CONTENTS

INTRODUCTION TO CELL INJURY

INTRODUCTION

CELL INJURY

→ disease taking place in the human body at microscopic level
→ because tissues are not functioning normally
  ↳ dlt cell damage or not able to funct^{n} properly

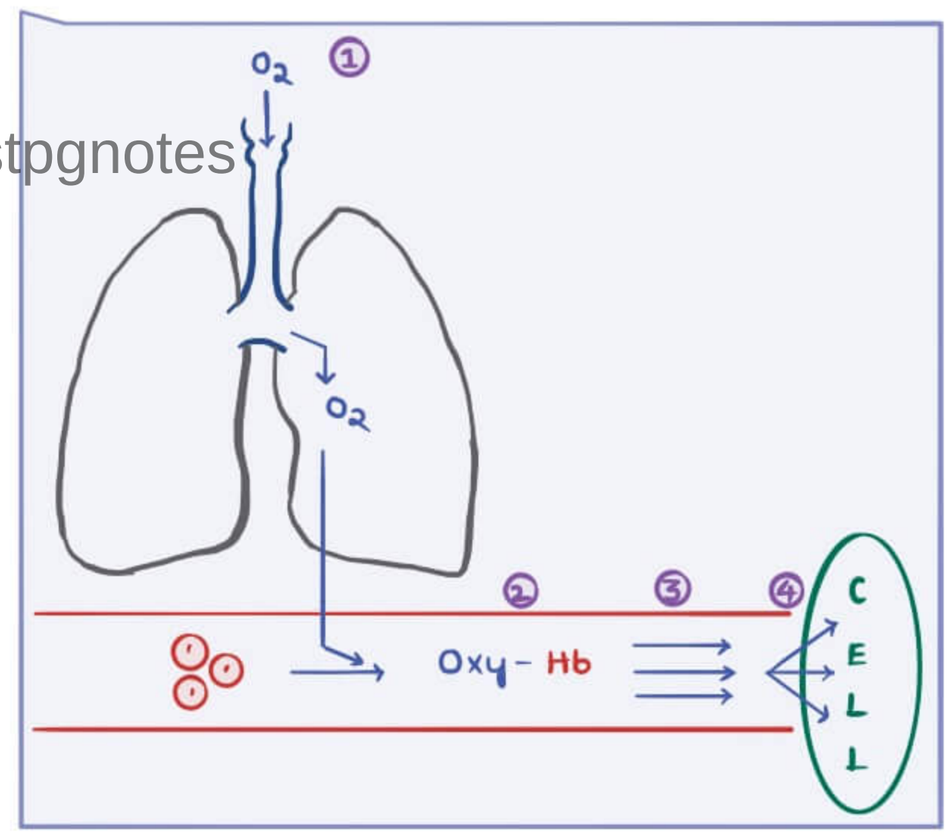
CAUSES OF CELL INJURY

1. PHYSICAL FACTOR
   → Eg: Temperature
     ↳ too high temperature → burn injury
     ↳ Less than normal → Sub zero temperature [frostbite]
2. EXPOSURE TO CHEMICALS
3. EXPOSURE TO INFECTIONS
4. GENETIC FACTORS

HYPOXIA

→ mc cause of cell injury
→ Hypo → Less
  Oxia → Oxygen
  } cell having less O_2 for utilizat^{n}

→ Alveolar O_2
  ↓ diffuses into
  Blood
  ↓
  Hb [RBC] + O_2
  ↓
  Oxy Hemoglobin
  ↓
  CELLS / TISSUES



4 COMMON CAUSES OF HYPOXIA ['HASH' - mnemonic]

1. Hypoxic Hypoxia
   → High altitudes
   → COPD
   → ILD [Interstitial Lung Disease]
   → Right → Left shunt

2. Anemic Hypoxia
   → dlt ↓ functional Hb
     • Anemia
     • Altered Hb
       ↳ CO Poisoning → CO - Hb → Headache, Cherry-red color tint
       ↳ Met Hb

MET Hb

Fe^{2+} —oxidation→ Fe^{3+} ⟹ MET Hb

(Cyt B5 reductase ←)

- Met Hb a/w NEWBORN on exposure to DRUGS like Nitrite, Sulfonamides & local anesthetics
- Met Hb also a/w ↓ individuals ↓ cytochrome B5 reductase deficiency
- Rx by IV Methylene Blue [Reducing agent]

3. Stagnant Hypoxia
   - → Ischemia [arterial obstruct^{n}] – more common cause of stagnant hypoxia
   - → congest^{n} [venous obstruct^{n}]

4. Histotoxic hypoxia
   - → Cytochrome ←⊖ Cyanide
     - a/w IV Nitroprusside longterm usage
     - Cyanide poisoning a/w Brick red discoloration
     - Rx by
       - B_{12} [methylcobalamine]
       - Amyl nitrate
       - Sodium Thiosulfate

MOST COMMON CAUSE OF HYPOXIA → ISCHEMIA

SEVERITY OF INJURY AFFECTED BY

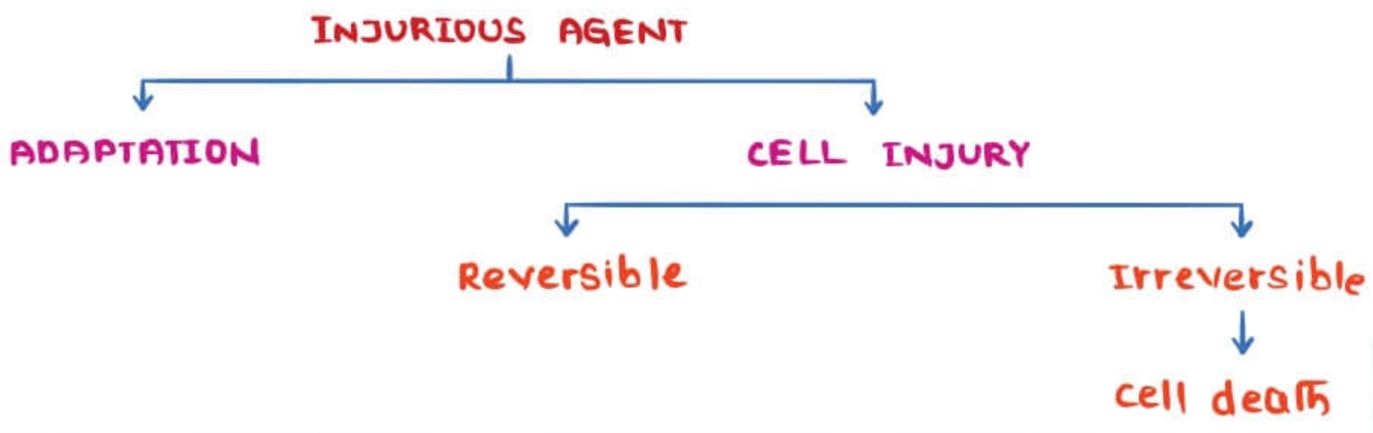
1. Nature of the cell
2. Duration

SENSITIVITY OF CELL IN BODY TO ANY KIND OF INJURY

Neuron [2min] > cardiac Fibre [20min] > Skeletal muscle fibre > Fibroblast
[most sensitive] [most resistant]

3. ORGANS [Specific Areas more susceptible to ischemic damage]
   a. CNS
      - Purkinje cells in Cerebellum
      - Cerebral cortical neurons in layers 3, 5 & 6

   b. CARDIAC TISSUE → Sub endocardial area
   c. GIT → Splenic Flexure

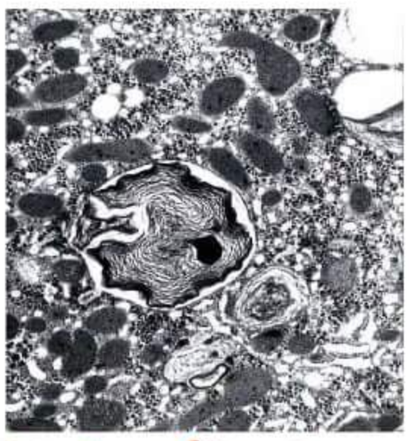


REVERSIBLE CELL INJURY

↓ O_2 → mitochondria affected → ↓ ATP → AFFECTS
1. cell membrane
2. ER
3. Misc. changes

1. CELL MEMBRANE

↓ ATP → ↓ Na^+ K^+ Pump activity [↑ Na^+ inside the cell]
↓
↑ water inside
↓
* CELLULAR SWELLING / HYDROPIC CHANGE [1° microscopic future]
* BLEB FORMATION
* LOSS OF MICROVILLI
* MYELIN FIGURES
  - ↳ small & spiral fragments derived either from cell membrane or membrane of organelles
  - ↳ made up of phospholipids [dlt denaturatⁿ of PL]
  - ↳ intracellular usually, can be seen extracellularly too


myeline figure

2. ER [ENDOPLASMIC RETICULUM] [particularly Rough Endoplasmic Reticulum]

↓ ATP → Ribosomes break away → ↓ Protein synthesis
→ misfolded Proteins accumulation

3. MISC. CHANGES

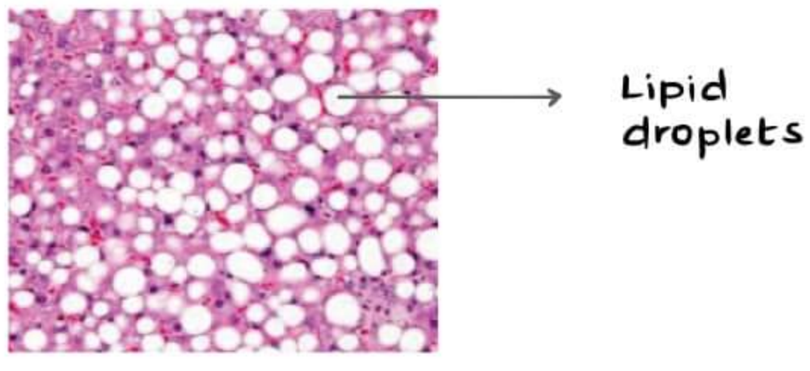
↓ O_2 → ↑ Glycolysis → ↑ Lactate → ACIDOSIS [↓ pH]

a. NUCLEUS

Homogenous appearance of nucleus

Clumping of chromatin
[Patchy deposit^n of chromatin material]

b. LIVER → FATTY CHANGE



c. MITOCHONDRIAL / AMORPHOUS DENSITIES ← ↑ ca^{2+} accumulat^n in mitochondria ← ↓ ATP

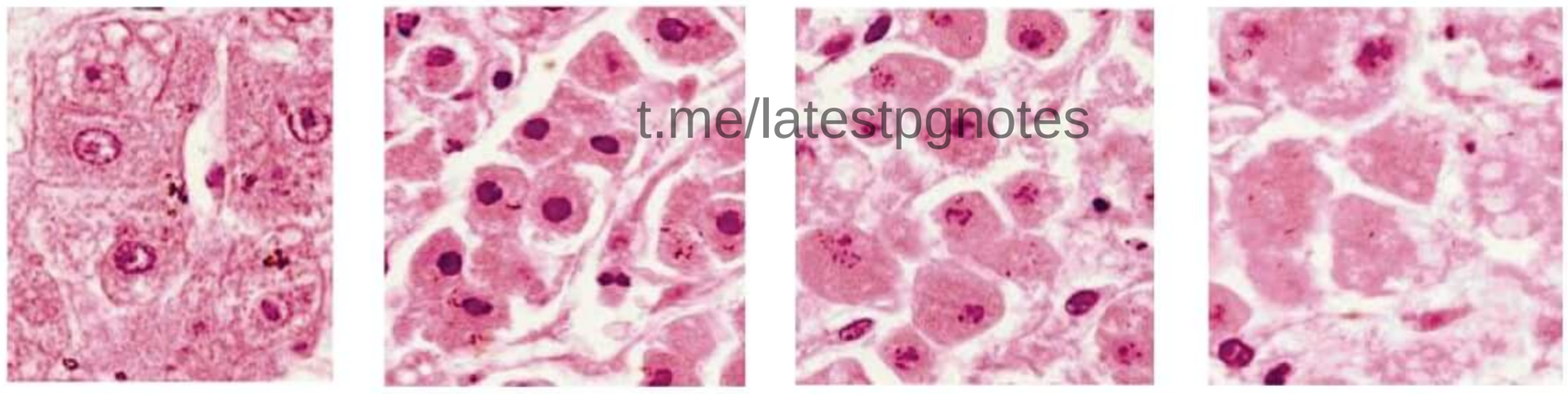
IRREVERSIBLE CELL INJURY

IRREVERSIBLE CELL INJURY

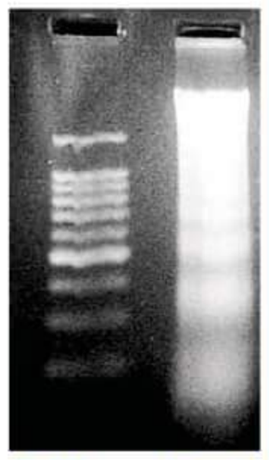
- MITOCHONDRIAL DYSFUNCTION
  - ↓
  - CYT 'C' LEAKAGE INTO CYTOPLASM
    - ↓
    - APOPTOSIS
      - ↓
      - CELL DEATH
- NECROSIS
  - ↓
  - ↓↓↓ ATP [d/t Hypoxia]
    - ↓
    - Energy dependent ca^{2+} pumps fails
      - ↓
      - ↑↑ ca^{2+} INSIDE THE CELL
        - MITOCHONDRIAL DENSITIES
          - ↓
          - CELL DEATH
        - ENZYME ACTIVATION
          - * Lysosomal enzymes
          - * Phospholipase
          - * Nucleases

LYSOSOMAL ENZYME ACTIVATION [m.imp] → CELL DEATH

NUCLEASE ACTIVAT^{n} →
- ● Pyknosis [ink dot nucleus]
- Karyorrhexis [Nuclear fragmentation]
- Karyolysis [Total Breakdown of nucleus]



NORMAL | PYKNOSIS | KARYORRHEXIS | KARYOLYSIS



STEP LADDER PATTERN | SMEAR PATTERN

→ On GEL ELECTROPHORESIS
- ↳ NORMAL NUCLEIC ACIDS → appear as Single band
- ↳ NECROTIC NUCLEIC ACIDS → appear as SMEAR PATTERN
- ↳ APOPTIC NUCLEIC ACIDS → appear as STEP LADDER PATTERN

PHOSPHOLIPASE ACTIVATION → cell membrane damage

Eg: cardiac cell [intracellular enzyme (Troponin)]

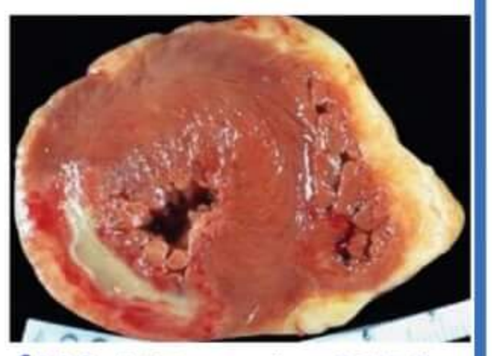
REVERSIBLE CELL INJURY
- → cell becomes bigger
- → no membrane damage
- → enzymes won't leak out
- → enzyme level normal in blood
- → Seen in Angina

IRREVERSIBLE CELL INJURY
- → membrane damage
- → enzymes in cardiac cells leaks out
- → ↑ enzyme level in blood
- → Seen in MI

TYPES OF NECROSIS

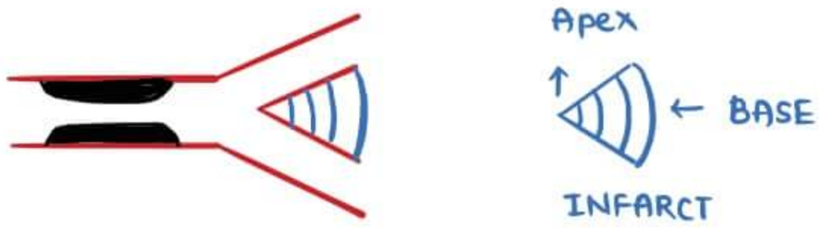
SUB TYPES

1. COAGULATIVE NECROSIS


COAGULATIVE NECROSIS

→ mc subtype of necrosis
→ mc cause is ISCHEMIA
→ denaturation or inactivation of hydrolytic enzymes
→ a/w "TOMBSTONE APPEARANCE"
→ commonly a/w ALL ORGANS except CNS
→ ZENKER'S DEGENERATION
  ↳ coagulative necrosis in skeletal muscle
  ↳ a/w Typhoid

→ commonly a/w neutrophilic infiltrat^{n}
→ INFARCT
  ↳ localized area formed dlt ischemia
  ↳ usually triangular in shape
  ↳ Apex of infarct pointing the direction of Site of Obstruction
  ↳ SUB TYPES

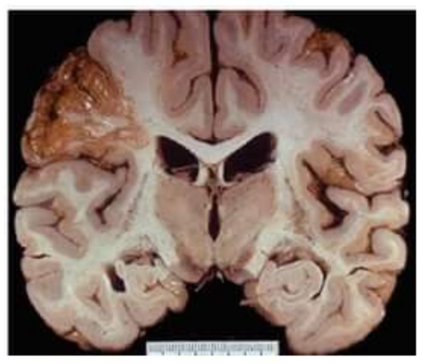


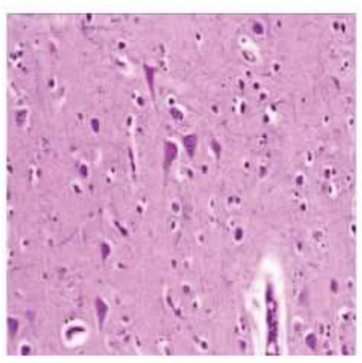
a. WHITE INFARCT
- Seen a/w organs ī end arterial blood supply particularly in solid organs
- Eg: Heart, Kidneys

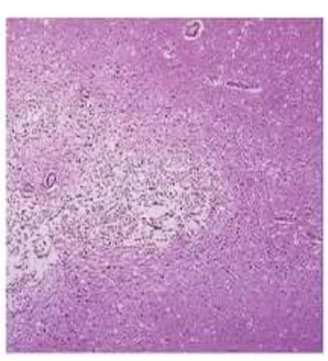
b. RED INFARCT
- Seen in organs ī loose connective tissues
- Seen in organs ī Dual blood supply like Lungs / Liver

2. LIQUEFACTIVE / COLLIQUATIVE NECROSIS

→ Hydrolytic Enzymes activation → Damage to tissue architecture
→ EXAMPLES
  → CNS ISCHEMIA
  → INFECTIONS [a/w pus formation] [a/w staphylococcus aureus infections]


LIQUEFACTIVE NECROSIS

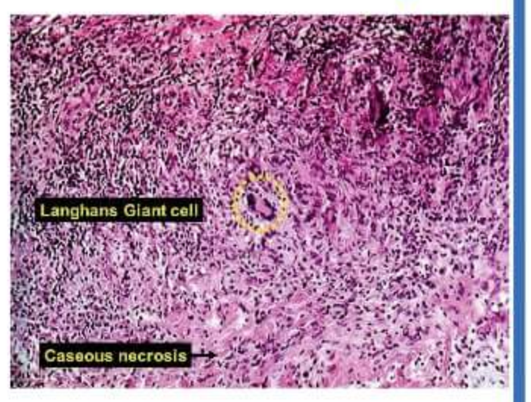

NORMAL BRAIN TISSUE


LIQUEFACTIVE NECROSIS

3. CASEOUS NECROSIS

→ 'cheese-like' necrotic material
→ structural outline not preserved
→ coagulative Necrosis + Liquefactive Necrosis
→ coagulative necrosis is the predominant contributor

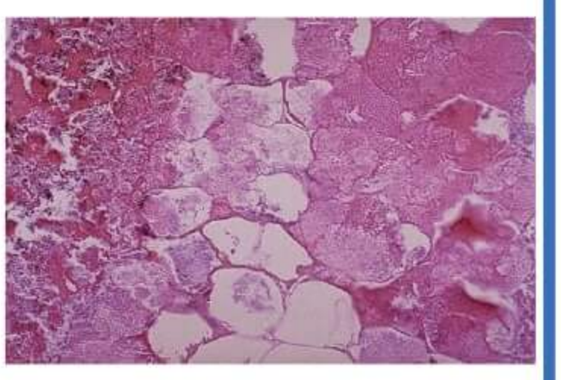
→ SEEN in a/w
  ↳ TB
  ↳ Fungi [Systemic] } NON - tubercular causes
  ↳ Syphilis



→ Granulamatous Reaction +nt
→ monocytes & Lymphocyte infiltration seen
→ Langerhans Gaint cells are a/w Tubercule [TB]

4. FAT NECROSIS

→ a/w organs ī high Fats or Lipase activation
→ SEEN ī
  • injury to breast tissue
  • injury to Omentum tissue
  • pancreatitis



→ EXAMPLE

ACUTE PANCREATITIS
↓
Gall stones / Alcohol
↓
Lipase activation
↓
Lipids → Fatty Acids + Ca^{2+}

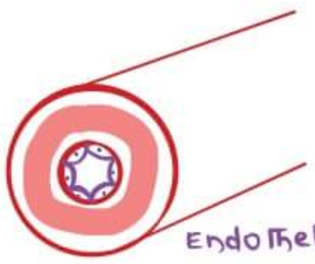
Sr. Ca^{2+} level is the important Prognostic factor to assess Severity of Pancreatitis

↓
SAPONIFICATION ['chalk-like' yellow white deposits]

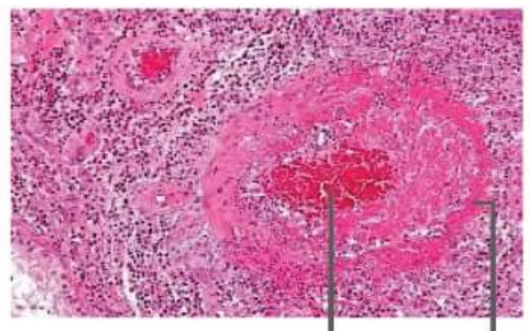
→ In PANCREATITIS, there is involvement of
  • Pancreas → Liquefactive necrosis seen
  • Peri Pancreatic fat → Fat necrosis seen

5. FIBRINOID NECROSIS

→ PATHOGENESIS



ENDOTHELIAL CELL INJURY
↓
Immune complex
↓
Damage to plasma protein in the vessel wall
↓
Inside the vessel wall deposition of plasma protein
↓
FIBRINOID NECROSIS

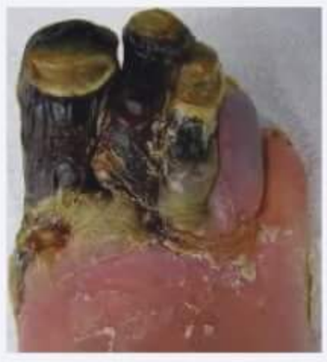


→ SEEN a/w

- Malignant Hypertension
- ASchoff Body
- Immune Complex Disorders ~ Type 3 hypersensitivity Reaction [PAN/HSP]

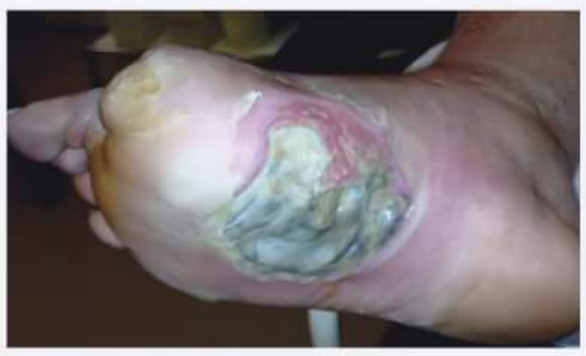
GANGRENE

DRY GANGRENE



→ Ischemia
→ coagulative necrosis

WET GANGRENE



→ Ischemia + secondary infect^{n}
→ liquefactive necrosis

GAS GANGRENE

→ Subtype of wet gangrene
→ a/w Clostridium welchii

APOPTOSIS

→ APOPTOSIS = falling of leaves
→ CASPASE DEPENDENT PROGRAMMED CELL DEATH
→ controlled by Genes
→ Affects Single cell or Small group of cells

GENES ASSOCIATED WITH APOPTOSIS

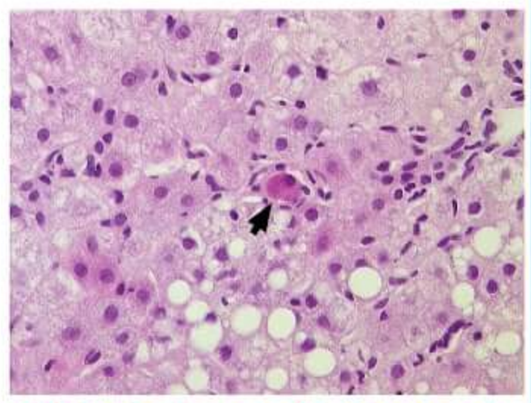
PRO - APOPTOTIC GENES	ANTI - APOPTOTIC GENES	SENSORS
→ BAK gene	→ Bcl - 2 gene [most imp]	→ BiM gene
→ BAX gene	→ Bcl - x_L gene	→ BiD gene
→ P_{53} gene [most imp]	→ MCl - 1 gene	→ PUMA gene
→ corticosteroids	→ Sex steroids	→ NOXa gene
→ Bcl - x_S		
→ Promotes apoptosis	→ inhibits apoptosis	→ Balances apoptosis

→ Bcl - 2 gene a/w Follicular lymphoma
→ MCl - 1 gene a/w development of resistance to chemotherapy
→ Bcl - x_S gene

APOPTOSIS AFFECTS SINGLE CELL | SMALL GROUP OF CELLS
NECROSIS AFFECTS LARGE GROUP OF CELLS
NECROSIS IS ALWAYS PATHOLOGICAL
APOPTOSIS CAN BE EITHER PHYSIOLOGICAL OR PATHOLOGICAL

PHYSIOLOGICAL APOPTOSIS SEEN IN

1. Embryogenesis
2. Females of Reproductive Age group [menstrual cycle]
3. Apoptosis of ↑↑↑ TLC after infection subsides
4. Self Reactive B & T cells



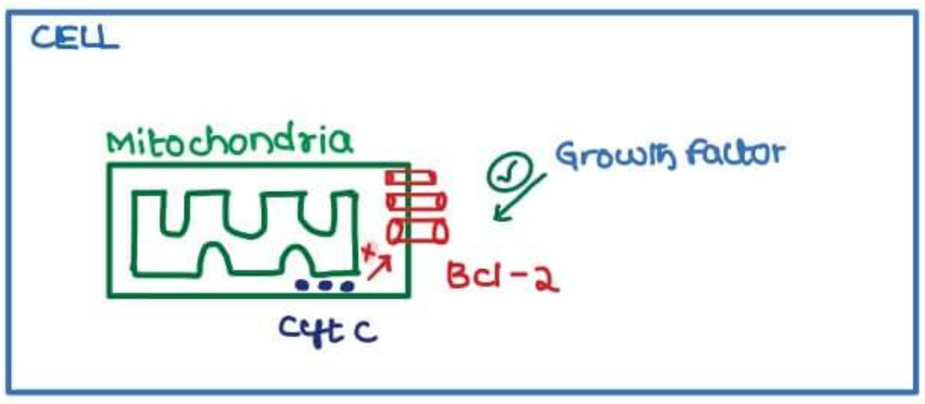
COUNCILMAN / APOPTOTIC BODY

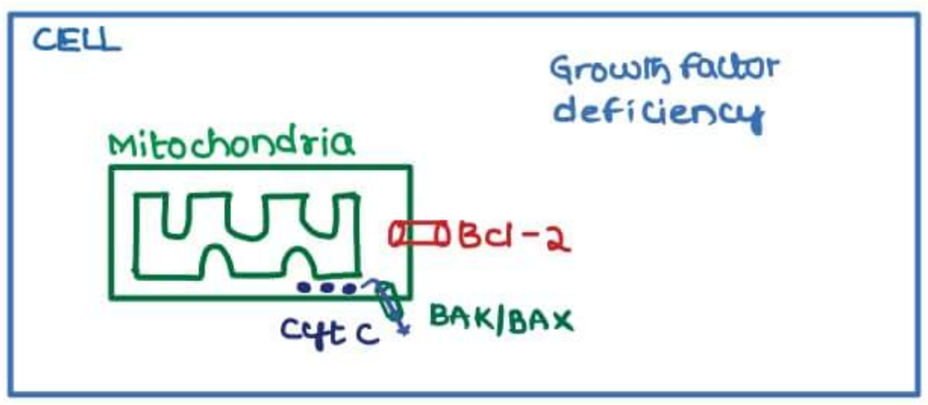
PATHOLOGICAL APOPTOSIS SEEN IN

1. DNA Damage
2. Duct Obstruction [Salivary glands | Pancreas]
3. Viral infection of hepatocytes → COUNCILMANN BODIES [APOPTOTIC BODY]
4. Transplant rejection | Graft vs Host Disease
5. Retinitis Pigmentosa
   - Rods → responsible for DIM LIGHT VISION [Rods → RAAT]
   - cones → responsible for DAY LIGHT VISION [Cones → COLOR]
   - Excessive apoptosis of rods +nt → NIGHT BLINDNESS

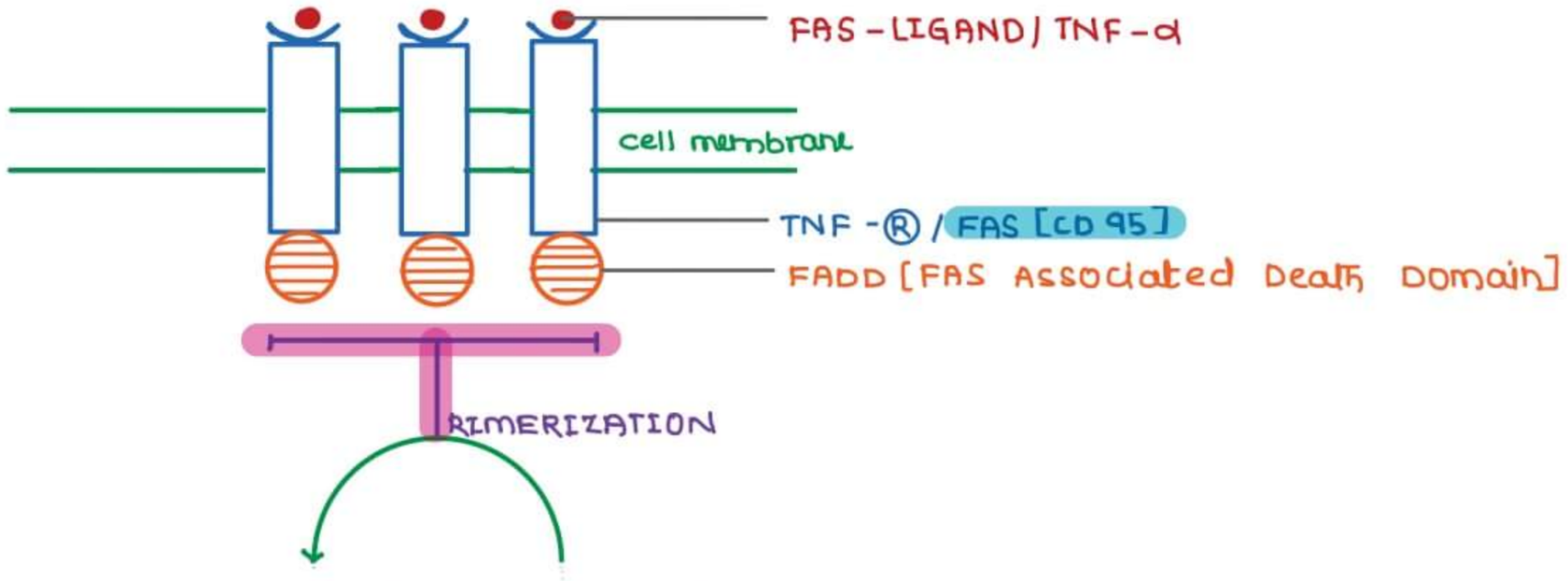
PATHWAYS OF APOPTOSIS

INTRINSIC / MITOCHONDRIAL PATHWAY





EXTRINSIC PATHWAY



- Caspase 8 +nt in animals
- Caspase 10 +nt in humans

INTRINSIC / MITOCHONDRIAL PATHWAY

↓ Growth factors
↓
↓ Bcl_2 Activat^n
↓
Bcl_2 replaced by BAK / BAX
↓
↑ mitochondrial Permeability
↓
↑ cytochrome c in cytoplasm
↓
↑ Activat^n OF APAF - 1
↓
↑ Activat^n OF CASPASE 9
↓
Stimulate CASPASES 3/6/7
↓
↑ Activat^n OF — PROTEASES, ENDONUCLEASES
↓
CELL DEATH

EXTRINSIC PATHWAY

FAS-L/TNFα Release [in severe damage]
↓
FAS - L / TNF - α + FAS / TNF - R
↓
TRIMERIZATION
↓
Activation OF FADD
↓
PRO CASPASE 8 ⟶ CASPASE 8
↓
↑ Activat^n OF CASPASES 3/6/7
↓
↑ Activat^n OF — PROTEASES, ENDONUCLEASES
↓
CELL DEATH

APAF1 → Apoptosis Activating factor 1

CASPASES

→ cystein containing , Protease , Acting at Aspartic Acid Residues

→ INTRINSIC / MITOCHONDRIAL PATHWAY
- initiator caspases → CASPASE 9 [NINE]
- Executioner caspases → CASPASE 3/6/7

→ EXTRINSIC PATHWAY
- initiator caspases → CASPASE 8 [EIGHT]
- Executioner caspases → CASPASE 3/6/7

SALIENT FEATURES OF APOPTOSIS

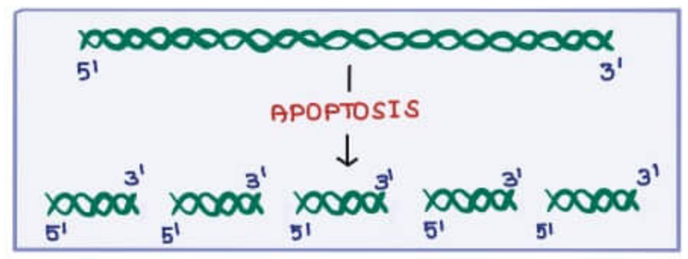
1. CELL SIZE

→ Cell size decreases [Shrinkage]
→ dlt Structural protein destruction by proteases
→ one of the earliest change

2. NO INFLAMMATION / CELL MEMBRANE INTACT [no phospholipase activation]

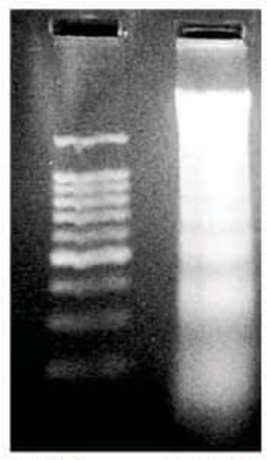
3. CHROMATIN CONDENSATION

→ dlt Endonuclease activation
→ Hallmark feature of apoptosis
→ most characteristic feature of apoptosis



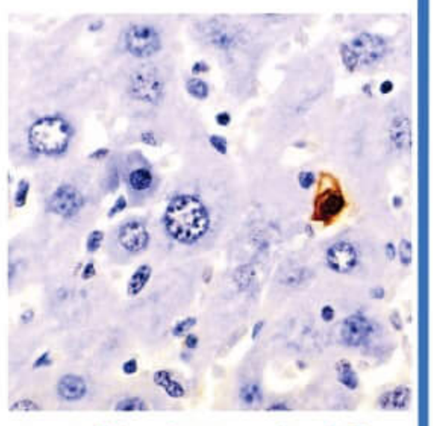
4. GEL ELECTROPHORESIS

→ NORMAL NUCLEIC ACIDS → appear as Single band
→ NECROTIC NUCLEIC ACIDS → appear as SMEAR PATTERN
→ APOPTOTIC NUCLEIC ACIDS → appear as STEP LADDER PATTERN


STEP LADDER PATTERN SMEAR PATTERN

5. TUNEL TECHNIQUE

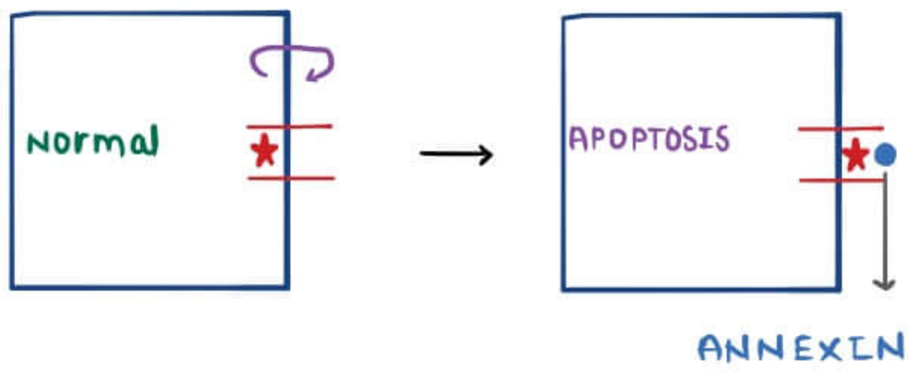
→ this technique uses dUTP
  ↳ attaches at 3'OH
  ↳ more amount of dye is attached in apoptosis
    • more intensified colour [Brown] occurs
    • can be picked up by light microscope


TUNEL STAINING

→ 'TUNEL' stands for
  • T → Tdt [Terminal Deoxynucleotide transferase]
  • U → dUTP
  • N → Nick
  • E → End
  • L → Labelling

6. STAINING done by ANNEXIN 'V'

FLIPPING CONCEPT



- attracts ↑↑ Phagocytic cells
- NO time for enzyme leakage } NO INFLAMMAT^{n}
- cell membrane intact

→ molecules that can flip over are [expression increases at the time of apoptosis]
  • Phosphotidyl serine
  • C1q
  • Thrombospondin

BOOSTER POINTS

→ MCl-1 gene a/w development of resistance to chemotherapy

→ In Traumatic Neuronal injury, AIF [Apoptosis Initiating factor] is Secreted
  ↳ no caspase activation
  ↳ directly activates endonucleases & Proteases

→ Di Amidino Phenyl Indole [DAPI] → Dye useful for detect^{n} of Apoptosis

EXCESSIVE APOPTOSIS SEEN IN

→ Neuro degenerative disorders

→ Virus infections

REDUCED APOPTOSIS SEEN IN

→ Auto immune disorders

p53 GENE

→ activates during DNA damage

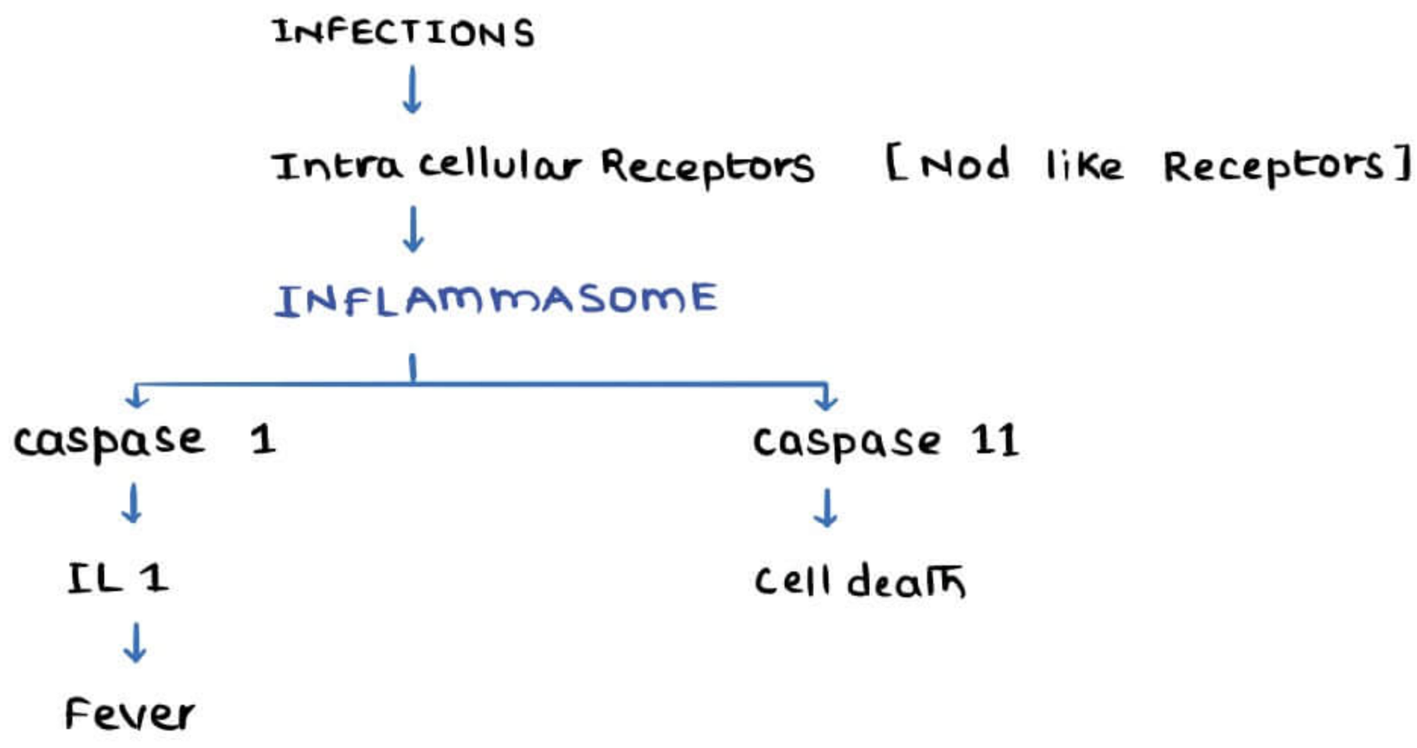
DNA damage $\xrightarrow{\text{p53 gene}}$ ↑ Apoptosis

→ Prevents the accumulation of altered cells → GUARDIAN OF GENOME

→ located on chr 17p

→ mutation in p53 → ↑ cancers
  • around 50% of human cancers are d/t p53 mutation

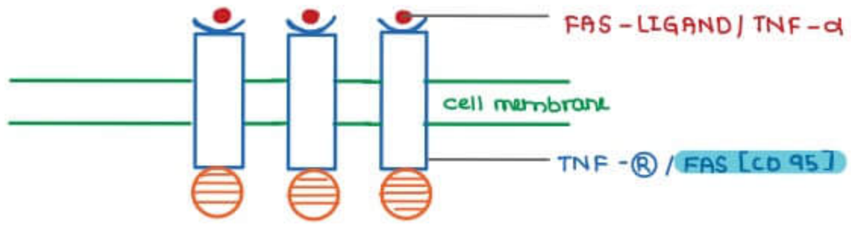
PYROPTOSIS



→ Overactivity of NLR → AUTO INFLAMMATORY SYNDROME

→ MORPHOLOGICAL FEATURES
  → cellular swelling ⊕
  → Inflammation ⊕

NECROPTOSIS



TNF + TNF - ®

↓

RIP 1/3 [Receptor associated Kinase]

- ROS [Reactive Oxygen Species]
  - Lysosomal / mitochondrial damage
  - ↓ ATP
  - CM damage ⊕ / Inflammation ⊕
- NO CASPASE ACTIVATION

→ caspase independent Programmed cell death

→ NECROSIS + APOPTOSIS → PROGRAMMED NECROSIS

SEEN IN

→ PHYSIOLOGICAL → mammalian growth plate

→ PATHOLOGICAL

↳ Pancreatitis / Reperfusion injury /

↳ Steatohepatitis / Parkinsonism

MICROBIOLOGY LINK

→ CMV avoid apoptosis by forming 'FLIP PROTEIN' → inhibit Caspase 8

→ CMV destroyed by Necroptosis

FREE RADICAL INJURY

→ Free radical have unpaired e^- in its structure

→ highly reactive molecules

→ FREE RADICAL FORMATION ASSOCIATED ī

↳ Radiation

↳ Reperfusion injury

↳ Heavy metal Injury [Cu/Fe]

↳ Infections

O_2 → Super oxide ion $[O_2^-]$ → Hydrogen Peroxide $[H_2O_2]$ → (Fe^{2+} / Fe^{3+} [FENTON'S REACTN]) → Hydroxyl Radical $[OH^-]$

↓

Free radical

↓

Damage to DNA / Proteins / Lipids

↓

AUTO CATALYTIC REACTION

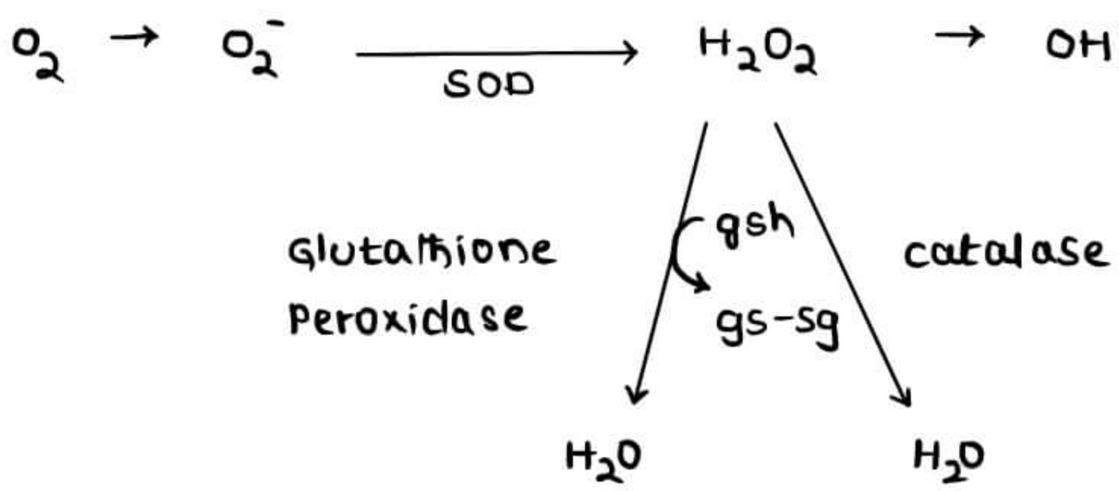
↓

Cell Death

→ Most dangerous free radical → Hydroxyl radical
→ Damage from free radicals can be prevented by → Anti oxidants

ANTI OXIDANTS

1. Vitamin A, C, E
2. Plasma proteins
   - ↳ Transferrin [Fe]
   - ↳ ceruloplasmin [Cu]
3. Enzymes



a. Superoxide dismutase [SOD]
b. catalase
c. Glutathione peroxidase

CELL ADAPTATION

SUB TYPES

1. ATROPHY

→ A ≅ absent ; Trophy ≅ growth
→ ↓ number & ↓ size of cells or tissues
→ Reason

Protein Degradation
↓
Proteins are attached to Ubiquitin
↓
PROTEASOME
↓
Proteasome destroy the proteins

In short, UBIQUITIN ATTACHED PROTEINS ARE GOING TO BE DESTROYED BY PROTEASOME

→ PHYSIOLOGICAL ATROPHY
   1. Atrophy of notochord
   2. Atrophy of ductus arteriosus

→ PATHOLOGICAL ATROPHY

1. Malnutrition
2. Disuse atrophy
3. Senile atrophy
   ↳ dlt old age, gradual deposition of lipids on blood vessels
   ↳ cerebral artery in brain going to develop atherosclerosis

↓

↓ Blood supply to brain → deficiency of Ach

↓

↓↓ Meyernet Nucleus ← Loss of memory
[reason]

↓↓ Neurons contain Acetyl choline → Senile Dementia [Alzheimer's Disease]

↓

↓↓ Memory

4. PRESSURE ATROPHY

Obstruction at urinary outflow level

↓

more urine accumulating inside the kidney

↓

compression of cortical part of Kidney

↓

cortical part undergoes atrophy

→ So ABSENCE OF GROWTH OF CELLS, either decrease in number or size of cells leads to atrophy

→ NEW CONCEPT REGARDING ATROPHY
   ↳ EARLIER considered as → TOTALLY BENIGN CONDITION
   NOW considered SOME as → PRE MALIGNANT CONDITION

Pre malignant condition

↓

Endometrial cancer [usually elder patients]

↓

Type I — Type 2

↑ Estrogen
[Females have
Endometrial hyperplasia]

Suffer from endometrial atrophy
Patients have P53 gene mutation
↓
↑ risk of Type 2 Endometrial cancer

2. HYPERTROPHY

→ Hyper ≅ Excessive ; Trophy ≅ growth
→ ↑ Size of individual cells
→ dlt oversynthesis of structural protein
→ Both Physiological & Pathological
→ PHYSIOLOGICAL
  1. Pregnancy [uterus, breast]
  2. Puberty
  3. Body builders

→ PATHOLOGICAL
  1. Cardiac patients → particularly Hypertension
  2. Stricture → narrowing of Lumen & Intestine
     ↓
     Area prior to it undergo hypertrophy

Heart pumps into Aorta
↓
Pressure in left ventricle is more than pressure in Aorta
↓
In case of HTN, LV have to exert more force
↓
overtime, LV gets hypertrophy
↓
Risk of cardiac failure

3. HYPERPLASIA

→ Hyper ≅ Increase ; Plasia ≅ number
→ ↑ number of cells
→ Both Physiological & Pathological

→ PHYSIOLOGICAL
  1. Pregnancy [Uterus & Breast tissue]
  2. Puberty [Uterus & Breast tissue]

→ PATHOLOGICAL
  1. Endometrial Hyperplasia [Pre - cancerous condition]
  2. Prostatic Hyperplasia [Benign prostatic hyperplasia]

Benign Prostatic Hyperplasia

Androgen dependent [Testosterone not responsible]

↓ 5α reductase

Di Hydro Testosterone [DHT]

↓

↑ NO. OF cells in the prostate

↓

Clinical Symptoms of patient

↳ elderly man

↳ delayed micturition

↳ problems i starting of stream

↳ stream is not of proper strength

↳ stream can't be controlled

↓

↑ Prostate size [Periurethral zone enlarges]

↓

compresses urethra

Important to know because of 2 reasons

(i) IF patients symptoms are seen i the help of DHT

↓

Relief can be provided to the patient by ↓ concentratn of DHT by FINASTERIDE [5α-reductase inhibitor]

↓

↓ Size of prostate in elderly male patients & provides symptomatic relief

(ii) BPH is not a risk factor for development of Ca prostate [as this is a benign condition]

→ So, Hyperplasia may or may not be a pre cancerous condition like atrophy

4 METAPLASIA

→ Meta ≅ Slightly altered ; Plasia ≅ Number

→ change in number of cells in presence of stress

→ EPITHELIAL METAPLASIA

→ CONNECTIVE TISSUE METAPLASIA

1. Myositis Ossificans [muscle replaced by bone]
2. Barrett's oesophagus [intestinal columnar metaplasia]

→ Metaplasia is a reversible change

↳ metaplasia persisting for longer periods → cancer

↳ Reversible metaplasia → Benign

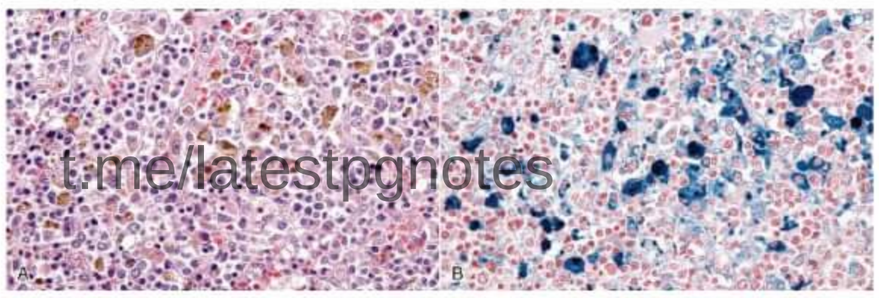
→ undifferentiated stem cells —stress→ New epithelium / connective tissue
→ EPITHELIAL METAPLASIA

Lungs, Ciliated Columnar Epithelium
↓ (smoking)
Squamous epithelial cells
↓
Squamous metaplasia
[MC Example of Epithelial metaplasia in Lungs]

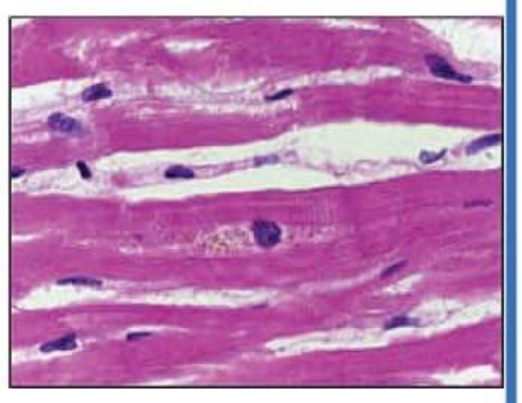
PIGMENTATION

1. MELANIN
→ Endogenous black pigment
→ Provides Hair & Skin colour
→ derived from TYROSINE

2. HEMOSIDERIN
→ derived from Iron
→ present at Storage sites of Iron [Bone marrow]
→ detected by PRUSSIAN BLUE
↳ Purple / violet granules
↳ Reaction Known as PERLS RXN



3. LIPOFUSCIN / LIPOCHROME
→ PERI NUCLEAR BROWN pigment
→ Lipid derived pigment
→ accumulated by LIPID PEROXIDATION
↳ a/w free radical injury
→ seen in
1. Aging → WEAR & TEAR PIGMENT
→ BROWN ATROPHY
2. PEM
3. Cancer



→ AGING is due to
1. Collagen - cross linking
2. Free radical injury [most accepted theory]
3. DNA damage [or defect in DNA HELICASE]
4. Telomere Shortening

→ WERNER SYNDROME
→ defect in DNA helicase → DNA damage
→ Pre mature aging

→ SIRTUINS

→ causes

1. DNA alteration } ↑ Lifespan
2. ↓ free radical injury }
3. ↓ Insulin resistance → ↓ DM

→ sirtulins increased by

1. ↓ calorie intake
2. Red wine consumption

4. CALCIFICATION

a. DYSTROPHIC CALCIFICATION

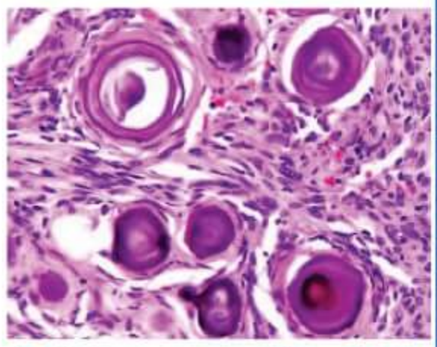
→ S. ca^{2+} → normal

→ deposited in Dead / Degenerated tissues

→ Ex:

1. TB of LN
2. Cardiac valves [RHD]
3. Atherosclerosis
4. Tumors / cancers [PSAMMOMA BODIES]

M → meningioma
O → Papillary CA of ovaries
S → Papillary CA of Salivary gland
T → Papillary CA of Thyroid



PSAMMOMA BODIES

b. METASTATIC CALCIFICATION

→ S. ca^{2+} ↑↑↑

→ deposited in Living tissues

→ Ex:

1. PTH ↑
   - ↳ Parathyroid adenoma [mcc of Primary hyperparathyroidism]
   - ↳ Chronic renal failure [secondary hyperparathyroidism]

2. vit D INTOXICATION
   - ↳ Granulomatous Disease

1-α Hydroxylase ↑
↓
↑ Calcitriol

3. MILK - ALKALI SYNDROME
4. CANCER
   ↓
   Osteolysis
   ↓
   Metastatic calcification

→ Ca^{2+} deposits in MITOCHONDRIA in majority OF cells EXCEPT in RENAL CELLS [deposits in Basement membrane]

→ Ca^{2+} has prediliction to deposit in following organs

1. Lungs
2. Gastric mucosa
3. Kidneys
4. Systemic arteries & Pulmonary veins

→ Ca^{2+} will not directly affect Parathyroid glands

→ Ca^{2+} → TETRACYCLINE [radiolabelled]
↓
used for the study OF BONE REMODELING

INFLAMMATION

BASIC CONCEPTS

INJURY
↓
RESPONSE OF BODY

1. CHANGES IN BLOOD VESSELS
2. CHANGES IN CELLS [connective tissue]

→ RESPONSE is usually protective, but some times harmful

CLASSIFICATION

→ mc type of Inflammation → CATARRHAL INFLAMMATION

SUB TYPES

1. ACUTE INFLAMMATION → Short Duration / Neutrophils
2. CHRONIC INFLAMMAT^{n} → Long duration / Mono nuclear WBCs [Lymphocytes | Monocytes]

CARDINAL FEATURES OF INFLAMMATION

→ Described by CELSUS

1. RUBOR – redness
2. CALOR – ↑ temp.
3. TUMOR – Swelling
4. DOLOR – Pain

→ VIRCHOW described LOSS OF FUNCTION / FUNCTIO LAESA

ACUTE INFLAMMATION

VASCULAR CHANGES

1. VASO CONSTRICTION → 1st change
2. VASO DILATION

NORMAL

Redness [RUBOR]
↑ Temperature [CALOR]

3. ↑ VASCULAR PERMEABILITY

Normal

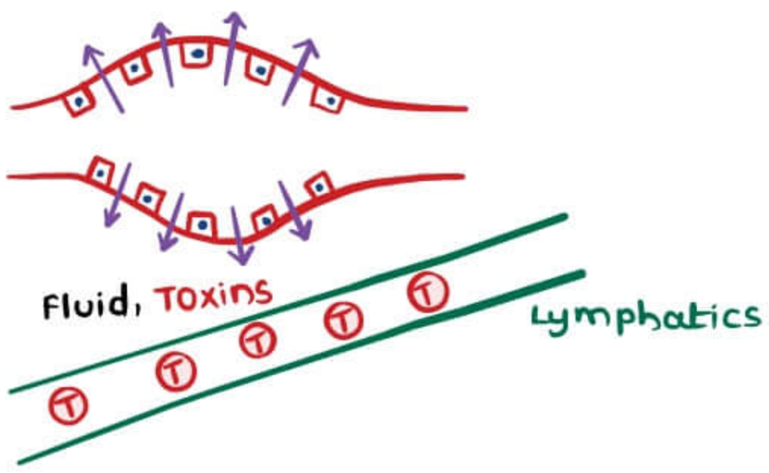
Fluids
Cells
Proteins
} EXUDATE [SG >1.020] → Swelling / edema [TUMOR]

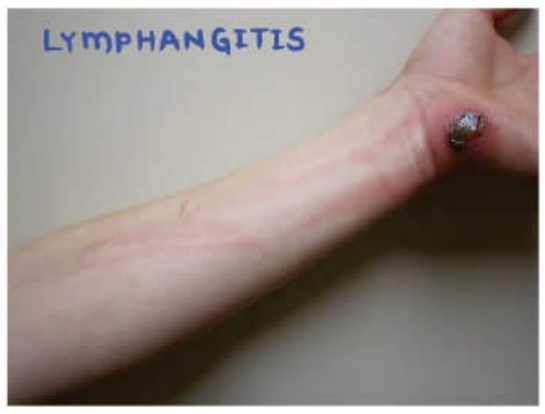
→ most characteristic feature of acute inflammat^n → ↑ vascular permeability
→ mc mechanism responsible → Endothelial cell contraction
→ Endothelial cell contract^n typically involves → Small Blood vessels
  ↳ Arterioles
  ↳ capillaries
  ↳ venules [mc involved]

MECHANISMS OF ↑ VASCULAR PERMEABILITY

1. EC CONTRCTION → Immediate transient Response → THORN PRICK
2. DIRECT EC INJURY → Immediate sustained Response → SEVERE BURN / SEPTICEMIA
3. EC RETRACTION → Delayed transient response → BACTERIAL INFECTIONS
4. EC DAMAGE → Delayed Prolonged leakage → LATE SUN BURN

LYMPHANGITIS can occur





→ Lymphatics drain excess extracellular contents
→ along ī Exudates, sometimes they also drain bacteria / toxins Leading to lymphangitis
→ mc bacterial infect^n responsible for lymphangitis → STREPTOCOCCUS PYOGENES

4. STASIS

↑ vascular permeability → ↑ Hemoconcentrat^n → ↓ Blood Flow → STASIS

VIRCHOW'S TRIAD [a/w THROMBUS formation]

ENDOTHELIAL CELL INJURY

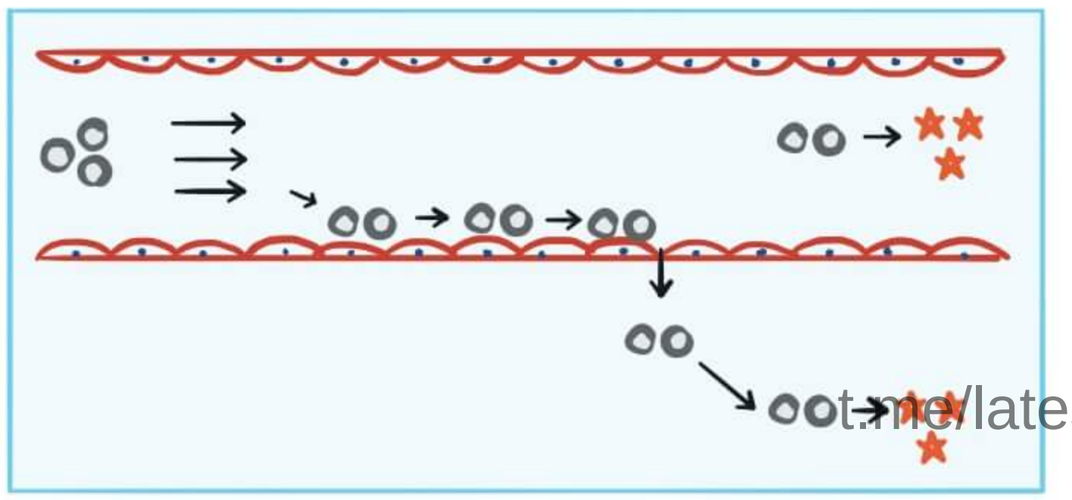
CHANGES IN BLOOD FLOW
- Stasis
- turbulence

INCREASED COAGULABILITY

VASCULAR CHANGES AT A GLANCE						
VASO CONSTRICTN	→	VASO DILATATN	→	INCREASED PERMEABILITY	→	STASIS

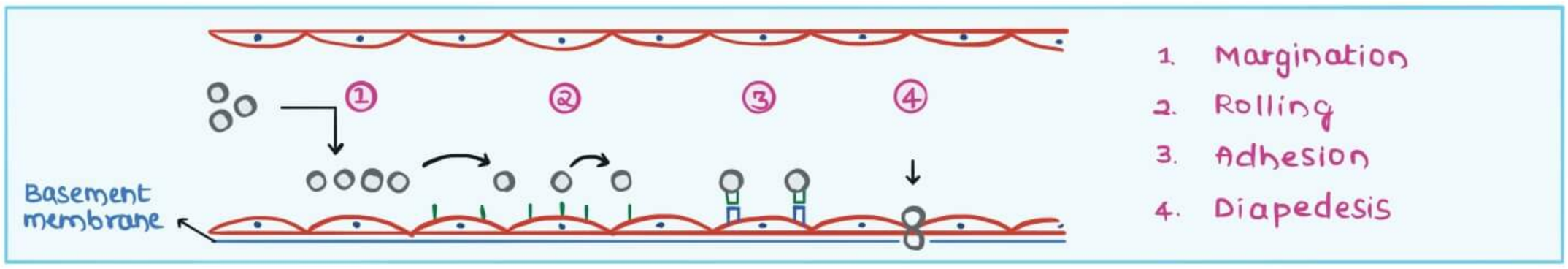
INTRA VASCULAR CELLULAR CHANGES

CELLULAR CHANGES



I. INTRA VASCULAR CELLULAR CHANGES
II EXTRA VASCULAR CELLULAR CHANGES

INTRA VASCULAR CELLULAR CHANGES



1. Margination
2. Rolling
3. Adhesion
4. Diapedesis

1. MARGINATION
2. ROLLING

} Interaction responsible for LOOSE ADHESION

→ Loose adhesion → ↓ Speed → ROLLING

→ SELECTINS

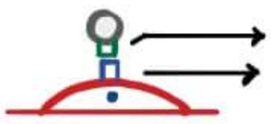
1. [redacted] → expressed on surface of
2. [redacted] → expressed on surface of
3. [redacted] → expressed on surface of [redacted]

↳ WEIBEL PALADE BODY

→ intra cellular body in endothelial cells [Low energy state]

→ contains Willebrand factor & Selectins

3. ADHESION



INTEGRIN
ICAM / VCAM
} interactn r/f FIRM ADHESION

→ ICAM - Inter cellular adhesion molecules

→ VCAM - vascular cellular adhesion molecules

→ Integrins → made of Sub units known as CD 11 a / LFA

4. TRANSMIGRATION / DIAPEDESIS

→ occurs d/t

↳ CD 31 [PECAM - Platelet Endothelial cell adhesn molecule]

↳ collagenase secreted by WBC & responsible for breaking of collagen of Basement membrane

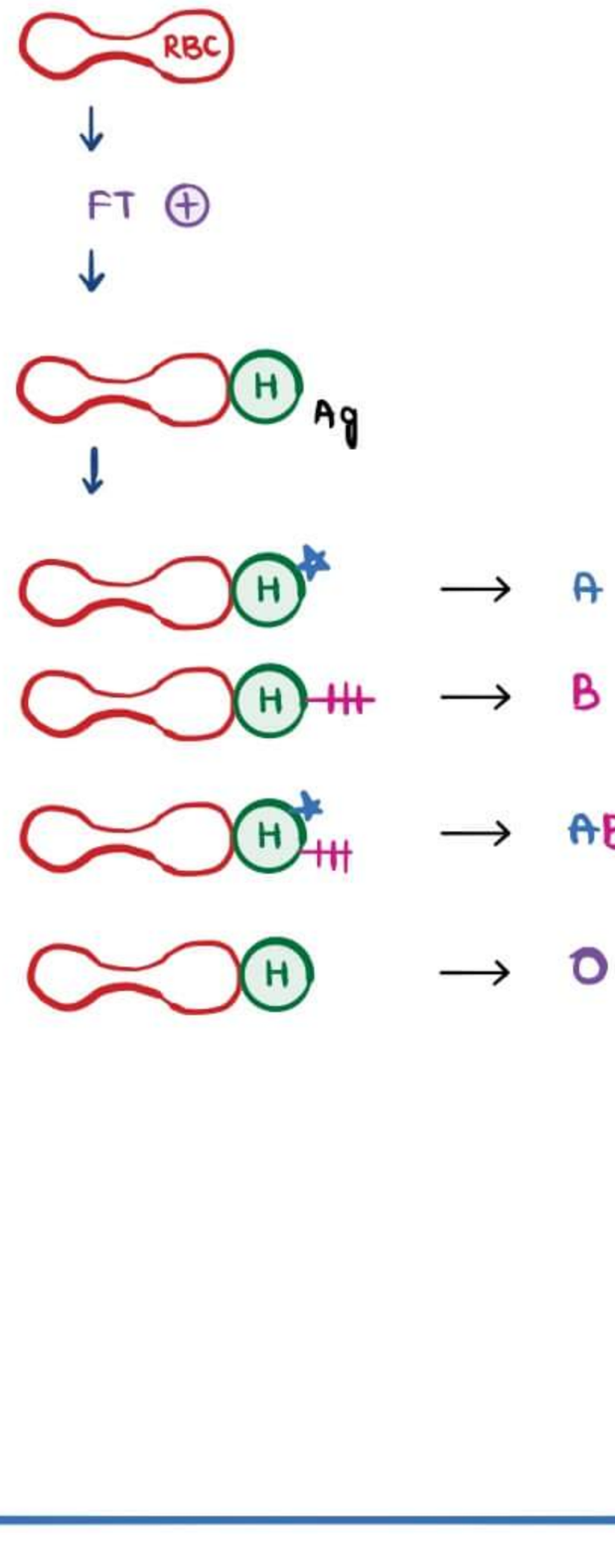
LEUCOCYTE ADHESION DISORDERS [LAD]

1. LAD I → Malfunctioning of INTEGRINS [LFA / CD 11] [firm adhesion]
2. LAD II → Malfunctioning of SELECTIN RECEPTORS [Sialyl - Lewis] [loose adhesn]

→ Both conditions lead to RECURRENT INFECTIONS

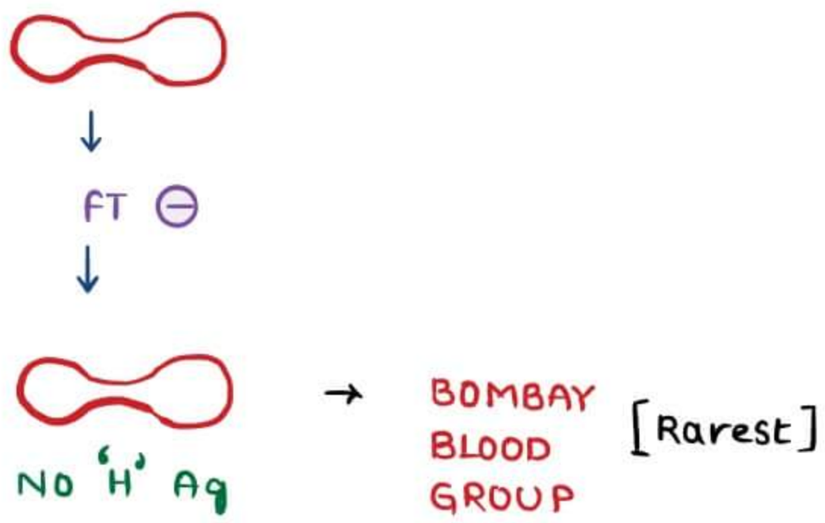
LAD I

→ H/O delayed separatn of umblical cord



LAD II

→ Fucosyl transferase defect



EXTRA VASCULAR CELLULAR CHANGES

5. CHEMOTAXIS

→ Chemo = chemicals ; Taxis = slow movement

→ UNIDIRECTIONAL MOVEMENT of WBC towards bacteria

→ CHEMICALS RESPONSIBLE :

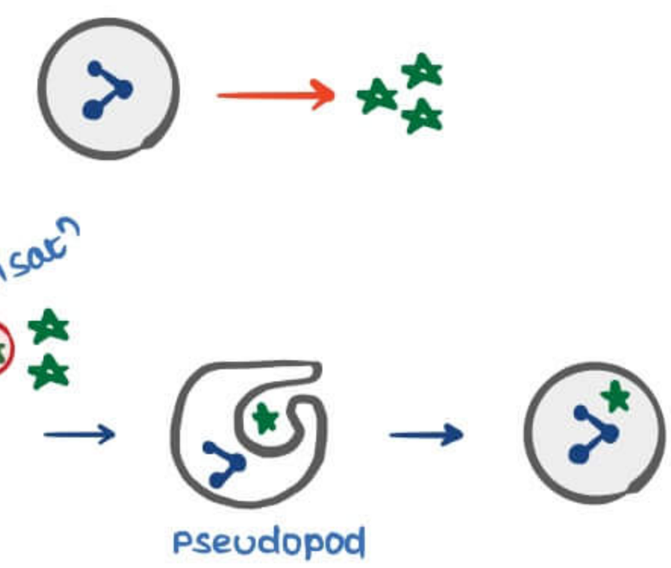
- ↳ Bacterial Products → Exogenous
- ↳ C_{5a} [Complement Protein] } Endogenous
- ↳ IL - 8 [Interleukin] }
- ↳ LTB_4 [Leukotriene B_4] }

→ Major action of STEROIDS → Chemotaxis Inhibition

6. LEUKOCYTE ACTIVATION

6a. RECOGNITION OF TARGET CELL

WBC		MICROBES
* Mannose ®	⟷	Mannose
* Scavenger ®	⟷	some particles



6b. ENGULFMENT

→ PSEUDOPODE FORMATION

↳ d/t Actin Polymerisation

→ OPSONISATION

↳ Bacteria becomes tastier → PREFERENTIAL EATING

↳ OPSONINS

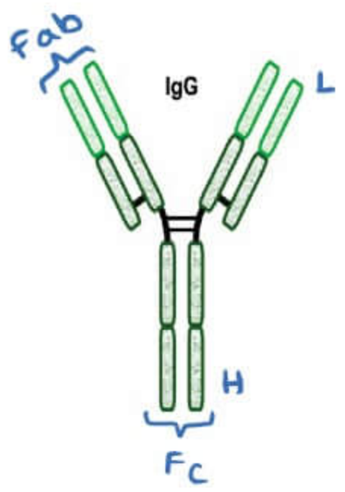
→ chemicals r/f Opsonisatn

→ Examples

↳ F_c fragment of Ig "G"

↳ C_{3b}

↳ Fibrinogen / CRP



→ ANTIBODY FORMATION

Immature B cell —(B cell Tyrosine Kinase)→ ↓Mature B cell ⟶ ↓Plasma cell ⟶ ↓Ig

↑ ⊖

BRUTON'S DISEASE

→ x linked recessive disorder

→ affects Boys

→ B - cell defect

→ Hypogamma globulinemia

→ Defective Opsonisation

→ CRP [C - Reactive Peptide]

↳ CRP is different from C - Peptide

C - PEPTIDE

↓

Pancreas

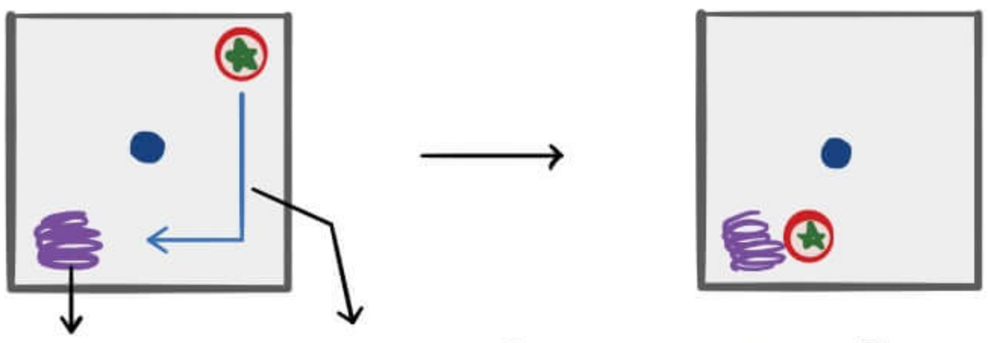
↓

β cells → I I I Insulin
C C C C - Peptide

↳ C - RP

→ C = carbohydrate Ag [derived from Pneumococcus]

6C. KILLING OF BACTERIA



C	→	CNS features
HE	→	HEmorrhage
DI	→	Decreased Immunity
A	→	Albinism
K		

↓

Defect

↓

CHEDIAK - HIGASHI SYNDROME

↳ RECURRENT INFECTIONS

↳ ↓ melanin → ALBINISM

↳ ↓ myelin → NEUROLOGICAL C/F

↳ Platelet defects → BLEEDING ↑

↳ Peripheral smear shows

→ GIANT GRANULE INSIDE THE CELLS

OXYGEN DEPENDENT BACTERIAL KILLING

KILLING OF BACTERIA

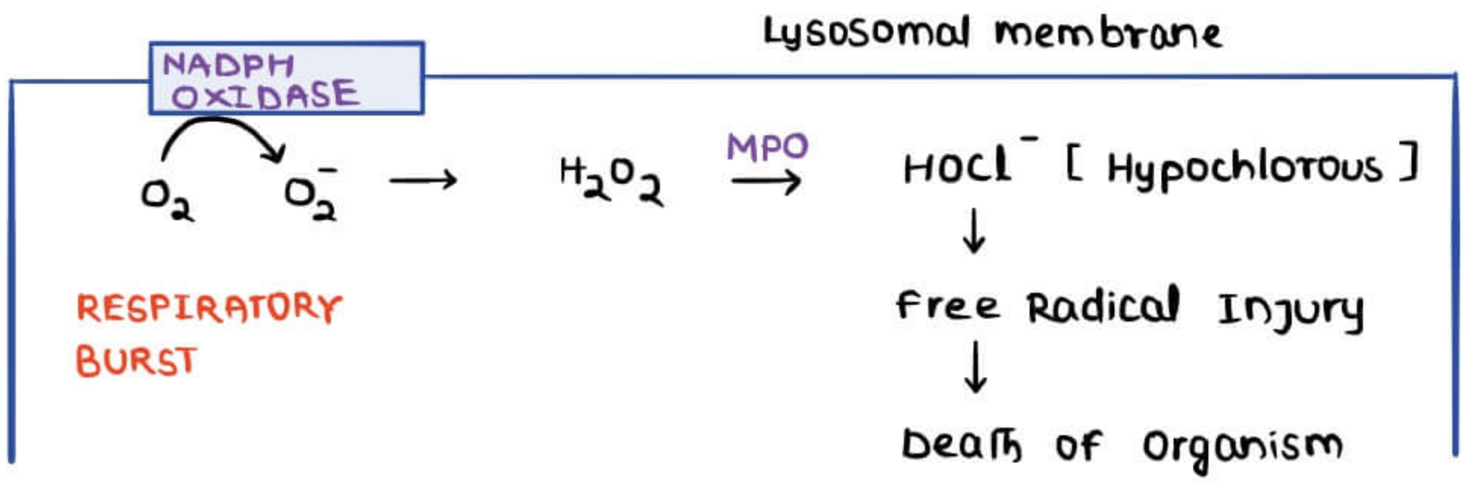
↓

LYSOSOMAL FORMATION

↓

O_2 FOR Killing

→ Most efficient bactericidal mechanism



NADPH OXIDASE / RESPIRATORY BURST OXIDASE & PHAGOCYTE OXIDASE

→ CHRONIC GRANULOMATOUS DISEASE

↳ d/t NADPH oxidase defect

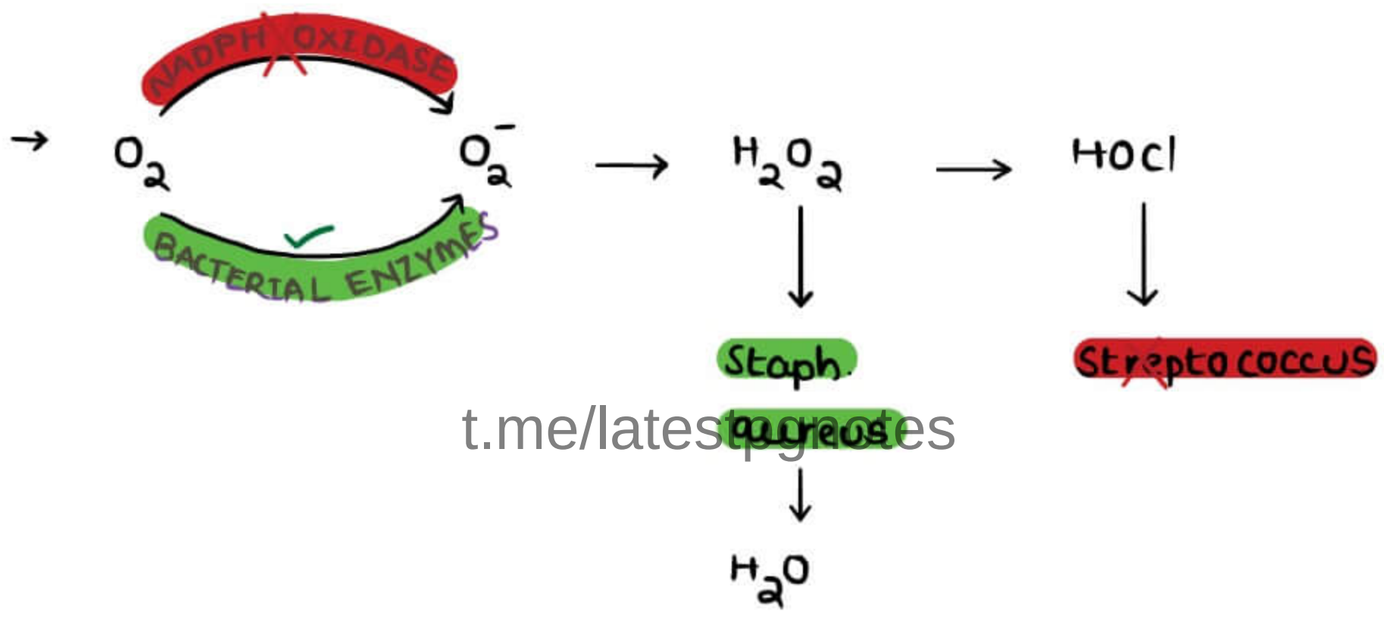
↳ SUB TYPES

1. X LINKED RECESSIVE
   → gp 91 PHOx defect [membrane bound component]

2. AUTOSOMAL RECESSIVE
   → gp 47 PHOx defect } cytosomal component defect
   gp 67 PHOx defect }

→ C/F

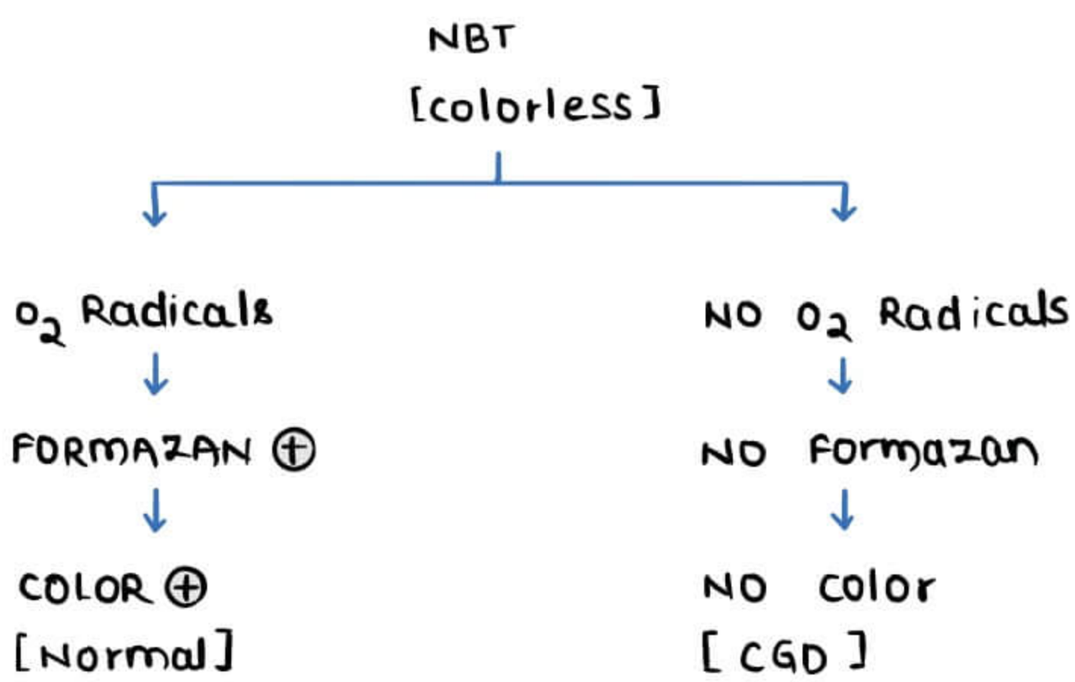
1. RECURRENT INFECTIONS
   → by catalase Positive organisms
   ↳ Eg: Staphylococcus aureus
   Pseudomonas
   Nocardia



2. GRANULOMA FORMATION

→ DIAGNOSIS

1. NITRO - BLUE TETRAZOLIUM TEST [NBT TEST]



2. FLOW CYTOMETRY
   → done using DHR [Di Hydro Rhodamine]
   → Better test than NBT Test

OXYGEN INDEPENDENT KILLING & NEUTROPHIL EXTRA CELLUR TRAP

OXYGEN INDEPENDENT KILLING

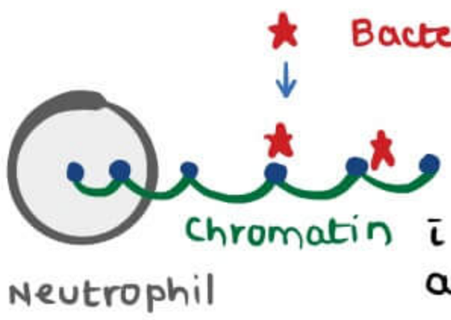
→ ACHIEVED ī THE HELP OF

1. CATHELICIDIN
2. LYSOZYMES
3. LACTOFERRIN
4. MAJOR BASIC PROTEIN
   → abundant in EOSINOPHILS
   → ơ/F parasitic killing

NEUTROPHIL EXTRA CELLULAR TRAP [NET]

→ NORMAL

→ SEPSIS → Platelet Activation → NET formation



→ FEATURES
↳ Killing of Bacteria
↳ Killing of WBC
↳ Nuclear Ag exposure
→ Anti Nuclear Antibodies will be formed
→ ↑ risk of Auto immune disorders [SLE (commonly associated]

PREFORMED CHEMICAL MEDIATORS

CHEMICAL MEDIATORS

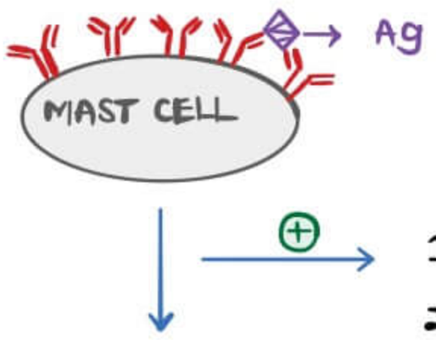
- CELLULAR
  - PREFORMED
    - ↳ Histamine
    - ↳ Serotonin
    - ↳ Lysosomal enzymes
  - FRESHLY FORMED
    - ↳ Nitric Oxide
    - ↳ Cytokines
    - ↳ Arachidonic Acid metabolites
- PLASMA
  - ↳ Kinin System
  - ↳ Coagulatory System
  - ↳ complementory System

CELLULAR PREFORMED MEDIATORS

HISTAMINE

→ SOURCE → Mast cells [Richest source] | Basophils | Platelets

→ FUNCTIONS →
1. vasodilatⁿ
2. ↑ vascular permeability
3. Itching
4. Bronchospasm



⊕
1. IgE Crosslinking
2. Physical factors → Temp.
3. Viruses
4. Anaphylotoxins
   - ↳ Bee venom / Insect venom
   - ↳ Proteins [C_{3a} / C_{4a} / C_{5a}]
5. DRUGS
   - ↳ morphine [should be used cautiously in Asthmatics]
   - ↳ D - tubocurarine
   - ↳ Vancomycin
     - → Should give Slow i.v.
     - → Rapid injection → RED MAN SYNDROME

SEROTONIN [5 - HYDROXY TRYPTAMINE (5-HT)]

→ SOURCE → GIT [Richest source, aka ENTERO CHROMAFFIN CELLS]
Platelets
CNS

→ FUNCTIONS → Same as Histamine
→ Responsible for
- ↳ vasoconstriction in small blood vessels
- ↳ vasodilation in large blood vessels

LYSOSOMAL ENZYMES

→ Responsible for oxygen dependent Killing of Bacteria

FRESHLY FORMED MEDIATORS : NITRIC OXIDE

1. NITRIC OXIDE [NO]

L - Arginine $\xrightarrow{\text{Nitric oxide synthase}}$ NO → ↑ Guanynyl cyclase
↓
↑ C - GMP
↓
Smooth muscle relaxation
↓
vasodilation

NO → Free radicals

NOS
→ ISOFORMS
↳ e NOS → Endothelial cells
↳ i NOS → Inducible / Inflammation
↳ n NOS → Neurons

MOA

NO → ↑ C GMP → vasodilation
↓ PDE - V
5' GMP

♂ → Impotency → Rx by VIAGRA [PDE - V Inhibitor] / SILDENAFIL

ARACHIDONIC ACID METABOLITES

→ Phospholipids
↓ Phospholipase A_2 [RLE] ⊖← STEROIDS
Arachidonic Acid
↓ Cyclo - oxygenase [COX] ⊖← NSAIDS
PG G_2 → PG H_2

PG I_2
↳ Endothelial cells
↓
1. vaso dilation
2. Platelet Inhibition

PG D_2 / E_2 / $F_{2\alpha}$
↓
1. Pain
2. Pyrexia [PG E_2]
3. ↑ Permeability

TXA_2
↳ Platelets
↓
1. ↑ Platelet aggregation
2. Vasoconstriction

→ CIF → ANTI - INFLAMMATORY DRUGS

1. Steroids
2. NSAIDs

→ COX

- COX - 1
  - → present in
    - ↳ stomach
    - ↳ Platelets
  - → PGs in Stomach
    - ↳ protective for gastric mucosa
    - ↳ ↓ gastritis
- COX - 2
  - → present in
    - ↳ Endothelial cells
    - ↳ Inflammation

→ NSAIDs

1. ⊖ COX 1 / COX 2 → NON - SELECTIVE
   - ↳ Anti inflammatory
   - ↳ ↑ gastritis
   - ↳ ↓ TXA_2 & ↓ PGI_2 → balance maintained

2. ⊖ COX 2 → SELECTIVE
   - ↳ Anti inflammatory
   - ↳ gastroprotective
   - ↳ ↓ PGI_2 & ↑ TXA_2 → ↑ myocardial infarct^{n} risk

→ STEROIDS → ARACHIDONIC ACID

- 5 - Lipoxygenase [5 - LOX]
  - ↑ ZILEUTON
  - → Leukotriene A_4 [LTA_4]
    - → LTC_4 / D_4 / E_4 → LT Receptors → Bronchospasm
    - → LTB_4 → chemotaxis
- COX
  - → PGs / TXA_2

LT Receptors ← LT® ANTAGONIST [monteleukast]

→ LTC_4 / D_4 / E_4 → SRS - A [Slow Reacting Substance - Anaphylaxis]
→ responsible for Asthma [LT induced]
↳ R/ by monteleukast

ARACHIDONIC ACID

5 LOX ↓ — COX

↑↑↑ LTs → BRONCHOSPASM

PGs

TXA_2

→ most prescribed drug for reducing the action of LT® → montelukast

→ DRUG INDUCED ASTHMA → COX Inhibitors → NSAIDs

ARACHIDONIC ACID

12 LOX | 5 LOX | COX

LIPOXINS | LTs | PGs / TxA_2

→ ↓ Inflammat^{n}

→ CAD [Coronary Artery Disease]

CAD

↓ AA ⟶ FISH OILS

↑↑↑ ↓↓

↓ CAD

CYTOKINES

→ Cyto = cells ; Kines = Peptides

→ INCLUDES

1. Interleukins
2. TNF - α
3. Interferons

→ PLEIOTROPIC → more than one action by one cytokine

→ REDUNDANCY → more than one cytokines having common action

→ LOCAL EFFECTS

↳ acts on Endothelial cells / fibroblasts

→ SYSTEMIC EFFECTS

IL 1, IL 6, TNF - α } acts on

1. Brain [central act^{n}]
   - ↳ ↓ appetite
   - ↳ ↑ Sleep
   - ↳ ↑ COX → Fever

2. Bone marrow
   - ↳ ↑↑↑ TLC
   - ↳ ↑ neutrophils
   - ↳ ↑ Lymphocytes
   - ↳ ↑ Eosinophils

3. Liver
   ↳ Acute Phase Reactants
      a. Positive APR
         → Fibrinogen
         → CRP
         → Lectin
         → Hepcidin
         → Ferritin
         → SAA Protein

      b. Negative APR
         → Albumin
         → Transferrin

   → ESR [Erythrocyte sedimentatn Rate]
      ↳ ESR ∝ Serum Fibrinogen
         → ↑ ESR → inflammation
         → '0' ESR → Afibrinogenemia

→ PYROGENIC CYTOKINES
   ↳ FEVER
      → caused by
         ↳ Exogenous → Bacterial toxins
         ↳ Endogenous → IL 1 / IL 6 / TNF - α
            CNTF [Ciliary Neuro Trophic factor]

      → eliminates viruses
      → O_2 dissociation curve shift to RIGHT
         ↳ ↑ O_2 → WBC → Respiratory Burst → Kills bacteria

→ SYSTEMIC INFLAMMATORY RESPONSE SYNDROME [SIRS]
   ↳ Diagnostic criteria [≥ 2 out of the following]
      1. RR > 24/min
      2. HR > 90/min
      3. TLC > 12000 / µl (or)
         < 4000 / µl (or)
         > 10% band / tab cells
      4. Temp > 38°C or < 36°C

→ SEPSIS
   ↳ SIRS + Documented Infection
   ↳ New Marker → PRO - CALCITONIN
      Old marker → C - RP

→ TNF - α [CACHETIN]
   ↳ ↓↓↓ Appetite
      ↓
      Cachexia
      ↓
      cancer
      chronic state

→ Most cytokines → ↑ Inflammation
↳ Exception → ANTI INFLAMMATORY CYTOKINES
→ IL - 10
→ TGF - β
} classical examples
→ IL - 6
→ IL - 4
→ Adiponectin
} in some conditions

→ IL 1 → Systemic Effects of Inflammation
IL 2 → Auto crine ; ↑ T - lymphocytes
IL 4
IL 5
} B cell proliferatⁿ & Differentiation
IL 6 → Systemic Effects of Inflammation
IL 7 → Normal functioning of B/T cell [defect causes SCID]
IL 11 → ↑ Platelets

IL 3 → Haematopoietic precurssor cell proliferatⁿ
IL 10 → Anti Inflammatory action

→ INTERFERONS [IFN]

		SOURCE	ACTION	CLINICAL USE
IFN α	→	Leucocytes	→ Anti viral	→ virus R_4
IFN β	→	Fibroblast	→ Immuno modulatory	→ Multiple Sclerosis
IFN γ	→	T cells	→ macrophage activatⁿ	→ Chr. granulomatus DS.

