form - pre-pro-insulin
• pre-pro-insulin - transferred to Golgi body - and cleaved into equal quantities of insulin, C-peptide.
• C-peptide levels - marker of endogenous insulin secretions.
• C-peptide - ↑ed → in Type II DM, ↓ed in Type I DM

PATHOGENESIS OF TYPE 1 DM
• Autoimmune β-cell destructn
• Genetic susceptibility -
  ↑/T - MHC class II
• HLA-DR-3, DR-4 - Haplotypes

Delta

- Non-MHC polymorphism - is also a/w disease susceptibility, CTLA-4, PTPN-22

→ Enviromental factors - Viral Inf^ns - coxsackievirus, mumps, CMV, Rubella

Mechanisms.

① Bystander damage - viral Inf^n causes islet injury and inflamm. l/t release of cryptic B-cell antigens and autoreactive T-cell activam.

② Molecular mimicry → viruses produce proteins that mimic B-cell antigens.

→ failure of self tolerance

→ CD4 TH1 → cytokines - IFN-γ, TNF

→ CD8 → KILL B-cells

→ Autoantibodies

- B-cell antigens are -
  - Glutamic acid decarboxylase (GAD)
  - Islet cell auto-antigen 512 (ICA-512)

PATHOGENESIS OF TYPE 2 DM

- Multifactorial causam, No auto-immune etiology
- Polymorphism in TCF7L2 genes (Transcription factor 7-like-2) are a/w B-cell f^n and insulin secrem - provides greatest genetic risk

① Insulin Resistance.

- NEFA (Non-esterified fatty acids)
  - ↓ fed in ms., liver of obese individuals
  - ↓ correlates to Insulin (R)esistance
  - ↓ NEFA accumulam forms "toxic" intermediates such as ceramide and diacylglycerol - which affect Insulin receptors.
  - ↓ NEFA competes with glucose for substrate oxidan causing feedback inhibition of glycolysis

Delta

- Adipokines → fat is a source of ~~adipokines~~ cytokines.
  1) Pro-glycemic cytokines – Resistin
     – Retinol binding protein-4
  2) Anti-glycemic cytokines – leptin
     – ~~ASD~~ Adiponectin.

(2) β-cell dysfunctn
- TCF 7 L2 gene
- Islet cell replaced by Amyloid in long standing cases.

MODY-3 → Alkla – HNF 1 α-mody
d/t mutatn of HNF-1-α gene,
homeobox gene on Chr. 12
↳ m/c type of MODY.

MONOGENIC forms of ~~Pre-Gest fn~~ DM
- Uncommon
- Results from defect in genes of
  - β-cell fn
  - Insulin action.

→ Genetic defects in β-cell fn
↳ 1-2% of Diabetes cases.
↳ AD
↳ Early onset
↳ No obesity
↳ ~~AB~~ No auto-antibodies
↳ MODY - largest subgroup
- Maternally Inherited Diabetes and Deafness (MIDD)
  ↳ Results from mitochondrial DNA mutatn
  ↳ Impaired ATP Synthesis in β-cells → I/t led Insulin relea
  ↳ Sensorineural deafness

(201)

* Genetic defects in insulin action -
  - Acanthosis nigricans
  - PCOS

Lipo-atrophic diabetes → Hyperglycemia + loss of s/c fat
→ A/w Dominant Negative mutants of PPAR-γ.

Complications
- M/c/c OO - CVS comp.
- Time - 15-20 yrs
- M/c earliest finding of DM nephropathy - Ted GFR, Renal hypert in 1st year
- Diabetic neuropathy -
  m/c pattern - Distal symmetric polyneuropathy affecting both motor, sensory function.
- Diabetic mononeuropathy may occur.

PANCREATIC NEOPLASMS
- A/k/a - islet cell tumors
- m/c → insulinoma.

- Insulinoma - → β-cell tumor
  → produce insulin to induce - hypoglycemia
  → BSL <50mg%, Hypoglycemic episodes

Morphology - · Mostly benign
· Solitary tumors
· Amyloid deposition.
· Ca - Ased based on mets, invasion

Zollinger Ellison Syndrome (Gastrinoma)

- ↑ed gastrin secretion
- Can occur in pancreas, duodenum, peri-pancreatic & soft tissue
- m/c site - Duodenum
- Triad - • peptic ulcer ——— • pancreatic islet lesions
  - • Gastric hypersecretion
- more than half of gastrinomas - locally invasive or already metastasized at time of Δsis
- >50% → diarrhoea
- Duodenal, gastric ulcer - often multiple
- 25% in MEN-I

★ m/c site for Glucaganoma - pancreas.
m/c site for mets of glucaganoma - Liver.

- m/c site for gastrinoma in MEN-1, ZES → Duodenum.

Nesidioblastosis

- Congenital β-islet cell hyperplasia
- Hyper-insulinemic hypoglycemia
- ↑ed expression of growth factors IGF-2Ø, IGF-1Rα, TGFBR.
- Also - • Beckwith-Wiedman Synd.
  - • Chronic pancreatitis
  - • Cystic fibrosis
  - • Endocrine neoplasms
  - • Gastric bypass ph.
  - • ZES.