CHEMICAL MEDIATORS IN PLASMA : KININ SYSTEM

→ INJURY TO BLOOD VESSEL

XII ⟶ XII a

PRE-KALLIKREIN ⟶ KALLIKREIN
↓
KININOGEN ⟶ BRADYKININ
↳ ↑ venular permeability [most imp]
↳ Pain
↳ vasodilatⁿ
↳ Bronchospasm

BRADYKININ ⟶ (Kininase / ACE) ⟶ METABOLITE

Angiotensin I ⟶ Angiotensin II
↳ ↑ BP

→ ACE INHIBITOR [↑ Bradykinin]
  ↳ ↓ BP
  ↳ SIE → Dry cough
  → Angio edema

COMPLEMENT SYSTEM

→ group of > 20 proteins
→ responsible for IMMUNITY
→ regulates normal functions of body

→ SUB UNITS

$C_3 \leftrightarrows C_{3a}, C_{3b}$

$C_5 \leftrightarrows C_{5a}, C_{5b}$

→ CLASSICAL PATHWAY

Ag - Ab [Ig M/G]

$C_1 \longrightarrow$ Activated C_1

↓

$C_4/C_2 \longrightarrow C_{4b2a}$

↓

C_3 Break Down → C_{3a}, C_{3b}

→ ALTERNATE PATHWAY

Endotoxin, Ig A } C_3 + factor B } C_{3bBb}

C_{3bBb} → C_3 Breakdown

C_5 Breakdown → C_{5a}

$C_{5b} + C_6/C_7/C_8/C_9$ → C_{5b6789} / C_{5b-9} complex

→ C_{5b-9} complex [MAC]

↳ MAC → Membrane Attack Complex
↳ causes Antigen destruction [main function of MAC]

→ Normal ⟶ ↓ Infections

DEFICIENCY	DISEASES
C_1 / C_2 / C_4 [Early proteins]	↑ Autoimmune disorders [SLE]
C_3	Severe pyogenic infections
C_5 / C_6 / C_7 / C_8 [Late proteins]	↑ Neisseria infection ↑ Toxoplasmosis
C_9	NO DISEASE

→ REGULATORY C PROTEINS

1. C_1 INHIBITOR [Blocks the activation of C1]

C_1 ⟶ Activated C_1 ⟶⊕ © SYSTEM

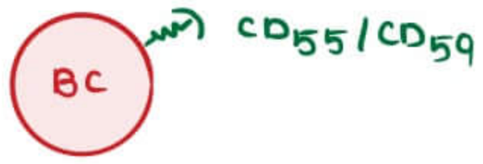
→ C_1 Inhibitor Deficiency

↑↑↑ © Activation
↓
Release of C_{3a} / C_{5a}
↓
HERLDITARY ANGIOEDEMA
↳ F >>t.me/latestpgnotes
↳ Edema [Oral [mc] / Larynx / GIT] [Emergency]
↳ Non pitting edema

2. CD_{46} / factor B / factor H

→ controls Alternate pathway
→ defect → +++ © system
↓
Endothelial cell damage
↓
ATYPICAL HEMOLYTIC UREMIC SYNDROME

3. CD_{55} / CD_{59}



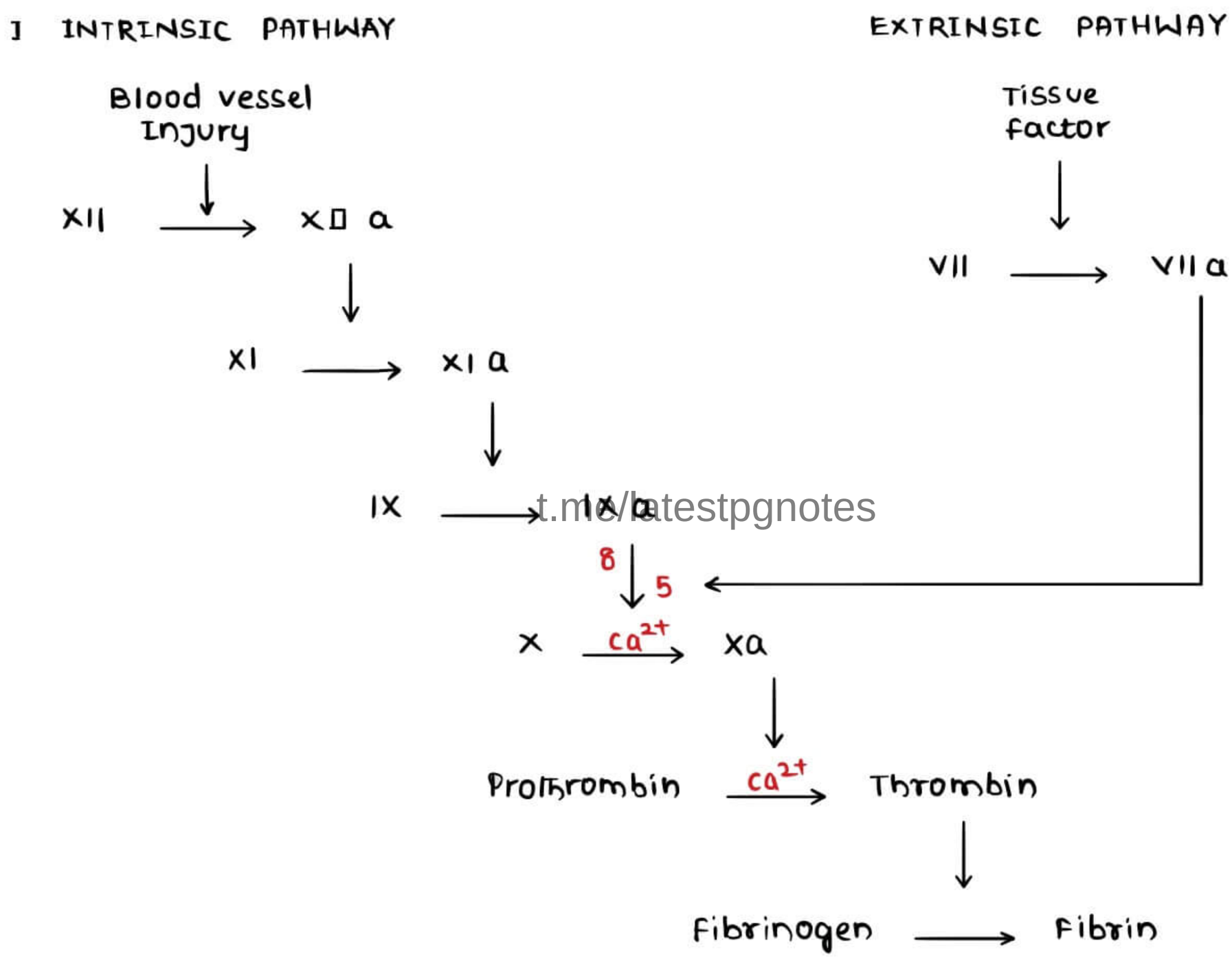
→ present on normal blood cell
→ Defect → ↓ RBC / WBC / Platelets
↓
Pancytopenia → PNH [Paroxysmal Nocturnal Hemoglobinuria]

→ C_{3a} ⟶ Anaphylotoxin
C_{3b} ⟶ Opsonisation

⟶ Anaphylotoxin
C_{5a}
⟶ Chemotoxis

C_{5b} ⟶ MAC [C_{5b-9}] ⟶ Antigenic destruction

COAGULATION CASCADE



→ FIBRINOGEN ⟶ FIBRIN
[Soluble] [Insoluble]

→ FIBRINOGEN
→ plasma protein
→ also required for Opsonisation

→ FIBRIN
→ plasma protein
→ required for chemotaxsis

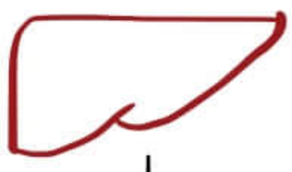
→ HEMOPHILIA
  → ↑ Bleeding
  → A ⟶ factor 8 Deficiency
    B ⟶ factor 9 Deficiency
    C ⟶ factor 11 Deficiency

→ PROTHROMBIN TIME [PT]
→ aPTT [ACTIVATED PARTIAL THROMBOPLASTIN TIME]

PERMORED
↳ using Platelet free plasma
↳ at room temp.
↳ within 2 hrs
↳ Additives added
  → For PT → Tissue Thromboplastin
  → For aPTT → Kaolin / Silica

↳ Plastic tube / Syringes used

PT	aPTT
↓	↓
monitors	monitors
Extrinsic	Intrinsic
Pathway	Pathway

→  Exception → IV

↓
Vit. K required
for ACTIVATION
↓
γ carboxylatⁿ of
Glutamate

↳ Vit K dependent clotting factors → 2 | 7 | 9 | 10
↳ Vit K dependent anticlotting factors → Protein c/s

→ Ca^{2+}
  → co-factor for clotting
  → ↓ Ca^{2+} ⟶ ↓ clotting
  → used in
    1. Blood Banks
      * ACD → Acid citrate Dextrose
      * CPD - A → citrate PO_4 Dextrose - Adenine
      * SAGM → Saline Adenine Glucose mannitol [⊕ cit./PO_4]

↳ citrate → ↓ Ca^{2+} → ↓ clotting

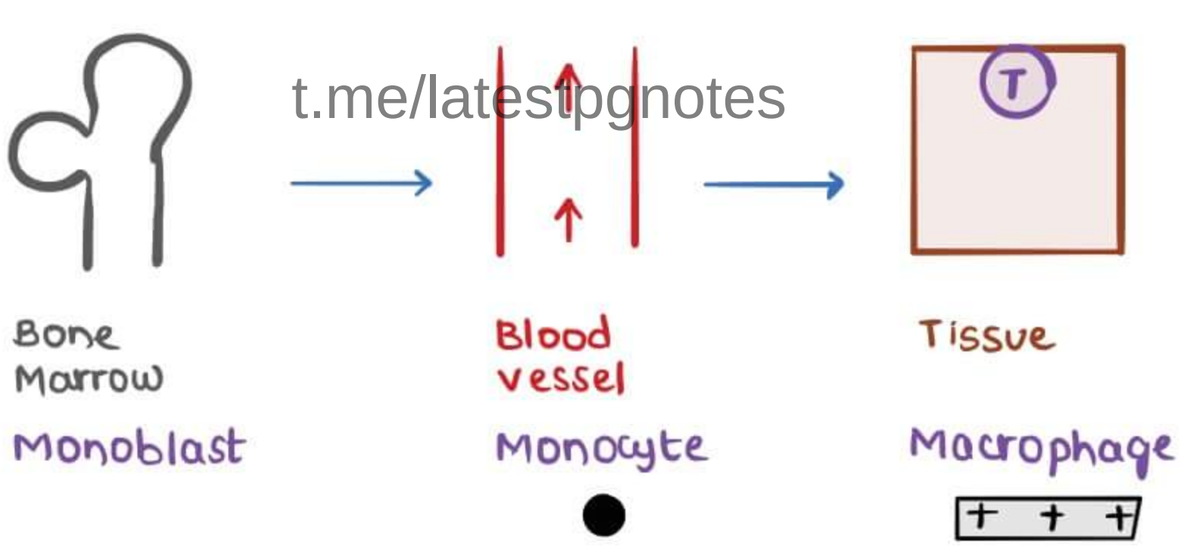
↳ SHELF LIFE
- → ACD → 21 days [3 weeks]
- → CPD - A → 35 days [5 weeks]
- → SAGM → 42 days [6 weeks]

CHRONIC INFLAMMATION

→ ongoing inflammation
→ a/w tissue destruction → Hallmark feature
→ a/w Repair or Healing

→ Longer Duration → NEUTROPHILS
↓
Mono Nuclear WBC [monocyte / Lymphocyte]
CHEMOKINES
1. α → IL 8 → attack Neutrophils
2. β → MCP / EOTAXIN → attract monocytes & Eosinophils
3. r → LYMPHOTAXIN → attract Lymphocytes

→ In Acute inflammation → α chemokines predominate
In Chronic inflammation → β & r chemokines predominate



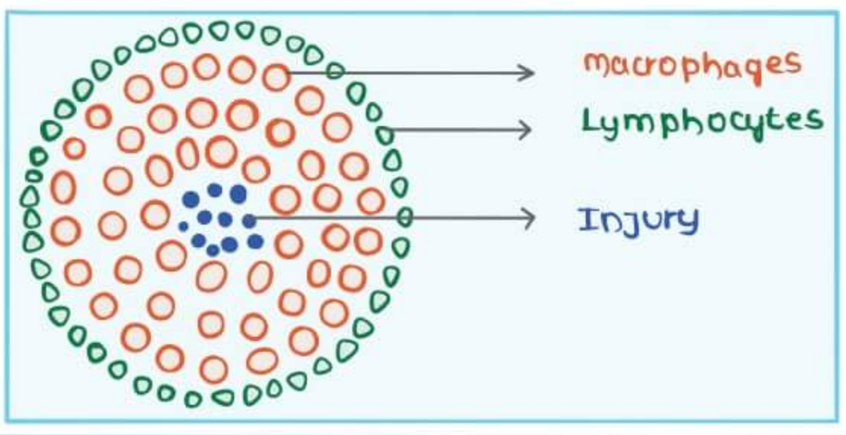
LIFE SPAN

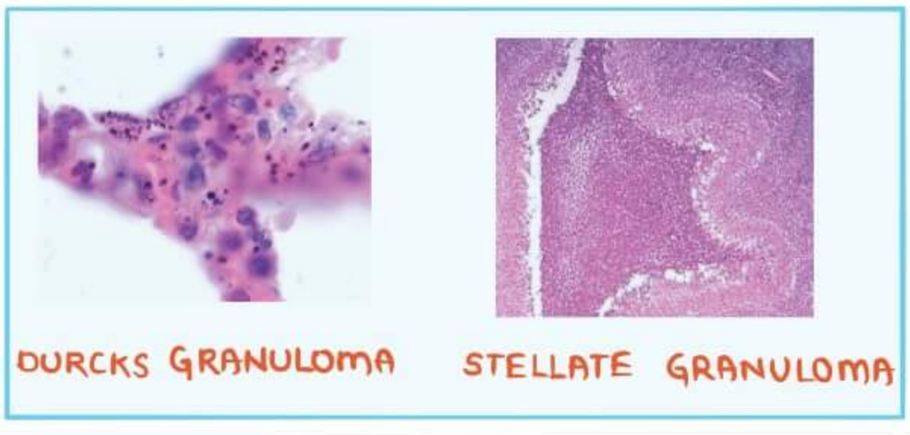
MACROPHAGE NAMES IN DIFFERENT SITES

1. Kidney → Mesangial cell
2. Liver → Kupffer cell
3. Brain → Microglia
4. Bone → Osteoclast
5. Spleen → Littoral cell
6. Placenta → Hoffbauer cell

GRANULOMATOUS INFLAMMATION

GRANULOMA





→ SEEN IN

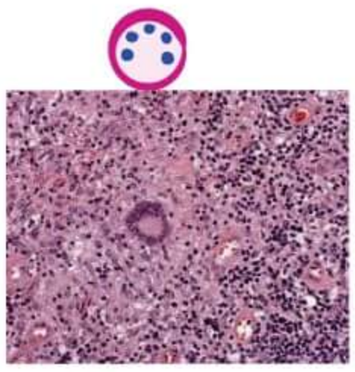
- ↳ TB → CASEATING GRANULOMA
- ↳ Sarcoidosis → NON - CASEATING GRANULOMA
- ↳ Syphilis → GUMMA
- ↳ malaria → DURCK GRANULOMA
- ↳ cat scratch disease → STELLATE GRANULOMA
- ↳ IBD
  - → crohn's disease → Granuloma ⊕
  - → ulcerative colitis → No Granuloma
- ↳ GRANULOMATOUS VASCULITIS
  - → Temporal Arteritis
  - → Takayasu Arteritis
  - → Churg Strauss Syndrome
  - → Granulomatosis ī polyangitis

→ EPITHELOID CELLS [ACTIVATED MACROPHAGES]

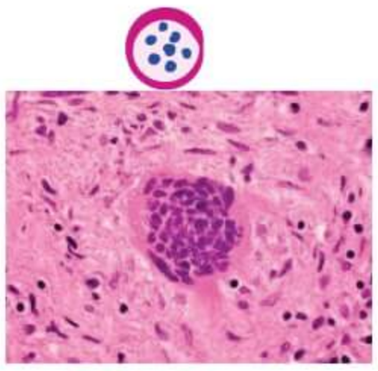
- ↳ derivative of macrophages
- ↳ do not line the body cavities
- ↳ present inside the granuloma
- ↳ have SLIPPER SHAPED NUCLEUS
- ↳ Secretory in function
- ↳ Fused to form 'GIANT CELL'

→ GIANT CELL - SUB TYPES

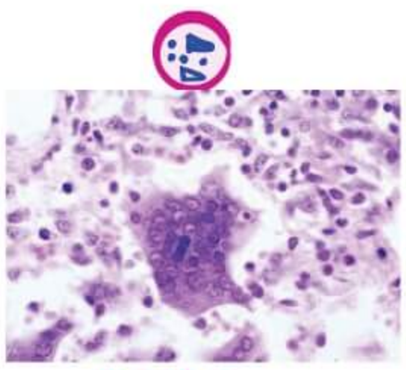
1.	LANGHANS GIANT CELLS	→ Seen in TB → LANGERHANS CELL → Normal
2.	FOREIGN BODY GC	→ Seen ī sutures & talc
3.	WARTHIN - FINKELDEY GC	→ Seen in measles
4.	REED - STERNBERG CELL/ TUMOR GIANT CELL	→ OWL - EYE APPEARANCE → Seen in Hodgkin's Lymphoma
5.	TOUTON CELLS	→ Fat droplets ⊕ → Seen in Xanthoma



LANGHAN CELL



FBGC



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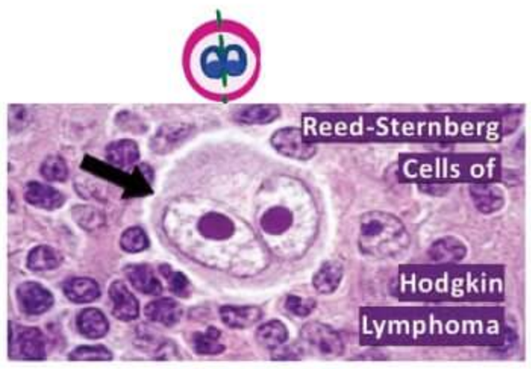
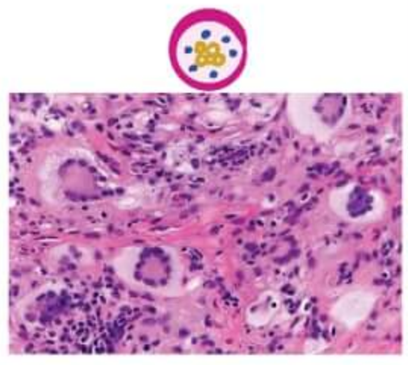


RS CELL



TOUTON CELL

→ GIANT CELLS PER SE ARE NOT DIAGNOSTIC

WOUND HEALING

DAY		
0	→	Blood clot
1	→	Blood clot + Neutrophilic infiltratⁿ
2	→	Day 1 + Thin Epithelial layer
3	→	Granulation tissue ↳ macrophages ⊕ ↳ Fibrous tissues ⊕ ↳ Angiogenesis
4|5	→	GT + collagen depositⁿ [Type III]
14	→	↑↑ collagen + Fibrous tissue

→ maximum angiogenesis seen at → DAY 5

→ COLLAGEN REMODELING
- ↳ 3-4 wks collagen III replaced by collagen 1
- ↳ dlt MMP [Matrix metallo Proteinases (zn)]

SUB TYPES

PRIMARY UNION
→ Seen in SHARP OBJECT INJURY

SECONDARY UNION
→ Seen in BLUNT OBJECT INJURY
→ more chance of SCAR FORMATION

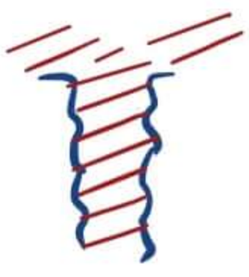
FIBROBLAST ⟶ MYO FIBROBLAST
- → has the contractⁿ ability
- → ↓ SIZE OF SCAR
  - ↳ scar contractⁿ/
  - ↳ wound contractⁿ

DELAYED WOUND HEALING

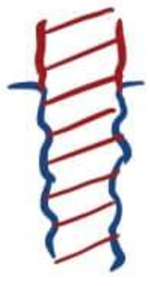
LOCAL FACTORS	SYSTEMIC FACTORS
→ foreign body	→ ↓ Immunity
→ persistent infections	→ DM
→ Radiation	→ DRUGS [Steroids]

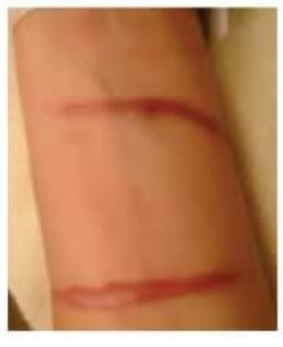
EXCESSIVE / ABNORMAL HEALING

KELOID



HYPERTROPHIC SCAR





→ more common in AFRO AMERICANS [genetic predisposition]
→ STEROIDS → causes ↓ fibroblast proliferatⁿ → ↓ SCAR SIZE

IMMUNITY 1
INTRODUCTION

IMMUNITY

INNATE IMMUNITY	ADAPTIVE IMMUNITY
→ non specific	→ Specific
→ no memory	→ memory ⊕

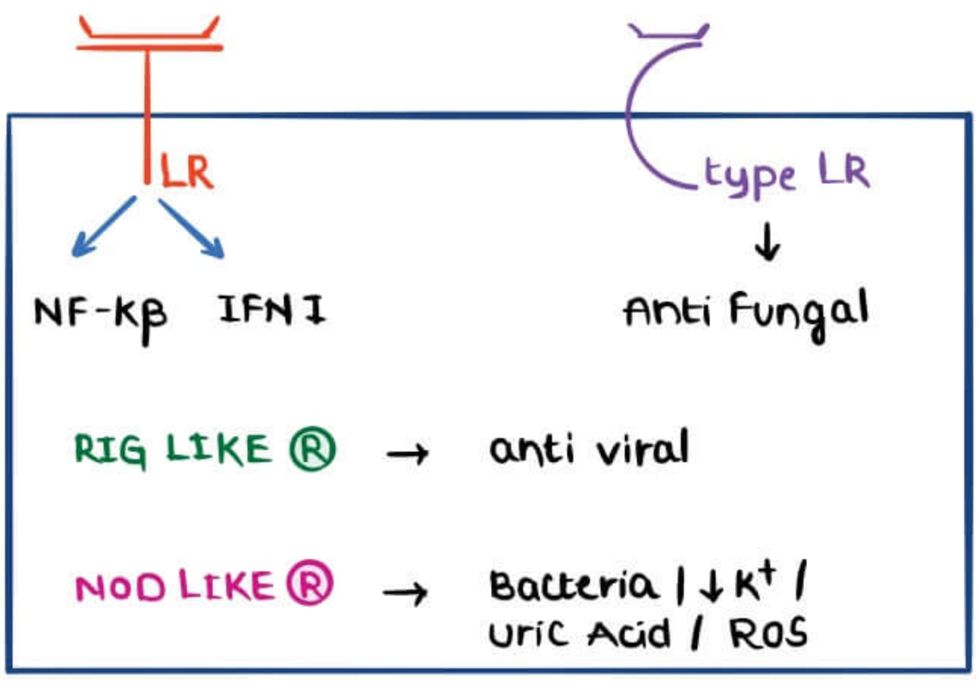
INNATE IMMUNITY

1. BARRIERS
   - → Anatomical [skin]
   - → Physiological [secretions]
2. PROTEINS
   - → C-RP
   - → Lectin
   - → Complement proteins
   - → Surfactants
3. CELLS
   - → Neutrophils
   - → macrophages
   - → NK cell
     - ↦ Kills virus infected cells
     - ↦ Kills tumor cells

BACTERIA	→	PAMP [Pathogen Associated Molecular Patterns]
INFLAMMATION	→	DAMP [Damage Associated Molecular Patterns]

PATTERN RECOGNITION RECEPTORS

- → recognises PAMP & DAMP
- → EXAMPLES



Nuclear factor Kβ
- → activatⁿ leads to more recruitement of WBC

IFN - 1 → Anti viral

- → NOD LIKE RECEPTOR
  - → identifies Bacteria | ↓K+ | Uric Acid | ROS [Reactive O_2 Species]
  - → acts by 'INFLAMMASOME'

INFLAMMASOME

CASPASE 1 ⊕ → IL 1 release → Fever inflammation

ADAPTIVE IMMUNITY

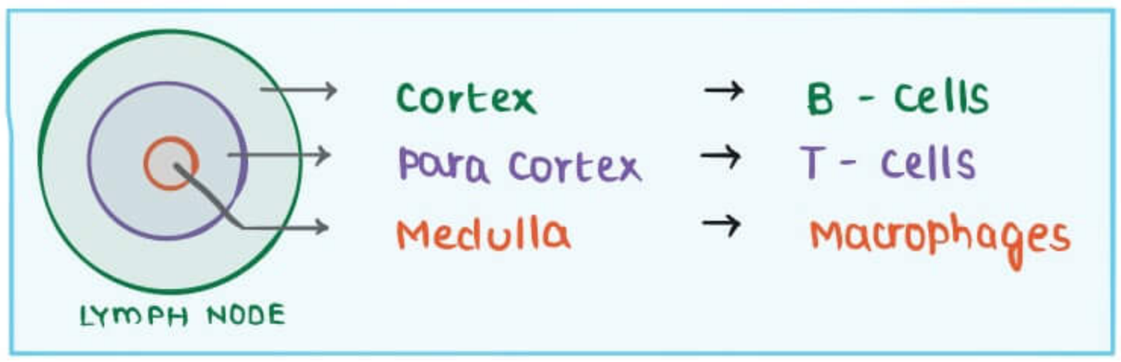
→ Contributed by T cells | B cells

→ B CELLS ⟶ PLASMA CELLS ⟶ Igs ⟶ HUMORAL IMMUNITY
→ T CELLS ⟶ CELLULAR IMMUNITY

→ HUMORAL IMMUNITY → effective against extra cellular microbes
→ CELLULAR IMMUNITY → effective against Intracellular microbes

B CELLS

→ Located in LN, Spleen, git, Tonsils



→ GIT → mucosal Tissue
↓
MALT
↓
PEYER PATCHES
↓
Ileum

Enteric fever
↓
ulceration of
Peyer patches

B CELL MARKERS

→ CD 19 | 20 | 21 | 22 | 23

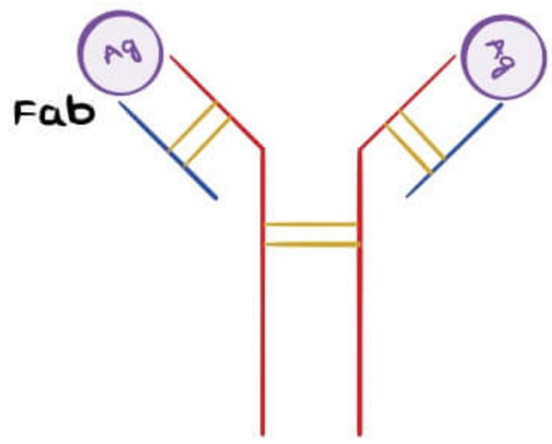
→ CD 40 | $\frac{\text{CD 80}}{\text{CD 86}}$

→ CD 19 → Pan B marker
→ CD 20 → Ⓡ for EBV

→ CD 40
↳ binds ī CD 40 - Ligand on T cells
↳ responsible for B ⟷ T cell interaction
↳ helps in quality antibody formation

→ $\frac{\text{CD 80}}{\text{CD 86}}$
↳ aka B7
↳ binds ī CD 28
↳ responsible for normal CO-STIMULATORY SIGNAL

B CELL → PLASMA CELL → Ig SECRETION



IMMUNOGLOBULINS [Ig]

→ LIGHT CHAINS → κ , λ
→ HEAVY CHAINS → γ , α , μ , δ , ε

IMMUNOGLOBULIN CLASSES [Based on heavy chains]

1. Ig G

→ Concentration in body → maximum
→ Cross placenta
→ Complement activation
→ Cell tastier [opsonigation]

2. Ig A

→ Forms
  a. Monomer [serum]
  b. Dimer [Secretions & mucosa] [two monomers joined by 'J']

→ FIRST LINE OF DEFENCE
→ activates ALTERNATE © PATHWAY

G	→	max. concentrat^{n}
A		
M		
D		
E	→	lowest concentrat^{n}

3. Ig M

→ Maximum size
→ maximum molecular weight
→ PENTAMERIC [mostly]
→ MILLIONAIRE ANTIBODY
→ component of PRIMARY IMMUNE RESPONSE [predominant component]
→ MONOMERIC FORM as B-CELL ®

4. Ig D → acts as B-cell ®

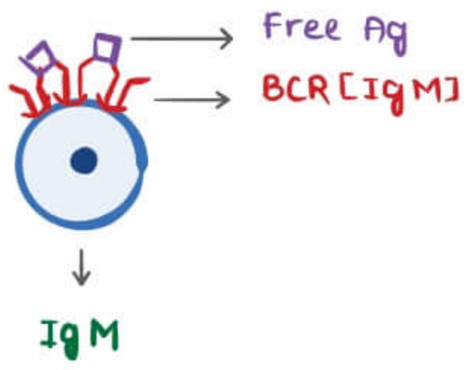
5. Ig E

→ LOWEST CONCENTRATION
→ attached on surface of MAST CELLS → Type 1 HSR
→ Heat labile antibody

TYPES OF ANTIGENS

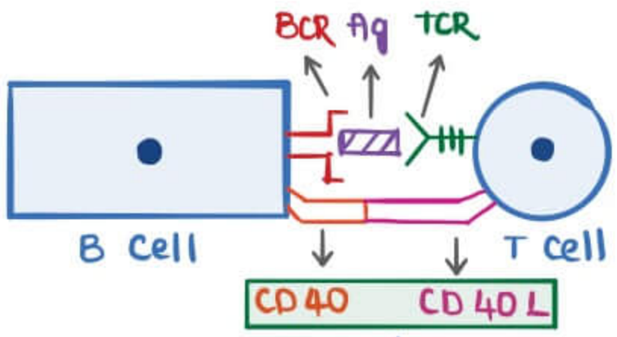
1. NON PROTEINACEOUS ANTIGENS

→ FREE ANTIGENS
  ↳ do not require support of any additional cells
  ↳ aka THYMIC / T CELL INDEPENDENT ANTIGENS
  ↳ interaction leads to Ig M production



2. PROTEINACEOUS ANTIGENS / T-CELL DEPENDENT ANTIGENS

→ requires the support of T-CELLS for proper activat^{n} of immune system



IL-4 / IL-5

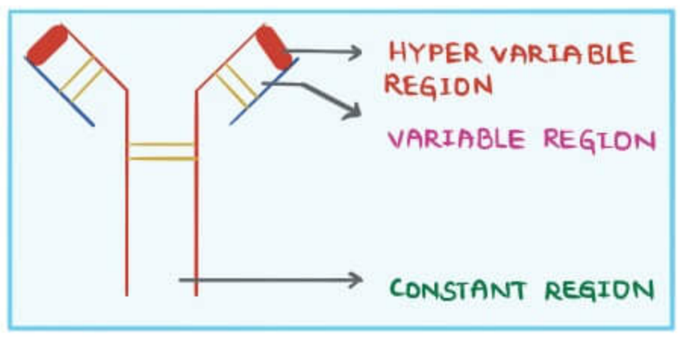
Ig M → Ig G/A/E → ISOTYPE / CLASS SWITCHING

ISOTYPE / CLASS SWITCHING

↳ Occurs d/t interactⁿ b/w CD 40 & CD 40 Ligand

↳ responsible for

* SOMATIC HYPERMUTATION
* AFFINITY MATURATION



ISOTYPE → Different classes of Antibodies in same person

ALLOTYPE → Difference in Antibody taken from 2 different people

IDIOTYPE → variable part of Antibody different in same person

T CELL

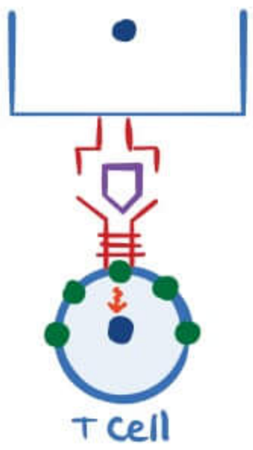
→ formed in Thymus

→ present at

↳ LN → Para cortex [PC]

↳ Spleen → Peri arteriolar Lymphoid sheath [PALS]

↳ GIT → Intra Epithelial lymphocytes [IELs]



APC [Ag Presenting cell]

TCR

CD [cluster Differentiating] Molecules

→ T Cell get activated by pre bound antigens, T Cells NEVER activated BY FREE ANTIGENS

→ CD MOLECULES USEFUL IN IDENIFICATION OF CERTAIN CELLS

↳ CD 1/2/3/4/5/7/8 → T cell markers

↳ CD 28 → CO stimulatory molecule

↳ CD 40 L → ī CD 40 → maintains proper quality of Ab

↳ CD 3

→ Pan T cell marker

→ Significant in signal transductⁿ mechanism

→ activatⁿ of T-cell assisted by Calcineurin & IL-2

T CELLS

CD4 T CELLS
[Helper]

CD8 T CELLS
[cytoToxic]

TH_1 → Type IV HR [IL2/IFN r]
TH_2 → Type I HR [IL4/5]
TH_{17} → IL 17
↳ Anti fungal
↳ Auto immune disorders

NK CELLS

LYMPHOCYTES

HSC → LYMPHOID STEM CELL

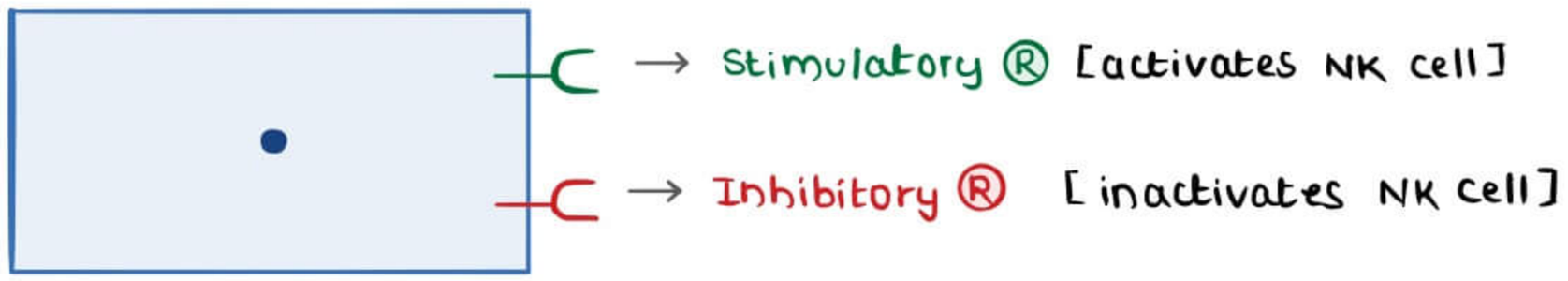
- T CELL [Thymus]
- B CELLS [Bone marrow]
- NKC [Natural Killer cells]

→ NK cells → Component of INNATE IMMUNITY
→ T & B cells → components of ADAPTIVE IMMUNITY

NK CELLS

→ Ex. of INNATE LYMPHOID CELLS [ILCs]
↳ no TCR
↳ Secretes cytokines like T cells

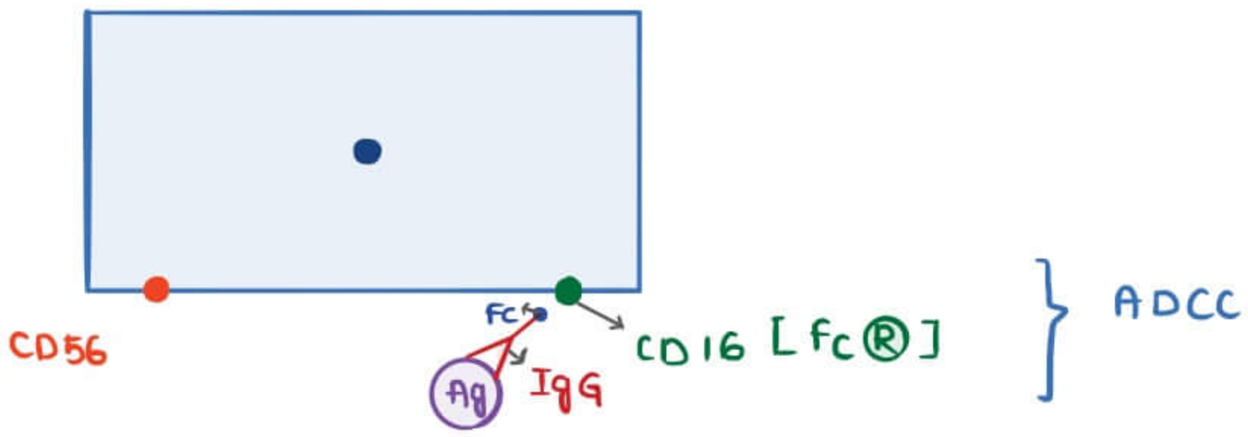
→ earlier known as LARGE GRANULAR LYMPHOCYTES [LGL]
→ Kills Virus infected cells & tumor cells



→ almost all Normal cells have MHC - I expression
→ MHC - I interacts ī Inhibitory ® → NK cells inactivated

→ In case of Virus infected cells / mutated [tumor] cells,
↳ ↓ expression of MHC I [virus infected cells] (or)
↳ ↑ expression of molecules overstimulating the Stimulatory ® [tumor cells]

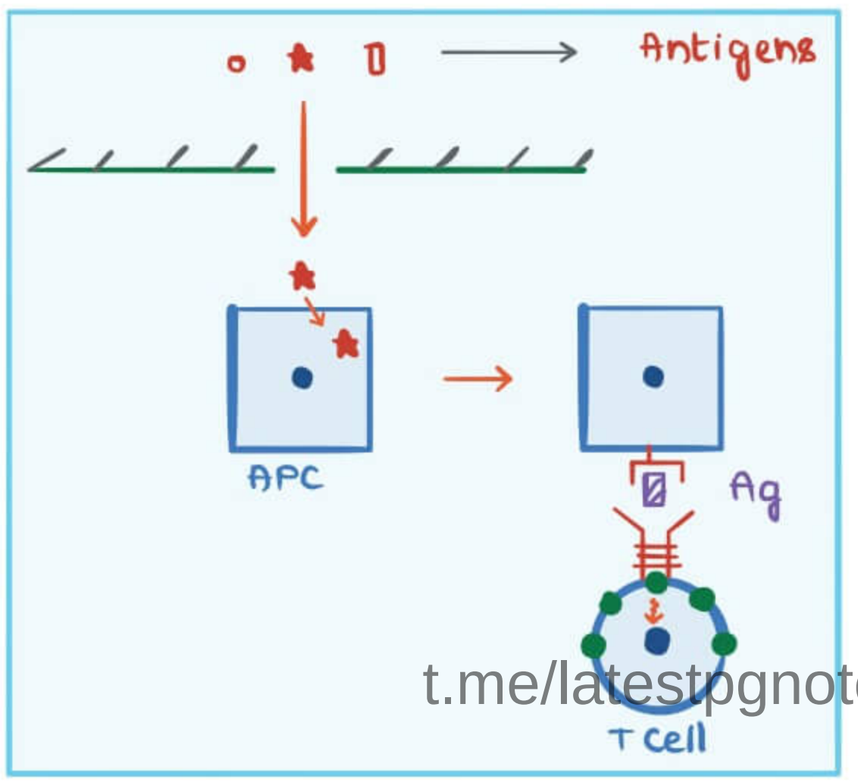
↳ both mechanisms activate NK cells & get destroyed



→ Fc of IgG + CD_{16} [F_c®] → activates NK cells → ADCC
→ ADCC → Antibody dependent cell mediated cytotoxicity

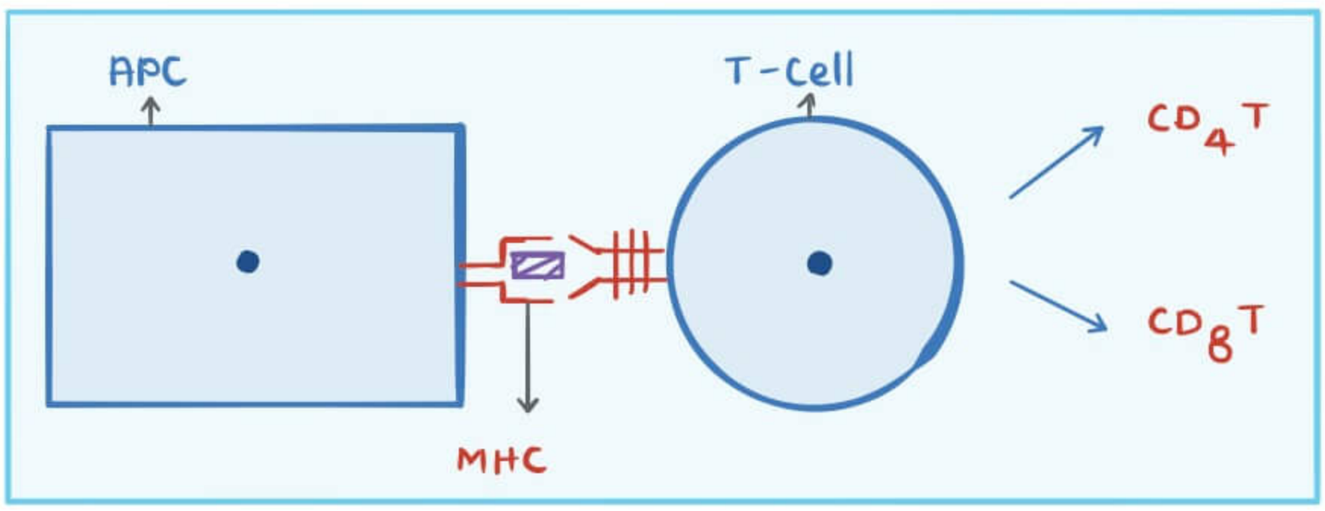
IMMUNE SYSTEM ACTIVATION

BASIC CONCEPTS



1. Entry of pathogen inside the body
2. Phagocytosis of pathogen by APC
3. Expression of Ag on the surface of APC & movement into circulation
4. T cell comes in contact ī Antigenic peptide presented by APC & T cell activation
5. T cell activation leads to production of
   a. EFFECTOR T - CELLS → deals ī present infection
   b. MEMORY T - CELLS → deals ī later infections

ANTIGEN PRESENTING CELLS [APCs]



→ MHC FUNCTIONS

↳ Let pathogenic Ag be expressed on Surface OF APC

↳ decision of activation of Sub types of T cells done based on MHC

→ MHC I → always activates CD_8 T cells

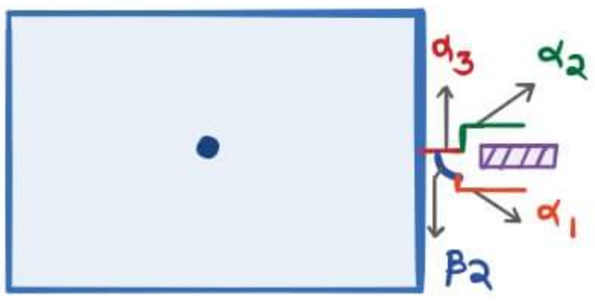
→ MHC II → always activates CD_4 T cells

→ CD_8 T cells are MHC I restricted cells

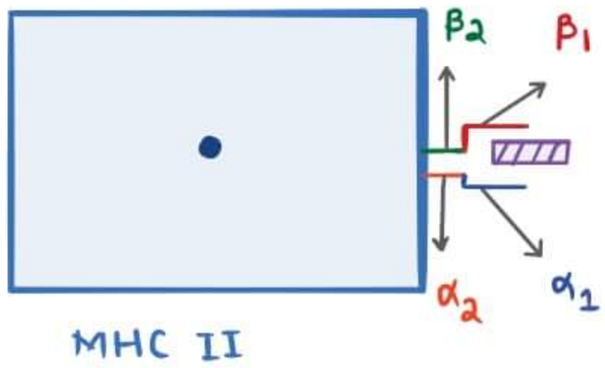
→ CD_4 T cells are MHC II restricted cells

→ NK cells are MHC Unrestricted cells

→ STRUCTURE OF MHC



MHC I



MHC II

→ ANTIGEN BINDING CLEFT

↳ part of MHC molecule, Where Ag binds

↳ on MHC I, ABC made up of → α_1 & α_2 chains [distal α chains]

↳ on MHC II, ABC made up of → α_1 & β_1 chains [distal α & β chains]

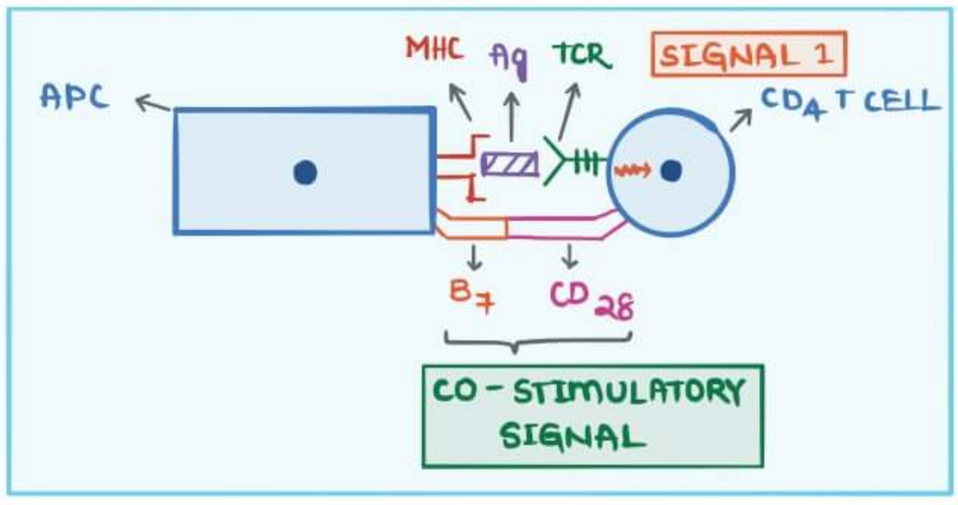
→ TYPES OF APC s

1. PROFESSIONAL APCs [+++ MHC]
   a. Dendritic cells
      skin & interstitial tissue → LANGERHANS CELL [most important]
      Lymphnode & spleen → FOLLICULAR DENDRITIC CELLS
      [acts as reservoir for HIV]
   b. B - cells
   c. Macrophages
2. NON PROFESSIONAL APCs [+ MHC]
   a. Fibroblasts
   b. Endothelial cells
   c. Thymic epithelial cells

ACTIVATION / INHIBITION OF T - CELLS

Ag ⟶ APC ⟶ Surface

CO - STIMULATORY SIGNAL IS MANDATORY FOR THE ACTIVATION OF T CELLS



→ EXTERNAL AG
  ↳ provides Signal 1 & costimulatory signal → T-CELLS ACTIVATED

→ SELF AG
  ↳ provides Signal 1 & no co-stimulatory signal → T-CELL ANERGY

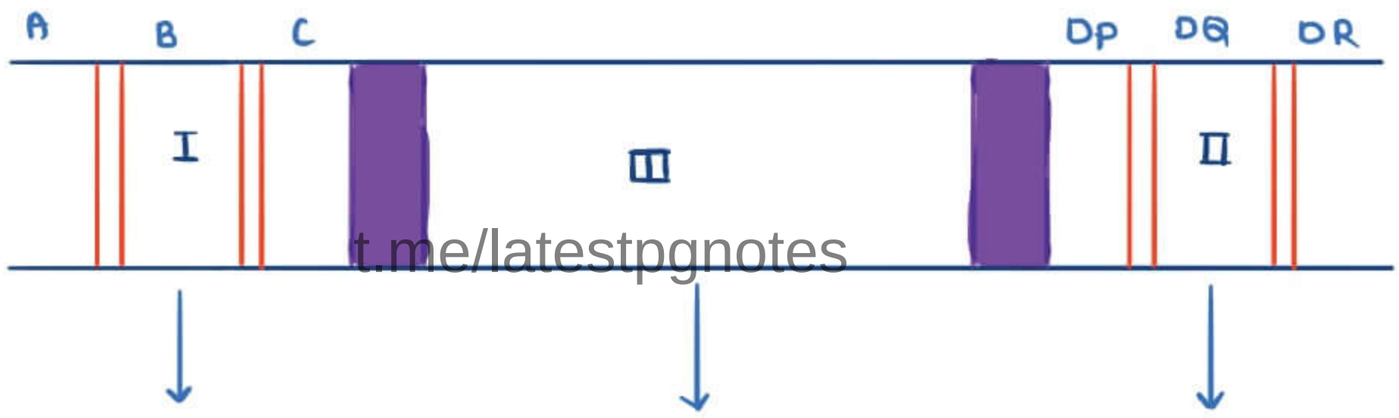
→ T-CELL ANERGY
  → NON ACTIVATⁿ OF T cell in the presence of SELF Ag
  → helps in prevention of Auto immune disorders

→ CO-STIMULATORY SIGNALS
  ↳ CD 28 interactⁿ → T cell activation [a/w external Ag]
  ↳ CTLA 4 / PD 1 interactⁿ → T cell inhibition [a/w Self Ag]

MAJOR HISTOCOMPATIBILITY COMPLEX [MHC]

→ aka HLA [Human Leukocyte Antigen] COMPLEX [discovered on Leukocytes]
→ these gene are located on CHROMOSOME 6p

CHROMOSOME 6p (short arm)



CODES FOR	MHC I	C_2 / C_4 / Ⓟ TNF α 21 α OHase	MHC II
PRESENT ON	All nucleated cells Platelets		All APCs [Prof. APCs [Non-prof. APCs]
ACTIVATES	CD 8 T-cells		CD 4 T cells
DETECTED BY	ALLO ANTISERUM		MIXED LEUKOCYTE REACTⁿ

USES OF MHCs

1. GENETIC ASSOCIATION OF DISEASE
   ↳ HLA-DR 3 / DR 4 → TYPE 1 DM
   ↳ HLA-B 27 → Ankylosing Spondiolytis

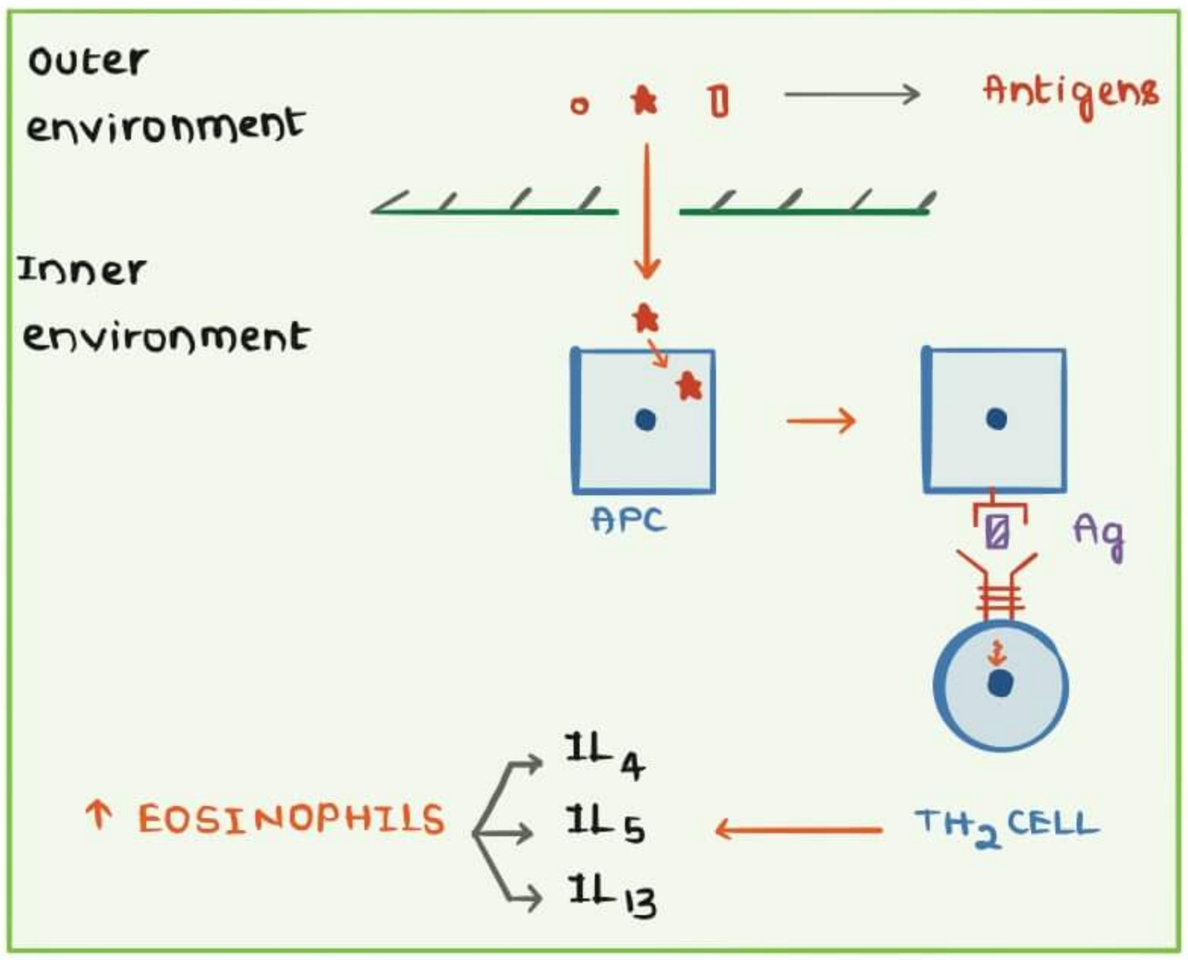
2. ORGAN TRANSPLANTATION
   ↳ HLA matching / gene matching done by TISSUE TYPING
   ↳ done ī
      → mixed Leukocyte Reactⁿ
      → micro cytotoxicity Assay

3. PATERNITY DISPUTES

TYPE 1 HYPERSENSITIVITY REACTION

→ aka ANAPHYLACTIC / IMMEDIATE HR

PATHOGENESIS



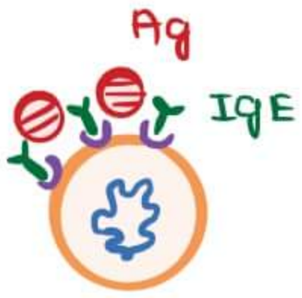
EOSINOPHILIA SEEN IN
- → Allergy
- → parasitic infection
- → Hodgkin's lymphoma
- → Type 1 HR

FIRST EXPOSURE

IL5 ⟶ IgE

STAGE OF SENSITIZATN / PRIMING
[NO symptoms]

2nd or REPEAT EXPOSURE



→ Release of CHEMICALS
- Pre formed → Histamine
- Freshly formed
  - ↑ AA → LTs / PGs
  - ↑ cytokins → IL-1 / TNF / IL4/5/13

- → Histamines, PGs } vasodilatn
- → Histamines, LTs } Bronchospasm
- → Histamines → Itching
  cytokines → ↑ inflammation

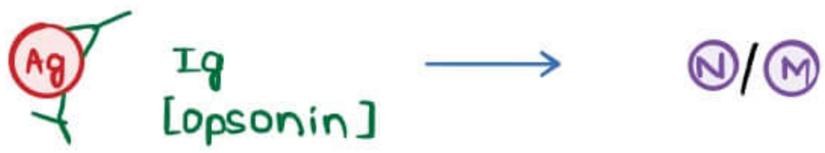
CLASSICAL EXAMPLE → BRONCHIAL ASTHMA
- → cause of Attack
  - ↳ in India → Dust particles
  - ↳ in western countries → Pollen grains

TYPE II HYPERSENSITIVITY / CYTOLYTIC HR

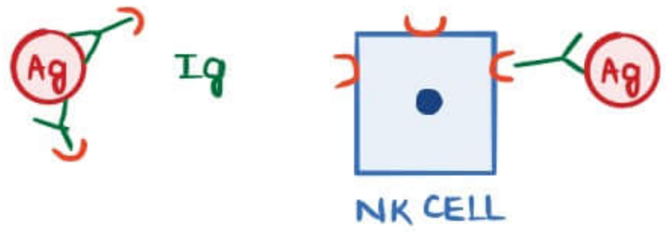
MECHANISMS

A. OPSONISATION & PHAGOCYTOSIS

1. Direct Antibody mediated Opsonisat^{n}

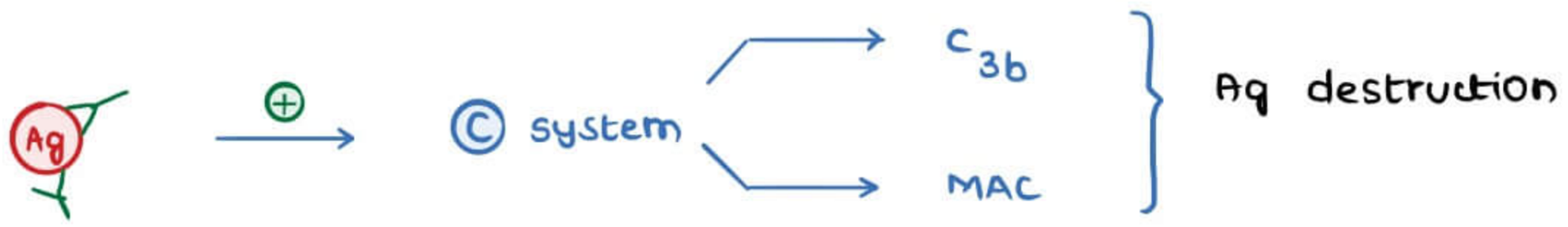


2. ADCC [Antibody Dependent cell mediated cytotoxicity]



ADCC [Antibody Dependent cell mediated cytotoxicity]

3. Via complement activation



EXAMPLES

- → RH INCOMPATIBILITY
- → BLOOD TRANSFUSION REACTION
- → AUTO IMMUNE HEMOLYTIC ANEMIA
- → AUTO IMMUNE THRDMBOCYTOPENIA
- → AUTO IMMUNE LEUCOPENIA

B. COMPLEMENT ACTIVATION & INDUCTION OF INFLAMMATION

Ag + Ab formation

C System Activation

↓

C_{5a} → ↑ N/M → CHEMICALS → TISSUE DAMAGE

EXAMPLES

- → ACUTE RHEUMATIC FEVER
- → GOODPASTURE SYNDROME
- → ANCA - mediated VASCULITIS

SORE THROAT

↓

Streptococcus pyogenes

↓

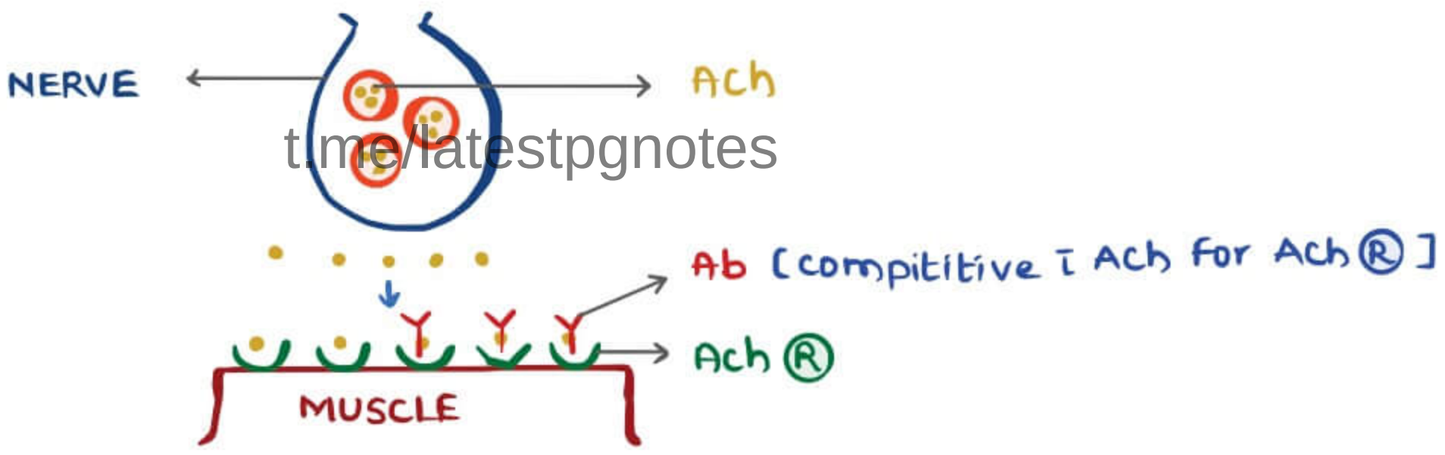
Ab formatⁿ → 'M' protein ≅ TISSUE GLYCOPROTEINS of } MOLECULAR MIMICRY

- heart
- Joints
- CNS
- Skin

C. Ab INDUCED TISSUE DYSFUNCTION

EXAMPLES

→ MYASTHENIA GRAVIS
→ GRAVES DISEASE
→ PERNICIOUS ANEMIA
→ INSULIN RESISTANT DIABETES



MYASTHENIA GRAVIS ↓ Muscle weakness

→ TYPE 2 HR takes place by
A. Opsonisatⁿ & phagocytosis
B. Inflammation
C. Antibody induced Tissue dysfunction

→ EXAMPLES

My	→	Myasthenia gravis
Blood	→	Blood transfusion Reactions
Group	→	Good pasture syndrome ; Graves disease
IS	→	Immune Hemolytic Anemia ; Immune Thrombocytopenia
R	→	Rheumatic Fever
H	→	Hyper acute transplant rejection
Positive	→	Pernicious anemia ; Pemphigus vulgaris

TYPE III HR / IMMUNE COMPLEX DISEASE

10 - 14 DAYS

Ag [mobile] ENTRY

↓

Ab FORMATION [Ig G / Ig M]

↓

PHASE I → Ag - Ab COMPLEX FORMATION

↓

PHASE II → DEPOSITION IN ORGANS

[Lymp nodes / Skin / Kidney / serosa / small Blood vessels]

&

TISSUE DAMAGE

Endothelial damage → Thrombus → ischemia

complement activat^{n} → ↑ inflamat^{n}

↓

PHASE III → CLINICAL MANIFESTATIONS

© Activat^{n} occurs → ↓ Serum C_3 indicates Active Immune complex Disease

EXAMPLES

S → Serum Sickness / SLE

H → Henoch - Schonlein Purpura

A → Arthus Reaction

R → Reactive Arthritis

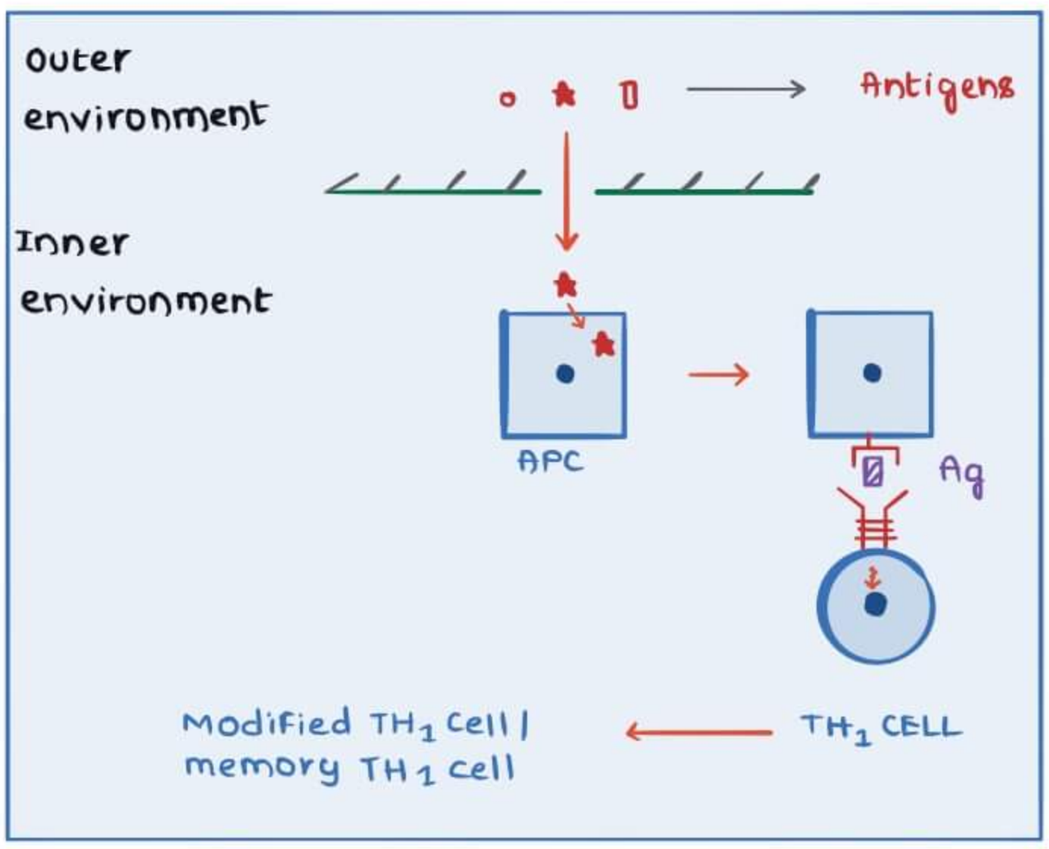
P → Post streptococcal Glomerulonephritis / PAN

TYPE IV HR / CELL MEDIATED HR [do not utilize Ab]

SUB TYPES

1. DELAYED TYPE

1st EXPOSURE



2nd EXPOSURE

Ag + APC

↓

TH_1 CELL ACTIVATION

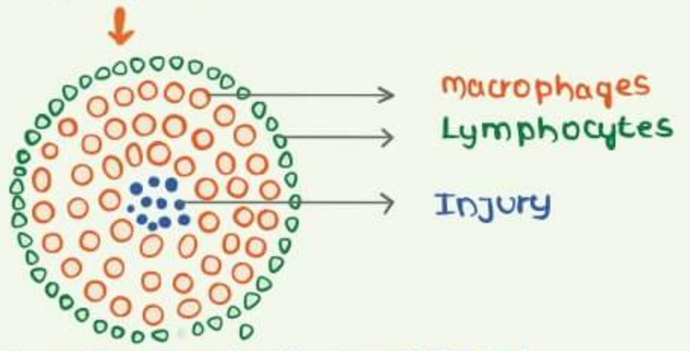
↓

IL 2 / IL 12 [↑ T lymphocytes | monocytes]

IFN γ [macrophage activation]

Lymphotoxin [influx of lymphocytes]

↓



GRANULOMA FORMATION

EXAMPLES

R, A } Rheumatoid Arthritis

m → multiple sclerosis

Chandra → contact dermatitis

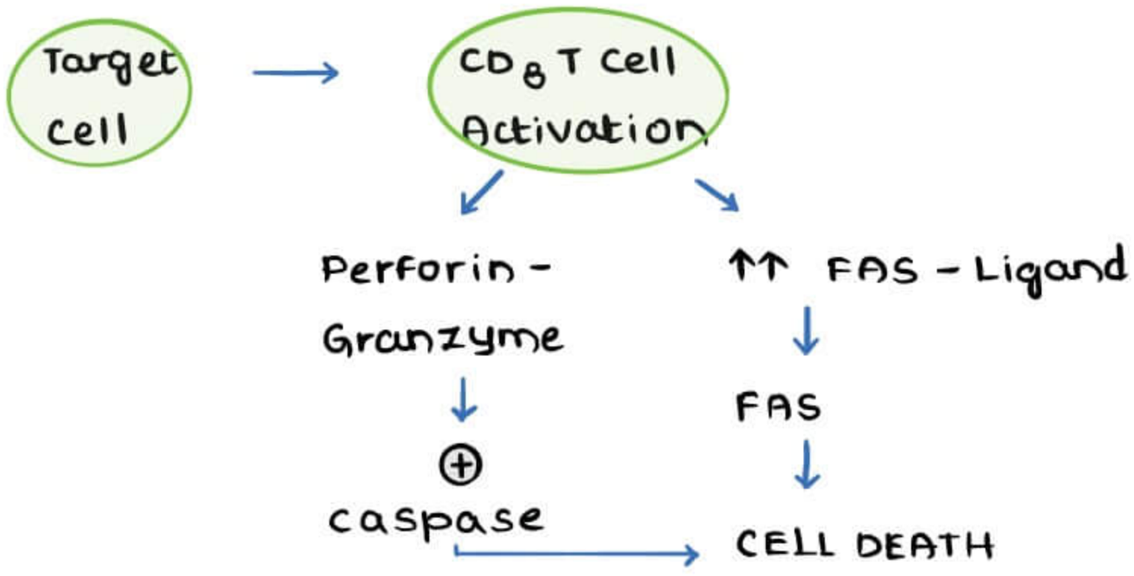
Is → IBD

Psoriatic → Psoriasis

Diabetic & → DM 1

TB → TB → mantoux test

2. MECHANISM OF CD_8 T CELL ACTIVATION



→ CD_8 T - CELLS → virus infected cell / cancer cells
→ Graft Rejection

IMMUNITY 2
TOLERANCE

↓ RESPONSE OF IMMUNE SYSTEM TO ANTIGENS [SELF]

SUB TYPES

1. CENTRAL TOLERANCE
2. PERIPHERAL TOLERANCE

1. CENTRAL TOLERANCE

→ takes place in thymus / Bone marrow

→ Deletion
Negative selection
↓
Self reactive B/T cells

→ T - Cells ⊖ → AIRE Gene → alteration → AUTO IMMUNE POLY ENDOCRINOPATHY
[Auto Immune Regulator Gene]

→ RECEPTOR EDITING → Seen in B cells

2. PERIPHERAL TOLERANCE

a. ANERGY

→ functional hyporesponsiveness

→ mechanisms

Self Ag $\xrightarrow{\oplus}$ $\frac{\text{CTLA-4}}{\text{PD-1}}$

↓ interact^{n} b/w B.7 & CD 28 → T CELL ANERGY
↓ interact^{n} b/w CD 40 & CD 40L → B CELL ANERGY

b. T - REGULATORY CELLS

CD_4 T CELLS → CD 25, foxp 3 gene

→ IL 10 / TGF β secreted
→ + CTLA - 4 & PD - 1

→ plays a role in ACCEPTANCE of FETUS at pregnancy

→ CD 25 Defect → ↑ MULTIPLE SCLEROSIS
→ fox p3 Defect → ↑ IPEX SYNDROME
- I → Immune dysregulat^{n}
- P → Poly endocrinopathy
- E → Enteropathy
- X → X Linked Syndrome

c. APOPTOSIS OF SELF-REACTIVE B/T CELLS

→ dlt ↑FAS – FAS-L

→ Defect → AUTO IMMUNE LYMPHO PROLIFERATIVE SYNDROME [ALPS]

d. ANTIGEN SEQUESTRATION

→ Ag ⟶ IMMUNE PRIVILEGED SITES

B → Brain
E → Eye
T → Testis

→ Trauma in B/E/T → AUTO IMMUNE DISEASE

CENTRAL TOLERANCE	PERIPHERAL TOLERANCE
→ ⊖ Selection [AIRE gene] → ® Editing	→ Anergy → T_{Reg} cells → Deletⁿ → FAS → Immune Priv. Sites

AUTO IMMUNE DISORDERS

ETIOLOGY

1. GENETIC FACTORS

→ FAILURE OF TOLERANCE

→ HLA – GENES DEFECTS → HLA B-27 [Ankylosing Spondylitis]

→ NON HLA GENES DEFECTS

↳ PTPN-22
- → most important
- → Abnormal Lymphocyte activatⁿ & proliferatⁿ
- → DM, RA & others

↳ NOD-2 → IBD [Inflammatory Bowel Disease]

↳ IL-2 ® → ↓ T_{Reg} cells

II. INFECTIONS

→ ↑ co-stimulatory signals [APC]

→ molecular mimicry → Rheumatic fever

→ Polyclonal B cell Activation

Ⓑ Ⓑ Ⓑ Ⓑ —mutation→ AUTO ANTIBODIES

Example → EBV & HIV

→ Spread of cryptic Epitope

→ Infections → ↓ IL-2 → T_{Reg} cells

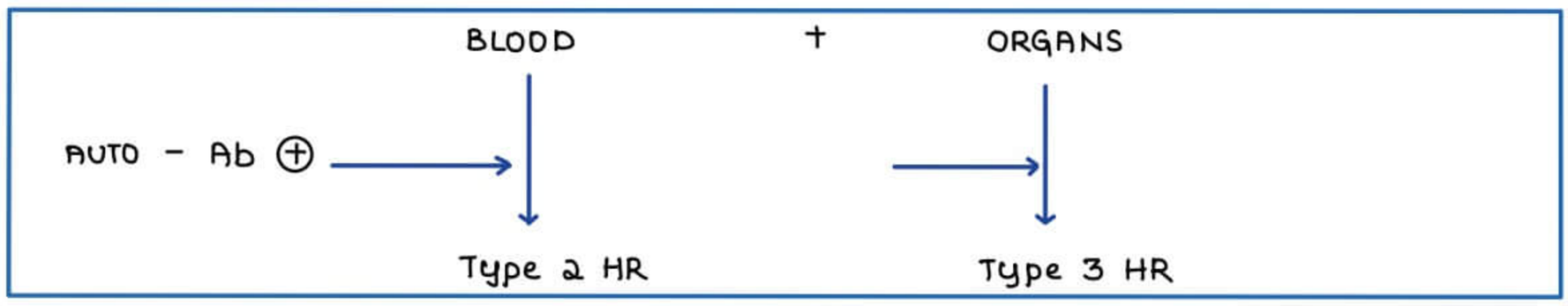
HYGIENE HYPOTHESIS → Disease

III MISCELLANEOUS

1. RELEASE OF SEQUESTERED Ag
2. SUN light [UV]
3. HORMONES [Estrogen | progesterone → ♀]
4. DRUGS
   - ↳ sulfonamide
   - ↳ Hydralazine
   - ↳ Isoniazid
   - ↳ Procainamide

SYSTEMIC LUPUS ERYTHEMATOSIS

MULTI SYSTEM DISORDER



RISK FACTORS

- → ♀ >> ♂
- → Reproductive age > extremes of age
- → HLA - DQ
- → UV Rays
- → Drugs [sulfonamides]
- → Infections → NETs [Neutrophil Extra cellular Traps]
- → Complement Protein [C_1 | C_2 | C_4] Deficiency

CRITERIA [≥ 4 Out of 11 are essential for Diagnosis]

- M → Malar Rash
- D → Discoid Rash
- S → Serositis
- O → Oral ulcers
- A → Arthritis
- P → Photosensitivity
- B → Blood Auto Ab
- R → Renal disorders
- A → ANA [Anti nuclear antibodies]
- I → Immunological defects → Other Ab → Anti DNA | Smith Ab
- N → Neurological manifestations [Epilepsy / psychosis]

- → Oral cavity involvement → Painless ulcers
- → Joints involvements → Non erosive Arthritis
- → Skin involvement → BUTTERFLY RASH
  [↑ in intensity on UV rays exposure]


Butterfly Rash

→ Pulmonary involvement → Pleuritis [more common]

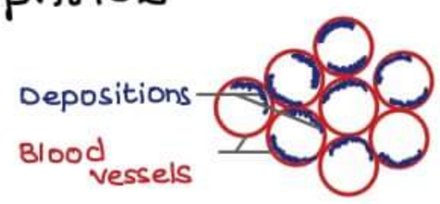
SHRINKING LUNG SYNDROME
[d/t weakness of diaphragm]

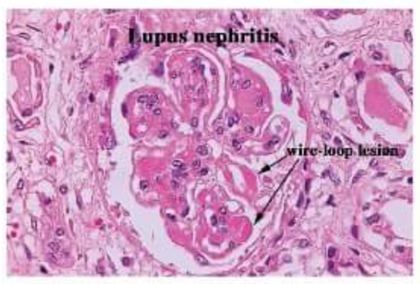
→ KIDNEY INVOLVEMENT

→ Type IV Glomerulonephritis / Diffuse proliferative Glomerulonephritis

→ mc sub type of glomerulonephritis

→ WIRE - LOOP LESIONS seen





→ CARDIAC INVOLVEMENT

→ Pericarditis [more common]

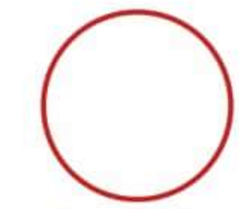
→ Endocarditis → LIBMAN-SACKS ENDOCARDITIS [LSE → SLE]

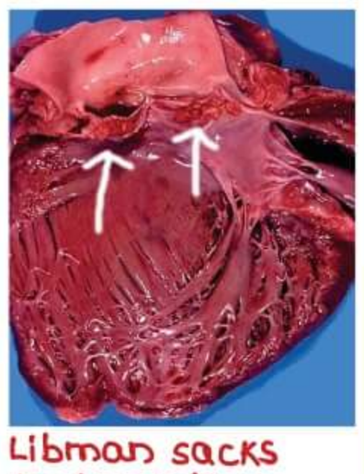
→ Lower Surface of Mitral valve [Endocardium] involved more

→ SPLEEN INVOLVEMENT

→ ONION SKIN APPEARANCE in Blood vessels seen

→ d/t reactions to immune complexes




Libman sacks Endocarditis

AUTO ANTIBODIES

① ANTI NUCLEAR ANTIBODIES → most sensitive Test for Dx

② ANTI SMITH ANTIBODIES } most specific Test for Dx

③ ANTI - dsDNA ANTIBODIES }

④ ANTI - RO ANTIBODY → a/w Neonatal lupus

→ high risk for congenital Heart Block

→ a/w sub acute cutaneous lupus

⑤ ANTI - P ANTIBODY → a/w Psychosis

⑥ ANTI - β_2 Glycoprotein Ab

→ seen in ♀ [Reproductive age group]

→ presents ī Recurrent Abortion

→ induces prothrombotic state

- predisposed to

DVT [Deep vein thrombosis]

HVT [Hepatic vein thrombosis]

stroke

→ aka ANTI PHOSPHOLIPID ANTIBODIES [APLA]

- responsible for APLA SYNDROME
  - 1°
  - 2° APLA mcly a/w SLE

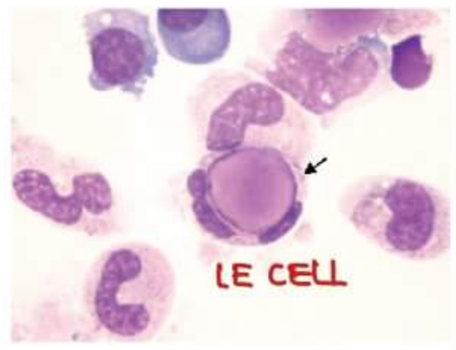
→ causes ↑aPTT [in vitro]

→ reacts ī CARDIOLIPIN Antigen

- responsible for false Positive VDRL

→ DRVVT [DILUTE RUSSELL VIPER VENOM TEST]
  → detects auto Ab more specifically

→ LE CELL seen in SLE
  → Neutrophil / Macrophage ī damaged cell in it
  → present in vitro



TREATMENT → STEROIDS

DRUG INDUCED LUPUS

→ DRUGS RESPONSIBLE :
  S → SULFONAMIDES [DAPSONE]
  H → HYDRALAZINE
  I → ISONIAZID
  P → PROCAINAMIDE

→ H/O drug intake +nt
→ NO kidney / Brain involved
→ ANTI HISTONE ANTIBODIES +nt
→ a/w HLA DR 4
  HLA DR 6

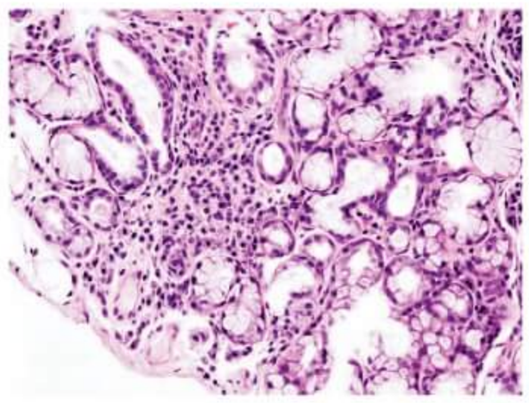
→ TREATMENT → Withdrawal of offending drug

OTHER AUTO IMMUNE DISORDERS

SJOGREN SYNDROME
→ Lacrimal glands, Salivary glands } damaged by Lymphocytic infiltratⁿ } Fibrosis

→ Dry eyes / Dry mouth Syndrome → SICCA SYNDROME [1°/2°]
→ a/w Rheumatoid Arthritis [cause of 2° Sicca Syndrome]

→ DIAGNOSIS
  1. AUTO ANTIBODIES
    ↳ ANA ⊕
    ↳ ANTI - RO Ab [SS-A] ⊕
    ↳ ANTI - LA Ab [SS-B] ⊕
    ↳ ANTI - RO Ab a/w
      → Vasculitis
      → Renal Inflammation
      → Longer duration of disease



  2. LIP BIOPSY
    ↳ confirmatory [IOC]
    ↳ Lymphocytic infiltratⁿ around glands & ducts

→ ↑ risk of MARGINAL ZONE LYMPHOMA

SYSTEMIC SCLEROSIS / SCLERODERMA

→ ↑ Fibrous tissue deposition → SKIN & OTHER ORGANS

VARIANTS

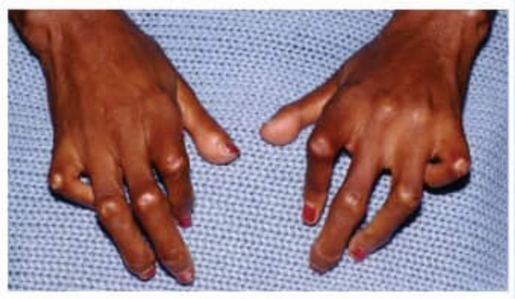
1. LINEAR SCLERODERMA / MORPHEA

→ Patches of hard skin ⊕
→ no other organ involvement

2. LIMITED SCLERODERMA

→ Initially → Blood vessels [Raynaud's disease] ⊕
→ Skin of Fingers / Skin of face / Fore arm ⊕

→ Later → Other Organs ⊕
→ a/w LATE VISCERAL INVOLVEMENT



CREST SYNDROME

- C → Calcinosis
- R → Raynaud's phenomenon
- E → Esophageal dysmotility
- S → Sclerodactyly
- T → Telangiectasia

→ a/w ANTI - CENTROMERE Ab ⊕
→ Limited Scleroderma → Good prognosis

3. DIFFUSE SCLERODERMA

→ Skin + other organs involved early

→ esophagus → Dysphagia
GIT → malabsorptⁿ
Cardiac → fibrosis
Lungs → cause of Death
Kidney

→ ANTI - DNA TOPOISOMERASE Ab ⊕ [Anti - SCL 70 Ab ⊕]
↳ Diffuse Scleroderma
↳ Total Organ involvement

→ ANTI ANA Ab ⊕
→ ANTI RNA POLYMERASE III Ab ⊕
↳ indicates Acute onset
↳ a/w Renal involvement [Scleroderma crisis]
↳ ↑ risk of cancer

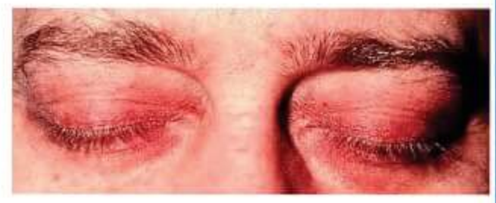
- R → Renal
- N → Neoplasia
- A → Acute onset

4. MIXED CONNECTIVE TISSUE DISEASE

→ Features of SLE / Sclerosis / Sjogren syndrome ⊕
→ ANTI - U_1 RNA Ab ⊕
→ Less Renal involvement
→ Better response to Steroids

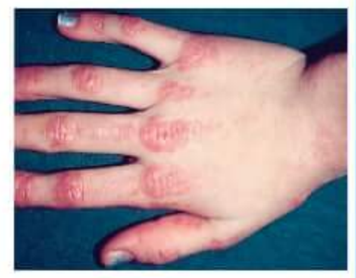
5. DERMATOMYOSITIS

→ Skin + Muscles + Surrounding Blood vessels
→ 1° or a/w cancers



→ C/F

SKIN → HELIOTROPE RASH [on upper eye lid]
→ GOTTRON PAPULES [Seen on extensor surface]



MUSCLE → proximal muscles involved predominantly
→ distal muscles involved later
[↑ Creatinine Kinase value]

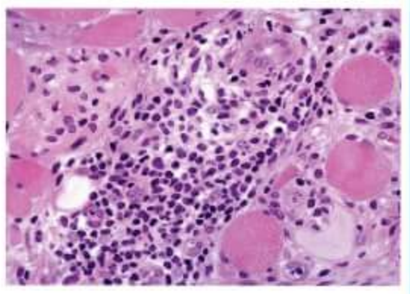
→ DIAGNOSIS

1. AUTO ANTI BODIES

→ ANA ⊕
→ ANTI - JO 1 Ab ⊕ → MECHANIC HANDS
→ ANTI - Mi_2 Ab ⊕ → a/w skin features
→ ANTI - P 155 Ab + } a/w Paraneoplastic syndromes
ANTI - P 140 Ab + } Juvenile variant

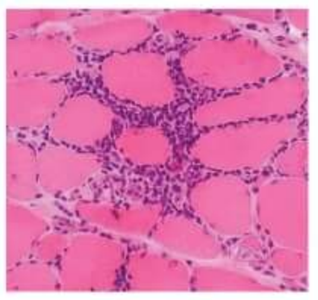
2. BIOPSY → confirmatory

Dermato Myositis
↓
PERI MYSIAL INFLAMMATION [CD_4 T C]
↓
PERI FASCICULAR ATROPHY



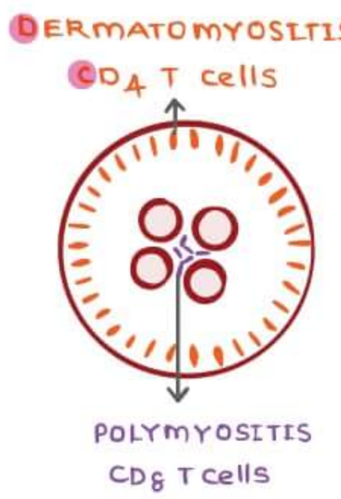
6. POLYMYOSITIS

→ Skeletal muscle involved
→ no Skin involved
→ BIOPSY → ENDOMYSIAL INFLAMMATION [CD_8 T cells]



Ig G_4 RELATED DISEASE

♀ ⟶ Plasma cells + T cells [tissues]
↓
Ig G_4



1. IDIOPATHIC RETRO PERITONEAL FIBROSIS / ORMOND DISEASE
2. RIEDEL THYROIDITIS
3. MIKULICZ SYNDROME
4. AUTO IMMUNE PANCREATITIS

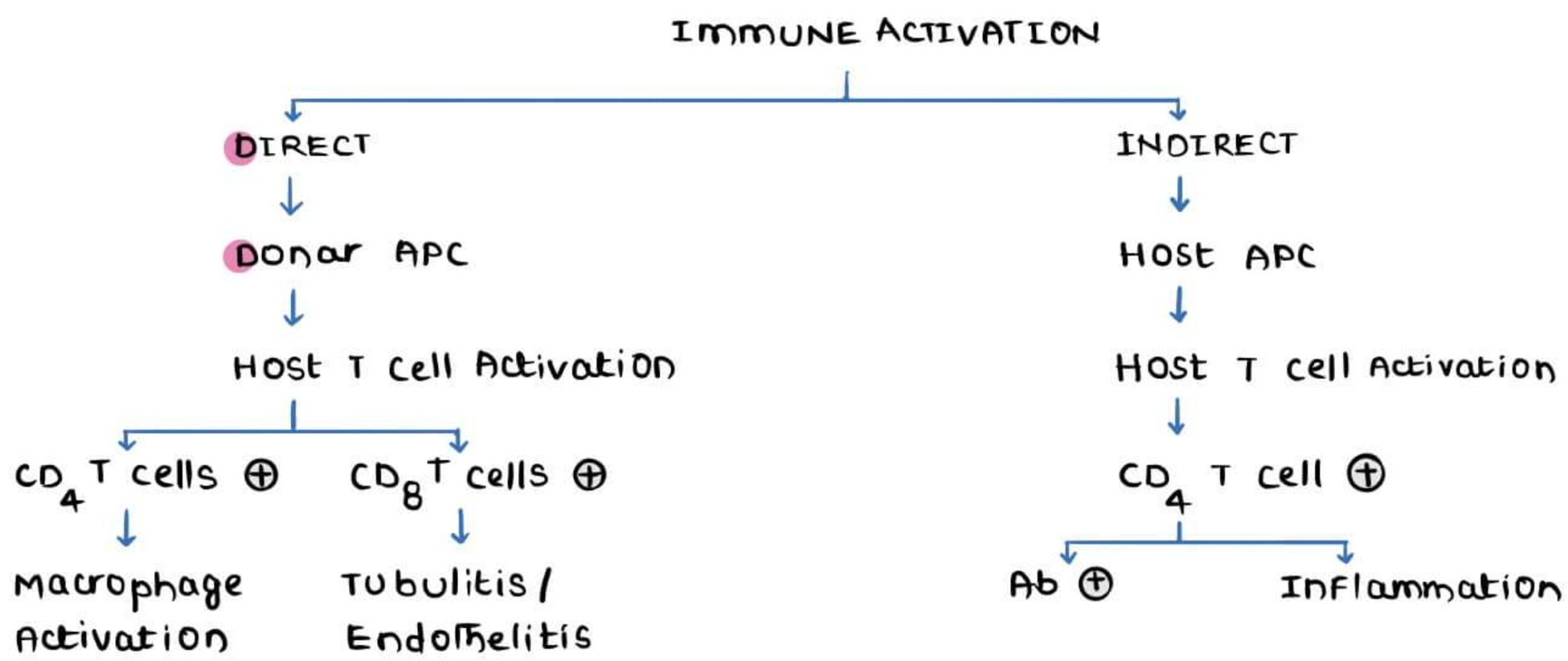
→ R_4 by RITUXIMAB

ORGAN TRANSPLANT & GRAFT

Transplant Rejection

Graft VS Host Disease

GRAFT REJECTION

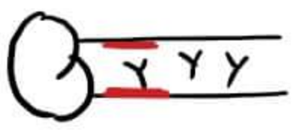


SUBTYPES

1. HYPER ACUTE TRANSPLANT REJECTION → GREAT VESSELS

→ dlt Preformed Ab
- ↳ multiparous ♀
- ↳ Previous recipient
- ↳ prior blood transfusion

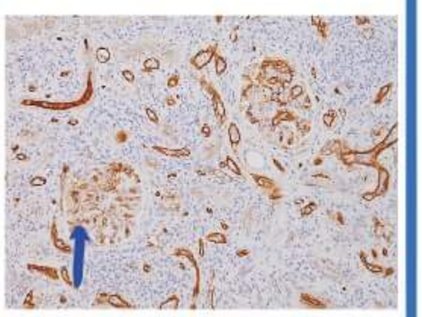
→ Endothelial cell injury + Thrombus
→ Neutrophilic infiltration



→ cross matching should be done to check for preformed Ab
→ Type 2 HR
→ rejected in minutes to hrs

2. ACUTE TRANSPLANT REJECTION

→ Type 2 ⊕ Type 4 HR
→ rejected in Days to weeks



SUB TYPES

a. ACUTE HUMORAL REJECTION

Ag + Ab → complement ⊕ → C_4d Deposition [marker] → Glumeruli damage vessel damage

b. ACUTE CELLULAR REJECTION

Direct Pathway → CD_4 / CD_8 T Cells → Tubulitis [Type I HR]; Endothelitis [Type II HR]

3. CHRONIC GRAFT REJECTION

→ occurs in months to years

→ Type 2 + Type 4 HR

→ CHRONIC HUMORAL → Ab ⊕ → Graft vasculature

CHRONIC CELLULAR → CD_4 T cell ⊕ → Inflammation

↘ ↙

Mononuclear infiltration
Glomerulopathy
↳ intimal thickening
↳ peritubular inflammatⁿ
↳ reduplication of Basement membrane

Intestial fibrosis
Tubular Atrophy

↓ RISK OF REJECTION

1. HLA MATCHING

→ HLA - A/B/C ; HLA - DRB 1 ; HLA - DQ

→ HLA - A/B/C & DRB 1 considered predominantly
↳ In Adults, atleast 6 out of 8 alleles should be matched
↳ In cord blood, A/B/DRB 1 → 4 out of 6 should be matched

→ Transplant rejection is maximum i HLA - DRB 1 mismatch

2. SOURCE OF GRAFT

→ Auto Graft → Self ; Skin / hair grafting
→ Allo Graft → Different person from same species
→ ISO Graft → Identical twin
→ xeno Graft → Different species ; valvular replacement

3. DRUGS

T cell Activation

1. ↓ inflammation → steroids
2. ↓ Lymphocyte proliferatⁿ → Mycophenolate mofetil [MMF]
3. ↓ T cell Activatⁿ → Tacrolimus [calcineurin ⊖]
4. IV Ig

B CELL ACTIVATION → B cell ⊕ ⟶ Ab ⊕ ⟵ PLASMAPHERESIS

→ RESULT

↓↓↓ T - CELL

↓

POST TRANSPLANT LYMPHOMA [B cell Lymphoma]

GRAFT VS HOST DISEASE / RUNT DISEASE [Animals]

→ Immuno compromised host & Immuno competent Graft

→ IMMUNOCOMPETENT GRAFT
- ↳ HSC [Hematopoietic stem cells] [mc]
- ↳ Solid organs [Liver]
- ↳ Unirradiated Blood Transfusion

SUB TYPES

ACUTE [< 100 days]		CHRONIC [> 100 days]
→ Skin	→ Rash [mc]	→ Fibrosis
→ Intestine	→ Bloody diarrhea	→ Stricture ⊕
→ Liver	→ Jaundice	→ Cholestatic Jaundice ↳ discolourat^{n} of Urine ↳ pruritis → Thymic abnormality [in some]

→ GRAFT → Destruct^{n} OF Leukemia cells → GRAFT VS LEUKEMIA EFFECT

IMMUND DEFICIENCY DISORDERS

SUB TYPES

1. PRIMARY DISORDERS
   - → LEUCOCYTE DISORDERS
   - → COMPLEMENT PROTEIN DEFECTS
   - → LYMPHOCYTE DEFECTS

2. ACQUIRED / SECONDARY DISORDERS

1 PRIMARY DISORDERS

I LEUCOCYTE DISORDERS
- → LAD 1/2
- → CHS
- → CGD
- → MPO Deficiency

II COMPLEMENT PROTEIN DEFECTS

III LYMPHOCYTE DEFECTS

1. DI - GEORGE SYNDROME

Chr 22q deletion → TBX 1 gene defect → Failure of 3rd / 4th Pharyngeal pouch development

→ 22 q 11 Deletion Syndrome

1. DI - GEORGE SYNDROME
2. VELLO - CARDIAL FACIAL SYNDROME

C → Congenital cardiac Defects
A → Abnormal facies
T → T- cell Defects
C → Cleft lip / Cleft palate
H → Hypo calcemia
22

↳ a/w defective protect^{n} against intra cellular infectious organisms

2. BRUTON'S DISEASE

→ B Cell defect
→ x - Linked
→ Boys >>> girls affected
→ BTK [B cell Tyrosine kinase] Defect

↓ B CELLS ⟶ ↓ Plasma cells ⟶ ↓ Igs

→ aka X - LINKED AGAMMAGLOBULINEMIA

↓ B CELLS ⟶ AREAS ⟶ UNDER DEVELOPED

External Organisms
[Extra cellular organisms]

↓↓ Ig OPSONISATION ↓↓

→ manifestations seen after 6 months of birth
→ Pneumococcal / H. influenzae ↑
→ Ig A → Enterovirus / Giardia ↑
→ LIVE POLIO VACCINE administrat^{n} → Paralytic Poliomyelitis
→ ECHO VIRUS → ↑ Encephalitis

3. COMMON VARIABLE IMMUNODEFICIENCY DISEASE [CVID]

B CELL MATURAT^{n} → BAFF, ICOS } ↓ T cell Activat^{n}

BAFF → cytokine Inducible co stimulator } require for B cell maturat^{n}

↓↓ Igs in Blood

→ ↑↑ sino pulmonary infections
→ ↑ Bacteria / viruses / Giardia

→ DD
1. childhood / Adolescent onset
2. ♀ = ♂
3. defect in B cell maturation → B cell Ⓝ

Ag → ↑ no. of B cells
↓
4. Hyperplastic areas

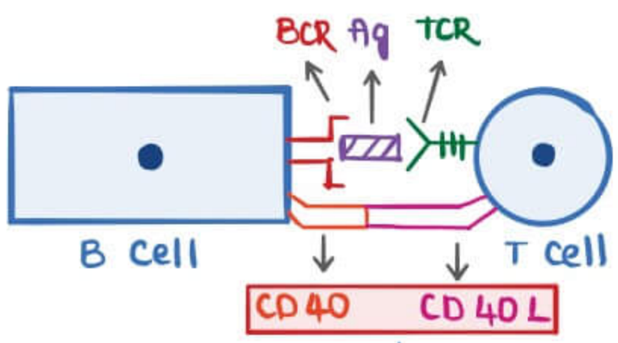
→ ↑ risk of → AUTO IMMUNE DISORDERS [RA]
→ MALIGNANCIES [Lymphoid ; Gastric cancer]

4. Ig A DEFICIENCY

→ mc Ig deficiency
→ ↑ respiratory / GIT / urogenital Infections
→ ↑ Auto immune disorders [SLE / RA]
→ ↑ Allergies
↳ during Blood transfusion → Anaphylaxis occurs

→ ↓ Ig A ; ↓ Ig G_2 / G_4

5. HYPER Ig M SYNDROME



Ig M → Ig G/A/E → ISOTYPE / CLASS SWITCHING

→ ↑↑↑ Ig M → React ī Blood cells → autoimmune hemolytic anemia
→ Thrombocytopenia
→ leucopenia

→ ↓ Ig G/A/E → ↓ Opsonisatⁿ → ↑ Bacterial infections
→ ↑ Fungal infections [Pneumocystitis Jiroveci]

→ x Linked >>> Autosomal Recessive

6. SEVERE COMBINED IMMUNODEFICIENCY DISEASE [SCID] [B / T CELLS]

DEFECT IN CYTOKINE RECEPTOR	ENZYME DEFICIENCY
→ X Linked	→ Adenosine deaminase defect
→ defect in γ chain unit	→ Autosomal recessive
→ ↓ IL-7 → ↓ T cells & ↓ Ig [Sec.↓]	→ Damage to T - Lymphocytes
→ ↓ IL-15 → ↓ NK cells	

→ Both B & T cells are defective ⟶ ↑ Bacterial Infections
↑ Viral / fungal infections

→ GENE THERAPY used for Rx

7. X-LINKED LYMPHOPROLIFERATIVE SYNDROME

→ SLAM protein [Surface molecule for Lymphocyte Activation molecules]
  ↳ requires for activatⁿ of B / T / NK cells
  ↳ defect causes ↓ clearance of EBV
  ↳ Leads to fulminant Infectious mononucleosis & B cell tumors

8. ATAXIA TELANGECTASIA

→ Ataxia
→ vascular malformations
→ neurological deficits
→ ↓ immunity [B/T cells]
→ ↑ Tumors

→ GENE → Chr 11

ATM Protein → DNA damage sensor protein → ⊕ P53 → involves in class switching

9. WISKOTT - ALDRICH SYNDROME

→ WASP GENE → X chromosome 'p' arm
→ Triad of
  ↳ Recurrent infections [↓ humoral & cellular immunity]
  ↳ ↓ platelets
  ↳ Eczema

→ Ig M → ↓
  Ig A → Ⓝ / ↑
  Ig E → ↑

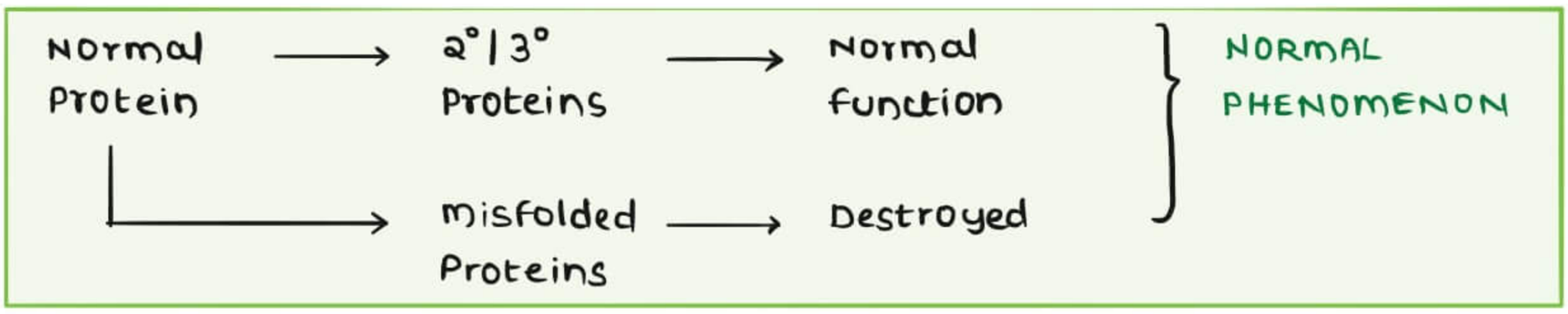
→ Peripheral Smear Shows → Small sized platelets

SECONDARY IMMUNODEFICIENCY DISORDERS

1. INFECTIONS [HIV]
2. PEM
3. MALIGNANCY / METASTASIS
4. ↓ SPLEEN FUNCTION

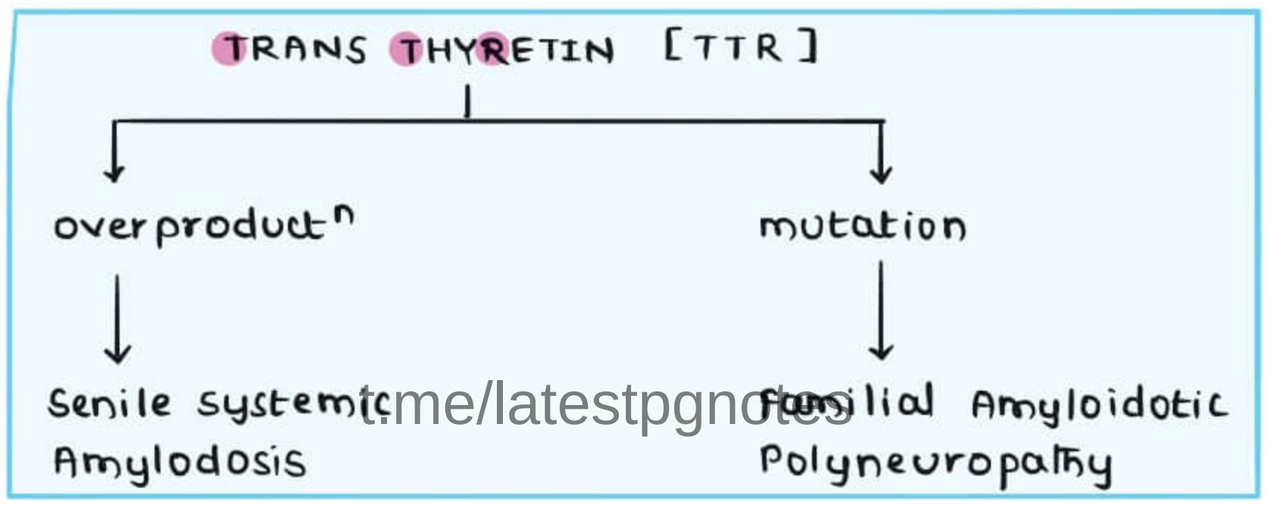
AMYLODOSIS

→ Group of conditions ī Extra cellular Fibrillar protein deposition
→ alw Organomegaly
→ pressure atrophy seen



→ **PATHOGENESIS**

→ over production of misfolding proteins
→ Altered / mutated protein ī ↑ misfolding
} not destroyed



→ **AMYLOID PROTEIN**
→ made up of
↦ Fibrillary protein [95%]
↦ P component [5%]

→ Structure → NON - BRANCHING FIBRILS

→ **CLASSIFICATION OF AMYLOIDOSIS**
I. Generalised / Systemic
II Localised
III Heriditary / familial

I GENERALISED / SYSTEMIC AMYLOIDOSIS

1. PRIMARY AMYLOIDOSIS [mc amyloidosis]
→ seen in PLASMA CELL DYSCRASIA [mc cause]

Plasma cell	→	Ig Secretion [Normal]	
Plasma cell dyscrasia	→	abnormal Ig Secretion [L >>> H]	→ Amyloid

→ chemical Nature → AL [Amyloid Light chain]

2. SECONDARY AMYLOIDOSIS

→ Risk factors
  ↳ chronic inflammation [RA / TB]
  ↳ cancers [Hodgkin Lymphoma / Renal cell carcinoma]

→ mc cause of 2° amyloidosis in Bharat → TB
→ mc cause of 2° amyloidosis in US → RA

→ Chronic Bronchitis not a/w Amyloidosis

→ ETIOLOGY

Cytokines
[IL-1 / IL-6]
↓

↓

↑↑ SAA Protein [Serum Amyloid Associated Protein]

→ Chemical nature → AA [Amyloid Associated Protein]

→ FAMILIAL MEDITTERRANEAN FEVER

↳ "PYRIN" ⟶ Fever + Serositis

↳ Rx by COLCHICINE

3. CHRONIC RENAL FAILURE [CKD]

DIALYSIS [previous machines]
↓
↑↑↑ β_2 - microglobulin
↓
chemical nature → $A\beta_2$

4. LOCALISED AMYLOIDOSIS

a. ALZHEIMER'S DISEASE

APP [Amyloid precurssor protein]

- α Secretase → DESTROYED
- β/γ Secretase → β - PLAQUE → Neuronal damage → Dementia

→ Chemical nature of Amyloid → Aβ
→ gene for APP located on → chr. 21
→ Down syndrome [Trisomy 21] has faster progression for developing dementia

b. MEDULLARY THYROID CANCER [MTC]
→ Para follicular cells / 'C' cells secretes CALCITONIN
→ Medullary thyroid cancer arises from 'C' cells

↑↑↑ 'C' → ↑↑↑ CALCITONIN

→ CALCITONIN
↳ ↑ calcitonin levels are used as a diagnostic marker in MTC
↳ ↑ calcitonin converts into amyloid
• Chemical nature of calcitonin → ACal

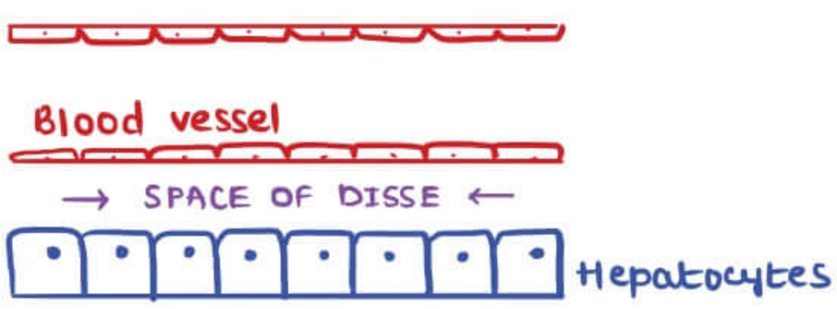
C. DIABETES MELLITIS TYPE 2
→ a/w Islet Associated Pancreatic Peptide [IAPP] / Amylin production
→ chemical nature of Amyloid → A IAPP

5. HERIDITARY AMYLOIDOSIS
a. FAMILIAL MEDITTERAANIAN FEVER
→ chemical nature of Amyloid → AA
b. FAMILIAL AMYLOIDOTIC POLYNEUROPATHY
→ Chemical nature of Amyloid → ATTR [A-Amyloid; TTR - Transthyretin]
→ ATTR is also seen in SENILE SYSTEMIC AMYLOIDOSIS
→ FAMILIAL AMYLOIDOTIC POLYNEUROPATHY a/w MUTATED TRANSTHYRETIN
→ SENILE SYSTEMIC AMYLOIDOSIS a/w overproduct^{n} of NORMAL TTR

ORGANS AFFECTED IN AMYLOIDOSIS
1. Cardiac tissue
→ a/w more commonly ī 1° amyloidosis
→ Extracellular amyloid deposited in Subendocardial tissue and interferes ī electric conduction of heart → ARRHYTHMIA occurs
→ RESTRICTIVE CARDIOMYOPATHY occurs
• mc cause of restrictive cardiopathy → Amyloidosis

2. KIDNEY
→ MC & most seriously affected organ dlt amyloid deposition
→ Amyloid deposition begins from Mesangium & involves other parts later
→ CLINICAL FEATURES → urinary casts ⊕ ; proteinuria ⊕ ; Kidney size ↑

3. HEPATIC TISSUE
→ hepatomegaly + nt
→ 1st part inside the liver involved is 'SPACE OF DISSE'



4. SPLEEN

SPLENIC SINUSES [Red Pulp]	SPLENIC FOLLICLES [White Pulp]
↓	↓
LARDACEOUS SPLEEN	SAGO SPLEEN

5. JOINTS

→ Knee joint involved
→ Wrist Joint involved → carpal tunnel syndrome

6. SKIN

→ Perivascular area involved → PINCH PURPURA

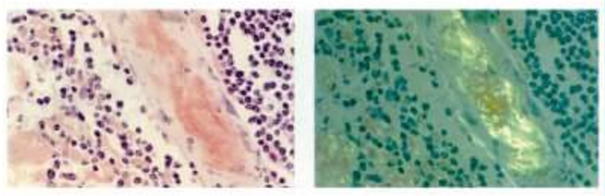
7. GIT

→ Tongue involved → MACROGLOSSIA [↑ Tongue size] → Protrudes from mouth
→ Oral / Rectal mucosa involved [easy areas to take Biopsy, rectal mucosa biopsy is preferred]
→ ABDOMINAL FAT ASPIRATION [Preferred now a days for diagnosis of amyloidosis]

DIAGNOSIS OF AMYLOIDOSIS

1. STAINING

→ congo red [mc used]
- under normal light → Pink red appearance
- under Polarised microscope → Apple green birefrinigens [Characteristic]



→ PAS ⊕
→ THIOFLAVIN T & THIOFLAFIN S [provides secondary immunoflorescence]

2. ELECTRON MICROSCOPY → Non-branching Fibrils are observed
3. SPECTROSCOPY & X-RAY CRYSTALLOGRAPHY → reveals β-plated structure
4. IMMUNO STAINING
5. SCINTIGRAPHY → done ī the help of Serum Amyloid P
6. GROSS SPECIMEN → shows waxy appearance
   → applying I_2 on it, gives Yellow color
   → if washed ī dilute H_2SO_4, it gives Blue | violet color

GENETICS

→ Genetics → study of genes
→ Genes → present on Chromosomes
→ Alleles → two different set of genes acquired from parents

→ No. of genes discovered → 20,000
→ % of genes for coding proteins → 1.5%

GENETIC DISORDERS

- CHROMOSOMAL
- SINGLE GENE
- MULTI FACTORIAL
  [genes + environment]
  ↳ DM
  ↳ HTN

CHROMOSOMAL DISORDERS

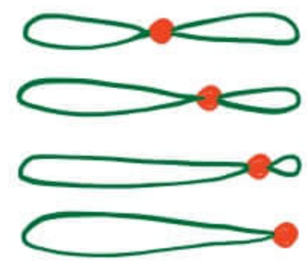
→ Sub divided based on

1. Number
   → Diploid [2n] [normal cell]
   → Haploid [n] [gamete]
   → Aneuploidy [An = absent ; Euploidy = multiples of 'n']

2. Structural Defect

→ SUB TYPES OF CHROMOSOMES [based on centromere]

1. METACENTRIC → centromere right in the middle
2. SUB-METACENTRIC → centromere side of middle
3. ACROCENTRIC → centromere towards one end
4. TELOCENTRIC → centromere towards tip



→ Telocentric → not seen in humans
→ Sub metacentric → X chromosome
→ Acro centric → Y chromosome , chromosome 13|14|15|21|22

→ SUB TYPES OF CHROMOSOMES [based on sex determination]

1. AUTOSOMES → not a/w determinat^{n} of sex → 1 to 22
2. SEX CHROMOSOMES → a/w sex determinat^{n} → X/Y

→ KARYOTYPING
→ Study of Chromosomes
→ SAMPLES CAN BE TAKEN FROM
↳ Amniotic cells
↳ Skin fibroblasts
↳ Peripheral blood lymphocytes

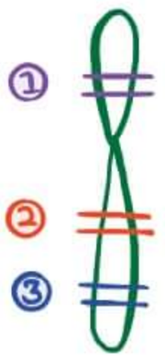
→ COLCHICINE added to sample → causes METAPHASIC ARREST
→ mc banding pattern → 'G' Banding [Giemsa]
→ CARNOY'S FIXATIVE → Methanol : Glacial acetic acid [3:1]

→ STRUCTURAL DEFECTS

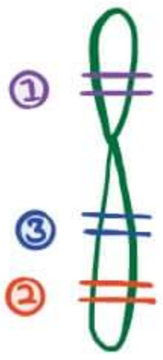
NORMAL

DELETION

INSERTION



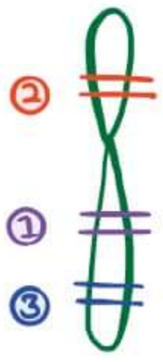
NORMAL



PARA CENTRIC INVERSION

↓

CHANGE IN GENES



PERI CENTRIC INVERSION

↳ inv (16) → AML - M_4

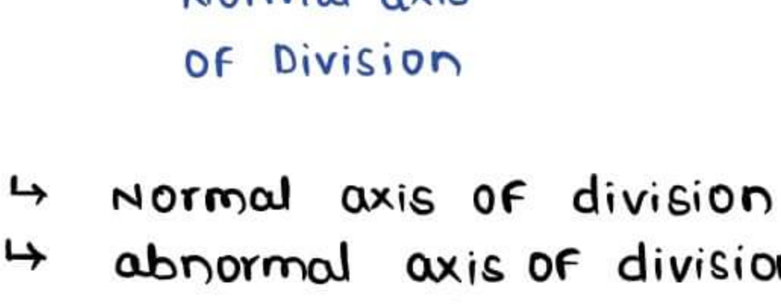
→ ISOCHROMOSOME - xq / 17q / 12p

Normal axis of Division

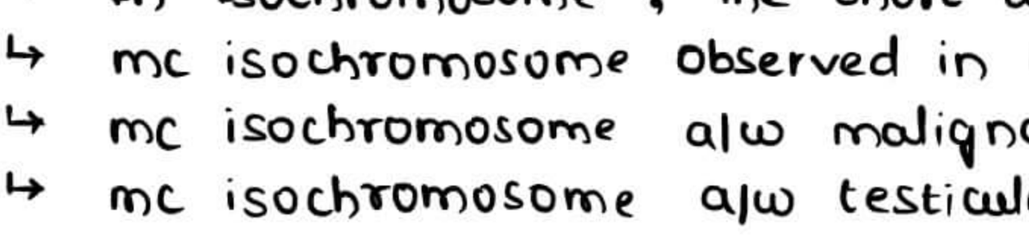
Abnormal axis of Division

↳ Normal axis of division → vertical
↳ abnormal axis of division → perpendicular to normal division
↳ abnormal division leads to ISOCHROMOSOMES
↳ In ISOCHROMOSOME, the short arm [p] will be lost usually
↳ mc isochromosome observed in humans → xq
↳ mc isochromosome a/w malignancy → 17q
↳ mc isochromosome a/w testicular tumor → 12p

→ TRANSLOCATION



BALANCED TRANSLOCATION
↳ no genetic loss
↳ t [8; 14] → Burkitt Lymphoma



ROBERTSONIAN TRANSLOCATION
↳ cell ↓ lesser genetic material will lost
↳ IF it affect Acrocentric chromosome, it can lead to DOWN SYNDROME [chr. 14/21]

RING CHROMOSOME

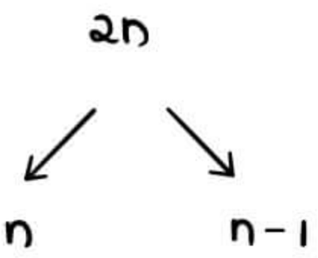
↳ defect lies at edges of chromosome & two ends will fuse ī each other

↳ involves 46 X r [x] → TURNER SYNDROME

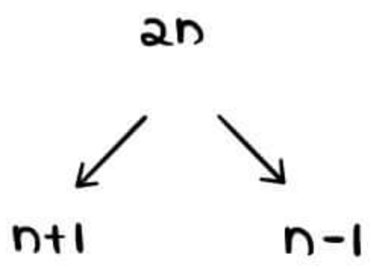
→ ANEUPLOIDY

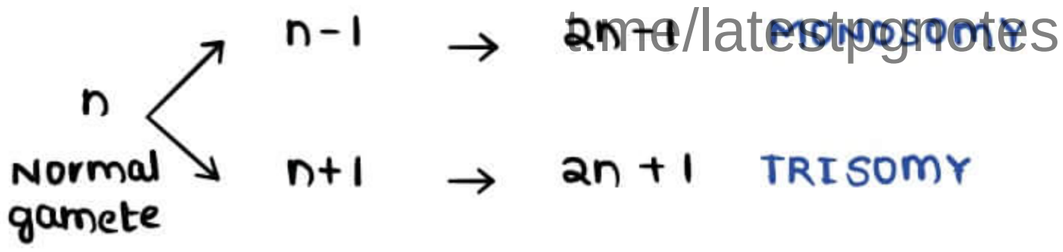
→ due to

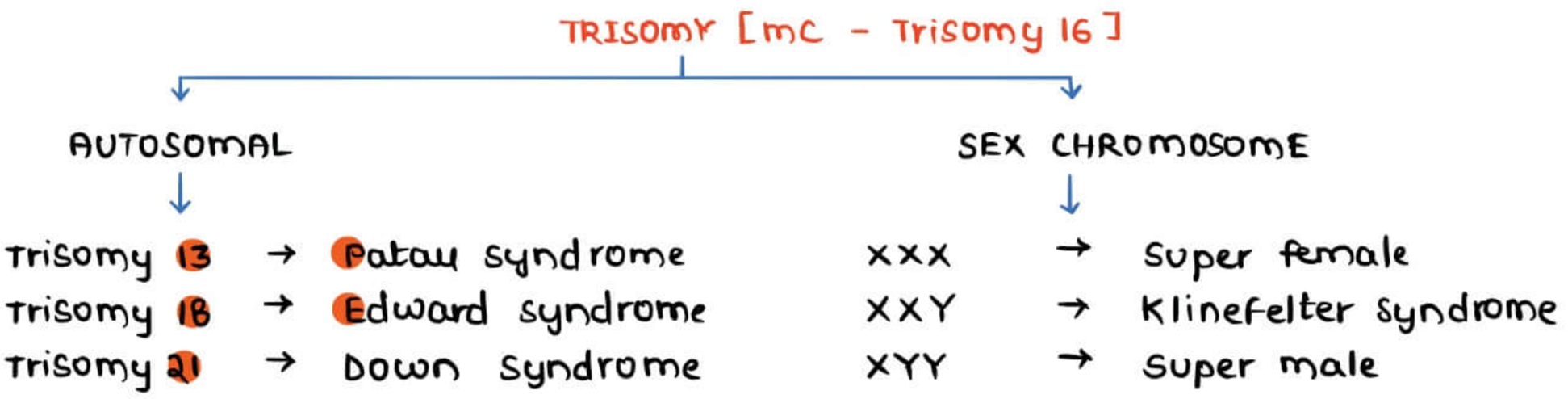
1. ANAPHASE LAG

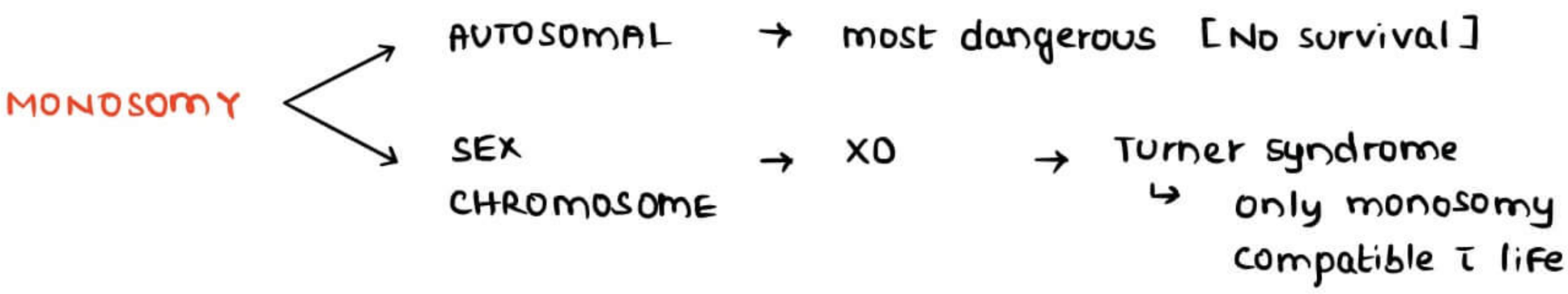


2. MEIOTIC NON - DISJUNCTION









SPECIFIC CYTOGENETIC DISORDERS

DOWN SYDROME

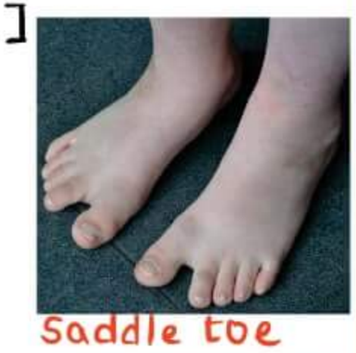
→ Trisomy 21
→ mc chromosomal disorder
→ mc inheritable cause of mental retardation

→ GENETIC BASIS
1. MEIOTIC NON - DISJUNCTION
   ↳ mc cause
   ↳ a/w ↑ maternal age
   ↳ takes place at Meiosis I
      → all trisomies occurs dlt defect at meiosis I, Except for TRISOMY 18 [Edward syndrome] [occurs at meiosis II
2. ROBERTSONIAN TRANSLOCATION → affects chr 14/21
3. MOSAICISM [MITOTIC NON - DISJUNCTION]
   ↳ least common cause
   ↳ unequal distribution of chromosome at mitosis

→ C/F
- C → Congenital cardiac defect
- H → Hypotonia
- I → Increased gap b/w great toe & second toe [SADDLE TOE]
- L → Leukemia [ALL, AML - M7]
- D → Duodenal atresia

- H → Hirschsprung disease
- A → Alzheimer's disease
- S → Simian crease [Single palmar crease]

- P → Protruding Tongue
- R → Rolling of Eyes
- O → Occiput [flat]
- B → Brushfield spots
- L → Low nasal bridge
- E → Epicanthal folds
- M → Mongolian slant


Saddle toe


Brushfield Spots


Epicanthal folds

→ SCREENING
↳ Sporadic down syndrome
   → dlt meiotic non-disjunction
   → a/w ↑ Maternal age
   → chances of having 2nd baby ī down syndrome are much lower

↳ Familial down syndrome
   → dlt Robertsonian translocatⁿ
   → chances of having 2nd baby ī down syndrome are much higher

→ TRIPLE TEST

AFP	HCG	ESTRIOL
↓	↑	↓

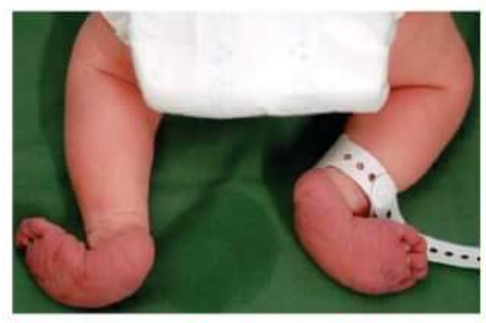
→ QUAD TEST

Triple Test + Inhibin - α ↑↑

FEATURES OF OTHER TRISOMIES [13/18]

COMMON DEFECTS [13/18]

→ congenital cardiac defects
→ Renal defects
→ Mental Retardation
→ Rocker Bottom Feet

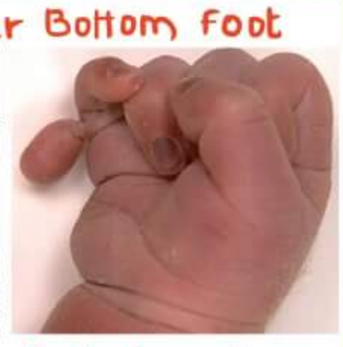


Rocker Bottom foot

PATAU SYNDROME [13]

→ Polydactyly
→ Palate defects
→ Eye defects
→ microcephaly

Palate defects



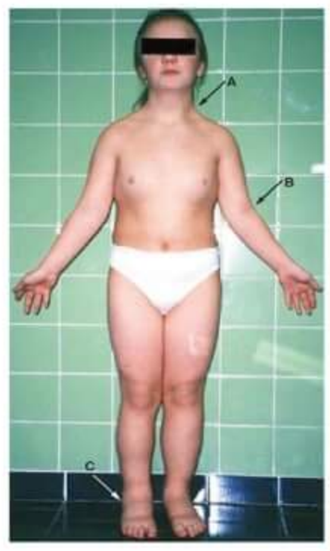
Polydactyly

EDWARD SYNDROME [18]

→ Extra / Prominent occiput
→ micrognathia [small chin]
→ Overlapping fingers

overlapping fingers

TURNER SYNDROME



→ Loss of 'x' chromosome
  1. 45 XO [classical] [more common]
  2. 46 X r [X]
  3. 46 X i [Xq]
  4. Mosaicism [46 XX / 45XO]

→ CIF
  ↳ mc cause of primary amenorrhea
  ↳ C → Cardiac defects [Bicuspid aortic valve > coarctat^{n} of aorta]
    L → Lymphedema [Hands & Feet involved]
    O → Ovaries [Streak] → ↓↓↓ fertility
    W → Webbed neck [low neck hair line]
    N → Nipples [widely spaced]
    S → Short stature [SHOX gene defect]

↳ 'O' BARR BODY

KLINEFELTER SYNDROME

→ ♂ Phenotype → 47 XXY

→ mc genetic cause of infertility

→ CIF
  ↳ tall stature
  ↳ ↓ IQ
  ↳ hypotonia

→ '1' Barrbody
  ↳ Feminine manifestations
    → gynecomastia
    → testicular atrophy
      ↳ ↓ Testosterone
      ↳ ↑ FSH
      ↳ ↑ LH

    → no 2° sexual characteristics

→ ↑ Auto immune disorders [SLE]
→ ↑ Cancers [Testicular tumors(teratoma) < Breast cancer [Ductal]]
→ ↑ congenital cardiac defects [Mitral valve prolapse]

→ DEFECTIVE GAMETOGENESIS → a/w ↑↑ Age [Both sex]

↑ maternal age → Down syndrome
↑ Paternal age → M → Marfan syndrome
O → Osteogenesis imperfecta
N → Neurofibromatosis
A → Achondroplasia

LYON'S HYPOTHESIS

→ only '1' X chromosome → active
→ 2nd Inactivation → dlt XIST gene [DNA methylation]
→ takes place at the level of BLASTOCYST

→ BARR BODY
  ↳ perinuclear structure observed in interphase
  ↳ No. of BARR BODIES [no. of X - 1]

1.	Normal Male	→	XY	→ 0
2.	Normal Female	→	XX	→ 1
3.	Turner syndrome	→	XO	→ 0
4.	Klinefelter synd.	→	XXY	→ 1
5.	Super female	→	XXX	→ 2

SINGLE GENE DISORDERS

Classical Mendelian Inheritance

Autosomal
- ↳ dominant
- ↳ Recessive

Sex chromosomal
- ↳ y Linked
- ↳ x Linked
  - → XLR
  - → XLD

Non - Mendelian Inheritance
1. Genomic Imprinting
2. Mitochondrial Inheritance
3. Trinucleotide repeat expansion
4. Germline mosaicism

MENDELIAN INHERITANCE

ALLELES

↳ individual copies of genes of a trait coming from both parents & present on same locus

Ⓝ gene → 2 ALLELES [same locus]

HAIR COLOR	HOMOZYGOUS TRAIT		HETEROZYGOUS TRAIT
GENOTYPE	AA	aa	Aa
PHENOTYPE	A [Black]	a [Brown]	A [Black]

↳ DOMINANT ALLELE → expressed even in heterozygous trait
↳ RECESSIVE ALLELE → expressed only in homozygous trait
↳ CO - DOMINANCE → Both alleles are expressed in heterozygous trait
  ↳ Ex: Blood grouping
  HLA | MHC genes

AUTOSOMAL DOMINANT DISORDERS

→ expressed in Heterozygous state
→ 50% progeny affected
→ Patient → atleast 1 parent affected [vertical Inheritance]
→ ♂ / ♀ equally affected
→ Structural proteins are affected
→ Loss of function mutation > Gain of function mutation
→ Incomplete penetrance
→ variable expressivity
→ Pleiotropy [> 1 system involved] ; Ex : NF
→ EXAMPLES

100
↓
80
↓
+/++/+++

Vo	→	VWD; VHL syndrome
familial	→	Familial adenomatus Polyposis ;
Hyperchol	→	Familial Hypercholesterolemia
Poora	→	Polycystic Kidney Disease
D	→	Dystrophia myotonica
O	→	Osteogenesis imperfecta
m	→	Marfan syndrome ; MEN
I	→	Intermittent porphyria [Acute]
N	→	Neurofibromatosis 1
A	→	Achondroplasia
N	→	Neurofibromatosis 2
T	→	Tuberous sclerosis
Hota	→	Huntington's disease [gain of funct^{n} mutat^{n}]
Hai	→	Hereditary Spherocytosis

AUTOSOMAL RECESSIVE DISORDERS

→ affects Enzymatic proteins [Inborn errors of metabolism]
→ expressed in homozygous state [Early onset] 100 ↓ 100
→ Complete penetrance
→ ↑ in consanguineous marriage [parsis / muslims]
→ Patient → Parents may be carriers
→ Siblings have higher chances [Horizontal Inheritance]

→ EXAMPLES
1. Inborn Errors of metabolism [Glycogen & Lysosomal Disorders]
2. Friedrich's ataxia
3. Sickle cell anemia
4. Thalassemia
5. Wilson's disease [Cu]
6. Hemochromatosis [Fe]
7. Homocystinuria
8. Alkaptonuria

SEX LINKED DISORDERS

Y LINKED DISORDERS

→ Only ♂ affected
→ Patient → Sons
→ Hair on pinna
→ Y chromosome → acrocentric chromosome → ↓ Fertility

X LINKED DISORDERS [father to son transmission is "zero"]

XLR [X Linked Recessive]
→ mc sex linked pattern of inheritance
→ x linked genes → encodes enzyme genes
→ more common in ♂
→ ♀ → $X X^{d}$ → heterozygous [not common]
→ EXAMPLES

Less → Lesch - Nyhan Syndrome
H → Hemophilia A & B
C → Color blindness [more i red] / CGD
G 6 → G6PD deficiency
Detected in → Duchhene muscular dystrophy
A → Agammaglobulinemia [Bruton Disease]
Fragile → Fragile X syndrome
Women → Wiskott - Aldrich Syndrome

XLD [X linked Dominant Disorders]
→ affects ♂ → Daughters [xx^d → 50% Progeny]
→ affects Structural proteins
→ less common
→ EXAMPLES
A → Alport Syndrome
V → vit D resistant Rickets
I } Incontinentia Pigmenti
P }

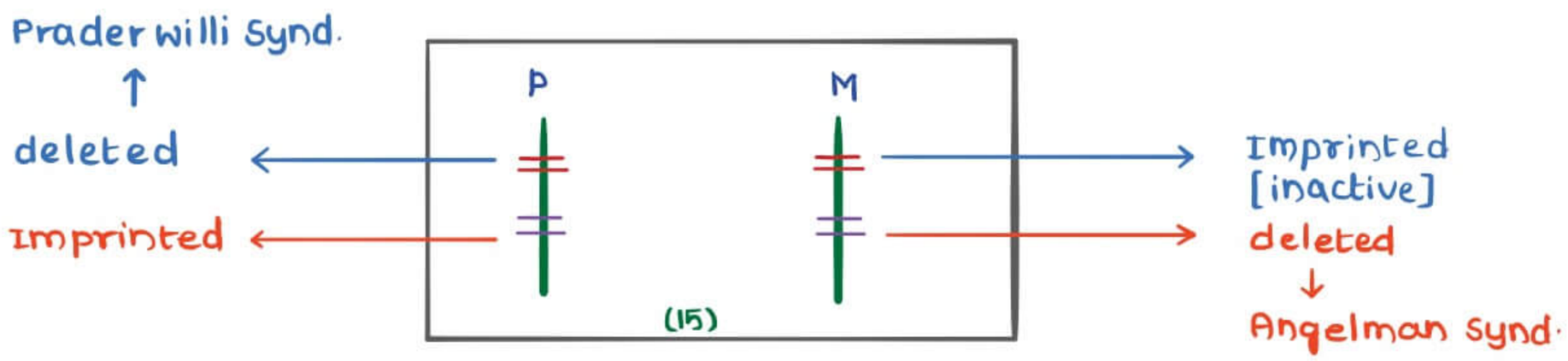
NON CLASSICAL / NON MENDELIAN INHERITANCE DISORDERS

1. GENOMIC IMPRINTING

→ DIFFERENTIAL GENE EXPRESSION based on PARENT OF ORIGIN
→

EPIGENETIC REGULATION → DNA Methylation
EPIGENETIC REGULATION → Histone Deacetylation

→



→ PRADER WILLI SYNDROME
↳ Normal → Maternal gene imprinted & paternal gene is active
↳ Etiology
1. in case of Deletion of Paternal chromosome [MC cause]
2. Uniparental Disomy [maternal chromosome]
3. ↓↓ SNORP [Small Nucleolar RNA Proteins]

↳ CIF
→ Mental Retardation
→ obesity [dlt ↑↑ ghrelin]
→ hypotonia
→ hypogonadism

→ ANGELMAN SYNDROME [AMS]

→ Normal → Paternal gene imprinted & Maternal gene is active

→ Etiology

1. Deletion of maternal chromosome [mc cause]
2. Uniparental disomy [paternal chromosome]

→ C/F

S → Seizures
A → Ataxia
R → Retardat^{n} [Mental]
I → Inappropriate laughter

} HAPPY PUPPETS

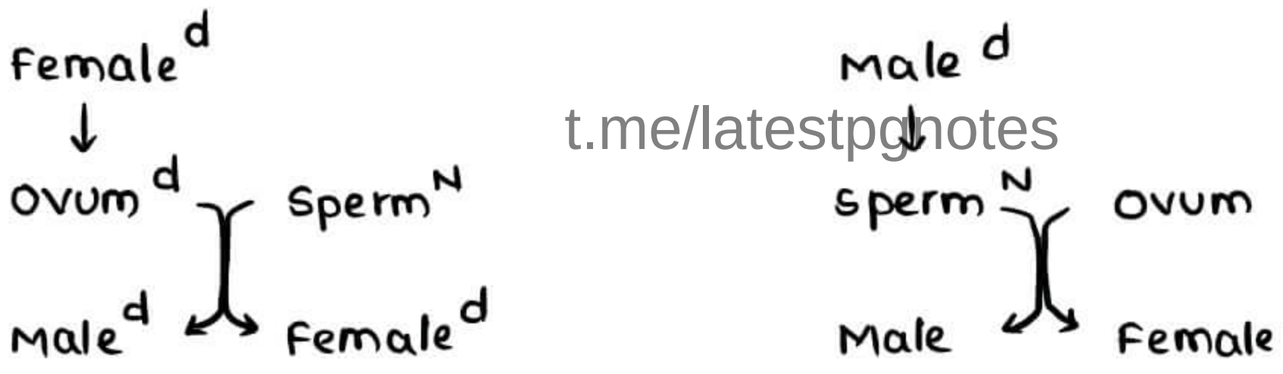
→ Genomic Imprinting seen in

1. PWS
2. AMS
3. Mc Cune Albright Dystrophy
4. Beckwith-wiedemann Syndrome

2. MITOCHONDRIAL / MATERNAL INHERITANCE

→ MATERNAL INHERITANCE

mt. DNA in ovum is preserved & in sperms not preserved



→ CLINICAL EXAMPLES

1. MELAS → Mitochondrial Encephalopathy, Lactic Acidosis, Stroke
2. LEIGH'S DISEASE
3. NARP SYNDROME → Neuropathy, Ataxia, Retinitis Pigmentosa
4. LEBER'S OPTIC NEUROPATHY

→ governed by Law of POPULATION GENETICS

3. GERMLINE MOSAICISM

AD → 1 Affected parent → Normal
→ No Affected parent → Rare

Person → N → Post zygotic mutat^{n} affecting gonadal cells → Progeny / next generation affected [>1 progeny]

→ Seen in Osteogenesis imperfecta
Tuberous sclerosis

4. TRIPLE REPEAT MUTATIONS

→ Long nucleotide repeats [affects Cytosine | guanosine]
→ causes Neurodegenerative disease
→ Dynamic in nature
  ↳ Amplificat n of nucleotide repeats at the time of gametogenesis

AMPLIFICATION
↓
Premutation [nex gen]
↓
Mutation [nex gen.]

→ HUNTINGTON'S DISEASE
  ↳ CAG repeats → Huntingtin
  ↓
  Caudate nucleus damage
  ↓
  Dementia / chorea

→ CAG repeats → Huntington's Disease
  GAA repeats → Friedrich Ataxia
  CTG repeats → Myotonic Dystrophy

→ FRAGILE X SYNDROME
  ↳ FMR - 1 gene mutation
  ↳ 2nd MCC OF MR
  ↳ Large face
  ↳ Large mandible
  ↳ Large Testis [Macro Orchidism]
  ↳ Large everted ears

→ CGG Repeats takes place at OOGENESIS

♂ → → → Grandson

SHERMAN'S PARADOX
  ↳ Chances of developing MR Far more i grandson by ANTICIPATION
  ↳ Nuclear repeats → Premutation → Mutation [ANTICIPATION]

HEMATOLOGY
HEMATOPOIESIS
BASIC CONCEPTS

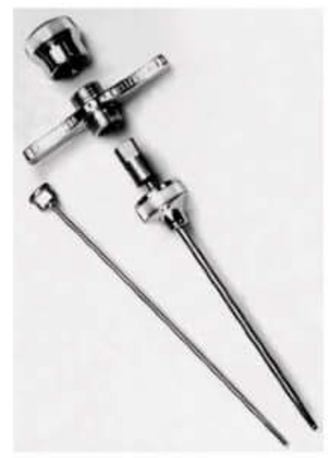
→ HEMATOPOIETIC STEM CELL [HSC]
- ↳ pluripotent cell [can give rise to multiple types of cells]
- ↳ Self - renewable

→ ERYTHROPOIESIS & HSC LOCATION

3 Weeks	→	3 months	→	Birth
Yolk sac mesoderm of → Aorta → gonads → mesonephros		Liver Spleen Lymph nodes		Bones

Birth	→	Puberty
Bone marrow of All Bones		Bone marrow of axial skeleton & ends of long bones

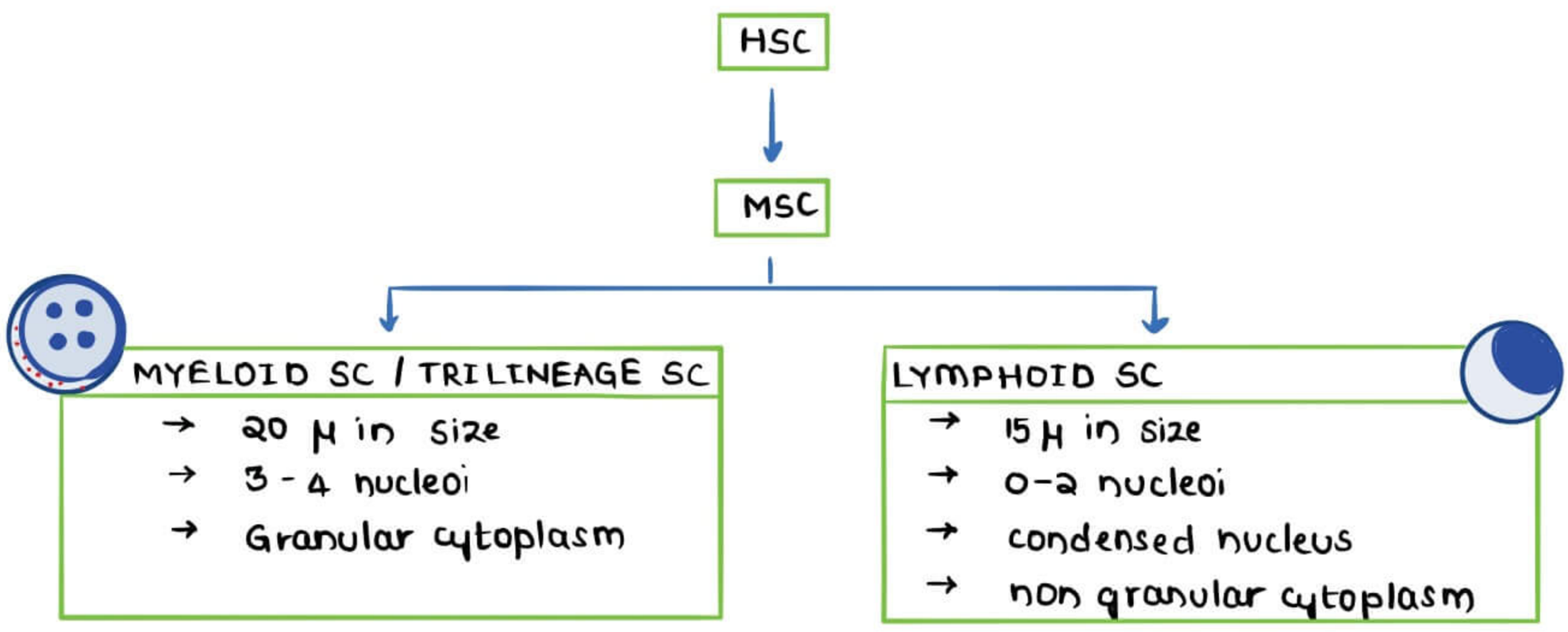
→ Bm EXAMINATION
1. Bm Aspirat^{n} → by KLIMA/SALAH'S NEEDLE
2. Bm Biopsy → by TREPHINE NEEDLE
   JAMSHEDI'S NEEDLE



TREPHINE & JAMSHEDI'S NEEDLES

→ Ideal Site of Bm BIOPSY
- ↳ Adults → posterior superior iliac spine [PSIS] except in obese people [ASIS
- ↳ CHILD → Anterior end [Tibia]

HEMATOPOIESIS / ERYTHROPOIESIS



HSC
↓
MSC
↓
MYELOID SC → Granulocyte / monocyte colony forming units → Granulocyte - CFU → Granulocytes (Neutrophils, Eosinophils, Basophils)
MYELOID SC → Granulocyte / monocyte colony forming units → monocyte - CFU → monocytes
MYELOID SC → Erythrocyte / megakaryocyte colony forming units → RBC
MYELOID SC → Erythrocyte / megakaryocyte colony forming units → Platelets
LYMPHOID SC → B cell
LYMPHOID SC → T cell
LYMPHOID SC → NK cell

→ HSC / MSC → SELF RENEWABLE CELLS
→ From Myeloid / Lymphoid SC → COMMITED CELLS

→ FROM TOP to Bottom OF Hierarchy Differentiation increases
↳ highly diffentiated cells affected by specified GF
↳ RBC → Erythropoietin [EPO] ← DARBOPOIETIN
↳ Platelets → IL 11 ← OPRELVEKIN
↳ Gm - CFU → Gm - CSF ← SARGRAMOSTIM
↳ G - CFU → G - CSF ← FILGRASTIM

→ PANCYTOPENIA Seen in → Aplastic Anemia
→ dlt damage to HSC

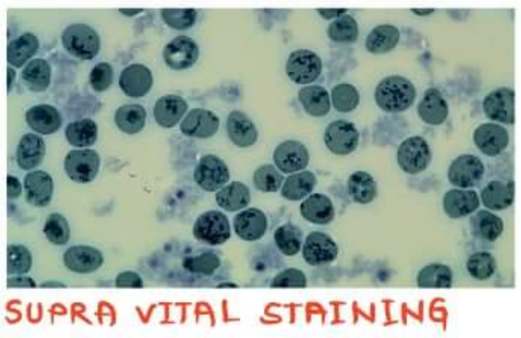
→ MYELOPROLIFERATIVE DISORDERS → ↑ RBC / P / WBC

RBC DEVELOPMENT & CLASSIFICATION OF ANEMIA

DEVELOPMENT

MYELOID STEM CELL
↓
ERYTHROBLAST
↓
NORMOBLAST
↓
RETICULOCYTE
↓
RBC

↑ differentiation
↓ Size
↓ Size of nucleus
↑ Hb concentratⁿ
} NUCLEAR CYTOPLASMIC SYNCHRONY


SUPRA VITAL STAINING

→ Hb detected Firstly in Erythroblast [only by e⁻ microscope]

NORMOBLAST

- ↳ Early
- ↳ Intermediate → Hb can be detected by routine staining
  → Polychromatophilic cell
- ↳ Late → NUCLEUS EXTRUSION occurs while it converting to Reticulocyte

RETICULOCYTE

- → mesh like appearance
- → FIRST NON - NUCLEATED CELL
- → detectⁿ requires SUPRA VITAL STAINING
  [detected Only in Living State]
  - ↳ New methylene blue [preferred]
  - ↳ Brilliant cresyl blue
  - ↳ Bm ACTIVITY → Reticulocyte count
  - ↳ Reticulocyte count Estimation gives Bm ACTIVITY
    aka 'POOR MAN'S Bm ASPIRATION'
    Normal → 0.5 - 2%

    Increased Reticulocyte count
    - → Hemolytic anemia
    - → Fe / FA / B_{12} Supplementation

    Decreased Reticulocyte count
    - → Aplastic anemia
    - → Deficiency of Fe/FA/B_{12}
    - → Leukemias / metastasis
    - → myelofibrosis

- → CORRECTED RETICULOCYTE COUNT

$$\frac{\text{Reticulocyte count} \times \text{Hb [patient]}}{\text{Hb [normal]}}$$

used to estimate compensatory increase of reticulocytes in certain conditions

RBCs

NORMAL RBCs [N - 7-8 μ]

- → Biconcave Shape
- → more Hb at periphery than center
- → Shape & Flexibility maintained by
  - ↳ Spectrin [most imp]
  - ↳ Band
  - ↳ Ankyrin

- → Variation in size of RBC can be known as → ANISOCYTOSIS
- → 11.5 - 14.5
- → Central 1/3rd Pallor

→ MCV → 80 - 100 FL
→ MCH → 27 - 33 pg
→ MCHC → $\frac{MCH}{MCV}$ → 34 - 37 g/dl

→ B_{12} deficiency | megaloblastic Anemia → MCHC → (N)

→ Hematocrit → 45% or 0.45
→ Red cell Distribution width [RDW]

MCH → gives color of RBC → ↓ → hypochromic RBC

MCV

→ 80 - 100 Fl
→ < 80 Fl → microcytic RBC
↳ S → Sideroblastic Anemia
↳ I → Iron deficiency Anemia
↳ T → Thalassemia
↳ A → Anemia of chronic disease
↳ L → Lead poisoning

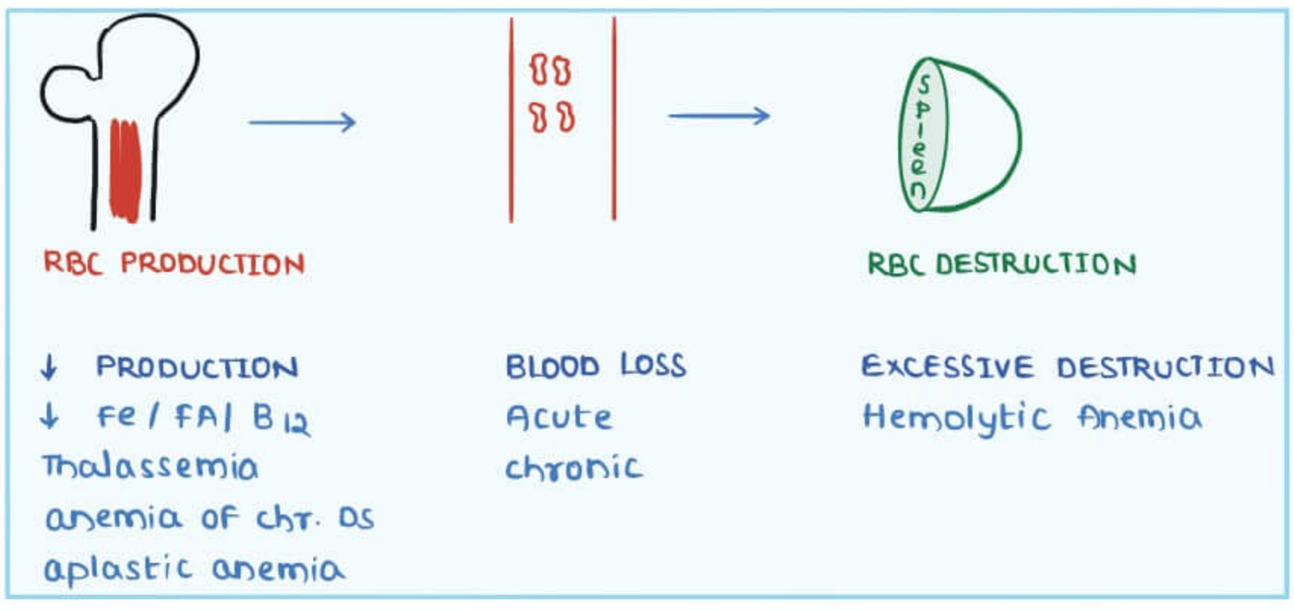
→ > 100fl → Macrocytic RBCs
↳ L → Liver disease
↳ H → Hypothyroidism
↳ M → Myelodysplastic syndrome
↳ C → Cytotoxic drugs
→ Cell Nutrient deficiency
↳ B_{12} deficiency
↳ FA deficiency
↳ Methotrexate
↳ Alcohol
↳ Phenytoin

↳ ↓ B_{12} } NUCLEAR CYTOPLASMIC
↓ FA } ASYNCHRONY

→ ↑ RBC Size } MEGALOBLAST
→ Nucleus is immature } [> 110Fl]

ANEMIA - CLASSIFICATION

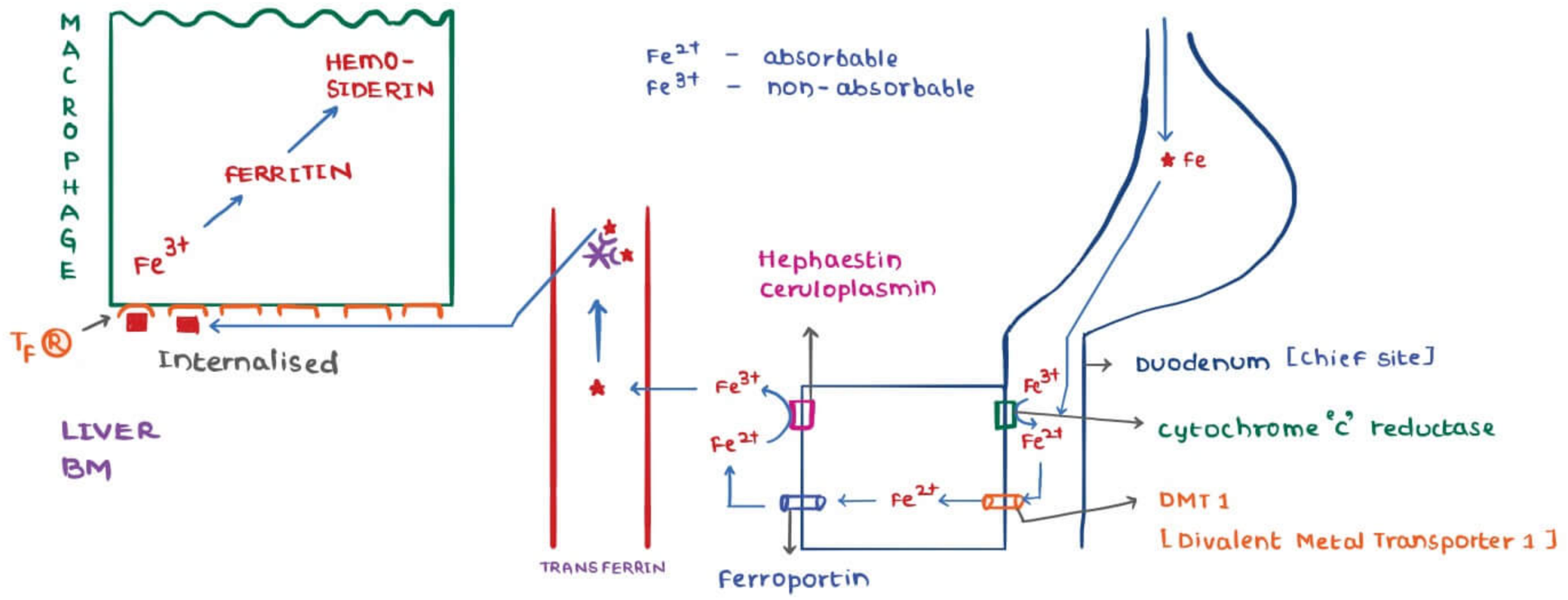
1. Size of RBC
   a. Microcytic Anemia
   b. Macrocytic Anemia
   c. Normocytic Anemia
      → myelofibrosis
      → Radiation
      → metastasis
      → Renal disease



IRON DEFICIENCY ANEMIA

→ mcc of microcytic anemia

IRON METABOLISM



ABSORPTION

→ chief site → DUODENUM

↑ ABSORPTION
- ↳ HCl
- ↳ Vitamin C
- ↳ Amino acid
- ↳ Sugars

↓ ABSORPTION
- ↳ Phytates [vegetables]
- ↳ carbonates
- ↳ Tannates
- ↳ Tetracyclines

→ PURE VEGETARIANS HAVE HIGHER CHANCES OF IRON DEFICIENCY

TRANSPORT

→ SERUM IRON → Iron attached i Transferrin [T_F]
→ N → 100 - 120 µg/dl

→ % TRANSFERRIN SATURATION

$\frac{2}{6}$ → 33 % or 1/3

→ TOTAL IRON BINDING CAPACITY [TIBC]
→ N → 300 - 360 µg/dl

STORAGE

→ FERRITIN $\propto \frac{1}{\text{TRANSFERRIN}}$

→ BM FERRITIN $\rightleftharpoons$ SERUM FERRITIN [indirector indicator of fe storage]

→ Serum Ferritin $\propto \frac{1}{\text{TRANSFERRIN}}$

IRON DEFICIENCY CAUSES

- → ↓ Intake
- → ↓ Absorption [Malabsorption, Diarrhea]
- → ↑ requirement
  - ↳ growing children
  - ↳ reproductive age group
  - ↳ pregnancy
  - ↳ Lactation

- → Blood loss
  - ↳ accidents / trauma
  - ↳ Hook worm infection
  - ↳ Peptic ulcer disease
  - ↳ colon cancer

STAGES OF IRON DEFICIENCY

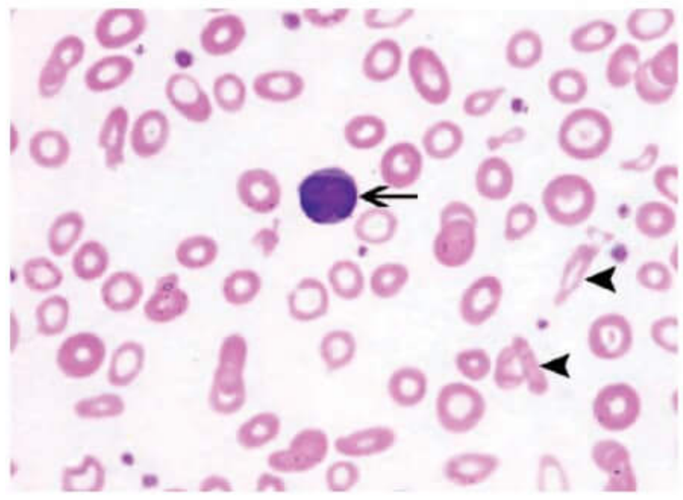
I ↓ STORAGE IRON → ↓ Bm IRON
→ ↓ Serum ferritin

II IRON DEFICIENT ERYTHROPOIESIS

→ Serum Iron	→ ↓↓
→ % T_f Saturation	→ ↓
→ TIBC	→ ↑

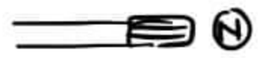
III IRON DEFICIENCY ANEMIA

→ RBCs AFFECTED } MICROCYTIC HYPOCHROMIA
ANISOCYTOSIS
POIKILOCYTOSIS



CLINICAL FEATURES

- → Fatigue
- → pallor
- → Dyspnea
- → palpitations
- → Stunted growth
- → Alopecia
- → Koilonychia
- → Pica



DIAGNOSIS

1. BM EXAMINATION
   - → Gold Standard
   - → ↓↓ staining ī prussian blue
   - → micro normoblasts ⊕

2. BLOOD
   - → ↓ Hb
   - → ↓ MCH / MCV / MCHC

3. PERIPHERAL SMEAR
   - → microcytic hypochromic RBCs
   - → Anisocytosis
   - → Poikilocytosis, Target cells

4. IRON PROFILE

→ S. ferritin → ↓
→ S. Iron → ↓
→ % T_f Saturation → ↓
→ TIBC → ↑

5. $\frac{S.T_f\ ®}{Log\ [S.ferritin]}$ → > 1.5

6. Fe 100 50 ↓ HEME 100 50 ↓ Hb 100 50 — Protoporphyrin 100 50

FREE ERYTHROCYTE PROTOPORPHYRIN [FEP] → ↑↑↑

∓ MENTZER INDEX → ↑ [> 13] — $\frac{MCV}{RBC\ count}$

→ IDA → ↓ Reticulocyte count
→ Distinguishes blw microcytic anemias [IDA vs Thalassemia Trait]
↳ Thalassemia trait → ↓

→ Index for Anisocytosis → RED CELL DISTRIBUTION WIDTH

ANEMIA OF CHRONIC DISEASE

→ CHRONIC INFLAMMATION ⟶ IL 1 | IL-6 | TNF-α

CYTOKINES

BM → ↓ EPO ACTION → Normocytic Normochromic anemia [mc]

LIVER → ↑ Hepcidin, ↑ ferritin } +ive APR; ↓ T_f → −ive APR → microcytic hypochromic anemia

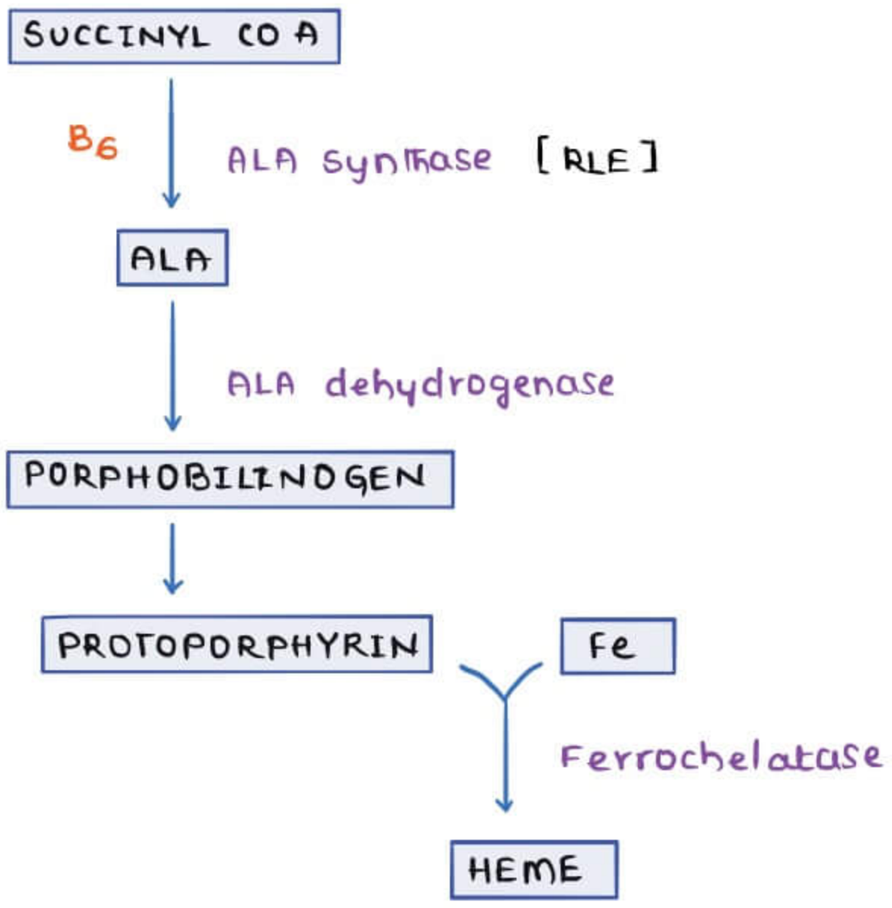
→ HEPCIDIN → inhibits Iron metabolism

→

	AOCD	IDA
S. ferritin	↑↑	↓↓
% T_f saturat^n	↓↓	↓↓
S. Iron	↓↓	↓↓
TIBC	↓↓	↑↑↑
$\frac{S.T_f\ R}{Log\ [ferritin]}$	< 1.5	> 1.5

SIDEROBLASTIC ANEMIA

HEME METABOLISM



CAUSES

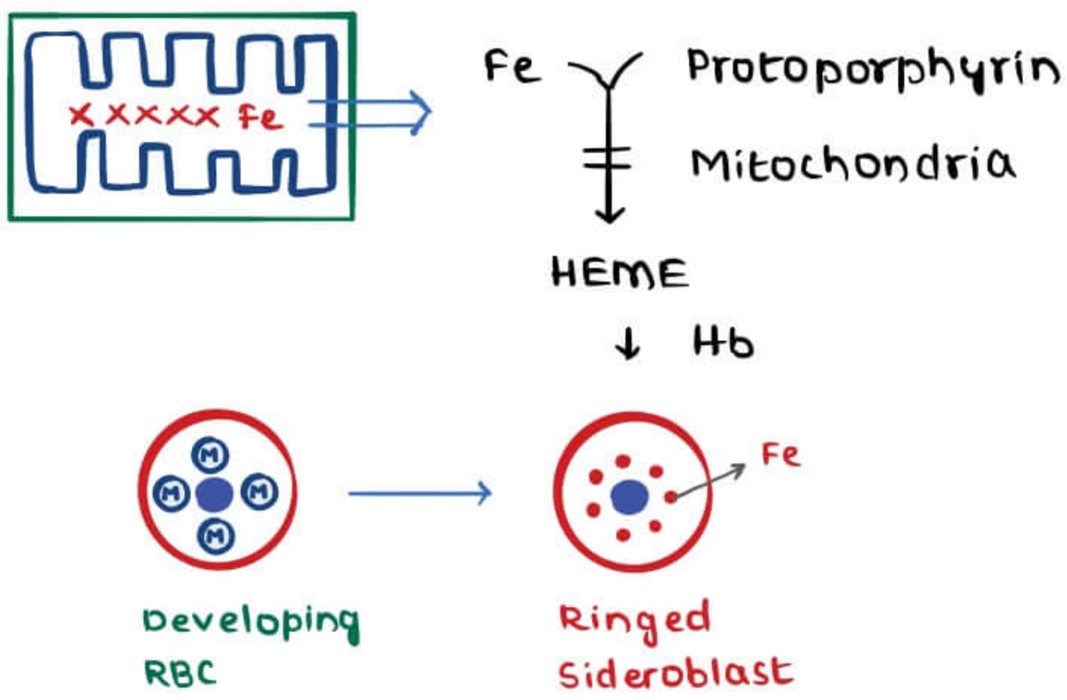
I. CONGENITAL → Enzyme defects

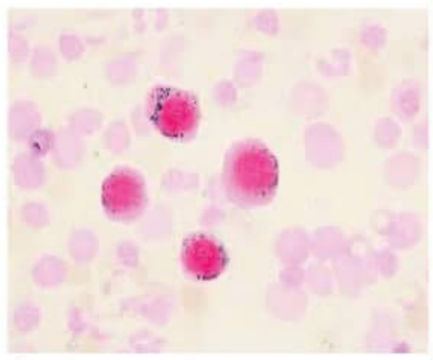
II. ACQUIRED [more common]

→ B_6 deficiency
  → primary
  → Isoniazid / dietary

→ Alcohol [mc]

→ Lead poisoning
  → damages ALAD & Ferrochelatase





RINGED SIDEROBLAST

Fe → damage to RBC precursor → Leakage of iron → IRON OVERLOAD

→ S. FERRITIN → ↑↑
  S. IRON → ↑↑
  % T_f SATURATION → ↑↑
  TIBC → ↓↓

SUMMERY TABLE OF MICROCYTIC HYPOCHROMIC ANEMIA

	IDA	AOCD	SID. AN.	THAL. TRAIT
S. FERRETIN	↓	↑	↑	N
S. IRON	↓	↓	↑	N
% T_f SATURATION	↓	↓	↑	N
TIBC	↑↑	↓	↓↓	N

MEGALOBLASTIC ANEMIA

→ Macrocytic Anemia → ↑ Size
→ megaloblastic anemia → ↑ Size & N:C Asynchrony

ETIOLOGY

1. Vit B_{12} deficiency
2. FA deficiency
3. Drugs

VITAMIN B12 DEFICIENCY

Normal functioning requires
→ Intrinsic factor [parietal cells]
→ Pancreatic enzymes [Duodenum]
→ Ileum [site]

Normal function [required for]
→ rapid division of cells
→ DNA synthesis

→ Homocysteine ⟶ Methionine

→ methyl malonyl CoA ⟶ Succinyl co A [req. for myelin synthesis]

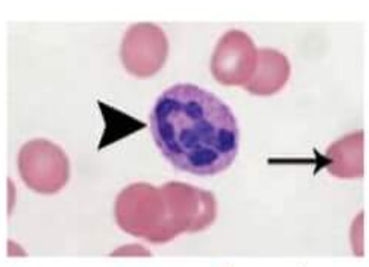
ETIOLOGICAL FACTORS

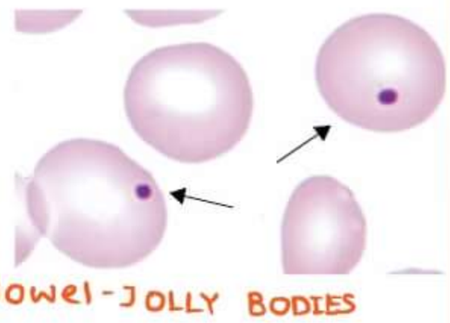
→ ↓ Intake → VEGANS [× no milk]
→ ↓ Absorptⁿ → ↓ IF
Pancreatic disease
Ileal disease
Fish tape worm [Diphyllobothrium latum] infectⁿ

→ ↑ Requirement → Children
→ Pregnancy
→ Lactation
→ Blind loop syndrome [overgrowth of bacteria]

CLINICAL FEATURES

1. BLOOD / Bm CHANGES
→ Pancytopenia
→ Dyserythropoiesis


Macro-ovalocyte

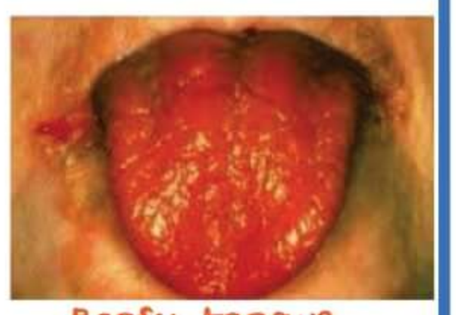

HOWEL-JOLLY BODIES

RBC → MACRO - OVALOCYTOSIS [earliest manifestatⁿ]
BASOPHILIC STIPPLING ⊕
HOWEL JOLLY BODIES

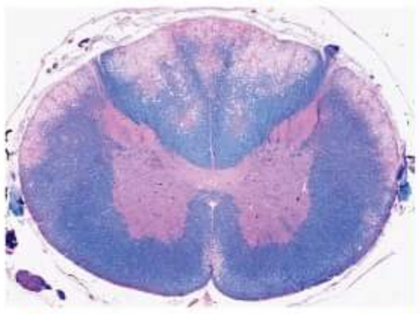
WBC  B12 Def. → 

Hypersegmented neutrophils
[≥ 5 nuclei]

PLATELETS → ↑↑ Size
→ Abnormal Shape


Beefy tongue

2. GIT
→ Mucosal Atrophy
→ Tongue → Smooth → BEEFY TONGUE


Sub acute combined degeneration of SC

3. CNS
→ ↓ myelin
↳ peripheral neuropathy
Ascending / descending tract involvement → SUB ACUTE COMBINED DEGENERATION OF SPINAL CORD
[also seen in neurosyphilis]

CLINICAL FEATURES → Anemia + Jaundice + Neurological Features

DIAGNOSIS

1. BLOOD
→ ↑ MCV
→ ↑ MCH
→ Ⓝ MCHC [MCV/MCH]
→ Basophilic stippling ⊕
→ Howell Jolly bodies ⊕
→ Hypersegmented neutrophils

2. SERUM VIT. B_{12} → ↓↓
S. Homocysteine → ↑
mm CoA → methyl malonylemia [Blood]
methyl malonyluria [urine]

3. BM → Hypercellular BM } INEFFECTIVE
↓↓↓ Reticulocytes } ERYTHROPOIESIS

PERNICIOUS ANEMIA
→ Auto immune
↳ I → ↓ [IF + B_{12}] [most specific]
↳ II → Ileal Ⓡ
↳ III → parietal cells

→ ↓↓ B_{12} absorptⁿ
→ Intestinalization occurs [predominant in fundus | Body] → ↑Cancer

→ DIAGNOSIS → Auto Abs ⊕
→ SCHILLING TEST
→ done for CAUSE OF B_{12} deficiency
→ not done for diagnosis of B_{12} deficiency

→ TREATMENT

1. B_{12} supplementation
   - → in pernicious anemia → Life time
   - → in other causes → for specific period

→ ON TREATMENT ↓ B_{12}

- → BLOOD PICTURE → Reversal
- → NEUROLOGICAL C/F → no further aggrevation / no reversal
- → CANCER → higher than normal

2. FOLATE DEFICIENCY

Poly glutamate form of folate [DIET]

mono glutamate form absorbed in SI [JEJUNUM]

ETIOLOGY

- → ↓ Intake
- → ↓ absorptⁿ
- → ↑ requirements

- → Drugs which ↓ absorptⁿ
  - → alcohol
  - → Methotrexate & OCPs

→ Chr 21 → location for FA ®

CLINICAL FEATURES

- → megaloblastic anemia
- → no neurological manifestations

DIAGNOSIS

1. S. Folate → ↓↓
2. RBC Folate → ↓↓ [Best test]
3. FIGLU TEST [Formimino glutamate]

Histidine → ↑ FIGLU ⫫ (FA) → Glutamate
↓
urine ⊕

MEGALOBLASTIC ANEMIA

↓ B_{12}
NS ⊕
MMCoA ↑

↓ FA
NS ⊖
MMCoA - (N)

Rx → Vit B_{12} + FA
never FA alone

HEMOLYTIC ANEMIAS : BASIC CONCEPTS & CLASSIFICATION

RBC DESTRUCTION → ↓ O_2 [Blood] → HYPOXIA [🫁] → ↑ EPO → (Bm) → ↑ RBC PRODUCTⁿ

ETIOLOGY

INTRA CORPUSCULAR HEMOLYTIC ANEMIAS

1. INHERITED
   1. Hereditary Spherocytosis
   2. G6PD Deficiency
   3. Thalassemia
   4. Sickle cell anemia
2. ACQUIRED
   - PNH [Paroxysmal nocturnal Hemoglobinuria]

EXTRA CORPUSCULAR HEMOLYTIC ANEMIAS

IMMUNE MECHANISM
1. ABO Incompatibility
2. Rh Incompatibility
3. autoimmune hemolytic anemia

NON - IMMUNE MECHANISM
1. Clostridium → Toxin
2. Snake venom → Toxin
3. Sequestration
4. mechanical damage
   - ↳ Angiopathic hemolytic anemia
   - ↳ march hemoglobinuria [Soldiers]

CLINICAL FEATURES

1. ↑ RBC LYSIS → ↑ LDH, ↑ unconjugated Bilirubin → JAUNDICE; Release of FREE Hb [TOXIC]

FREE Hb + Haptoglobin / Hemopexin → Haptoglobin - Hb → ↓ S. HAPTOGLOBIN

FREE Hb → Blood hemoglobinemia → urine hemoglobinuria [altered color urine]

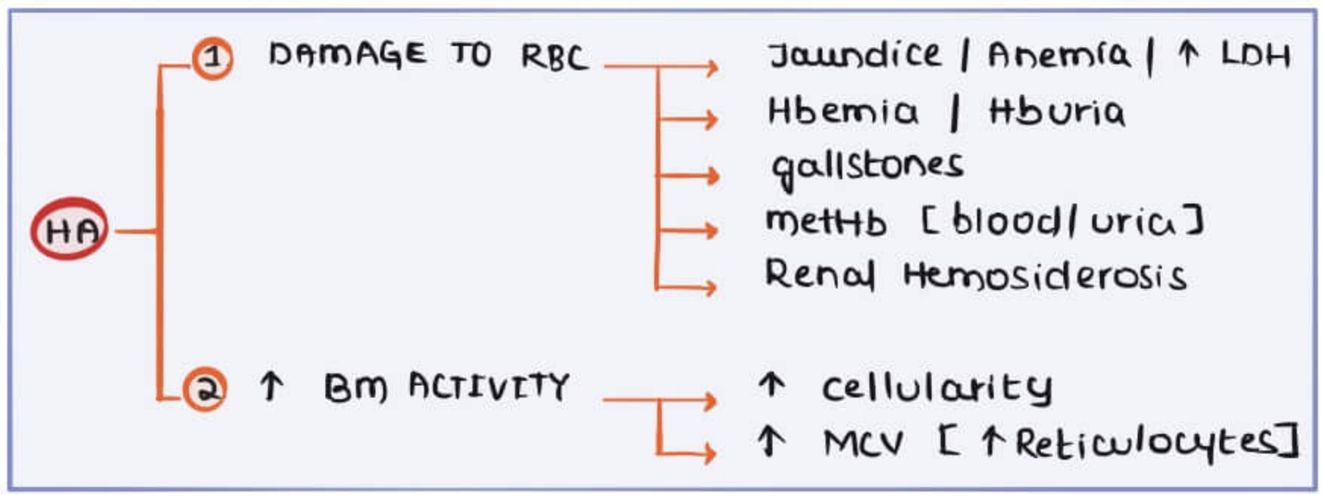
FREE Hb —(Fe^{2+} → Fe^{3+})→ METHEMOGLOBIN → Methemoglobinemia & MetHburia

→ RENAL HEMOSIDEROSIS

Chronic Hemolytic anemia → ↑↑↑ UCB → Ca^{2+} Bilirubinate → PIGMENT GALL STONES

2. ↑ EPO → ↑ Bm activity [compensatory] → Hypercellular Bm & ↑ Reticulocytes [↑MCV]

EXCEPTION → in Fe / B_{12} / FA deficiency → no reticulocytosis



SITES OF RBC DAMAGE

INSIDE SYSTEMIC CIRCULATION [INTRAVASCULAR HA]

- → Hbemia ⊕ ⊕ ⊕
- → Hburia ⊕ ⊕
- → S. haptoglobin ↓↓↓
- → no hepatomegaly
- → no splenomegaly
- → Ex:
  - G6PD DEFICIENCY
  - PNH

INSIDE REC | SPLEEN [EXTRA VASCULAR HA]

- → Hbemia ⊕
- → Hburia ⊕
- → S. haptoglobin ↓
- → hepatomegaly ⊕
- → splenomegaly ⊕
- → Ex:
  - SICKLE CELL ANEMIA
  - HERIDITARY SPHEROCYTOSIS

INTRA CORPUSCULAR HEMOLYTIC ANEMIA

INHERITED

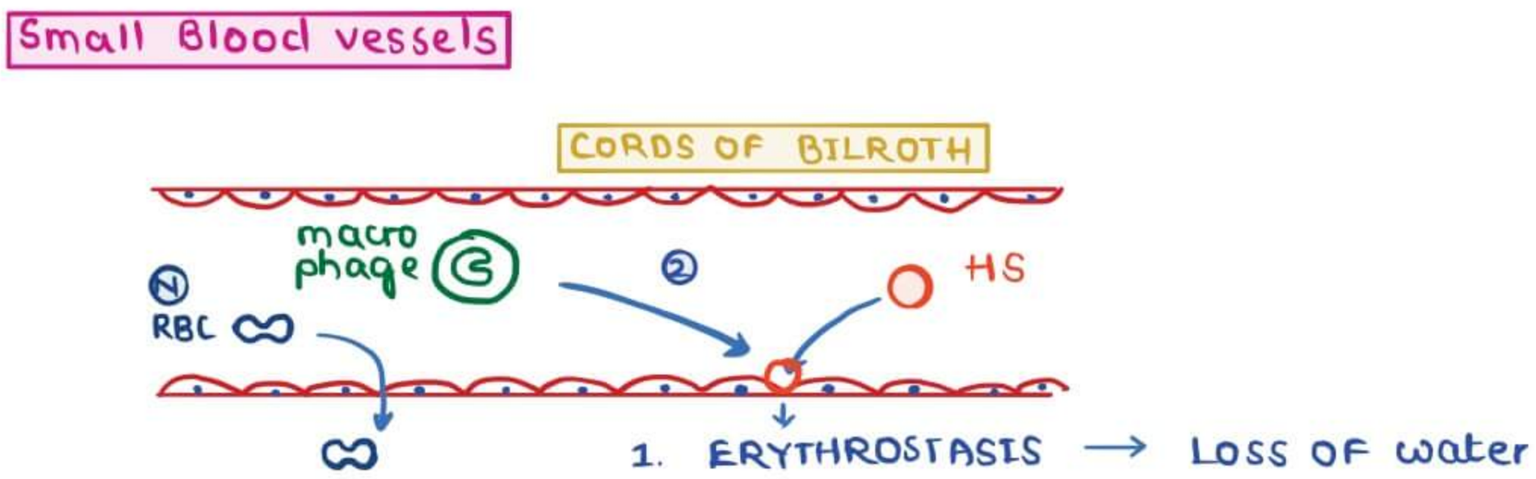
1. Membrane defects → HS | HE
2. Enzyme defects → G6PD DEFICIENCY
3. Hb defects → THALASSEMIA

HERIDITARY SPHEROCYTOSIS

PATHO PHYSIOLOGY

→ NORMAL RBC
- → Biconcave → Flexible
- → Biconcavity is dlt → Spectrin | Ankyrin | Band 3 | Band 4.1

→ HERIDITARY SPHEROCYTOSIS
- → membrane defect dlt Ankyrin > Band 3 > Spectrin



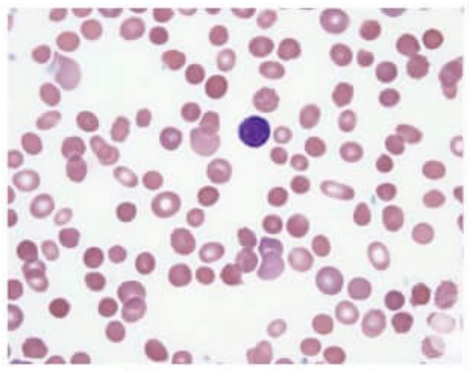
HS → Spherical RBC → 1. Loss of water → but can reach P. circulat^{n}
2. Eaten up by Splenic macrophages
↳ Leads to Extravascular hemolytic anemia

CLINICAL FEATURES

→ Anemia [t ½ ↓↓]
→ Jaundice
→ Splenomegaly
→ Autosomal Dominant → H/o in family ⊕

DIAGNOSIS

1. BM EXAMINATION → ↑ Cells / ↑ reticulocytes
2. BLOOD
   → ↓ Hb | ↑ LDH / ↓ S. haptoglobin
   → MCH → Ⓝ
   → MCV → ↓
   → MCHC → ↑↑↑ [$\frac{MCH}{MCV}$]


SPHEROCYTES

→ P/I SMEAR shows Spherocytes [no central pallor]
→ OSMOTIC FRAGILITY TEST [RBC in hypotonic solution]


NORMAL RBC


Heriditary Spherocytosis [↑ osmotic fragility]

→ AUTOHEMOLYSER [0.9% Nacl [Kept RBC for 48 hrs]]
   ↳ Ⓝ → < 4% RBC destruct^{n}
   ↳ HS → > 15% RBC destruct^{n}

→ EKTACYTOMETRY
   ↳ can detect the shearing stress OF RBC
   ↳ Recent test

TREATMENT

1. ELECTIVE SPLENECTOMY
   1. Severity of anemia → ↓
   2. Shape of RBCs → no change [Spherical]
   3. Chance of infection → ↑ [by capsulated bacteria]
      ↳ pneumococcus
      ↳ H. influenzae

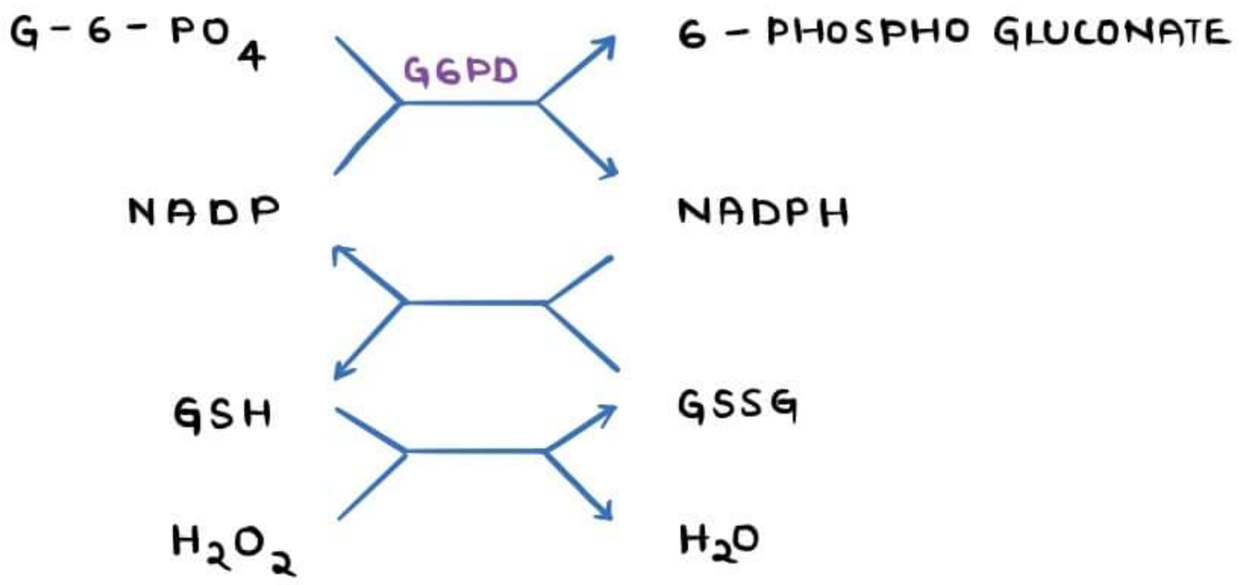
COMPLICATIONS

1. APLASTIC CRISIS
   ↑ BmA → ↑ Erythroid precursors → Susceptible to Parvo virus

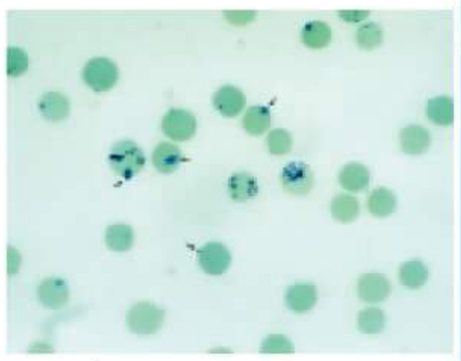
2. ↑ INFECTIONS [post splenectomy]
3. HS → Chronic Hemolysis → Pigment gallstones

2. HERIDITARY ELLIPTOCYTOSIS [d/t SPECTRIN defect]

G6PD DEFICIENCY

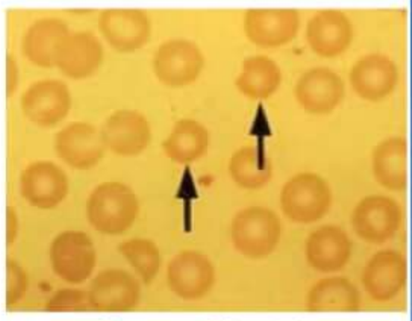


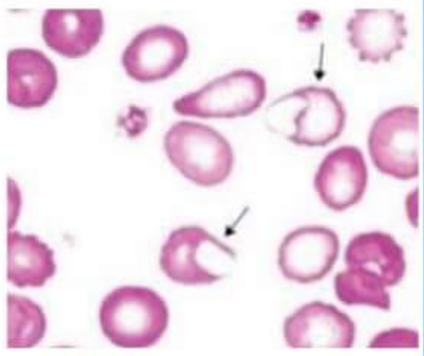
G-6-PD DEFECT
↓
RBC → ↑ Susceptibility to Oxidative damage
↓
Denaturath of Hb chains
↓
HEINZ BODY ⊕


HEINZ BODIES

Direct Damage to RBC
↓
I/V Hemolysis

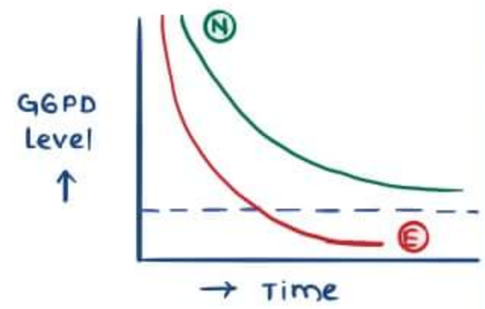
↓ Flexibility of RBC
↓
in Splenic circulath
↓
1. BITE CELL
2. SPHEROCYTE
3. BLISTER CELL
↓
E/V HEMOLYSIS


BITE CELLS


BLISTER CELLS

→ OXIDATIVE STRESS ⟶ HEMOLYSIS
↓
1. Infections [pneumonia / sepsis]
2. Drugs [Anti malarials [primaquine], sulfa drugs, anti TB drugs]
3. Foods [Fava beans]

G6PD DEFICIENCY
→ x Linked Recessive Disorder
→ unstable enzyme
→ ↓↓↓ $t_{1/2}$



G6PD DEFICIENCY → STRESS → Elderly RBC destroyed → SELF LIMITING HEMOLYSIS

VARIANTS

G6PD - B > G6PD - A+ > G6PD - A- > G6PD - m

↓ ↓ ↓ ↓

Normal $t_{1/2}$ ↓ $t_{1/2}$ ↓↓ $t_{1/2}$ ↓↓↓↓ $t_{1/2}$

↓ ↓

most common most severe

DIAGNOSIS

1. HISTORY [♂ > ♀]
2. BLOOD → ↓ Hb
   → MCH → N
   MCV → N
   MCHC → N

   → PI smear
   ↳ Bite cells ⊕
   ↳ Blister cells ⊕
   ↳ Spherocytes ⊕
   ↳ Heinz Body ⊕ [visualised by Crystal Violet]

→ SPHEROCYTES IN PERIPHERAL SMEAR

DID

1. HS
2. G6PD Def
3. Infections [clostridium]
4. Auto Immune hemolytic anemia [mc]

3. G6PD LEVEL ESTIMATION

↳ Electrophoresis → Sub type

↳ Sodium nitrite

↓

Methemoglobin Reduction assay

→ G6PD DEFICIENCY → Rapid clearance of RBC

↳ P. falciparum → PROTECTIVE

℞ → NO drugs required [Self Limiting]

HEMOGLOBINOPATHIES - SICKLE CELL ANEMIA

HB DEFECTS

→ ↓ quantity → Thalassemia

→ ↓ quality → Sickle cell anemia

SICKLE CELL ANEMIA

PATHOPHYSIOLOGY

Point mutation → β_6 Amino Acid

Glutamic Acid [Normal] (GOES) (β) Polar AA	Valine [Sickle cell anemia] (VELCOME) (β^S) Neutral AA

→ Hb → TETRAMER → 2 α
→ 2 β

2α →
- $\beta|\beta$ → $\alpha_2\beta_2$ → Hb A [Normal]
- $\beta|\beta^S$ → $\alpha_2\beta_2$ → Hb A [60%] } SICKLE CELL TRAIT [heterozygous
- $\beta^S|\beta^S$ → $\alpha_2\beta_2^S$ → Hb S [40%] }

↳ $\alpha_2\beta_2^S$ → Hb S → SICKLE CELL DISEASE
→ no Hb A

→ HbS → RBC → ↓ Solubility of Hb → Precipitation → Polymerization → SICKLING

FACTORS AFFECTING SICKLING

1. AMOUNT OF HbS [most important]
   - → HbS → ↑ Sickling [SCD >>> SCT]
   - → HbF, → HbA } ↓ Sickling
   - → HYDROXYUREA, → DECITABINE } ↑↑ HbF → ↓ Sickling
2. ACIDOSIS
3. EXERCISE
4. DEHYDRATION → ↑ MCHC
5. TIME OF RBC FOR CIRCULATION
   - ↳ Spleen / BM → Sluggish flow → ↑ Sickling

↓ O2 / ↓ H2O

O2 / H2O

REVERSIBLE SICKLING

↓ O2 / ↓ H2O

IRREVERSIBLE SICKLING

↑ Stiffness → ↓ Flexibility → Trapped in Spleen → EV HA

↑ Stickiness → ↑ Adhesion to Endothelial cells → MICROVASCULAR OCCLUSION → 

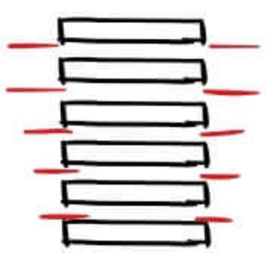
C/F

- → Jaundice
- → anemia
- → splenomegaly
- → retarded growth

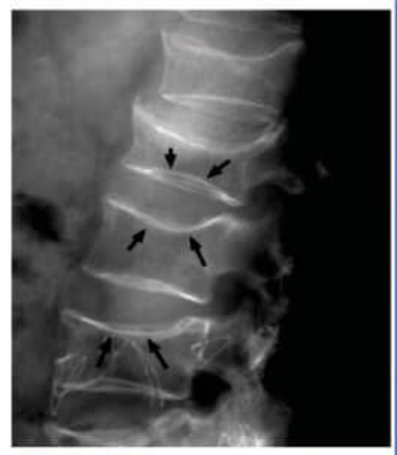
COMPLICATIONS

1. VASO OCCLUSIVE CRISIS

- → Brain → coma / ↓ conciousness / Stroke
- → Bones
  - ↳ small bones of hands & feet → HAND - FOOT SYNDROME
  - ↳ Long bones → Avascular necrosis of neck of femur
  - ↳ Vertebral column

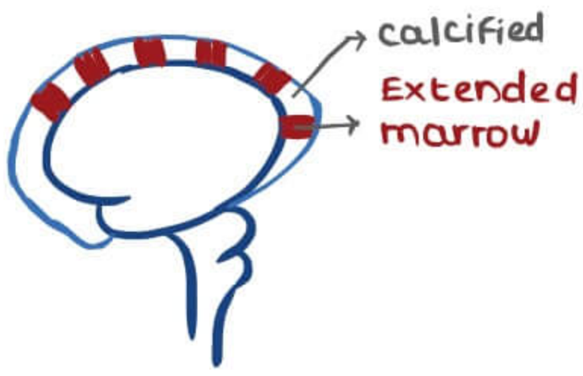


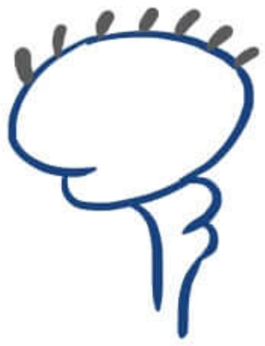
H - SHAPED VERTEBRA
COD FISH VERTEBRA
FISH MOUTH VERTEBRA



COD FISH VERTEBRA

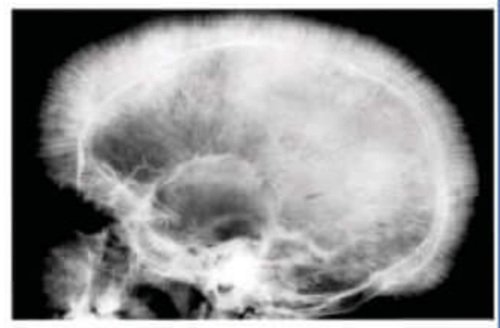
- → SKULL





calcified area

HAIR ON END APPEARANCE
CREW CUT APPEARANCE



CREW CUT APPEARANCE

- → SKIN → chronic non healing leg ulcers
- → SPLEEN → ↑↑ size initially → congestive splenomegaly
  Later → Arterial occlusⁿ → Ischemic damage → FIBROSIS OF SPLEEN
  [AUTO SPLENECTOMY]

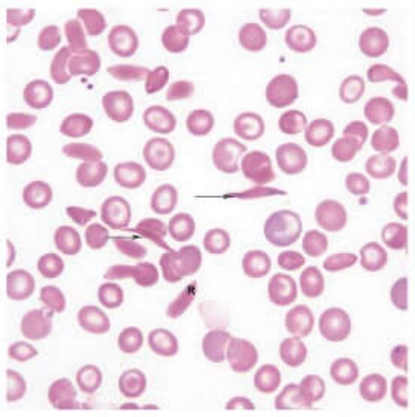
→ PULMONARY CIRCULATION
  → ACUTE CHEST SYNDROME
    ↳ pain in chest
    ↳ Dyspnea
    ↳ ↓ O_2 in blood

→ ♂ → Painful erection → PRIAPISM

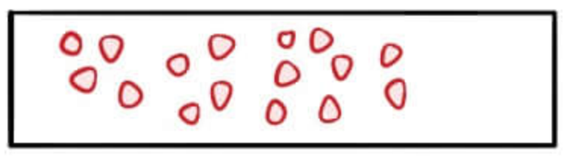
2. APLASTIC CRISIS → ↑ BMA → Parvo virus infection
3. HEMOLYTIC CRISIS → Infection → ↑↑ Splenic activity
4. SEQUESTRATION CRISIS → ↑↑↑ Splenic Size → hypovolemia

DIAGNOSIS

1. BM → ↑ cells / ↑ Reticulocyte count
2. BLOOD → ↑ LDH / ↑ S. Bilirubin
   → ↑↑↑ TLC
   → ↓↓↓ ESR


SICKLED CELLS

→ PERIPHERAL SMEAR shows → SICKLED CELLS (±)

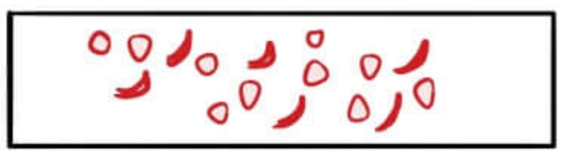


↓

Add DITHIONITE METABISULFITE TEST

↓

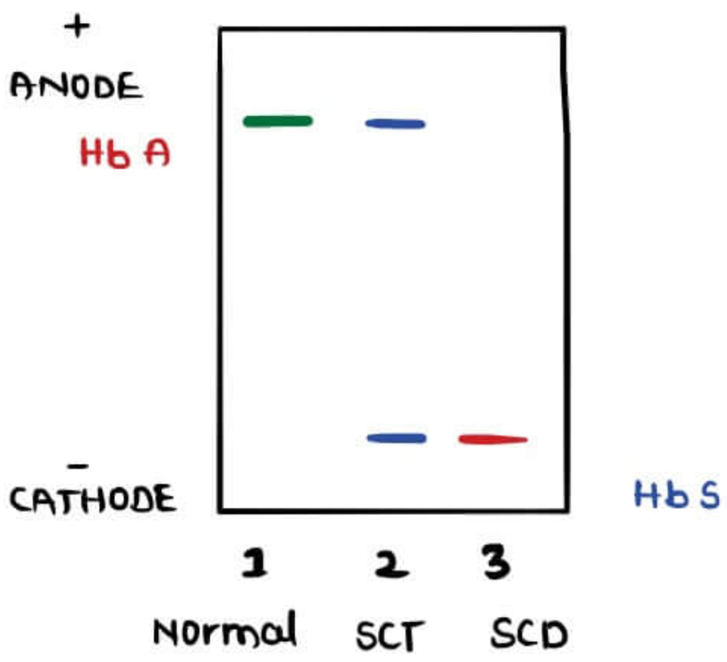
can't distinguish blw SCT/SCD



3. Hb ELECTROPHORESIS

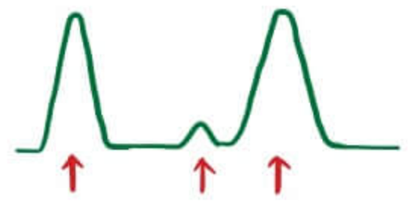
Glutamic acid [Polar] [HbA]

Valine [Neutral] [HbS]



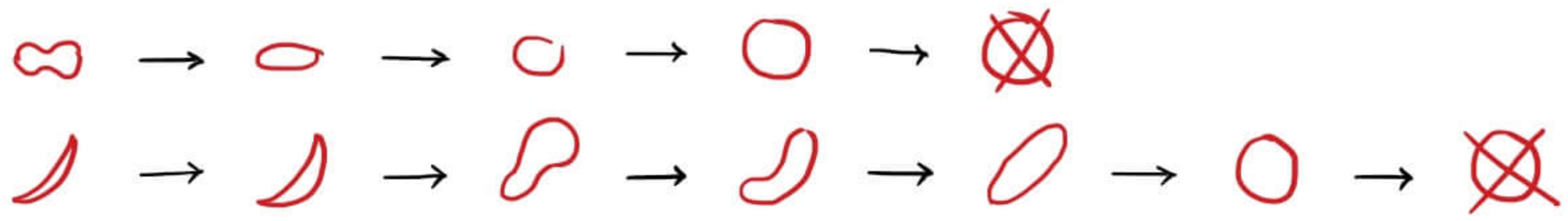
→ require expertise
→ quantification of different Hb types not possible

4. HPLC [HIGH PERFORMANCE LIQUID CHROMATOGRAPHY]



→ can be differentiate the types of Hb
→ quantity of Hb can be known
→ IOC FOR ALL TYPES OF HEMOGLOBINOPATHIES

5. OSMOTIC FRAGILITY TEST



→ SCA → ↓ Osmotic Fragility
↳ also seen in Hemoglobinopathies
→ Thalassemia
→ Severe IDA
→ HbC [β_6 → glutamic acid → Lysine]

6. X RAY → Skull → HAIR ON END APPEARANCE
Vertebra → FISH MOUTH APPEARANCE

TREATMENT

1. O_2
2. IVF
3. ANALGESICS
4. ANTIBIOTICS
5. HYDROXYURIA, DESITAMINE } ↑ HbF

MORTALITY COMMONLY DUE TO → SEPSIS

β THALASSEMIA

→ Quantitative disorder of Hb

Hb → 2α → 4 α genes → Chr 16
2 β → 2 β genes → Chr 11

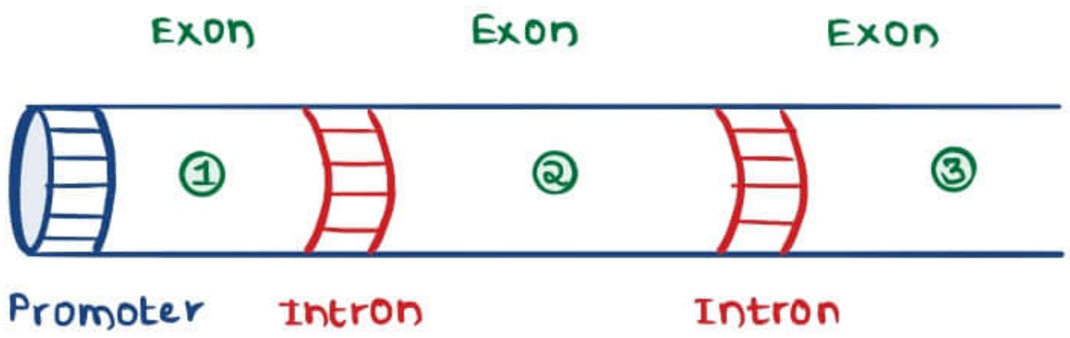
α THALASSEMIA → dlt gene deletion
β THALASSEMIA → dlt gene mutation [more common]

β THALASSEMIA

NORMAL [adult] → Hb A / Hb F / Hb A_2
↓ ↓ ↓
$\alpha_2\beta_2$ $\alpha_2\gamma_2$ $\alpha_2\delta_2$

95% 1% 3%

β → normal β chain formation
β^+ → partial β chain formatⁿ
β^0 → no β chain formatⁿ



SPLICING [Introns removed]

mRNA

RIBOSOMES

↓

translation

↓

β FORMATION

INTRON → Intervening region

EXON → Expressive sequence

PROMOTOR → increases the no. of β chains

→ MUTATIONS

1. SPLICING MUTATIONS → $\beta^+ >>> \beta^0$
   [Intron > Exon]

2. PROMOTER MUTATIONS → β^+

3. CHAIN TERMINATION MUTATION → β^0

CLINICAL POSSIBILITIES

β/β → NORMAL → 14 - 17 g/dl

1. β/β^+ → mild → THALASSEMIA MINOR / THALASSEMIA TRAIT
   ↳ Hb > 10 g/dl
   ↳ Asymptomatic

2. β^+/β^+ → moderate → THALASSEMIA INTERMEDIA
   ↳ Hb → 6 - 7 g/dl
   ↳ Blood transfusions ±

3. β^0/β^+
   β^0/β^0 → Severe → THALASSEMIA MAJOR
   ↳ Hb < 6 g/dl
   ↳ multiple blood transfusions

β THALASSEMIA MAJOR

BONE MARROW

Relative excess of α chains

↓

α - Chain precipitation

- Direct damage to Normoblast → ↓ No. of actual RBCs [INEFFECTIVE ERYTHROPOIESIS]
- Escape in circulation → Trapped in Spleen → EVHA

→ SEVERE ANEMIA

ANEMIA +++

↓

↑↑ EPO

- ↑ Bm ACTIVITY
- EXTRA MEDULLARY HEMATOPOIESIS
  - L / S → Hepato & Splenomegaly
  - BONES → Facial bones ⊕, SKULL ⊕

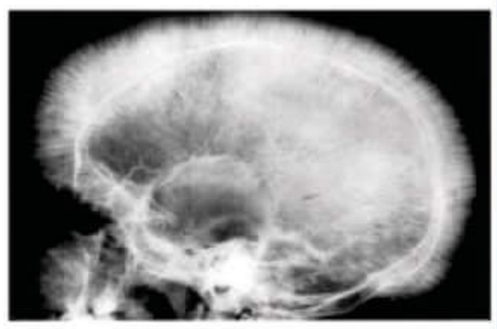
FACIAL BONES INVOLVEMENT

→ Frontal Bossing
→ Malocclusion of teeth

} CHIPMUNK FACIES

SKULL INVOLVEMENT

→ CREWCUT / HAIR ON END APPEARANCE



CREW CUT APPEARANCE

→ ↑ Release of Iron From BM → ↑ Iron absorption → Multiple Blood transfusions

IRON OVERLOAD

Heart | Pituitary | Pancreas | Liver | Parathyroid

→ CARDIAC / ENDOCRINE FAILURE → DEATH

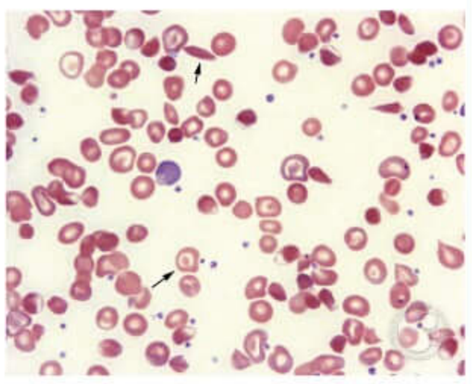
C/F

→ Anemia +++
→ Stunted growth
→ chipmunk facies
→ Hepato & Splenomegaly

DIAGNOSIS

1. BLOOD

→ ↓↓↓ Hb
MCV ↓↓
MCH ↓↓
MCHC ↓↓



→ PERIPHERAL SMEAR
↳ microcytosis
↳ anisocytosis
↳ poikilocytosis
↳ target cells 
↳ basophilic stippling [dlt abnormal RNA]
↳ ↑ Reticulocyte count [not proportional to severity of anemia]
↳ Normoblasts ⊕

2. OSMOTIC FRAGILITY ↓↓↓
3. HPLC → IOC

α — $\beta \rightarrow \alpha_2\beta_2 \rightarrow$ ↓↓↓ HbA
α — $\gamma \rightarrow \alpha_2\gamma_2 \rightarrow$ ↑↑↑ HbF [highly suggestive]
α — $\delta \rightarrow \alpha_2\delta_2 \rightarrow$ ↑ HbA_2

α : β RATIO → 1 : 1 [Normal]
30 : 1 [Thalassemia major]

THALASSEMIA TRAIT / MINOR

→ ↓ Intensity
→ mild anemia
→ no H/O Blood transfusion
→ P/ SMEAR → Mild ⊕

♂ ♀ Thalassemia major → do not marry
T.trait T. trait → AR → Thalassemia major [25%]

→ SCREENING
→ osmotic fragility → ↓

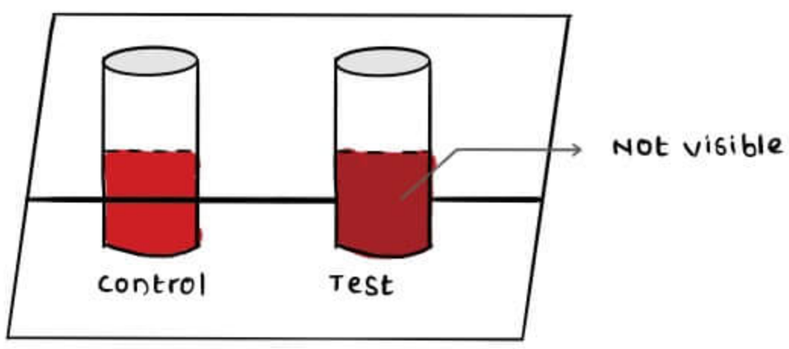


image @ 55:45

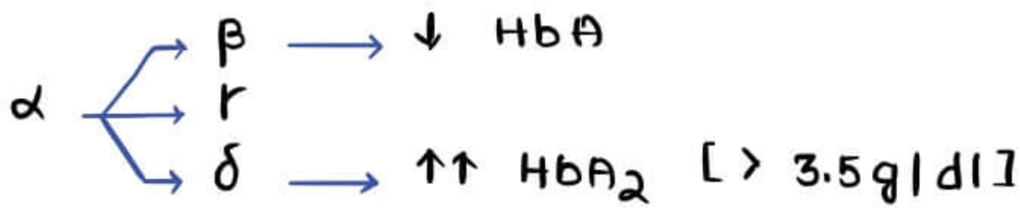
SCREENING

→ Hypotonic saline [5ml]
→ 0.2 ml Blood
→ Wait for 30 minutes

NESTROF TEST

→ NE → Naked Eye
ST → Single tube
R → Red cell
OF → Osmotic fragility
TEST → Test

→ Diagnosis confirmed by HPLC of Hb



→ THALASSEMIA TRAIT VS IDA by HPLC
other parameters

RDW	N	↑↑↑
mentzer index MCV / RBC count	< 13	> 13
HPLC	↑↑ HbA2	↓ HbA

ALPHA THALASSEMIA

→ dlt GENE DELETION
→ Chr 16 → 4α genes → 2 α Chains

αα / αα → Normal [100% α chains]
1. αα / α_ → Asymptomatic [75% α chains]

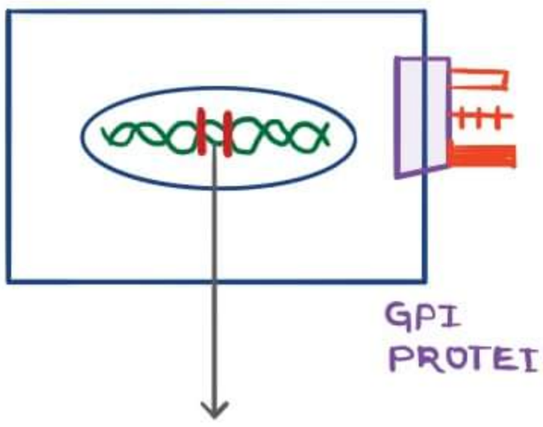
2. α_ / α_ → Asymptomatic [50% α chains]
αα / __ → Asymptomatic [ASians] [50% α chains] [CIS α Thalassemia] [marriage not advised]

3. α_ / __ → [25% α chains]
↓
β_4 TETRAMER [HbH]
↳ high precipitat^{n} → EVHA
↳ high O_2 affinity → Tissue hypoxia

4 __ / __ → Fetal life
↓
γ_4 TETRAMER [BARTS Hb]
↳ IUD → HYDROPS FETALIS

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA [PNH]

→ ACQUIRED INCORPUSCULAR HEMOLYTIC ANEMIA [only cause]



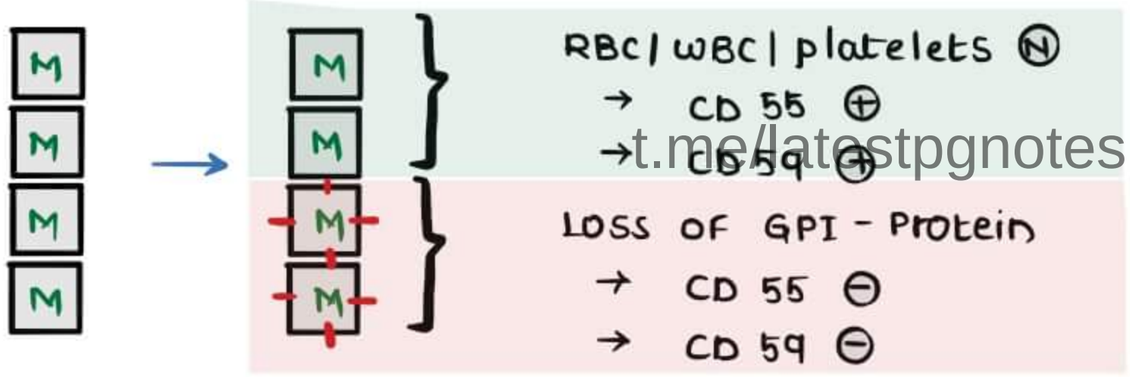
CD55 [DAF]
CD59 [MIRL]
C_8 Binding protein
} ↓ Spontaneous
© protein activation

PIG-A Gene [x chr]
[Phosphatidylinositol glycan complementation A gene]

→ Synthesizes GPI Link protein [Transmembrane protein]
→ serves as ANCHOR

DAF – Decay Accelarating factor
MIRL – Membrane Inhibitor of Reactive Lysis

→ In PNH, PIGA gene defect ⊕

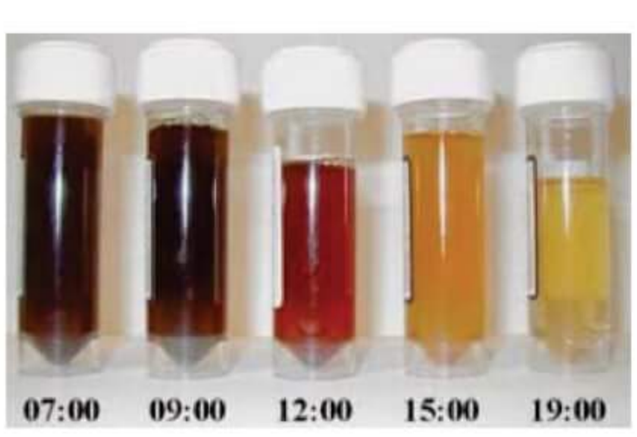


→ BIPHENOTYPIC CELLS

Myeloid Stem cells

→ COMPLEMENT ACTIVATION → DESTRUCTION OF RBC / WBC / PLATELETS → PANCYTOPENIA

→ RBC Destruction
[Night] → ↓ RR → ↑ CO_2 → ↑ H^+ [ACIDOSIS]
↓
© SYSTEM
↓
RBC Damage
↓
IV HEMOLYSIS
↓
HbURIA
[altered color of urine]

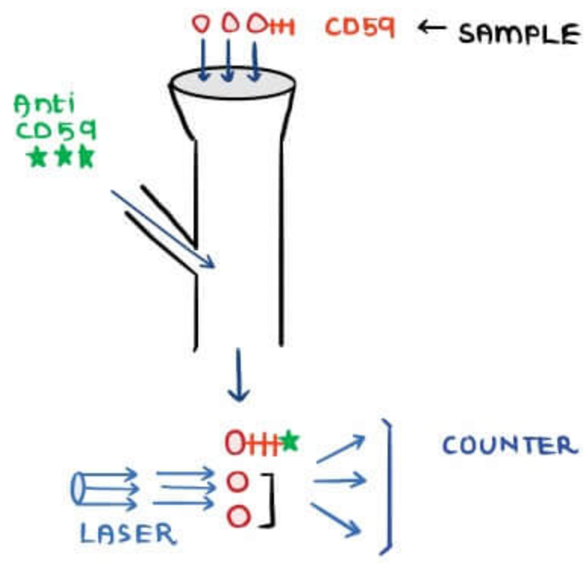


→ WBC → Dysfunction → ↑ INFECTIONS

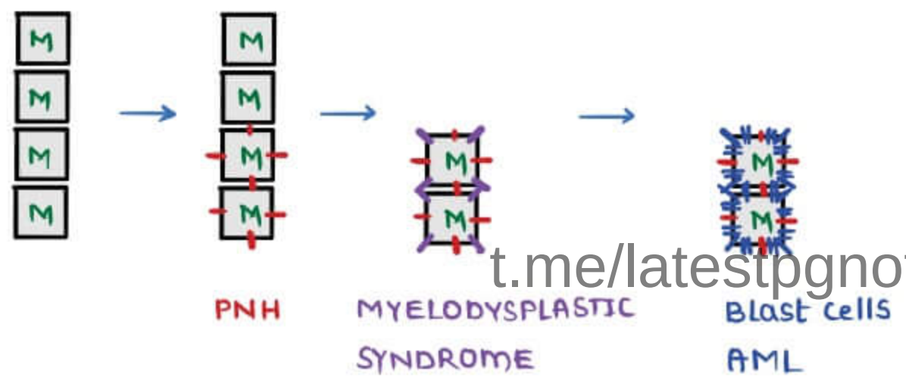
→ PLATELETS → ↓ platelet count
→ Altered function
↓
↑ Aggregation ← Free Hb [d/t IVH]
+
NO
↓
↑ THROMBOSIS
[cerebral veins | Hepatic veins] → DEATH
↓
BUDD CHIARI SYNDROME

→ DIAGNOSIS

1. FLAER - FLOW CYTOMETRY [IOC]
→ Fluorescein - Labelled Pro - Aerolysin
→ PNH → 2 DIFFERENT CELLS
BIPHENOTYPIC APPEARANCE



2 ↑ © ACTIVITY → Sugar / ACID [presence]
→ HAM'S ACIDIFIED SERUM TEST
→ SUCROSE LYSIS TEST



→ PNH also a/w APLASTIC ANEMIA

Auto Ab ⊕ → GPI-P → PNH
→ Stem cell Ag → APLASTIC ANEMIA

→ TREATMENT

PNH → ↑↑ © Proteins Damage

C_5 CONVERTASE INHIBITOR → ECULIZUMAB

STEM CELL TRANSPLANTATION [definitive R_x]

AUTO IMMUNE HEMOLYTIC ANEMIA

→ EXTRA CORPUSCULAR HEMOLYTIC ANEMIA
→ IMMUNE MEDIATED
  ↳ Auto immune HA

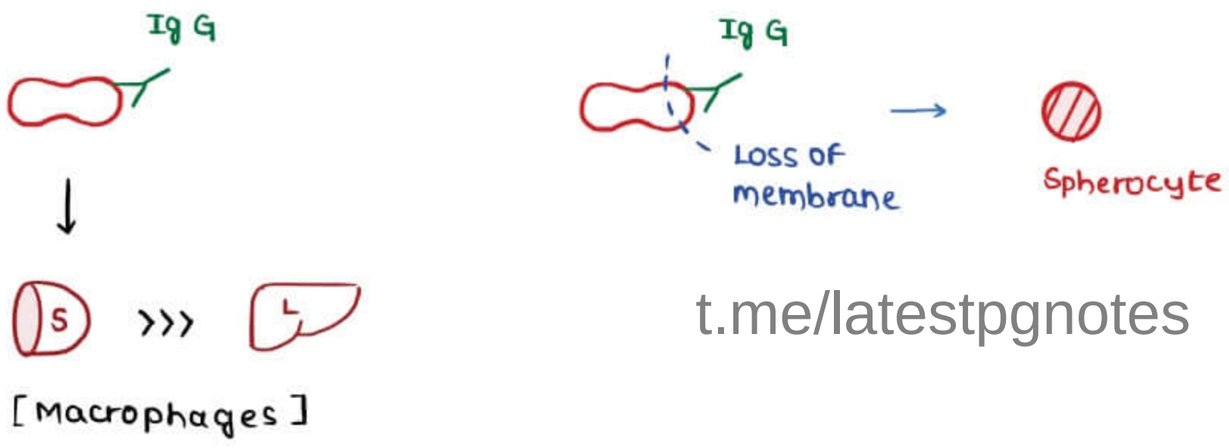
AUTO IMMUNE HA - SUB TYPES

WARM AHA [GOA - Hot]
↓
Ab attach at 37°C
Ig G >>> Ig A

COLD AHA [MUSSOORIE - cold]
↓
Ab attach at lower temp.
Ig M >>> Ig G

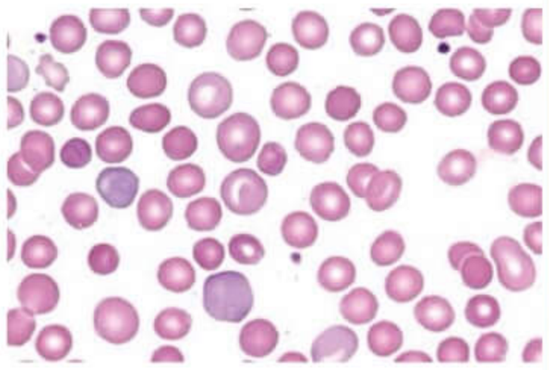
WARM AHA

→ Ig G / Ig A
→ bind at 37°C
→ Idiopathic
→ a/w auto immune disorders [SLE / RA]
→ a/w malignancies [CLL]
→ a/w Drugs [d methyl dopa / Penicillin / Quinidine]

→ 

[Macrophages]
↓
EVH

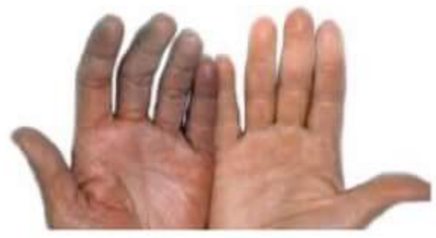
→ C/F → Anemia
→ Jaundice
→ Severe splenomegaly
→ Spherocytes



→ DIAGNOSIS
1. ↑ LDH / ↑ UC Bilirubin / ↓ Hb
2. BLOOD → Pl smear → Spherocytes
→ Auto - Ab ⊕
  - On RBC surface → DIRECT COOMBS TEST
  - Serum [Free] → INDIRECT COOMBS TEST

→ Jaundice | Anemia | Splenomegaly | Spherocytosis seen in
↳ Auto immune Hemolytic Anemia → coomb's Test → + ive
↳ Heriditary Spherocytosis → coomb's Test → − ive

COLD AUTO IMMUNE HA – @ <37°C



1. COLD AGGLUTININ DISEASE

→ Ig M against 'I' Ag of RBC
→ attaches at cold temperature
→ results in CLUMPING / AGGLUTINATION → ACROCYNOSIS

At body temp [37°C] → detachment of Ig M

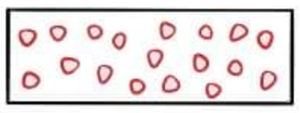
Ig M $\xrightarrow{+}$ © proteins → C_{3b} attachment

↓
Hepatic circulation [Kuppercells]
[Hepatomegaly ⊕]
↓
EVH

→ a/w Ig M
→ a/w → Mycoplasma infection
→ malignancies
→ infectious mono nucleosis
→ waldenstrom macroglobulinemia

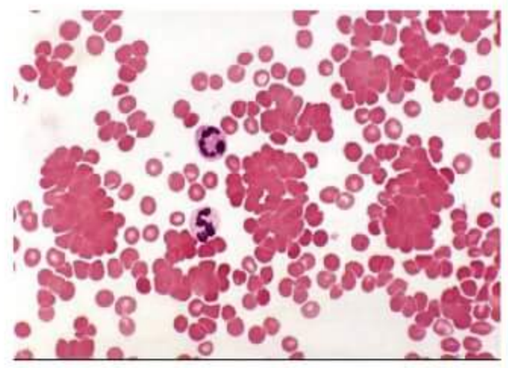
→ DIAGNOSIS

1. COLD SLIDE TEST



Ⓝ temp

chilled slide



2. COLD HEMOLYSIN TYPE

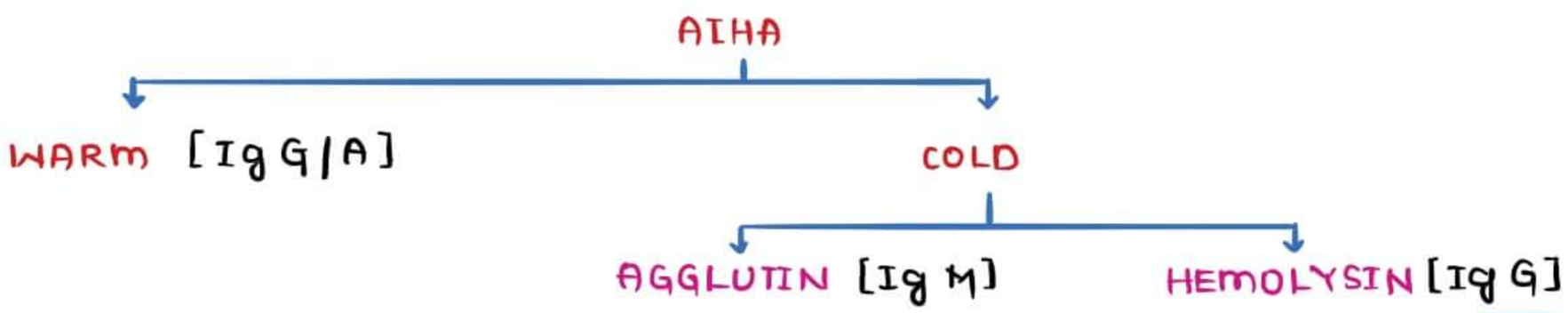
→ Ig G against 'P' antigen of RBC
→ binds at 4°C

→ © activation at 37°C

→ 37°C → © Activation → MAC formatⁿ → IVH → Hburia

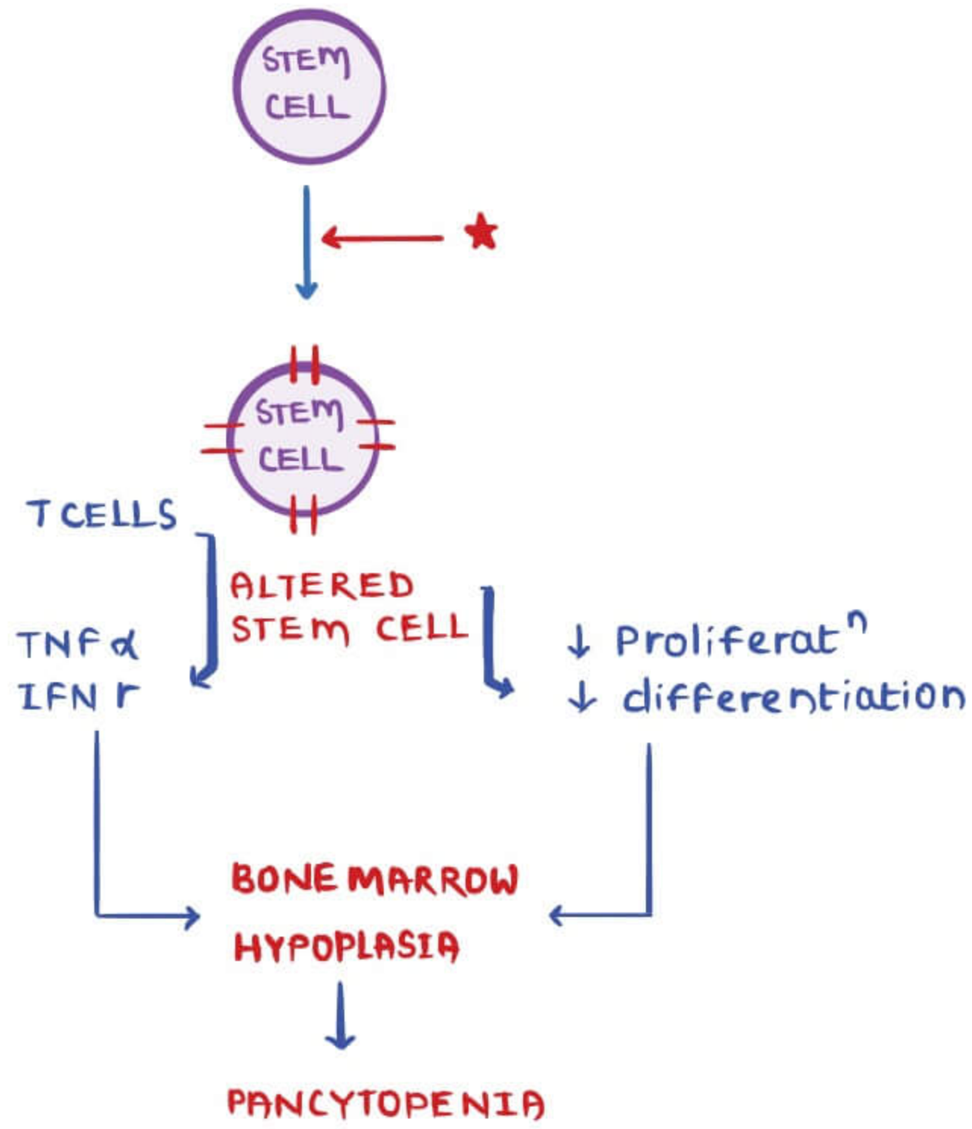
→ COLD HEMOLYSIN DISEASE [PARAOXYSMAL COLD HBURIA (PCH)]

→ COLD HEMOLYSIN Ab aka → DONATH – LANDSTEINER Ab
↳ seen in children ī viral infection
↳ a/w Syphilis
↳ aka BIPHASIC Ab



APLASTIC ANEMIA

→ a/w Hematopoietic Stem Cell defect → PANCYTOPENIA



IMPORTANT INFO

→ DRUGS
  → Anti Thymocyte Globulin [ATG] } ↓ T cell activity → useful in Aplastic anemia
  → Cyclosporine }

→ AA can progress to
  → MDS
  → AML

→ AA also a/w PNH [dlt T cell activity against GPI-linked protein]

APLASTIC ANEMIA - CAUSES

1. INHERITED
   → Telomerase defect
   → Fanconi Anemia
      - AR
      - Defect in DNA Repair genes
      - Hypoplasia [Kidney | Spleen]
      - Bone defects [Radius | thumb]

      - FANCONI SYNDROME IS A/W RENAL TUBULAR DAMAGE [different from FA]

2. ACQUIRED
   a. IMMUNE MEDIATED
   b. IDIOPATHIC [mcc]

3. CHEMICALS
   a. DOSE RELATED → Alkylating Agents / Anti Metabolites / Chloramphenicol
   b. DOSE UNRELATED [IDIOSYNCRATIC S/E] [even 1 Single dose can cause AA]
      - Gold salts
      - chloramphenicol

4. PHYSICAL
   → Radiation
   → viruses [EBV, VZV, CMV]

CLINICAL FEATURES

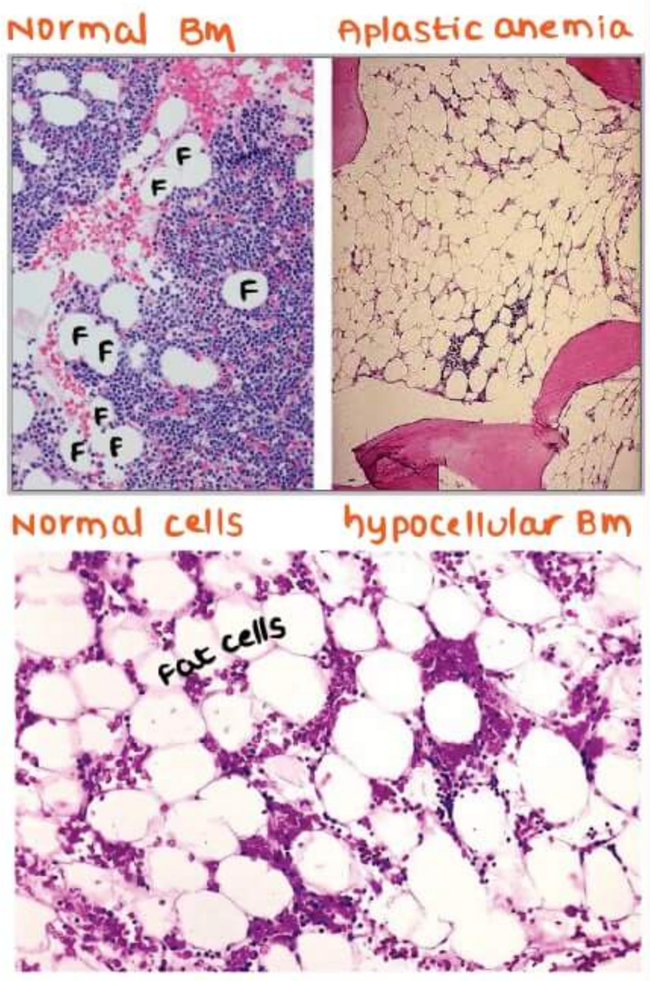
→ no age prediliction
→ no sex prediliction
→ FEATURES OF PANCYTOPENIA
   ↳ Fatigue
   ↳ Fever
   ↳ Hemorrhage [bleeding manifestations]

→ SPLENOMEGALY NEVER SEEN

DIAGNOSIS

1. BLOOD
   → Pancytopenia
   → Reticulocytopenia
   → macrocytic, normochromic RBCs

2. Bm ASPIRATION → DRY TAP
3. Bm BIOPSY
   → ↓ cellularity
   → this feature differentiates AA From
      - MDS
      - Aleukemic leukemia
      } hyper-cellular



APLASTIC ANEMIA

TREATMENT

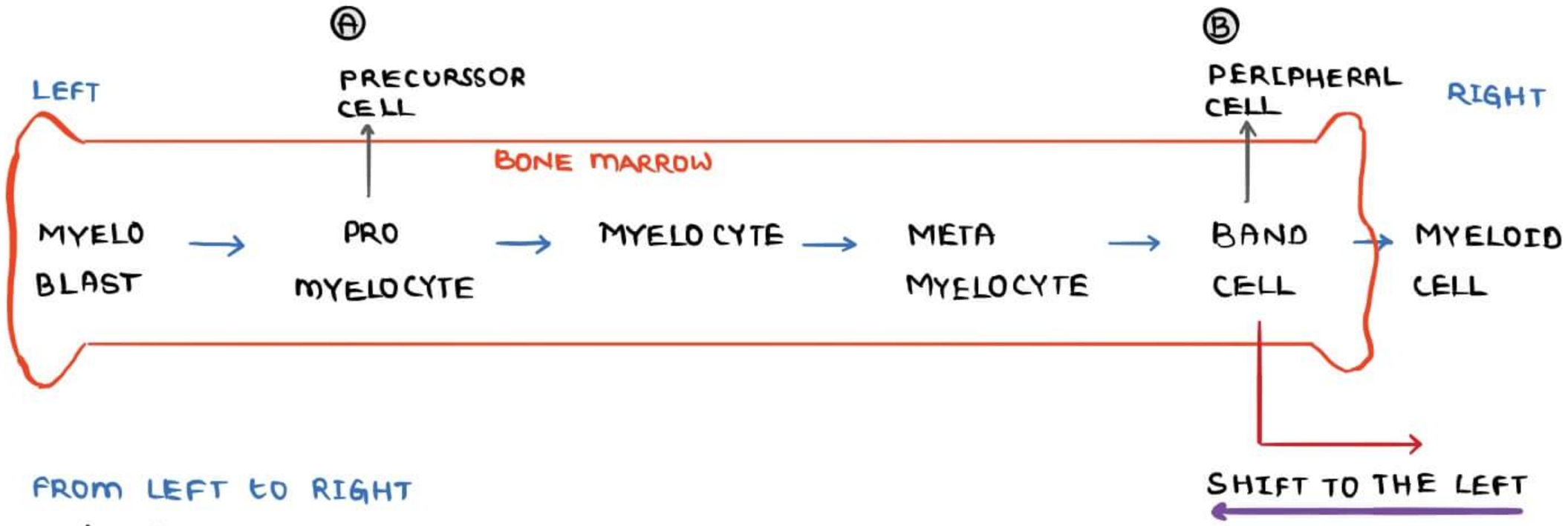
→ TOC → Bone marrow Transplantation
→ DRUGS → Anti Thymocyte Globulin [ATG], Cyclosporine

CLASSIFICATION OF APLASTIC ANEMIA

NON - SEVERE / MODERATE AA	Bm Cellularity < 25%
SEVERE AA	Bm Cellularity < 25% + Any 2 out of 3: Absolute neutrophil count < 500/mm^3; Platelet count < 20,000/mm^3; Reticulocyte count < 60,000/mm^3
VERY SEVERE AA	SEVERE AA ī Absolute neutrophil count < 200/mm^3

→ common cause of death in patients ī severe & very severe AA → Septicemia

WHITE BLOOD CELLS
INTRODUCTION TO WBC DISORDERS



FROM LEFT TO RIGHT
- ↓ Size
- ↓ Rate of Replication
- ↑ maturation

DISORDERS AFFECTING WBCs

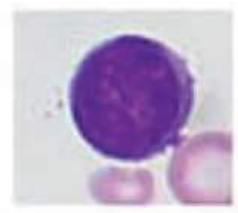
I ↓ WBCs → LEUCOPENIA

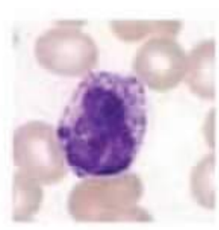
II ↑ WBCs → BENIGN & NEOPLASTIC

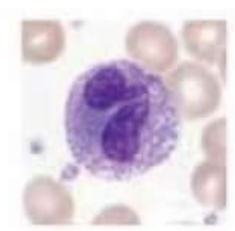
↑ WBCs - BENIGN

1. LEUCOCYTOSIS [↑↑↑ TLC]
   - → TLC → Ⓝ 4,000 - 11000 /μL
   - → DLC [Differential Leucocyte Count]


Monocyte


Lymphocyte


Basophil


Eosinophil


Neutrophil

Never → Neutrophils [50-70%]
Let → Lymphocytes [20-40%]
Monkeys → Monocytes [8-10%]
Eat → Eosinophils [0-5%]
Bananas → Basophils [0-2%]

→ NEUTROPHILIA
- → Bacterial infections
- → necrosis
- → Acute inflammation
- → DRUGS
  - ↳ Steroids
  - ↳ Lithium

→ Lymphocytosis
- → viral infections
- → chronic inflammation

→ monocytosis
- → chronic inflammation
- → cancers

→ EOSINOPHILIA
- → Allergy
- → parasitic infections
- → Hodgkin Lymphoma

→ Basophilia
- → allergy
- → CML

2. LEUKEMOID REACTION

→ TLC → 40,000/μl

→ Seen in

↳ Pneumonia
↳ Infective Endocarditis
↳ Sepsis
↳ Kawasaki Disease

} ↑ Mature white Blood cells

→ D/D → CML

→ differentiated by LAP SCORE

→ LAP SCORE

→ ↑ed in Leukemoid reaction
↓ed in CML

→ Dohle Bodies & toxic granules are also Leukemoid reactions
Dohle Bodies → Dilated Endoplasmic reticular structures

↑ WBC — NEOPLASTIC WBC PROLIFERATION

LEUKEMIA

SEQUENCE OF INVOLVEMENT

Extensive Bm involvement
↓
SYSTEMIC circulation
↓
Liver / LN / Spleen / Brain
[organs]

LYMPHOMA

SEQUENCE OF INVOLVEMENT

LN / Liver / Spleen [Organs]
↓
SYSTEMIC CIRCULATION

LEUKEMIA ⇌ LYMPHOMA

CLINICAL FEATURES — LEUKEMIA

→ ↓ RBC / WBC / platelets → PANCYTOPENIA

↳ fatigue / pallor
↳ recurrent fever
↳ petechiae / purpura

→ HYPERVISCOSITY OF BLOOD
→ LYMPHADENOPATHY / HEPATOSPLENOMEGALY
→ HEADACHE / CRANIAL NERVE PALSY

CLINICAL FEATURES — LYMPHOMA

→ LYMPHADENOPATHY / HEPATOSPLENOMEGALY
→ BLOOD & Bm INVOLVEMENT

LEUKEMIA - PATHOGENESIS

NORMAL

IMMATURE WBC → ① → MATURE WBC

IMMATURE WBC → ② → APOPTOSIS

LEUKEMIA

IMMATURE WBC → ① (blocked) → MATURE WBC

IMMATURE WBC → ② (blocked) → APOPTOSIS

① MATURATION ARREST [most important]
② RAPID RATE OF PROLIFERATION

LEFT — BONE MARROW — RIGHT

MYELO BLAST → PRO MYELOCYTE → MYELOCYTE → META MYELOCYTE → BAND CELL → MYELOID CELL

PRO MYELOCYTE → (A)
BAND CELL → (B)

(A) → Acute onset → ACUTE LEUKEMIA → Precursor cell leukemia

(B) → Gradual Onset → CHRONIC LEUKEMIA → Peripheral cell Leukemia

ACUTE LYMPHOBLASTIC LEUKEMIA

HSC

MYELOBLAST

- → prominent nucleoli
- → granular cytoplasm [AUER RODS]
- → stained by MPO ⊕

↓

AML

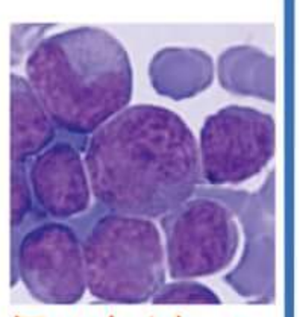
LYMPHOBLAST

- → condensed nucleoi [0-2]
- → no granular cytoplasm
- → Stained by TdT ⊕

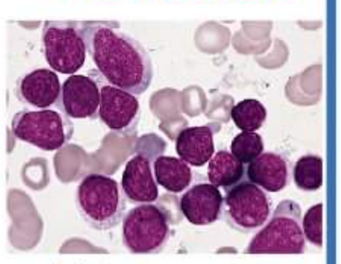
↓

ALL

MPO → myeloperoxidase
TdT → Terminal deoxynucleotidyl transferase



myeloblast



LYMPHOBLAST

BLAST CELLS IN BM

- → (N) → 1-2%
- → Acute leukemias → > 20% [WHO]
- → IOC → BM Examination

RISK FACTORS OF ACUTE LEUKEMIAS

GENETIC	ACQUIRED
↳ Fanconi anemia ↳ Bloom Syndrome ↳ Ataxia telangiectasia ↳ Down Syndrome ↳ ALL [overall] ↳ AML [< 3yrs]	↳ Radiation exposure ↳ Chemicals [Benzene | Smoking [PHC]] ↳ Infections [EBV / HTLV 1] ↳ Drugs [Anti cancer drugs]

ACUTE LYMPHOBLASTIC LEUKEMIA [ALL]

→ mc leukemia in children

→ C/F → Sudden onset of clinical symptoms
- ↳ Fatigue | fever | petechiae
- ↳ hepatosplenomegaly | Lymphadenopathy
- ↳ Sternal tenderness ⊕

→ GENETIC DEFECT
- → Hyperploidy | hypoploidy
- → Trisomy 4 | 7 | 10
- → t [12;21] , t [4;11] , t [9;22]

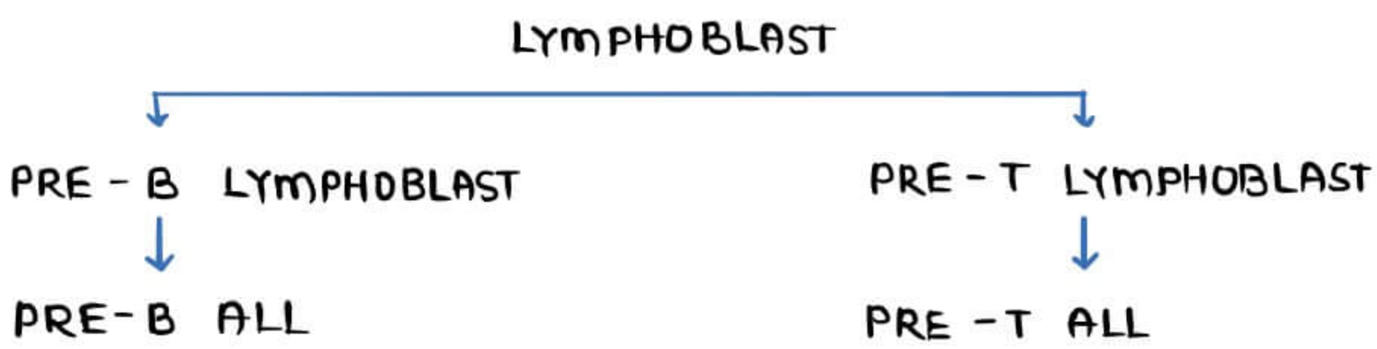
→ DIAGNOSIS

1. BONE MARROW EXAMINATION [IOC]
   - → Hypercellular
   - → Blasts
     - ↳ > 20%
     - ↳ lymphoblasts → TdT ⊕ , PAS ⊕

2. BLOOD
   - → ↑↑↑ TLC
   - → ↓ Hb
   - → ↓ platelets
   - → Lymphoblasts ⊕
   - → ALEUKEMIC LEUKEMIA → absence of WBC in Blood

3. IMMUNOPHENOTYPING

→ WHO CLASSIFICATION



PRE - ● ALL	PRE - ● ALL
→ more common	→ Less common
→ Bm ⊕ ⊕ ⊕	→ Thymus ⊕ ⊕ ⊕
→ Peak @ 3 yrs	→ Peak @ Puberty
→ Pancytopenia ⊕	→ Retrosternal mass ⊕
→ EBF / PAX-5 mutation	→ NOTCH gene mutation
→ [Loss of function]	→ [Gain of function]
→ Good prognosis	→ Poor prognosis
→ CD 19 / 20 ⊕	→ CD 1/2/5/7 ⊕

PROGNOSTIC FACTORS FOR ALL

	GOOD PROGNOSIS	POOR PROGNOSIS
PLOIDY	→ Hyperploidy t [12;21] → Trisomy 4/7/10	→ t [9;22]
RACE	→ White	→ Black
OLD	→ 1 - 10 years	→ < 1 year or > 10 years
GENDER	→ Girl	→ Boy
No. of Cells	→ Less Blasts	→ more Blasts
ORGANS	→ Less involvement	→ more involvement ↳ Thymus ↳ Testis
SUB TYPE	→ Pre-B ALL	→ Pre T - ALL
INFILTRAT^{n}	→ Lesser	→ Higher
STEROIDS / DRUG RESPONSE	} ⊕	} ⊖

TREATMENT

ANTI CANCER DRUGS

V → VINCRISTINE
A → ASPARAGINASE
P → PREDNISOLONE
D → DAUNORUBICIN
Mtx → METHOTREXATE
↳ intra thecally
↳ for brain metastasis

ALLOGENIC BONE MARROW TRANSPLANTATION [Definitive Rx]

CHRONIC LYMPHOCYTIC LEUKEMIA [CLL]

→ mc leukemia in adults
→ ETIOLOGY UNKNOWN
→ Radiation not associated ī CLL

→ GENETIC DEFECTS
  ↳ 11q deletion
  ↳ 17p deletion
  ↳ 13q deletion
  ↳ Trisomy 12q
  ↳ NOTCH - ® gain function

→ B CELL ⟶ PLASMA CELL ⟶ Ig

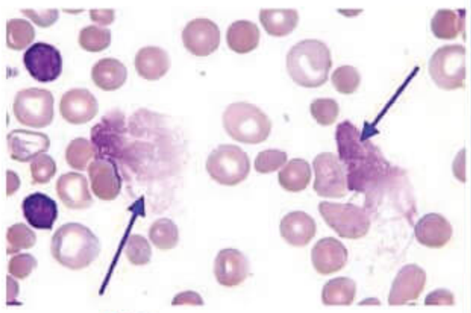
B CELL mutation ⟶ abnormal Plasma cells ⟶ abnormal Igs

ABNORMAL Igs → ↑↑↑ Infections
→ Auto - Abs [IgG] ⟶ RBCs ⟶ AIHA

↳ PERIPHERAL SMEAR →

B cells

SMUDGE CELLS / PARACHUTE CELLS / BASKET CELLS



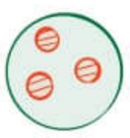
SMUDGE CELLS

→ C/F
  → Elderly [age group]
  → Gradual onset
  → ASymptomatic mostly
  → Fatigue / Cervical Lymphadenopathy / fever / hepatosplenomegaly

→ DIAGNOSIS

1. BLOOD EXAMINATION
   → Absolute lymphocyte count [ALC] → > 5000 cells / Ml
   → ↓ Hb / ↑ TLC
   → Peripheral smear shows SMUDGE CELLS
   → Auto Abs ⊕ detected by coomb's Test

2. BM EXAMINATION → Hypercellular [↑ Lymphoid cells]
3. LN EXAMINATION
   → GROSS → Effaced
   → MICROSCOPIC → Proliferation centres



4. IMMUNO PHENOTYPING

B CELL CANCER → CD_{19} ⊕ , CD_{23} ⊕
→ CD_{20} ⊕ , CD_5 ⊕

→ CLL
↓
Additional mutations
↓
DIFFUSE LARGE
B CELL LYMPHOMA
↓
Sudden LN & Spleen
Enlargement ⊕

} RICHTER SYNDROME

→ PROGNOSTIC FACTORS

POOR PROGNOSIS

1. 11 q ⊖ / 17 p ⊖
2. ZAP 70 ⊕
3. NOTCH – ® mutation
4. Somatic hypermutation ⊖

→ TREATMENT

1. FLUDARABINE [DOC] → anti metabolite
2. IBRUTINIB → B cell tyrosine kinase ⊖

ACUTE MYELOGENOUS LEUKEMIA

RISK FACTORS

→ ANTI - CANCER DRUGS
→ poor a/w viruses
→ t [8;21] , t [15;17] , inv 16 [t [16;16]]
→ 50 - 60 yrs age
→ MYELOBLAST ⊕

AML - CLASSIFICATION

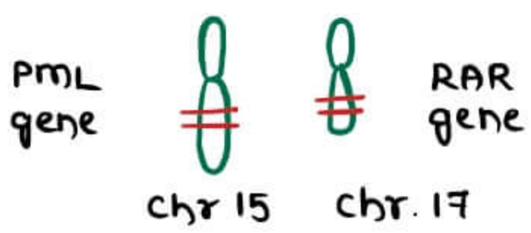
FAB CLASSIFICATION [BLASTS → > 30%]

M_0 → Minimally Differentiated AML
M_1 → AML without maturation
M_2 → AML with maturation
M_3 → Acute Promyelocytic leukemia
M_4 → Acute myelomonocytic leukemia
M_5 → Acute monocytic leukemia
M_6 → Acute Erythroleukemia
M_7 → Acute megakaryocytic leukemia

→ M_1 , M_2 , M_3 , M_4 → MPO ⊕
→ M_5 → Non Specific Esterase ⊕
→ M_6 → PAS ⊕
→ M_7 → CD_{41} / CD_{61} ⊕

ASSOCIATIONS

→ AML - M_2 → t [8;21] → CHLOROMA
→ AML - M_3 → t [15;17] → AUER RODS +++



t [15;17]
↓
PML - RAR gene
↓
↓ Vitamin A activity
↓
↓ Differentiation of cells
↓
↑ immature / cancer cells
↓
Mucin +++
→ Endothelial Cell Damage
→ DIC
→ DEATH

→ Rx by → 1. Vitamin A [All Trans Retinoic Acid]
↳ induce differentiatⁿ of cells
↳ useful in AML - m_3 [APL]

2. ARSENIC TRIOXIDE → for AML - m_3

→ M_7 - AML
  ↳ mc AML seen in Down Syndrome
  ↳ tumor cell secretes PDGF → responsible for MYELOFIBROSIS

→ MC AML seen in clinical practice → m_2 - AML
→ mc AML seen in infants → m_5 - AML
→ mc AML in children → m_7 - AML

WHO CLASSIFICATION [> 20% BLASTS]

I AML with Specific Genetic Defects → t [8;21] → t [15;17] → t [16;16]
II AML [Therapy related]
III AML with multi Lineage dysplasia → with or without MDS
IV AML [NOS - Not Otherwise specified]

→ AML i Specific gene defects can be diagnosed as AML even if there are < 20% of blasts

PROGNOSIS

I. AML i specific genetic defects → Good
IV. AML [NOS] → Intermediate
III. AML i multilineage dysplasia → poor
II AML [Therapy related] → worst prognosis

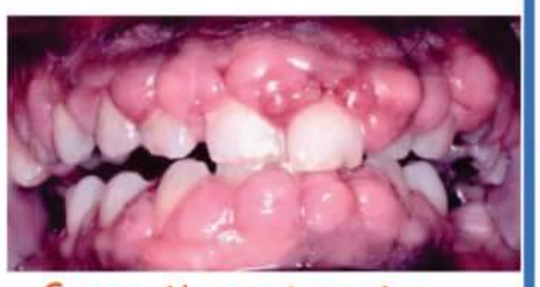
Clf

→ Acute onset of clinical symptoms
→ t [8;21] → Chloroma [green]
  → mc site → Retro orbital tissue
  → Proptosis ⊕
  → CD 45, CD 43, Lysozyme ⊕
  → aka GRANULOCYTIC SARCOMA


Proptosis

→ M_4, M_5 } GUM HYPERTROPHY, LEUKEMIA CUTIS

→ t [15;17] → ↑ DIC → Death


Gum Hypertrophy

DIAGNOSIS

1. Bm EXAMINATION [IOC]
  → myeloblasts ⊕ → MPO⊕ / NSE⊕ / Sudan Black B ⊕

2. IMMUNO PHENOTYPING → CD_{41} / CD_{61} → AML - m_7
  → CD_{45} → AML - m_2

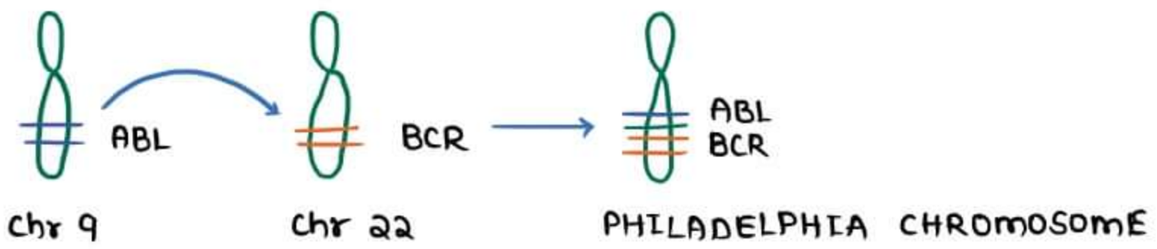
3. CYTOGENETICS

CHRONIC MYELOGENOUS LEUKEMIA [CML]

→ Myeloproliferative disorder

→ RISK FACTORS
1. Radiation
2. Benzene

→ t [9;22] →

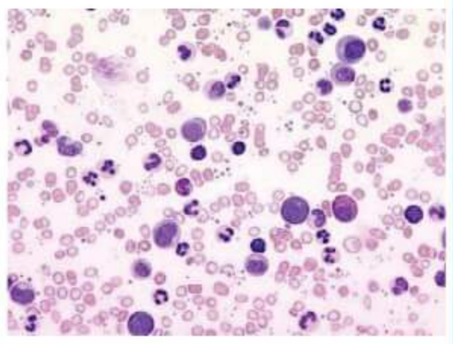


PHILADELPHIA CHROMOSOME
↓
BCR - ABL FUSION GENE
↓
210 KDa protein
↓
↑↑ Myeloid proliferation
⊖ Apoptosis
↓
CML

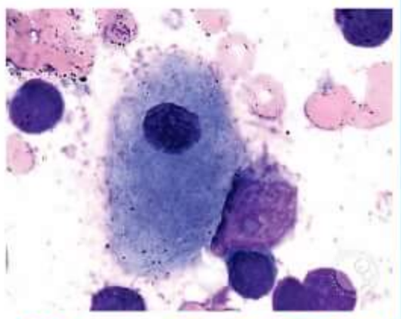
→ CIF
- → middle age [40-60 yrs]
- → mostly Asymptomatic [incidental finding]
- → massive splenomegaly > hepatomegaly > Lymphadenopathy [rare]

→ DIAGNOSIS

1. BLOOD EXAMINATION
   - → ↑↑ TLC / ↑ Platelets
   - → ↑ DLC → ↑ Eosinophils
   - → ↑ Basophils



- → D/D → LEUKEMOID REACTION → ↑ LAP SCORE
- → CML → ↓ LAP SCORE


PSEUDO - GAUCHER CELL

2. BM EXAMINATION
   - → Hypercellular
   - → WBC at different stages
   - → ↑ Reticulin
   - → PSEUDO - GAUCHER CELLS [Histiocytes ī sea blue granules in cytoplasm]

3. CML → Serum B_{12} ↑
4. CYTOCHEMISTRY → ↓↓ LAP SCORE
5. DETECTION OF PHILADELPHIA CHROMOSOME
   - → confirmatory
   - → done by FISH [FLUORESCENT IN SITU HYBRIDIZATION] → IOC

- → BCR ABL fusion DNA also detected by SOUTHERN BLOT

→ STAGES

1. CHRONIC PHASE → ACCELERATED PHASE → BLAST PHASE

↑ Mutations →

<10% Blasts → 10 - 19% Blasts → >20% Blasts

3-6 yrs course → 6 months course → 3 months course

Sudden Splenomegaly
Sudden Lymphadenopathy →

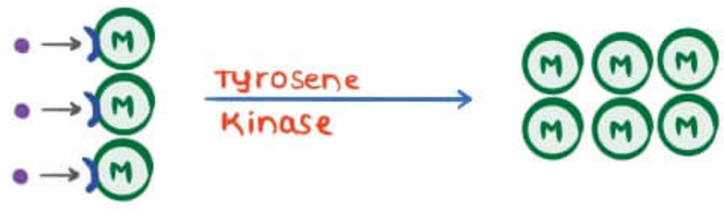
BLAST PHASE
↓
PLURIPOTENT STEM CELL [cell of origin] → Lymphoblasts [30%]
myeloblasts [70%]

ONCOGENE ADDICTION
↓
CML → PHILADELPHIA CHROMOSOME → ↑ Tyrosine Kinase activity → ↑ cancer cells
↑⊖
IMATINIB

MYELOPROLIFERATIVE DISORDERS

→ ↑↑↑ TYROSINE KINASE ACTIVITY ⟶ ↑ Cell numbers [usually one type]
[RBC | WBC | platelets]

→ MYELOFIBROSIS [SPENT PHASE] OF BM
↓
Extra medullary hematopoiesis



→ ADDITIONAL MUTATIONS ⟶ ACUTE LEUKEMIA

EXAMPLES

1. CML → ↑ WBC [predominant]
2. POLYCYTHEMIA VERA → ↑↑ RBCs
3. ESSENTIAL THROMBOCYTHEMIA } ↑ Platelets
4. 1° MYELOFIBROSIS

POLYCYTHEMIA VERA

→ JAK 2 Tyrosine Kinase ⊕
→ Valine Substituted by PHENYL ALANINE [at 617 position]
→ ↑↑↑ RBCs
↑ WBCs
↑ Platelets

→ CIF → Hyper viscosity OF Blood
↓
Neurological manifestations
↳ headache
↳ dizziness
↳ visual disturbance

→ Peripheral circulation
↳ ischemia
↳ cyanosis

→ ↑ venous thrombosis → Hepatic vein thrombosis & DVT
→ ↑ Arterial thrombosis

→ ↑ PLATELETS [dysfunctional] ↑ BLeeding

→ ↑ WBCs [nearly mature] → no risk of Infections
↳ ↑ Neutrophils → ↑ LAP SCORE
↳ ↑ Basophils

ALL MYELO PROLIFERATIVE DISORDERS EXCEPT CML → ↑ LAP SCORE

→ ↑ BASOPHILS → HISTAMINE
↳ pruritus [after hot water bath]
↳ Flushing
↳ Peptic ulcer disease

→ DIAGNOSIS

1. DEMONSTRATION OF JAK 2 MUTATION
2. ↑↑ Hb

↓ Serum EPO ← EPO → RBC → Hb

↑ ⊖

	RBC MASS	EPO	SaO_2	
Dehydration	Normal	Normal	Normal	→ relative polycythemia
Polycythemia vera	↑↑	↓	Normal	
COPD / High altitude	↑	↑	↓	
Ectopic EPO [tumors]	↑	↑↑	Normal	

→ POLYCYTHEMIA VERA ⟶ ACUTE LEUKEMIA

→ Rx

1. PHLEBOTOMY
2. DRUGS
   - ↳ Hydroxyuria
   - ↳ Anagrelide

ESSENTIAL THROMBOCYTHEMIA

ETIOLOGY

1. JAK 2 mutation [mc]
2. MPL mutation
3. Calreticulin mutation

ET ⟶ ↑↑↑ PLATELETS

C/F

→ ↑ venous Thrombosis
→ ↑ Bleeding
→ ERYTHROMELALGIA → Small vessel occlusion
→ Throbbing & burning pain of hands & feet
→ Less chance of going into spent phase
→ Lesser chances of myelofibrosis transformation
→ mild splenomegaly

PRIMARY MYELOFIBROSIS

JAK2 mutation > MPL mutation

↓

↑↑ No. of Neoplastic megakaryocytes

↓

BM fibrosis / ↑↑ collagen

↓ Ineffective EPO → ↓ Anemia

↓ Extra medullary hematopoiesis → ↓ massive splenomegaly → ↓ LEUCO ERYTHROBLASTS [Immature WBC & RBCs]

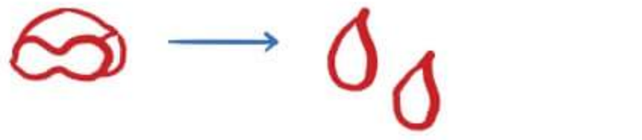
→ CIF

→ CLASSICAL TRIAD

↳ TEAR DROP RBCs

↳ LEUCO ERYTHROBLAST

↳ AB NORMAL PLATELETS



→ Elderly / Anemia / Splenomegaly

→ DIAGNOSIS

Bm EXAMINATION

→ BM ASPIRATION → DRY TAP

→ Bm BIOPSY [IOC]

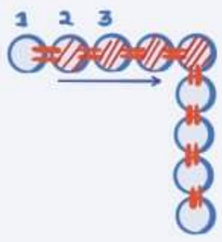
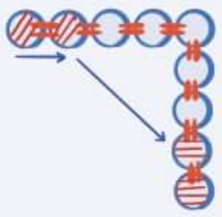
→ 1° MYELOFIBROSIS ⟶ ACUTE LEUKEMIA

→ Least Risk of progression to Acute leukemia among myeloproliferative disorders } ESSENTIAL THROMBOCYTOSIS

→ Least Risk of complications → ET

HODGKIN'S LYMPHOMA

LYMPHOMAS

HODGKIN'S LYMPHOMA	NON HODGKIN'S LYMPHOMA
→ LN involvement ⊕	→ LN involvement ⊕
→ Extra nodal Involvement ⊖	→ Extra nodal Involvement ⊕
→ Cervical / mediastinal LN ⊕	→ Waldeyer Ring ⊕ Mesenteric LN ⊕
	
→ contiguous spread ⊕	→ Non - contiguous spread
→ Staging predictable	→ Staging unpredictable
→ response to Rt ⊕	→ response to Rt ⊖
→ Good prognosis	→ Poor Prognosis

HODGKIN'S LYMPHOMA

ETIOLOGY

→ EBV [mc association]

→ OTHER FACTORS

↳ B CELL → ↑↑ NF - Kβ → ↑↑ cancer cells

Germinal / Post Germinal → ↓↓ I - Kβ [Inhibitor - Kβ]

REED STERNBERG CELL

CLASSICAL RS CELL

→ 15 - 45 μ

→ OWL - EYE APPEARANCE

→ Aneuploidy ⊕ → ↑↑↑ chr. 2p

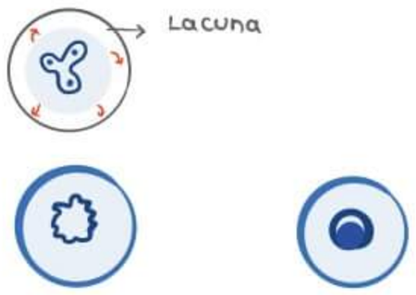
→ CD 15 ⊕

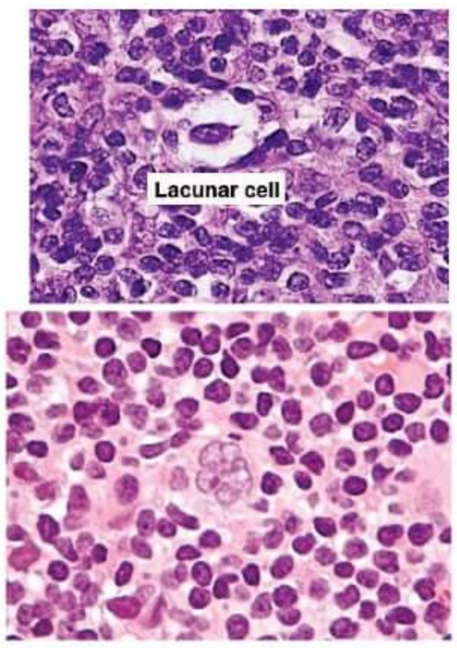
CD 30 ⊕ - marker of Lymphocyte activation


RS CELL

VARIANTS OF RS CELL

1. LACUNAR CELL → a/w TGF - β release → Fibrosis
2. MONONUCLEAR CELL → prominent nucleous
3. LYMPHO HISTIOCYTIC / POPCORN CELL
   - → irregular indentation of nucleus
   - → CD 15 & CD 30 ⊖
   - → CD 20 ⊕
   - → BCL - 6 ⊕





POPCORN CELL

RS CELLS & CYTOKINES

IL - 13	→	↑ Reed Sternberg cells
IL - 5	→	↑ Eosinophils
TGF - β	→	Bands [nodules]
M - CSF	→	↑ monocytes

HL [Hodgkin Lymphoma] → RS cell + Inflammatory cells

RS - LIKE CELLS SEEN IN

- → Infectious mononucleosis
- → Solid tissue cancer
- → Immunoblastic lymphoma

C/F

- → PAINLESS RUBBERY LYMPHADENOPATHY [Cervical LN mostly]
- → CONSTITUTIONAL [B] SYMPTOMS
  - ↳ Fever
  - ↳ Night sweats
  - ↳ wt loss
- → FEVER — PEL - EBSTEIN FEVER
- → PARANEOPLASTIC SYNDROME
  1. Alcohol consumpt^{n} causes PAIN
  2. 2^{o} Amyloidosis

DIAGNOSIS

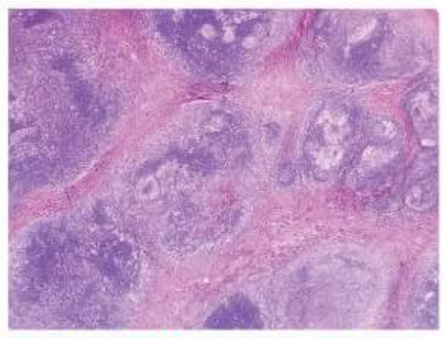
1. CUTANEOUS ANERGY
2. EXCISIONAL LN BIOPSY
   - → IOC
   - → diagnostic & therapeutic
   - → on m/E

CLASSICAL HL			NON-CLASSICAL HL		
→ RS cell	→	CD 15 ⊕	RS cell	→	CD 15 ⊖
		CD 30 ⊕			CD 30 ⊖

SUB TYPES

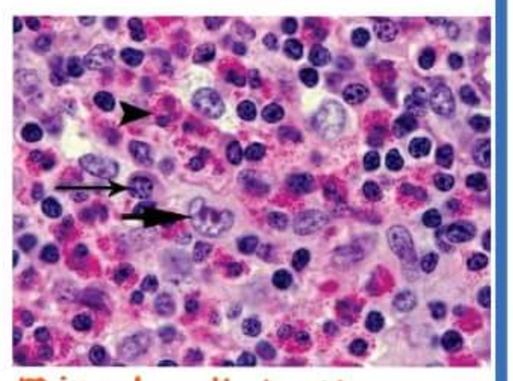
1. NODULAR SCLEROSIS

- → MC HL in the world
- → M = F
- → Nodules ⊕
- → young adults ⊕
- → Lacunar RS cells ⊕


NODULAR SCLEROSIS

2. MIXED CELLULARITY

- → mc HL in India
- → RS cells / plasma cells / Eosinophils / Lymphocytes ⊕
- → mono nuclear RS cells ⊕
- → BIMODAL DISTRIBUTION → young & > 55 yrs
- → maximum incidence of 'B' symptoms


mixed cellularity

MIXED CELL HL
- Bharat
- B symptoms +++
- Bimodal distribution

3. LYMPHOCYTE RICH HL

- → Elderly age group
- → classical RS cells < mono nuclear RS cells ⊕
- → Better prognosis

↑ RS CELLS → Poor Prognosis

↑ Lymphocytes → Good prognosis

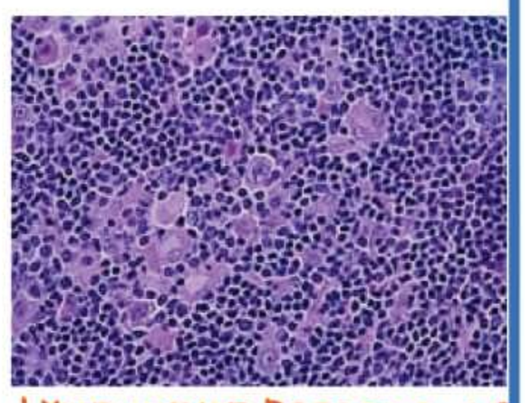
4. LYMPHOCYTE DEPLETED HL

- → Elderly age group
- → a/w HIV ⊕
- → HODGKIN CELLS ⊕ [Atypical Histiocytes]
- → worst prognosis

NON CLASSICAL HL

LYMPHOCYTE PREDOMINANT HL

- → RS cells → CD15 ⊖
  - CD 30 ⊖
  - CD 20 ⊕
- → Best prognosis overall
- → Popcorn / Lympho - histiocytic cells ⊕


LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA

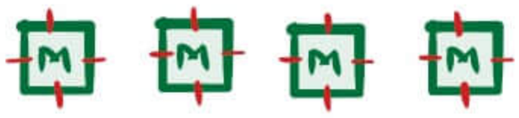
METASTASIS → Nodal disease >> Spleen >> Liver >> Bm

TREATMENT → ANTI - CANCER DRUGS
- A → Adriamycin
- B → Bleomycin
- V → Vinblastine
- D → Dacarbazine

MYELODYSPLASTIC SYNDROME

→ Hypercellular Bone marrow + CYTOPENIA [BLASTS → < 10%]

→



↓

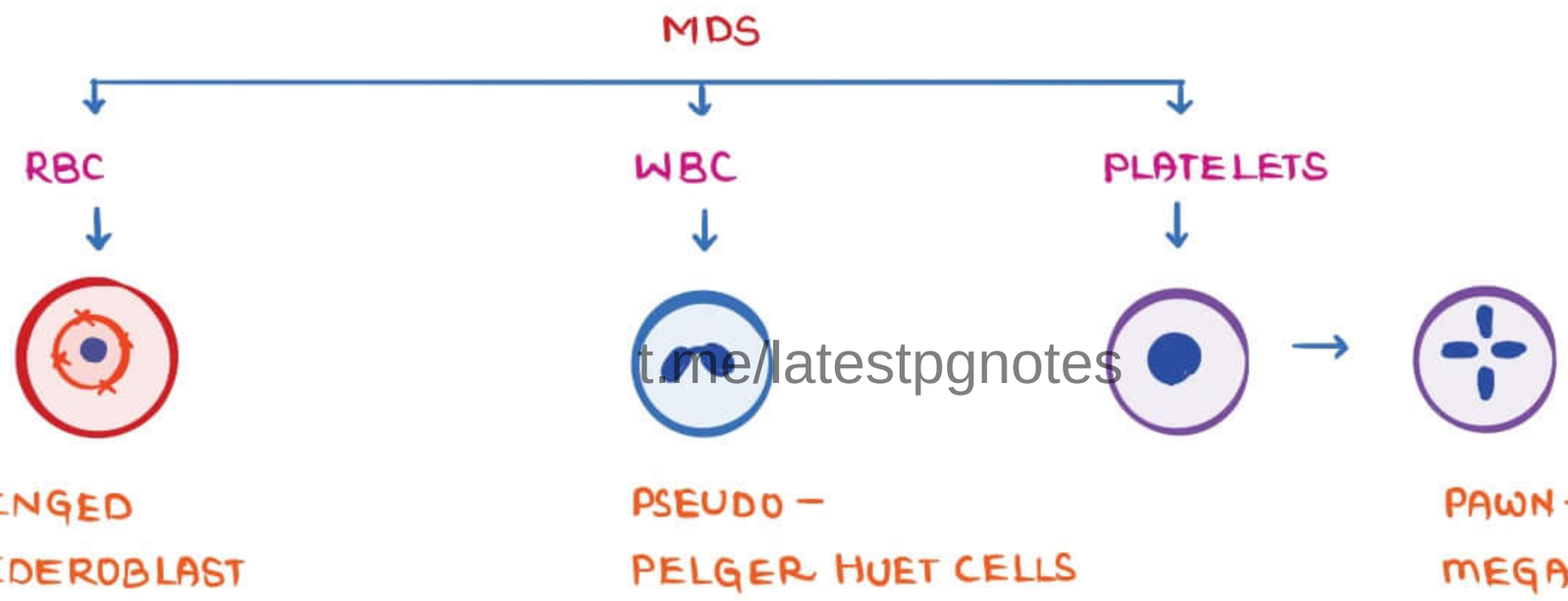
MATURATION DEFECT

↓

INEFFECTIVE ERYTHROPOIESIS

SUB TYPES

1. 1° MDS → Elderly [mean age 70 yrs]
2. 2° MDS
   a. H/O exposure to Drugs / Radiations —2-8 yrs→ MDS
   b. GENETIC DEFECTS
      → chr 5q deletion → Seen in Adults [mc overall]
      → monosomy 7 → Seen in children
      → Trisomy 8 [MYC]

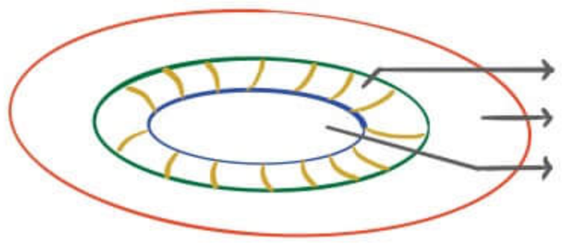


→ C/F → Fatigue / petechiae / fever

→ DIAGNOSIS
   1. BM EXAMINATION → hyper cellularity
   2. PERIPHERAL SMEAR → Pancytopenia
      Ringed sideroblasts
      Pseudo pelger huet cells
      Pawn - ball megakaryocytes

→ TREATMENT
   1. ALLOGENEIC BM TRANSPLANTATION → for young patients
   2. AZACITIDINE, DECITABINE ⊖ DNA methylation
   3. LENALIDOMIDE → for 5q deletion
   4. ANTIBIOTICS
   5. REPEATED BLOOD TRANSFUSIONS

NON HODGKIN LYMPHOMA



MANTLE ZONE
MARGINAL ZONE
GERMINAL CENTRE
→ FOLLICULAR LYMPHOMA
→ DLBCL
→ Burkitt's Lymphoma

MANTLE ZONE LYMPHOMA

→ arises from NAIVE 'B' CELLS
→ t [11;14] → Chr 14 → has locus for Ig gene
→ Chr 11 → has locus for Cyclin D1

→ t [11;14] → ↑↑↑ cyclin D1 ⟶ ↑ cells

C/F → diffuse lymphadenopathy
LN Bx → CD 5 ⊕
CD 23 ⊖
cyclin D_1 ⊕
→ In the absence of cyclin D_1, SOX-11 acts as marker

MARGINAL ZONE LYMPHOMA

→ Site of origin
↳ MALT → GIT, Lungs
↳ Extra nodal → orbit, stomach

→ INDOLENT TUMOR
→ Chronic B cell stimulation dlt
↳ H. pylori
↳ Auto Immune Disorders [RA / Sjogren syn / Hashimoto's thyroiditis]

→ t [11;18]

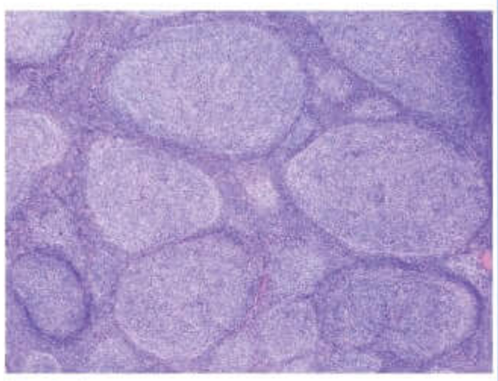
→ INITIALLY → good response to AntiBiotics
LATER → poor response to AntiBiotics

→ mc site for
MALT → Ileum
MALTOMA → stomach

GERMINAL CENTRE LYMPHOMAS

1. FOLLICULAR LYMPHOMA

→ t [14;18] → ↑↑ bcl-2
MLL-2 gene mutation ↓
↑ cells [follicles]
↓
Painless LN ⊕
Indolent

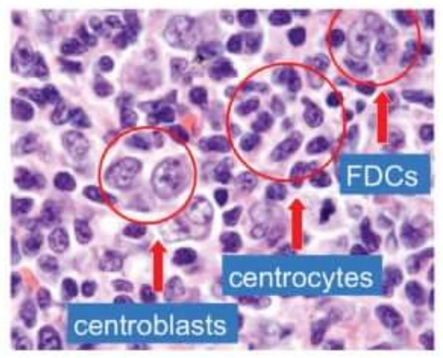


FOLLICULAR LYMPHOMA

→ DIAGNOSIS

1. IMMUNO PHENOTYPING

→ CD 15 / 20 → ⊕
bcl - 2 → ⊕
CD 5 → ⊖



2. Tumor cells shows

→ CENTROBLASTS & CENTROCYTES → aka BUTTOCK CELLS

→ FL ⟶ ⟶ ⟶ ⟶ DLBCL

2. DIFFUSE LARGE B CELL LYMPHOMA

→ ETIOLOGY

↳ Idiopathic [50%]
↳ Over expression of BCl - 6 [30%]
↳ a/w follicular lymphoma [20%]

→ MC NHL
→ Seen in immuno suppression [HIV / Transplant] ← EBV
HHV - 8 [AIDS] → 1° EFFUSION LYMPHOMA

3. BURKITT'S LYMPHOMA

→ t [8 ; 14] → ↑↑ C-MYC [transcription factor]
t [2 ; 8] ↓
t [8 ; 22] ↑↑↑ MITOSIS

→ most aggressive NHL
→ mc a/w Tumor Lysis Syndrome

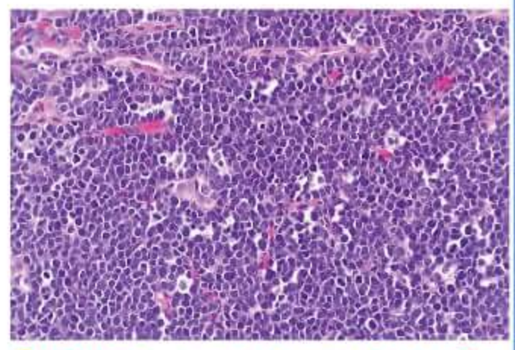
→ DIAGNOSIS

LN BIOPSY

STARRY SKY APPEARANCE

↓ ↓

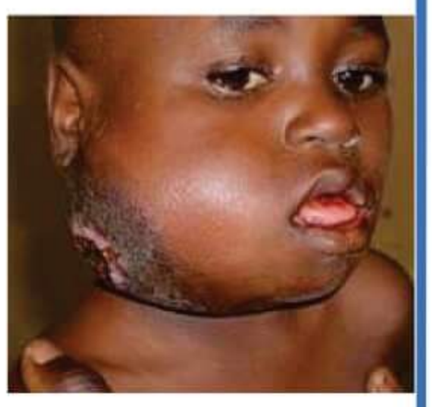
macro-phages — Tumor cells [chromatin]



STARRY SKY APPEARANCE

→ SUB TYPES

1. ENDEMIC → 100% a/w EBV
→ affects Jaw bones & maxilla
→ seen in AFRICANS



2. SPORADIC → seen in developed countries
→ Abdominal mass ⊕

3. A/w HIV → dlt immuno suppression

→ worst prognosis

HAIRY CELL LEUKEMIA

→ B - cell tumor
→ involves BM ; Spleen ; Liver
→ M >> F

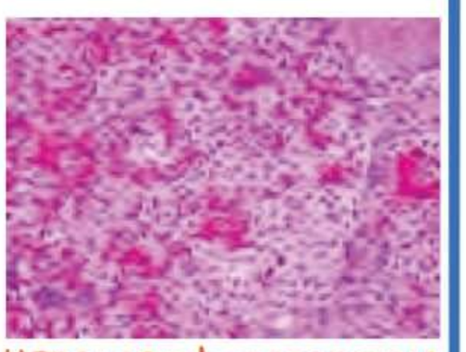
→ CIF
  → massive splenomegaly [RED PULP INVOLVED]
  → ↑ Infections [by MAC - mycobacterium avium complex]

  → RED PULP OF SPLEEN INVOLVED IN
    1. Hairy cell Leukemia
    2. Hepato Splenic Lymphoma

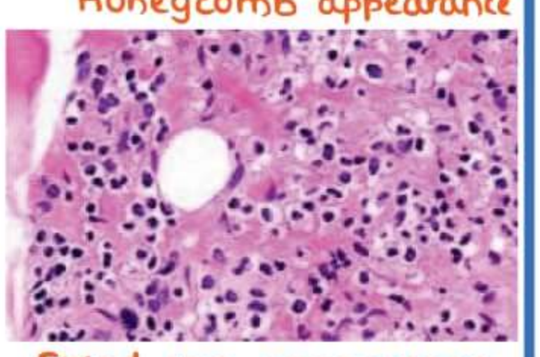

TRAP STAIN

→ DIAGNOSIS
  1. BLOOD
    → Pancytopenia
    → Phase contrast microscopy → HAIRY - PROJECTIONS ⊕
    → Staining → Tartrate Resistant Acid Phosphatase [TRAP] ⊕

  2. IMMUNO PHENOTYPING
    → CD 11 ⊕
      CD 25 ⊕
      CD 103 ⊕
      ANNEXIN A1 ⊕ [Best marker]


Honeycomb appearance

  3. BM EXAMINATION
    a. Bm ASPIRATION → Dry Tap
    b. Bm BIOPSY
      ↳ HONEY COMB APPEARANCE
      ↳ FRIED EGG APPEARANCE

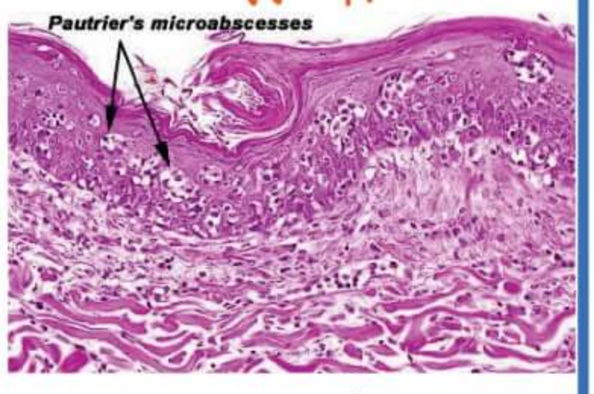

Fried egg appearance

→ R_I → CLADRIBINE [DOC]

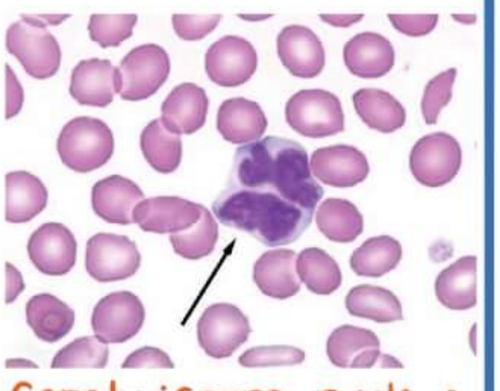
CUTANEOUS T-CELL LYMPHOMA

→ CD_4 T CELL TUMOR

→ Involves
  Blood → SEZARY SYNDROME
  Skin → Epidermotropism → PAUTRIER'S MICROABSCESS
  ↓
  MYCOSIS FUNGOIDES
  [Skin → LN / BM]

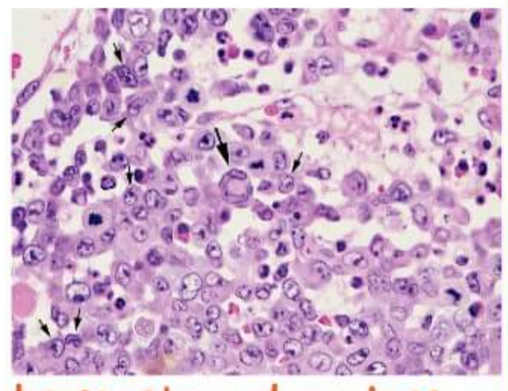


→ CEREBRIFORM NUCLEI ⊕⊕
→ CLA ⊕ / CCR_4 ⊕ / CCR 10 ⊕
→ a|w GENERALISED EXFOLIATIVE ERYTHRODERMA


Cerebriform nucleus

ANAPLASTIC LARGE CELL LYMPHOMA

→ children & young adults
→ HALL MARK CELLS → Horse shaped nucleus ī abundant cytoplasm

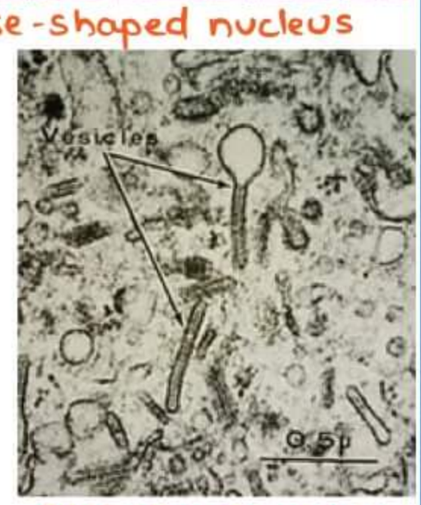


horse-shaped nucleus

→ ALK gene [chr 2p] expressed
→ CD 30 ⊕ [R/ by Anti - CD 30]
→ Good prognosis

LANGERHANS CELL HISTIOCYTOSIS

→ BRAF mutation ⊕
→ arises from Langerhans cells
→ contains BIRBECK GRANULES
↳ TENNIS - RACKET APPEARANCE ON E/m

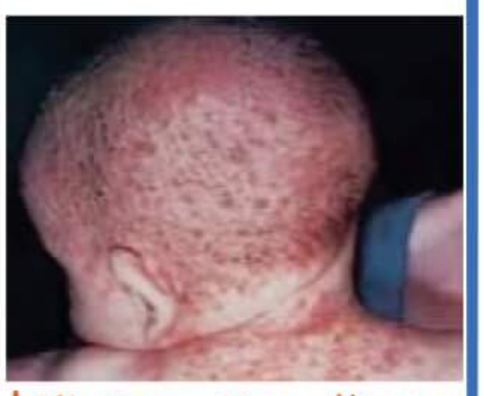


Birbeck Granules

→ MARKERS → CD 1a / S-100 / HLA - DR ⊕

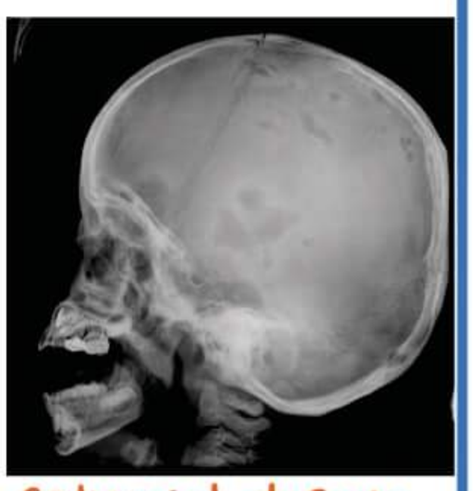
→ DISORDERS

1. LETTERER - SIWE DISEASE
→ < 2yrs age
→ multifocal & multi system
→ Lytic lesions [multiple bones involved]
→ Skin lesions [Seborrheic dermatitis]



Letterer - Siwe disease

2. EOSINOPHILIC GRANULOMA
→ Unisystem
→ TRIAD [HAND SCHULLER CHRISTIAN TRIAD]
↳ Exophthalmos
↳ Calvarial Defects
↳ Diabetes Insipidus



calvarial defects

3. PULMONARY LANGERHANS CELL HISTIOCYTOSIS
→ seen in Adult smokers
→ Cessation of smoking → Regression of disease

PLASMA CELL DYSCRASIAS

→ NORMAL PLASMA CELLS

B CELL —Ag→ PLASMA CELLS ⟶ Ig ⊕ [L/H] [POLYCLONAL]

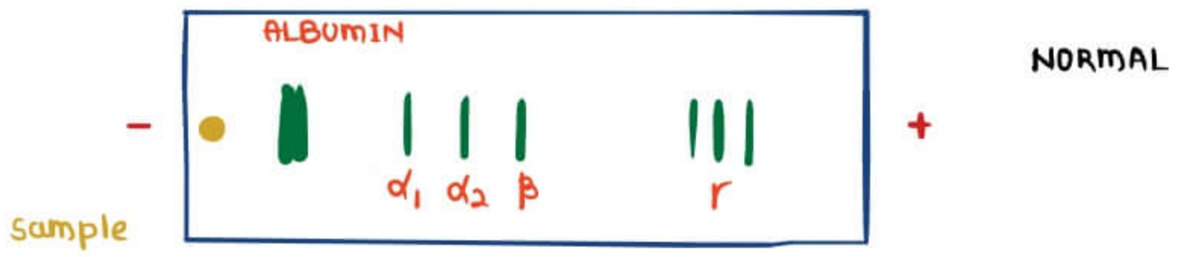
→ PLASMA CELL DYSCRASIAS [MONOCLONAL GAMMOPATHY / PARA PROTEINEMIA]

Mutation of Plasma cells ⟶ over production [L/H] [MONOCLONAL]

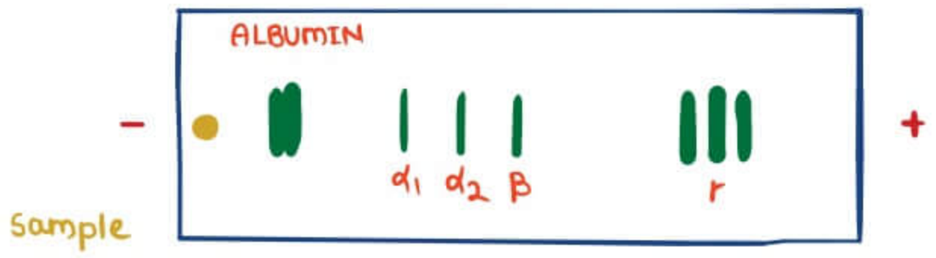
→ DIAGNOSIS

1. PROTEIN ELECTROPHORESIS → Quantity estimated
2. IMMUNO FIXATION ELECTROPHORESIS → Quality estimated

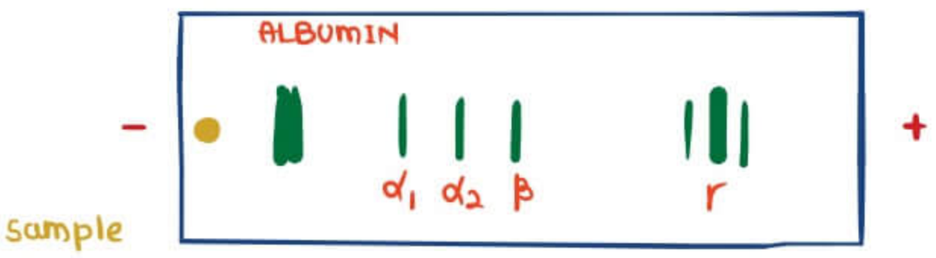
PROTEIN ELECTROPHORESIS



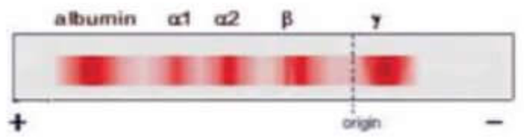
NORMAL



INFECTIONS

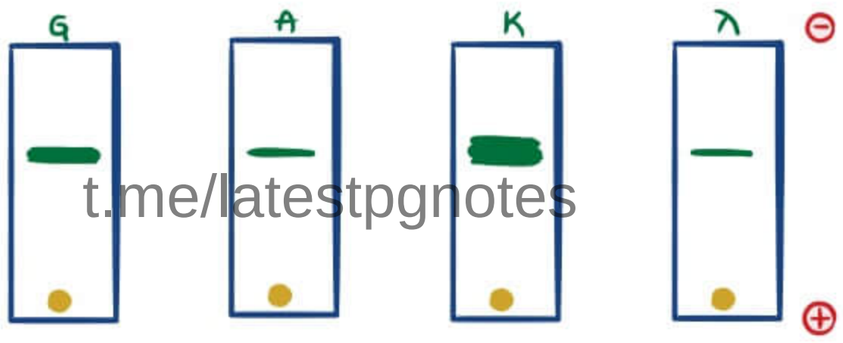


PLASMACELL DYSCRASIA

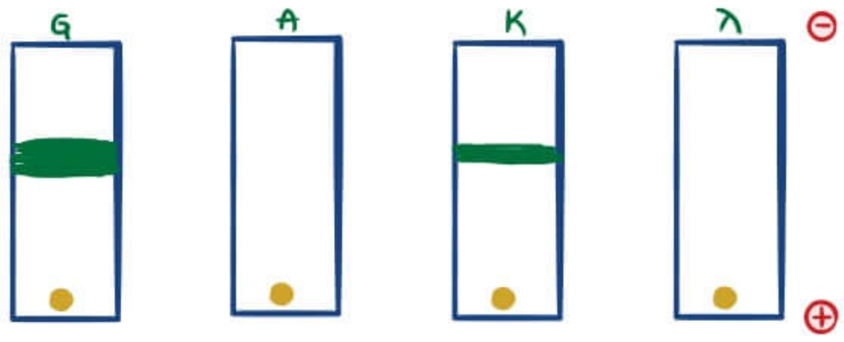


IMMUNO FIXATION ELECTROPHORESIS

NORMAL



PLASMA CELL DYSCRASIAS



MONOCLONAL GAMMOPATHY [MG] CLASSIFICATION

1. MGUS [MG of Unknown significance] [most common]
2. MULTIPLE MYELOMA [Light chains > Heavy chains]
3. LYMPHOPLASMOCYTIC LYMPHOMA [↑ plasma cells & lymphocytes ; LC = HC]
4. HEAVY CHAIN DISEASE [↑ Heavy chains]

MULTIPLE MYELOMA

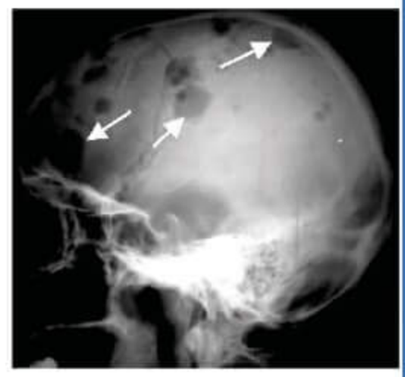
→ Multi Focal in Bones
→ r chain > α chain

→ PATHOGENESIS

B - CELL
↓
mutation → 13q⊖ [mc] / t [11; 14] / 17p⊖
↓
BM PLASMACYTOSIS
↓
IL - 6 Secretion [Autocrine cytokine]
↓
PLASMA CELLS ⊕⊕⊕

1. Replacement of cells
Ⓝ cells
↳ Pancytopenia
↳ ↑ infections
↳ normocytic normochromic anemia
↳ ↑ Bleeding

2. IL-6 & TNF-α
↓
↑ Osteoclast
↓ Osteoblast
↳ Pathological fractures
↳ vertebral column >
↳ Ribs >
↳ Skull
Backache
Pain on deep inspiratn
Headache
Punched out lesions of skull



3. ↑ MONOCLONAL PROTEINS
→ ↑ Bleeding
→ ↑ coagulatn defects
→ ↑ viscocity of Blood
↳ Ⓝ → 1.8
↳ neurological manifestations

→ ↑ Infections → DEATH

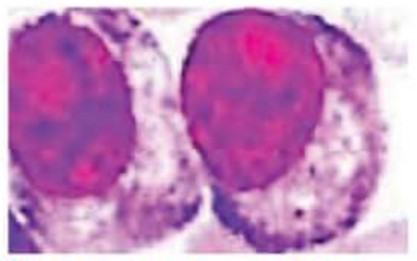
→ Light chains >>> Heavy chains
↓

↓
1. Renal Failure
2. Renal Amyloidosis [myeloma Kidney]
3. Bence - Jones Proteins [urine] [99%]
↳ 1% → NON - SECRETORY MULTIPLE MYELOMA [no Light chains]

→ S. calcium ↑↑ [Hypercalcemia]
↑ Thirst
Polyurea
Renal failure

Ⓝ Alkaline Phosphatase

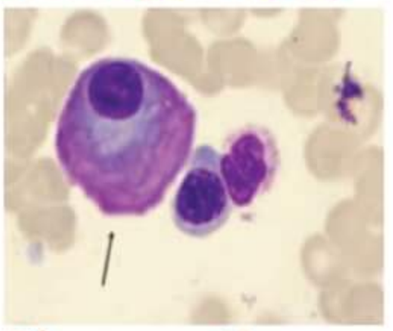
NORMAL PLASMA CELL → CART WHEEL NUCLEUS [Eccentric]



Cart wheel nucleus

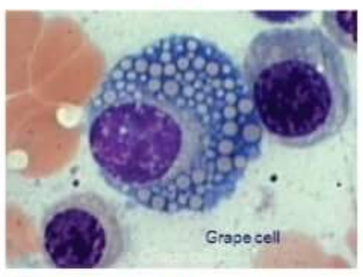
MULTIPLE MYELOMA [PCD]

→ FLAME CELL
[Ig deposit^{n} in cytoplasm]



Flame cell

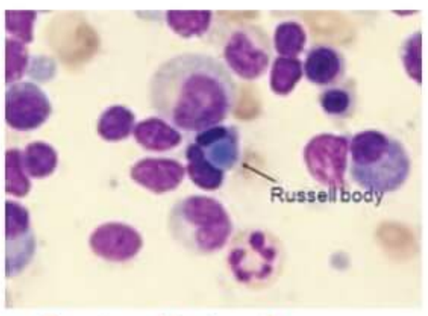
→ MOTT CELL
[Fibrils / gobules in cytoplasm]



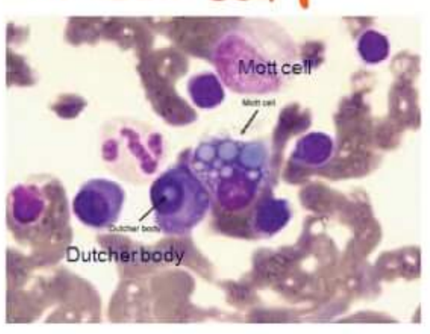
Mott cell

RUSSEL BODY
[Intra cytoplasmic inclusion]

DUTCHER BODY
[intra nuclear inclusion]



Russell body



DIAGNOSIS

1. Bm BIOPSY
   → IOC
   → International Myeloma working group CRITERIA
      → Bm Plasma cells → ≥ 10%
      ⊕
      Any one of myeloma defining events

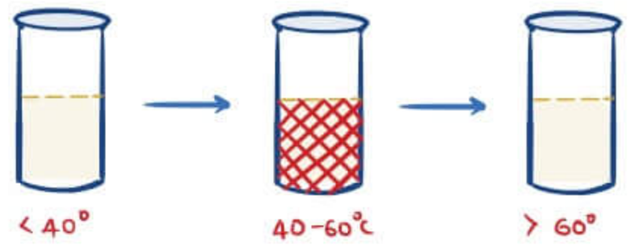
   → Ⓐ → Evidence of Tissue impairement
      C → ↑↑ ca^{2+} [> 11 mg/dl]
      R → Renal Insufficiency
      A → Anemia [< 10 gm/dl]
      B → Bony lesions [≥ 1 lesion]

   → Ⓑ → ≥ 1 out of the following
      → ≥ 60% clonal plasma cells
      → > 1 focal lesion [on MRI, > 5mm]
      → Serum involved : uninvolved
         free light chain ratio
            → > 100

2. BLOOD
   → ↑ ESR
   → Normocytic Normochromic Anemia
   → ↑↑ S. ca^{2+}
   → Ⓝ S. Alkaline phosphatase level

3. SERUM / URINE } Protein Electrophoresis & Immuno fixation Electrophoresis

4. URINE → Bence – Jones Proteins
→ Less Soluble at 40 – 60°C



HEAT COAGULABILITY / HEAT SOLUBILITY TEST

5. X-RAY

Skull
Spine
Pelvis
} OSTEOLYTIC LESIONS ⊕

5. IMMUNO PHENOTYPING

Ⓝ → CD 19 / 38 / 45 ⊕

Plasma cells [mm] → CD 138 ⊕
CD 45 ⊖

CD 19	⊕	CD 19	⊖
CD 56	⊖	CD 56	⊕

MONOCLONAL PROTEINS → on Electrophoresis

↓

'M' Spike [m – monoclonal protein]

→ MC antibody seen in mm → Ig G > Ig A

TREATMENT → LENALIDOMIDE + BORTEZOMIB + STEROIDS

D/D

1. MGUS
→ Asymptomatic
→ Bm plasma cells → < 10%
→ S. para proteins → < 3g/dl
→ 3% of MGUS [aged > 50yrs] can develop multiple myeloma
→ 5% of MGUS [aged > 70yrs] can develop multiple myeloma

2. SMOLDERING MYELOMA
→ Bm plasma cells → 10 – 60%
→ S. para proteins → > 3g/dl
→ no myeloma defining event

MGUS	SMOLDERING MYELOMA	MULTIPLE MYELOMA
→ < 10%	→ 10 – 60%	→ > 60%
→ < 3g/dl	→ > 3 g/dl	
	→ MDE ⊗	→ MDE ⊕

WALDENSTROM'S DISEASE & HEAVY CHAIN DISORDERS

LYMPHOPLASMACYTIC LYMPHOMA / WALDENSTROM'S MACROGLOBULINEMIA

→ a/w MYD 88 mutation
→ a/w 'M' Spike → Ig M

MULTIPLE MYELOMA	LYMPHOPLASMACYTIC LYMPHOMA
→ Ig G >> Ig A → Plasma cells ⊕	→ Ig M → Plasma cells ⊕ Lymphocytes ⊕ mast cells ⊕
→ C → ↑↑ ca^{2+} R → ⊕⊕ A → ⊕⊕ B → ⊕⊕	→ N ⊖ ⊖ ⊖
→ INFILTRATION OF Liver / LN / Spleen ⊖	⊕

→ TREATMENT → Ig M can be removed by PLASMAPHARESIS

HEAVY CHAIN DISEASE

1. α HCD / SELIGMANN DISEASE [MC HCD]

∝ MEDITERANIAN LYMPHOMA
GIT ⊕ >>> Respiratory tract ⊕

2. γ HCD / FRANKLIN'S DISEASE

Hepatomegaly, Splenomegaly → LN +++

→ Fever / Malaise / Anemia

→ affects waldeyer Ring → Palatal edema ⊕
→ a/w Rheumatoid Arthritis

3 μ HCD → a/w CLL

PLATELETS & BLOOD TRANSFUSION
CONCEPT OF BLEEDING DISORDERS

HEMOSTASIS

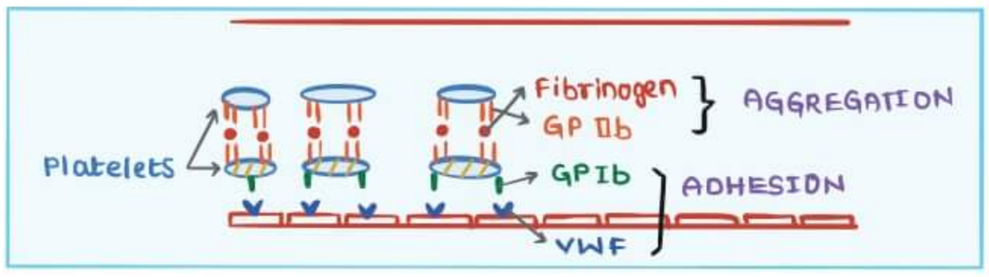
Contributed by

1. Blood vessels → vaso constriction
2. Platelets → Temporary plug
3. Coagulatⁿ cascades → Permanent plug

TEMPORARY HEMOSTATIC PLUG

Temporary plug formatⁿ requires

1. ADHESION → Gp Ib, vWF
2. ACTIVATION → TXA_2, ADP
3. AGGREGATION → Gp IIb, fibrinogen



FUNCTIONAL PLATELET DISORDERS [↑ Bleeding ; N platelet count]

1. ADHESION DEFECTS
   - a. Gp Ib Defect → BERNARD SOULIER DISEASE [BS Disease]
   - b vWF Defect → vWD
2. DRUGS
   - → ⊖ TXA_2 → Aspirin
   - → ⊖ ADP → Clopidogrel
3. Gp ●b defect → GLANZMANN'S DISEASE
   Fibrinogen defect → HYPOFIBRINOGENEMIA

aDhesion	→	Gp Ib defect	→ BERNARD SOULIER DISEASE
aGgregation	→	Gp IIb defect	→ GLANZMANN'S DISEASE
BERNARD SOULIER DISEASE	→	Big size Platelets ⊕ in peripheral circulatⁿ	

PLATELET DEFECTS	→	↑	BLEEDING TIME
COAGULATION DEFECT	→	↑ PT	[Extrinsic pathway indicator]
		↑ a PTT	[Intrinsic pathway indicator]

BLEEDING DISORDERS - SUB TYPES

●LATELET DEFECTS [spontaneous bleeding ⊕]

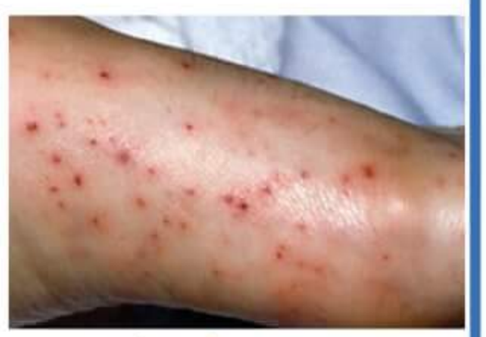
→ SUPERFICIAL [Skin | mucosa] BLEEDING ⊕

- ↳ petechiae [<1mm] / purpura [1-2mm]
- ↳ Hematuria
- ↳ ↑ menstrual loss
- ↳ gum bleeding
- ↳ melena

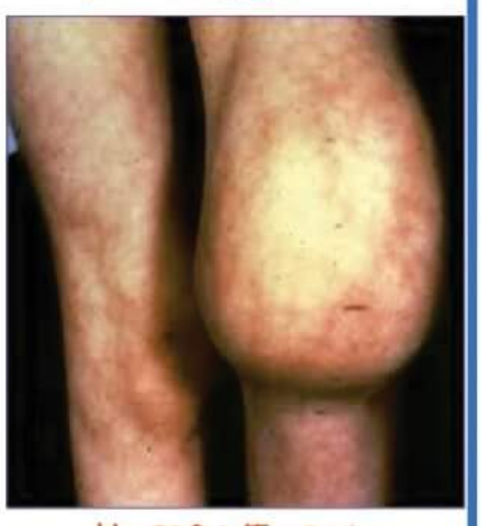
COAGULATION DEFECTS [H/O trauma ⊕]

→ DEEP TISSUE BLEEDING ⊕

- ↳ Joints → Hemarthrosis
- ↳ Muscles → Hematoma



petechiae



Hemarthrosis

INTRODUCTION TO PLATELET DISORDERS

PLATELET DEFECTS

↑ BT Normal platelet count	↑ BT ↓ Platelet count
↓	↓
FUNCTIONAL DEFECT	QUANTITATIVE DEFECT / THROMBOCYTOPENIA
↓	↓
BS disease vWD Glanzmann's disease ↓ Fibrinogen Drugs	↓ Platelets ⊕ → BM
	↓ Active → megakaryocytic Thrombocytopenia
	↓ ↓ Activity → Amegakaryocytic thrombocytopenia

Ⓝ Platelets → 1.5 Lakh – 4.5 Lakh / mm^3
Thrombocytopenia → < 1 Lakh / mm^3

MEGAKARYOCYTIC THROMBOCYTOPENIA

1. IMMUNE DISORDES [coombs TEST ⊕]
   a. ITP
   b. Dengue
   c. SLE
   d. B cell cancers
   e. Drugs [Quinidine]
2. NON IMMUNE DISORDERS [coombs TEST ⊖]
   a. DIC
   b. HUS
   c. TTP

AMEGAKARYOCYTIC THROMBOCYTOPENIA

1. BM FAILURE [Fibrosis / Radiation]
2. B_{12} / FA Deficiency
3. Leukemia
4. Drugs [Anti cancer Drugs]

ITP [IMMUNE THROMBOCYTOPENIC PURPURA]

SUB TYPES

1. ACUTE ITP
   → Short duration history
   → Severe
   → Sudden onset
   → Seen in children
   → HIV viral infection ⊕
2. CHRONIC ITP
   → longer duration History
   → less severe
   → seen in adults
   → Sub types
      1° / Idiopathic
      2° [SLE / HIV / CLL]

PATHOGENESIS

ITP → Ab formation → Platelet Ag

→ circulation → SPLENIC PHAGOCYTOSIS

C/F

→ Petechia
→ Purpura
→ Hemorrhagic Bullae [more in Acute ITP]
→ Gum bleeding
→ Hematuria
→ melena

→ NORMAL SIZED SPLEEN

DIAGNOSIS → ITP IS DIAGNOSIS OF EXCLUSION

→ BT ↑ / P/C ↓
→ PT } Normal
→ aPTT }
→ Coombs Test ⊕
→ BM EXAMINAT^{n} → Active → MEGAKARYOCYTIC THROMBOCYTOPENIA

TREATMENT

1. SYMPTOMATIC m$_x$ for Acute ITP
2. CHRONIC ITP
   → steroids
   → IV Igs
   → Splenectomy

HEMOLYTIC UREMIC SYNDROME [HUS]

SUB TYPES

1. TYPICAL HUS → Acute Gastro-enteritis

   1. E.coli 0157/H7
   2. Shigella dysenteriae

   } → Release TOXIN —EC damage→ PLATELET-THROMBI

2. ATYPICAL HUS

   1. mutation of © Proteins [CD 46/ factor H]
   2. Drugs [Mitomycin / Ticlopidine]

   } —EC damage→ PLATELET-THROMBI

CLINICAL FEATURES

→ CLASSICAL Triad
   1. Renal failure [K/A/T or R/A/T syndrome]
   2. microangiopathic HA
   3. Thrombocytopenia

→ Child ↓ H/O Bloody Diarrhea → Renal Dysfunction + Purpura

DIAGNOSIS → ↑ BT
→ PT } Normal
aPTT }

THROMBOTIC THROMBOCYTOPENIC PURPURA [TTP]

→ NORMAL

→ ADAM TS 13 [metallo protease] → damage to VWF clumps

→ TTP

1. DEFICIENCY OF ADAM TS 13 [UPSHAW - SCHULMAN SYNDROME]
2. Ab Formatn against ADAM TS 13
   → seen i Auto immune disorders & certain Drugs

↓

↓ ADAM TS Activity

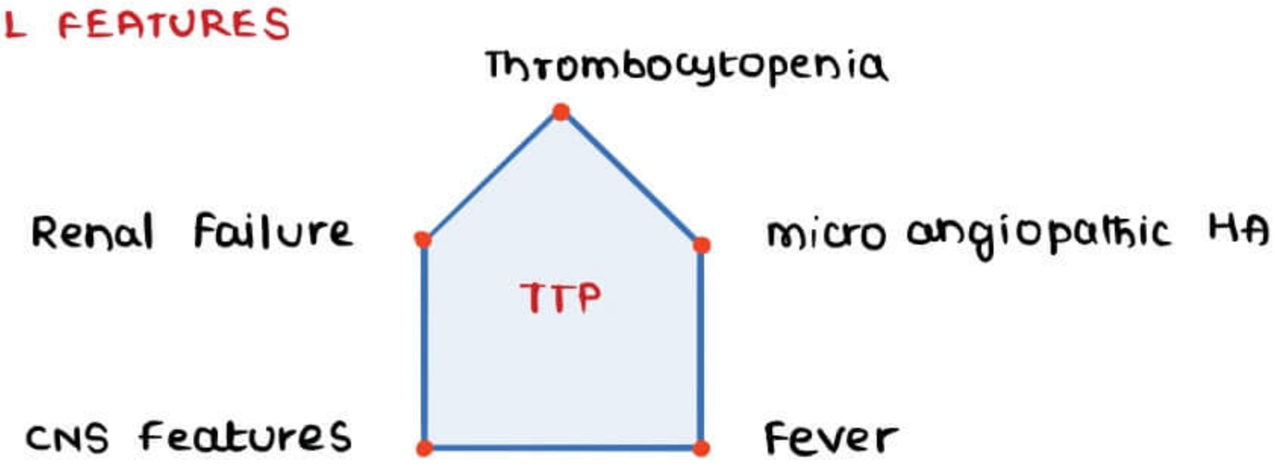
↓

↑ VWF Clumping

↓

Platelet - Thrombi ⊕⊕⊕

→ CLINICAL FEATURES



→ TREATED BY PLASMAPHERESIS

DISSEMINATED INTRA VASCULAR COAGULATION [DIC]

→ Thrombo - Hemorrhagic disorder

→ Acute | Sub acute | Chronic disorder

→ RISK FACTORS

1. OBSTETRIC CAUSES [mc]
   → Retained placenta
   → Dead fetus
   → Amniotic fluid embolism
2. INFECTIONS
   CANCERS
   → stomach
   → colon
   → Pancreas
   → AML - m3
3. BURNS / SURGERY / TRAUMA

PATHOGENESIS

Obstetric causes
Infections
cancers
} Endothelial cell Injury

↓ Intrinsic pathway ⊕

Wide Spread THROMBI

↑ Extrinsic pathway ⊕

Surgery
Burns
Trauma
} TISSUE FACTOR

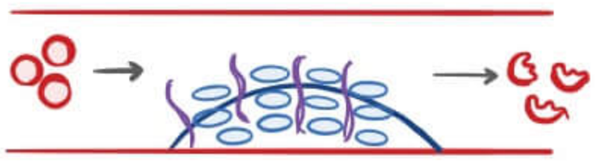
1° EVENT → [redacted]

VASCULAR OCCLUSION → Ischemic damage → Micro angiopathic HA

PLATELETS / CLOTTING FACTOR CONSUMPTION → PLASMIN ACTIVATION → ↑ BLEEDING [2° Event]

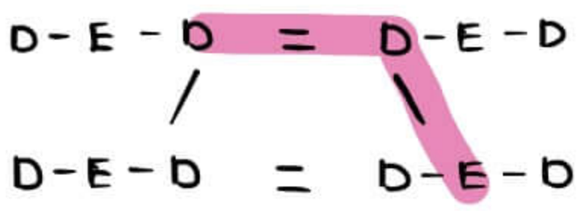
DIAGNOSIS

1. ↓ Hb ↑ LDH
   ↓ PC ↑ UC Bilirubin



2. PERIPHERAL SMEAR shows SCHISTOCYTES [MAHA]
3. ↑ BT ↑ PT ↑ aPTT
4. D-DIMER ASSAY [Specific]

D - E - D [Fibrinogen]



Cross linked

↓ Plasmin ⊕

D = D D-DIMER
E

D-Dimers suggests
→ ↑ Plasmin
→ Fibrin

CIF

1. BRAIN → mc affected → Confusion, altered sensorium, Dizziness, Coma
2. HEART → ↓ CO / Dyspnea
3. KIDNEY → Acute tubular necrosis
4. LUNGS → difficulty in breathing, hypoxemia
5. ADRENAL GLAND → Hemorrhage [MeningoCOCCEMIA]
   ↓
   WATERHOUSE - FRIDERICHSEN SYNDROME

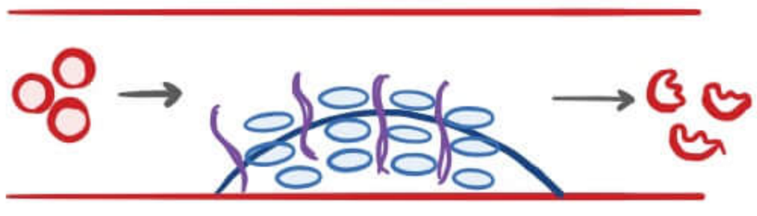
TREATMENT

1. TREAT PRIMARY CAUSE
2. FRESH FROZEN PLASMA
3. ANTI COAGULANTS

INSPITE OF BEST EFFORTS, DIC Q/W HIGH MORTALITY

ANGIOPATHIC HEMOLYTIC ANEMIA : BASIC CONCEPTS

→



SUB TYPES

1. MACRO ANGIOPATHIC HA
   - → a/w Prosthetic cardiac valves [Aortic valve >>> mitral valve]
   - → a/w Severe Aortic Stenosis
   - → a/w Synthetic vascular grafts
   - → a/w Cavernous Hemangioma

2. MICRO ANGIOPATHIC HEMOLYTIC ANEMIA
   - → a/w HUS / TTP / DIC
   - → a/w Eclampsia
   - → a/w Scleroderma
   - → a/w malignant HTN
   - → a/w march hemoglobinuria [Soldiers]

CLOTTING FACTOR DISORDERS [HEMOPHILIAS] & CONCEPT OF FACTOR INHIBITORS

HEMOPHILIA SUB TYPES

A	→	Factor	8	defect [mc]
B		Factor	9	defect
C		factor	11	defect

FACTOR 8

SOURCE

- → LIVER
  - ↳ Sinusoidal Endothelial cells
  - ↳ Kupffer cells
- → KIDNEY
  - ↳ Tubular Epithelial cells

HEMOPHILIA - A

- → x Linked disorder
- → 90% → ↓↓↓ factor 8
  10% → functional defect of factor 8
- → Intrinsic pathway affected

VARIANTS

1. MILD → 6-50% factor 8 ⊕
2. MODERATE → 2-5% factor 8 ⊕
3. SEVERE → < 1% factor 8 ⊕

C/F

- → children [♂ >>> ♀]
- → H/O trauma
- → HEMARTHROSIS
- → HEMATOMA
- → H/O Excessive Bleeding
  - ↳ Circumcision
  - ↳ Tooth Extraction

DIAGNOSIS

1. P/C → Normal PT → Normal
   BT → Normal aPTT → Elevated

2. Factor 8 level → ↓↓↓ [confirmatory]

TREATMENT

1. MILD → Desmopressin
2. Severe → rFactor 8 [HUMATE]
3. CRYOPRECIPITATE

HEMOPHILIA B [CHRISTMAS DISEASE]

→ ↓↓ Factor 9
→ X Linked Recessive
→ Similar c/f as Hemophilia A
→ DIAGNOSIS
   1. BT → N PT → N
      P/C → N aPTT → ↑

→ Rx 1. r factor 9
   2. FRESH FROZEN PLASMA

FACTOR INHIBITORS

→ Abs ⟶ ↓ clotting factor activity
→ CAUSES

1. RECIPIENTS OF CLOTTING FACTORS
2. PREGNANCY
3. AUTO IMMUNE DISORDERS
4. B CELL CANCERS

C/F → Similar to Hemophilia
→ ↑ aPTT

ISOLATED ↑ aPTT

Add HEPARINASE ↓ N aPTT ⟶ ↑ aPTT ↓ Hemophilia factor Inhibitor

MIXING STUDY [distinguishes Hemophilia & factor inhibitor]
→ 1 : 1 patient & normal Plasma

- Hemophilia ↓ Ⓝ aPTT
- Factor Inhibitors ↓ ↑ a PTT [DELAYED PROLONGATⁿ]

VON WILLEBRAND DISEASE

VON WILLEBRAND FACTOR

SOURCE

→ Endothelial cells
→ megakaryocytes
→ Hepatocytes [small quantity]

→ Gene Located on Chr. 12

FUNCTIONS

1. Transport of Factor 8
   ↳ $t_{1/2}$ → 2.4 hrs
   ↳ $t_{1/2}$ ↓ vWF → 12 hrs

2. PLATELET ADHESION

↓ vWF
- ↓ Platelet Adhesion → ↑ BT
- ↓ Intrinsic pathway Activity → ↑ aPTT

SUB TYPES OF VON WILLEBRAND DISEASE

1. TYPE I vWD → ↓ vWF [mc] → Autosomal Dominant
2. TYPE II vWD → Ⓝ vWF → Qualitative Defect
3. TYPE III vWD → ↓↓↓ vWF [most severe] → Aut. Recessive

TYPE 2

SUB TYPES

Type 2A [mc] Type 2C
Type 2B Type 2D

→ Autosomal Dominant

CIF

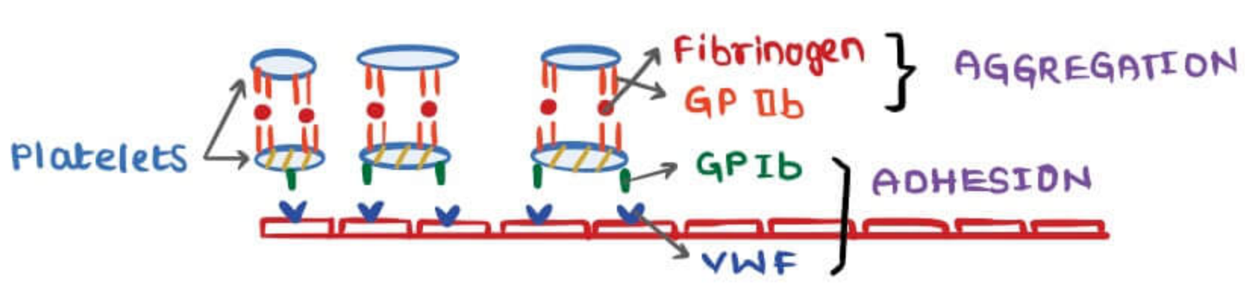
→ MUCOSAL BLEEDING → Petechiae / purpura
Epistaxis / melena

→ TISSUE BLEEDING [rare]

DIAGNOSIS

1. P/C → N PT → N
   BT → ↑ aPTT → ↑

2. RISTOCETIN AGGLUTINATION TEST [RAT] [confirmatory test]



RISTOCETIN
↓ ⊕
GP Ib & VWF

RISTOCETIN TEST

Formalin - fixed Platelets + Plasma
Ristocetin [person]

Normal → RAT ⊕ [elicited by AGGREGOMETER]
VWD → RAT ⊖

VWD
→ ↑ BT & ↑ aPTT → RAT ⊖
Ⓝ PT & Ⓝ PlC → VWF ASSAY

R_x → 1. DESMOPRESSIN for mild form
2. CRYOPRECIPITATE for Severe form

BLOOD TRANSFUSION

HEALTHY VOLUNTARY → 350 ml in CHITRA BAG + Anticoagulant Solution [49 ml]

450 ml Blood → 63 ml anticoagulants

ANTI COAGULANTS — SHELF LIFE

1. ACD → Acid Citrate Dextrose — 21 Days
2. CPD → Citrate Phosphate Dextrose — 21 Days
3. CPD-A → Citrate Phosphate Dextrose - Adenine — 35 Days
4. SAGM → Saline Adenine Glucose mannitol & Citrate & Phosphate — 42 Days

Saline → Isotonic
Adenine → ATP generation
Glucose → RBC nutrition
Mannitol → ↓ Lysis
CITRATE → ↓ Ca^{2+} → ↓ clot formation
Phosphate → Buffer [maintains PH]

WHOLE BLOOD [< 6 hrs] → [2-6°C] → 42 Days

Packed RBC	Platelets	FFP	Cryoprecipitate
2-6°C	20-24°C	-18°C	-18°C
	5 days	1 year	1 year

CRYOPRECIPITATE RICH IN

1. VWF
2. Factor 8
3. Factor 13
4. Fibrinogen

FFP RICH IN

→ Other clotting factors

WHOLE BLOOD TRANSFUSION - INDICATIONS

1. Massive Blood transfusion
2. Exchang transfusion

1 unit transfusion → ↑ 1 gm/dl Hb & 3% ↑ HCT

PACKED RBC INDICATION → Anemia

FROZEN RBCs ī Glycerol (↓ lysis) indicated for Autologous transfusion

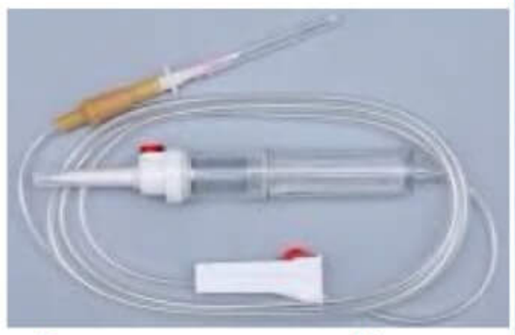
PLATELETS INDICATION → ↓ Platelet count

FFP INDICATIONS → Burns
→ clotting factor deficiencies

CRYOPRECIPITATE INDICATIONS → clotting factor deficiencies

BLOOD TRANSFUSION SET

→ Transfusion needle → 18 - 19 gauge
→ Filter → 170 - 200 μ
→ microaggregates can enter



BLOOD TRANSFUSIⁿ SET

	START	FINISH
WHOLE BLOOD	ī in 30 min	4 hrs
FFP	ASAP	ī in 20 min
CRYOPRECIPITATE	ASAP	ī in 20 min

PLATELETS

→ Random Donor Platelets → ↑↑ 5000 - 10000 ī 1 unit
↑ Alloimmunization

→ Single Donor Platelets → Plateletpheresis
↳ 6 units can obtained
↳ ↓ Immune Reactions
↳ transient hypocalcemia can occur
↳ peri oral numbness/tingling ⊕

COMPLICATIONS

DONOR

1. pain, bruise, hematomy
2. vasovagal Syncopy
→ countered by 1. raising the foot end of donor
2. Supplementing ī fluids

3. APHERESIS → Citrate → Transient hypocalcemia
→ prevented by slow infusion
→ Rx by Oral Ca^{2+} Supplementation

RECIPIENTS

1. Fever → > 1°C than Ⓝ
   → aka febrile NOn Hemolytic Transfusion Reaction [fNHTR]
   → mc blood transfusion Reaction

2. HEMOLYTIC TRANSFUSION REACTION
   → dlt mismatching [mostly dlt clerical error]
   → Acute Reaction
   → takes place ī whole blood, Platelets, FFP } should be ABO compatible
   → clf
      → High grade fever ī chills & rigors
      → Flank pain [Hemoglobinemia & Hemoglobinuria ⊕]
      → OOzing OF blood from veni puncture [in comatose patient]
   → MANAGEMENT
      1. stop BT
      2. maintain IV line ī Ⓝ Saline
      3. Blood Bank → Sampling for mismatch

3. ANAPHYLACTIC REACTION
   → Recipient may be ī Ig A deficiency

4. TRALI [Transfusion Related Acute Lung Injury]
   → seen ī in 6 hrs of FFP infusion
   → dlt antibodies against WBCs
   → Non - cardiogenic pulmonary edema ⊕

5. POST TRANSFUSION PURPURA
   → seen ī platelet transfusion after 7-10 days

6. GRAFT VS HOST DISEASE
   → dlt donor T cells
   → seen after 8 - 10 days

7 INFECTIONS
   → maximum ī Platelets
   → malarial trophozoites transmits through all components
   → seen ī
      Bacteria
      ↳ Yersinia enterocolitica
      ↳ Pseudomonas
      ↳ coagulase negative Staphylococcus

   → Prevented by Screening

MASSIVE BLOOD TRANSFUSION

→ > 1 Blood volume in 24 hrs
> 50% Blood volume in 3 hrs

COMPLICATIONS

1. HYPOTHERMIA [prevented by inline warmers]
2. ELECTROLYTE DISTURBANCES
   ↳ ↑↑ K^+
   ↳ Citrate → ↓↓ Ca^{2+}
   → → HCO_3^- → metabolic Alkalosis

3. DILUTIONAL COAGULOPATHY → DIC → Death

1 : 1 : 1 PROTOCOL (RBC Plasma Platelets) → Protective against Dilutional coagulopathy related mortality

ALTERNATIVES

1. Hb solutions
2. perfluoro carbons

} ↓ $t_{1/2}$

→ used at Balloon angioplasty

BLOOD GROUPING

ABO BLOOD GROUPING

→ mc Blood grouping system
→ A/B antigen genes Located on → chr 9
→ H antigen genes located on → chr 19
→ Full expression of these genes occur at → 1 yr of age
→ ABO antigens are → Glycoproteins
→ ABO Antigens expressed On the surface of → RBCs & platelets

NAG → A → ↑ Gastric cancer

Galactose → B

NAG / Glycosamine → AB → Least H Substance, Least common

× → O → max. H Substance, mc → ↑ PUD, ↓↓ vWF

SECRETORS [80%] → Saliva | sweat | Plasma | semen
→ Except CSF

NON-SECRETORS

→ mc specimen used to check secretors & non-secretors → Saliva

BLOOD GROUP	Ag on RBC	Ab in plasma
A	A, H	anti-B Ab
B	B, H	anti-A Ab
AB	A, B, H	NO Ab
O	H	anti-A & anti B Ab

AB → universal recepient
O → universal donar

Safest blood group for transfusⁿ in emergency → O -
Safest plasma for transfusⁿ in emergency → AB +

BOMBAY BLOOD GROUP

→ discovered by BHENDE
→ rare blood group
→ anti A | B | H Ab in plasma
→ Even "O" can't be given to these patients
→ Safest for transfusⁿ for these patient → Bombay
→ detected by REVERSE GROUPING [detectⁿ of Ab in plasma]

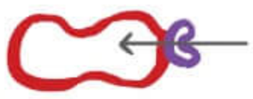
OTHER BLOOD GROUPS

1. RHESUS | Rh

→ antigens expressed since birth
→ C | D | E Antigens
→ D → most important
→ genes located on Chr. 1
→ 85% → Rh ⊕
15% → Rh ⊖

→ HEMOLYTIC DISEASE OF NEW BORN
↳ Ig G Antibodies
↳ dlt mismatch b/w Rh group of mother & fetus
→ mother → Rh ⊖
→ Fetus → Rh ⊕

2 DUFFY ANTIGEN



P. vivax
P. Knowelsii

→ Duffy ⊖ RBCs have resistance to P. vivax | P. Knowelsii infection

3. P ANTIGEN

→ a|w Parvovirus 19 infection
→ P ⊖ → resistant to Parvovirus B19 Infection

Auto - Ab → P ⟶ DONATH LANDSTEINER Ab
[Biphasic Ab]
- attaches at 4°C
- hemolysis at body temp.

↓

PAROXYSMAL COLD HEMOGLOBINURIA

4 I ANTIGEN

Ab formation → COLD AGGLUTININ DISEASE

5 LEWIS ANTIGEN

→ gene located on chr 19
→ Ab → Ig M
→ do not cross placental barrier
→ do not cause hemolytic disease of new born

Ab formation → mc cause of incompatibility during Pretransfusion testing

KELL ANTIGEN

→ KELL Ag + K_x Ag → Mc Leod Phenotype
→ ↓ RBC life span
→ cardiac defects ⊕
→ muscular dystrophy ⊕
→ Acanthocytes ⊕

GASTROINTESTINAL TRACT

HISTOLOGY - LAYERS OF GIT

1. MUCOSA [EPITHELIUM]

Oesophagus	→	Stratified squamous non Keratinized
Stomach	→	columnar
Small Intestine Large Intestine [upto colon]	}	columnar
Anal canal	→	Squamous

2. SUB MUCOSA

→ contains MEISSNER'S PLEXUS [secretory & absorptive in funct^{n}]

3. MUSCULARIS PROPRIA

→ Inner → circular
→ In b|w → AUERBACH'S / MYENTERIC PLEXUS [motor in funct^{n}]
→ OUTER → Longitudinal

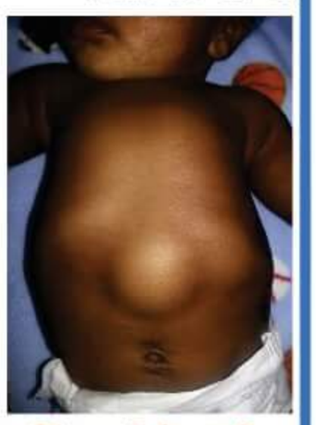
4. SEROSA → absent in OESOPHAGUS

GALL BLADDER DO NOT HAVE MUSCULARIS MUCOSAE [not mus. propria]

INFANTILE HYPERTROPHIC PYLORIC STENOSIS

→ EARLIER NAME → CONGENITAL HYPERTROPHIC PYLORIC STENOSIS
→ But this condition, **NOT PRESENT AT THE TIME OF BIRTH**
→ more common in Male babies
→ ASSOCIATED WITH
- Trisomy 18 [Edward Syndrome]
- Trisomy 21 [Down Syndrome]
- Exposure to ERYTHROMYCIN [motilin receptor agonist] in 1st two wks of life

→ CLINICAL FEATURES
- present at 3-6 WKS after birth
- New onset regurgitation
- Non-bilious, projectile vomiting after feeding
- Demands refeeding
- OLIVE LUMP [1-2 cm firm, ovoid, abdominal mass]


OLIVE LUMP

→ DIAGNOSIS by USG
→ TREATMENT by PYLOROMYOTOMY

HIRSHSPRUNG DISEASE

→ AKa CONGENITAL AGANGLIONIC MEGACOLON

→ Prevalence → 1 : 5000 live births

→ dlt failure of migration of neural crest cells into the bowel

↓

Absence of ganglionic cells [particularly Nitric oxide releasing cells] in bowel

↓

Affected part of bowel not able to relax

↓

Proximal part of affected bowel will be dilated

→ SHORT SEGMENT HIRSHPRUNG DISEASE → if it involves part of large intestine

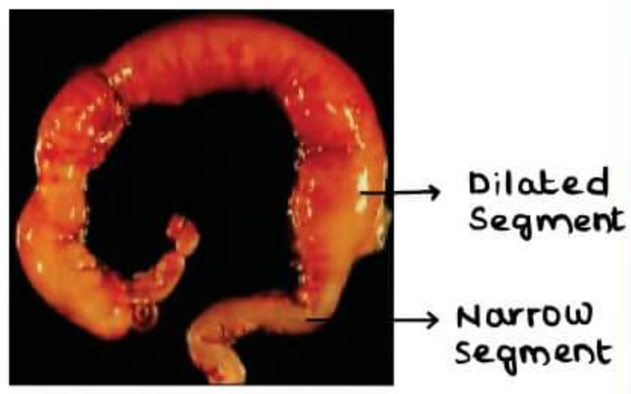
→ LONG SEGMENT HIRSHPRUNG DISEASE → if it involves entire colon

→ MC SITE INVOLVED → RECTUM

→ more common in male babies

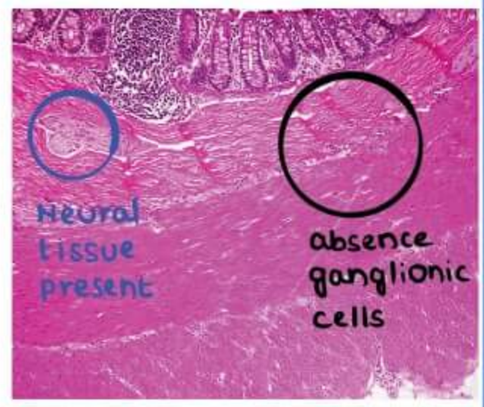
→ GENETICS

- Loss | under activity of RET gene
- in 10% , a|w Down Syndrome



→ CLINICAL FEATURES

- Failure of passage of meconium / abdominal distension
- constipation
- Dilatatⁿ of segment leads to thinning of bowel wall
  - cecum is prone for rupture



→ DIAGNOSIS confirmed by RECTAL SUCTION BIOPSY

- Absence of ganglionic cells
- nerve fibres are hypertrophied

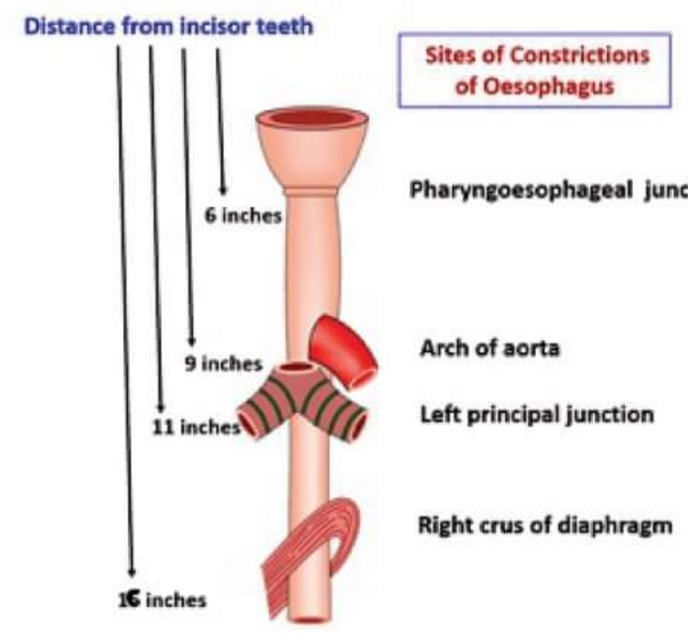
- SPECIAL STAINS

	NORMAL	HIRSHSPRUNG
AChE	−	+ + +
CALRETININ	+	−

ESOPHAGUS APPLIED ANATOMY

→ 25 cm → in adult
10 cm → in New born

→ 4 CONSTRICTIONS
↳ at Upper esophageal Sphincter [by Cricopharyngeus]
↳ dlt Aortic Arch cross over
↳ dlt Left Bronchus cross over
↳ at Lower esophageal Sphincter



→ Distance from Incisor teeth
1. 6" [15 cm]
2. 9" [22.5 cm]
3. 11" [27.5 cm]
4. 16" [40 cm]

→ maximum narrowing at → Upper esophageal Sphincter
→ mc site for perforation → Upper esophageal Sphincter
→ common causes of perforat^{n} → Iatrogenic / Instrumentat^{n}

→ Stratified Squamous non-Keratinized epithelium [acid Sensitive]

→ LES
→ a/w HIGH TONE → helps in Unidirectional movement of food
→ LES DYSFUNCT^{n} → REFLUX ESOPHAGITIS

GERD

REFLUX ESOPHAGITIS

RISK FACTORS

→ Transient Lower Esophageal Sphincter Relaxat^{n} [TLESR] [most important]
→ Smoking
→ Alcohol
→ Obesity
→ Over eating
→ Pregnancy
→ Hiatal Hernia

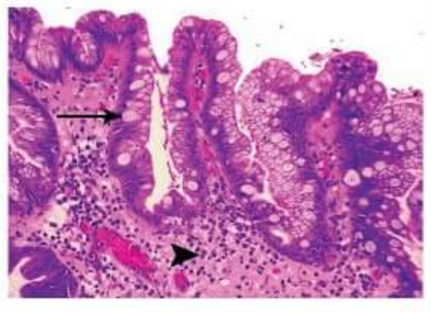
CLINICAL FEATURES

→ Retro sternal pain [Burning]
→ Sour brash
→ teeth discoloration

RE ≅ GERD

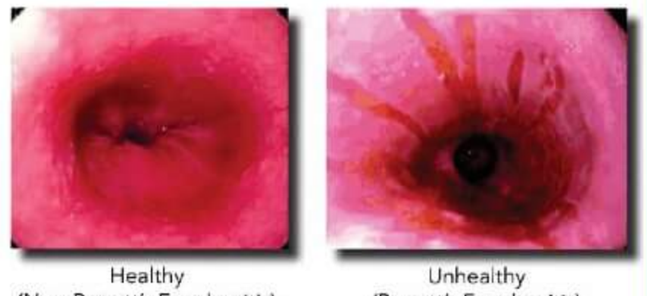
DIAGNOSIS

1. 24 HOUR pH STUDY
2. MANOMETRY → ↓ LES pressure
3. ENDOSCOPY + BIOPSY → confirmed Dx



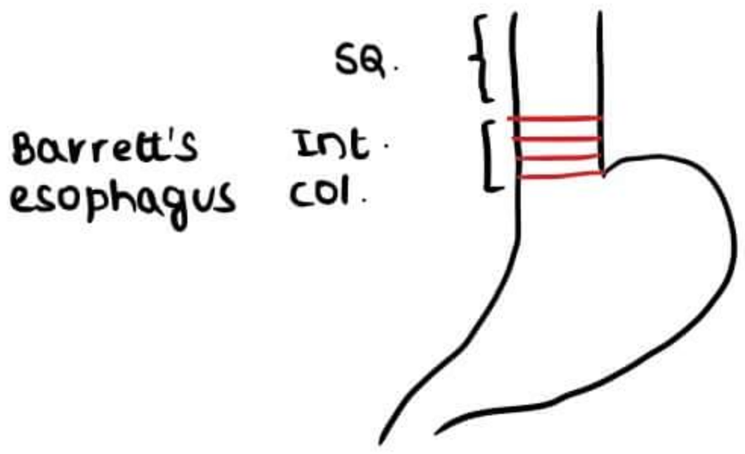
STEM CELLS

SSq. E → Intestinal Columnar E [ACID RESISTANT] → METAPLASIA



Healthy (Non-Barrett's Esophagitis)

Unhealthy (Barrett's Esophagitis)



BARRETT'S ESOPHAGUS

[Intestinal Metaplasia]

↳ Dysphagia

↳ cancer → Adeno carcinoma of Lower part of oesophagus

MANAGEMENT

1. ↓ HCl → PPI's [DOC]
2. PROKINETIC DRUGS
3. SURGERY → FUNDOPLICATION

ICE → Goblet cells ⊕

TRACHEO - ESOPHAGEAL FISTULA

→ FISTULA
- → abnormal connection blw 2 epithelial surfaces
- → can be blw 2 tubings or blw 1 tubing & skin

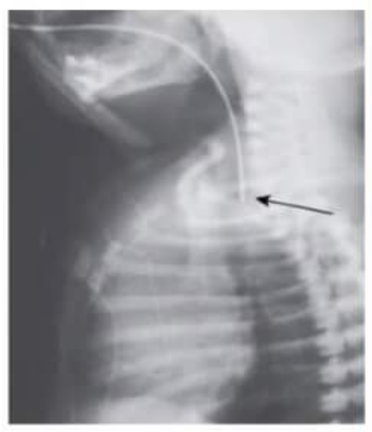
→ congenital defect

→ MOST COMMON VARIANT
- → upper end of esophagus end in a blind pouch
- → Lower end of esophagus communicates ī part of trachea just above the bifurcation

MC VARIANT

→ CLINICAL FEATURES
- → Polyhydramnios
- → Abdominal distension
- → Aspiration [pneumonia]

→ SUSPECTED WHEN
- → When newborn baby not able to swallow milk
- → When not able to pass NG tube in newborn baby



ALCOHOL INDUCED ESOPHAGEAL DISORDERS

ALCOHOLICS

MALLORY-WEISS TEAR

- → Superficial [involves only mucosa]
- → Located below the GEJ [90%]

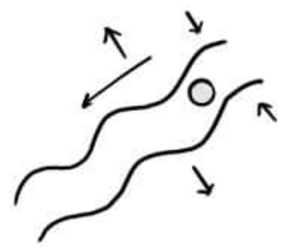
BOERHAAVE SYNDROME

- → Muscles rupture on postero-lateral part on Left side
- → Located above the GEJ [3-5cm above]

CIF

- → Chest pain
- → Hemetemesis [painful]
- → Sub cutaneous emphysema [esply in Boerhaave syndrome]
- → PAINLESS HEMATEMESIS seen in Esophageal varices [Portal HTN Liver Cirrhosis]

ACHALASIA CARDIA

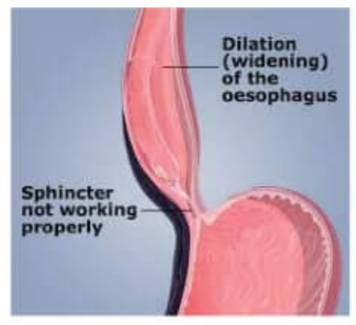


- → GIT → ⊕ neurons — Ach
- → GIT → ⊖ neurons — NO / VIP

- → Selective loss of ⊖ neurons → ↑↑ Muscle tone → Abnormal Motility

ETIOLOGY

- → 1. PRIMARY
- → 2. SECONDARY
  - ↳ Chagas disease
  - ↳ Varicella Zoster virus



CIF

- → dysphagia [Liquids >>> solids]
- → wt Loss

Pre malignant condition

DIAGNOSIS

- → 1. MANOMETRY → IOC ; ↑ LES tone
- 2. BARIUM SWALLOW → BIRD BEAK APPEARANCE

MANAGEMENT

1. DRUGS
   - → Botulinum toxin
   - → Ca^{2+} channel blocker
2. HELLER'S MYOTOMY [definitive Rx]

COMPLICATIONS

1. Aspiration pneumonia
2. chronic Achalasia cardia → Squamous cell carcinoma [in lower part]

ESOPHAGEAL CANCER

ADENOCARCINOMA
- → lower 1/3 rd
- → mc in USA

SQUAMOUS CELL CARCINOMA
- → upper & middle 1/3 rd
- → mc in India

RISK FACTORS

SQUAMOUS CELL CARCINOMA
- → smoking / Alcohol
- → intake of Nitrosamines [Grilled / smoked foods]
- → intake of Hot drinks
- → chronic achalasia cardia
- → Plummer Vinson syndrome [Patterson Kelly Brown Syndrome]
  - ↳ IDA
  - ↳ Atrophic glossitis
  - ↳ esophageal webs
  - ↳ seen in middle aged female
  - ↳ web located in upper 1/3 rd

- → TYLOSIS et PALMARIS
  - ↳ congenital
  - ↳ thickened palms & soles

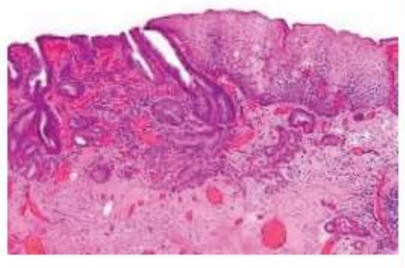
- → Deficiency of Zn / Mo / vit A / vit C

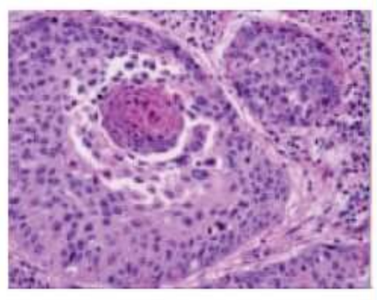
ADENOCARCINOMA → Barrett's esophagus

CLINICAL FEATURES
- → Progressive dysphagia [solids >>> Liquids]
- → weight loss
- → chest pain
- → hoarseness of voice [d/t recurrent laryngeal nerve involvement]
- → cough [d/t tracheal involvement]

DIAGNOSIS

1. ENDOSCOPY + BIOPSY
   - → Goblet cells ⊕ → Adenocarcinoma
   - → Squamous cells ⊕ → Squamous cell carcinoma





2. BARIUM SWALLOW → RAT - TAIL APPEARANCE

SPREAD OF ESOPHAGEAL CANCERS
- → mc site → Liver
- → LN
  - ↳ upper 1/3 rd → cervical LN
  - ↳ middle 1/3 rd → Mediastinal LN / Tracheobroncheal LN
  - ↳ lower 1/3 rd → cardiac / gastric / Celiac LN

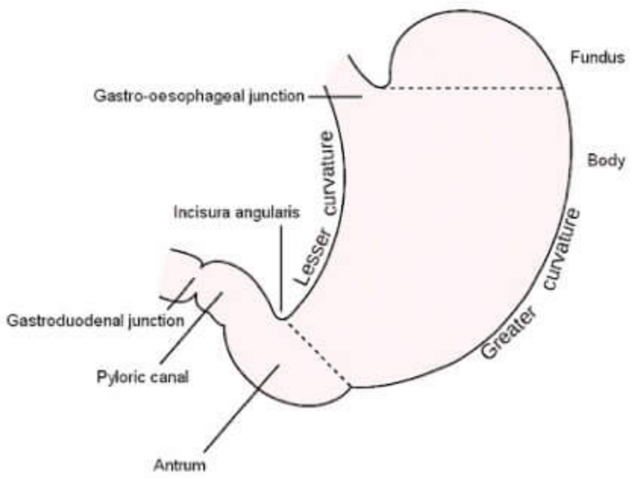
MANAGEMENT → Partial / total esophagectomy

STOMACH

CELLS

1. PARIETAL CELLS
   - → Secrets Intrinsic factor
   - → secrets HCl [Secretⁿ a/w Ach / Histamine / Gastrin → ⊕]

2. CHIEF CELLS → secretes pepsinogen
3. FOVEOLAR CELLS → secretes mucin [protective]
4. G - CELLS
   - located in antrum
   - Secretes GASTRIN ⊕→ HCl ⊖



FACTORS

DAMAGING FACTORS
- → HCl
- → COX ⊖ [NSAIDS] → Gastric mucosal damage

PROTECTIVE FACTORS
- → Epithelial regenerative capacity
- → MUCUS
- → HCO_3^-
- → PGs
  - ↳ ↑ MUCUS
  - ↳ ↑ HCO_3^-
  - ↳ ↑ ERG
  - ↳ ↓ HCl secretion

ACUTE & CHRONIC GASTRITIS

ACUTE GASTRITIS [imbalance b/w Protective & damaging factors]

RISK FACTORS
- → Alcohol
- → Drugs → NSAIDs & ANTI CANCER DRUGS
- → uremia
- → Stress
  - → ICU
  - → Burns → CURLING ULCER
  - → ↑ ICT → CUSHING ULCER

C/F → Epigastric pain, Nausea & vomiting

CHRONIC GASTRITIS

RISK FACTORS
- → H. pylori
- → Autoimmune gastritis
- → uremia
- → Radiation
- → GVHD

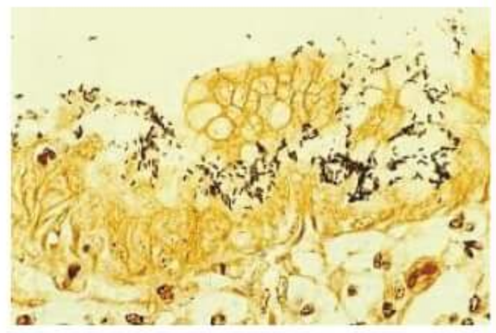
TYPE A GASTRITIS
- → Auto immune
- → self reactive CD_4 T cell
- → a/w Type I DM
  - Addison's Disease
  - Hashimoto's thyroiditis

→ parietal cells are damaged → Achlorhydria
↓
↑ G - CELL ⊕
↓
↑ Gastrin [hypergastrinemia]
↑ neuro endocrine tumor

→ mc ly involves Fundus & Body

TYPE ● GASTRITIS [90%]

→ dlt H. pylori
→ mc ly involves Antrum
→ H. pylori secretes
↳ Urease
CAG - A
VAC - A
} Gastric mucosal inflammatⁿ



→ CLINICAL MANIFESTATIONS OF H. pylori associated inflammatⁿ
1. DUODENAL ULCER [dlt hypersecretⁿ OF acid → Gastric metaplasia]
2. STOMACH CANCER
3. REACTIVE T- CELLS → FACTORS → Polyclonal B - cell proliferatⁿ
↓
MALTOMA

PEPTIC ULCER DISEASE

→ damage to mucosal lining
→ complicatⁿ of chronic gastritis
→ COMMON SITES
1. Duodenum [1st part]
2 Antrum [Lesser curvature]
3. GE]

DUODENAL ULCER	GASTRIC ULCER
→ Located in anterior wall of D_1	→ at Lesser curvature [B-A junctⁿ
→ H. pylori +++	→ H. pylori ⊕ / NSAID & ⊕ / smoking ⊕
→ ↑ Acid	→ Ⓝ Acid & ab Ⓝ mucosal sensitivity
→ Epigastric pain ↳ ↓ ī food ↳ Wt. gain	→ Epigastric pain ↳ ↑ ī food ↳ wt. loss
→ Brunner gland hypertrophy ⊕	→ Brunner gland hypertrophy ⊖
→ not premalignant	→ Pre malignant
COMPLICATIONS	COMPLICATIONS
1. Bleeding	1 Bleeding
↳ melena ↳ From Gastroduodenal artery	↳ Hematemesis ↳ source - Left gastric artery
2. MALIGNANCY	2. Malignancy
↳ benign always	→ can be malignant

3. PERFORATION

→ mcly involves anterior wall

→ can lead to pancreatitis, peritonitis } poor prognosis mortality

4. GASTRIC OUTLET OBSTRUCTION

→ occurs at D_1

→ clw repeated episodes of vomiting

↓ Hcl → ↓ Cl^- → metabolic Alkalosis

↓ FLUID → Intra vascular dehydrat^n → + RAAS → ↑ Na^+ / H_2O, ↓ K^+ / H^+ [in urine] → ↓ hypokalemia → ACIDURIA

→ © HYPOCHLOREMIC
HYPOKALEMIC
METABOLIC ALKALOSIS ī
PARADOXICAL ACIDURIA

→ common site → D_1

→ mc cause in adults → stomach cancer

PUD

1. Bleeding [mc]
2. Perforat^n [mc alw mortality]
3. GOO [hypochloremic hypokalemic metabolic alkalosis ī ACIDURIA]
4. Malignancy [ī gastric ulcer]

DIAGNOSIS

1. UREA BREATH TEST

Urea ^{14}, Water } Breath Analyzer → detects $CO_2{}^{14}$

H. pylori → Urease → Urea ^{14}, $CO_2{}^{14}$

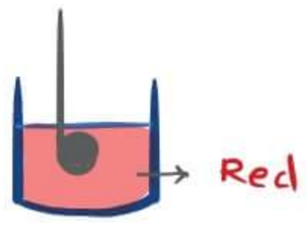
2. ENDOSCOPY + BIOPSY → confirmatory

BENIGN ULCER	MALIGNANT
→ small [<4cm]	→ big
→ flat	→ irregular
→ regular folds	→ Heaping margins
→ clean base	
→ at LC commonly	→ at GC commonly

3. CLO TEST [campylobacter like organisms]

→ indicator → Phenyl Red

→ discoloratⁿ → positive



TREATMENT

1 PPI
2 ANTI BIOTICS
} TRIPLE DRUG THERAPY

GASTRIC TUMORS

→ MC Benign tumor → LEIOMYOMA

→ mc malignant tumor → ADEND CARCINOMA

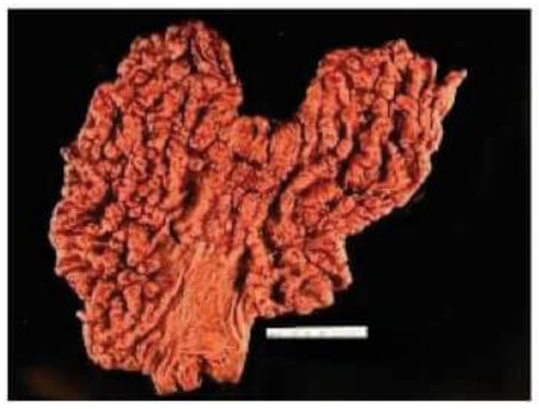
→ mc malignant tumor which bleeds → LEIOMYOSARCOMA

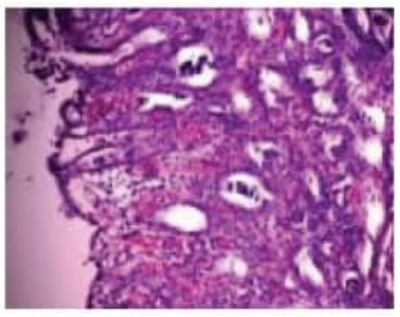
→ mc mesenchymal tumor → GIST

ADENOCARCINOMA

RISK FACTORS

→ Tobacco / Alcohol
→ Nitrosamines
→ H. pylori
→ Autoimmune gastritis [A & B]
→ Blood group A
→ HIO previous gastric Sx
→ Nutritional Deficiency
→ menetrier's disease
  ↳ foveolar hypertrophy
  ↳ ↑ TNF α
  ↳ Prominent gastric rugal folds





→ CDH_1 mutation → E - cadherin

→ APC mutation → ↑ adenomatous polyps

→ LOCATION → Antrum

C/F

→ Early satiety [Post prandial heaviness] [earliest]
→ wt loss [mc]
→ abdominal pain

DIAGNOSIS

1. ENDOSCOPY + BIOPSY [IOC]

↓ ↓

ulcer

1. Early → mucosa & sub mucosa involved
2. Late → muscle & Serosa also involved

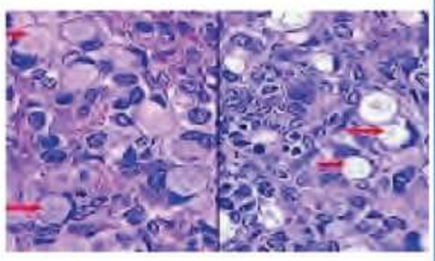
Early → better prognosis
Late → poor prognosis

LAUREN'S CLASSIFICATION

INTESTINAL TYPE	DIFFUSE TYPE
→ Localised cancer 	→ diffuse infiltration 
→ APC mutation ⊕	→ CDH1 mutation ⊕ 
	→ mucinous vacuole ⊕
	→ SIGNET - RING APPEARANCE
	→ a/w DESMOPLASIA
	→ LINITIS PLASTICA [leather bottle appearance]
→ Better prognosis	→ Poor prognosis

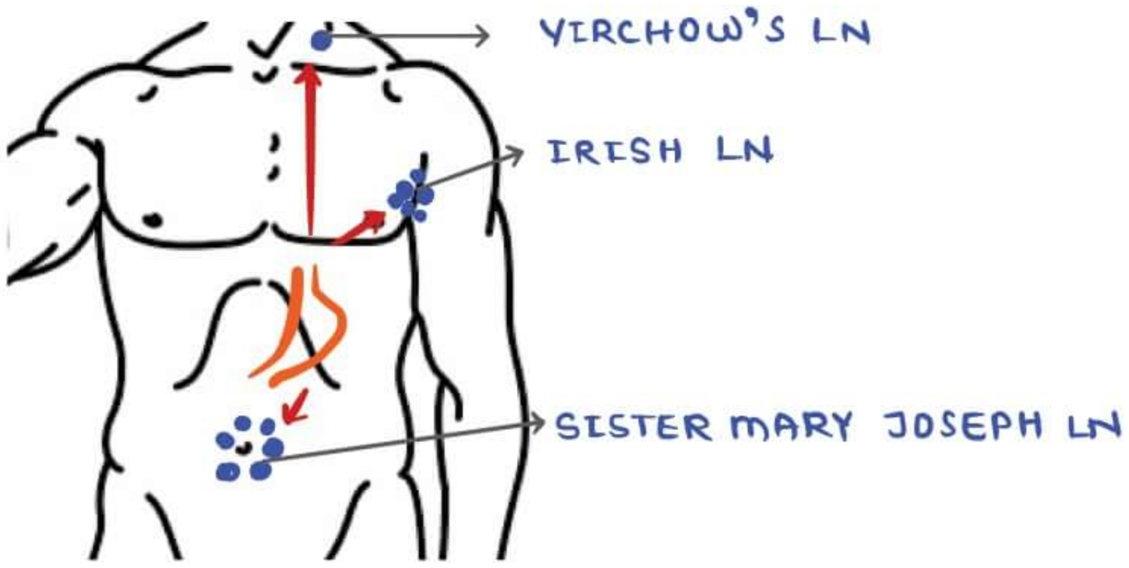
BEST PROGNOSIS → SUPERFICIAL SPREADING VARIANT

SPREAD



common organs involved

↳ Liver → mc
↳ Lungs
↳ overies → B/L ;  KRUKENBERG TUMOR
→ mi reason → 1° Gastric cancer
↳ LN



→ POD Involvement → BLUMER'S SHELF

GASTRO INTESTINAL STROMAL TUMOR

CELLS OF CAJAL

→ component of MYENTERIC PLEXUS
→ Pacemaker cells of GIT
→ mutation of cells → ↑↑↑ Proliferatn [dlt Tyrosine kinase]

→ Definitive markers
CD 117 / C-KIT [more specific]
CD - 34 [non - specific]

→ Other markers → DOG - 1 [detected on GIST 1]
→ R/ by IMATINIB [Tyrosine Kinase ⊖]
→ mc mesenchymal tumor of stomach

NHL → m/c Extranodal site → Stomach [immuno competent]
→ CNS [immuno compromised / AIDS]

SMALL INTESTINE MALABSORPTION DISORDERS DIARRHEA ⊕

CELIAC SPRUE

→ a/w HLA - DQ_2 / DQ 8

→ PATHOGENESIS

1. Cereals ↓ GLUTEN → GLIADIN

act on

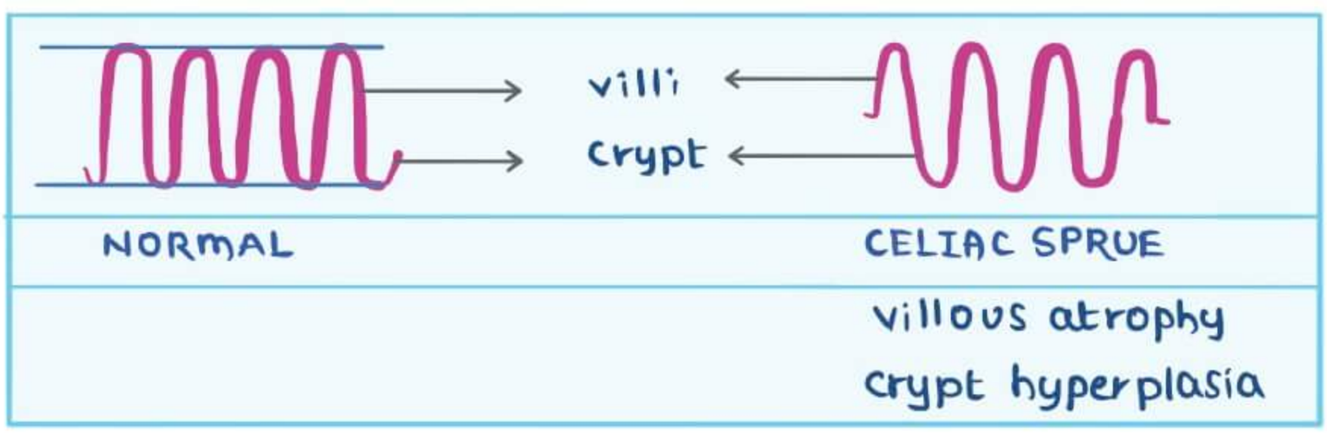
T Cells → Abs [Ig A]
↳ Anti-Gliadin Ab ⊕
↳ Anti - tissue transglutaminase Ab
↳ Anti - endomysial Ab ⊕

GLUTEN CONTAINING CEREALS
↳ Wheat
↳ oat
↳ Barley
↳ Rye

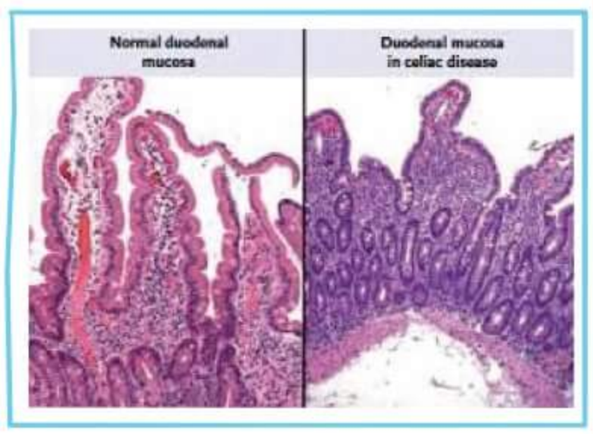
2. Ig A → DERMAL PAPILLAE ⊕ → DERMATITIS HERPETIFORMIS

→ CLINICAL FEATURES
↳ Diarrhea
↳ Abdominal pain
↳ Dermatitis herpetiformis

→ DIAGNOSIS
1. INTESTINAL BIOPSY [Duodenal Bx]



DUODENAL BIOPSY



THICKNESS MUCOSA NOT ALTERED
Lymphocytic infiltration ⊕

→ repeated duodenal biopsies are indicated [at least 2]

→ COMPLICATIONS OF CELIAC SPRUE
  → Malabsorptⁿ & Skin manifestations
  → DUODENAL COMPLICATION → IDA
  → ↑ Enteropathic T-cell lymphoma

2. ANTI ANTIBODIES
  → Anti TTG Ab + + + [preferred]
    Anti endomysial Ab

3. SKIN Bx

→ MANAGEMENT
  1. CEREAL SUBSTITUTION → maize & Rice
  2 DAPSONE for Dermatitis Herpetiformis
  3. STEROIDS

→ clinical manifestations instead of good dietary control indicates →
↑ Enteropathic T cell lymphoma

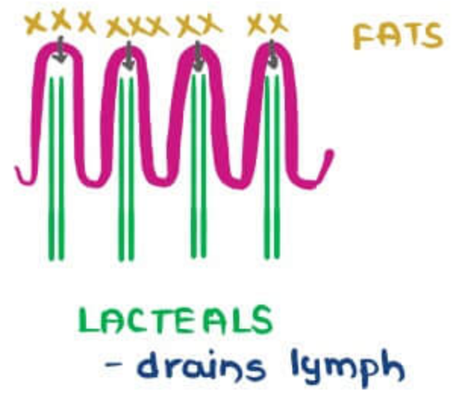
TROPICAL SPRUE

→ Infectious disease [E. coli]
→ Tropical distribution
→ Total Intestinal involvement ⊕
  ↳ deficiency of Fe | FA | B_{12}

→ Benign condition
→ good response to antibiotics

WHIPPLE DISEASE

→ Causative Agent → TROPHERYMA WHIPPELII
→ MULTI SYSTEM INVOLVEMENT
  ↳ Intestine
  ↳ CNS [late involvement]
  ↳ Joints [early involvement]
  ↳ LN



→ TROPHYREMA WHIPPELI INFECTION → Macrophage infiltratⁿ in Lamina propria → ROD SHAPED BACILLI ⊕ Inside macrophages → LACTEAL COMPRESSION & OBSTRUCTⁿ OF LYMPHATIC DRAINAGE → DIARRHEA

→ DIAGNOSIS
  1. BIOPSY
    a. PAS ⊕ , Diastase resistant granules inside macrophages
    b. Rod shaped bacilli ⊕

→ Rx by ANTIBIOTICS

CARCINOID TUMOR

→ arises from NEURO ENDOCRINE CELLS
  ↳ Chromogranin ⊕
  ↳ NSE ⊕

→ mc site involved → GIT > Bronchus

CASE I

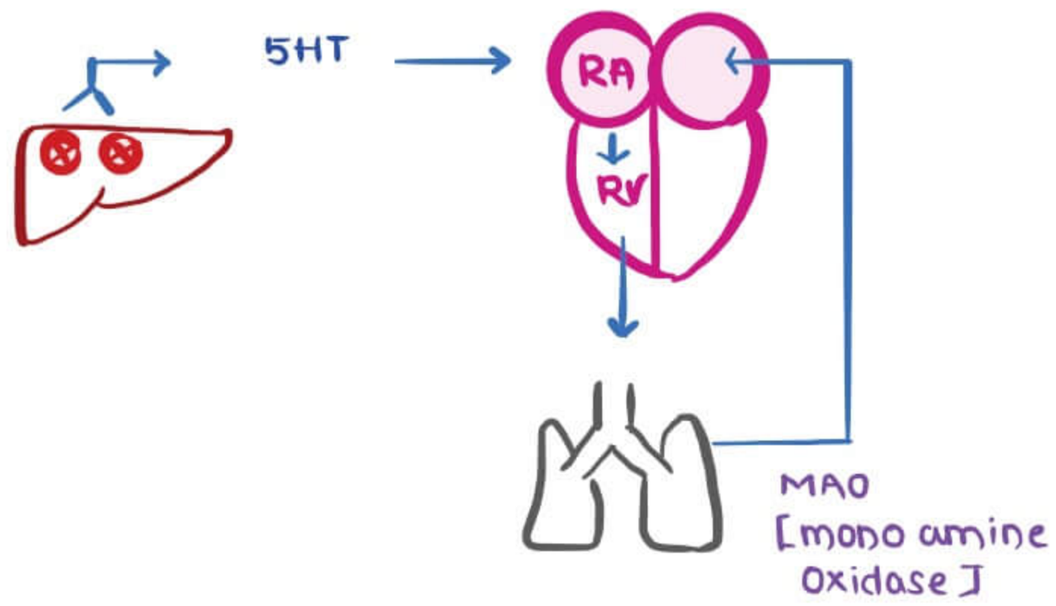
ILEUM → 5 HT →  → metabolised to 5-HIAA → Urine

CASE II

MID GUT [malignant carcinoid tumor] → 5 HT →  → 5 HT into circulatⁿ [CARCINOID SYNDROME]

CARCINOID SYNDROME

→ ↑ 5 HT in circulatⁿ by cancer cells
→ CLINICAL FEATURES
  → Flushing
  → Diarrhea
  → Asthma like symptoms
  → Systemic fibrosis → Isolated Rt heart involvement
    ↳ Tricuspid valve → Regurgitatⁿ / Insufficiency
    ↳ pulmonary valve → Stenosis



T	}	Tricuspid valve
I	}	Insufficiency
P	}	Pulmonary valve
S	}	Stenosis

S	→	Systemic fibrosis [Rt ♡]
H	→	hepatomegaly
I	→	Intestine [Diarrhea]
V	→	vasomotor [Flushing]
A	→	Asthma like symptoms

DIAGNOSIS

1. SCREENING TEST → 24hr HIAA levels in urine
2. PLASMA CHROMOGRAMIN - A Levels → ↑↑↑
3. BIOPSY & ELECTRON MICROSCOPY
   → Granules
     ↳ chromogranin A ⊕
     ↳ NSE ⊕

TREATMENT

1 Drugs for small tumors
2. Surgery for big tumors

INFLAMMATORY BOWEL DISEASE

young Females [20-30 yrs]
↓
Immune system Activation
↓
Normal Gut Bacteria

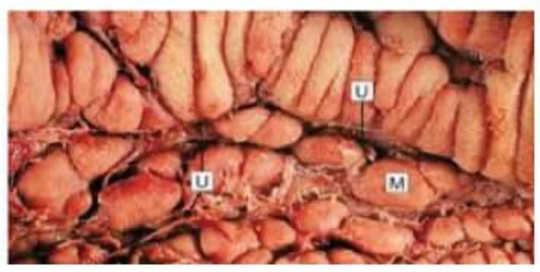
AFFECTS

GIT → Abdominal pain [colicky], diarrhea [bloody]
Eyes → Uveitis
Bile ducts → Obstructive Jaundice
Joints → migratory arthritis
Skin → Erythema nodosum, pyoderma gangrenosam

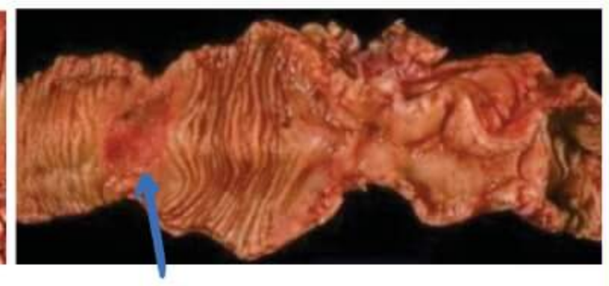
CROHN'S DISEASE

→ Involves ANY PART OF GIT
  ↳ mcly → ILEUM
  ↳ Lcly → RECTUM

→ SKIP LESIONS ⊕
→ COBBLE - STONE MUCOSA ⊕

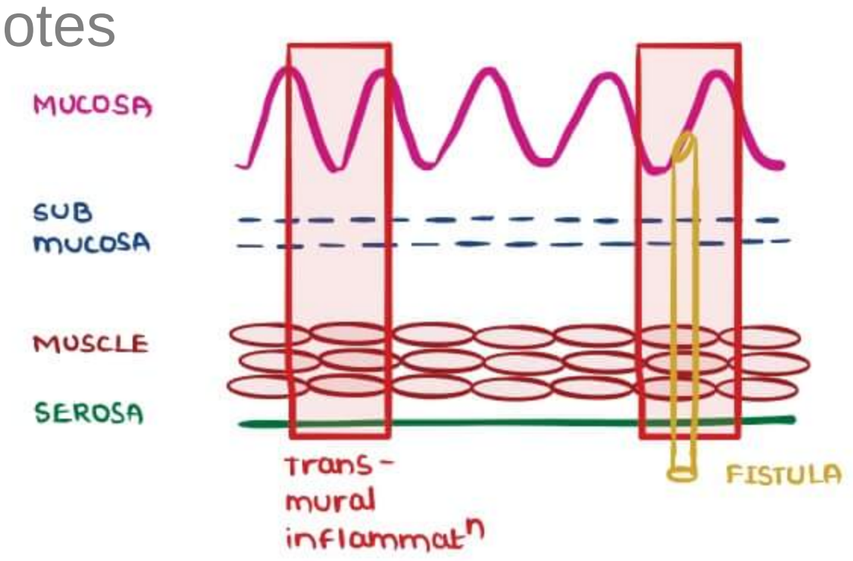


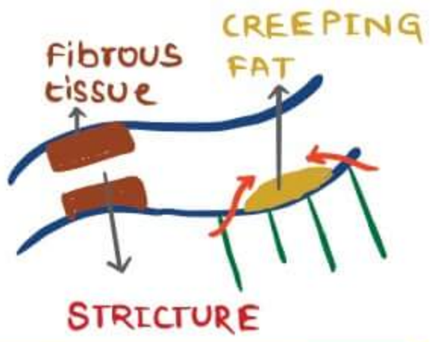
COBBLESTONE MUCOSA


SKIP LESION

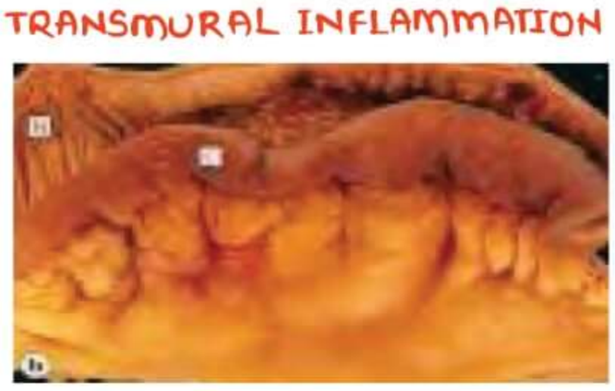
→ TRANSMURAL INFLAMMATION
  ↳ a/w granuloma formatⁿ
  ↳ a/w Fistula formatⁿ
  ↳ a/w Stricture formatⁿ
  ↳ CREEPING FAT ⊕

→ SACCHAROMYCES CEREVISAE
↓
Ab ⊕
↓
ASCA ⊕



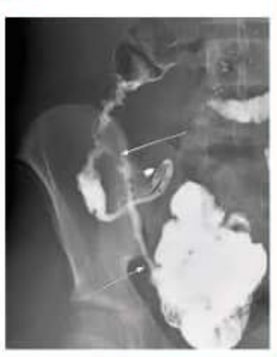



TRANSMURAL INFLAMMATION


CREEPING FAT

CROHN'S DISEASE		
S	→	Skip lesions
I	→	Ileum [mc]
S	→	S.C. → ASCA ⊕
T	→	Transmural Inflammation [granuloma ⊕]
E	→	Extra Fibrosis → Stricture / creeping fat
R	→	Rectum spared

→ STRICTURE → STRING SIGN
on Barium investigation


STRING SIGN

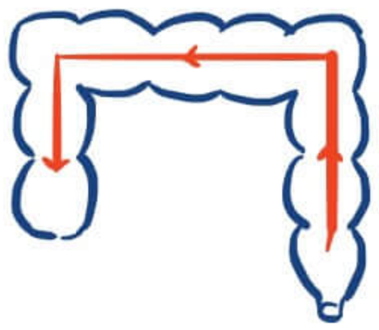
→ CLINICAL FEATURES
- → Abdominal pain [Rt lower quadrant]
- → Diarrhea
- → Eyes ⊕
- → Skin ⊕

→ ↑ oxalate absorptⁿ in ileum → Systemic circulation → Kidney → RENAL STONES

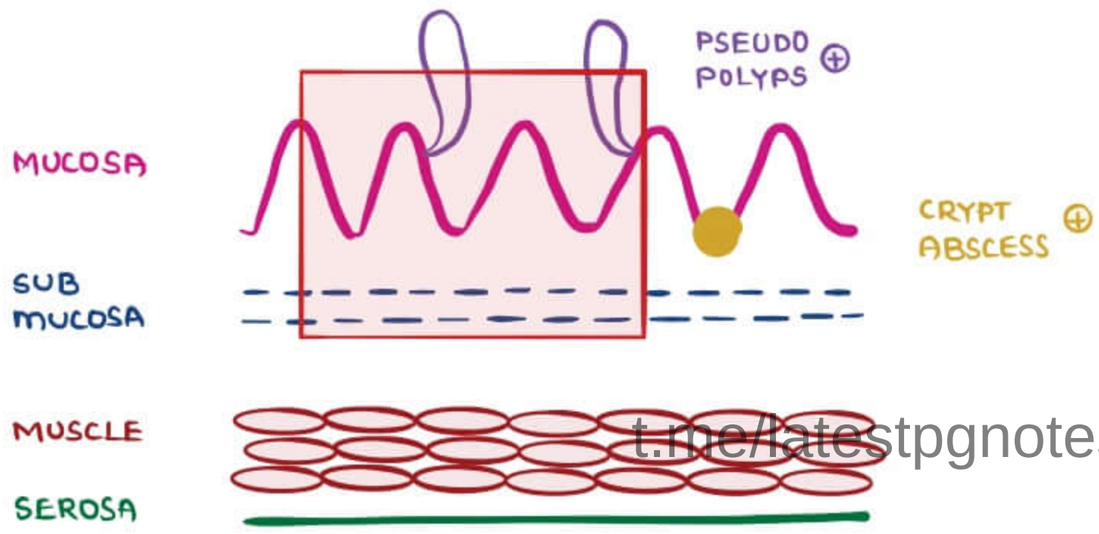
→ ↑ colon cancer

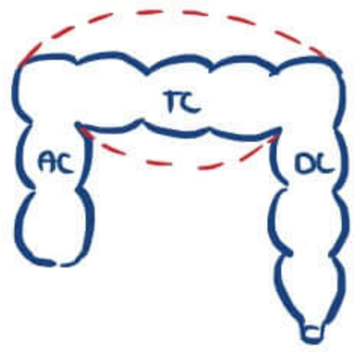
ULCERATIVE COLITIS

→ involves COLON → Rectum [Retrograde spread]
↓
PAN COLITIS [severe form]

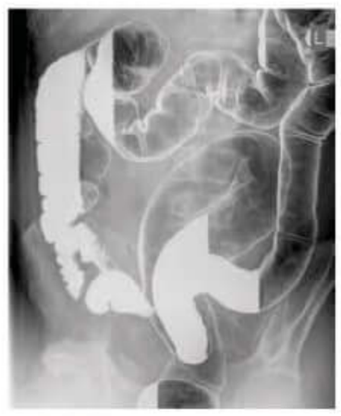


RETROGRADE SPREAD





TOXIC MEGACOLON



LEAD-PIPE APPEARANCE

- → SUPERFICIAL INVOLVEMENT [mucosa & Sub mucosa]
- → CRYPT Abscess ⊕
- → PSEDO POLYPS ⊕
- → TOXIC MEGACOLON [may rupture]
- → LOSS OF HAUSTRATIONS ⊕ → LEAD - PIPE APPEARANCE
- → p - ANCA ⊕ [also seen in vasculitis]

→ CLINICAL FEATURES
- ↳ Abdominal pain [Lt. lower quadrant]
- ↳ Diarrhea
- ↳ Jaundice
- ↳ Joint involvement
- ↳ ↑ colon cancer [UC > CD]

ULcerative	→	ulcers [mucosa & Sub mucosa]
C	→	Continuous involvement
O	→	Origin
L	→	Lead pipe appearance
I	→	↑ growth [pseudopolyps]
T	→	Toxic mega colon
I S	}	↑ severity / ↑ colon cancer

p ANCA ⊕
Granuloma ⊖

INTESTINAL POLYPS, COLON & ANAL CANCER

POLYPS

NON-NEOPLASTIC POLYPS

1. Inflammatory polyps
2. Hyperplastic polyps → mc, Recto sigmoid locat^{n}
3. Hamartomatous polyps
   - a. PEUTZ-JEGHERS POLYP → origin → Jejunum
   - b. JUVENILE → Origin → Rectum
     → < 5 yrs age group
     → Solitary

JUVENILE POLYPOSIS SYNDROME
→ ↑ Stomach | colon cancer
→ multiple polyps

PJ SYNDROME

NEOPLASTIC POLYPS → Adenomatous Polyps

COLON CANCER

→ Elderly
→ Rectum >> Sigmoid colon
→ Adeno carcinoma

RISK FACTORS

A. GENETIC

1. HNPCC / LYNCH SYNDROME

→ a/w DNA Repair genes defect [MSH | MLH]
↓
microsatellite instability
↓
↑ cancer

→ LYNCH SYNDROME / C|E|O SYNDROME
→ C → Colon cancer [Rt]
E → Endometrial cancer
O → Ovarian cancer

→ < 50 yrs age group

2. FAMILIAL ADENOMATOUS POLYPOSIS [FAP]

APC gene → Chr 5q → ↓ Adenoma

mutation → ↑↑ Adenomatous Polyps → ↑ Colon Ca

SUB TYPES

1. CLASSICAL
   → >/ 100 Adenomas + Retinal Pigment Epithelium hypertrophy

2. TURCOT SYNDROME
   → classical FAP + CNS tumors [medulloblastoma | glioma]

3. GARDNER SYNDROME
   → FAP
   → Osteoma
   → Fibromatosis
   → Epidermal cysts

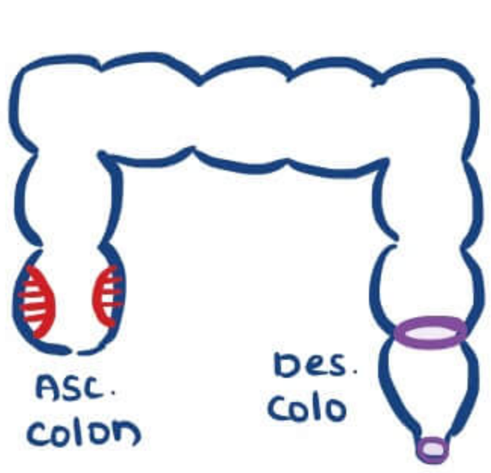
B. ENVIRONMENTAL RF

↑ RISK	↓ RISK
Dietary lipids	Dietary fibers
Pelvic irradiation	NSAIDs
Streptococcus bovis endocarditis	HRT
Ureterosigmoidostomy	

C. IBD
→ CD → ↑↑
→ UC → ↑↑↑

CLINICAL FEATURES

ULCERATIVE | FUNGATIVE
↳ SIS of Anemia



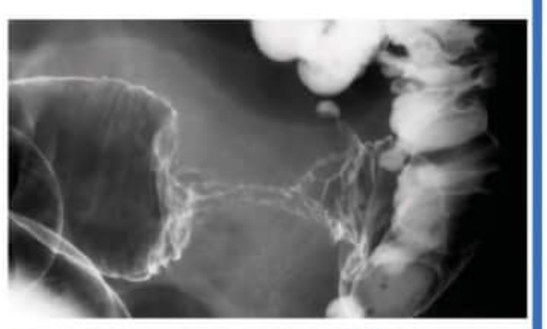
CIRCUMFERENTIAL | NAPKIN RING APPEARANCE
→ Alteration of bowel habits
→ Bleeding per rectum [Rectal cancer]
   ↳ tenesmus
   ↳ Spurious diarrhea

DIAGNOSIS

1. COLONOSCOPY + BIOPSY [IOC]
2. FECAL OCCULT BLOOD TEST
   → detected by
      a. Microscopic Examination of Stool sample
      b. GUAIAC TEST

3. TUMOR MARKERS
   → ↑↑ S. CEA [carcino Embryonic Antigen] → useful to check recurrence

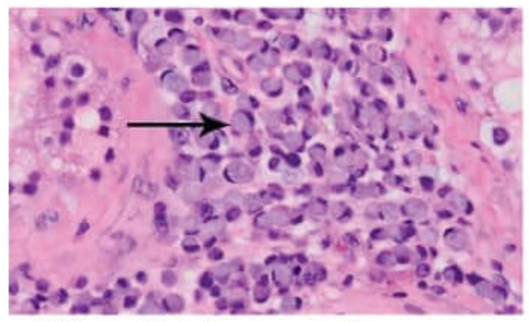
4. APPLE CORE APPEARANCE ON Barium enema


Apple core lesion

SCREENING TEST
1. colonoscopy
2. Fecal occult Blood Test

METASTASIS

1. Liver
2. Lymph nodes
3. Ovaries [Krukenberg tumor - signet-ring appearance]



Signet ring cell

Rx

1. SURGERY
2. ANTI CANCER DRUGS
   - a. FOLFOX REGIME
     - → Folinic Acid
     - → 5-FU
     - → Oxaliplatin
   - b. FOLFIRI REGIME
     - → Folinic Acid
     - → 5-FU
     - → Irinotecan

ANAL CARCINOMA

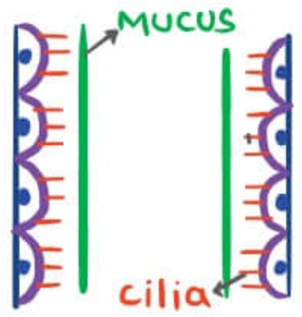
→ Squamous cell carcinoma

→ Rx by CHEMO-RADIATION → NIGRO'S REGIME

RESPIRATORY SYSTEM
INTRODUCTION

BASIC CONCEPTS

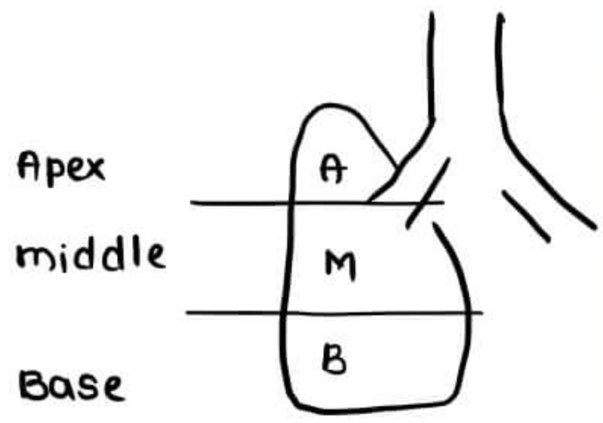
→ RIGHT BRONCHUS IS MORE ALIGNED ī TRACHEA THAN LEFT → FB impactn is more
→ Airway is lined by PSEUDO STRATIFIED CILIATED COLUMNAR EPITHELIUM
→ DEFENCE MECHANISMS WHICH HELPS IN REMOVAL OF DUST | BACTERIA | Ag
  1. Upward movement of MUCUS dlt CILIARY movement
  2. Alveolar MACROPHAGES → helps in phagocytosis



→ ↓ CILIARY ACTIVITY SEEN IN
  1. SMOKING
  2. KARTAGENER SYNDROME [dlt DYNEIN defect]
     → TRIAD OF
       ↳ Bronchiectasis
       ↳ Situs inversus [dextro cardia]
       ↳ Sinusitis

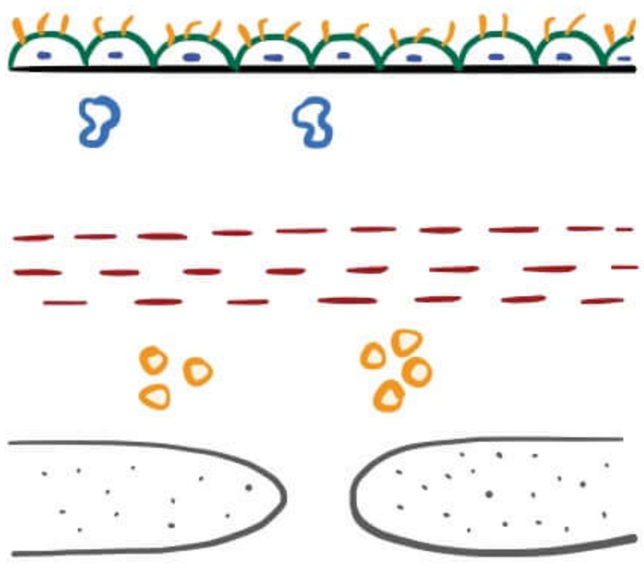
     → ↓ Fertility

→ Ventilation is maximum at BASE
→ Perfusion is maximum at BASE
→ V/P Ratio is maximum at APEX



→ PNEUMOCYTES
  1. TYPE I → Lining of airway
  2. TYPE II → Secretes surfactant [↓ ST] & has repair function

→ HISTOLOGY



→ Pseudo stratified columnar Epithelium
→ Venules
→ Smooth muscle
→ mucus secreting glands
→ cartilage [absent in bronchioles]

REID'S INDEX

$\frac{A}{B}$ [Thickness of mucus gland layer]
B [distance blw epithelial cell & cartilage]

→ N → < 0.4

→ Increased in PULMONARY BRONCHITIS

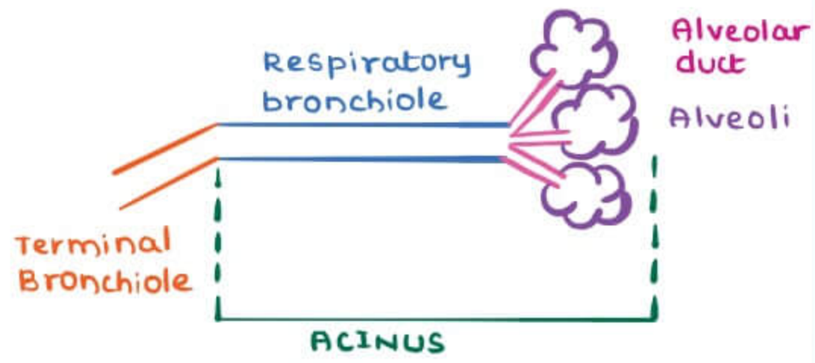
OBSTRUCTIVE LUNG DISEASE

SPIROMETRY

→ FEV_1 ↓↓↓ & FVC ↓

→ $\frac{FEV_1}{FVC}$ ↓

→ RV ↑↑ → ↑ TLC



EMPHYSEMA

ACINUS

→ Functional unit of lung

→ DAMAGING FACTORS

↳ Elastase [N/m] → Elastin damage

→ PROTECTIVE FACTORS

↳ Anti Elastase activity

→ α_1 anti trypsin

→ α_1 macroglobulin

EMPHYSEMA → Permanent abnormal dilatation of Acinus

ETIOLOGY

→ Smoking

→ α_1 - anti trypsin deficiency

↳ PiMM gene

↳ α_1 - anti trypsin misfolded

↳ causes micro nodular cirrhosis + Emphysema

→ PiMZ gene defect → heterozygous

→ Pizz gene defect → homozygous → total absence of enzyme

SUB TYPES

1. CENTRI ACINAR EMPHYSEMA

→ dlt smoking

→ Upper lobes of Lungs are affected

→ mc clinically seen emphysema

2. PAN ACINAR EMPHYSEMA

→ whole acinus involved

→ dlt α_1 - anti trypsin deficiency

→ base of Lung involved

→ a/w micro nodular cirrhosis

→ autosomal recessive

3. DISTAL ACINAR EMPHYSEMA

→ seen in smokers

→ a/w Spontaneous pneumothorax

→ Upper lobe involved

4. IRREGULAR EMPHYSEMA

→ patchy involvement
→ mc microscopic emphysema

CLINICAL FEATURES

→ ELASTIN FIBRES
  ↳ Alveolar recoil maintained
  ↳ maintain patency
  } dilatatⁿ of Alveoli, airway collapse

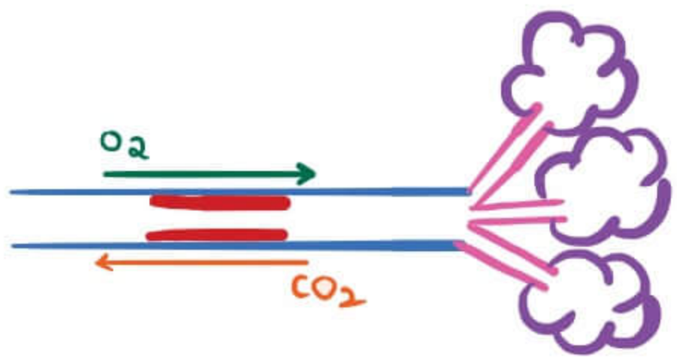
→ Dysphea
→ weight loss
→ H/O smoking
→ PURSED LIP BREATHING
→ AIR TRAPPING Leads to
  ↳ Flat diaphragm
  ↳ Barrel chest

→ pO_2 → (N) → PINK PUFFERS
→ Later → pO_2 ↓ → Rt. ventricular failure

CHRONIC BRONCHITIS

→ productive cough i Sputum for atleast 3 months in 2 consecutive years
→ seen in SMOKERS

SMOKING
↓
INFLAMMATION
↑ MUCUS PRODUCTION
→ Stasis
→ Productive cough
→ mucus gland thickness ↑
2° INFECTION



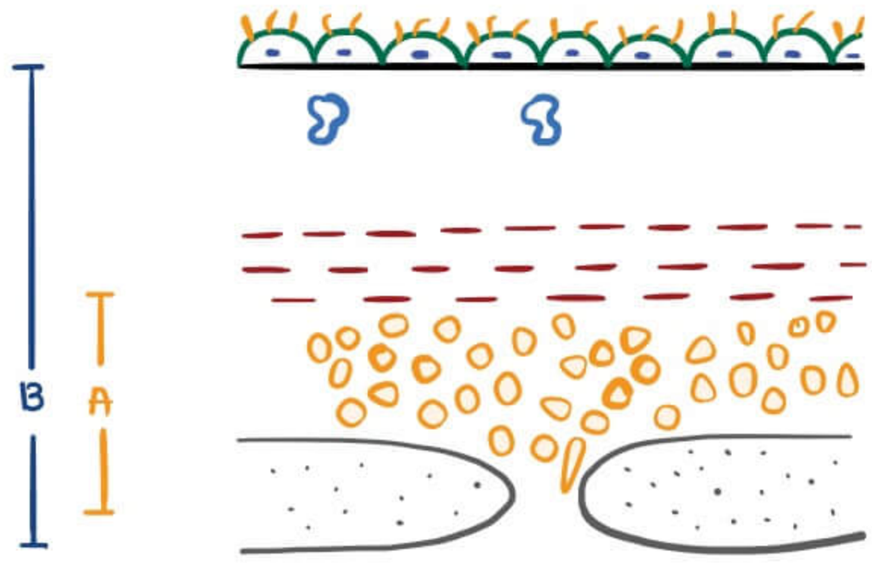
↑↑ $pA\,CO_2$
↓ $pA\,O_2$ → $pa\,O_2$ ↓↓ → cyanosis

CLINICAL FEATURES

→ Productive cough
→ Fever
→ Cyanosis
} BLUE BLOATERS

↓ paO_2 → vaso constrict^{n} → ↑ Tissue Peripheral Resistance → Pulmonary HTN → Rt. ventricular failure → cor pulmonale

REID'S INDEX = $\frac{A}{B}$ → ↑↑



→ Pseudo stratified columnar Epithelium
→ venules
→ Smooth muscle
→ mucus secreting glands
→ cartilage [absent in bronchioles]

→ Squamous metaplasia ⟶ Dysplasia ⟶ ↑ Bronchogenic cancer
→ NO amyloid deposition → NO AMYLOIDOSIS
→ CHEST X-RAY → Prominent markings [dlt Pulm. HTN]

COPD → Emphysema + Chronic Bronchitis

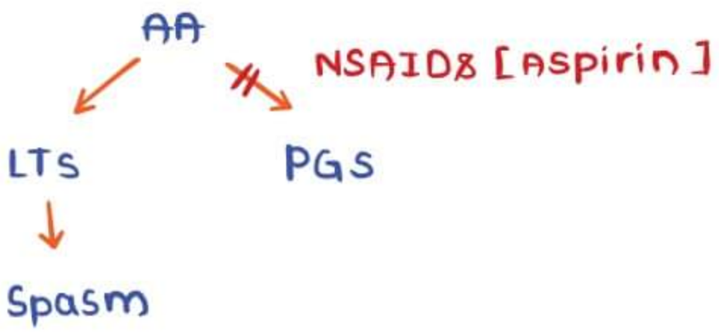
Smoking
↓
↑ Ach [vagal]
↓
↑ Bronchospasm

Rx
1. Quit smoking } ↑ Longevity
2. O_2 Supplementat^{n} }
3. Ipratropium
4. Antibiotics
5. mucolytics

BRONCHIAL ASTHMA [Reversible]

EXTRINSIC
→ dlt Ext. antigen [dust / pollen]
→ Type 1 HR
→ ↑ Ig E
→ seen in children
→ HIO Eczema ; atopy

INTRINSIC
→ dlt viruses [↓ Spasm threshold]
occupational disorders
Exercise
Drugs [NSAIDs]



→ SAMTER'S TRIAD
  ↳ ASA intolerance [Aspirin]
  ↳ Asthma
  ↳ Adult Nasal polyps

  ↳ Child Nasal polyps → CYSTIC FIBROSIS

→ CIF
  → Wheezing
  → dyspnea
  → nocturnal cough
  → respiratory alkalosis

MICROSCOPIC EXAMINATION
  → Airway remodelling

SPUTUM FINDINGS [3 C's]
  → CURSCHMANN SPIRALS
  → CREOLA BODIES
  → CHARCOT - LEYDEN CRYSTALS

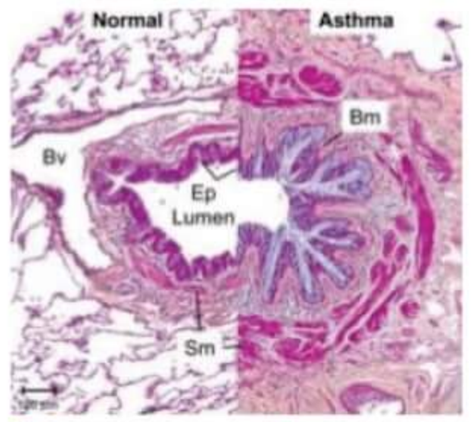
→ ADAM 33 gene a/w ↑ Fibrosis & ↑ smooth muscles

→ YKL - 40 PROTEIN → directly related ∝ Severity of Asthma

BRONCHIECTASIS
→ chronic necrotising infection → Abnormal permanent dilatation of airways

ETIOLOGY
→ Kartagener Syndrome
→ cystic fibrosis
→ Obstruction → FB or tumor
→ Necrotising infection [TB [mc] | Staph. aureus | Adenovirus]
→ Allergic Broncho pulmonary Aspergillosis

CIF
→ Productive cough → clubbing
→ Dyspnea → ↓ paO_2 → Cor pulmonale

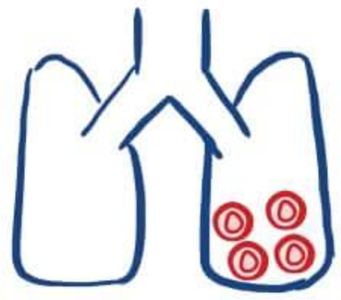


Airway remodelling


Curschmann spirals


Creola bodies


Charcot - leyden crystals



Dilated Airways upto pleura

→ AFFECTS Left lower lobe commonly [others involves Right lung]

→ GROSS → Dilated airways upto pleura
→ HRCT SCAN → HONEY COMB / TRAM TRACK APPEARANCE

→ BRONCHIECTASIS → Benign & ↑↑ 2° Amyloidosis
→ CHRONIC BRONCHITIS → ↑ cancer & no amyloidosis

RESTRICTIVE LUNG DISEASE

Honey combing of lungs

SPIROMETRY

→ FVC ↓↓
→ TLC ↓
→ FEV1 ↓
→ $\frac{FEV1}{FVC}$ ↑
→ ↓ compliance
→ ↓ Diffusion capacity

C|F
→ Cough
→ Dyspnea
→ ↑ RR
→ HONEY COMBING OF LUNGS [later stages]

ETIOLOGY

1 CHEST WALL DISORDERS
- a. NEURO MUSCULAR
  - → Polio
  - → muscular dystrophies
- b. OBESITY
- c. KYPHOSCOLIOSIS

2. INTERSTITIAL DISORDERS
- a. Intestitial fibrosis
- b Pneumoconiosis
- c. Hypersensitivity Pneumonitis
- d. Sarcoidosis

1. IDIOPATHIC PULMONARY FIBROSIS / CRYPTOGENIC FIBROSING ALVEOLITIS

ETIOLOGY

→ cause unknown
→ Alveolar Epithelial Injury → ALVEOLITIS ⊕
↓
TGF - β
↓
INTESTITIAL FIBROSIS
↙ ↘
Lower Lobes Sub pleural

RISK FACTORS
- → Age → Elderly
- → GENETIC FACTORS → Telomerase / mucin / Surfactant
- → ENVIRONMENTAL FACTORS → Smoking

CIF
- → cough
- → Dyspnea
- → ↑ RR

MIE → USUAL INTERSTITIAL PNEUMONIA → Hall mark

Early stages → ↑↑ Fibrosis → FIBROBLASTIC FOCI
Later Stages → ↑↑ collagen
↓ cellular component

Both Stages CO - Exist - - - - → HONEY COMB FIBROSIS

PROGNOSIS → POOR
TOC → PULMONARY TRANSPLANT
RULE OUT → Drugs Exposure → Bleomycin / Methotrexate / Amiodarone
→ Radiation

NON SPECIFIC INTESTITIAL PNEUMONIA

ETIOLOGY → Idiopathic / connective Tissue Disease

CIF → Eldery ♀ [non-smoker]
→ Dyspnea / cough

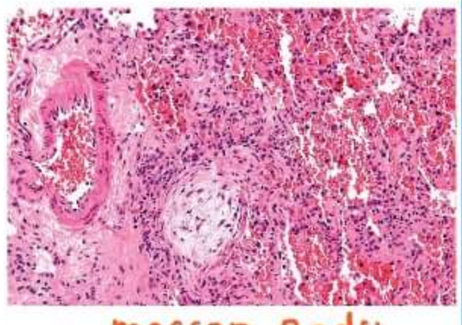
MIE
- → Cellular pattern } Same stage lesions
- → Fibrosing pattern } co-exist

→ NO Fibroblastic foci
→ NO honey combing

→ BIL Reticular opacities On HRCT ⊕

CRYPTOGENIC ORGANISING PNEUMONIA

ETIOLOGY → unknown
CIF → cough & Dyspnea
MIE → MASSON BODY ⊕ [organised connective tissue in Alveolar ducts & bronchioles]


masson Body

→ NO honey combing
→ NO Intestitial fibrosis

→ Good response to STEROIDS

PNEUMOCONIOSIS

Occupational Disorder

PATHOGENESIS → DUST PARTICLES INHALAT^{n} [1-5 μ] → Alveolar macrophages ⊕ → FIBROSIS

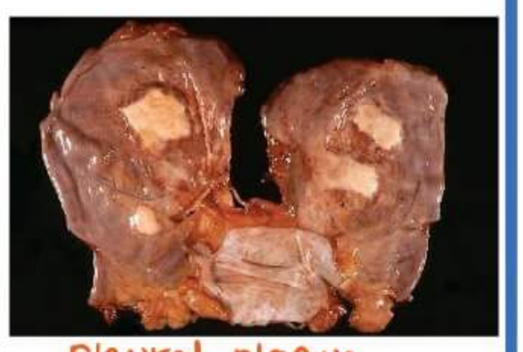
1 SILICOSIS / GRINDER'S DISEASE / SAND BLASTING DISEASE

→ mc
→ dlt QUARTZ [SiO_2]
→ upper lobes
→ ↑↑ TB / ↑ cancer
→ CXR → EGG SHELL CALCIFICATION [calcificat^{n} on Hilar LN]

2. ASBESTOSIS

→ Insulation / Plumbing
→ TYPES OF PARTICLES
  1. Serpentine [curvy particles]
  2. Amphibole [more pathogenic] [straight particles]

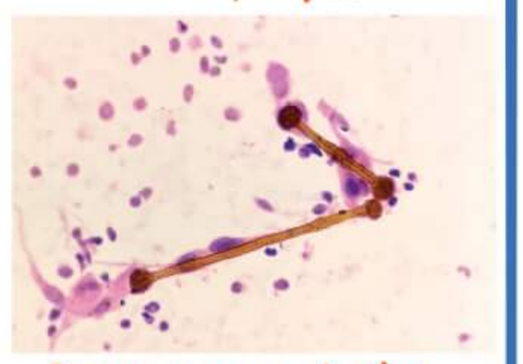
→ LESIONS
  → PLEURAL PLAQUE
    ↳ mc lesion
    ↳ seen at Basal area



Pleural plaque

  → INTESTITIAL FIBROSIS

Protenaceous material + Fe
FERRUGINOUS BODY /
ASBESTOS BODY



Ferruginous body

→ involves BASE
→ ↑↑ cancers → acts as Initiator & promotor
  1. Bronchogenic carcinoma [15-20 yrs exposure] → mc
  2. mesothelioma [25-35 yrs exposure] → most specific

3. BERYLLIOSIS

→ Nuclear
  Aerospace

→ Intertitial fibrosis ⊕
  non caseating granulomas in different organs

→ ↑ cancer

4. COAL WORKER'S PNEUMOCONIOSIS

→ Coal Dust
→ PRESENTATIONS

A. PULMONARY ANTHRACOSIS
  → NO clinical symptoms
  → DUST CELLS ⊕ [macrophages ī coal dust]

Black Lung

B SIMPLE COAL WORKER PNEUMOCONIOSIS
→ nodules +
→ Elastase → centri Acinar Emphysema
C. PROGRESSIVE MASSIVE FIBROSIS [Risk factors – Smoking & coal dust]
→ complicated coal workers pneumoconiosis
→ BLACK LUNG

5. BAGASSOSIS

Sugar cane Dust
↓
Fungal Spores

2% Propionic Acid Spray → Non - Pathogenic

6. BYSSINOSIS | TEXTILE WORKER DISEASE | MONDAY CHEST DISEASE

cotton dust

PNEUMOCONIOSIS
+
Rheumatoid Arthritis

CAPLAN SYNDROME
↓
Coal worker pneumoconiosis
Arthritis

INFECTIOUS LUNG DISEASE

PNEUMONIA [Infection of Pulmonary Parenchyma]

TYPICAL | AIR-SPACE PNEUMONIA

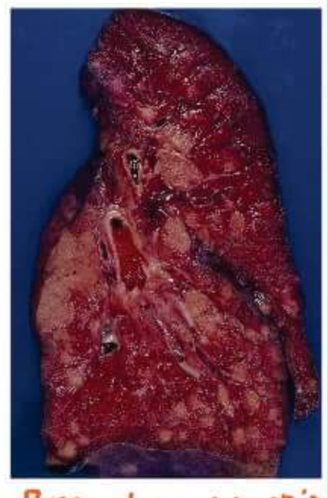
→ Alveolar Exudate ⊕ Neutrophilic infiltration
→ C|F
→ high grade fever
→ productive cough
→ pleuritis
→ Signs of consolidation

→ SPUTUM → Gram stain ⊕ & culture ⊕
→ SUB TYPES

LOBAR PNEUMONIA

BRONCHO PNEUMONIA
→ Basal Lobe +
→ B|L
→ 2 extremes of ages


Lobar pneumonia


Bronchopneumonia

TYPICAL PNEUMONIA - CAUSATIVE ORGANISMS

Streptococcus pneumoniae	→	CAP [Community Acquired Pneumonia]
	→	Rusty Sputum
Staphylococcus aureus	→	2° pneumonia
	→	abscess +
Klebsiella pneumoniae	→	Alcoholic
	→	↑ Aspiration
	→	Red currant Jelly Sputum +
H. Influenzae	→	a/w Chronic bronchitis [Type 'b']
Pseudomonas	→	Burns
	→	Cystic fibrosis
	→	Immunosuppression
LEGIONELLA	→	humidified Air exposure
	→	ICU
	→	causes pneumonia/Diarrhea/CNS ⊕
	→	PONTIAC FEVER [URTI]
	→	Silver Stain for identification
	→	JG CELL damage
	↳	↓ Aldosterone
	↳	↑ K^+ / H^+
	↳	↓ Na^+

STAGES OF PNEUMONIA

1. CONGESTION [1-2 days]	
→	Alveolar fluid ⊕ ĩ bacteria & neutrophils
2. RED HEPATIZATION [3-4 days]	
→	RBCs ⊕ [in fluid]
→	Fibrin ⊕
3. GRAY HEPATIZATION [5-8 days]	
→	Lysis of RBCs
→	Fibrin ⊕⊕⊕
4. RESOLUTION [> 8 days]	
→	Neutrophils / macrophages ⊕

ATYPICAL PNEUMONIA

→ Non - Bacterial etiology
→ Interstitial tissue Inflammation
→ mono nuclear cell infiltration

C/F

→ Low grade Fever
→ Dry cough
→ malaise / myalgia
→ no signs of consolidation

INVESTIGATION

SPUTUM → staining ⊖
CXR

ATYPICAL PNEUMONIA – CAUSATIVE ORGANISMS

1. MYCOPLASMA	→	mc
	→	Ig M → AIHA (cold)
	→	♂ residing in closed spaces
2. CHLAMYDIA	→	2nd MC
	→	↑ CAD
3. PNEUMOCYSTIS JIROVECI	→	Fungus
	→	a/w HIV
	→	Silver stain ⊕
4. COXIELLA BURNETII	→	causes Rickettsial infection ī out a vector
	→	causes 'Q' fever
5. VIRUSES		
INFLUENZA TYPE A	→	complicated by Staph. aureus
	→	Aspirin CI (causes Reye syndrome)
RSV	→	children
	→	causes Bronchiolitis
CMV	→	OWL – EYE Inclusions
	→	seen Immunosuppression [AIDS / Post transplantation]
MEASLES	→	KOPLIK SPOTS / Rash
	→	WARTHIN – FINKELDEY CELLS ⊕

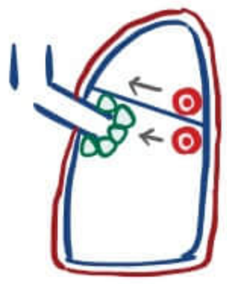
PULMONARY TB & LUNG ABSCESS

1° PULMONARY TB

→ Droplet infection

→ GHON'S COMPLEX

SUBPLEURAL LESION
+
LYMPHATICS
+
HILAR LN



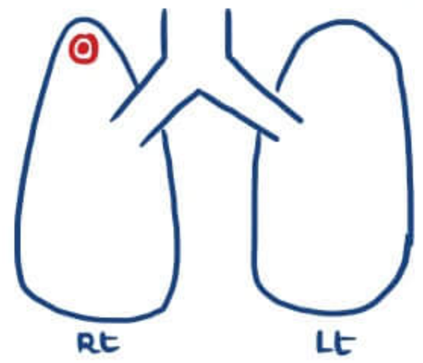
PATHOGENESIS

1. LAM [Lipo Arabino Mannan] $\xrightarrow{\ominus}$ Alveolar macrophages

2. > 3 WEEKS → Cytokines [From APC] → IFN – γ → Macrophage Activation → Granuloma → Obligate aerobe Inactivation

→ RAENKE COMPLEX → calcified Ghon's complex

2° PULMONARY TB



- → Occurs due to
  - → Reactivation [mc] } a/w ↑ age & AIDS
  - → Fresh infection }
- → Apical lesion
  - → Supra clavicular → PUHL'S FOCUS
  - → Infra clavicular → ASSMANN'S FOCUS
- → Immune activation ⊕⊕⊕ → Airway → Cavitation
- → Hilar LN not affected

ORGANS AFFECTED

LN	→	mc extrapulmonary organ affected ; cold abscess ⊕
Kidney	→	Sterile pyuria
Eyes	→	Phlyctenular conjunctivitis
Ears	→	multiple perforations in TM
CVS	→	Constrictive pericarditis
Bones	→	POTT'S spine
ADRENAL	→	adrenal insufficiency [mc cause of Chronic adrenal insufficiency]
LIVER	→	Simmond'S focus [simon'S focus found in Lungs]
GIT	→	Transverse ulcers in Ileum
Brain	→	RICH FOCUS
	→	Basal surface involved
	→	TB meningitis → COBWEB COAGULUM ⊕

CIF

- → Cough [> 2 weeks]
- → Fever [low grade evening rise]
- → Hemoptysis [mcly from bronchial artery
  rarely from pulmonary artery → RASMUSSEN'S ANEURYSM]
- → Weight loss

DIAGNOSIS

1. ↑↑ ESR
2. ↑ TLC
3. SPUTUM
   - → Early morning sample
   - → PETROFF'S METHOD → Sputum concentration method
   - → STAINING → ZN Stain → Acid fast bacilli
   - → CULTURE → LJ media [slow growth]
     BACTEC MEDIA [Faster growth]
   - → PCR → Nucleic Acid Amplification

4. PLEURAL TAP → Straw colored fluid → ↑↑ Adenosine Deaminase [ADA]

Rx → Anti Tubercular Therapy

LUNG ABSCESS

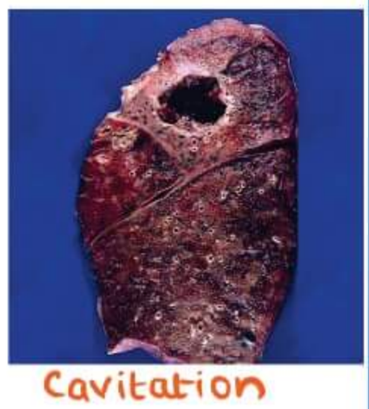
CAUSES

1. ASPIRATION	→	↓ consciousness
	→	Alcoholics
	→	hasty intake of food particles [mc]
2. SEPTIC EMBOLISM	→	Infective endocarditis
3. POST PNEUMONIA	→	Staph. aureus
	→	Klebsiella
4. OBSTRUCTIVE NEOPLASM		

CLINICAL FEATURES

→ high fever
→ productive cough
→ foul smelling Sputum

CXR → Cavitation + Air fluid level


Cavitation

PULMONARY HYPERTENSION

→ Normal Pulmonary artery pressure → 10 mm Hg
→ Pulmonary HTN → > 25 mm Hg

1° PULMONARY HTN

→ young ♀
→ BMPR 2 Gene Inactivation mutation

Normal gene	→	Smooth muscle cell apoptosis
mutation	→	↑↑ Proliferation of Smooth muscle cell → Pulmonary HTN

2° PULMONARY HTN

ETIOLOGY → Hypoxemia → high altitude / pulmonary disease
→ Left ventricular failure / mitral Stenosis
→ Recurrent Pulmonary Embolism
→ Obstructive Sleep apnea

MIE → MEDIAL HYPERTROPHY OF Elastic & muscular arteries
→ PULMONARY ARTERIAL ATHEROSCLEROSIS
→ RIGHT VENTRICULAR HYPERTROPHY

} PLEXIFORM LESION [tuft of capillaries]

CLINICAL FEATURES → Dyspnea / Fatigue / chest pain
CXR → Tapering OF pulmonary arteries
Rx

1. O_2
2. Diuretics
3. Vasodilators → Endothelin Antagonists
   → Prostanoids
4. Lung transplantation

RESPIRATORY DISTRESS SYNDROME

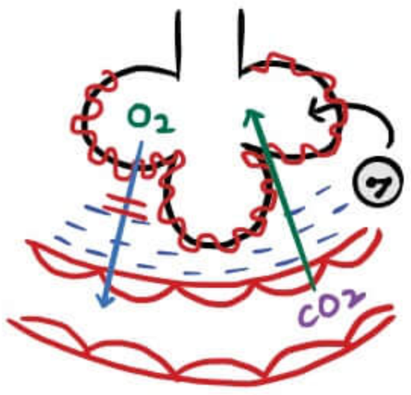
ACUTE LUNG INJURY [Seen in ADULTS]

→ Sudden onset of severe hypoxemia
→ Bil pulmonary infiltrate
→ NO H/O cardiac disease

ARDS / STIFF LUNG / SHOCK LUNG / HYALINE MEMBRANE DISEASE [Severe ALI]

ETIOLOGY

1. DIRECT LUNG INJURY
2. INDIRECT LUNG INJURY
   → Gram ⊖ Septicemia [most important]
   → Aspiration
   → Shock
   → DIC | Heroin | pancreatitis



PATHOGENESIS

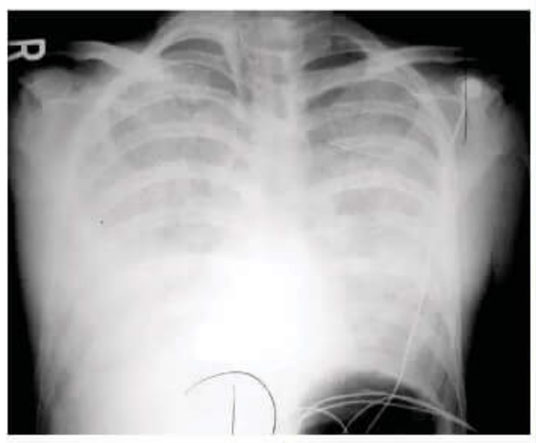
ENDOTHELIAL CELL INJURY
- I/□ Pneumocytes Damage → ↓ST → Alveolar collapse
- Exudative fluid ⊕ Accumulates in interstitial area → Hyaline membrane → STIFF LUNG

→ HYPOXEMIA [↓ paO_2]
→ ↓ $paCO_2$

CLINICAL FEATURES

→ Dyspnea
→ ↑↑ RR
→ Intestitial fibrosis

CXR → BIL Infiltrates ⊕ [WHITE OUT LUNG]
PCWP → < 18 mm Hg [non - cardiac cause]



White out lung

→ DIFFUSE ALVEOLAR DAMAGE
→ REFRACTORY TO O_2 THERAPY dlt → ↓ ST → Alveolar collapse
→ Hyaline membrane ⊕

TREATMENT

1. TOC → R_x the Primary cause
2. PEEP → ↑ O_2 diffusion & Alveolar opening
   → Positive End Expiratory pressure
3. STEROIDS

NEONATAL RESPIRATORY DISTRESS SYNDROME [Seen in NEONATES]

SURFACTANT

→ begins at 28 Weeks of gestation [in Lamellar bodies]
→ max. Secretion at 32 - 34 wks of gestation
→ Type II Pneumocytes Secrete it
→ chemically it is → LECITHIN = DPPC [DiPalmitoyl Phosphatidyl choline]
→ ↓ Surface tension → ↓ Alveolar collapse
→ ↑ → steroids & Thyroxine
→ ↓ → Insulin

RISK FACTORS

→ C - Section
→ Prematurity
→ maternal hyperglycemia [Fetal hyperglycemia]
→ ↓ Surfactant → ↑ Surface Tension

CIF

→ Respiratory distress [in few hours of birth
→ ↑↑ RR
→ Hypoxemia

CxR

→ WHITE OUT LUNG
→ GROUND GLASS LUNG

Rx

→ 1. STEROIDS to MOTHER
→ 2. ARTIFICIAL SURFACTANT to BABY
→ 3. CPAP [via Endotracheal tube]

COMPLICATIONS

1. ↓ O_2 → ↑↑ PDA & ↑↑ NEC
2. Supplemental O_2 → ↑ free radicals [Retinal damage & Bronchopulm dysplasia]
3. Hypoglycemia

SARCOIDOSIS

Unknown Ag → CD_4 T cell ⊕ → Non - caseating Granulomas

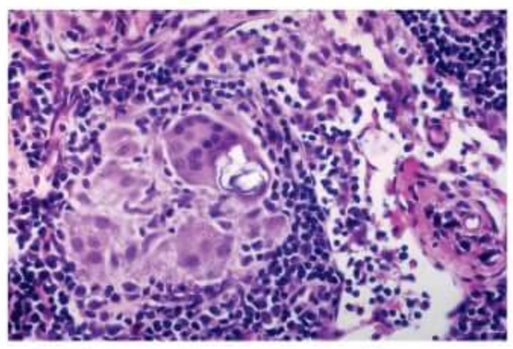
MULTISYSTEM DISORDER

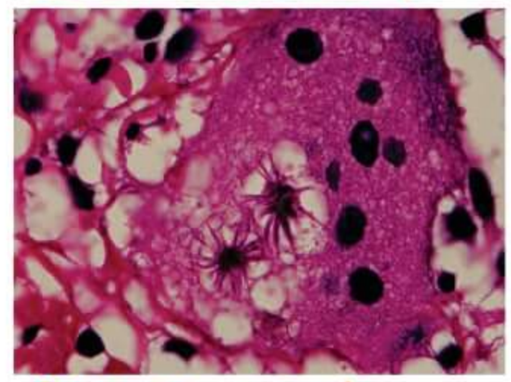
LUNGS	→	mcly involved organ → Interstitial fibrosis → UIL pleural effusion → CIF → Dyspnea [mc]
LN	→	BIL hilar lymphadenopathy → POTATO NODES ⊕
SKIN	→	LUPUS PERNIO [violet colored rash on nose & cheeks] Erythema nodosum [painful, Lower Limbs ⊕]
EYES	→	Uveitis → CANDLE WAX DROPPINGS
LIVER BM SPLEEN	}	mc cause of non - infectious granulomatous lesion in Liver Granulomatous Lesions ⊕
ENDOCRINE	→	Pituitary
MUSCLES	→	weakness | fatigue

DIAGNOSIS

1. S. ACE ↑↑↑
2. S. Ca^{2+} ↑↑↑ → ↑ 1-α OHase → Vit D
3. CUTANEOUS ANERGY
4. Non-caseating granuloma ⊕ [most characteristic]

S → Schaumann Body [Ca^{2+}]
A → Asteroid Body [stellate inclusions]
R → Residual Body


Schaumann Body


Asteroid body

5. BAL FLUID → ↑↑ CD_4 : CD_8 T cells [5:1 to 15:1]

R_4 → 1. Spontaneous Recovery
→ 2. Steroids

HYPERSENSITIVITY PNEUMONITIS / EXTRINSIC ALLERGIC ALVEOLITIS

→ known Ag → ALVEOLITIS & INTERSTITIAL PNEUMONITIS

PATHOGENESIS

1. ACUTE	→ 1st time → Ab formation
	→ Repeat Exposure (Ag, Ab) → Immune complexes ⊕ [Type III HR]
2. CHRONIC	→ Non-caseating granuloma → Type IV HR [more imp]
	→ TYPE IV >>> TYPE III

SUB TYPES

1. FARMER'S LUNG → Actinomyces [Thermophilic]
2. PIGEON BREEDER'S LUNG → Proteins from bird feathers | excreta
3. HUMIDIFIER'S LUNG → Bacteria

C|F

ACUTE PHASE → Ag —(4-6 hrs)→ cough | Dyspnea | Fever [few hrs - few days]

CHRONIC PHASE → Ag → Interstitial fibrosis
↳ progressive dyspnea
↳ Respiratory failure
↳ cyanosis

R_4 → Avoid the allergen & Steroids

DESQUAMATIVE INTERSTITIAL PNEUMONIA

→ Smokers
→ macrophages in air spaces ⊕
→ misnomer

→ C|F → Cough & Dyspnea
→ Interstitial Fibrosis

→ R_4 → Steroids

LUNG TUMORS

BENIGN TUMORS

BRONCHIAL ADENOMA

→ type of carcinoid tumor
→ well differentiated Neuro endocrine cells ⊕ → chromogranin ⊕
→ Recurrent hemoptysis +
→ biopsy contra indicated

HAMARTOMA

→ common site → Lungs
→ CxR → Popcorn calcification
→ Pre neoplastic lesion

MALIGNANT TUMORS

I 1° → BRONCHOGENIC CARCINOMA
II 2° → METASTASIS
↳ Breast [mc]
↳ colon
↳ choriocarcinoma
} CANNON BALL METASTASIS

BRONCHOGENIC CARCINOMA

RISK FACTORS

1. GENETIC
→ p53 mutation [mc]
→ L-MYC mutation
→ K-RAS mutation
→ EGFR mutation
→ ALK mutation
→ RET | MET mutation

2. NON GENETIC
→ Smoking [most dangerous] → PAH [more prone for CYP1A1 polymorphism]
→ Air pollution
→ Asbestos
→ Radiation [Radon [decay of uranium], xenon]

CIF

→ cough [mc]
→ Weight loss
→ Dyspnea
→ Hemoptysis
→ RLN → Hoarseness

CLINICAL FOLLOW UP

→ Radiological Exam
→ Sputum cytology
→ Bronchoscopy ĩ Bx [Best]

Bx

→ 1. M|E or HPE
→ 2. Immunohistochemistry

1. Keratin ⊕ → Intercellular Bridge → Pearls } Squamous cell carcinoma } p 40 ⊕, p 63 ⊕

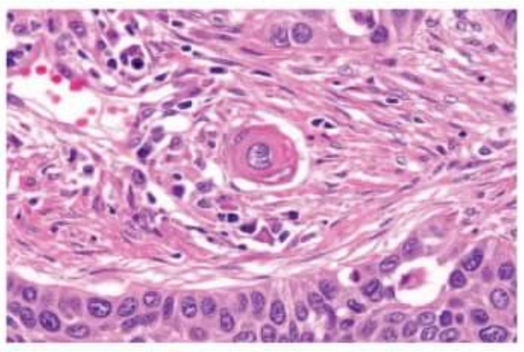
2. Mucin ⊕, Glands ⊕ } Adeno carcinoma } TTF [Thyroid Transcription factor] ⊕, NAP-A ⊕ & CK 7 ⊕

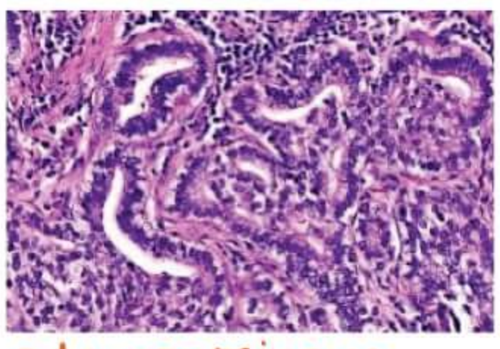
3. SMALL CELLS ī Neuro Secretory granules ⊕, Salt & pepper chromatin ⊕, Basophilic staining [AZZOPARDI EFFECT] } Small cell cancer

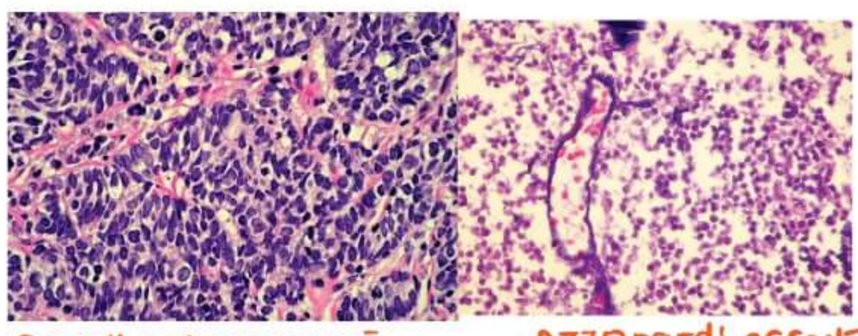
↓

Chromogranin ⊕
TTF ⊕
NAP-A ⊖
Low molecular wt CK 7|8|18 ⊕

4. Large cells ⊕ → Diagnosis of Exclusion → Large cell carcinoma
   → CD 56 ⊕
   → Synaptophysin ⊕
   → Chromogranin ⊕


Squamous cell carcinoma [Keratin ⊕]


Adenocarcinoma


Small cell cancer ī neuro secretory granules

Azzopardi effect

1. SQUAMOUS CELL CARCINOMA

→ mc bronchogenic cancer in India
mc bronchogenic cancer in males
mc bronchogenic cancer in smokers

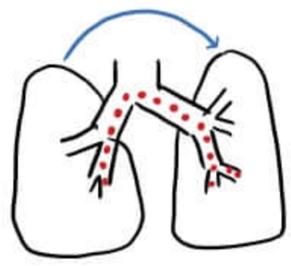
→ CENTRAL LOCATION
→ Cavitation ⊕
→ Late metastasis
→ Good prognosis
→ CELLS → PTHrp → Hypercalcemia

2. SMALL CELL CARCINOMA

→ ♂, Smokers [strongest association]
→ Central location
→ Best response to Chemotherapy & Radiotherapy
→ WORST PROGNOSIS
→ maximum metastasis ⊕ [early metastasis]
→ Aggressive
→ Surgery can't be performed
→ Neuro secretory granules ⊕
  ↳ ACTH → Cushing Syndrome
  ↳ ADH → SIADH [↓ Na^+]
  ↳ Calcitonin → hypocalcemia

3. ADENOCARCINOMA

- → overall mc Lung cancer
- → ♀ >> ♂
- → non - smokers
- → Peripheral cancer
- → Mucin ⊕ → Thrombophlebitis ⊕
- → clubbing ⊕
- → SCAR CANCER



Aerogenous Spread ⊕

ADENOCARCINOMA IN SITU

- → Excellent prognosis
- → Suffocation ⊕ → Mortality

4. LARGE CELL CARCINOMA

- → non - smokers
- → peripheral location
- → Secretes Estrogen → Gynecomastia

METASTASIS

- → Adrenal gland [mc]
- → CNS [by small cell cancer]
- → Bones
- → Liver

COMPLICATIONS

1. PANCOAST TUMOR

- → peripheral cancer
- → Sympathetic plexus compression ⊕
- → Adeno cancer
- → Horner Syndrome ⊕ ['MAPEL']
  - ↳ miosis
  - ↳ Anhidrosis
  - ↳ Ptosis
  - ↳ Enophthalmos
  - ↳ Loss of Ciliospinal reflex

2. SUPERIOR VENA CAVA SYNDROME → Bluish dusky congest^{n} of head
3. RLN Involvement → hoarsness of voice
4. C_8 / T_1 / T_2 Involvement → Shoulder pain
   Pain on inner side of the arm

PARANEOPLASTIC SYNDROME

↑↑ Ca^{2+}	→	Squamous cell carcinoma
cushing syndrome	→	Small cell carcinoma
SIADH	→	small cell carcinoma
↓↓ Ca^{2+}	→	Small cell carcinoma
Lambert - Eaton Syndrome	→	Small cell carcinoma
Acanthosis nigricans	→	Small cell carcinoma
SVC syndrome	→	small cell carcinoma

SMALL CELL CARCINOMA	→	poor prognosis
NON SMALL CELL CARCINOMA	→	good prognosis

MESOTHELIOMA & PLEURAL TUMORS

PLEURAL TUMORS

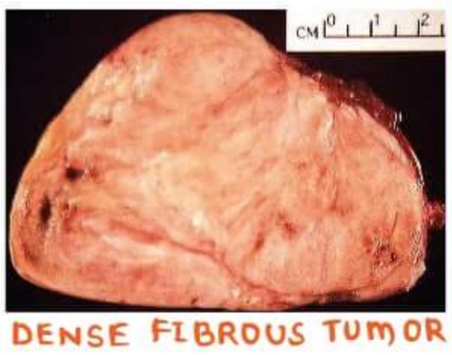
1° <<< 2° [metastasis]

- SOLITARY FIBROUS TUMOR
- MALIGNANT MESOTHELIOMA

- mc cause → Lung cancer
- 2nd mcc → Breast cancer
- ipsilateral involvement of pleura +nt

SOLITARY FIBROUS TUMOR

→ Earlier called as BENIGN MESOTHELIOMA
→ Asbestos exposure is not a risk factor
→ Chr. 12 inversion → NAB 2 STAT 6 FUSION GENE
→ GROSS → Dense fibrous tumor
→ microscopically, SPINDLE CELLS [resemble fibroblasts] +nt


DENSE FIBROUS TUMOR

	SFT	MM
CD 34	⊕	⊖
Keratin	⊖	⊕

MALIGNANT MESOTHELIOMA

RISK FACTORS

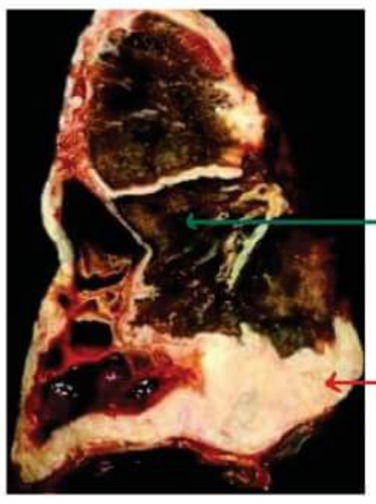
→ Asbestos exposure
  ↳ a/w AMPHIBOLE
  ↳ incubation period → 25 - 45 yr

→ Radiation exposure
→ NO A/W SMOKING

CLINICAL FEATURES

→ 50 - 60 yrs
→ Chest pain, Difficulty in breathing, pleural effusion
→ Rt Lung >>> Lt Lung
→ along ↑ pleura, Lungs & Hilar Lymphnodes are involved

→ GROSS APPEARANCE



LUNG ENCASED BY CANCER

→ M|E

1. EPITHELIOID TYPE [mc type, 60%]
2. SARCOMATOID TYPE [20%]
3. MIXED / BIPHASIC TYPE [15-20%]

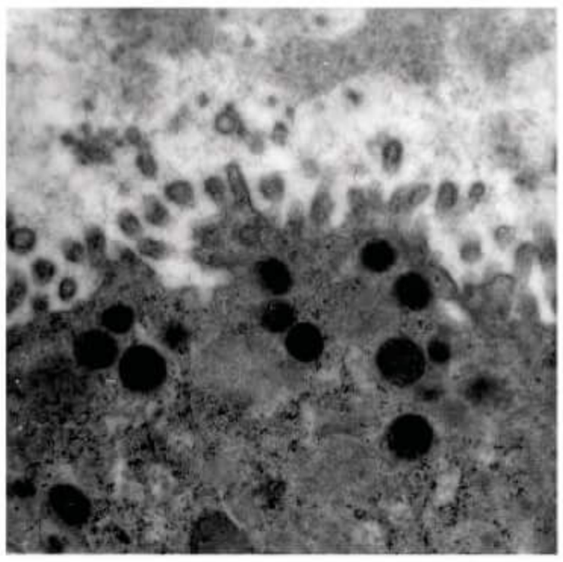
→ EPITHELIOD TYPE

→ forms papillary & tubular structures

→ resembles ADENO CARCINOMA OF LUNG

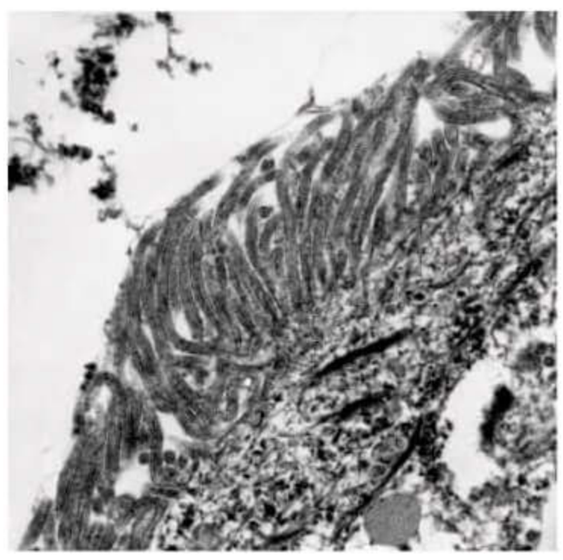
→ distinguished from Adenocarcinoma of Lung by

1. ELECTRON MICROSCOPY



ADENOCARCINOMA

- short,
- Non - branching microvilli



MESOTHELIOMA

- Long, thin,
- branching microvilli

2. IMMUNO HISTOCHEMISTRY MARKERS

	ADENOCARCINOMA	MESOTHELIOMA
CALRETININ	−	+ +
WT_1	−	+ +
CK 5/6	−	+ +
MOC 31	+ +	−

- marker OF choice → Calretinin
- CALRETININ POSITIVITY ASSOCIATION ī VARIOUS MESOTHELIOMA VARIANTS
  - → EPITHELIOID TYPE → Extremely associated
  - → SARCOMATOID TYPE → Less intensely positive
  - → MIXED / BIPHASIC TYPE → Less intensely positive

BOOSTER INFO - MALIGNANT MESOTHELIOMA

→ Deletion OF CDKN 2A / INK 4a [tumor Suppressor gene] on Chr 9P

→ Confirmed by FISH TECHNIQUE

PULMONARY HAMARTOMA

→ TRUE NEOPLASM

→ COMPONENTS

NODULES OF MESENCHYMAL TISSUE | ENTRAPPED RESPIRATORY EPITHELIUM

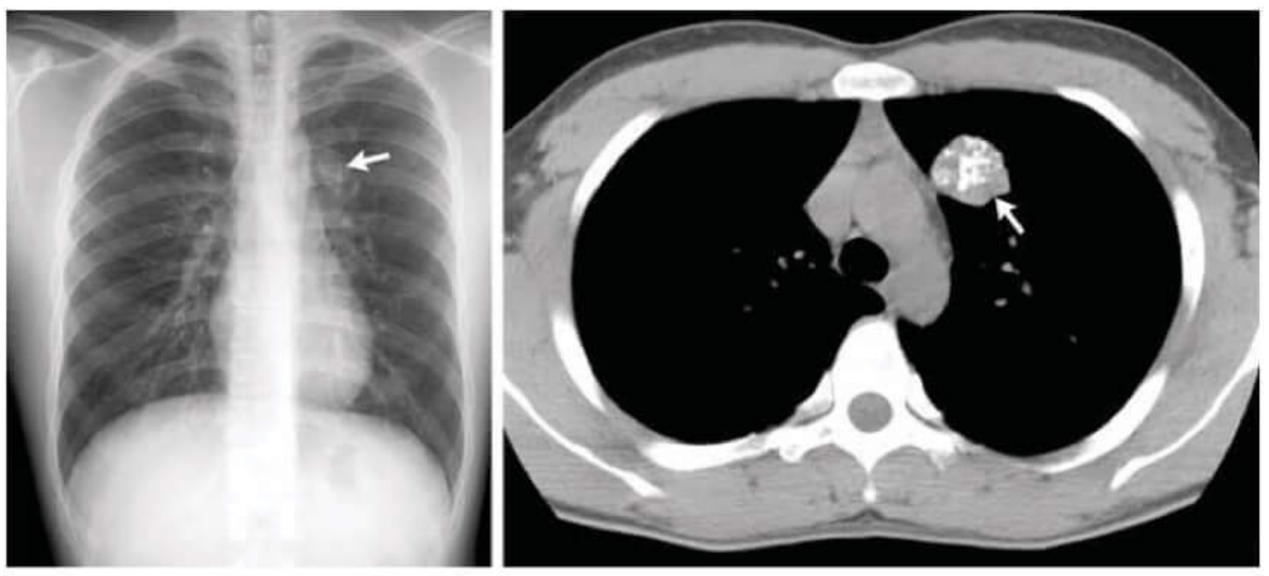
↓

connective tissue | fat |
cartilage [predominant] |
Smooth muscles

→ a/w t [3; 12]

→ NO Specific Signs & Symptoms → Example of INCIDENTAL FINDING

→ RADIOLOGICAL FINDING



POP CORN CALCIFICATION

→ TREATMENT → Surgical Excision

INFLAMMATORY MYOFIBROBLASTIC TUMOR

→ disease of children

→ NO Sex prediliction [m=F]

→ dlt ALK Gene activation on Chr 2p 23

→ CIF → Fever, cough, chest pain, hemoptysis

→ GROSS → Peripheral firm mass [in 25% patients, Ca^{2+} deposit^{n} +nt]

→ M/E

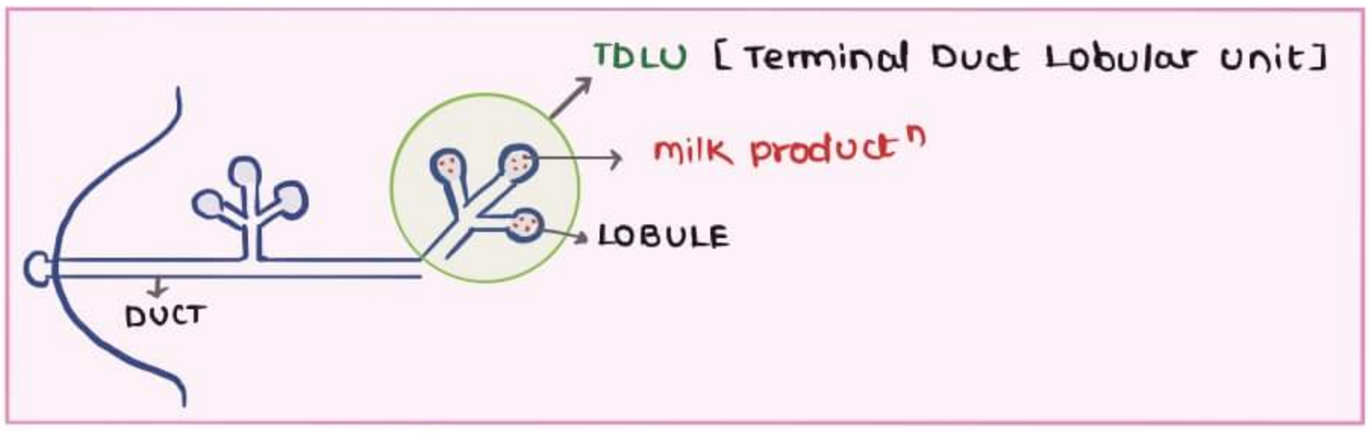
- SPINDLE SHAPED CELLS [made up of fibroblasts & myofibroblasts]
- Infiltration of lymphocytes & plasma cells +nt
- Peripheral fibrosis +nt

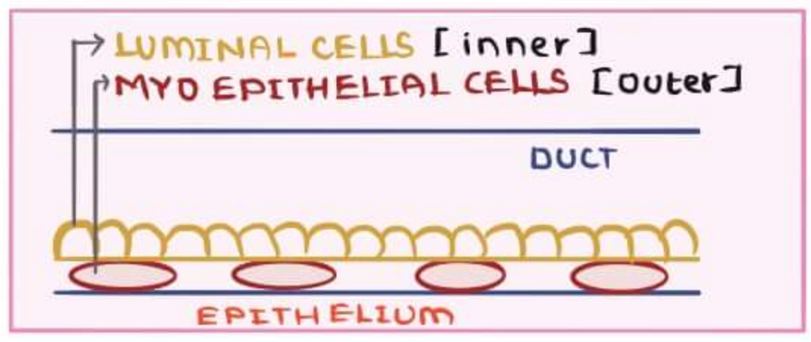
BREAST

HORMONE SENSITIVE TISSUE

Estrogen → Alveolar & ductal growth
Progesteron → Alveolar differentiation

LACTATION → Oxytocin → milk ejection
→ Prolactin → Lactogen



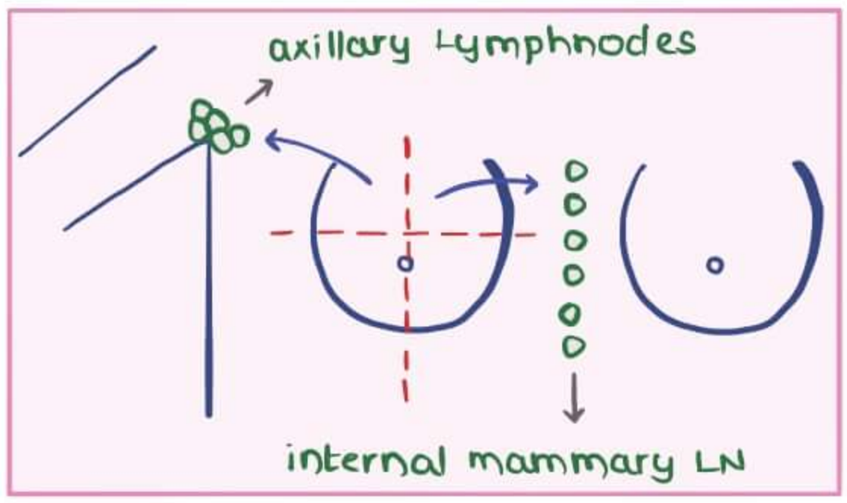


TDLU → Functional unit of Breast tissue

COMPONENTS OF BREAST TISSUE

1. STROMA
2. EPITHELIUM
   → Luminal cells requires vitamin A for differentiation
   → Vitamin A Deficiency → Squamous metaplasia
   → EPITHELIAL HYPERPLASIA → > 2 layers of cells

QUADRANTS OF BREAST



→ Outer quadrant of breast tissue drains into → Axillary LN
→ Inner quadrant of breast tissue drains into → Internal mammary LN

→ Maximum dense tissue is present in → Upper outer quadrant
→ most common site for malignancy → Upper outer quadrant
→ Least common site for malignancy → Lower inner quadrant

NIPPLE DISCHARGE - SUB TYPES

1. BLOODY
   → Intra Ductal Papilloma [mc cause]
   → Ductal carcinoma

2. GREENISH → mammary duct ectasia
3. PURULENT → Acute mastitis

4. GALACTORRHEA

→ mechanical stimulatⁿ [mc physiological cause]

→ Drugs
  ↳ OCP
  ↳ H_2 anti histaminic drugs
  ↳ Antipsychotic drugs

→ Endocrinological disorders
  ↳ prolactinoma [mc pathological cause]
  ↳ Hypothyroidism

INFLAMMATORY CONDITIONS

1. ACUTE MASTITIS

→ Breast feeding young female

→ dlt staphylococcus areus → Pus ⊕

→ clf → Pain, fever, nipple discharge [purulent]
→ Swelling

→ Diagnosis → Ultrasound

→ treatment
  1. NSAIDs
  2. ANTI BIOTICS for staph. areus [Penicillin group]
     → Flucloxacillin / dicloxacillin / amoxiclav
  3. ASPIRATION [guided by ultrasound]
  4. INCISION & DRAINAGE

→ BREAST FEEDING IS NOT CONTRAINDICATED

2. ZUSKA'S DISEASE [PERIDUCTAL MASTITIS]

→ Smoking female

Smokers → Vit A ↓↓ → Squamous metaplasia → Obstruction → Dilatation of duct

→ clf
  → Sub areolar mass
  → Pain & Redness
  → nipple retraction
  → Fistula formation

→ may mimic MALIGNANCY

3. MAMMARY DUCT ECTASIA

→ Multiparous Elderly female

DILATATION → Accumulatⁿ of Secretions → Nipple discharge
                                      → Rupture → Inflammation

→ not a/w smoking
→ no metaplasia

→ C/F
  → Green brown nipple discharge
  → Sub areolar mass

→ M/E → CHRONIC GRANULOMATOUS INFLAMMATION
[Lymphocytes, macrophages & plasma cells ⊕]

→ aka PLASMA CELL MASTITIS

4 FAT NECROSIS

→ a/w Trauma & Surgery

LIPASE → FFA, Ca^{2+} → Dystrophic calcification

→ mammography mimics malignancy

→ M/E → FAT NECROSIS → FB Gaint cells, Lipid Laden macrophages
→ Dystrophic calcification

5. LYMPHOCYTIC MASTOPATHY

→ Auto immune etiology
♀ ↑ Type 1 DM / Auto immune thyroid disease

→ C/F → ≥ 1 Hard mass in breast tissue
→ BIOPSY
1. Duct & lobular Atrophy
2. Dense collagen
3. Lymphocytic infiltration

BENIGN EPITHELIAL LESIONS OF BREAST TISSUE

CLASSIFIED AS

1. NON PROLIFERATIVE BREAST CHANGES / FIBROCYSTIC CHANGES [RR 1]
2. PROLIFERATIVE BREAST CHANGES
   a. With out Atypia [Relative Risk of cancer - 1.5-2]
   b. With Atypical hyperplasia [Relative Risk of cancer - 4-5]
3. CARCINOMA IN SITU
   → Bm not involved
   → RR - 8-10

RISK OF BREAST CANCER	RELATIVE RISK	ABSOLUTE RISK
Fibrocystic changes of Breast	1	3%
Proliferative Breast changes ī out Atypia	1.5 - 2	5 - 7 %
Proliferative Breast changes ī Atypia	4 - 5	15 - 17 %
carcinoma In Situ	8 - 10	25 - 30 %

1. NON PROLIFERATIVE / FIBROCYSTIC BREAST CHANGES

a. CYSTS → BLUE - DOME CYST [ī fluid]

b. FIBROSIS → Leakage of fluid from cyst → Inflammation → Fibrosis

c. ADENOSIS → ↑ NO. of Acini per lobule

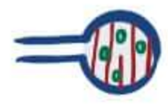
APOCRINE METAPLASIA ⟶ no progression to cancer

CLINICAL FEATURES → painful 'LUMPY - BUMPY BREAST' in a < 50 yr ♀

2. PROLIFERATIVE BREAST DISEASE ī OUT ATYPIA

a. EPITHELIAL HYPERPLASIA → > 2 layers of cells
→ Incidental finding

b. SCLEROSING ADENOSIS



→ ↑ collagen & Fibrosis
→ micro calcification ≅ malignancy

c. COMPLEX SCLEROSING LESION

→ at microscopy / Radiological level → RADIAL SCAR
→ mimics invasive cancer

Epithelial component
Stroma

d. PAPILLOMA [INTRADUCTAL]

→ Incomplete compression → serous discharge
→ complete compression → Bloody discharge

Fibrovascular scar
papillary growth

3. PROLIFERATIVE BREAST DISEASE ī ATYPIA

a. ATYPICAL LOBULAR HYPERPLASIA [ALH] [< 50% Acini involved per lobule]

b. ATYPICAL DUCTAL HYPERPLASIA [ADH]

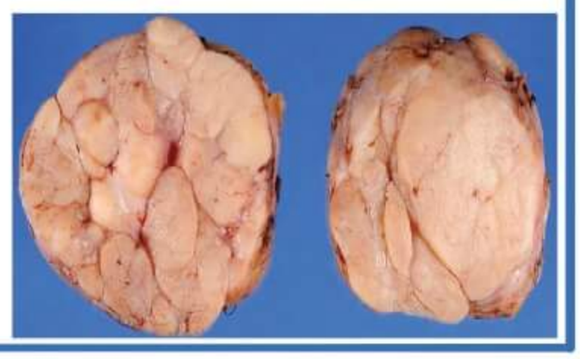
→ MONOMORPHIC CELLS ⟶ Partial Involvement of either lobes or ducts

STROMAL TUMORS

A. INTRA LOBULAR TUMORS

1. FIBROADENOMA / BREAST MOUSE

→ mc benign tumor
→ young ♀
→ Single usually
→ can be multiple & BIL
→ Renal transplant → R/ by Cyclosporine → BIL & multiple fibroadenomas
→ cyclosporine discontinuation causes → Regression of the tumor
→ well circumscribed
→ freely mobile mass
→ GROSS FEATURES → Well defined margins
→ grey white nodules
→ Slit like space ⊕



→ MICROSCOPIC FEATURES → Pericanalicular Stroma
→ Intracanalicular stroma

→ R_x by SIMPLE EXCISION

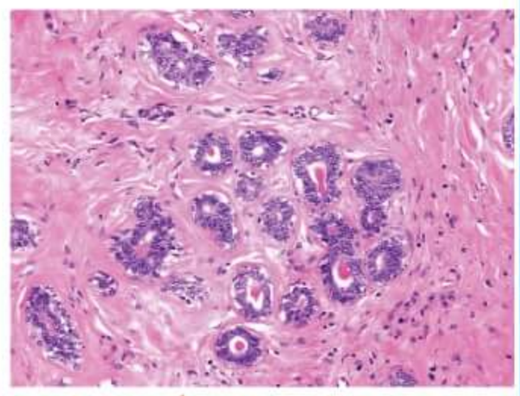
2. PHYLLODES TUMOR

→ ↑↑ Stroma ī leaf like projections → BULKY BREAST
→ Gain of Function mutation [1q]
→ HOXB 13 Overexpression → Higher grade tumor
→ CIF → > 60 yrs Female, palpable mass

→ most are Low grade tumors → no metastasis
→ High grade tumors → metastasis [hematogenous spread] ⊕
→ Axillary LN Dissection is contra indicated
→ Only stromal component can spread

→ DID FROM FIBROADENOMA

Histologically → ↑ Stroma, ↑ mitosis, ↑ cellularity


Pericanalicular Fibro-adenoma

B. INTER LOBULAR STROMAL TUMORS

1. MYOFIBROBLASTOMA → M = F
2. ANGIOSARCOMA

→ mc stromal malignant tumor
→ Sporadic → < 35 yrs ♀, high grade, poor prognosis
→ 2° tumor → after Radiation | Edema

INTRODUCTION & IN SITU CANCER

BREAST CANCER

→ mc cancer in females in INDIA

RISK FACTORS

1. ↑ Estrogen exposure [most important]
   ↳ ♀
   ↳ early menarche & Late menopause
   ↳ exogenous estrogens → HRT
   ↳ post menopausal obese ♀
   ↳ Endometrial cancer

2. AGE → post menopausal
3. Radiation exposure
4. Family H/O → 1° Relatives
5. Pregnancy → 1st pregnancy < 20 yrs → protective
6. Lactation → protective [× ovulation & maturation of cells]
7. Dietary → ↑ Lipids, Alcohol → ↑ risk

PATHOGENESIS

FAMILIAL BREAST CANCER → DNA Repair Genes

→ BRCA 1 gene [17q] → ♀ >>> ♂ Breast cancer ; ↑ ovarian cancer
→ BRCA 2 gene [13q] → ♂ >>> ♀ Breast cancer ; ↑ prostate cancer
→ p 53 gene [17p]
→ CHEK 2 gene [22q]

→ BRCA 1 Gene a/w Basal like cancer & Medullary cancer
→ BRCA 2 Gene a/w fanconi Anemia
→ p53 gene a/w Sporadic cancer
→ p 53 gene is mc genetic mutation a/w breast cancer [overall]
→ p 53 gene a/w Li - Fraumeni Syndrome
→ CHEK 2 gene a/w ↑ renal cancer / colon cancer / Thyroid cancer
→ CHEK 2 gene a/w post radiation risk of cancer

SPORADIC BREAST CANCER [mc]

→ Hormone Exposure [Estrogen]
↓
Potential cells
↓
↑ risk of cancer

→ a/w p 53 gene mutation

TYPES OF CANCER

BM ⊖
↓
Carcinoma In Situ
↓
Ductal CIS | Lobular CIS

BM ⊕
↓
Infiltrating cancer
↓
molecular classification → depends on gene expression profiling
Histological Classification →
- NO Special Type [Ductal carcinoma]
- Special carcinoma

CARCINOMA IN SITU

→ SITE → TDLU

1. DUCTAL CIS

→ Bm ⊖
→ cells in ducts [myoepithelial cells] preserved
→ Secretion, Necrosis } Ca^{2+} → picked up on mammography

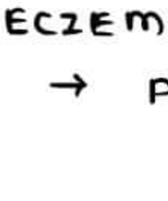
→ DCIS —1%/1yr→ Invasive cancer

TREATMENT → MASTECTOMY
→ Radiotherapy & Tamoxifen for recurrence prevention

DCIS - VARIANTS

1. COMEDO DCIS
   - → high grade tumor cells ⊕ ; central necrosis ⊕
   - → Linear / branching calcification on mammography

2. NON - COMEDO DCIS



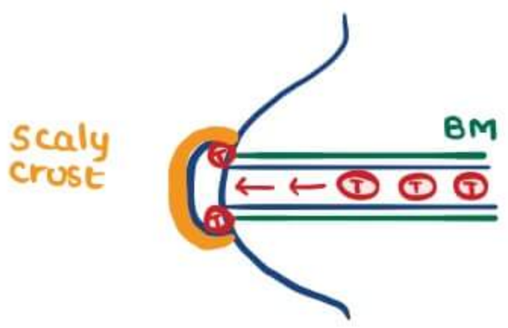
tumor cells
calcified area

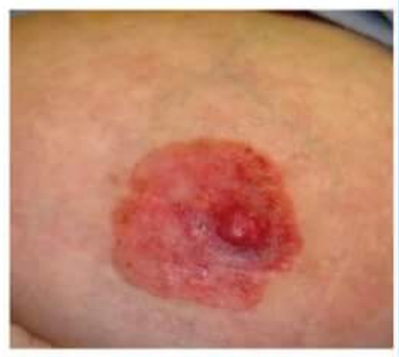
CRIBRIFORM PATTERN

micropapillary structures

MICROPAPILLARY PATTERN

3. PAGET'S DISEASE OF NIPPLE
   - → type of DCIS
   - → UIL Lesion
   - → Pruritis ⊕
   - → ulceration of nipple ⊕
   - → Palpable mass [50%] ⊕ [↑ Invasive cancer]
   - → aka ECZEMATOID LESION
   - → M/E → PAGET CELLS ⊕
     - ↳ abundant cytoplasm
     - ↳ prominent nucleus & nucleoli
     - ↳ mucin ⊕
     - ↳ Her2 ⊕
     - ↳ ER / PR ⊖





Paget Disease

2. LOBULAR CARCINOMA IN SITU
   - → malignant cells → DISCOHESIVE FASHION
   - → CDH_1 mutation → ↓ E-cadherin → DISCOHESIVE

E-cadherin
Normal

DISCOHESIVE FASHION

   - → no secretions, no necrosisis } no calcification → Incidental finding
   - → BIL
   - → LOBULAR CIS —1% / 1 year→ INVASIVE CANCER [Ipsilateral & Contralateral]
   - → M/E → Discohesive cells
     - → mucin ⊕ → Signet Ring cells
     - → ER / PR ⊕
     - → Her 2 ⊖
   - → R_1 → BIL mastectomy

INFILTRATING BREAST CANCER

→ MC SITE → Terminal Duct Loblar Unit [TDLU]
→ mc Breast cancer → Adenocarcinoma

1. MOLECULAR CLASSIFICATION → Based on Gene expression profiling
2. HISTOLOGICAL CLASSIFICATION → Special sub type
   → no Special sub type

MOLECULAR CLASSIFICATION

	LUMINAL A	LUMINAL B	HER 2 ENRICHED	BASAL LIKE
ER / PR	⊕	⊕	⊖	⊖
Her 2 / Neu	⊖	⊖	⊕⊕	⊖
Marker	Low proliferatⁿ rate K;67→low	high proliferatⁿ rate K;67 → High		Triple ⊖ cancer [other name]

LUMINAL A BREAST CANCER
→ Elderly females
→ mc sub type
→ Best prognosis among sub types

LUMINAL B BREAST CANCER
→ BRCA 2 gene mutation ⊕
→ Bad prognosis

HER 2 ENRICHED
→ young females
→ Worst prognosis among sub types

BASAL LIKE
→ young female
→ BRCA 1 gene mutation ⊕

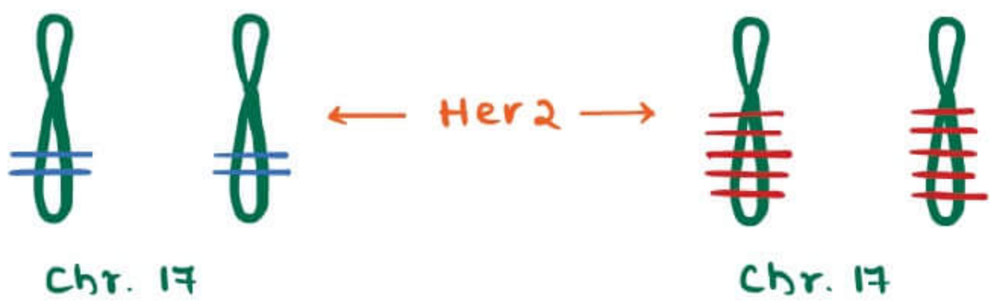
ER / PR → ⊕ → Nuclear Staining

Her2 / Neu → ⊕ → Surface/membrane Staining

[IHC] [Immunohistochemistry]

	Negative	Equivocal	Positive
Score	0/1	2	3

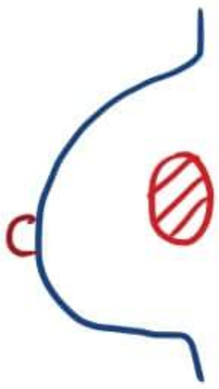
FISH TEST [flourescence insitu hybridization]
→ ↑ Her 2 / Neu
→ $\frac{\text{Her 2 / Neu}}{\text{CEP 17}}$ [Better Indicator]



HISTOLOGICAL CLASSIFICATION

1. NST INVASIVE CANCER [DUCTAL INVASIVE CANCER] [mc subtype]

CLINICAL PRESENTATION



BREAST LUMP [mc]

→ upper outer quadrant [mc site]
→ SKIN RETRACTⁿ ⊕
→ NIPPLE RETRACTⁿ ⊕
→ FIXATⁿ OF CHEST WALL ⊕
→ PEAU D ORANGE ⊕

SPECIAL SUBTYPES

A. INVASIVE LOBULAR CANCER

→ ↓ CDH → ↓ E-cadherin
→ B/L
→ multifocal
→ OCCULT PRIMARY [mc cancer]

→ m/E → 1. → DISCOHESIVE CELLS

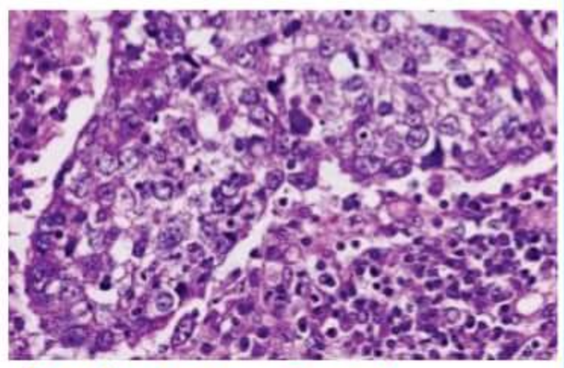
→ INDIAN FILE PATTERN

→ little Stroma

→ 2. ↑ SIGNET RING CELL CANCER OF STOMACH

B. MEDULLARY CANCER

→ Hypermethylatⁿ of BRCA 1 gene promoter
→ MIE
  → Sheets of cancer cells
  → ↑ mitosis ⊕
  → Lymphoplasmacytic infiltration



Medullary cancer

C. MUCINOUS CANCER

→ CELLS present in a pool of MUCIN
→ Soft, GEL Like consistency
→ elderly females
→ Good prognosis

D. TUBULAR CANCER → Best prognosis

E. PAPPILLARY CANCER → least common

INFLAMMATORY BREAST CANCER

→ involve LYMPHATICS → Redness & Swollen
→ mimics MASTITIS
→ no response to Antibiotics
→ poor prognosis

MALE BREAST CANCER

→ 1% of breast cancers

→ RISK FACTORS

- B → BRCA 2 gene >> 1
- R → Radiation
- E → Estrogen
- A → Age
- S → Syndrome [Klinefelter syndrome]
- T → Tumor in 1° relative

→ CIF → Sub areolar mass
→ Skin ⊕
→ Nipple discharge ⊕

→ MIE → ♂

→ DUCTAL CARCINOMA → ER ⊕ TUMORS

PROGNOSTIC FACTORS OF CARCINOMA BREAST

→ CIS → Excellent

→ Invasive cancer → variable

→ METASTASIS → most important factor

→ LN STATUS → Axillary LN Status ⊕ [sentinel LN] → Poor prognosis

→ SIZE OF TUMOR → ↑ size → Poor prognosis
→ Exception → HER 2 ENRICHED CANCER

→ LOCALLY ADVANCED DISEASE → Poor prognosis

→ INFLAMMATORY CANCER → Her 2 ⊕ → Poor prognosis

→ LYMPHO VASCULAR INVASION → Poor prognosis

→ MOLECULAR SUB TYPES
- → Luminal A → Best prognosis
- → HER 2 Enriched → worst prognosis

→ HISTOLOGICAL SUB TYPES
- → Tubular cancer → Best prognosis

→ GRADE → NOTTINGHAM SCORE

Low grade → Good prognosis

High grade → Bad prognosis

components
- → Tubule formatⁿ
- → mitotic counts
- → Nuclear pleomorphism

→ ANEUPLOIDY → poor prognosis

→ RECEPTORS

1. ER
   - ⊕ → hormone therapy ✓
   - ⊖ → chemotherapy ✓
2. Her2/ NEU → Poor prognosis
   → Predicts the response to TRASTUZUMAB (Herceptin)

BONE DISORDERS

INTRODUCTION TO BONE TUMORS

BONE TUMORS

I. PRIMARY [1°] BONE TUMORS

II. SECONDARY [2°] BONE TUMORS [more common]

SECONDARY [2°] BONE TUMORS | METASTASIS

→ commonly occur from Prostate cancer, Breast cancer, Renal cancer, Lung cancer

→ MC cancer responsible for bony metastasis → Breast cancer

→ MC cancer in Females responsible for bony metastasis → Breast cancer

→ MC cancer in males responsible for bony metastasis → Prostate cancer

→ MC cancer in children responsible for bony metastasis → Neuroblastoma

→ OSTEOBLASTIC SECONDARIES → Prostate cancer, Carcinoid tumor

→ OSTEOCLASTIC | OSTEOLYTIC 2° → Breast cancer, Lung cancer

→ In Breast & lung cancer both Osteoclastic & Osteoblastic 2° are seen
[Osteoclastic 2° > Osteoblastic 2°]

→ MC bones involved in metastasis → vertebral column

→ multifocal EXCEPT Renal & Thyroid cancers

- Renal & Thyroid cancers are Pulsatile in nature

PRIMARY [1°] BONE TUMORS

	BENIGN TUMORS	MALIGNANT TUMORS
AGE	Young	Elderly
PREVALENCE	more	Less
BONE BIOPSY	Uniform	Variable

Bone Biopsy [confirmatory test for diagnosis]

CLASSIFICATION

	MALIGNANT	BENIGN
HEMATOPOIETIC	Myeloma	
	Lymphoma	
CARTILAGE FORMING	chondrosarcoma	osteochondroma
		Chondroma
		chondroblastoma
		Chondromyxoid fibroma
BONE FORMING	osteosarcoma	osteoid osteoma
		osteoblastoma
UNKNOWN ORIGIN	Ewing sarcoma	Giant cell tumor
	Adamantinoma	Aneurysmal bone cyst
NOTOCHORDAL	CHORDOMA	

→ CHORDOMA → NOTOCHORD ORIGIN, AGGRESSIVE BONE TUMOR

→ CHONDROMA → BENIGN CARTILAGE TUMOR

→ MC 1° MALIGNANT BONE TUMOR → MYELOMA > OSTEDSARCOMA

RISK FACTORS [↑ cancer]

→ Chronic osteomyelitis
→ Bone infarct
→ Radiation exposure
→ Paget's disease
→ metal implant / prosthesis

} a/w chronic inflammatⁿ → ↑ cells → ↑ cancer risk

SPECIFIC INDIVIDUAL TUMORS

OSTEOSARCOMA

→ 2nd MC 1° malignant bone tumor
→ Mineralised Bone deposition is charecteristic finding

RISK FACTORS

1. Rb gene / P53 gene mutation & MDM2 / CDK4 overactivity
2. H/O previous Bone lesion [Paget's disease / Bone infarct]
3. Chemicals ; Radiation exposure

1°	2°
young [75%]	Elderly [25%]
more	H/O Radiation exposure / Bony lesion

→ BIMODAL AGE DISTRIBUTION present

SITE

→ Femur [Lower end] >> Tibia [upper end] >> Humerus [upper end]
→ Metaphyseal region involved commonly

CLINICAL FEATURES

→ Gradually growing painful MASS around the knee joint
→ NIGHT PAIN
→ PATHOLOGICAL FRACTURE

SUB TYPES OF OSTEOSARCOMA

A. GRADE
- Low grade
- High grade

B. 1° & 2°

C. SITE
- Intramedullary
- Intra cortical
- Surface [Better Prognosis]
  - Parosteal → Surface of cortex involved
  - Periosteal → surface of periosteum involved

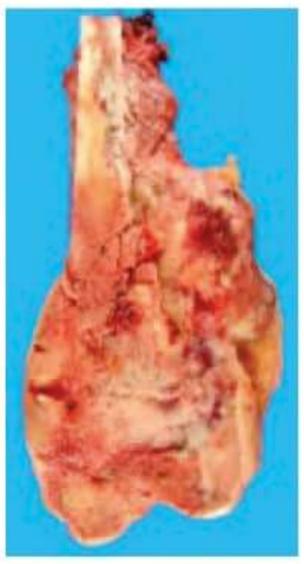
D. HISTOLOGICAL SUB TYPES
- osteoblastic
- chondroblastic
- Fibroblastic
- telangiectatic
- Small cell
- Giant cell

MC OSTEOSARCOMA → HIGH GRADE / 1° / INTRAMEDULLARY / OSTEOBLASTIC

DIAGNOSIS

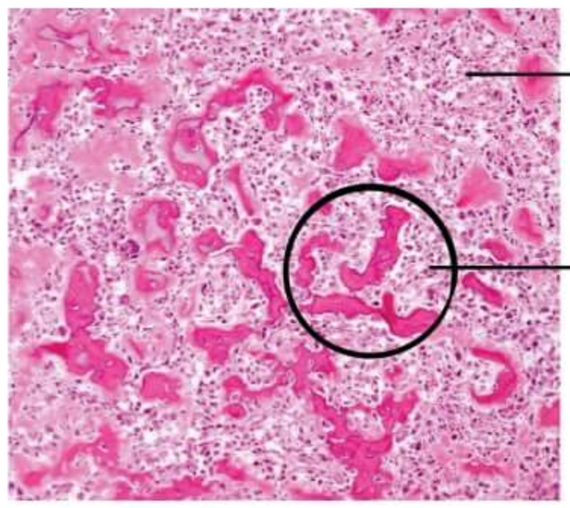
→ BONE BIOPSY IS CONFIRMATORY

→ Diagnostic finding → Bone formation by tumor cells



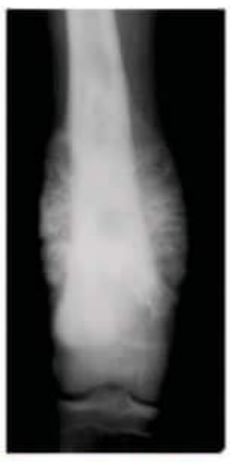
Gross

- Bulky
- Gritty
- Hemorrhage / necrosis + nt



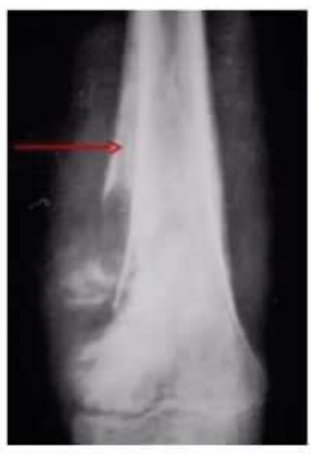
Histology

→ RADIOLOGICAL FEATURES



SUN BURST APPEARANCE

- dlt Ca^{2+} deposition



CODMAN'S TRIANGLE

- dlt lifting of periosteum by tumor
- indicates the aggressive nature of tumor

→ METASTASES TO Lungs >> Bones / Brain

→ RADIO RESISTANT IN NATURE

→ TREATEMENT

1. Surgery
2. Methotrexate

GIANT CELL TUMOR

→ aka OSTEOCLASTOMA

→ Benign tumor but Locally aggressive

→ Tumor cells → PRIMITIVE OSTEOBLASTIC PRECURSOR CELLS

↓

Express RANK - L

↓

attaches to RANK on osteoclasts

↓

EXCESS OSTEOCLAST ACTIVATION

↓

LOCALLY DESTRUCTIVE LESIONS

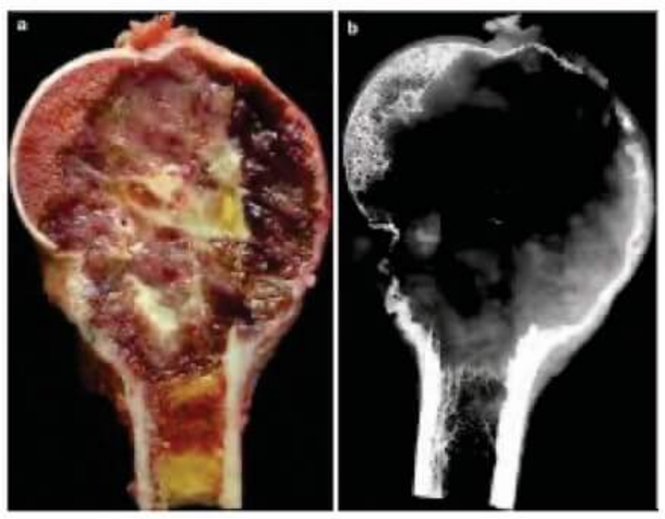
CLINICAL FEATURES

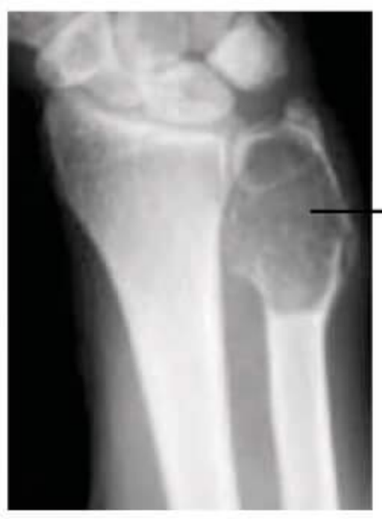
→ 20 - 40 yrs
→ commonly affect KNEE JOINT
  • distal end of femur > upper end of Tibia / lower end of Radius

→ arises from EPIPHYSIS, but can extend into METAPHYSIS [articular cartilage involved]

→ Arthritis - like manifestations +nt
→ Pathological fractures occurs

DIAGNOSIS





→ SOAP BUBBLE APPEARANCE

BONE MARROW BIOPSY

→ CLUB SHAPED TUMOR
→ a/w single layer of Periosteal reaction
→ Red Brown mass [d/t Hemorrhage & necrosis]
→ Cystic degeneration +nt → SOAP BUBBLE APPEARNCE on radiographs
→ Bone marrow biopsy shows
  ↳ GIANT CELLS Surrounded by STROMAL CELLS
    • GIANT CELLS → normal cells
    • STROMAL CELLS → cancer cells

  ↳ Hemorrhage & necrosis + nt

→ 9n about 4% of patients, pulmonary metastasis seen
→ GCT have high chances to undergo malignant transformation

TREATMENT

1. CURETTAGE [40-60% have recurrence]
2. DENOSUMAB
   • monoclonal activity
   • inhibit osteoclast activity

CHONDROSARCOMA

→ Malignant tumor → Cartilage formation + nt
→ GENES
  ↳ IDH_1 / IDH_2 gene mutation
  ↳ CDK2NA gene Silencing
  ↳ EXT mutation a/w MULTIPLE OSTEOCHONDROMA SYNDROME

→ arises from METAPHYSIS Except clear cell chondrosarcoma [Epiphyseal origin]

CLINICAL FEATURES

- → Males >> females
- → > 40 yrs age
- → Painful enlarging mass
- → involves Axial skeleton
  - Pelvis [mc]
  - Shoulder
  - Ribs

CLASSIFICATION OF CHONDROSARCOMA

Based on Histology

1. CONVENTIONAL [Hyaline cartilage]
2. CLEAR CELL
3. MESENCHYMAL
4. DEDIFFERENTIATED

clearcell & mesenchymal variants are seen in relatively young patients
mc variant → Grade 1 Intramedullary conventional / classical chondrosarcoma

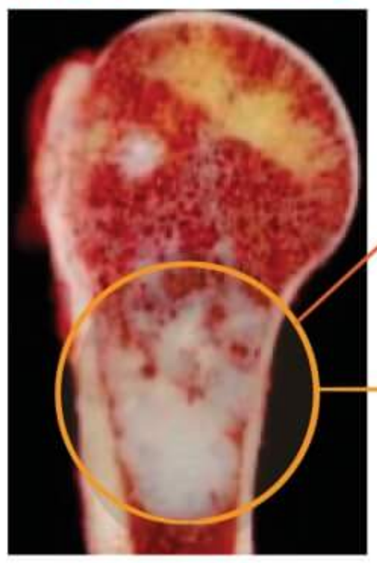
CLASSICAL | CONVENTIONAL CHONDROSARCOMA

Based on SITE → INTRA MEDULLARY / CENTRAL CHONDROSARCOMA
Based on SITE → JUXTA CORTICAL / PERIPHERAL CHONDROSARCOMA

GRADING OF CHONDROSARCOMA [Based on cellularity , Atypia , mitotic activity]

- → GRADE 1 → most common
- → GRADE 2
- → GRADE 3 → high chance of metastasis

GROSS FEATURES

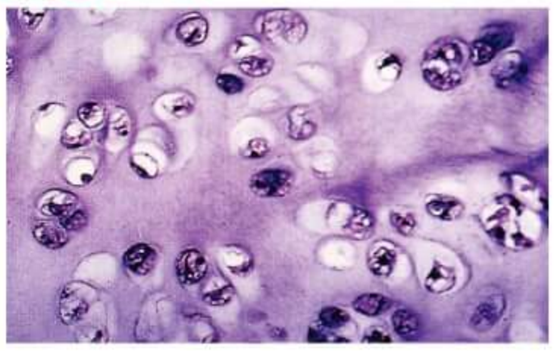


Firm in consistency

NODULES OF GREY-WHITE CARTILAGE

INTRA MEDULLARY TYPE

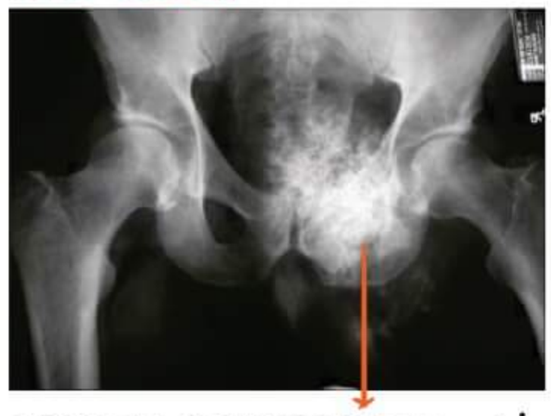
HISTOLOGY



Malignant cartilage cells

Permeating marrow

RADIOLOGY



SPOTTY CALCIFICATION/ FLOCCULENT DENSITIES

- → chondrosarcoma a/w Paraneoplastic syndrome → ↑ GLUCOSE [Hyperglycemia]
- → metastasis to Lungs >> Brain | Kidney

- → CHEMO & RADIO RESISTANT TUMOR , Rx by Surgery
- → Chondrosarcoma has the best prognosis among all other bone tumors

EWING SARCOMA

→ Malignant tumor i Primitive Round cells without differentiation

EWING SARCOMA FAMILY OF TUMORS [ESFT]

SMALL ROUND BLUE CELLS

- With Neuroectodermal diffentiation → PNET → S-100 | chromogranin | NSE ⊕
- Without Neuroectodermal differentiation → EWING SARCOMA → S-100 | chromogranin | NSE ⊖

EWING SARCOMA

→ GENETICS

↳ t [11;22] [mc]

[on chr 11] FLT 1 gene + EWS gene [on chr 22] → FUSION GENE → CANCER

↳ t [21;22]

↳ Trisomy 8 / 12

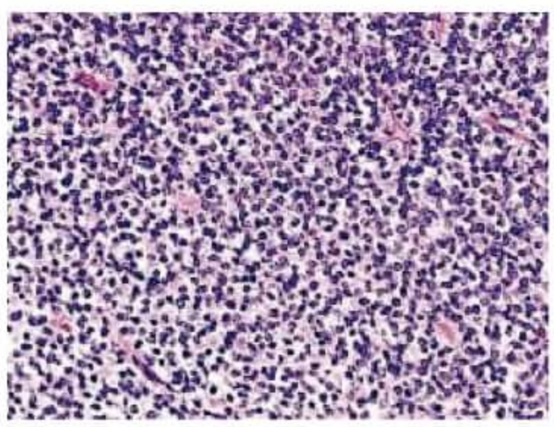
→ arises from DIAPHYSIS
→ mc affects Femur
→ Flat bones of pelvis also involved

CLINICAL FEATURES

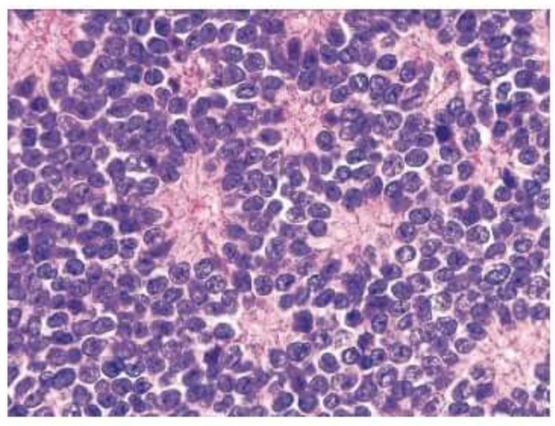
→ < 20 yrs
→ presents painful, tender swelling & fever
→ mimics Osteomyelitis

INVESTIGATIONS

1. ↑ TLC , ↑ ESR , ↑ CRP
2. Bm BIOPSY

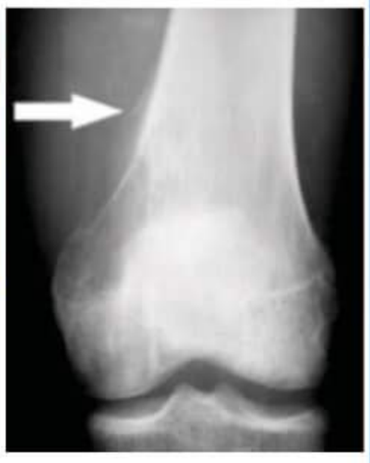


- small round blue cells
- Little stroma
- clear cytoplasm



HOMER WRIGHT PSEUDO ROSETTES

ONION SKIN APPEARANCE



→ Lytic lesion
→ Tan grey mass involving medulla [Hemorrhage & necrosis +nt]
→ Periosteal Reaction present → ONION SKIN APPEARANCE ON X RAY
→ IMMUNO HISTO CHEMISTRY → mic-2 ~ CD 99 ⊕
→ METASTASIS → BONE TO BONE METASTASIS SEEN
→ mc tumor ī Bone to Bone metastasis → EWING SARCOMA

NEOPLASIA
GENERAL CONCEPTS

PROPERTIES OF TUMOR CELLS

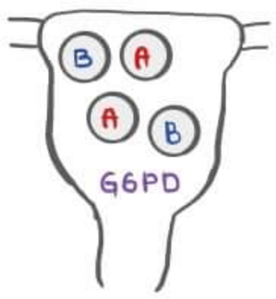
1. CONTINUE TO REPLICATE EVEN AFTER THE ABSENCE OF STIMULUS / GROWTH FACTOR

→ NORMAL CELL → CANCER CELLS

GF - Growth factor

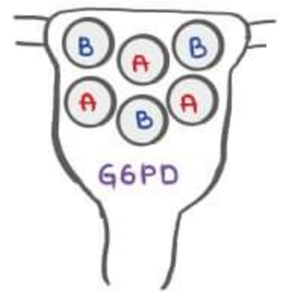
2. MONOCLONAL GROWTH

NORMAL



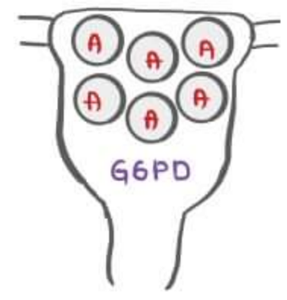
- Normal no. of cells
- isoforms of G6PD - are equally distributed

PREGNANCY



- ↑ no. of cells
- isoforms of G6PD - are equally distributed

CANCER [monoclonal growth]



- ↑ no. of cells
- isoforms of G6PD are unequally distributed

→ monoclonality shown by both BENIGN & MALIGNANT TUMORS
→ MC ENZYME whose isoforms are useful for detect^{n} OF MONOCLONALITY is G6PD ENZYME

3. COMPONENTS OF NEOPLASM

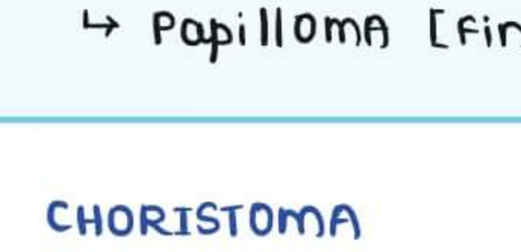
a. PARENCHYMA [proliferating neoplastic cells]
b. STROMA [connective tissue]

→ MORE STROMA → FIRM appearance
→ MORE PARENCHYMA → MEDULLARY appearance

→ DESMOPLASIA
↳ Excessive amount of stroma
↳ contributed by parenchymal chemicals

↳ Ex: LINITIS PLASTICA
COLON CANCER
BREAST CANCER

4. TUMOR CLASSIFICATION

BENIGN	MALIGNANT
→ slow growth	→ Rapid growth
→ capsule ⊕	→ capsule ⊖
→ well differentiated 	→ poorly differentiated
→ Good prognosis	→ poor prognosis
→ NOMENCLATURE uses suffix "OMA" ↳ fibroma ↳ osteoma ↳ Chondroma ↳ Adenoma [glandular] ↳ Papilloma [finger like]	→ NOMENCLATURE CARCINOMA [from epithelial cells] SARCOMA [from connective tissues] ↳ AdenoCARCINOMA [glandular] ↳ ChondroSARCOMA

CHORISTOMA

→ ECTOPIC REST OF NORMAL TISSUE [normal tissue at abnormal site]

HAMARTOMA

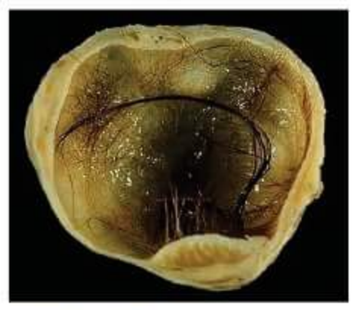
→ ABNORMAL TISSUE at NORMAL SITE
→ Commonest Site → LUNGS
→ Preneoplastic lesions [Latest Studies]


HAMARTOMA

TERATOMA

→ arises from ≥1 GERM CELL LAYER
→ usually arises from TOTIPOTENT CELLS

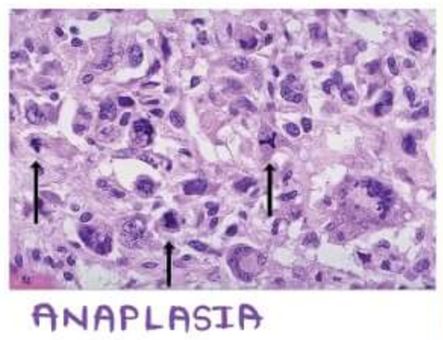
→ mc site	→ GONADS
→ mc extra gonadal site	→ MEDIASTINUM
→ if well diffentiated	→ BENIGN
→ if poorly differentiated	→ MALIGNANT


TERATOMA

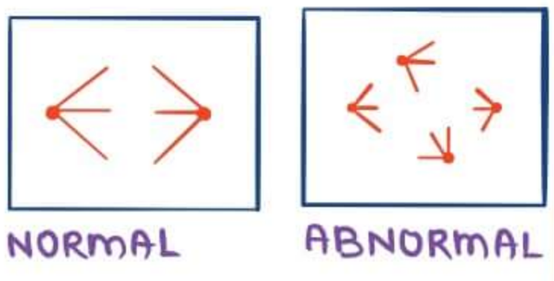
FEATURES OF NEOPLASIA

1. ANAPLASIA

→ TOTAL ABSENCE OF DIFFERENTIATION
↑↑↑ NC RATIO [Nucleo : cytoplasmic Ratio]
↳ Normal N:C Ratio → 1 : 4
↳ Anaplastic N:C Ratio → 1 : 1


ANAPLASIA

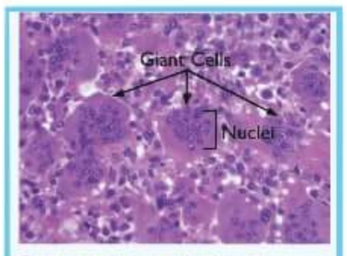
→ PLEOMORPHISM
→ ABNORMAL MITOSIS
↳ NORMAL [2 mitotic spindles]
↳ ABNORMAL [>2 mitotic spindles]
• 4 mitotic spindles → Quadripolar spindles
• 3 mitotic spindles → Tripolar spindle


NORMAL ABNORMAL

→ ABNORMAL GAINT CELL

↳ REED STERNBERG CELLS → 

[Hodgkin Lymphoma]



GAINT CELLS

→ IRREVERSIBLE

→ HALLMARK OF MALIGNANT TRANSFORMATⁿ

AN	→	Abnormal [high] N:C Ratio
A	→	Abnormal mitosis
PL	→	Pleomorphism
A	→	Abnormal Gaint cells
SIA	→	Irreversible

Ⓝ CELL ⇌ METAPLASIA (reversible) → DYSPLASIA (↑ N:C Ratio, Pleomorphism ⊕) → ANAPLASIA [cancer] (↑↑↑ N:C Ratio, Pleomorphism ⊕⊕⊕, Irreversible)

2. RATE OF GROWTH ↑↑

→ No. of divisions required for clinical manifestations → 30

→ minimum mass of tumor cells to be detected clinically → 10^9 cells (1g)

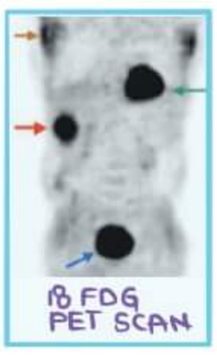
→ maximum no. of cells compatible i the life → 10^{12} cells (1kg)

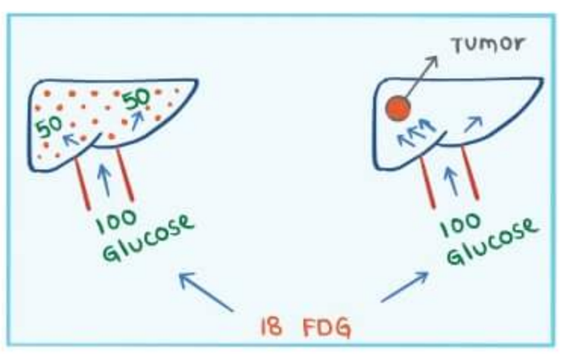
→ Glucose metabolism

NORMAL CELLS → Glycolysis
TCA / Kreb cycle

CANCER CELLS $\xrightarrow{O_2 \oplus}$ Aerobic Glycolysis → WARBURG EFFECT

Pyruvate → Intermediates → GF ↓ Tumor cells proliferatⁿ





18 FDG

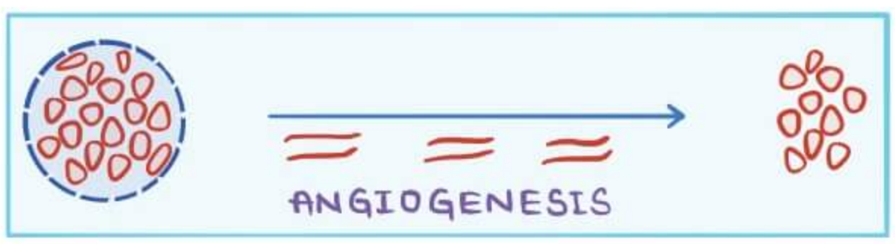
→ non metabolised

→ sub type of glucose

→ radio active

→ PET scan is done to LOCALISE TUMOR CELLS

3. INVASION



VEGF - vascular Endothelial GF

FGF - fibroblast GF

→ due to VEGF, FGF ⟶ ANGIOGENESIS [r/f invasion]

→ i out angiogenesis, tumor cells can grow only upto 1-2 mm

→ ANTI ANGIOGENETICS
  ↳ ANGIOSTATIN } Natural
  ↳ ENDOSTATIN }
  ↳ BEVACIZUMAB → Drug

→ CARCINOMA IN SITU → Basement membrane not affected
→ CARCINOMA → Basement membrane affected

4. METASTASIS

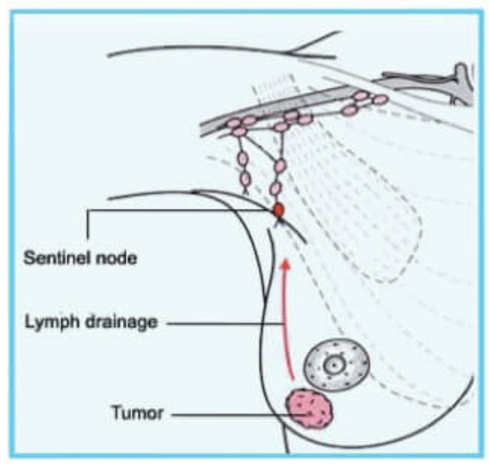
→ MOST RELIABLE FEATURE OF MALIGNANCY
→ Distinguishes b/w benign & malignant tumor
  ↳ EX: • PHEOCHROMOCYTOMA
  • FOLLICULAR THYROID TUMOR

→ EXCEPTIONS [malignant ↑out metastasis]
  1. Basal cell carcinoma [skin]
  2. Glioma

→ Spred through
1. Lymphatic spread
  ↳ Property of CARCINOMAs
  ↳ Except RCC, HCC, choriocarcinoma → Hematogenous
  ↳ SENTINEL [GATE KEEPER / CARE TAKER] LYMPH NODES
    ↳ tumor cells spread first to these LN

EXAMINATION

Negative	Positive
↓	↓
Good prognosis	Poor Prognosis
↓	↓
limited Sx	more extensive Sx



↳ Tells about
  • EXTENT OF DISEASE SPREAD [prognosis]
  • EXTENT OF SURGERY

↳ Useful for • Breast cancer
  • vulval cancer
  • Melanoma

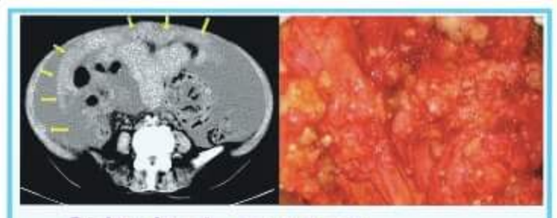
2. HEMATOGENOUS SPREAD

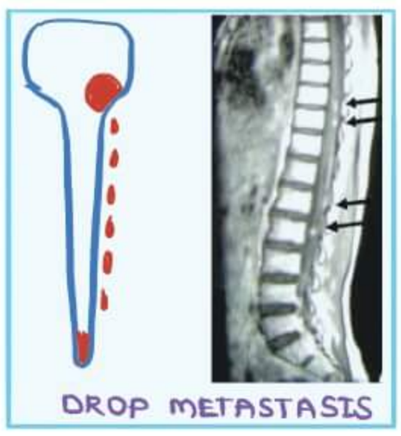
→ feature of SARCOMAs
→ Exceptions
  • clear cell sarcoma } lymphatic spread
  • Rhabdomyo sarcoma }

→ can spread through → Vein >>> Artery
→ commonly affect parts recieving more blood [common sites]
  • Liver
  • Lungs

3. DIRECT SEEDING

- → Body cavities are involved directly
  - ↳ pleural cavity [seen in lung cancer, mesothelioma]
  - ↳ pericardial cavity [seen in lung cancer, cardiac cavity]
  - ↳ peritoneal cavity
    - → most commonly affected in direct seeding
    - → responsible for
      - ↳ OMENTAL CAKING
      - ↳ MALIGNANT ASCITIS
        - → common in ovarian tumors
        - → D_x by ASCITIC TAP ± the help of
          - tumor markers
          - HPE [Histopathological Examination]


OMENTAL CAKING


DROP METASTASIS

4. CSF SPREAD

- → a/w 'DROP METASTASIS'
- → involves lower spinal cord
- → seen in MEDULLOBLASTOMA

GENETIC BASIS OF CARCINOGENESIS I

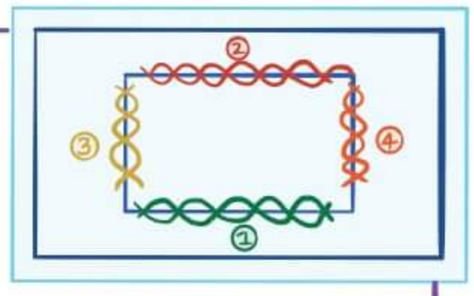
HALL MARKS OF CANCER

- → Self Sufficiency of Growth factors
- → Insensitivity to Growth Inhibitors
- → Altered metabolism
- → Evasion of Apoptosis
- → Immortality
- → Sustained Angiogenesis
- → Invasion & metastasis
- → Evasion of Host Immune response

GENETIC DEFECTS

1. PROTO - ONCOGENES

- → causes ↑ replicat^n of normal cells
- → mutation / overactivity → GAIN OF FUNCTION
- → Single gene mutat^n is sufficient



2. TUMOR SUPPRESSOR GENES

- → controls the replicat^n of normal cells
- → mutation / underactivity → LOSS OF FUNCTION
- → Both genes of allelle should be involved

3. DNA REPAIR GENES

- → defect → cancer
- → Both genes of allelle should be involved

4. REGULATION OF APOPTOSIS GENES

- → Defect → cancer

1. SELF SUFFICIENCY IN GROWTH SIGNAL

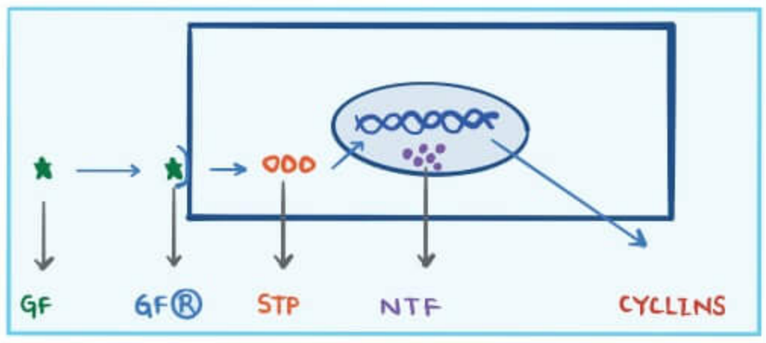
PROTO - ONCOGENES [normal] $\xrightarrow{\text{mutation}}$ ONCOGENES [↑↑↑ Gain of function]

→ due to
- → Point mutation
- → Over expression
- → Translocation

} ↑ Activity

→ NORMAL CELL GROWTH INVOLVES [ONCOGENES]

1. Growth factor [GF]
2. GF Receptors [GF®]
3. Signal Transduction proteins [STP]
4. Nuclear Transcription factors [NTF]
5. ↑ cyclins



ANY HYPERACTIVITY OF FIRST 4 FACTORS } ↑↑↑ CYCLINS } ↑↑↑ PROLIFERATION OF CELLS

1. GROWTH FACTORS

→ PDGF → SIS gene → GLIOMA
→ HGF → HGF gene → LIVER CANCER

2. GF RECEPTOR [® Associated Tyrosine kinase]

→ ERB B_1 gene → Lung cancer ← GEFITINIB, ERLOTINIB (used in Rx)
→ ERB B_2 / HER-2 gene → Breast cancer ← TRASTUZUMAB
→ RET gene → MEN II Syndrome
- ↳ Pheochromocytoma
- ↳ medullary carcinoma Thyroid

3. SIGNAL TRANSDUCTION PROTEINS

→ RAS [most imp. STP involved in cancer]
→ ABL
→ β catenin
→ BRAF

GDP - RAS [Inactive] $\underset{\text{GTPase}}{\overset{\text{GF}}{\rightleftharpoons}}$ GTP-RAS [active]

↓ [NEURO FIBROMIN]

MAP K pathway
PI3K / AKT pathway

↓

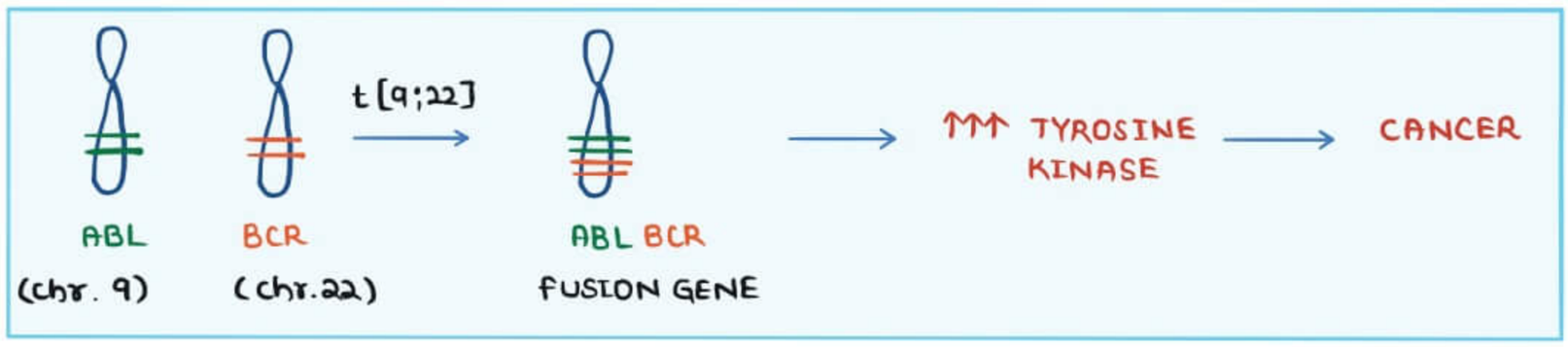
Cell replicates

→ RAS MUTATION

↳ Colon cancer → K - RAS
↳ Kidney & bladder cancer → H - RAS
↳ melanoma → N - RAS

↳ MC TYPE PROTO-ONCOGENE MUTAT^{n} a/w HUMAN CANCER → K - RAS

→ ABL GENE [have non-receptor tyrosine kinase activity]



↳ t [9;22] → CML & ALL

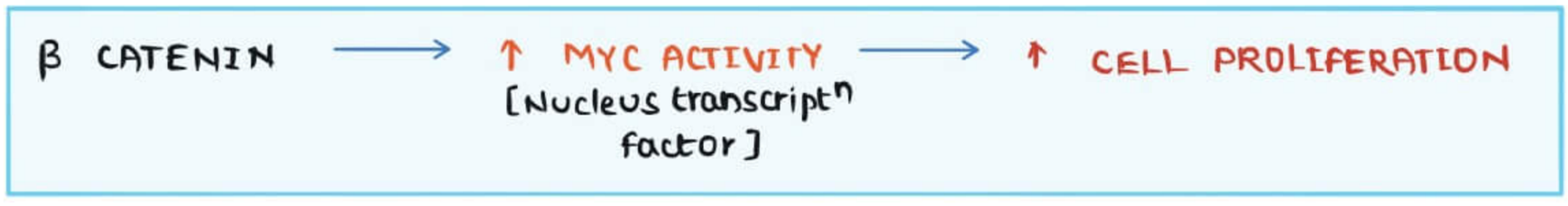
↳ ONCOGENE ADDICTION [ABL] → addicted to Tyrosine kinase for proliferat^{n}
↳ TARGETED THERAPY by IMATINIB [directs against TYROSINE KINASE]

↳ ALL [Acute] replicates faster than CML
↳ IMATINIB is more effective against CML than ALL
↳ therefore, t [9;22] CML has good prognosis
t [9; 22] ALL has poor prognosis

→ B RAF gene

↳ BRAF mutation a/w
- Hairy cell leukemia [100%.]
- Benign nevi [80%.]
- melanoma [60%]

→ β CATENIN



↳ APC gene] ↓ β catenin
↳ E-Cadherin] activity

↳ β catenin mutat^{n} a/w → COLON CANCER

4. NUCLER TRANCRIPTION FACTORS

1. MYC GENE

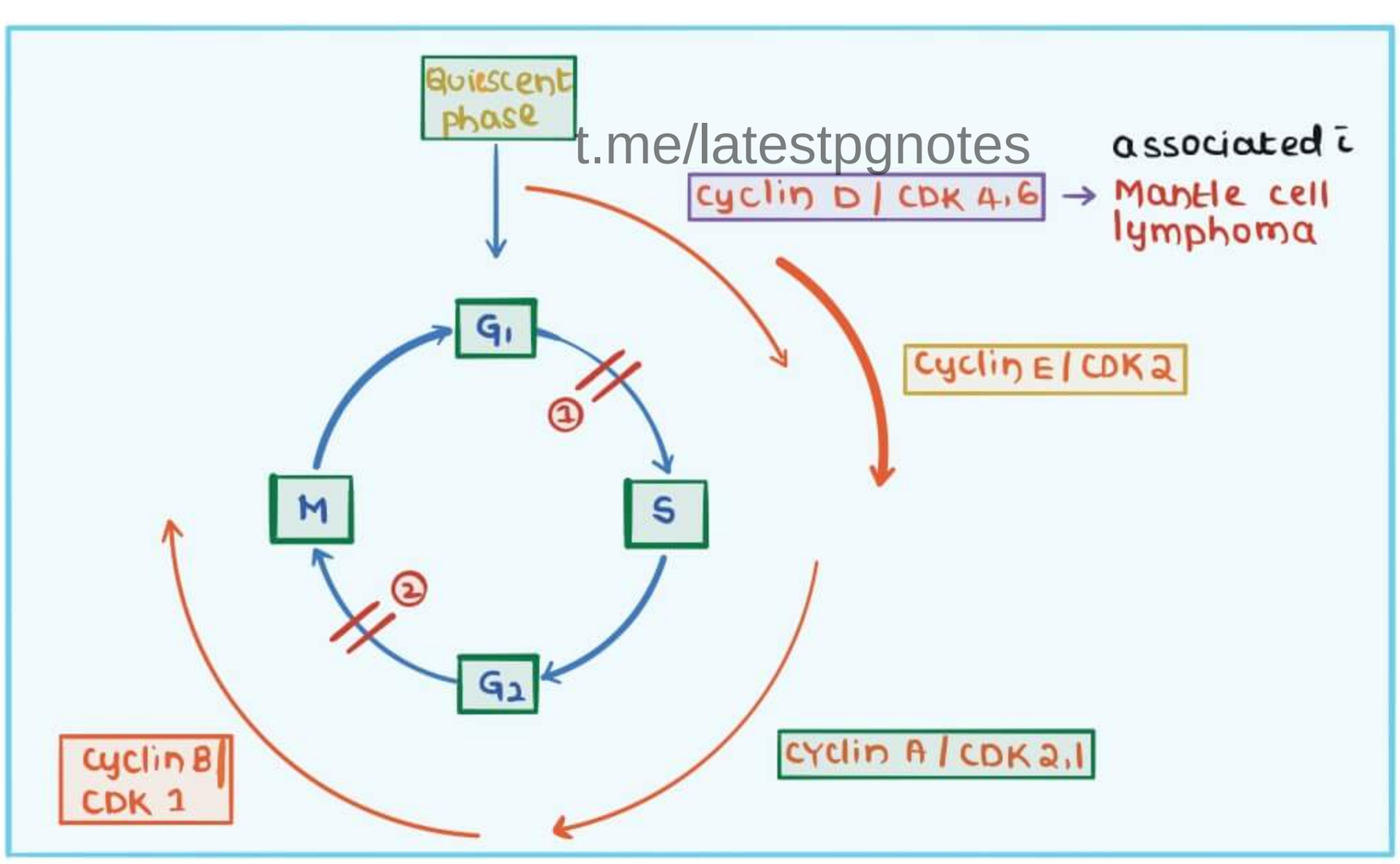
→ ↑ cyclin activity
→ ↑ Telomerase
→ Reprogram → "STEMNESS"
→ aka "MASTER REGULATOR" of cell

→ SUB TYPES
→ C - MYC → Burkitt's lymphoma [fastest rate of replicatn]
→ N - MYC → Neuroblastoma
→ L - MYC → Lung cancer [small cell]

5. CYCLINS [OFF/ON] → CDKs → causes Phosphorylation

→ CDKs [Cyclin Dependent Kinases]
↳ SUB TYPES & ACTIVATION SEQUENCE
→ D → 4, 6
→ E → 2
→ A → 2
→ B → 1

→ CELL CYCLE PHASES & REGULATION



→ CELL CYCLE PHASES ARE REGULATED BY
↳ From Quiescent stage to just beyond check point 1 → CYCLIN D / CDK4,6
↳ From just beyond check point 1 to 'S' phase → Cyclin E / CDK2
↳ From 'S' phase to 'G_2' Phase → Cyclin A / CDK 2,1
↳ From 'G_2' phase to 'M' phase incl. check point 2 → cyclin B / CDK 1

→ cell cycle also regulated by
↳ Rb gene ; p 53 gene → G_1 / S
↳ p 53 gene → G_2 / S

→ CDK activity → ↑ by cyclins ; ↓ by CDK inhibitors

CDK INHIBITORS

p 21	p 15
p 27	p 16
p 57	p 18
	p 19
↓	↓
non specific	Specific for
All CDKs	CDK 4/6

GENETIC BASIS OF CARCINOGENESIS 2

2. INSENSITIVITY TO INHIBITORS

→ Tumor Suppressor genes ⟶ ↓ Cell Replication

→ DOUBLE - HIT HYPOTHESIS
- ↳ proposed by Knudson
- ↳ explained ī Retinoblastoma
- ↳ both copies of genes should be involved

→ FUNCTIONS
- ↳ Regulation of G_1|S Transition → RB / P53 gene
- ↳ DNA Repair → P53 / BRCA - 1/2 genes
- ↳ mitogenic pathway ⊖ → APC genes, NF 1/2, PTEN genes
- ↳ Angiogenesis ⊖ → VHL genes

1 RB GENE
- ↳ located on chr 13q 14
- ↳ proposed by Knudson in Retinoblastoma
- ↳ most important tumor suppressor gene in humans
- ↳ mc tumor suppressor gene a|w cancers

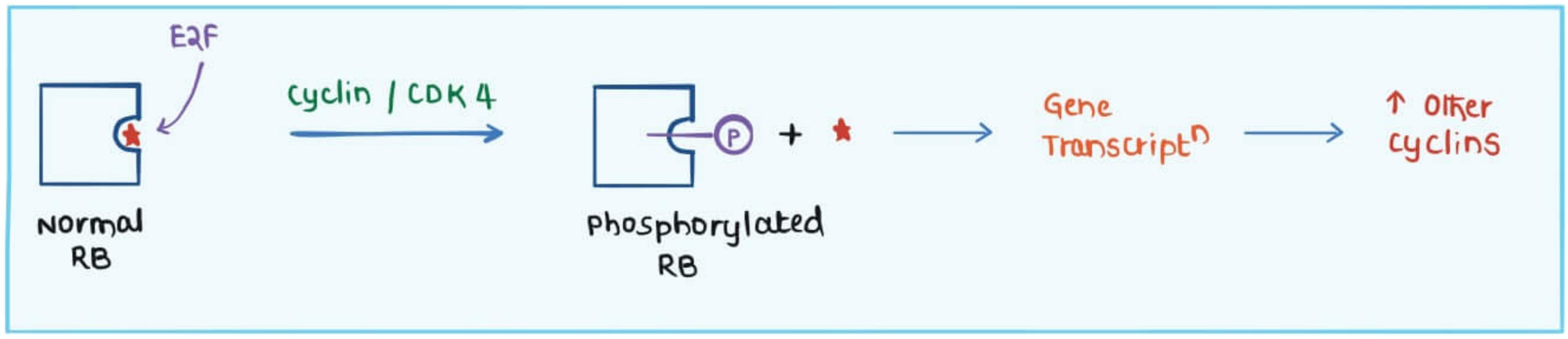
↳ Retinoblastoma
- a. Sporadic → no alterat^n of genes at the time of birth
  → ① ② → UIL Retinoblastoma
- b. Familial → 1 gene of allelle is mutated at the time of birth
  → BIL Retinoblastoma

↳ RB gene is RECESSIVE in nature but

↳ FAMILIAL RB is AUTOSOMAL DOMINANT
- → as only 1 mutath required after birth
- → LOSS OF HETERDZYGOSITY occurs
  - ↳ 1 defective & 1 normal gene → heterozygous
  - ↳ 2 defective genes → Loss of heterozygosity [homozygous for defective gene]

↳ Sporadic RB [60%] more common than familial RB [40%]

↳ FUNCTION

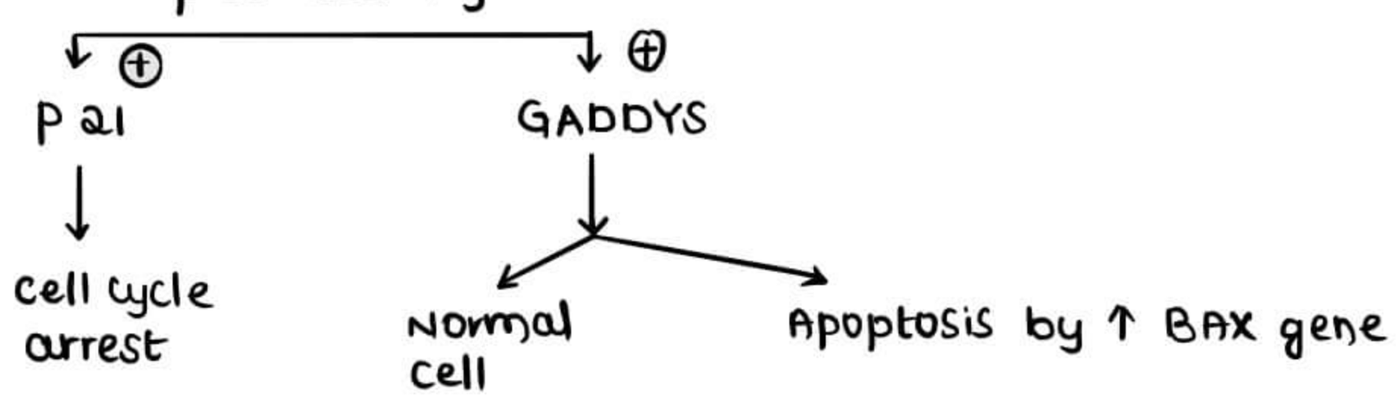


↳ aka 'GOVERNOR OF CELL REPLICATION'

↳ EBV → E_7 protein → ↓ Rb gene → ↑ cell Replication [CA CERVIX]

2. P53 GENE / GUARDIAN OF GENOME
   → (N) cells → MDM gene destroys P53

   → DNA damage → ↑ p53 activity



   → FORMS OF p53 gene
      a. WILD TYPE → (N) → Located on chr 17p
      b. GERMLINE p53 GENE MUTATION
         ↳ causes LI FRAUMENI SYNDROME → ↑ cancers

      c. SPORADIC p53 GENE MUTATION
         ↳ mc genetic mutation seen in human cancers

3. BRCA 1 → chr 17q → ♀ Breast cancer / ovarian cancer
   BRCA 2 → chr 13q → ♂ Breast cancer / Prostate cancer

   BRCA 1, BRCA 2 } involved in DNA Repair

   BRCA 1 → play a important role in familial variant of cancer
   → documented presence of BRCA 1 gene mutation → indicatn for prophylactic mastectomy & oopherectomy

4. NF 1 → chr. 17q → Neurofibromatosis 1
   → cafe au lait spots

   NF 2 → chr. 22q → ↑ Acoustic Neuroma
   → leash modules
   → cafe au lait spots
   → CNS tumors

5. WT 1
   → mesenchymal to epithelial transition (normal)
   → mutation causes wilms tumor
   → located on chr 11 p

6. VHL GENE
   → (N) → ↓ HIF [Hypoxia Inducible factor] → ↓ VEGF
   → located on chr 3p
   → a/w VHL SYNDROME
      ↳ Kidney cancers
      ↳ Brain tumors [cerebellar hemangioblastoma]
      ↳ Pheochromocytoma

7. APC GENE
   → ↓ β catenin Activity → ↓ Adenomas (normal)
   → located on chr 5q
   → ↑ Adenomas → familial Adenomatous Polyposis → ↑ colon cancer
   → aka GATE KEEPER OF COLONIC NEOPLASIA

III GENES REGULATING APOPTOSIS

→ INTRINSIC PATHWAY AFFECTED
→ BCL-2 OVER ACTIVITY → ↓ APOPTOSIS → ↑ CANCER
→ Ex: Follicular lymphoma

IV DNA REPAIR GENE DEFECTS

→ Nucleotide Excision Repair defect [NERD]
→ Mismatch repair defect [MRD]
→ Homologous Recombination Repair defect [HRRD]

→ NERD	→	Xeroderma pigmentosa [UV Rays] → ↑ Skin Cancers	Autosomal Recessive

→ MRD → LYNCH Syndrome
   ↳ Autosomal Dominant
   ↳ dlt MICRO SATELITE INSTABILITY
   ↳ aka CEO Syndrome
      ∘ ↑ Colon Cancer
      ∘ ↑ Endometrial cancer
      ∘ ↑ Ovarian cancer

HRRD	→	BLOOm Syndrome	← Ionising Radiation	Autosomal Recessive
		Fanconi's anemia	← Alkalising agents	
		Ataxia-telangiectasia	← Ionising Radiation	

→ BRCA 1|2 gene defects → involved only in FAMILIAL BREAST CANCER

OTHER HALLMARKS OF CANCER

1. ALTERED METABOLISM
   → WARBURG EFFECT → Aerobic glycolysis → GF → ↑ cell proliferatⁿ

2. IMMORTALITY
   → normally ONLY GERM CELLS have TELOMERASE
   → cancer cells have telomerase activity

3. SUSTAINED ANGIOGENESIS
   → VEGF, FGF } ↑
   → Angiostatin, Endostatin } ↓

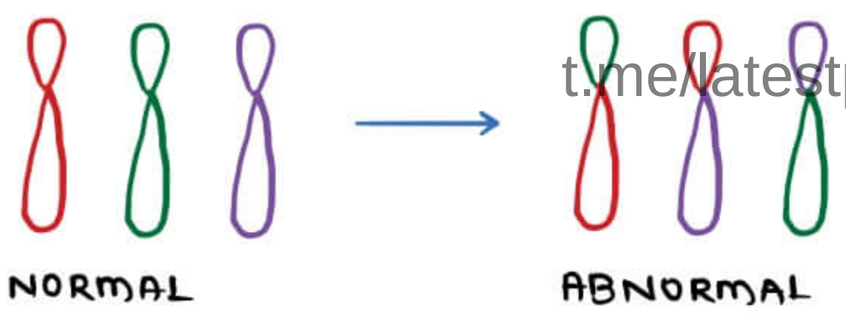
   → BEVACIZUMAB → Anti Angiogenetic drug

4. INVASION & METASTASIS
   → TWIST | SNAIL → Epithelial to Mesenchymal Transition [EMT]

5. ESCAPE IMMUNE SURVEILLANCE
   → proposed by LEWIS THOMAS & M. BURNETT

ADVANCED CONCEPTS OF GENETIC DEFECTS

CHROMOTHRYPSIS



Chromosomes are shattered & fused i each other

→ a|w GLIOMA & OSTEOSARCOMA

EPIGENETIC CHANGES

→ Some genes influence the activity of other genes by
   ↳ DNA HYPER METHYLATION
   ↳ HISTONE ACETYLATION

MICRO RNAs ⊖→ mRNA Translation

→ ↑ Cancer → ONCO miRNAs → miR 155 → B cell lymphoma
→ ↓ Cancer → Tumor suppressor miRNA → miR 15 (defect→) CLL
   miR 16

→ DICER → For functional miRNA → defect → ↑ cancer

ETIOLOGICAL FACTORS OF NEOPLASIA

CHEMICALS

INITIATORS → Ⓝ DNA ⟶ Mutated DNA
- → DIRECTLY ACTING ⟶ damage DNA ī out any alterations
- → INDIRECTLY ACTING ⟶ damage DNA, forming reactive interme-diates in Liver

PROMOTORS → Mutated DNA ⟶ ↑ cells

SUB TYPES OF CHEMICAL MEDIATORS

1. SMOKERS → PAH [Polycylic Aromatic Hydrocarbons]
   - → a|w → Squamous cell cancer OF Lungs & Larynx
   - → transitional cancer OF Bladder [by β - Napthylamine]
   - → Adenocarcinoma OF Pancreas

2. NITROSAMINES
   - → Stomach Cancer
   - → Oesophageal cancer
   - → more in Japan

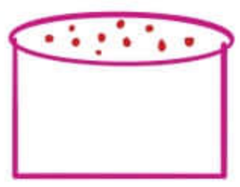
3. AZODYES → GIT cancers

4. VINYL CHLORIDE → Angiosarcoma of Liver
   - → also seen in
     - ↳ Arsenic → Skin cancer
     - ↳ Thorotrast

5. ASBESTOS
   - → 'UNIQUE CARCINOGEN' → acts as both Initiator & Promotor
   - → Mesothelioma [25 - 35 yrs exposure] [most specific]
   - → Bronchogenic carcinoma [15-20 yrs exposure] [mC]

6. DRUGS
   - → ALKYLATING AGENTS } 2° Leukemia
   - → TOPOISOMERASE INHIBITORS }
   - → CYCLOPHOSPHAMIDE [Alkylating agent] → Urinary Bladder cancer

AMES TEST / CARCINOGENICITY/ MUTAGENIC TEST



① ② Chemical ⊕ growth ⊕

S.typhimurium [modified - can't produce histidine]
NO histidine provided in petri dishes

→ carcinogenicity / mutagenesity OF a chemical can be tested

SIR PERCIVAL POTT

→ chimney sweepers ⟶ scrotal skin cancer

↓ suggested daily bath [removes soot regularly]

↓ Scrotal skin cancer

RADIATION EXPOSURE

1. NON IONISING → UV RAYS → A
   → B [more powerful than A]
   → C [max. chance of causing cancer]
   [filtered by ozone layer]

↳ causes DNA damage → PYRIMIDINE DIMERS
↳ dimers repaired by Nucleotide Excision Repair Genes [NER]
↳ defect in NER genes → ↑ cancer
→ a/w XERODERMA PIGMENTOSA
↳ ↑ Basal cell carcinoma
↳ ↑ Squamous cell carcinoma } Skin Cancers
↳ ↑ melanoma

2. IONISING RADIATION
→ more powerful & causes DNA damage
→ includes X / Y / β rays ⟶ OH° ⟶ DNA DAMAGE
→ Radiology / Atomic Bomb

↓ Lead Aprons [protective]

↓ max. in G_2/m phase

→ ↑ Leukemias → AML, CML, ALL [not a/w CLL]
→ ↑ Papillary Thyroid cancer
→ THOROTRAST → ↑ Angiosarcoma of Liver

→ Least affected Organs by Ionising radiation
↳ SKIN
↳ GIT
↳ Bones

INFECTIOUS MICRO ORGANISMS

1. H. PYLORI
→ contains CAG & A^{9} [cytotoxin] → Gastric Adeno carcinoma
→ Polyclonal B cell activat^{n} → t [11;18] → Gastric MALToma

2. FUNGI
→ Aspergillus flavus → AFLATOXIN → Hepato cellular cancer

3. VIRUSES [most notorious

a. RNA VIRUSES

1. HTLV 1 → Adult T-cell leukemia [TAX protein]

↓

↑ cyclins
interferes ↓ DNA repair gene functⁿ

→ takes 4-6 decades to cause cancer
→ involves CD_4 T cells
→ transmitted by Sexual, vertical & parenteral route
→ more in CARIBBEAN ISLANDS

2. HEPATITIS C → Liver cancer

b. DNA VIRUSES

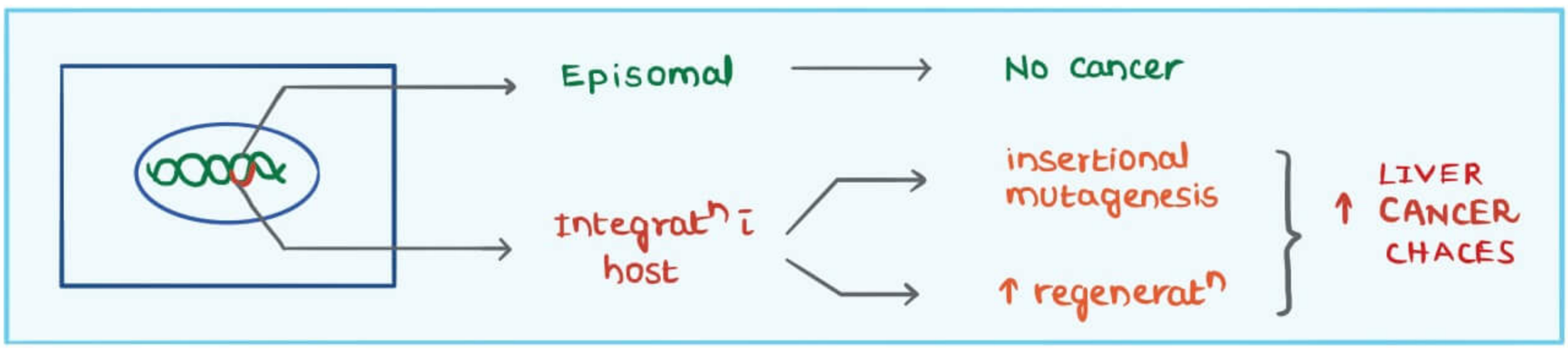
1. HPV [Human Papilloma Virus]
   - ↳ 6, 11 → Low risk → Warts [condyloma acuminata] [STD]
   - ↳ 16, 18 → higher risk → secrets E_6 → ⊖ p53
     E_7 → ⊖ Rb gene
     ⊖ p21 | p27
     ⊕ Cyclin A|E

→ ↑ cancers
   - ↳ Cervical cancer
   - ↳ Anal canal cancer
   - ↳ Oral cavity cancer

2. KAPOSI SARCOMA HERPES VIRUS [HHV-8]
   → affects Immuno compromised persons

   → causes
   - ↳ Kaposi's Sarcoma
   - ↳ 1° Effusion Lymphoma [a|w HIV]
     - ↳ affects body cavities [a|w HIV]
     - ↳ component of DLBCL [Diffuse Large B cell Lymphoma]

3. HEPATITIS B VIRUS



4. EBV
   → dlt
      ↳ LMP 1 gene → ↑ NF-Kβ & ↑ BCL-2
      ↳ EBNA protein → ↑ Cyclin D
      ↳ VIL-10 → ↓ T cell activity

      ⇒ B CELL IMMORTALIZATION → ↑ cancer

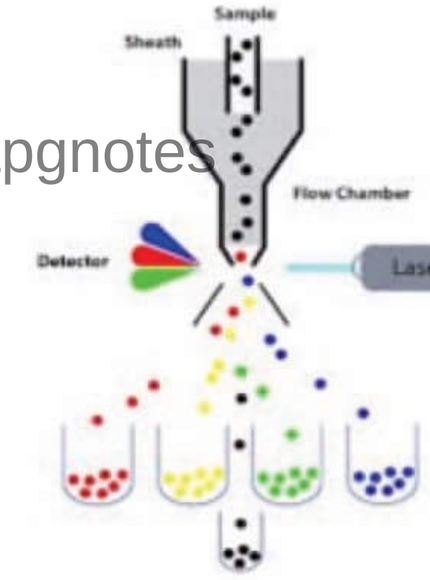
   → ↑ Hodgkin's Lymphoma
     ↑ Non Hodgkin's Lymphoma
     ↑ Burkitt's lymphoma [African / Endemic]
   } B CELL CANCERS

↑ Nasopharyngeal carcinoma [china] → T CELL CANCER

PARASITES
1. CLONORCHIS SINENSIS → cholangio carcinoma
2. SCHISTOSOMIASIS → urinary Bladder cancer

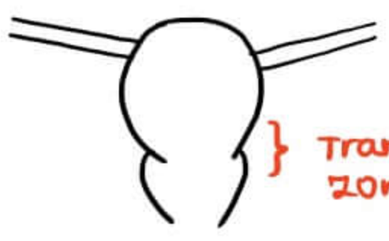
DIAGNOSIS OF TUMORS

1. FLOW CYTOMETRY
→ flowing stream of cells are used
→ detects certain surface molecules on cells
→ useful in detection of CD molecules
→ useful in Dx of
   ↳ haematological malignancies
   ↳ Nucleic acid content



2. CYTOLOGICAL METHODS
a. FNAC
→ 22-26 Gauge needle is used
→ Advantage → OPD procedure
→ Disadvantages
   ↳ need other procedures [USG etc] for assistance at times
   ↳ CI in bleeding disorders & vascular growths
   ↳ can't differentiate b/w benign & malignant tumors
      → Ex: Follicular Thyroid Tumor
         ↳ Adenoma } not differentiated
         ↳ Follicular carcinoma } by FNAC

b. EXFOLIATIVE CYTOLOGY
→ Shed cells obtained either
   ↳ Spontaneously or by
   ↳ Scraping



→ used in
  ↳ bronchial washings
  ↳ Oral cavity
  ↳ cervical tissue ⟶ PAP SMEAR

↓

Squamo - columnar junction

↓

Fixed ī ETHER + 95% ETHANOL

↓

microscopy for
  → maturation index
  → Nuclear features

VIA
  → Visual inspection after the application of Acetic acid
  → BEST SCREENING METHOD FOR CERVICAL CANCER

PAP SMEAR

3. HISTOLOGICAL METHODS

→ MC METHOD used for diagnosis of cancer
→ MICROSCOPIC EXAMINATION OF FIXED TISSUE AFTER BIOPSY

→ SOLID CANCERS [Cx CANCER] } not appropriate
  [High contamination] } method

→ LIGHT MICROSCOPE → formalin used
→ ELECTRON MICROSCOPE → Glutaraldehyde used

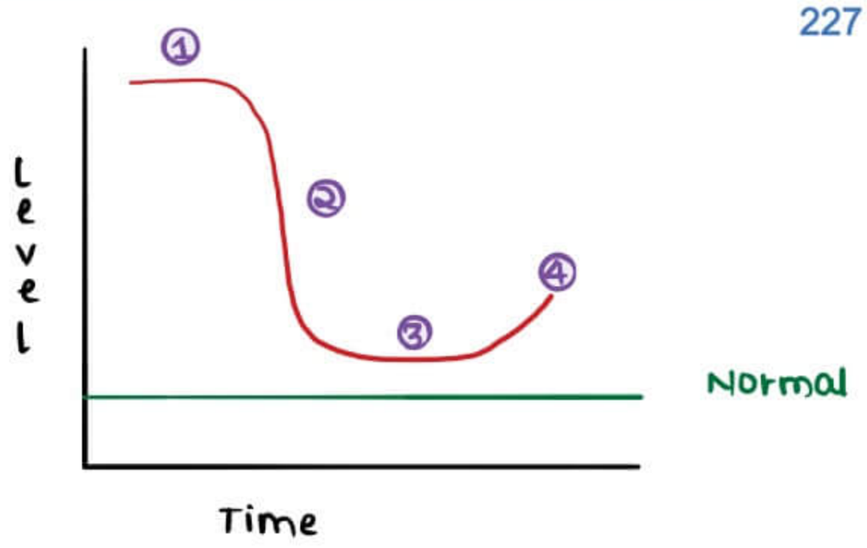
→ STAINING
  a. Routine
  b. Special

4. IMMUNO CYTOCHEMISTRY

→ SURFACE MARKERS are identified using FLUORESCEIN ANTIBODIES
→ useful in Δ& of UNDIFFERENTIATED TUMORS
  ↳ EXAMPLES
    → Keratin → carcinoma
    → Desmin → myogenic tumor
    → Vimentin → sarcoma
    → GFAP → glial tumor [GFAP - Glial fibrillary associated protein]

→ useful in IDENTIFICATION OF Δs OF PRIMARY, particularly in METASTASIS
→ useful in PROGNOSIS/ THERAPY
  ↳ EXAMPLE → Breast cancer
    ↳ ER ⊕ → Good prognosis / Anti Estrogenic drugs used
    ↳ HER 2/Neu ⊕ → poor prognosis / Trastuzumab used

5. TUMOR MARKERS



→ acts as SURROGATE MARKERS

→ NOT FOR DEFINITIVE DIAGNOSIS

→

1 → Suggestive of cancer
Start therapy

2 → indicates Response to therapy

3 → indicates Stage of Remission

4 → indicates Stage of Recurrence

→ EXAMPLES

↳ PSA	→	Prostate cancer
↳ Ig	→	Multiple myeloma
↳ HCG	→	Chorio carcinoma
↳ Calcitonin	→	Medullary Thyroid cancer
↳ Catecholamines	→	Pheochromocytoma
↳ CEA	→	Colon cancer, pancreatic cancer
↳ AFP	→	Hepatocellular cancer, NON-Seminomatus GCT
↳ CA 15.3	→	Breast cancer
↳ CA 19-9	→	Pancreatic cancer
↳ CA 125	→	Ovarian cancer
↳ NSE	→	Neuroblastoma

PSA – Prostate Specific Antigen
NSE – Neuron Specific Enolase
CEA – Carcino Embryonic Antigen
AFP – Alfa Feto Protein

PARANEOPLASTIC SYNDROMES

→ NOT EXPLAINED ON THE BASIS OF
- ↳ Direct Spread
- ↳ metastasis
- ↳ indigenous hormones

SIGNIFICANCE
- ↳ may be initial manifestation
- ↳ may mimic metastasis
- ↳ may indicate worsening condition

→ TYPES

I. ENDOCRINOPATHIES

1. Hypercalcemia
   - ↳ mc paraneoplastic syndrome
   - ↳ dlt PG & / PTHrP [PTH related Peptide]
   - ↳ seen in Lung cancer [Squamous cell carcinoma]
     Kidney cancer
     Breast cancer

2. CUSHING SYNDROME
   - ↳ seen in Lung cancer [Small cell cancer]
     Carcinoid tumor

3. SIADH
   ↳ Seen in Lung cancer [Small cell cancer]
   CNS tumors

4. HYPOGLYCEMIA
   ↳ Seen in Fibrosarcoma
   Hepatocellular cancer

5. POLYCYTHEMIA
   ↳ dlt EPO [Erythropoietin like substance]
   ↳ seen in Hepatocellular carcinoma
   Kidney cancer
   Fibromyoma
   Cerebellar hemangioblastoma

II VASCULAR ; HEMATOLOGICAL

1. VENOUS THROMBOPHLEBITIS
   → dlt MUCIN
   → causes MIGRATORY VENOUS THROMBOPLEBITIS / TROUSSEAU SIGN
   → Seen in Pancreas cancer
   AML-M3
   Bronchogenic cancer

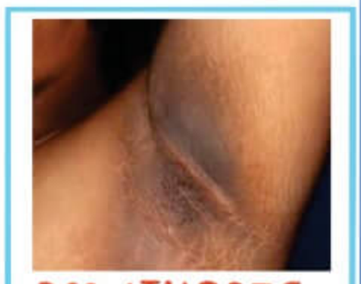
2. MARANTIC ENDOCARDITIS / NON BACTERIAL THROMBOTIC ENDOCARDITIS [NBTE]
   → Seen in Pancreatic cancer
   AML - M3

   → dlt mucin

3. ANEMIA → Seen in Thymoma

III DERMATOLOGICAL

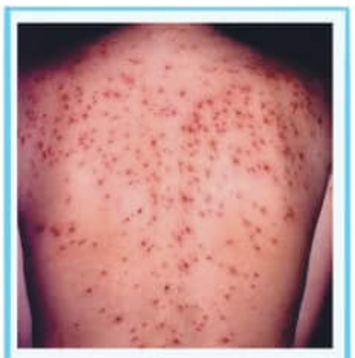
1. ACANTHOSIS NIGRICANS
   → Seen in Stomach cancer
   Lung cancer
   Uterine malignancy


ACANTHOSIS NIGRICANS

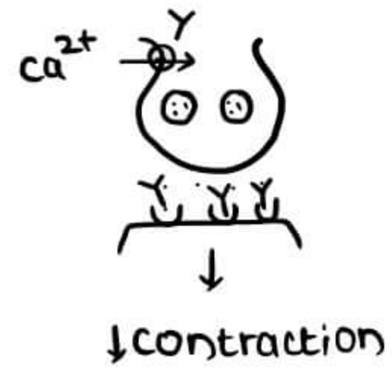
2. DERMATOMYOSITIS
   → Contains Anti p 140 Ab
   Anti P 155 Ab
   VS
   Auto Immune Dermatomyocitis
   contains Anti - Jo 1 Ab

   → Seen in Lung cancer
   Breast cancer

3. SEBORRHEIC KERATOSIS /
   → SIGN OF LESER TRELAT
   ↳ Seen in Stomach cancer [mc]
   Colon cancer
   Breast cancer



IV NEURO MUSCULAR



1. MYASTHENIA GRAVIS
   - → Ab against Ach ® [post synaptic]
   - → Seen in Thymoma

2. LAMBERT – EATON SYNDROME
   - → Ab against ca^{2+} channel [pre synaptic]
   - → Seen in Lung cancer [small cell cancer]

L → Late
E → Entry of ca^{2+} in
S → small cell cancer

3. OPSOCLONUS [rapid eye movement] → seen in Neuroblastoma
4. LIMBIC ENCEPHALITIS
   - → Anti - HU Ab ⊕
   - → Seen in Lung cancer [Small cell cancer]

5. SUB ACUTE CEREBELLAR DEGENERATION
   - → Anti - YO Antibodies ⊕
   - → Seen in Uterine cancer
     Ovarian cancer
     Breast cancer

V. OSSEUS ; SOFT TISSUE CHANGES

1. HYPERTROPHIC OSTED ARTHROPATHY
   - → causes clubbing of fingers
   - → Seen in Lung cancer

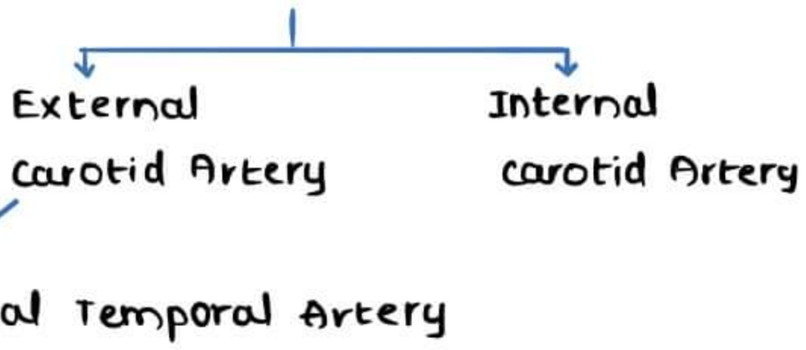
VASCULITIS

→ Non - Infectious
→ Immunological
→ C/F → ISCHEMIA

LARGE VESSEL VASCULITIS [Aorta & its major branches involved]

TEMPORAL ARTERITIS

→ mc vasculitis in Adults
→ ♀ , > 50 yrs
→ Aorta ⊕ carotid artery ⊕

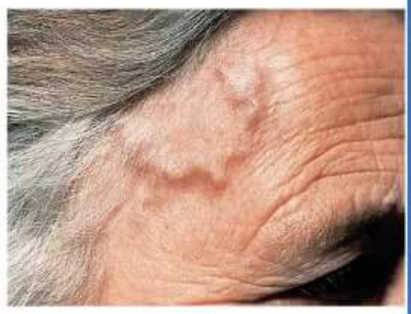


C/F

→ Headache [localised] [mc symptom]
→ Jaw claudication [most specific]
→ Fever, malaise, joint & muscle pain

↓

POLYMYALGIA RHEUMATICA
[shoulder girdle >> Pelvic girdle]


Temporal arteritis

DIAGNOSIS

→ ↑↑ TLC
→ ↑↑ ESR [> 50 mm | 1 hr]
→ BIOPSY
  ↳ IOC
  ↳ atleast 1 cm should be taken
  ↳ Patchy involvement ⊕
  ↳ Granuloma ⊕ → Gaint cells ⊕ → aka GAINT CELL ARTERITIS
  ↳ Negative biopsy do not rule out disease

ICA ⟶ OPHTHALMIC ARTERY ⟶ ↓ Blood ⟶ BLINDNESS [sudden onset]

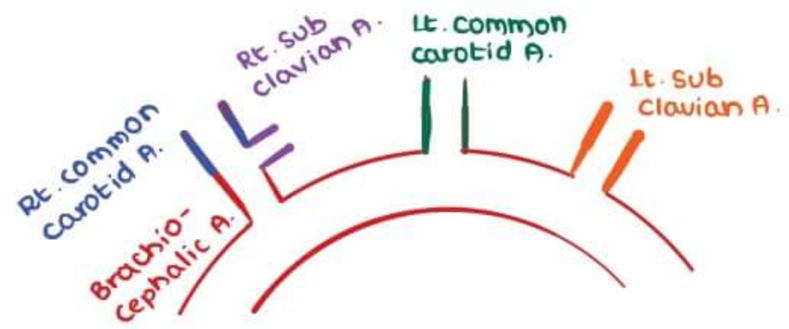
Rx

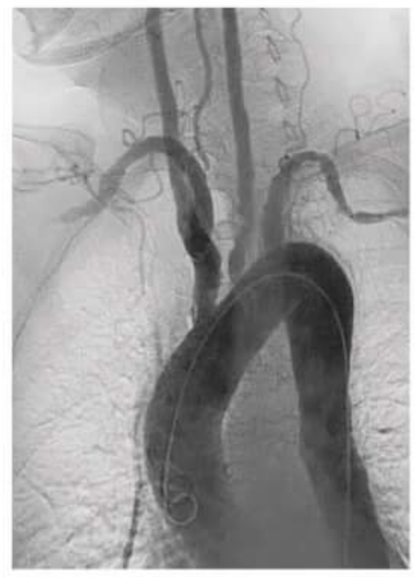
1. STEROIDS → DOC
2. Inhaling & Exhaling in plastic bag at the event of S/O Blindness

2. TAKAYASU ARTERITIS

→ < 50 yrs
→ discovered in Japan
→ Aortic Arch involved
→ AORTIC ARCH SYNDROME
→ Origin point of vessels involved
  → Feeble pulse → PULSELESS DISEASE

→ MIE → Granuloma ⊕
→ CIF → Neurological SIS
→ Weak pulse
→ SIO Blindness





→ Poor prognosis
→ Renal artery involvement → RAAS activation → HTN

REND VASCULAR HTN

Elderly → Atherosclerosis

Young → India → Non-Specific Aortic Inflammation [Takayasu arteritis]

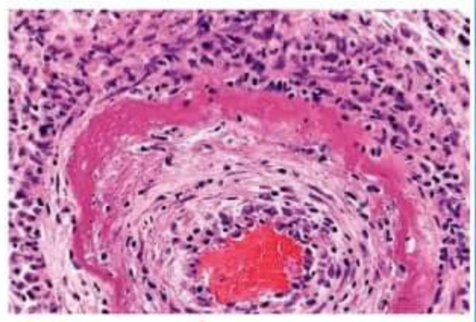
MEDIUM SIZED VESSEL VASCULITIS → Renal | popliteal | coronary artery involved

POLYARTERITIS NODOSA

→ Young Adults
→ Immune complexes ⊕ → Fibrinoid necrosis ⊕
→ HBS Ag ⊕ anti-HBS Ag → Many organs ⊕
→ Small vessels are Spared

→ MULTI ORGAN INVOLVEMENT [Except LUNGS]
→ Kidney → Renal artery → RABS ⊕ → HTN
→ no glomerulonephritis [RBC casts ⊖ in urine]

→ GIT → Pain | melena
→ SKIN → nodules | papules | ulcers
→ NERVES → mono neuritis multiplex
→ JOINTS → Arthralgia
→ CNS → Seizures

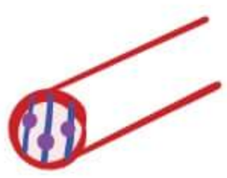

Fibrinoid necrosis

→ MIE → EARLY PHASE → Fibrinoid necrosis ⊕
→ Transmural Inflammation
→ LATE PHASE → Fibrosis ⊕

→ RX → 1. STEROIDS
→ 2. CYCLOPHOSPHAMIDE

BUERGER DISEASE

→ NECROTISING INFLAMMATION → Arteries > veins > Nerves
→ Lymphatics not involved


Thrombo angitis Obliterans

→ Tibial Artery ⊕ → ↓ Blood
- ↳ at rest → no symptoms
- ↳ walking → pain +
- ↳ stopped walking → no symptoms

} Intermittent claudication

→ Young ♂ smokers

→ Rx
1. Quit smoking
2. vasodilators
3. Surgery
4. Amputation

KAWASAKI DISEASE

→ < 4 yrs age group

→ FEVER ⊕
- Conjunctivitis [non exudative]
- Rash [on extensor surface]
- Edema [hands & feet]
- Adenopathy [cervical LN]
- Mucosal ulcers [STRAWBERRY TONGUE]

} atleast 4

→ Thrombocytosis ⊕
→ Coronary vaswlitis ⊕

} mc cause of myocardial Infarctⁿ in child


Strawberry tongue

→ DIAGNOSIS
- → ↑↑ TLC
- → ↑ ESR
- → ↑ PLC

→ Rx
- → IV Ig + ASPIRIN
- → steroids should be avoided

SMALL VESSEL VASCULITIS

→ ANCA auto Ab ⊕

MPO [Ag]
↓
p - ANCA Ab
↓
MPO - ANCA
↓
- microscopic polyangiitis
- churg - strauss syndrome
- Good pasture syndrome
- ulcerative colitis

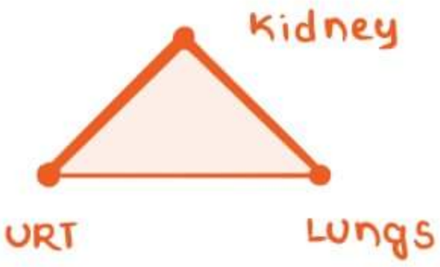
[against nuclear envelop Ag]

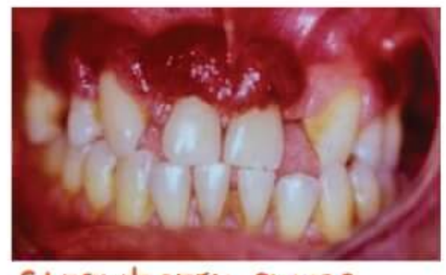
Proteinase - 3 Ag
↓
c - ANCA Ab
↓
PR - 3 ANCA
↓
- wegener granulomatosis

WEGENER GRANULOMATOSIS / GRANULOMATOSIS ī POLYANGIITIS

→ Necrotising granuloma ⊕

→ AFFECTS




Strawberry gums

KIDNEY → Crescent GN [RPGN] [RBC casts ⊕]

URT [mc] → Ear → Om
Nose → Septal perforation , saddle nose
Throat → strawberry gums, sub glottic stenosis

LUNGS → Cough
Hemoptysis
Cavitatory lesions ⊕

→ DIAGNOSIS → 1. C - ANCA / PR - 3 ANCA ⊕
2. BIOPSY → Crescentic GN

→ Rx → CYCLOPHOSPHAMIDE [DOC] , STEROIDS

→ Death → Renal failure

MICROSCOPIC POLYANGIITIS

→ Small vessels ⊕

→ PAN vs MP

	PAN	MP
small vessels	⊖	⊕
Lungs	⊖	⊕
Kidneys	⊕	⊕
Glomerulonephritis	⊖	⊕
p - ANCA	⊖	⊕

→ MP vs WEGENER GRANULOMATOSIS

MP	WEGENER
p - ANCA ⊕	C - ANCA ⊕
no nasopharyngeal involvement	Kidney ⊕
	Lungs ⊕
	URT ⊕

→ MIE → SAME STAGE OF INFLAMMATION ⊕
→ NO GRANULOMA FORMATⁿ

→ a/w → INFECTIONS
→ PENICILLIN [Drugs]
→ SLE

→ Rx → STEROIDS

HENOCH - SCHONLEIN PURPURA

→ children

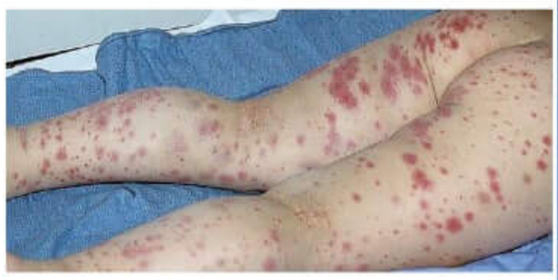
→ mc vasculitis in children

URTI ⟶ Ig A ↑↑

↓

Immune complexes ⊕ → III HR

Kidney	Skin	GIT	JOINTS
↓	↓	↓	↓
GN ⊕	Purpura	abdominal pain	pain
microscopic Hematuria	↓	melena	
	Rash [Ext. surface]		
	↳ Limbs		
	↳ Buttocks		



→ Rash is dlt vasculitis

→ Platelet count is Normal → NON THROMBOCYTOPENIC PURPURA / ANAPHYLACTOID PURPURA

CHURG STRAUSS SYNDROME

→ Necrotising vasculitis

→ Granuloma ⊕ ⟶ Eosinophilia ⊕ ⟶ Type I HR

→ alw Asthma & Drugs [montelukast]

→ multiple organ involvement → Lungs , Skin , Heart

→ p - ANCA ⊕

ANGINA

ISCHEMIC HEART DISEASE

→ ANGINA

→ MI

→ CHRONIC IHD

→ SUDDEN CARDIAC DEATH

→ < 1 hr

→ mostly dlt Ventricular fibrillation

ANGINA → Reversible

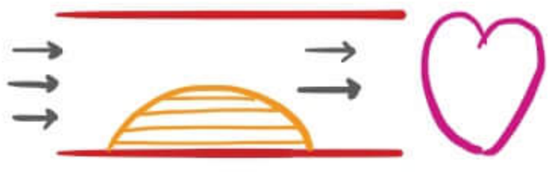
STABLE ANGINA → ST depression [Sub endocardial ischemia]

→ CIS present on EXERTION

→ IF coronary artery obstruction

> 75 % → CIS appear on exertion

> 80% → CIS appear even at rest



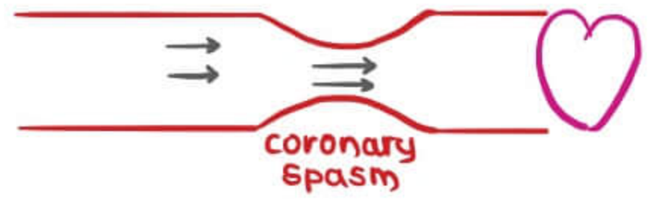
→ Rl by

1. Nitrates
2. β blockers
3. Ca^{2+} channel Blockers

PRINZMETAL ANGINA

→ dlt CORONARY ARTERY SPASM

→ coronary spasm persists at → Rest | Exertion

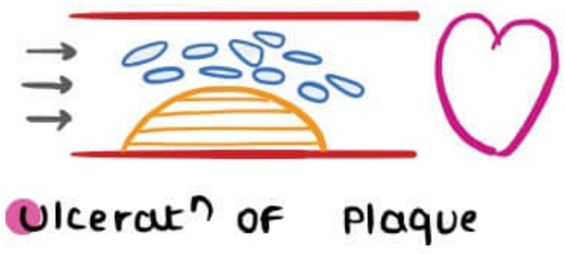


→ Rl by NITRATES

→ β Blockers contraindicated

UNSTABLE ANGINA

→ c/s → New pain
→ worse pain
→ Severe pain



Ulceratⁿ of Plaque

↓

↑ platelets | fibrin | spasm

→ Aggressive in nature

→ may lead to Myocardial Infarction

→ Most dangerous angina

→ aka PRE - INFARCTION ANGINA

→ Rl by NITRATES
ANTI PLATELET DRUGS

MYOCARDIAL INFARCTION

→ IRREVERSIBLE

→ ULCERATION | RUPTURE | HEMORRHAGE OF PLAQUE

↓

THROMBUS | SPASM OF CORONARY VESSEL

↓

INFARCTION

↓ ↓

TRANSMURAL MI — SUB ENDOCARDIAL MI [inner 1/3 rd]

C/F

→ CHEST PAIN
→ radiates to inner arm / Jaw / Epigastrium
→ Squeezing pain
→ LEVINE SIGN → clenched fist on chest

→ MI → NO PAIN → Elderly & DM → SILENT MI

→ DIAPHORESIS

→ ↑ PULSE

→ DYSPNEA

→ NAUSEA & VOMITING

BLOOD VESSEL → LAD

↓

Apex — Anterior wall of LV — Anterior inter ventricular septum

↓

ANTERIOR WALL MI [mc]

DIAGNOSIS

1. ECG
   - → Hyperacute 'T' waves
   - → ST segment elevation
   - → 'Q' wave [old MI]

2. CARDIAC ENZYMES
   - → MYOGLOBIN
     - → first enzyme to increase in MI
     - → normal in 24 hrs
     - → not specific

   - → CREATINE KINASE
     - → CK - MM | CK - MB | CK - BB
     - → CK - MB → useful for MI Dx
       - → also increases in myocarditis

   - → TROPONIN → increases in 24 - 48 hrs & elevated for 7 - 10 days

     cTn T

     cTn I [more important]

     - → Best enzymes for Dx of MI → most specific & sensitive
     - → also useful in the Dx of RE - INFARCTION

   - → LDH

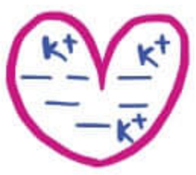
     - → in normal person, $LDH_2 >> LDH_1$
       in MI, $LDH_1 >>> LDH_2$ [FLIPPING OF LDH RATIO]
     - → Last enzyme to ↑ in MI
     - →

       TTC [Triphenyl Tetrazolium chloride] Stain + LDH
       - → Normal [intra cardiac LDH] → Brick Red color
       - → MI [leaked out LDH] → PALE or YELLOW

       - → useful to know cause at the time of autopsy

3. ECHO
   - → hypokinesia
   - → Akinesia

4. THALLIUM SCAN → K^+



Diffuse staining

Infarcted area is picked up against the normal background of viable area

5. BIOPSY

< 4 hrs	no change
4 - 24 hrs	Inter cellular edema [WAVINESS OF FIBRES]
	Pale on TTC staining
24 - 72 hrs	COAGULATIVE NECROSIS
	NEUTROPHILIC INFILTRATION
	INFARCT ī YELLOW BORDER
3 - 7 days	Macrophages ⊕⊕⊕
	Neutrophils ↓↓
	Hyperemic borders
≠ - 10 days	Granulation tissue
	Red - Brown margins
	Scar ↓↓
4 - 6 WKS	Scar
	white scar

REPERFUSION INJURY

→ STREPTOKINASE [thrombolytics] worsens the condition in some
→ also a/w coronary artery stenting or other invasive procedure
→ dlt sudden influx of WBC | free radicals | Ca^{2+}
→ m/E → CONTRACTION BANDS [dlt Ca^{2+}]

COMPLICATIONS

1. ARRHYTHMIAS
   → ↓ HR [Bradyarrythmia]
   → ventricular fibrillation
      ↳ mostly occur ī in 1 hr
      ↳ mortality → 25%
      ↳ Rx by Defibrillatⁿ | cardioversion or LIGNOCAINE
      ↳ mcc of death in the 1st hour of MI

2. CARDIAC FAILURE
3. CARDIAC RUPTURE SYNDROME
   → seen after 3 - 7 days after MI
   → Affects 1. free wall rupture [mc]
   2. Inter ventricular septum
   3. Mitral Regurgitatⁿ

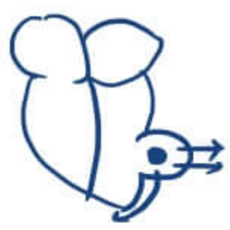
Free wall Rupture → CARDIAC TAMPONADE

4. AUTO IMMUNE PERICARDITIS / DRESSLER SYNDROME

NEO ANTIGENS → after 2-3 weeks usually
→ Immune system activatⁿ ⊕

presents ī chest pain
Symptomatic relief occur by anti inflammatory drugs

5. VENTRICULAR ANEURYSM
   → clot or thrombus can develop
   → may rupture



CHRONIC ISCHEMIC HEART DISEASE [with HF]

LEFT VENTRICULAR FAILURE [Ischemia]

1. Renal tissue → RAAS ⊕
2. Brain → HIE
3. Pulmonary system → mc affected
   → First system to be affected
   → pulmonary edema ⊕
   → Dyspnea ⊕

→ chronic failure → HEART FAILURE CELLS [macrophages ī hemosiderin]
↳ seen in pulmonary tissue

RIGHT VENTRICULAR FAILURE

→ mc cause → LVF
→ Pulmonary HTN → COR PULMONALE

CIF

Liver → congestive hepatomegaly [Acute]
→ NUTMEG LIVER [chronic]

Spleen → congestive splenomegaly
GANDY GAMMA BODY ⊕

Pedal edema ⊕
Anasarca ⊕

RHEUMATIC FEVER

→ children [5-15 yrs]
→ Immunological disorder
→ also Sore throat by Group A β Hemolytic Streptococcus
↓
Ab → 'm' protein
→ = Glycoproteins of ♡ | CNS | Joints

CROSS REACTIVITY dlt MOLECULAR MIMICRY

→ Type II HR
→ DIAGNOSIS

EVIDENCE OF RECENT STREPTOCOCCAL INFECTION
+
REVISED JONES CRITERIA [2 major or 1 major + 2 minor]

REVISED JONES CRITERIA

MINOR CRITERIA

- → Fever
- → Arthralgia
- → ↑ ESR
- → ↑ PR interval
- → ↑ C - RP

MAJOR CRITERIA

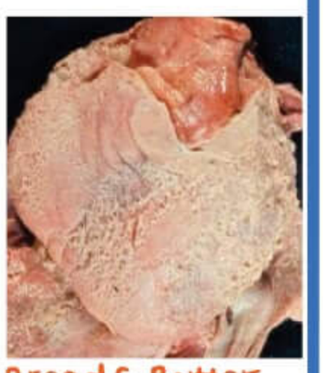
J, O } JOINTS [mc] → large joints → MIGRATORY POLY ARTHRITIS
NON - EROSIVE ARTHRITIS → dramatic response to ASPIRIN

- N → Nodules [subcutaneous, painless, seen on extensor surface]
- E → Erythema marginatum
- S → Sydenham's chorea [Late sign, CNS (Basal ganglia) involved]
- C → Carditis [Pancarditis]

PANCARDITIS

PERICARDITIS

- → Fibrin deposition
- → BREAD & BUTTER PERICARDITIS [sero fibrinous]
- → Pericardial rub ⊕


Bread & Butter Pericarditis

MYOCARDIUM & MYOCARDITIS

ASCHOFF BODY

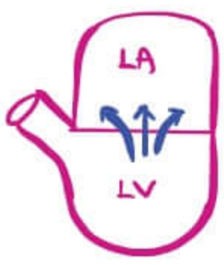
- → Seen around the blood vessels
- → Seen in any layer of heart [mcly in myocardium]
- → Seen in acute phase (Acute RHD)
- → Fibrinoid Necrosis Surrounded by
  - ↳ plasma cells
  - ↳ T - cells
  - ↳ Plump macrophages
    [ANITSCHKOW / CATERPILLER CELL]

→ MYOCARDITIS → HEART FAILURE → MORTALITY [COD]

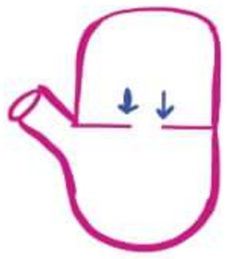
ENDOCARDITIS

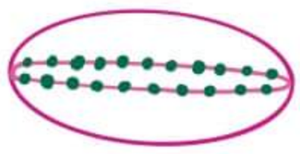
- → VALVES INVOLVEMENT → mitral > Aortic > Tricuspid > Pulmonary
- → ACUTE RHD

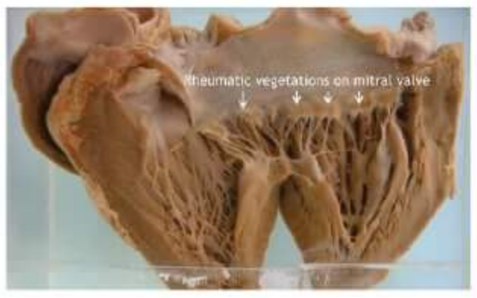
mitral Regurgitation ⊕
↓
Atrial wall damage
↓
Mc CALLUM PLAQUE



→ CHRONIC RHD → Fibrosis → mitral stenosis







VEGETATIONS IN RHD

→ small
→ Sterile (Fibrin, platelets, inflammatory cells)
→ present along line of closure
→ no embolisation

MITRAL STENOSIS ⟶ FISH-MOUTH / BUTTON HOLE STENOSIS
[Seen only in Chronic RHD]

INFECTIVE ENDOCARDITIS

NORMAL PROTECTIVE FACTORS

1. Normal Endothelial Lining
2. Transient Bacteremia
3. normal activity of Immune System

RISK FACTORS

→ RHD [mc] } Damage to Endothelial Lining
→ Congenital cardiac defect
→ Ventricular Septal defect
→ artificial cardiac valve

→ IV Drug abusers } Prolonged bacterial Presence
→ Septisemia

→ Immuno Suppression → abnormal Immune system activity

SUB TYPES

ACUTE IE

→ NO previous damage
→ dlt Staph. areus (highly virulent)

SUB ACUTE IE

→ Previous damage ⊕ [RHD | VSD]
→ dlt Streptococcus viridans

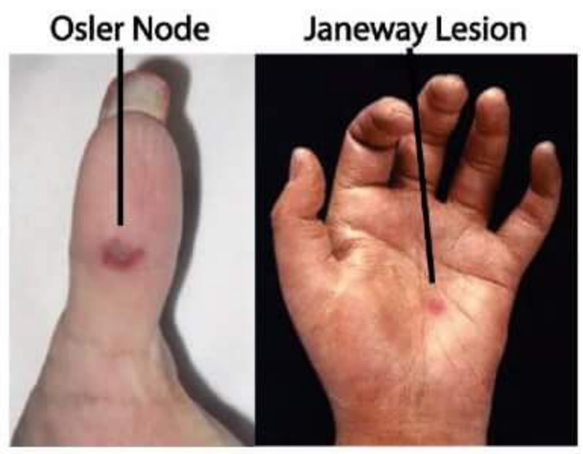
PROSTHETIC VALVE → dlt Staph. epidermidis
IV DRUG ABUSERS → dlt Staph. aureus
→ mc valve involved → Tricuspid valve

ULCERATIVE COLITIS } dlt Streptococcus bovis
COLON CANCER

HACEK BACTERIA → negative on blood culture

CLINICAL FEATURES

- → High grade fever
- → Murmurs ⊕ [changing | dynamic nature]
- → Weight loss
- → ROTH SPOTS ⊕
- → OSLER NODES ⊕ [painful]
- → JANEWAY LESION ⊕ [painless]

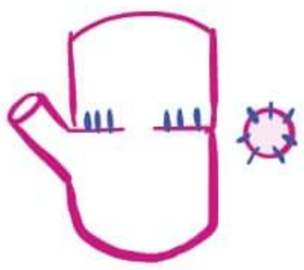


DIAGNOSIS → DUKE'S CRITERIA

- → Blood culture ⊕ [minimum of 2 cultures, 12 hrs apart]
- → ECHOCARDIOGRAPHY FINDINGS
- → Fever | ♡ predisposition | vascular & Immunological features

VEGETATIONS

INFECTIVE ENDOCARDITIS



im - 13, 14.55

- → Large
- → multiple
- → Friable
- → Embolism ⊕
- → seen on valvular cusps
- → seen on peripheral aspect
- → a/w RING ABSCESS

RHEUMATIC HEART DISEASE

- → small
- → Sterile
- → Firm
- → no embolism
- → seen on Line of closure

SLE [LIBMANN SAC ENDOCARDITIS]

- → Small — im-15.50
- → Sterile — 17.20
- → Lower surface of valve affected more
- → Firm
- → no embolism

NON BACTERIAL THROMBOTIC ENDOCARDITIS / MARANTIC ENDOCARDITIS

- → seen on Line of closure
- → small
- → fibrin & platelets ⊕
- → Sterile
- → Embolism ⊕
- → Seen in Pancreatic cancer & AML - M_3

CARDIAC TUMORS

I PRIMARY CARDIAC TUMORS

II SECONDARY CARDIAC TUMORS

- → more common than 1° tumors
- → mc 1° → Lung cancer
- → pericardium affected

PRIMARY CARDIAC TUMORS

1. MALIGNANT

- → Adult → ANGIOSARCOMA
- → children → RHABDOMYOSARCOMA

2. BENIGN

- → Adult → MYXOMA
- → children → RHABDOMYOMA

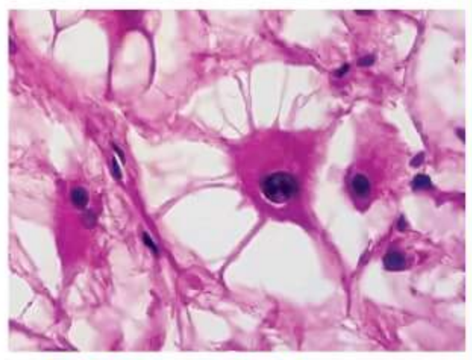
MYXOMA

Site of origin → Atrium [LA >> RA]

TYPES

1. SPORADIC → Single , mc
2. FAMILIAL → BIL
   → a/w CARNEY SYNDROME
   - ↳ myxoma
   - ↳ skin lesions
   - ↳ ↑ Endocrine activity

M/E → LEPIDIC CELLS in MYXOID MATRIX



SPIDER CELLS

RHABDOMYOMA

SITE OF ORIGIN → ventricles [RV = LV]

HISTOLOGY → SPIDER CELLS

a/w TSC_1 & TSC_2 genes

KIDNEY & URINARY BLADDER
BASIC CONCEPTS

KIDNEY

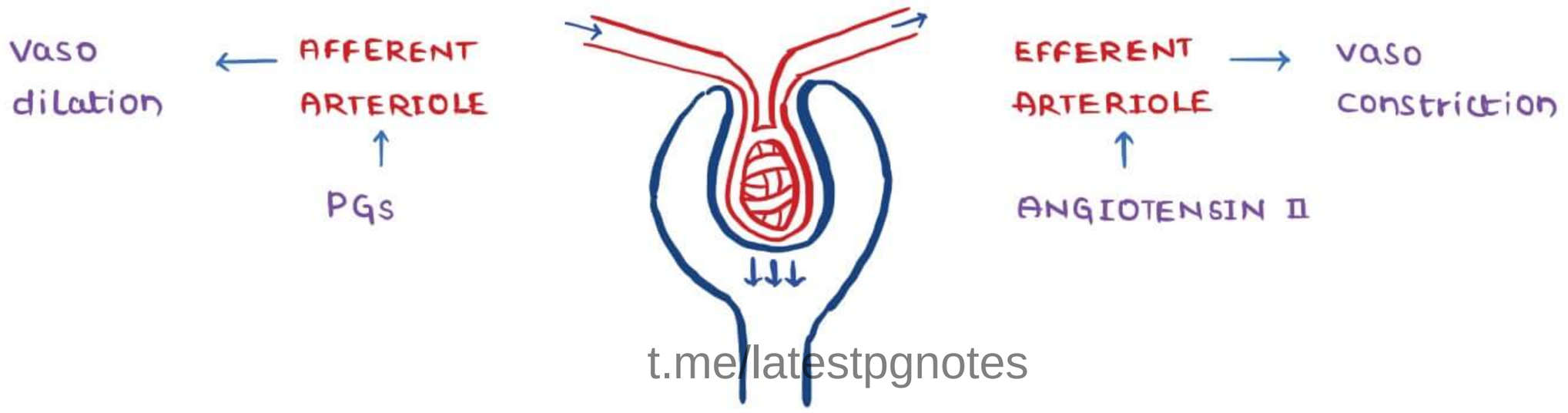
PELVIS

→ From Anterior to Posterior

Vein ⟶ Artery ⟶ Pelvis

→ determines the approach during surgery
→ Nitrogenous waste excretion
→ Acid Base Balance maintainance
→ EPO [from peritubular cells]
→ Renin [From Juxta glomerular cells]
→ 1 α OH ASE → aids in the formatn of active form of vitamin D

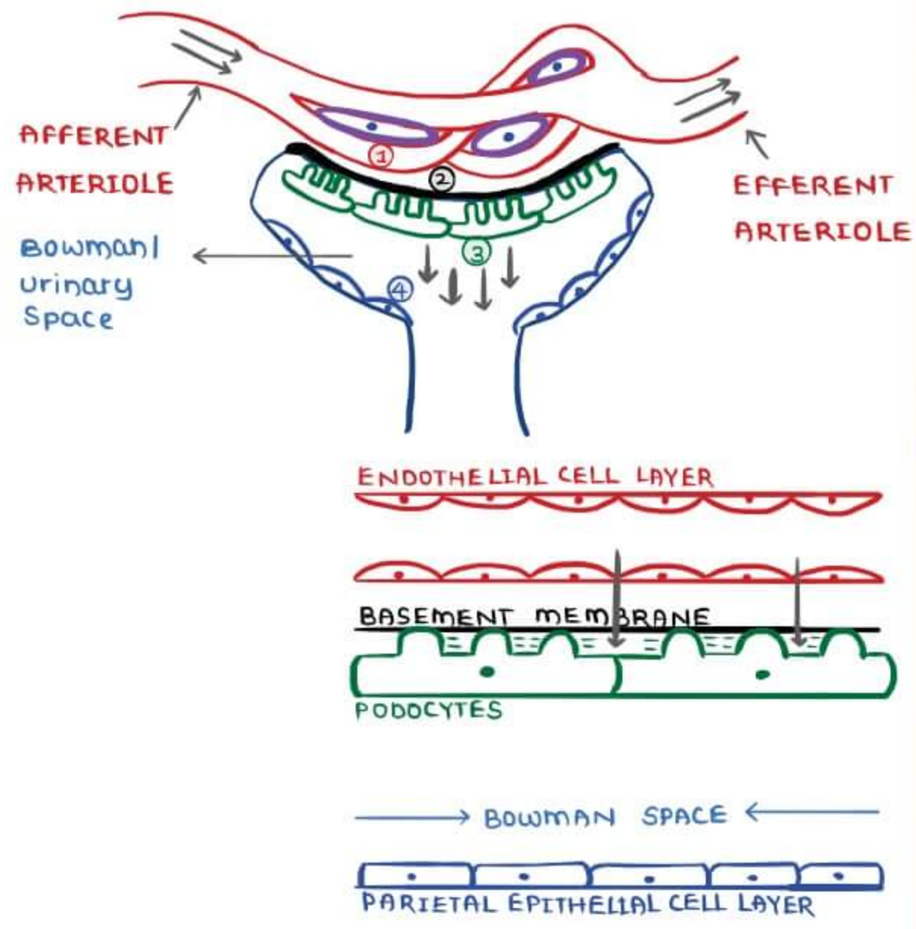
GLOMERULAR DISORDERS



→ Diameter of Afferent arteriole is under the control of → PGs
→ Diameter of Efferent arteriole is under the control of → Angiotensis II
→ GFR → 125 ml | min

GLOMERULAR UNIT - COMPONENTS

1. ENDOTHELIAL LAYER
2. BASEMENT MEMBRANE
3. VISCERAL EPITHELIAL CELLS | PODOCYTES
4. PARIETAL EPITHELIAL CELLS
5. MESANGIAL CELLS



LAYERS OF GLOMERULAR FILTRATION BARRIER

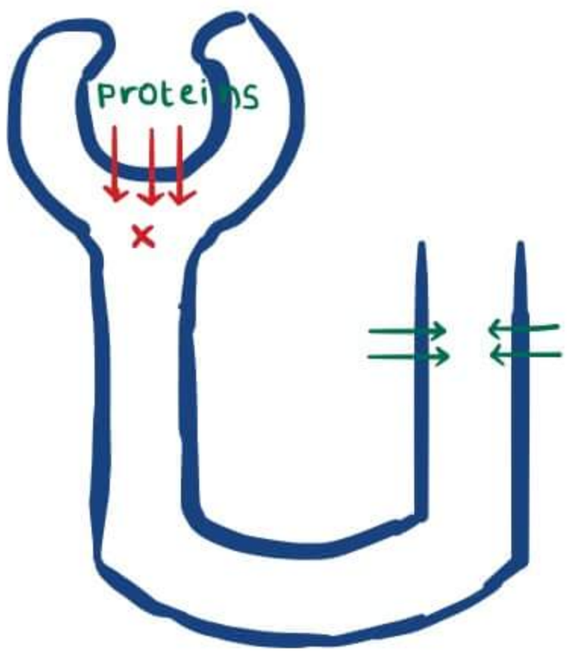
1. ENDOTHELIAL LAYER
2. BASEMENT MEMBRANE
3. VISCERAL EPITHELIAL CELLS | PODOCYTES

FILTRATION AT GLOMERULUS DEPENDS ON

1. Size of molecule
2. Charge of molecule
   → Podocytes contributes → Negative charge
   ↳ Anions ⊖ → not Filtered easily
   ↳ Cations ⊕ → Filtered easily [Glucose | AA | Na^+]

NON PRESENCE IN URINE DUE TO

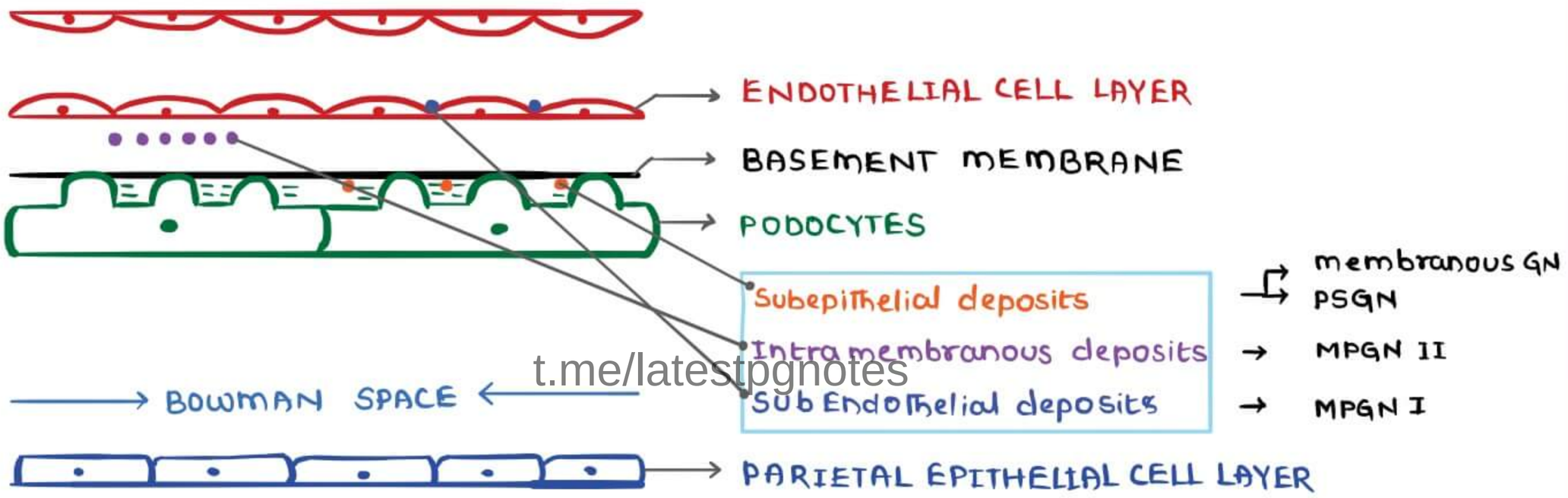
1. Albumin → negative charge
2. Globulin → Size & negative charge
3. Fibrinogen → Size & negative charge



TAMM HORSFALL Protein

- → tubular protein
- → Filtered from ascending Limb OF LH
- → < 150 mg | day urine
- → Hyaline cast ⊕
- → Physiological cast
- → Seen in normal persons

IMMUNO COMPLEX DEPOSITS - LOCATION



ADULT POLYCYSTIC KIDNEYS

- → Autosomal Dominant
- → BIL

GENETICS

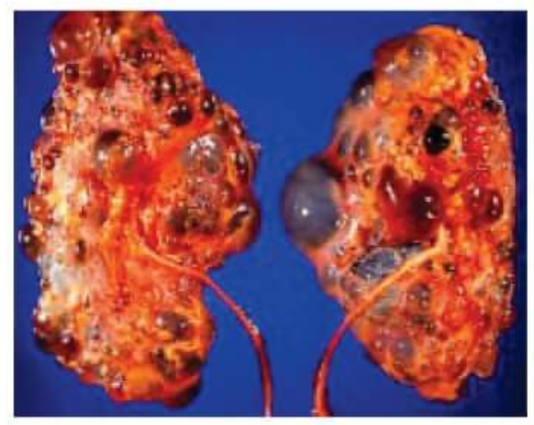
- → PKD_1 gene [chr. 16p] → codes for Polycystin 1 Protein
- → PKD_2 gene [chr 4q] → codes For Polycystin 2 Protein [BADE]

- → Polycystin 1 expressess mainly on distal tubule cells & play a role in cell - cell & cell - matrix interactions
- → Polycystin 2 expresses on all cells of nephron & play a role in Ca^{2+} channel function

- → Mutation in above genes → ↑ cell proliferat^n → ↑ secret^n → CYSTS

GROSS FEATURES

- → BIL Enlarged Kidneys
- → multiple cysts +nt in cortex & medulla
- → variable lining of cysts



C|F

→ Asymptomatic till adult life
→ FLANK PAIN [mc manifestation]
→ HEMATURIA
→ HTN
→ PROTEINURIA

EXTRA RENAL MANIFESTATIONS

→ Cysts in other organs
  ↳ Liver [mc]
  ↳ Spleen
  ↳ Pancreas
  ↳ Ovary
  ↳ Lungs [extremely rare]
  ↳ NO CYSTS IN BRAIN

→ BERRY ANEURYSM
→ MITRAL VALVE PROLAPSE
→ COLONIC DIVERTICULOSIS

COMPLICATIONS

→ HTN | Coronary Artery Disease [commonest cause of Death]
→ ↑ Infections
→ ↑ Nephrolithiasis [a|w Uric acid stones]
→ ↑ Renal cancer [BIL, multifocal & Sarcomatoid type]

TREATMENT

→ BP control
→ Renal Transplantation

CHILDHOOD POLYCYSTIC KIDNEY

→ Autosomal Resistant
→ PKHD$_1$ gene located on chr. 6p [KIDDE | BACCHA]
→ PKHD$_1$ gene mutation → Fibrocystin defect
→ Mainly involves Kidney & Liver

→ KIDNEY INVOLVEMENT

→ Enlarged Kidney
→ multiple cysts tnt in cortex & medulla
→ CYSTS PRESENT AT RIGHT ANGLE TO CORTEX → SPONGE APPEARANCE
→ Epithelial lining of cysts → cuboidal Epithelium [collecting duct origin]

→ LIVER INVOLVEMENT
  → cysts + nt
  → congenital hepatic fibrosis
    - can develop Splenomegaly Secondary to Portal HTN
    - Bad prognosis [fatal]

→ one of the cause OF 'POTTER SEQUENCE'
  → OLIGOHYDRAMNIOS → pulmonary hypoplasia, facial anomolies

MEDULLARY CYSTIC KIDNEY

→ Shrunken Kidney → End stage Renal Diseas
→ cortico - medullary cysts + nt

ADULT VARIANT

→ Autosomal Dominant
→ aka AUTOSOMAL DOMINANT TUBULO - INTERSTITIAL KIDNEY DISEASE
  ↳ interstitial fibrosis
  ↳ tubular atrophy
  ↳ Glomeruli preserved

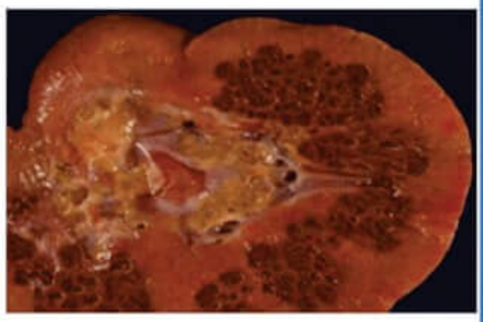
→ MCKD $_{1/2}$ Gene mutation → Polyuria, salt wasting

FAMILIAL JUVENILE NEPHRONOPHTHISIS

→ Autosomal recessive
→ ciliopathy

MEDULLARY SPONGE KIDNEY

→ seen in adults
→ Sporadic
→ Renal medulla involved
→ cystic dilatations involving collecting ducts → SPONGE APPEARANCE



→ usually asymptomatic
→ Some may have
  - ↑ infections
  - ↑ calcium oxalate & calcium phosphate stones → Hematuria

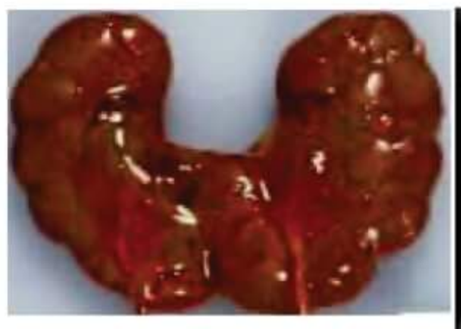
→ BOOSTER INFO :
  → DD → NEPHRONOPHTHISIS
  → Diffentiating features of MEDULLARY SPONGE KIDNEY
    - always involves papillary tips
    - IVP shows PAINT BRUSH APPEARANCE

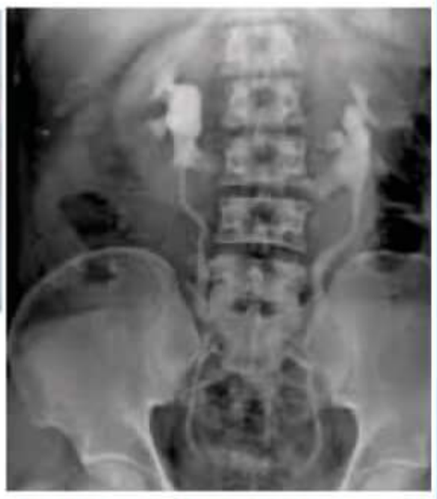
ECTOPIC KIDNEY

→ mcly involves left kidney
→ mc abnormal location → PELVIC BRIM
→ a/w ureteric obstruction → ↑ infections

HORSE-SHOE KIDNEY

- → mc congenital renal anomaly [1 in 500 live births]
- → Fusion of Kidney at the lower pole occurs during embryological development
  - → 'U' shaped Kidney
  - → Failure of Ascent of Kidney
  - → Ectopic site of Kidney → Anterior to L_4 | great vessels
  - → ureteric obstruction + nt → ↑ infections & ↑ stones





FLOWER VASE APPEARANCE

- → ASSOCIATE WITH
  - → Edward syndrome
  - → Down s syndrome
  - → Turner syndrome

- → RADIOLOGICAL FEATURES
  - → FLOWER VASE APPEARANCE
  - → HAND JOINING SIGN

NEPHRITIC SYNDROME

Ag → Ab formation → Immune complex formation

↓

compliment Activation

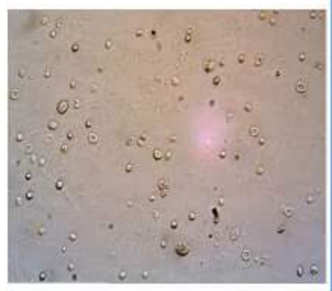
↓

GLOMERULONEPHRITIS

↓ GFR — PROTEINURIA — RBC + in urine

↓ GFR:
- ↓ Urine output → OLIGURIA [<400 ml / 24 hr]
- RAAS⊕ → HTN

RBC + in urine → HEMATURIA



bysmorphic RBC

HEMATURIA → > 3 RBC / hpc in 3 samples, 1 week apart

bysmorphic RBCs → glomerular hematuria

isomorphic RBCs → NON glomerular hematuria

POST STREPTOCOCCAL GLOMERULO NEPHRITIS [PSGN]

- → pediatric age group
- → H/O Skin | Sore throat ī Group A β Hemolytic Streptococcus [4,12,1]
- → DIFFUSE GLOMERULAR INVOLVEMENT ī WBC INFILTRATION
- → Type 3 HR
- → time taken from H/O Skin | Sore throat to clf of GN → 10 - 14 days

CLINICAL FEATURES

- → HTN | Hematuria [cola colored urine] | Oliguria | proteinuria

DIAGNOSIS

1. URINE EXAM

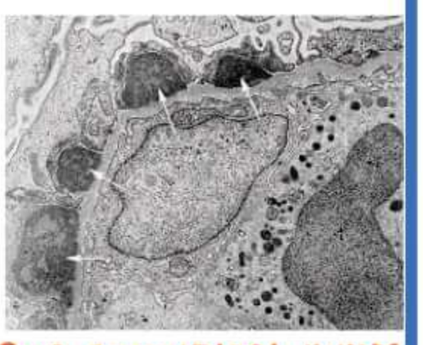
→ Altered color of urine
→ ↓↓ urine output
→ RBC cast ⊕

2. BLOOD

→ Anti - DNase B Ab [more significant]
→ Anti - Streptolysin O Ab
→ ↓ C_3 protein at active stage → Transient hypocomplementemia

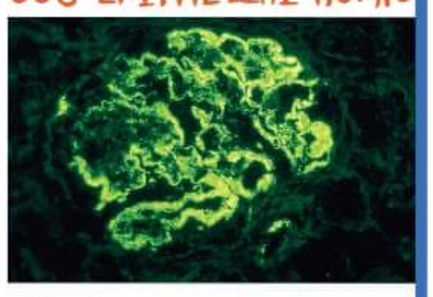
3. RENAL BIOPSY

→ confirmatory
→ Immune complexes ⊕
  ↳ Sub endothelial
  ↳ Intra membranous
  ↳ Sub epithelial HUMPS [mc]



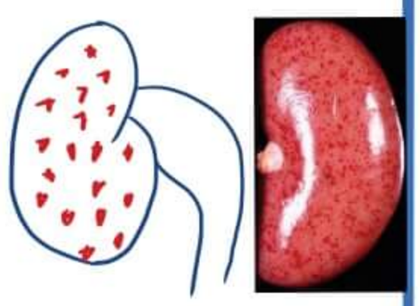
SUB EPITHELIAL HUMPS

→ STARRY SKY APPEARANCE ⊕



STARRY SKY APPEARANCE

→ FLEABITTEN KIDNEY [non specific]
  ↳ PSGN
  ↳ vasculitis
  ↳ IE
  ↳ malignant HTN
  ↳ Leukemia



FLEABITTEN KIDNEY

TREATMENT

→ mostly → complete Recovery ⊕
→ Symptomatic Rx

DIFFUSE PROLIFERATIVE GN [ACUTE GN]

1. POST INFECTIOUS → PSGN
2. NON INFECTIOUS → SLE

RPGN & BERGER'S DISEASE

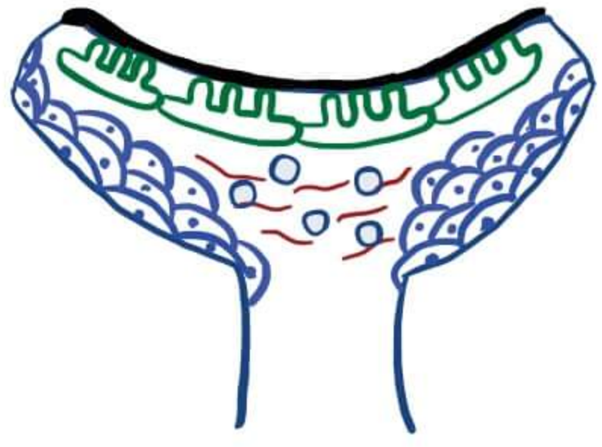
RAPIDLY PROGRESSIVE GN

ONSET OF SIGNS & SYMPTOMS —Months→ Renal Failure

PATHOGENESIS

Severe glomerular inflammation
↓
Leakage of Thombin & Fibrinogen

Fibrin Deposition
WBC Infiltration
Parietal cells ⊕
} CRESCENT FORMATION



↓ GFR → Renal Failure

Normal

RPGN [CRESCENTIC GN]

Obliterat^{n} ⊕

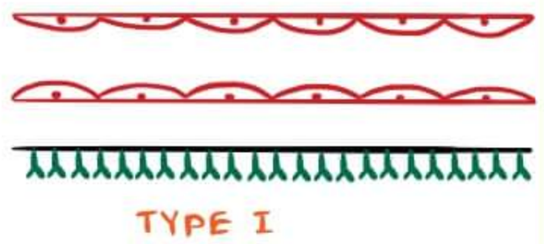
SUB TYPES

TYPE I → ANTI GBM DISEASE

GOOD PASTURE SYNDROME [Example]

→ IF → Linear Immuno Florescence

→ R_I → Plasmapharesis



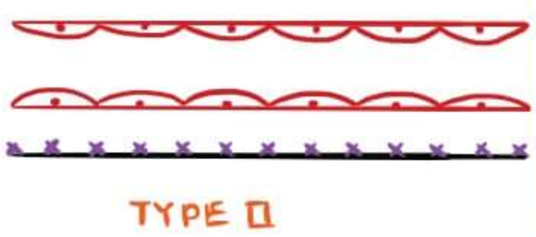
TYPE I

TYPE II → Immune complex deposition ⊕

↳ SLE

↳ Ig A Nephropathy

↳ HSP



TYPE II

→ Granular IF ⊕

→ R_I → R_I the primary cause

TYPE III → PAUCI IMMUNE RPGN

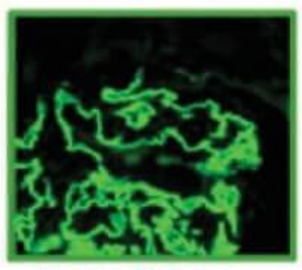
→ NO GBM Ab

→ NO Immuno complexes

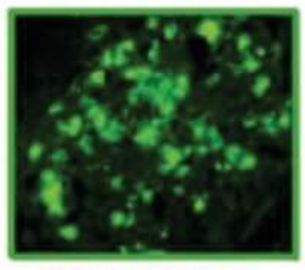
→ ANCA ⊕

↳ c-ANCA ⊕ → wegener's granulomatosis

↳ p-ANCA ⊕ → microscopic Polyarteritis



LINEAR



GRANULAR

ABSENT

CIF → HIO disease → Rapid deteriorat^{n} of Renal function

DIAGNOSIS → 1. Urine exam 2. Blood exam 3 Renal Bx

BERGER'S DISEASE / Ig A NEPHROPATHY

→ mc cause of GN in ADULTS

→

HIO Mucosal Infection [Resp. [mc] | GIT | urogenital tract]

↓

↑↑ Ig A

↓

< 72hrs

Immune complex [mesangium] ⊕

↓

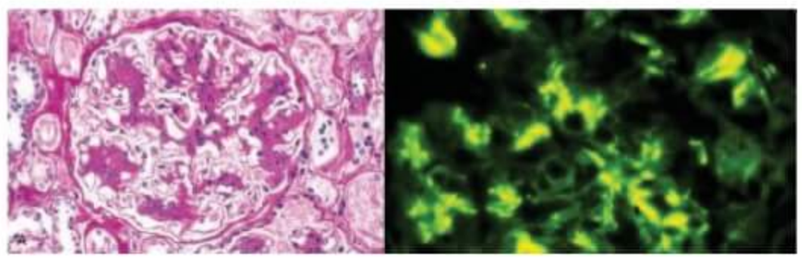
Glomerular Injury

PSGN	Ig A NEPHROPATHY
→ Pediatric	→ Adults
→ 10 - 14 days	→ < 72 hrs
→ ↓ S. C_3 levels	→ normal complement protein

C/F → RECURRENT HEMATURIA [Gross > microscopic]

DIAGNOSIS

RENAL BIOPSY → mesangium
↳ hypercellularity ⊕
↳ Electron dense deposits ⊕



MEMBRANOUS GLOMERULOPATHY & MEMBRANOPROLIFERATIVE GLOMERULOPATHY

MEMBRANOUS GLOMERULOPATHY

→ mc cause of nephrotic syndrome in Elderly
→ mc cause of nephrotic syndrome in SLE
→ mc cause of nephrotic syndrome in Hepatitis B
→ mc cause of nephrotic syndrome in Solid cancer

ETIOLOGY

→ 1° IDIOPATHIC [mc]

→ 2° Drugs [NSAIDS, Penicillamine]
Infections [Hepatitis B, malaria, Toxoplasmosis]
SLE, Auto Immune Thyroiditis
Cancers [melanoma, colon cancer]

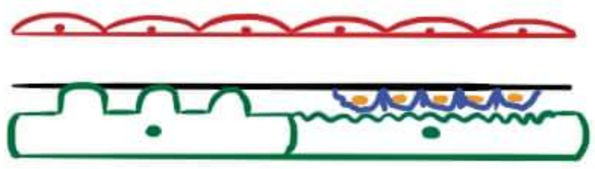
PATHOLOGY

AUTO - Ab ⊕ [HLA - DQ A1] ⟶ Phospholipase ® on visceral epithelial cell
↓
podocyte damage
↓
C/F [Non selective Proteinuria]

HEYMANN NEPHRITIS [Study model in Rat Kidney]
↓
Ab against
MFGALTN

DIAGNOSIS

1. URINE
2. BLOOD
3. KIDNEY BIOPSY
↳ LM → Thickened glomeruli [non-specific]
↳ EM → Effacement of podocytes ⊕
→ Spike & Dome appearance ⊕
↳ IF → sub epithelial I/C



→ Poor response to STEROIDS
→ Rx the primary cause

MEMBRANOPROLIFERATIVE GLOMERULOPATHY / MESANGIO - CAPILLARY GLOMERULOPATHY

→ MIXED PICTURE [Nephrotic Syndrome (predominant) & Nephritic syndrome]

ETIOLOGY

→ 1° → IDIOPATHIC [mc]

→ 2° → Hepatitis C | Leprosy | Hepatitis B → CLL
→ Partial Lipodystrophy syndrome → d_1 AT deficiency | SLE

PATHOLOGY

TYPE I

↓

© Activation by
classical & Alternate pathways

↓

↓ C_1 / C_3 / C_4

↓

Subendothelial I/C

TYPE II

↓

C_3 Nephritic factor ⊕

↓ stabilizes

C_3 convertase
[Alternate pathway]

↓

↓ C_3

↓

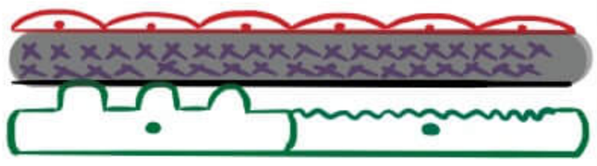
Intramembranous I/C

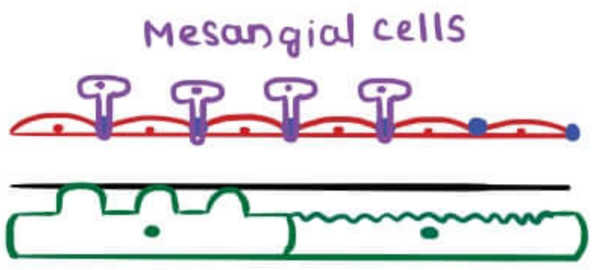
↓

DENSE DEPOSIT DISEASE

DIAGNOSIS

1. Blood
2. Urine
3. Renal Bx
   - LM → Thickened membrane
   - EM → Effacement of podocytes
     Intramembranous dense deposits [MPGN II]





- TRAM TRACK APPEARANCE / SPLITTING OF BM
- MESANGIAL RINGS ⊕

MPGN I

R_4 → Poor response to STEROIDS

ANTI - GBM DISORDERS

→ GBM → Collagen IV

→ collagen 1 → Bone
→ collagen II → cartillage [car TWO lage]
→ Collagen III → Blood vessels
→ collagen IV → GBM [Kidneys & Lungs]

→ COLLAGEN IV → 

GOODPASTURE SYNDROME

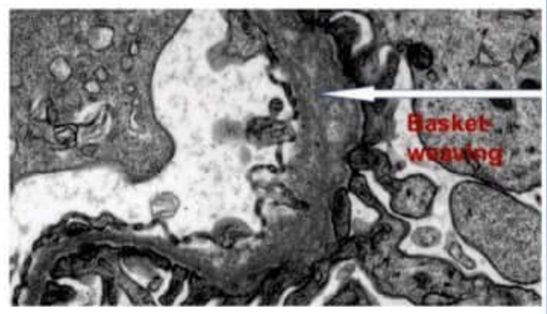
→ type II HR
→ Ab against α_3 chain
→ collagen IV involved

→ causes HEMORRHAGIC INFLAMMATION
↳ Kidneys → Hematuria
↳ Lungs → Hemoptysis

→ Renal Bx → Linear IF ⊕
→ can progress to RPGN & Renal failure [cause of death]

ALPORT SYNDROME

→ X Linked disorder [XLD | XLR] & Autosomal Disorder [AD | AR]
→ mc → XLD
→ α_5 chain of collagen IV defect [XLD]



ORGANS AFFECTED

1. KIDNEYS [mc] → Hematuria
→ BASKET WEAVE APPEARANCE on EM [dlt Splitting of BM]
2. EAR → SNHL
3. EYE → Anterior Lenticonus

NEPHROTIC SYNDROMES : BASIC CONCEPTS

T - Cell Injury + IIC Injury

→ Podocyte damage

→ MASSIVE PROTEINURIA [> 3.5g / 24hrs]

- ↓ Albumin
- ↓ ANP
- → EDEMA

- AT III ↓
- Protein C/S ↓
- Ig ↓

→ ↑ Liver activity

- ↑ Lipids [Blood]
- ↑ LIPIDS [UREA]
- → LIPID CAST / OVAL FAT BODY ⊕
- under polarised microscope
- → MALTESE CROSS ⊕

EDEMA

↓ ALBUMIN → ↓ Oncotic pressure

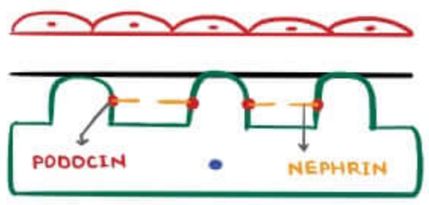
↓ ANP → ↓ Na^+ / water excretion

→ EDEMA [mainly due to ↑ Na^+ & H_2O]

↓ Transferrin [T_f] → IDA [Iron resistant]

↓ TBG → Hypothyroidism [not responsive to T_3 & T_4 Supplementat^n]

PODOCYTE



NPSH 1 gene mutation → Nephrin deficiency → Congenital / Finnish NS

NPSH 2 gene mutation → Podocin deficiency → FSGS

PODOCYTOPATHY

MILD	SEVERE
↓	↓
Loss of Albumin	Loss of Albumin / Ig / Protein C / AT-III
↓	↓
SELECTIVE PROTEINURIA	NON SELECTIVE PROTEINURIA
↓	↓
Responsive to steroids	not so responsive to steroids

MINIMAL CHANGE DISEASE

→ mc cause of nephrotic syndrome in children

ETIOLOGY

→ Idiopathic
→ Drugs [NSAIDS]
→ Hodgkin Lymphoma
→ Respiratory Infections
→ Atopy

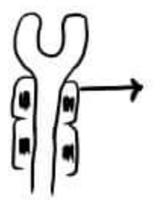
→ PODOCYTE DAMAGE ⊕ → c/s → child → Frothiness in urine ⊕⊕⊕ Swelling

DIAGNOSIS

1. BLOOD → ↓ Albumin
   → ↑ Lipids

2. URINE → 24 Hr
   → OFB ⊕ / LC ⊕

3. Renal BIOPSY
   a. LM → Normal [minimal change disease]
   b. EM → EFFACEMENT OF PODOCYTES [confirmatory]
   c. IF → NO I/C [Nil Deposite Disease]



LIPOID NEPHROSIS

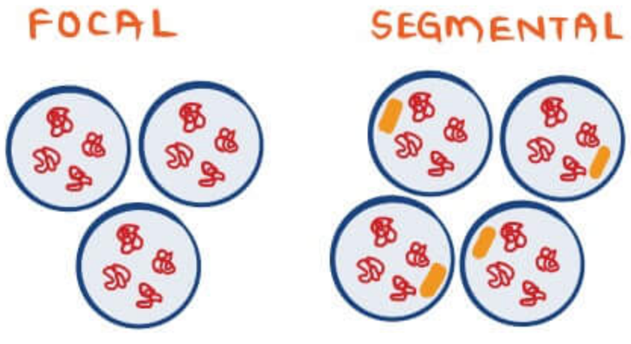
Rx → Selective proteinuria R/ by Steroids [Excellent Response]

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

1° → Idiopathic
2° → Reflux Nephropathy → HIV
→ HTN → IV drug abusers
→ Sickle cell Disease → U/L Renal agenesis

→ Adults → mc cause of Nephrotic Syndrome in adults
→ Non - Selective proteinuria ⊕

DIAGNOSIS



EM → Effacement of Podocytes

HIV → HIVAN [HIV ASSOCIATED NEUROPATHY]

FSGS → Glomerular Tip → Good prognosis
Collapsing Type

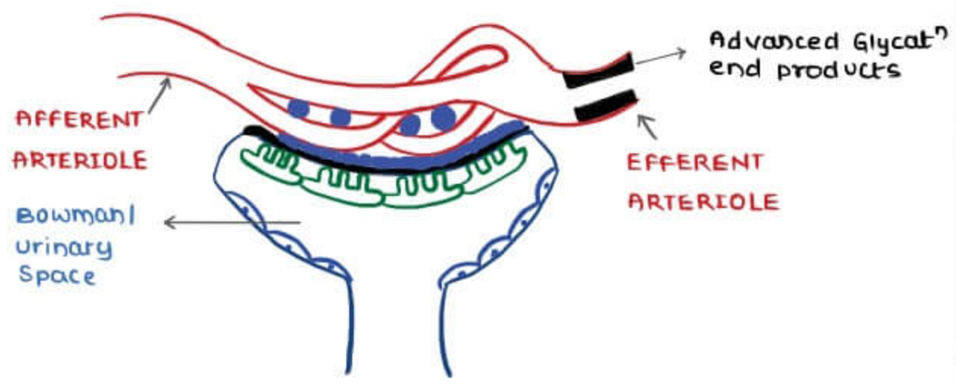
HIV → Glomerular damage
Tubular cystic lesions
visceral Epithelial cell hypertrophy
↓
Poorer prognosis
Not Responsive to Steroids

SYSTEMIC DISORDERS AFFECTING GLOMERULUS

DIABETES MELLITUS [mc]

→ MC cause of chronic kidney disease globally

PATHOLOGY



DM → ↑↑↑ GLUCOSE
↓
Non Enzymatic Glyosylation
↓
ADVANCED GLYCATION END PRODUCTS
↓
Efferent Arteriole
↓
↑ Filtration Injury
↓
NODULAR GLOMERULOSCLEROSIS [most characteristic]
[KIMMEL STEIN WILSON LESION]
↓
DIFFUSE GLOMERULOSCLEROSIS
[↓ GFR]

→ Angiotensin II → Efferent vessel constriction

→ ACE Inhibitors
→ Angiotensin Receptor Blockers [ARB] } ↓↓ Diabetic nephropathy

RENAL PAPILLARY NECROSIS CAUSES

1. DM [mc]
2. Obstruction of Urinary tract
3. Sickle cell disease
4. Analgesics [↓ PGs]

SLE → membranous Glomerulopathy >>>> MPGN [Nephrotic Syndrome]
→ Diffuse Proliferative Glomerulonephritis [Nephritic Syndrome]
↳ WIRE LOOP LESIONS ⊕

AMYLOIDOSIS

→ 2° Amyloidosis affects Kidney

KIDNEY [mc & most severely affected]
↓
Mesangial deposition [1st affected]
↓
Glomerular deposition
↓
NEPHROTIC SYNDROME

RENAL TUMORS : RENAL CELL CARCINOMA

BENIGN TUMORS

1. ANGIOMYOLIPOMA
   - → Spontaneous haemorrhage ⊕
   - → a/w Tuberous Sclerosis
     - ↳ Epilepsy
     - ↳ Angiomyolipoma
     - ↳ Rhabdomyoma [cardiac]
     - ↳ macules

2. ONCOCYTOMA → Large Eosinophilic cells ± prominent mitochondria

MALIGNANT TUMORS

RENAL CELL CARCINOMA [RCC] | HYPERNEPHROMA | GRAWITZ TUMOR

- → 6-7ᵗʰ decade
- → M > F
- → Upper pole involved mcly

RISK FACTORS

1. Tobacco [most important]
2. Asbestos
3. HTN / obesity
4. Estrogen
5. Sickle cell trait
6. ESRD → Dialysis [Dysplasia in cystic lesion]

FAMILIAL VARIANTS

1. VHL SYNDROME
   - → VHL gene on Chr. 3p → ↓ HIF [Hypoxia Inducible factor]
   - → VHL gene mutation → ↑ HIF → ↑ VGF → ↑ cancer
   - → TRIAD
     - ↳ Renal cancer
     - ↳ Pheochromocytoma
     - ↳ Cerebellar hemangioblastoma

2. HERIDITARY LEIOMYOMATOSIS + RCC → FH gene mutation

3. BIRT - HOGG DUBE SYNDROME

TRIAD

- S → Skin cancer
- R → Renal cancer
- P → Pulmonary cysts

4. HERIDITARY PAPILLARY CANCER → MET Gene [proto oncogene] mutation

CIF

- → Hematuria [painless] } CLASSICAL TRIAD
- → Palpable mass
- → costo - vertebral pain
- → Fever
- → weight loss
- → malaise

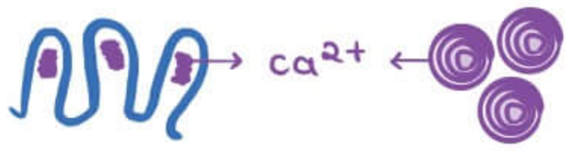
DIAGNOSIS → Renal Biopsy & HPE

SUB TYPES

1. CLEAR CELL CANCER
   - → mc
   - → arises from proximal tube
   - → VHL gene mutation ⊕

clear cytoplasm
ī granules

2. PAPILLARY CANCER
   - → arises from distal tubular cells
   - → multifocal & BIL
   - → Trisomy 7 | 16 | 17
   - → Trisomy 7 alw → sporadic & familial variants
   - → alw Dialysis associated cystic disease



PSAMMOMA BODIES

3. CHROMOPHOBE CARCINOMA
   - → alw Hypoploidy
   - → alw BHD Syndrome
   - → Best prognosis

perinuclear halo

4. BELLINI DUCT CANCER
   - → arises from collecting duct [medulla]
   - → Anaplasia ⊕⊕⊕
   - → worst prognosis

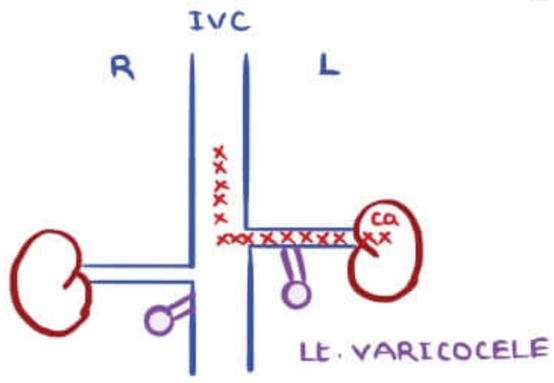
5. MEDULLARY CARCINOMA → alw Sickle cell trait
   → arises from collecting duct

6. XP 11 TRANSLOCATION CANCER
   - → TFE Gene involved
   - → young patients

METASTASIS

→ Lungs > Bones > Liver > Adrenal gland

→ RCC → VENOUS SPREAD



PARANEOPLASTIC SYNDROME

→ ↑ ESR
→ Anemia
→ Polycythemia
→ Leukemoid Reaction
→ Non metastatic Hepatic dysfunct^{n} [STAUFFER SYNDROME]
→ Amyloidosis
→ ↑ Ca^{2+}
→ feminization / masculanization
→ Cushing syndrome

WILMS TUMOR

→ children

RISK FACTORS

1. WAGR SYNDROME
   → Wilms tumor
   → Aniridia
   → Genital anomaly
   → Retardation [mental]

   → WT_1 Gene, WT_2 Gene } tumor suppressor genes
   ↓ mutation
   ↑ WILMS TUMOR

   → located chr 11p

2. BECKWITH - WIEDEMANN SYNDROME → Wilms tumor + hemihypertrophy
3. DENYS - DRASH SYNDROME → WT + Gonadal dysgenesis

Clf → Abdominal mass [earliest]
→ Fever
→ Hematuria
} TRIAD

DIAGNOSIS

Renal Bx ī HPE

TRIPHASIC TUMOR → Blastemal components, Epithelial components, Stromal components

NEPHROGENIC REST → ↑ cancer in opposite kidney

PROGNOSIS → Anaplasia ⊕⊕⊕
↳ a/w p53 mutation
↳ poorer prognosis

ACQUIRED CYSTIC KIDNEY DISEASE

→ a/w Dialysis → DIALYSIS ASSOCIATED CYSTIC DISEASE
→ cortico medullary renal cysts + nt
→ usually asymptomatic
→ ↑ risk of Kidney stones [calcium Oxalate]
↑ risk of Kidney cancer [papillary renal carcinoma]

RENAL AGENESIS

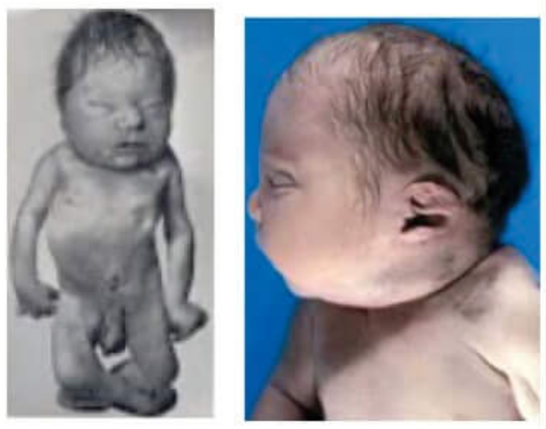
U/L AGENESIS [compatible i life]

usually Left Kidney absent
↓
compensatory enlargement of right kidney
↓
Glomerulosclerosis
↓
CHRONIC KIDNEY DISEASE

BIL AGENESIS [incompatible [life]
↓
1. AMNION NODOSUM
2. POTTER SEEQUENCE

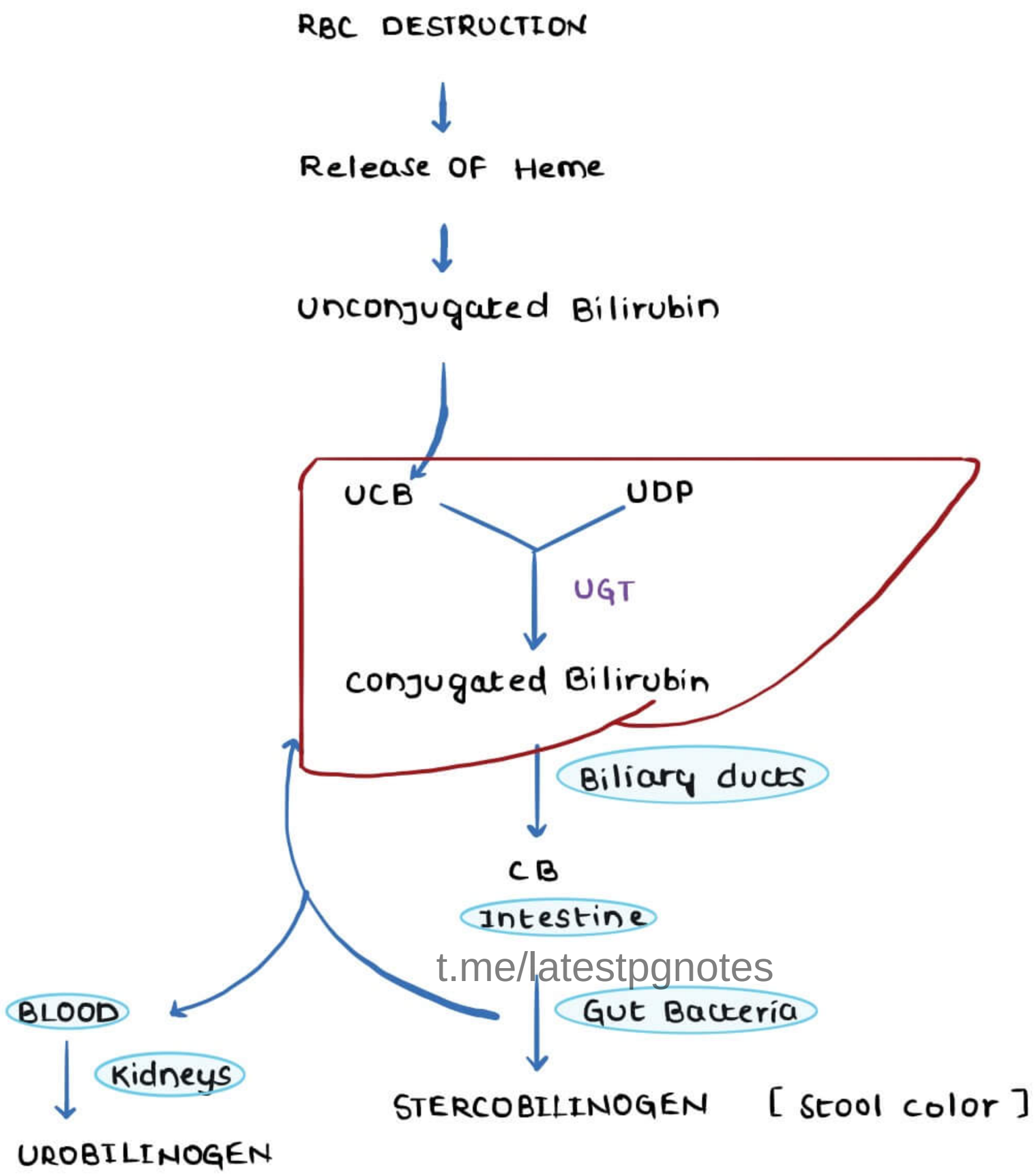
Oligohydramnios →
- Pulmonary hypoplasia [mcc death]
- Limb defects → club feet
- POTTER FACIES
  - Flat face
  - Low ears
  - micrognathia

P → Pulmonary hypoplasia
O → Oligohydramnios
T → Twisted limbs / face
T → Twisted skin
E → Extremity defects
R → Renal agenesis

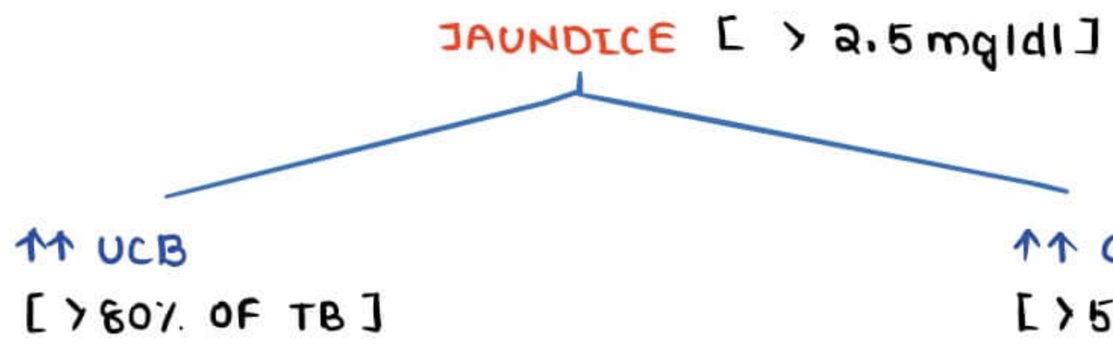


POTTER FACIES

LIVER , BILIARY SYSTEM & PANCREAS
BILIRUBIN METABOLISM



→ UGT – UDP Glucuronyl Transferase
→ UCB – Lipid Soluble
→ CB – water soluble



Yellowish discoloration of skin & Sclera is dlt → affinity of Bilirubin for ELASTIN FIBERS

→ UNCONJUGATED HYPERBILIRUBINEMIA → UCB → > 80% OF TB
→ CONJUGATED HYPERBILIRUBINEMIA → CB → > 50% OF TB

UNCONJUGATED HYPERBILIRUBINEMIA

→ ↑ RBC DESTRUCTION → Hemolytic anemia
→ LIVER IMMATURITY → NewBorn
→ UGT DEFECT [↓] → Genetic Defects

NEW BORN JAUNDICE

1. PHYSIOLOGICAL JAUNDICE → Seen from 2nd Day onwards
2. BREAST MILK JAUNDICE → d/t Glucoronidase | Pregnanediol in breast milk

GENETIC DEFECTS [↓ UGT activity]

1. GILBERT SYNDROME → Adult [Guy] ī Stress
2. CRIGGLER NAJJAR SYNDROME
   a. CNS I → no activity OF enzyme [↑↑ mortality]
   b. CNS II
      → ↓ activity of enzyme
      → ↑ Neurological symptoms d/t UCB deposition in Basal ganglia
      → Rx by Phenobarbitone & Phototherapy
      → Seen in Children | New born
      → Autosomal Recessive

CONJUGATED HYPERBILIRUBINEMIA

→ Jaundice | Pruritis | Pale colored | clay colored Stools
→ Steatorrhea | dark colored urine

CAUSES

1. BILE DUCT OBSTRUCTION
   → Stones
   → Cancer
   → Infections

2. BILIARY TRACT DISEASE
   → Primary Biliary Cirrhosis
   → Primary Sclerosing cholangitis

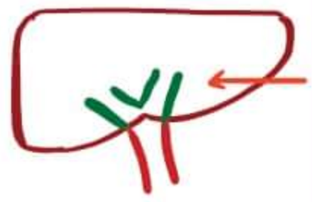
3. GENETIC DISEASE (↓ Excretⁿ OF CB)
   → DUBIN - JOHNSON SYNDROME
      ↳ AR
      ↳ MRP - 2 Defect ⊕
      ↳ Dark pigmented liver [d/t Epinephrine metabolites]

   → ROTOR SYNDROME
      ↳ Normal Liver

VIRAL HEPATITIS → ↑ UCB & ↑ CB

BILIARY TRACT DISORDERS

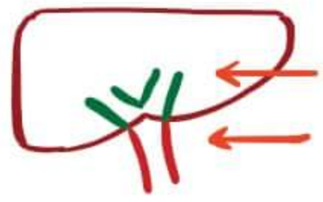
1° BILIARY CIRRHOSIS



→ Auto Immune granulomatous destruction of INTRAHEPATIC BILE DUCT

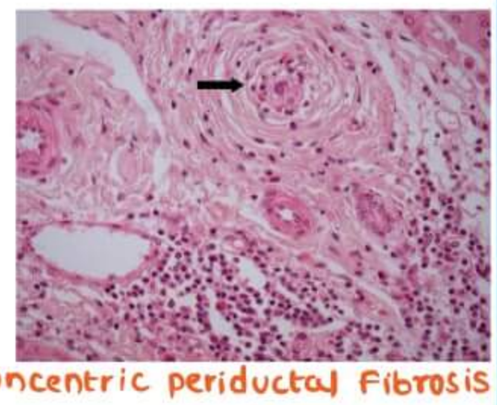
→ F >> M
→ 40 - 50 yrs
→ a|w SJOGREN SYNDROME
→ ANTI MITOCHONDRIAL ANTIBODY [AMA] against Pyruvate Dehydrogenase
→ ↑ CB ⟶ ↑ CIRRHOSIS | MALIGNANCY

1° SCLEROSING CHOLANGITIS



→ M > F
→ Damage to INTRA & EXTRA HEPATIC BILE DUCT

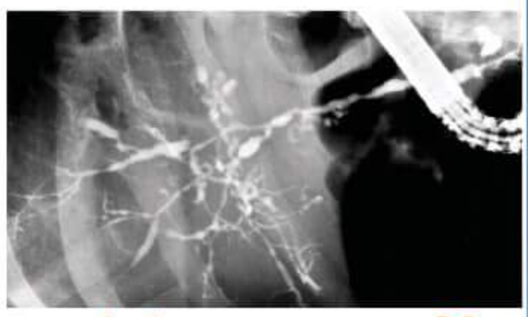
→ Bile ducts undergo CONCENTRIC PERIDUCTAL FIBROSIS



concentric periductal Fibrosis

ONION SKIN APPEARANCE

→ BEADED APPEARANCE on cholangiogram
→ a|w Ulcerative colitis
→ p ANCA ⊕
  ↳ p ANCA in vasculitis is against MPO
  ↳ p ANCA in 1°SC is against Nuclear envelop protein



Beaded appearance on cholangiogram

→ obstructive Jaundice ⊕
→ ↑ cirrhosis | ↑ cancer

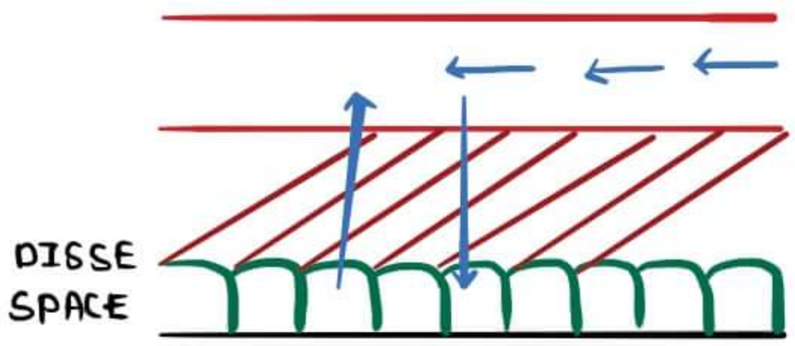
CIRRHOSIS

RISK FACTORS

→ Alcohol [mc]
→ NAFLD [mc reason for cryptogenic cirrhosis]
→ Viral Hepatitis
→ Metabolic diseases

PATHOLOGY

→ Damage to liver parenchyma
→ Bridging fibrous Septa formation
→ Regeneration of Parenchyma nodules ⊕



STELLATE ITO CELL ⟶ (TGF-β) MYOFIBROBLAST

FEATURES

1. PORTAL HTN

↳ congestive splenomegaly
↳ Ascites
↳ Porto systemic shunts
→ esophagus varices
→ Hemorrhoids
→ Caput medussae

2. ↓ PROTEIN SYNTHESIS

→ ↓ Albumin → Ascites
→ ↓ clotting factors → ↑ Bleeding, ↑ PT, ↑ aPTT
→ ↑ r globulins [IgS] [in response to ↑ed Infections]

3. ↓ METABOLISM

→ ↑↑ ESTROGEN
↳ Palmar erythema
Spider angioma
Gynecomastia
↓ gonadal function

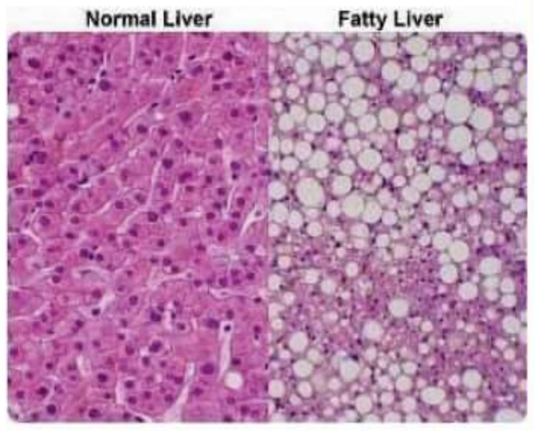
→ ↑ NH_3 → Neurotransmitter → Hepatic Encephalopathy

HEPATIC ENCEPHALOPATHY

→ Precipitated by
↳ GI Bleed
↳ ↓ K^+
↳ ↓ H^+
↳ ↓ Na^+
↳ ↓ O_2

4. HEPATO-RENAL | HEPATO-PULMONARY SYNDROME

ALCOHOLIC LIVER DISEASE



1. ALCOHOLIC STEATOSIS / FATTY LIVER

→ accumulation of fat droplets in hepatocytes

FAT DROPLETS

1. MICRO VESICULAR STEATOSIS CAUSES [no displacement of nucleus]

→ ALD
→ Reye Syndrome
→ Acute fatty liver of Pregnancy
→ Chronic viral hepatitis
→ Tetracyclin / valproate

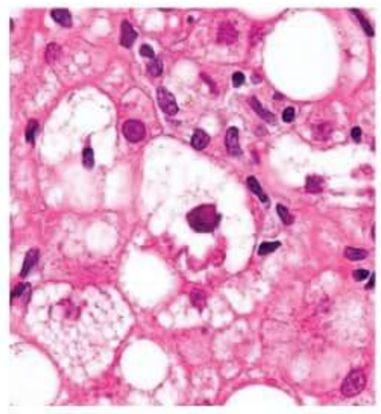
2. MACRO-VESICULAR STEATOSIS CAUSES [Displace nucleus]

→ ALD
→ PEM
→ TPN
→ Jejeno-ileal bypass
→ DM
→ Lipodystrophy

2. ALCOHOLIC HEPATITIS

→ Perivenular / Peri Sinusoidal fibrosis ⊕

→ MALLORY DENK BODY ⊕ → cytokeratin filaments ⟶



→ also seen in

New → Non Alcoholic fatty Liver Disease
Indian → Indian childhood cirrhosis [dlt Copper toxicity]
W → Wilson's Disease
A → Alcoholic Liver Disease , α_1 - AT Deficiency
T → Tumor [Hepatocellular cancer]
C → Chronic Cholestasis [1° Biliary Cirrhosis]
H → Focal nodular Hyperplasia

→ Not seen in 2° Biliary cirrhosis & Hemochromatosis

3. CIRRHOSIS / LAENNEC CIRRHOSIS

→ Irreversible nodular damage to Liver

Cirrhosis

NON - ALCOHOLIC FATTY LIVER DISEASE

→ IDIOPATHIC / CRYPTOGENIC

→ RISK FACTORS
- ↳ Obesity
- ↳ Dyslipidemia
- ↳ Insulin Resistance

→ Asymptomatic → Diagnosis of Exclusion

→ mc cause of Death → cardiovascular cause

→ MIE → Steatosis
→ Non Alcoholic Steato Hepatitis [NASH]

DD

1. HISTORY
2. TESTS

ALD → $\frac{AST}{ALT}$ → > 2 NAFLD → $\frac{AST}{ALT}$ → < 2

HEPATITIS

HEPATITIS A → Acute Hepatitis
HEPATITIS B
HEPATITIS C
HEPATITIS D
HEPATITIS E → Acute Hepatitis

HEPATITIS A

→ transmitted by FECO - ORAL ROUTE
→ MC cause of Hepatitis in CHILDREN

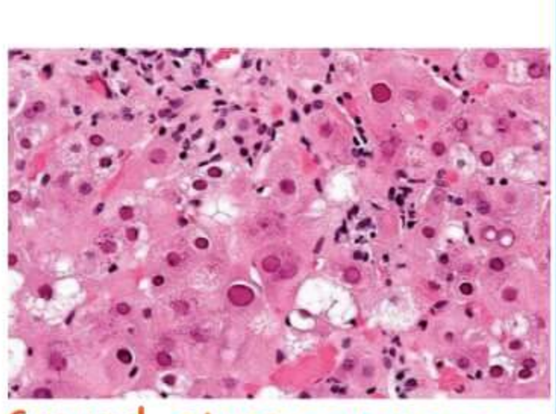
HEPATITIS E

→ transmitted by FECO - ORAL ROUTE
→ MC cause of Hepatitis in ADULTS
→ a/w FULMINANT DISEASE in PREGNANCY

HEPATITIS B

→ TRANSFUSION ASSOCIATED HEPATITIS VIRUS
→ CARRIER STATE ⊕
→ ↑ HCC
→ only DNA virus causing hepatitis

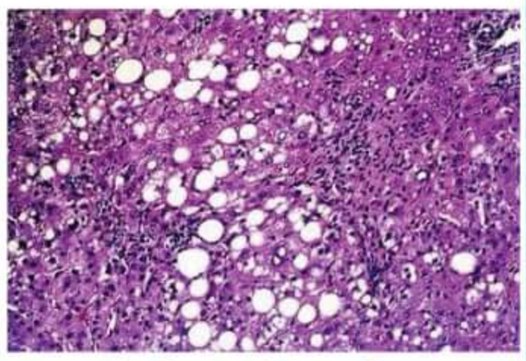
→ MICROSCOPIC FEATURES
1. GROUND GLASS APPEARANCE [HBs Ag]
2. SANDED NUCLEI [HBc Ag]


Ground Glass appearance

HEPATITIS C

→ maximum chance of CHRONICITY
→ a/w CIRRHOSIS [RNA virus causing cirrhosis]

→ MICROSCOPIC FEATURES
1. FOCAL FATTY CHANGE
2. BILE DUCT DAMAGE
3. LYMPHOCYTE AGGREGATION IN PORTAL TRACT


Fatty change

HEPATITIS D

→ defective virus → requires Hepatitis B for pathogenesity

→ CO - INFECTION → Simultaneous infect^{n} [Fulminant]
SUPER - INFECTION → Hep. B → Hep D [↑ chronicity]

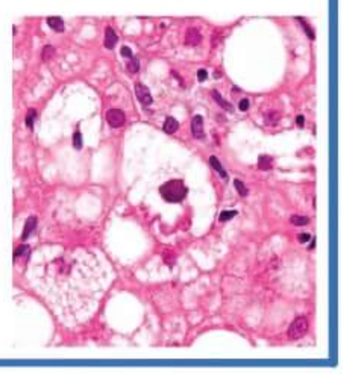
METABOLIC DISEASES OF LIVER

1. α_1 - ANTI TRYPSIN DEFICIENCY [α_1 AT Def.]


→ α_1 - ANTI TRYPSIN →  Protect from PROTEASES

IN NORMAL PERSON → PiMM Allele
ABNORMAL → PiZZ Allele } misfolding of Proteins } CIRRHOSIS, PAN ACINAR EMPHYSEMA
→ PiMZ Allele

→ AR
→ DIAGNOSIS
1. PAS ⊕ / Diastase Resistant granules [pink inclusions]
2. Mallory Denk Bodies [non - specific]



2. HEMOCHROMATOSIS

→ Defect in regulation of Iron absorption

→ HEPCIDIN
  ↳ negative Iron Regulatory protein
  ↳ ↓ Hepcidin → Iron overload

→ 1° → HFE gene defect on chr. 6p.21 [mc] } HEMOCHROMATOSIS
  HJV gene defect

→ 2° → multiple blood transfusions } HEMOSIDEROSIS
  → Africans [dlt Iron utensil usage for cooking]

→ IRON OVERLOAD CAUSES → FREE RADICAL INJURY

→ CIF
  ↳ cirrhosis [↑ mortality]

  ↳ SKIN → ↑ melanin
  PANCREAS → ↓ Dm
  ↑ melanin + Dm → BRONZE DIABETES

→ CARDIAC → Arrythmia, Restrictive cardiomyopathy
  → ↑ mortality

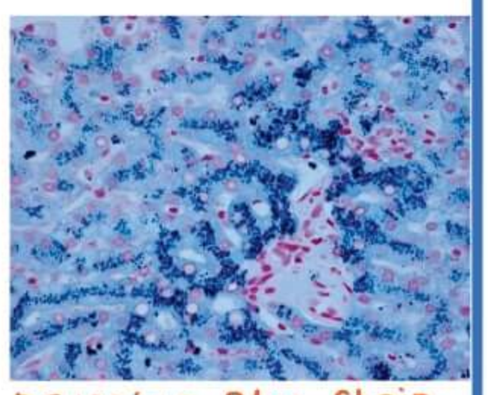
→ GONADS → ♂ → Gonadal Dysfunction
  ↳ Testicular atrophy
    → dlt Iron deposition in PITUITARY
    & ↓ It's function [not dlt Iron deposition in testes]

→ PSEUDO - GOUT

→ ↑ HEPATO CELLULAR CANCER [not common]

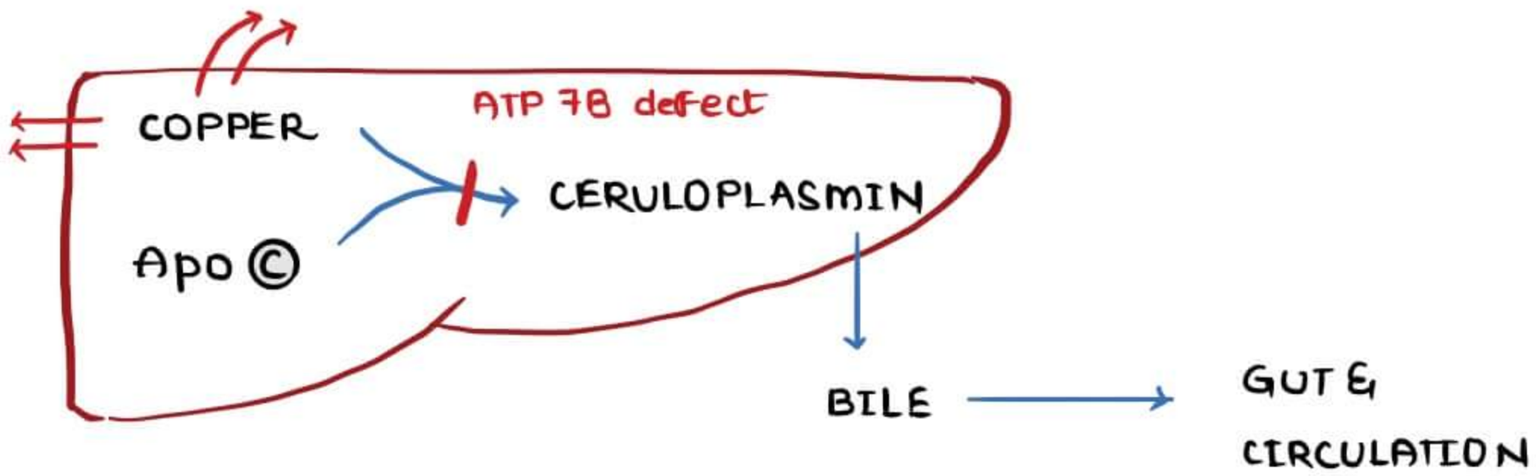
→ DIAGNOSIS → IRON OVERLOAD
  ↳ ↑ S. Iron
  ↳ ↑ % T_F [earliest]
  ↳ ↑ S. Ferretin
  ↳ ↓ Iron binding capacity

  → LIVER BIOPSY
    → Prussian Blue stain used
    → Bluish violet granules ⊕


Prussian Blue Stain

→ Rx → 1. IRON CHELATOR
  → 2. PHLEBOTOMY

WILSON'S DISEASE

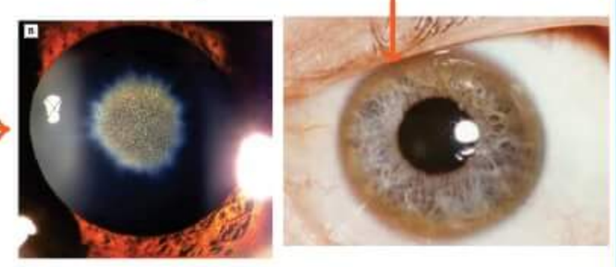


→ Autosomal recessive disorder
→ ATP 7B gene defect [located on chr. 13]

↓

Hepatic Damage → Cirrhosis / ↑ cancer
CNS damage → Basal ganglia damage → Parkinsonism
→ Astrocyte damage [ALZHEIMER II CELLS]

EYES → cornea → decemet membrane → KF RING
→ Sunflower cataract



DIAGNOSIS

1. ↑ urinary copper [most specific]
2. Copper level in 1gm of dried Liver → > 250 µg Cu [confirmatory]
3. S. copper → ↓ / N / ↑

R_I → DMT_1 → ZINC [competitive inhibitor]
[competes i Cu for DMT_1]

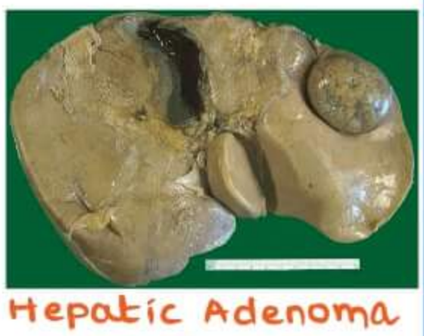
TUMORS

BENIGN TUMORS

CAVERNOUS HEMANGIOMA → mc benign tumor of liver

HEPATIC ADENOMA

→ young female i OCP intake
→ Sub capsular
→ During pregnancy, may rupture → ↑ Hemorrhage
→ β CATENIN MUTATION ⊕ ⟶ HCC [in 10%]


Hepatic Adenoma

MALIGNANT LIVER TUMORS

SECONDARY MALIGNANT TUMORS

→ Metastasis [mc malignant tumors of Liver]
→ CAN BE FROM
↳ Pancreas
↳ Colon [mc 1° causing 2° tumor in Liver]
↳ Breast

→ HEPATOMEGALY i NODULAR EDGES

PRIMARY MALIGNANT TUMORS

1. HEPATOBLASTOMA → mc malignant liver tumor in children
2. ANGIOSARCOMA

RISK FACTORS

- → Arsenic
- → Thorotrast
- → Poly vinyl chloride

3. HEPATOCELLULAR CARCINOMA

→ mc malignant liver tumor in adults

RISK FACTORS

1. Chronic hepatitis [Hep B > C]
2. Alcohol intake
3. Aflatoxins [Peanut ingestion ī Aspergillus flavus]
4. Hemochromatosis
5. Wilson's Disease
6. Heriditory tyrosinemia

PATHOLOGY

1. β CATENIN ACTIVATION
2. ↓ p53 ACTIVITY
3. ↑ IL-6 → ↑ multiplication , ↓ Differentiation

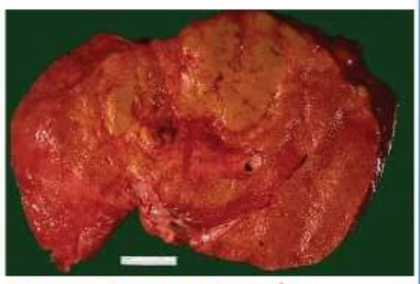
4. DYSPLASTIC NODULE
   a. Low Grade → + cancer
   b. High Grade → +++ cancer

5. CHRONIC LIVER DISEASE ī CELLULAR CHANGE
   a. Small cell change
      → N:C Ratio ↑↑↑
      → +++ cancer
   b. Large cell change
      → N:C Ratio ↑
      → + cancer

→ HBV ⟶ HBX PROTEIN ⟶ ONCOGENIC

C/F

- → M > F
- → Elderly
- → malaise
- → Abdominal pain [mc symptom]
- → weight loss
- → hepatomegaly [mc sign]

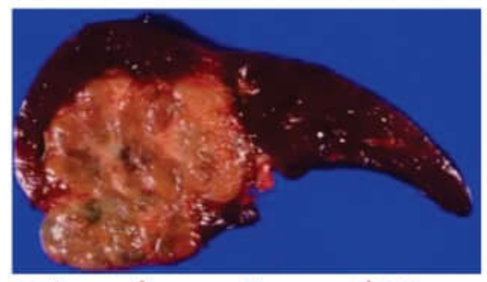


Hepatomegaly

DIAGNOSIS

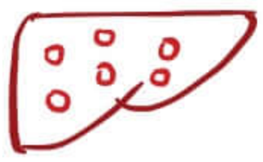
1. α - FETO PROTEIN ↑↑↑
2. ARGINASE - 3 [most sensitive & specific]
3. HEP - PAR - 1
4. GLYPICAN - 3

FIBROLAMELLAR VARIANT OF HCC


Fibrolamellar HCC

- → Young adults
- → m = F [India → F >>m]
- → not a/w Hepatitis B or cirrhosis
- → Left lobe predilection
- → slow growth ⊕
- → Good prognosis
- → Normal AFP levels
- → NEUROTENSIN is the marker
- → M/E → ONCOCYTES ⊕ ↑ collagen

METASTASIS OF HCC

1. 
2. 

- → SATELLITE NODULES ⊕ ↑ central umblication [depression]
- → also spreads to LUNGS
  PERI HILAR LN
  PERI PANCREATIC LN
  PERI AORTIC LN

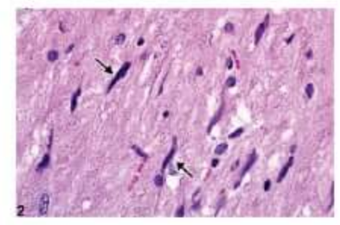
TREATMENT

1. SORAFENIB
2. TRANSPLANTATION

CENTRAL NERVOUS SYSTEM
GENERAL INTRODUCTION

CELLS → NEURONS + GLIAL CELLS

1. OLIGODENDROCYTES → form& myelin in CNS
2. ASTROCYTES → forms blood brain Barrier
   → post injury cells responsible for gliotic React^{n}
3. EPENDYMAL CELLS → ventricular lining
4. MENINGOTHELIAL CELLS → cover brain [protective]
5. MICROGLIA → Phagocytosis
   → aka GITTER CELLS
   → aka ROD CELLS [Neuro Syphilis]


ROD CELLS

MENINGITIS

CSF FINDINGS

	GROSS	CELLS/HL	PROTEIN [mg/dL]	GLUCOSE [mg/dL]	Cl^- [mEq/L]
NORMAL	Clear	0-5	15-40	40-70	115-120
BACTERIAL	Turbid	↑↑↑ [Neut]	↑↑↑	↓↓↓	↓
TB	COB WEB COAGULUM	↑↑ [N+M]	↑↑	↓	↓↓↓
VIRAL	Clear	↑ [L]	↑↑	Normal	↓
FUNGAL	clear	↑ [m]	↑↑	↓	↓


COB WED COAGULUM

TB → CSF PLEOCYTOSIS

VIRAL → Glucose levels are normal
Except for mumps & Herpes virus [↓]

BACTERIAL CAUSES OF MENINGITIS

- → Streptococcus pneumoniae
- → Streptococcus agalactiae
- → E. coli
- → Neisseria meningitidis

VIRAL MENINGITIS

- → commonly caused by Enterovirus
- → Spreads by feco oral route

NEURODEGENERATIVE DISORDERS

→ Neuronal loss + Intra cellular Protein aggregates

ALZHEIMER'S DISEASE

→ mc cause of memory loss

- → SPORADIC → a/w ↑ Age, ↑ Apo E_4 [Apo E_2 ↓ → protective]
- → FAMILIAL → a/w Down Syndrome [Trisomy 21]
  Presenilin 1 gene on chr 14
  Presenilin 2 gene on chr 1

1.

Chr. 21
↓
APP [Amyloid Precursor Protein]
↓
DIFFERENTIAL SECRETASE ACTIVITY

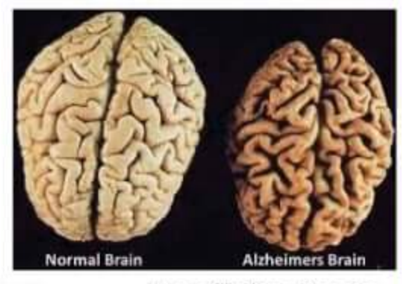
α/r Secretase	β/r secretase
↓	↓
Soluble peptide	Insoluble peptide [Aβ peptides]
	↓
	Amyloid β plaques
	↓
	ALZHEIMER'S DISEASE

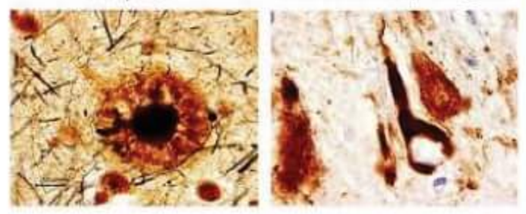
2. TAU PROTEIN → attaches to microtubules & stabilizes them

Tau Phosphorylat^{n} → do not attaches to MT → TANGLES

FINDINGS

1. DIFFUSE CEREBRAL ATROPHY
   - → Affects frontal lobe, parietal lobe, Temporal lobe
   - → Occipital lobe is spared





2. NEUROFIBRILLARY TANGLES
   - → hyperphosphorylated Tau protein
   - → Number correlates ī Severity of dementia
   - → best visualized by Silver stain

3. NEURITIC PLAQUES [Aβ peptides]
   - → central core of amyloid ⊕ → Stained by CONGO RED
   - → DIFFUSE PLAQUE → Only amyloid ī out neuritic process around it

4. CEREBRAL AMYLOID ANGIOPATHY
   - → Aβ plaques around blood vessels → Fragile BV → ↑ Hemorrhage

CIF

→ Short term MEMORY LOSS
  LOSS OF SMELL
} Early stage

→ Language & Behavioral Defect → Advance stage

DEATH → dlt Pneumonia

Rx → AChE Inhibitors
  MEMANTINE

FRONTO TEMPORAL LOBE DEGENERATION

→ Frontal involvement → Behavioral defects
Temporal involvement → language defects
} Early features

→ LATE DEMENTIA

SUB TYPES

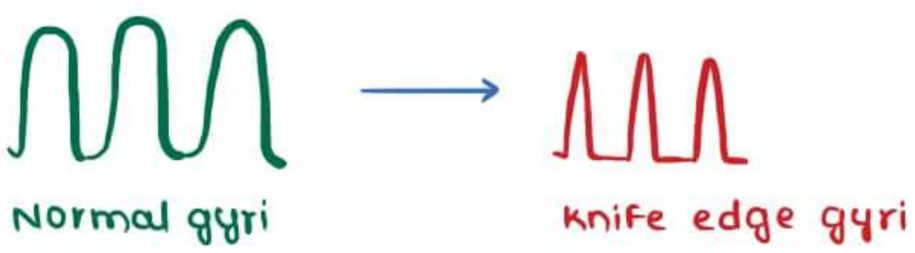
1. FTLD - Tau / PICK'S DISEASE
2. FTLD - TDP

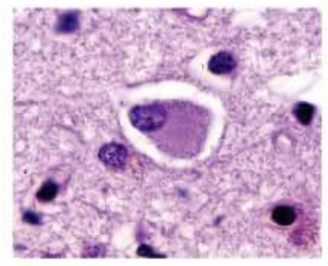
1. FTLD - Tau / PICK'S DISEASE

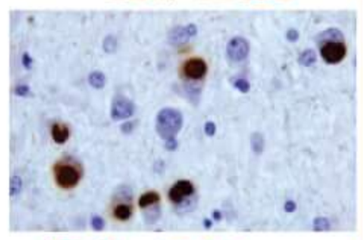
→ Atrophy → Frontal & Temporal lobe
→ Parietal / Occipital lobes are spared


Knife Edge gyri

→ KNIFE - EDGE GYRI / WAFER-THIN GYRI




PICK CELLS


PICK BODY

→ PICK CELLS → swollen up neurons
PICK BODY → Intracellular 3R Tau protein

PARKINSONISM

→ Loss of Dopaminergic neurons in Substantia nigra

FACTORS

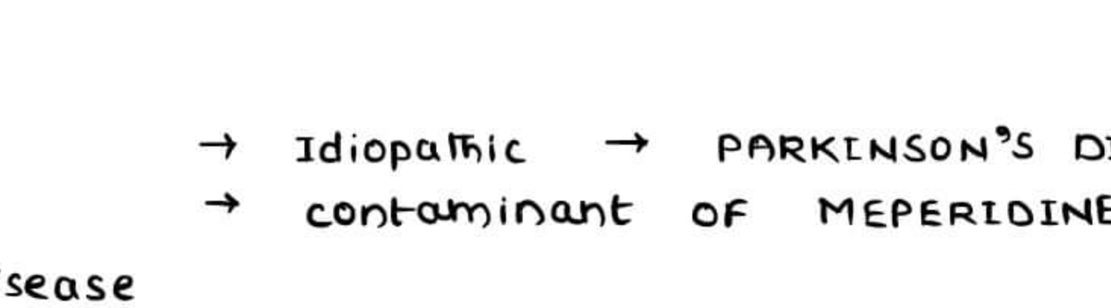
Risk factors

Age → Idiopathic → PARKINSON'S DISEASE
MPTP → contaminant OF MEPERIDINE
Wilson disease
CO poisoning
Drugs → Anti psychotic Drugs

Protective factors → Caffeine & Nicotine

PATHOLOGY → NIGRO - STRIATAL PATHWAY AFFECTED

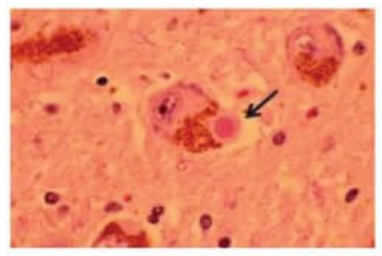
CLINICAL FEATURES



→ mask like facies
→ Stooping posture
→ ↑ Seborrheic dermatitis
→ Dementia [Late feature]

FINDINGS

- → Pallor of Substantia nigra
- → LEWY BODY
  - ↳ made up of α - SYNUCLEIN
  - ↳ Located in Substantia nigra



LEWY BODY

HUNTINGTON'S DISEASE

GENETICS

- → Autosomal dominant
- → CAG Repeats

↑↑↑ [Spermatogenesis]

↓

ANTICIPATION [early onset in next generatⁿ]

- → Chr. 4
- → 4ᵗʰ - 5ᵗʰ decade
- → CAUDATE NEUCLEUS ATROPHY

CIF

- → Chorea - Athetosis [involuntary purposeless movements ī writhing property]
- → Occulomotor abnormality
- → Depression

DEATH → Recurrent Infections

CNS TUMORS

2° → MESTASTASIS [mc]
- → small cell Lung cancer [mc]
- → Breast cancer
- → malignant melanoma
- → Renal cancer

1° TUMORS

RISK FACTORS

I. Smoking | Radiation

II FAMILIAL SYNDROMES

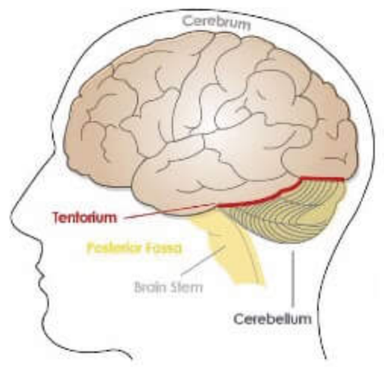
1. TURCOT SYNDROME → APC mutation [↑ colorectal carcinoma]
2. LI-FRAUMENI SYNDROME → P53 mutation
3. GORLIN SYNDROME → PTCH mutation
4. COWDEN SYNDROME → PTEN mutation

CLINICAL FEATURES

- → Headache
- → vomiting
- → seizures
- → ↑ ICT

GENERAL PRINCIPLES

- → mostly SUPRATENTORIAL in location in ADULTS
  mostly INFRATENTORIAL in location in CHILDREN



- → WHO CLASSIFICATION
  - ↳ Based on → Histology + molecular parameters
    - ↳ Atypical cells
    - ↳ mitotic activity
    - ↳ necrosis
    - ↳ microvascular invasion
  - ↳ GRADE I [Slow growth] ⟶ GRADE IV [Aggressive]

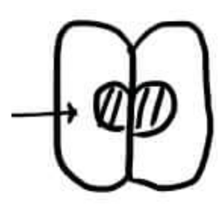
ADULT CNS TUMORS → Supra tentorial [cerebral Hemispheres] involvement

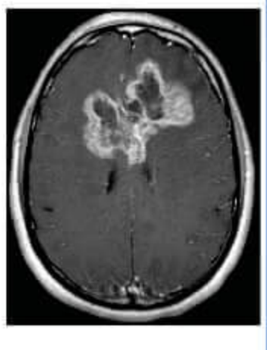
INFILTRATING ASTROCYTOMA

- → LOW GRADE → p53 mutation | PDGF-α overactivity
- → HIGH GRADE → Rb mutation | CDK2NA overactivity

GLIOBLASTOMA

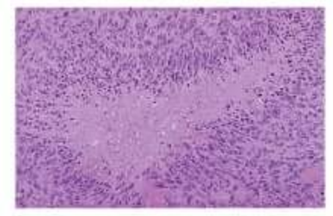
- → high grade tumor → WHO GRADE IV
- → mc 1° malignant tumor in adults
- → BUTTERFLY GLIOMA or BLOOD BUTTERFLY TUMOR





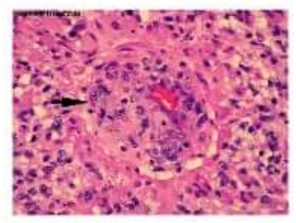
- → 1° → denovo
  - → Wild IDH1 mutation
  - → mc [90%], Elderly age

2° → Low grade astrocytoma dedifferentiation
→ IDH_1 mutation
→ 10%, young age



MIE

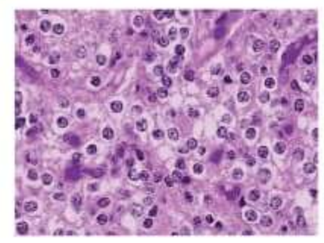
PSEUDOPALISADING → Necrosis surrounded by tumor cells
GLOMERULOID BODY → Endothelial cell proliferation ⊕⊕⊕



TREATMENT → TEMOZOLOMIDE

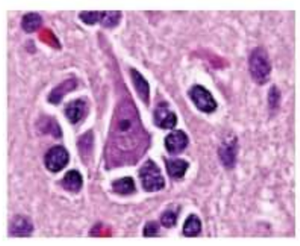
OLIGODENDROGLIOMA

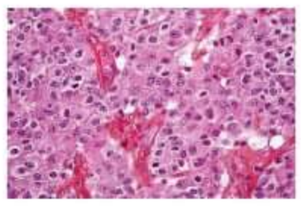
→ arises from FRONTAL LOBE
→ 4th - 5th decade
→ CALCIFICATION +



MIE

→ FRIED EGG APPEARANCE
→ PERINEURONAL SATELLITOSIS
→ CHICKEN WIRE CAPILLARIES [Thin capillaries ⊕⊕⊕]





GENETICS

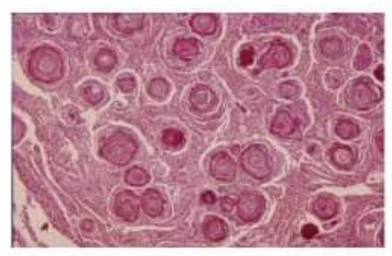
→ IDH_1 | IDH_2 mutation [mc]
→ 1p deletion, 19q deletion } co-deletion → ↑↑ Response Rate to R_x
→ Better prognosis

MENINGIOMA

→ arises from ARACHNOID MENINGOTHELIAL CELLS
→ m/c 1° brain tumor of adults
→ Benign
→ F >> M
→ Progesterone ® on tumor cells ⊕ → ↑ in Size during pregnancy

RISK FACTORS

→ Radiation
→ Gene mutation
  1. NF 2 gene [mc]
  2. TRAF - 7 gene



→ U/L ⟶ BIL, Acoustic neuroma } Neurofibromatosis 2 [NF2 gene mutation]

M/E → PSAMMOMA BODY ⊕

VARIANTS

I. LOW GRADE
1. Fibroblastic
2. Syncytial
3. Secretory
4. Transitional

II. HIGH GRADE
1. Atypical
2. Anaplastic [most aggressive]

SCHWANNOMA

→ Benign

→ arises from Schwann cells of

↳ Peripheral Nerves

↳ Cranial nerves

↳ V th

↳ VIII th [vestibular part] → ACOUSTIC NEUROMA

→ Tinnitus

→ SNHL

→ Sensory findings

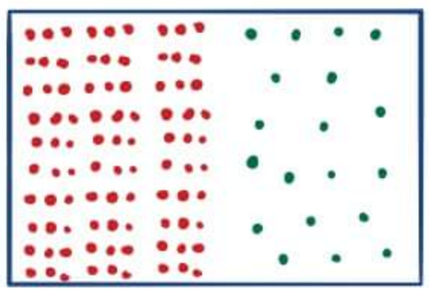
→ SITE - Cerebello - pontine angle

→ U|L [B|L Acoustic neuroma a|w NF2]

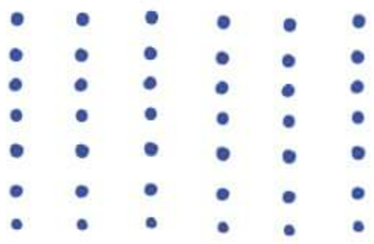
→ M|E

ANTONI 'A' AREA
[↑ Cells]

ANTONI 'B' AREA
[↓ cells]



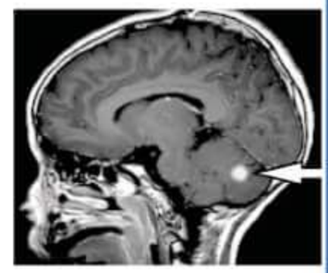
VEROCAY BODY [nuclei free area]



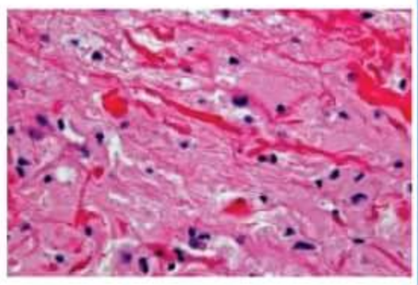
→ 5 100 ⊕

PEDIATRIC CNS TUMORS

1. PILOCYTIC ASTROCYTOMA



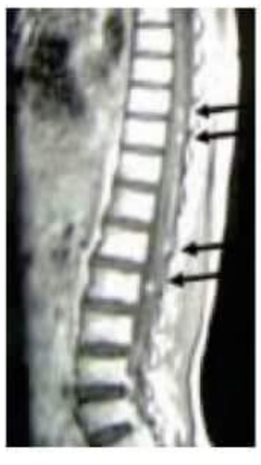
"C" ⇔ children [mc 1° benign brain tumor of children]
Cerebellar location
cystic mass
p 53 mutation is rare



M|E → ROSENTHAL FIBERS
[intra cytoplasmic Red - pink fibers]

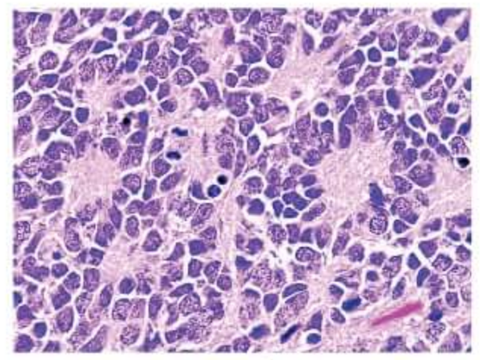
→ Good prognosis

2. MEDULLOBLASTOMA



→ malignant
→ mc 1° malignant brain tumor in children
→ arises in cerebellum
→ arises from neuro ectodermal cells [poor differentiatn]
→ metastasis occurs through CSF → DROP METASTASIS

→ M/F
  ↳ Atypical cells ⊕
  ↳ ↑ mitosis ⊕ → Ki-67 ⊕
  ↳ HOMER WRIGHT ROSETTES [fibrillary structure surrounded by tumor cells


Homer wright rosettes

→ WHO CLASSIFICATION
  1. WNT TYPE
    → have monosomy 6 & β catenin overactivity
    → a/w Best prognosis

  2. SHH TYPE
  3. GROUP 3 MEDULLOBLASTOMA → a/w Worst Prognosis
    → a/w MYC gene mutation | Isochromosome 17q presence → WORST PROGNOSIS

  4. GROUP 4 MEDULLOBLASTOMA

→ TREATMENT
  ↳ Radiosensitive tumor
  ↳ Surgery + Radiotherapy

3. EPENDYMOMA

→ malignant tumor
→ arises from EPENDYMAL CELLS

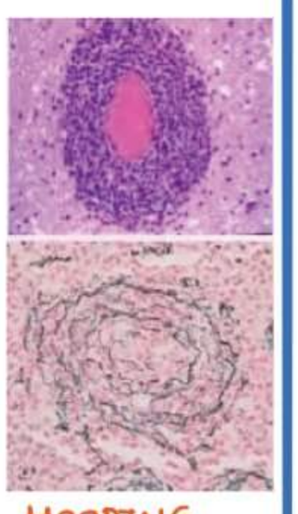
- 4th ventricle [child] → HYDROCEPHALUS ⊕, CSF spread ⊕
- SPINAL CORD [Adults] → a/w NEUROFIBROMATOSIS 2

→ M/E
  → Perivascular Pseudorosettes ⊕ [TUMOR cells surrounding a blood vessel]
  → GFAP [Glial fibrillary Acidic Protein] ⊕

→ a/w POOR PROGNOSIS

4. 1° CNS LYMPHOMA

→ a/w Immunosuppression
  ↳ AIDS
  ↳ Post-transplant patient


HOOPING

→ B-cell tumor [DLBCL]
→ a/w EBV infection
→ multifocal tumor
→ M/F → "HOOPING"
  - characteristic Finding [distingushes it from 2° CNS lymphoma]
  - blood vessel surrounded by tumor cells, tumor cells are seperated by silver staining material

GENITAL SYSTEM

MALE GENITAL TRACT

TESTIS

CRYPTORCHIDISM

→ MC genito urinary disorder in male child
→ Failure of testicular descent
→ LEYDIG CELLS are SPARED

COMPLICATIONS [dlt ↑ temp]

→ Atrophy → ↓ Fertility
→ Tumor → ↑ Seminoma
→ Torsion

TREATMENT

→ Orchidoplexy
  → age recommended → 6 m - 2 years
  → risk of development of tumor → not decreased

ORCHITIS

→ Inflammation of testis & Epididymus
→ CAUSES
  → E. coli
  → Chlamydia
  → mumps → involves testis, parotid gland & pancreas
  → TB → granulomatous orchitis
  → Syphilis

In TB → Epididymus → Testis
↑
T E S T I S
↓
Epididymus ← Testis ← In Syphilis

→

	ORCHITIS	TORSION
Scrotum elevation	↓↓ Pain	↑↑ Pain [PREHN SIGN]
cremasteric reflex	+	-

TESTICULAR TUMORS

→ Adult age group
→ CIF → Painless enlargement of testes
→ SPREAD → Lymphatic → Para aortic LN
→ Hematogenous → Lungs [mc] / CNS / Liver / Bones

→ BIOPSY IS CONTRAINDICATED [dlt disseminatⁿ]

RISK FACTORS

- → Gonadal dysgenesis & Genetic defects — G
- → Opposite Testis — O
- → Temp. [Cryptorchidism] — T
- → Intra Tubular Germ cell Neoplasia [ITGCN] — I

GONADAL DYSGENESIS

CAUSES

- → Klinefelter syndrome
- → Testicular feminization
- → isochrome 12 p
- → overexpression of NANOG & OCT 3/4
- → Cryptorchidism [Abdominal >> Inguinal]

Pre cancerous condition

not a/w Teratoma & Spermatocytic seminoma

CLASSIFICATION [Based on cell of origin]

GERM CELL TUMOR

- → common site → Gonads
- → mc extragonadal site → mediastinum

SEMINOMATOUS GERM CELL TUMORS

- → slow growth
- → Sparing of Tunica albugenia
- → Radio sensitive
- → Lymphatic spread
- → Good prognosis

NON SEMINOMA GERM CELL TUMORS

- → Examples
  - Chorio carcinom
  - Embryonal carcinoma
  - Teratoma
  - yolk sac tumors
- → Poor Prognosis
- → Hemorrhage & necrosis ⊕
- → Hematogenous spread

NON GERM CELL TUMORS

STROMAL TUMORS
- → Leydig cell tumor
- → sertoli cell tumor

LYMPHOMA

SEMINOMA

VARIANTS

1. CLASSICAL
2. ANAPLASTIC
3. SPERMATOCYTIC

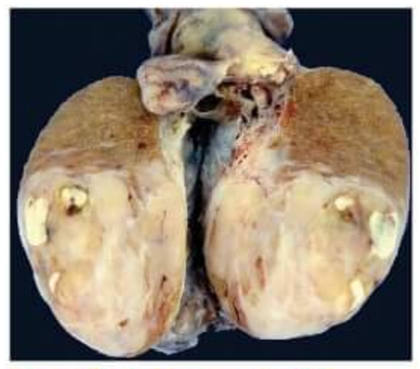
CLASSICAL SEMINOMA

- → mc testicular tumor in adults
- → malignant tumor
- → OVER EXPRESSION OF GENES → OCT 3/4 / NANOG / c-KIT

GROSS FEATURES

→ Grey tumor

→ no hemorrhage or necrosis

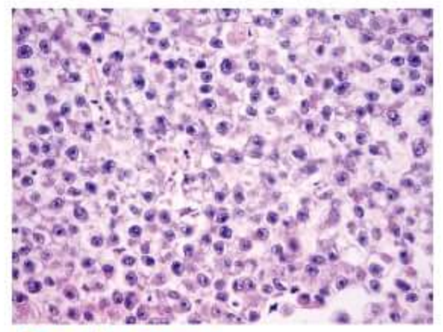


Seminoma - Gross

MICROSCOPIC FEATURES

→ Sheets of cells ī clear cytoplasm [dlt glycogen]
ī prominent nucleoli

→ Lymphocytic infiltration in stroma



Seminoma

ANAPLASTIC SEMINOMA

→ Anaplasia ⊕
mitosis ⊕

SPERMATOCYTIC SEMINOMA

→ Elderly

→ Excellent prognosis

→ no LN metastasis

→ M/E → Similar to 2° spermatocytes
no Lymphocytic infiltration

NSGCT

EMBRYONAL CANCER

→ 20 - 30yrs age

→ Primitive cells ⊕

→ ↑ β HCG

→ ↑ AFP

→ Hemorrhage & necrosis ⊕

TERATOMA

→ arises from > 1 germ cell layer

→ Origin from Totipotent cells

→ Pediatric → Pure [rare]
→ mixed → a/w Embryonal cancer

Adult → malignant [unless proved otherwise]

→ M/E → Ectoderm derivatives [mc] → ↑ Squamous cell cancer
→ mesoderm derivatives
→ Endoderm derivatives

→ MARKERS → ↑ AFP , ↑ β HCG

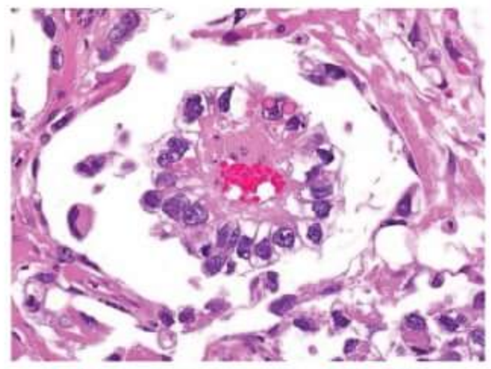
YOLKSAC TUMOR / ENDODERMAL SINUS TUMOR

→ mc testicular tumor in a < 4 yr child

→ ↑ AFP
↑ α_1 - Anti trypsin

→ MIE → SCHILLER – DUVAL BODY ⊕ / GLOMERULOID BODY ⊕

GLOMERULOID BODY



GLOMERULOID BODY

CHORIOCARCINOMA

→ derived from TROPHOBLAST
  ↳ Cytotrophoblast
  ↳ Syncytiotrophoblast → ↑↑↑ β-HCG
    ↳ Hyperthyroidism
    ↳ Gynecomastia

→ Small palpable mass ⊕
→ Early spread ⊕ ⊕⊕
→ Poor prognosis

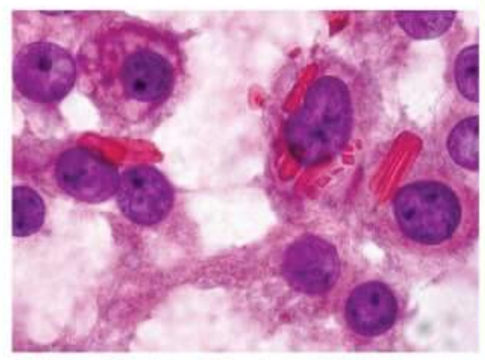
NON-GERM CELL TUMORS

STROMAL TUMORS

LEYDIG CELL TUMOR

→ Hormone secretion ⊕
  ↳ Androgen → Precocious Puberty
  ↳ Estrogen → Gynecomastia

→ MIE → Lipid droplets ⊕
→ REINKE CRYSTALS ⊕
  ↳ rod shaped eosinophilic inclusions



REINKE CRYSTALS

SERTOLI CELL TUMOR

→ SILENT TUMOR
→ a/w ↑ Estrogen → Gynecomastia

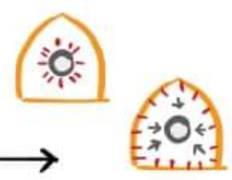
LYMPHOMA

→ MC testicular tumor seen in Elderly
→ B/L
→ MIE → DIFFUSE LARGE B CELL LYMPHOMA
→ malignant tumor
→ poor prognosis

PROSTATE

PROSTATE GLAND

→ Peri urethral zone ⟶ BHP ⟶ Early presentat^{n} →
→ Peripheral zone ⟶ CANCER ⟶ Late presentat^{n} ⟶



BENIGN HYPERPLASIA OF PROSTATE

→ mc cause of enlarged prostate in > 50 yrs

→ HORMONE DEPENDENT

→ Androgen

Testosterone $\xrightarrow{5\alpha \text{ reductase}}$ Di Hydro Testosterone [DHT]

↓

↑ CELLS [glandular & stromal cells]

→ Estrogen → ↑ no. & sensitivity of DHT Receptors

→ GROSS → Nodularity ⊕

→ MIE → Hyperplasia of Stromal cells & glands

GLANDS → Basal layer ī cuboidal cells

→ columnar cells

CLINICAL FEATURES → URETHRAL COMPRESSION

→ Urine Retention

→ ↑ frequency

→ Difficulty in starting & Stopping the Stream

MC complication → OBSTRUCTIVE UROPATHY

→ medial lobe hypertrophy

→ Bladder diverticula

→ hydroureter

→ hydronephrosis

RISK OF CANCER → No association

R_x → 1. FENASTERIDE / DUTASTERIDE [5-α Reductase inhibitors]

→ 2. TAMSULOSIN [Selective α, blockers]

→ 3. TURP [Transurethral Resection of Prostate] [Definitive R_x]

PROSTATE CANCER

RISK FACTORS

→ Age → Advancing age [most important]

→ Diet → ↑↑ Lipids

↓↓ vitamin A , vitamin C , Soya foods]

→ Androgens

→ Genes

→ BRCA - 2 gene mutation

→ 1° relatives

→ Hypermethylation of GLUTATHION - S - TRANSFERASE

→ ↓↓ E - CADHERIN

→ TMPRSS2 - ERG FUSION

CIF

→ Asymptomatic

→ Pain → Back | Pelvis

METASTASIS

→ LN → Obturator LN

→ HEMATOGENOUS → Bones
- Lumbar Spine [mc]
- Pelvis
- Proximal femur

→ Lungs & Liver

→ OSTEOBLASTIC METASTASIS

CORE BIOPSY

m/E → Adenocarcinoma → single layer of cells ⊕
→ no basal cells

→ GRADING → GLEASON SCORING

SERUM PSA PARAMETERS [sensitive but not Specific]

1. S. PSA Levels → > 10 ng/ml [Ⓝ → < 4 ng/ml]
2. PSA DENSITY → $\frac{\text{S. PSA}}{\text{volume}}$
3. PSA VELOCITY → > 0.75 ng/ml

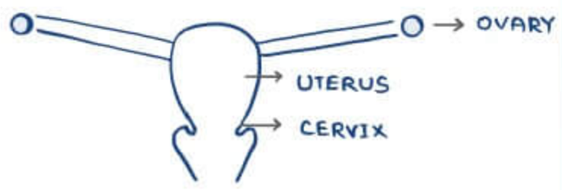
SUB TYPE

Free form → BHP
Bound form → cancer

NEW BIOMARKERS

1. Urinary PCA-3 ↑
2. TMPRSS 2 – ERG FUSION DNA ⊕

FEMALE GENITAL TRACT : CERVIX



FEMALE GENITAL TRACT

CERVIX

→ Endocervix → columnar cells
→ Exocervix } squamous cells
→ [cervical os]

→ Transformat^{n} zone → Squamous dysplasia [Pap smear taken from here]

CERVICAL INTRA EPITHELIAL NEOPLASIA [CIN]

Dysplastic changes
→ ↑↑ N:C Ratio
→ ↑ mitosis

RISK FACTOR

HPV INFECTION

→ most important

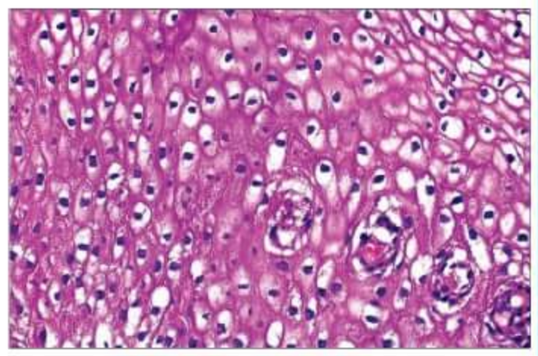
→ Low risk sub types → 6, 11 → condyloma acuminata

→ High risk sub types → 16, 18, 31, 33 → cancer

HISTOLOGY → KOILOCYTOSIS

→ Shrunken / pyknotic nucleus

→ perinuclear halo



koilocytosis

→ Ki-67 / p16 ⊕

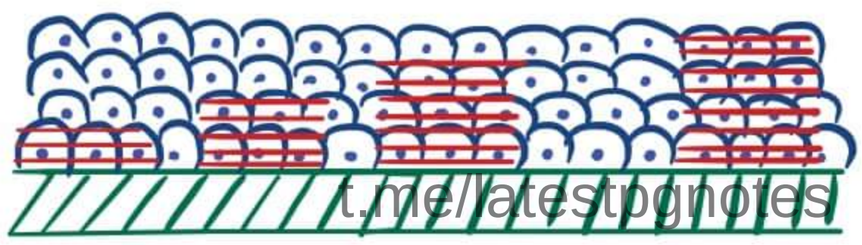
→ E_6 protein → ↓ p53 / ↑ Telomerase

→ E_7 protein → ↓ Rb

} ↑ cancer

↑ HPV Infection } Early age of Intercourse
multiple partners
High risk partner
multiparity

CIN



CIN I CIN II CIN III carcinoma In situ

→ LOW GRADE SIL [Squamous Intraepithelial lesion] → Mild dysplasia

→ HIGH GRADE SIL → moderate / severe dysplasia

LSIL $\xrightarrow[10\text{yrs}]{10\%}$ HSIL

HSIL $\xrightarrow[10\text{yrs}]{10\%}$ CANCER

→ COLPOSCOPY [VIA] → Acetic Acid → mosaic pattern ⊕, Abnormal vasculority ⊕ } dysplasia

CERVICAL CANCER

RISK FACTORS

1. HPV Infection [most important]
2. Smoking [Polycyclic aromatic hydrocarbons]
3. Immunodeficiency
4. OCPs

→ 2nd mc cancer of Females

CIF → Post-coital Bleeding [mc]
→ Foul smelling discharge

EXTENSION → 1. Vagina → Ureteric obstruct^{n} → Post renal Azotemia → Renal failure → Death
→ 2. Bladder
→ 3. Lungs

MIE → Squamous cell cancer [mc]
→ Adeno carcinoma
→ mixed carcinoma


Ayre spatula

SCREENING [For squamous dysplasia]
1. VIA [visual Inspection after Acetic Acid] & Colposcopy [Best]
2. PAP SMEAR
→ ♂ → Transformat^{n} zone
→ ♀ → H/O HPV vaccination → Screening still adviced
→ Screening donot pick up Adenocarcinoma

VAGINA

EMBRYONAL RHABDOMYOSARCOMA / SARCOMA BOTRYOIDES

→ children (< 5 yrs) c H/O grape like mass from vagina

→ MIE → TENNIS - RACKET CELLS ⊕
→ Myoglobin ⊕
Desmin ⊕


Sarcoma botryoides

CLEAR CELL ADENOCARCINOMA

→ Precursor lesion → VAGINAL ADENOSIS

♀ → Intra uterine exposure of DES [DiEthyl Stilbestrol]

- Incompetent cervix
- Mullarian duct differentiat^{n} ⊖
- Abnormal uterine shape

SQUAMOUS CELL CANCER

→ a/w HPV 16 infection
→ extension of carcinoma cervix

UTERUS

COMPONENTS
1. MYOMETRIUM
2. ENDOMETRIUM
↳ Estrogen → ↑ growth
↳ Progesteron → Implantation

ENDOMETRIAL DISORDERS

ENDOMETRIOSIS

→ ECTOPIC ENDOMETRIAL TISSUE

→ SITES

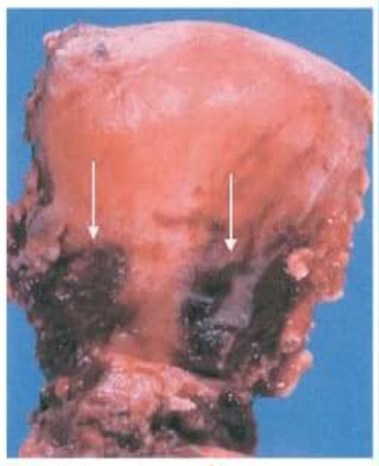
↳ Ovary [mc] → CHOCOLATE CYST → ↓ fertility
↳ uterine ligament → Pelvic pain & dysmenorrhea
↳ Recto-uterine pouch → pain on defecation
↳ Bladder / Bowel → pain on urination / defecation / abdominal pain
↳ mucosa of fallopian tube → ↓ fertility

→ PATHOGENESIS

1. REGURGITATION THEORY [mc accepted] [during menstruat^n]
2. METAPLASTIC THEORY
3. LYMPHATIC DISSEMINATION
4. STEM CELL THEORY

Aromatase, PGE_2 ⟶ Estrogen → Cell survival


CHOCOLATE CYST OF OVARY


Burn powder appearance

→ COMPLICATIONS

→ ↑↑ ovarian cancer
→ chocolate cyst ⊕ / BURN POWDER APPEARANCE

ADENOMYOSIS

→ Endometrial tissue in myometrium
→ > 2.5 mm below Endo myometrial Junction

ENDOMETRIAL HYPERPLASIA

→ ↑↑ Estrogen → ↑↑ Endometrial glands → Heavy Bleeding
→ PTEN GENE MUTATION ⊕

→ WHO CLASSIFICATION

1. NON - ATYPICAL EH → 1 - 3 % risk of cancer
2. ATYPICAL EH → 23 - 48 % risk of cancer

→ Atypical EH aka → ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA [EIN]

ENDOMETRIAL CARCINOMA

→ MC invasive cancer of female genital tract
→ C/F → Post menopausal bleeding [mc]
→ METASTASIS → Lungs [mc]
→ WHO CLASSIFICATION

1. TYPE I ENDOMETRIAL CARCINOMA
2. TYPE II ENDOMETRIAL CARCINOMA

	TYPE I	TYPE II
AGE	→ 55 - 65 yrs	→ 65- 75 yrs
CLINICAL SETTING	→ Unopposed estrogen exposure → Obesity → HTN → DM	→ Atrophy → Thin physique
GENETICS	→ PTEN mutation	→ p 53 mutation
	→ Indolent in nature	→ Aggressive nature
	→ LN spread ⊕	→ Intra peritoneal spread
	→ Better prognosis	→ poor prognosis
	→ ENDOMETROID CANCER	→ PAPILLARY SEROUS CANCER

MYOMETRIAL DISORDERS

LEIOMYOMA / FIBROID

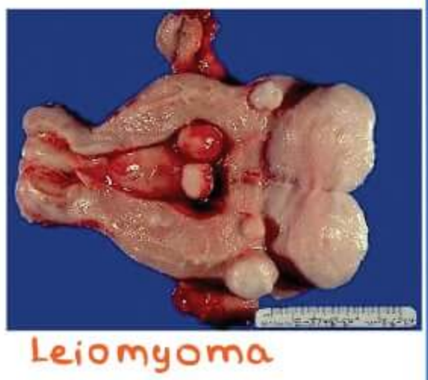
→ Smooth muscle mass
→ Benign
→ Reproductive age group

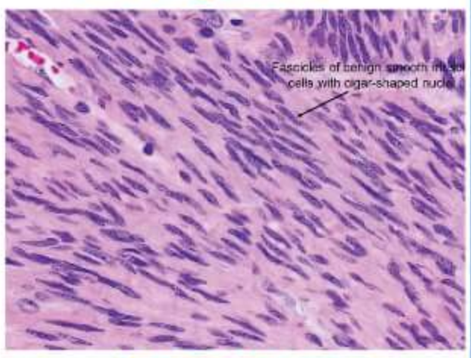
→ SUB TYPES
  → SUB MUCOSAL
  → INTRA MURAL
  → SUB SEROSAL

→ CLINICAL FEATURES
  → Asymptomatic usually
  → menorrhagia
  → ↓ fertility
  → Pressure symptoms

→ GROSS FEATURES → well circumscribed ; multiple
→ whorled mass ⊕ → Grey white

→ MIE → Smooth muscle cells ± whorled ⊕
→ Advanced Info → MED 12 mutation ⊕


Leiomyoma



Leiomyoma

LEIOMYOSARCOMA

→ DE-NOVO Origin
→ mc sarcoma of uterus
→ GROSS → Single ; Brown
→ MIE → Hemorrhage & necrosis
→ Atypical mitosis → ≥ 10 mitosis / hpf

OVARIES

OVARIAN TUMORS

1° OVARIAN TUMORS
2° OVARIAN TUMORS

Surface Epithelium
Germ cell
Sex cord stromal cell

OVARY

COMPONENTS	1° TUMORS
Surface Epithelial cells	→ Surface Epithelial tumors [mc]
Germ cells	→ Germ cell tumors
Sex - cord Stromal cells [theca | granulosa | fibrosa cells]	→ Sex cord stromal tumors

RISK FACTORS

NON GENETIC	→	Nulliparity
	→	Asbestos
GENETIC	→	BRCA 1/2 mutat^{n} ; K-RAS mutat^{n}
	→	LYNCH / TURNER / PJ SYNDROMES

BRCA 1 → Serous surface epithelial tumor
Turner Syndrome → dysgerminoma
PJ Syndrome → Sex cord stromal tumors

PROTECTIVE FACTORS → pregnancy & OCPs

SURFACE EPITHELIAL TUMORS

→ mc 1° ovarian tumors
→ may be Benign / Borderline / malignant
→ usually cystic

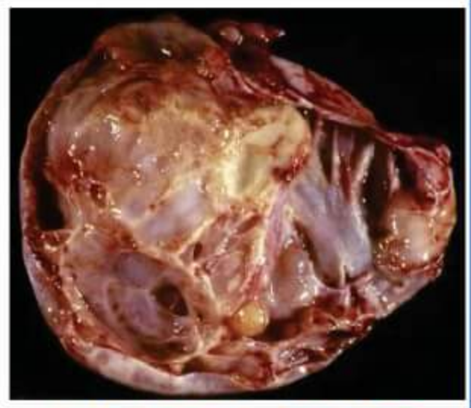
→ Benign a/w → young female
malignant a/w → Elderly female & Atypia, Hemorrhage & necrosis ⊕

→ SUB TYPES

My → Mucinous Tumor
servant → Serous tumor
Began → Brenner tumor
Experiencing → Endometroid tumor
Cancer → Clear cell tumor

1. MUCINOUS TUMOR

→ cystic tumor ī columnar non-ciliated epithelium [secretes mucus]
→ Benign → mucinous cystadenoma
→ malignant → mucinous cystadenocarcinoma


mucinous tumor

FEATURES

→ U/L
→ ↑↑↑ Size
→ multiple cysts ⊕
→ PSEUDO MYXOMA PERITONEI [mucin in peritoneal cavity]

RISK FACTORS

→ Smoking
→ K-RAS mutation

2. SEROUS TUMOR

→ cyst mass ī ciliated epithelium [≅ fallopian tube]
→ BENIGN → mc benign ovarian tumor
→ MALIGNANT → mc BIL malignant ovarian tumor
→ SEROUS CYSTADENOCARCINOMA [malignant]
→ BRCA 1 gene mutation
→ PSAMMOMA BODIES ⊕

3. BRENNER TUMOR

→ UIL
→ WALTHARD NESTS ⊕ → Transitional Epithelium [≅ Bladder]

4. ENDOMETROID CANCER

→ PTEN gene mutation
→ ≅ Endometrial adenocarcinoma
→ a/w Endometriosis

5. CLEAR CELL CANCER → clear dlt glycogen

CLINICAL FEATURES OF SURFACE EPITHELIAL TUMORS

→ Abdominal Enlargement [↑ ovarian size / Ascites]
→ Abdominal pain
→ Palpable ovaries [in post menopausal ♀]
→ malignant pleural effusion
→ hepatic metastasis

MARKERS

→ CA 125 → indicates the progression of disease
→ OSTEOPONTIN

GERM CELL TUMORS

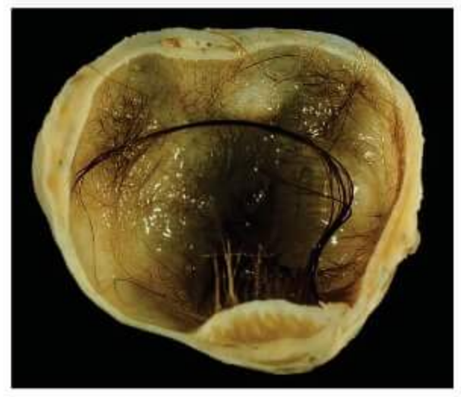
1. DYSGERMINOMA
2. ENDODERMAL SINUS TUMOR
3. TERATOMA
4. OVARIAN CHORIOCARCINOMA

1. DYSGERMINOMA

→ ♀ counterpart of SEMINOMA
→ mc malignant GCT
→ Radiosensitive
→ UIL
→ a/w Turner Syndrome
→ marker → ↑↑ S. LDH
→ Good prognosis

2. TERATOMA

→ arise from totipotent cells
→ arise from > 1 germ cell layer

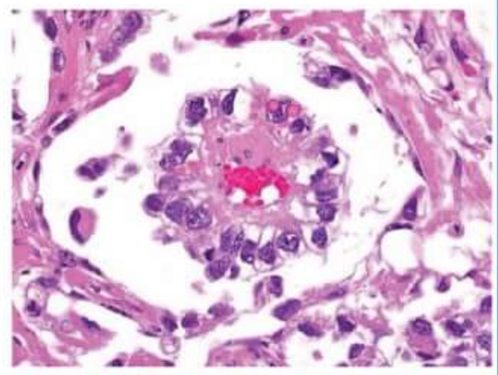

Teratoma

→ MATURE TERATOMA → DERMOID CYST
  ↳ skin / hair / cartilage / sebaceous gland ⊕
  ↳ Reproductive age group
  ↳ 46 xx
  ↳ skin —1%→ Squamous cell carcinoma

→ IMMATURE TERATOMA
  ↳ Adolescent females
  ↳ malignant

→ SPECIALISED TERATOMA
  ↳ STRUMA OVARII [contains functional thyroid tissue / hyperthyroidism ⊕]
  ↳ ↑ 5 HT → CARCINOID [U/L]

ENDODERMAL SINUS / YOLK SAC TUMOR


SCHILLER DUAL BODY

→ mc malignant ovarian tumor of children [< 4 yr]
→ 2nd mc malignant GCT
→ M/E → SCHILLER DUVAL BODY
→ TUMOR MARKERS → AFP ⊕ / α_1-AT ⊕

OVARIAN CHORIDCARCINOMA

→ co-exist ↓ other GCT
→ Placental Origin
→ Marker → β HCG ↑↑↑
→ non responsive to chemotherapy
→ poor prognosis

III SEX CORD STROMAL TUMORS [FUNCTIONAL TUMORS]

1. THECOMA - FIBROMA

→ SPINDLE CELLS ⊕
→ Theca cells → OIL RED 'O' +
  Fibroma → OIL RED 'O'

→ FIBROMA a/w
  1. MEIG SYNDROME
    → Fibroma
    → Ascites
    → Rt sided pleural effusion
  2. BASAL CELL NEVUS SYNDROME
    → > 6 cm fibroma

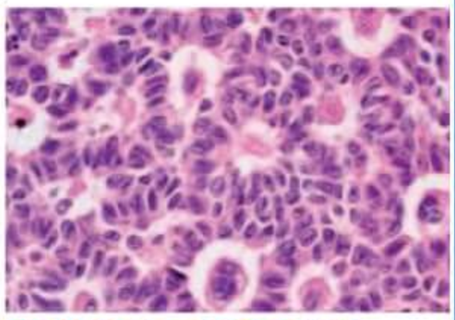
2. GRANULOSA – THECA CELL TUMORS

→ FOX L2 mutation

→ Hormone Secretion → Estrogen
- → precocious puberty
- → Endometrial hyperplasia
  Endometrial malignancy

→ MIE

1. CALL EXNER BODY
   - → acidophilic inclusion centre
   - → surrounded by tumor cells



Call Exner Bodies

2. COFFEE BEAN NUCLEUS

→ STAIN → Inhibin ⊕

3. SERTOLI – LEYDIG CELL TUMOR

→ Functional tumors [Androgen → masculinization]

→ PURE LEYDIG CELL TUMOR → m/E → REINKE CRYSTALS ⊕

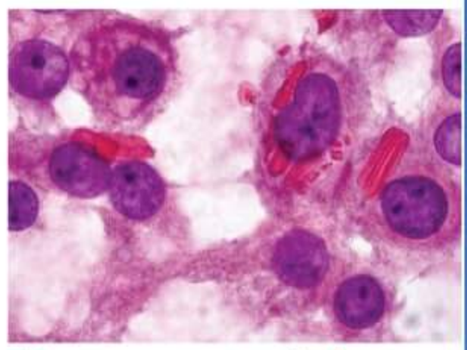
4. GONADOBLASTOMA

→ Mixed tumor [Stroma + Germ cell]

→ Abnormal sexual development [♀ (80%) ; ♂ (20%)]

→ Rx by surgical excision

→ Good Prognosis



Reinke crystals

2° OVARIAN TUMORS

→ mc metastasis → mullerian origin tumor
- ↳ Uterus
- ↳ Fallopian tube
- ↳ Opposite ovary
- ↳ pelvic peritoneum

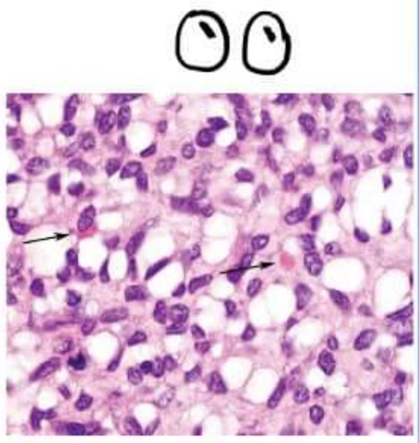
→ EXTRA – MULLERIAN ORIGIN
- ↳ stomach cancer
- ↳ colon cancer
- ↳ Breast cancer

1 KRUKENBERG TUMOR

→ B/L [dlt lymphatic spread]

→ ORIGIN
- ↳ Stomach [mc] → Diffuse variant
- ↳ Breast → infiltrating lobular carcinoma
- ↳ Colon
- ↳ Pancreas

→ M/E → SIGNET-RING APPEARANCE
[dlt mucinous vacuole]

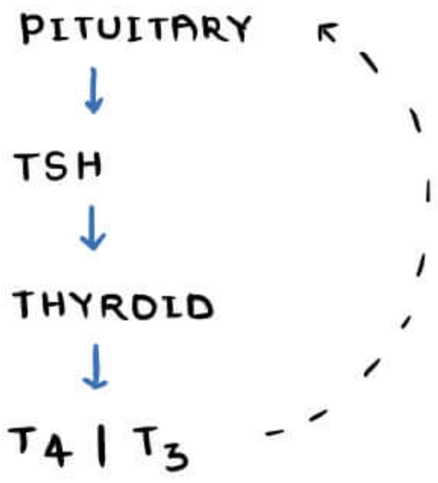


Signet-ring cells

2. PSEUDO-MYXOMA PERITONEI [mucus in peritoneum]

→ can be Appendiceal tumor → mc
mucinous ovarian tumor

THYROID



THYROID HORMONES

→ more produced form → T_4
→ more active form → T_3

→ FUNCTIONS
  → ↑ BMR
  → proper bone growth
  → ↑ β adrenergic receptors on CVS
  proper Brain growth

THYROID FUNCTION TESTS

1. S.TSH → ↑ [seen in hypothyroidism]
  → ↓ [seen in hyperthyroidism]
  → preferred parameter in thyroid disorders

SUB CLINICAL DISEASE

→ sub clinical hypothyroidism → ↑ TSH & Ⓝ T_3 | T_4
→ sub clinical hyperthyroidism → ↓ TSH & Ⓝ T_3 | T_4

2. S.T_4 LEVELS
  a. FREE FORM → Symptoms depends on free form
  b. PROTEIN [TBG] FORM

Increased in
- OCPs
- Pregnancy
- HRT

↓

↑ S.T_4 levels

Decreased in
- Nephrotic Syndrome
- anabolic steroids

↓

↓ S.T_4 levels

3. I^{131} UPTAKE

↑ Synthetic capacity
↓
HOT NODULE
→ Graves Disease
→ Toxic Nodular goitre

↓ Synthetic capacity
↓
COLD NODULE
→ Thyroiditis
→ Excess intake of Thyroid hormones
→ Malignancy

4. S.THYROGLOBULIN → marker for Thyroid cancer

THYROIDITIS [Initial hypothyroidism $\xrightarrow{F/b}$ Hyperthyroidism]

1. ACUTE THYROIDITIS

→ dlt Bacterial infection

→ C|F → Fever / Tender thyroid / Cervical Lymphadenopathy

→ INVESTIGATIONS

↳ S. T_4 ↑

↳ S. TSH ↓

↳ I^{131} ↓

→ R_x → Antibiotics

2. HASHIMOTO'S | CHRONIC LYMPHOCYTIC THYROIDITIS

→ Auto Immune Disorder → PTPN-22 | CTLA-4 gene mutation

↓

CD_4 T cells | CD_8 T cells [main reason for pathogenesis]

Auto Ab ⊕ [useful for Dx]

→ ♀

→ HLA DR3 | DR5 ⊕

→ a/w

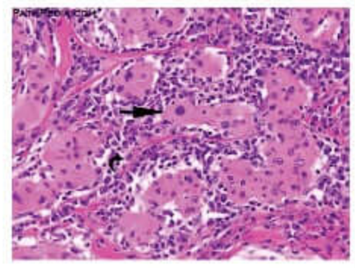
- Klinefelter Syndrome → Pernicious anemia
- Down Syndrome → SLE
- Turner Syndrome → Type 1 DM
- → myasthenia gravis
- → Rheumatoid Arthritis

→ C|F → middle aged ♀ → HASHITOXICOSIS → → HYPOTHYROIDISM

→ Painless enlargement of thyroid

→ mc cause of hypothyroidism in iodine-sufficient areas

→ DIAGNOSIS



1. FOLLICULAR DAMAGE ⊕
2. LYMPHOCYTIC INFILTRATION ⊕
3. Well formed GERMINAL CENTERS ⊕
4. HURTHLE CELLS / ASKANAZY CELLS ⊕
   - → pink granular eosinophic cytoplasm ⊕
   - → ONCOCYTIC METAPLASIA

→ ↑ Risk for B-CELL CANCER → MARGINAL ZONE LYMPHOMA

3. REIDEL'S THYROIDITIS

→ Ig G_4 related disease → young ♀ → Fibrosis of Thyroid & Extra thyroid structures [Trachea & esophagus]

→ FEATURES → HARD-ROCK LIKE THYROID → Hypothyroidism

→ Dysphagia

→ Stridor / Dyspnea

→ mimics THYROID CANCER [DD → young ♀ → RT]

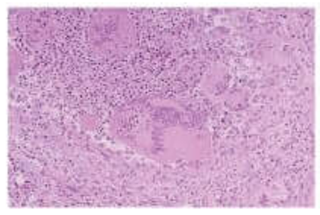
→ R_x → RITUXIMAB / TAMOXIFEN / STEROIDS

4. DEQUERVAIN'S / GRANULOMATOUS

→ ♀ ī HIo viral infection [fever, malaise, pain in neck]
→ mc cause of tender thyroid

→ CIF
  → Tender Thyroid
  → Transient Hyperthyroidism
  → Cervical Lymphadenopathy ±

→ MIE → Granuloma → Gaint cells + around colloid



→ S. T_4 ↑
S. TSH ↓
I^{131} ↓

→ R_x → NSAIDs
→ Self limiting → do not cause permanent hypothyroidism

5. SUB - ACUTE LYMPHOCYTIC THYROIDITIS

→ Autoimmune Disease
  ↳ painless
  ↳ post - partum ♀

→ Painless thyroiditis
Transient hyperthyroidism → hypothyroidism

→ NO Fibrosis
NO Hurthle cells

HYPERTHYROIDISM & GOITRE

THYROTOXICOSIS [↑ Thyroid hormones by any cause]

→ ↑ gland activity → Graves disease
[Hyperthyroidism] → Toxic multinodular goitre

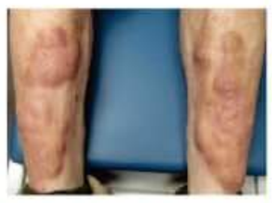
→ Normal activity → External supplementation [Iatrogenic]
→ Stress
→ Strauma Ovarii

GRAVE'S DISEASE

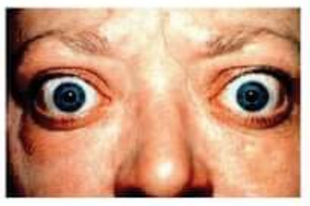
→ mc cause of Thyrotoxicosis & Hyperthyroidsm → GRAVE'S DISEASE
→ Auto Immune disease
→ ♀ >>> ♂
→ 20 - 40 yrs
→ HLA DR3 | B-8
→ ↑ SLE | Type 1 DM | pernicious anemia | Addison disease
Auto - Ab ⊕ → TSIg → ⊕⊕⊕ TSH R → Hyperthyroidism

TRIAD

THYROID → Hyperthyroidism

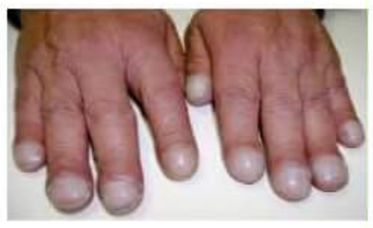


SKIN → PRE TIBIAL myxedema
↳ Shin involved
↳ non - pitting edema



EYE → PROPTOSIS
→ Extra Ocular Muscle weakness

CIF

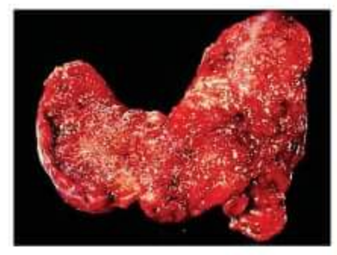


→ Weight loss a/w good appetite
→ Heat Intolerance
→ Diarrhea
→ oligomenorrhea
→ Osteoporosis
→ Systolic HTN
→ Sinus tachycardia
→ AF ↑

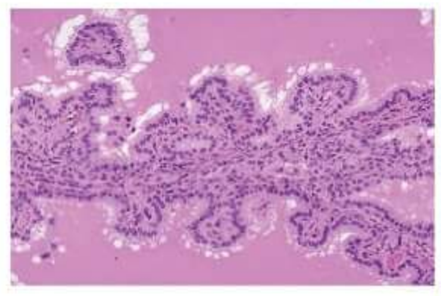
→ THYROID ACROPACHY → Swelling of digits & Clubbing
→ APATHETIC HYPERTHYROIDISM
↳ Elderly
↳ ↑ Skeletal & CVS manifestation

DIAGNOSIS

1. S. T_4 → ↑ } Thyroiditis
S. TSH → ↓ } External hormone intake
I^{131} Uptake → ↑↑



2. MIE → Diffuse increase in the size of the gland
→ Follicular hypertrophy & hyperplasia
↓
PAPILLAE FORMATION
[no fibro vascular core]
↓
SCALLOPING OF COLLOID



℞ THIOAMIDES
Non Selective β blockers

GOITRE

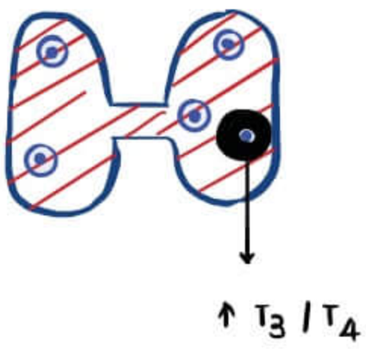
→ Enlargement of thyroid gland
→ ↓ Hormones → ↑ Size

1. ENDEMIC → > 10 % are affected
→ Himalayan, Andes

2. SPORADIC

- → ♀
- → puberty , pregnancy
- → goitrogens
- → Drugs [Lithium , Amiodarone , PAS]
- → PENDRED SYNDROME
  - ↳ Pendrin defect
  - ↳ SNHL + ↓ function of thyroid

PATHOGENESIS



Endemic / Sporadic

↓ T_3 / ↓ T_4

↓

↑↑ TSH

↓

follicular hyperplasia [DIFFUSE GOITRE] } NON TOXIC GOITRE

↓

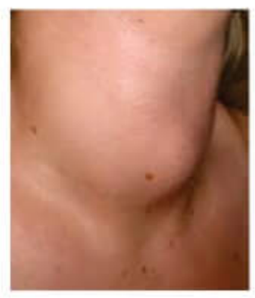
MULTI NODULAR GOITRE

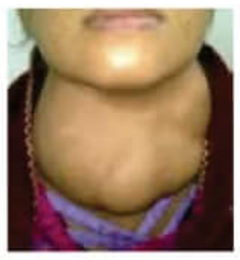
↓

Autonomous

↓

Toxic multinodular goitre





CIF → mostly hypo | Euthyroid
→ Hyperthyroid in toxic multinodular goitre

COMPLICATIONS

1. Cyst formation
2. Hemorrhage
3. Jugular venous compression → PEMBERTON SIGN
4. Hoarsness [RLN⊕]
5. Dyspnea [trachea compression]
6. TOXIC MNG → PLUMMER SYNDROME
   ↓
   hyperthyroidism
   NO skin involvement
   NO Eye involvement

PLUMMER VINSON SYNDROME
→ ♀
→ IDA
→ esophageal webs
→ atrophic glossitis

MIE

1. Hyperplastic Stage
2. Involution

THYROID TUMOR

BENIGN

FOLLICULAR ADENOMA

→ mc benign thyroid tumor
→ G protein couple receptor mutation ⊕

MALIGNANT

RISK FACTORS

1. GENETIC

→ RET gene mutation	→ Medullary Thyroid cancer
→ RAS gene mutation	→ Follicular Thyroid cancer
→ RET / PTC gene mutation	→ Papillary Thyroid cancer
→ p 53 gene mutation	→ Anaplastic Thyroid cancer

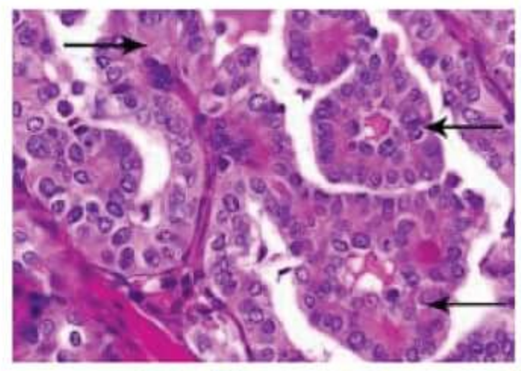
2. ENVIRONMENTAL

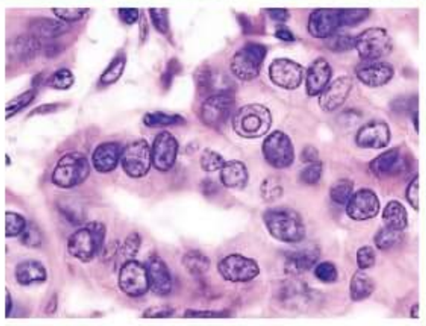
→ Radiation	→ Papillary Thyroid cancer
→ TSH ⊕⊕⊕	→ Follicular Thyroid cancer

PAPILLARY THYROID CANCER

→ mc thyroid cancer
→ a/w Post Radiation
RET - PTC gene mutation

→ young patients [20 - 30 years]
→ Lymphatic Spread → Palpable LN ⊕ [cervical LN]





DIAGNOSIS

MIE

1. PAPILLE FORMATION ⊕ [fibro vascular core ⊕]
2. PSAMMOMA BODIES ⊕
3. NUCLER FINDINGS ⊕ [Hall mark]
   → Orphan - Annie Eye nuclei
   → Pseudo inclusions
   → Nuclear grooving

SUB TYPES

1. Follicular variant [mc]
2. Diffuse sclerosing variant
3. Tall cell variant → BRAF mutation ⊕ , more aggressive , ↑ metastasis
4. Papillary micro carcinoma → < 1 cm

2. FOLLICULAR THYROID CANCER

RISK FACTORS

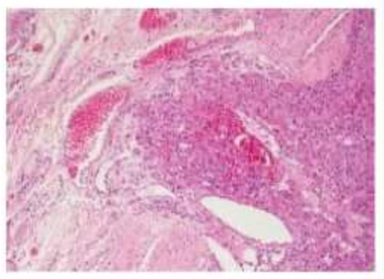
→ RAS mutation
→ Endemic goitre

→ 40 - 50 yr ♀
→ Hematogenous Spread ⊕ → Bones, Lungs, Liver
→ FNAC NOT USEFUL → can't differentiate b/w Adenoma & carcinoma

DIAGNOSIS

1. BIOPSY → metastasis ⊕

Follicular carcinoma → Capsular invasion ⊕
Vascular invasion ⊕



2. S. Thyroglobulin ↑ → marker of Recurrance

HURTHLE CELLS ⊕

→ Seen in Follicular adenoma
Follicular carcinoma
Hashimoto's Thyroiditis

→ if > 50% → HURTHLE CELL TUMOR → poorer prognosis

3. MEDULLARY THYROID CANCER

→ arises from Para - follicular cells / 'C' cells

→ 'C' cells Secretes → calcitonin [best tumor marker]
→ ACTH / 5-HT / VIP [alw Cushing Syndrome, Diarrhea]

→ Only thyroid cancer alw Amyloid deposition
→ RET mutation ⊕

SUB TYPES

1. SPORADIC
→ U/L, Unicentric
→ 60 - 70 yrs

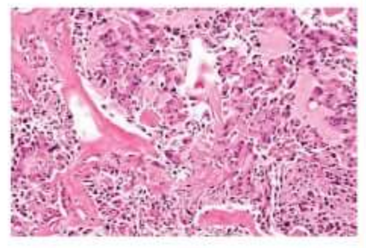
2. FAMILIAL
→ B/L, multicentric
→ Indolent
→ Better prognosis

MEN SYNDROME - MEN 2A & 2B [more aggressive]
→ more aggressive
→ younger age group affected
→ poor prognosis

→ Prophylactic Thyroidectomy indicated in a patient ī family H/O RET mutation

DIAGNOSIS

1. FNAC → MIE → POLYGONAL CELLS + in AMYLOID STROMA
2. CALCITONIN
3. CEA → used in calcitonin negative medullary cancer
→ Tumor Burden can be Known



4. ANAPLASTIC THYROID CANCER

→ p 53 mutation
→ highly aggressive → metastasis +++
→ Elderly
→ Firm Non - Tender gland
→ THYROGLOBULIN ⊖ CYTOKERATIN ⊕

→ Extra thyroidal structures also involved
  ↳ Esophagus [dysphagia]
  ↳ Trachea [stridor]
  ↳ Laryngeal Nerve [Hoarsness]

1° B CELL LYMPHOMA → Marginal zone Lymphoma
→ alw Hashimoto's Thyroiditis

PARA THYROID

PARATHYROID GLAND

→ ④ → Superior [4th pharyngeal pouch]
→ Inferior [3rd pharyngeal pouch]

→ PTH → Distal tubules of Kidney → Ca^{2+} reabsorption [↑ Ca^{2+}]
→ 1-α OHase ⊕ → calcitriol [vit D]
→ BONES → Osteoblasts → Osteoclast → ↑ Ca^{2+}
→ NET EFFECT → ↑ S. Ca^{2+}, ↓ S. PO_4^{3-}

→ ↓ Ca^{2+} ⟶ Ca^{2+} Sensing ® ⟶ ↑ PTH ⟶ ↑ S. Ca^{2+}
[parathyroid gland]

HYPERPARATHYROIDISM
1° HYPERPARATHYROIDISM

→ PTH ↑↑ → ↑ S. Ca^{2+} → Asymptomatic hypercalcemia [Incidental]
↓ S. PO_4^{3-}

→ post menopausal females

ETIOLOGY

1. Parathyroid adenoma [mc]
2. Parathyroid hyperplasia
3. Parathyroid Carcinoma

PARATHYROID ADENOMA

→ mcc 1° Hyper PTH
→ mc site → Rt. Inferior gland
→ Remaining glands undergo atrophy

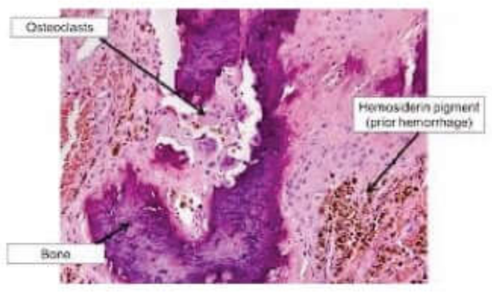
→ M|E → sheets of cells ⊕ ī no adipose tissue in blw

→ GENETICS
  1. Cyclin D_1 overactivity
  2. MEN 1 gene under activity

→ Sporadic also

CIF

→ Kidneys → ↑ stones , polyuria
→ GIT → nausea , Constipation , ↑ PUD , ↑ Pancreatitis
→ CNS → confusion , anxiety
→ BONES → osteoporosis
↳ concavity on radial side of phalanges
↳ X Ray skull → salt & pepper appearance



→ CYST + HEMORRHAGE → OSTEITIS FIBROSA CYSTICA / BROWN TUMOR

→ JOINTS → PSEUDO GOUT

DIAGNOSIS

1. S. PTH → ↑↑↑
S. ca^{2+} → ↑↑
S. PO_4^{3-} → ↓↓

GLANDS

Adenoma	Hyperplasia
One → ↑↑↑	4 → ↑↑↑
Others → ↓↓	WASSERHELLE CELL HYPERPLASIA

→ ↑↑ ca^{2+} seen in
D → Drugs [Thiazides] / Vit D intoxication
I → Immobilisation
S → Sarcoidosis [↑ 1α OHase]
C → Cancers [Symptomatic hypercalcemia]
→ multiple myeloma
→ metastasis
↳ Squamous cell Lung cancer
↳ Renal cancer
↳ Breast cancer

2° HYPER PARATHYROIDISM [↓↓ ca^{2+} ⟶⟶ ↑ PTH]

ETIOLOGY

1. Renal failure [mc]
2. Vit D Deficiency
3. GIT [steatorrhea]

HYPO PARATHYROIDISM

ETIOLOGY

→ Surgical Removal [Thyroid Sx] [mc]
→ Auto immune Disease [Autoimmune Polyendocrinopathy Syndrome I (APS I)]
→ hypomagnesemia
→ Di - GEORGE Syndrome

APS I

→ dlt AIRE gene defect
→ adrenal insufficiency ⊕
muco cutaneous candidiasis ⊕

Hypomagnesemia

→ a/w Diuretics
Alcohol
aminoglycoside
diarrhea

CIF → ↓ Ca^{2+} ; ↑↑ PO_4^{3-} ; S. PTH ↓

→ TETANY → Carpo pedal Spasm
↳ Chvostek sign
↳ Trousseau sign

→ CVS → ↑ QT interval

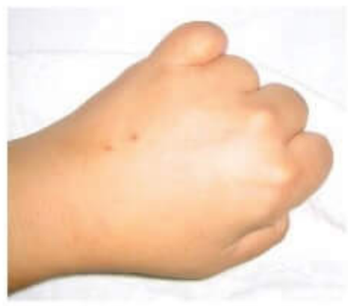
→ Calcification [Basal ganglia]
→ Dental Caries
→ Cataract

PSEUDO - HYPOPARATHYROIDISM

→ S. Ca^{2+} ↓
S. PO_4^{3-} ↑
S. PTH ↑↑

→ End organ resistance +

→ CIF → mental Retardation
Calcification
Short stature
Small 4th/5th meta carpals → KNUCKLE KNUCKLE DIMPLE DIMPLE SIGN / ARCHIBALD SIGN



→ a/w Maternal Imprinting

PSEUDO - PSEUDO HYPO PARATHYROIDISM

→ S. Ca^{2+}
S. PO_4^{3-}
S. PTH
} Normal

→ CIF → MR, Obesity, Skeletal defects
→ a/w Paternal Imprinting

ADRENAL GLAND

ADRENAL CORTEX

1. Zona glomerulosa → Aldosterone
2. Zona fasciculata → Cortisol
3. Zona Reticulosa → Sex-steroids

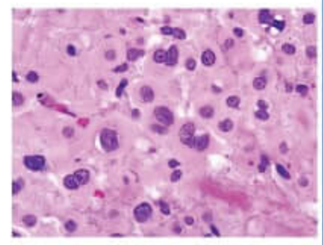
CUSHING SYNDROME

→ ↑ Cortisol

CIF

→ central obesity
→ moon facies
→ HTN
→ muscle wasting
→ skin atrophy
→ osteoporosis

ETIOLOGY



1. EXTENAL [IATROGENIC] SUPPLEMENTAT^{n} [mc]

⊖ ACTH secretion → BIL adrenal atrophy

2. ENDOGENOUS CAUSES

i. Pituitary adenoma

→ ↑↑ ACTH → BIL adrenal hyperplasia → CUSHING DISEASE
→ MIE → N → Basophilic granular cytoplasm
CD → Intermediate filaments → CROOKS HYALINE CHANGE

ii ECTOPIC ACTH SECRETION

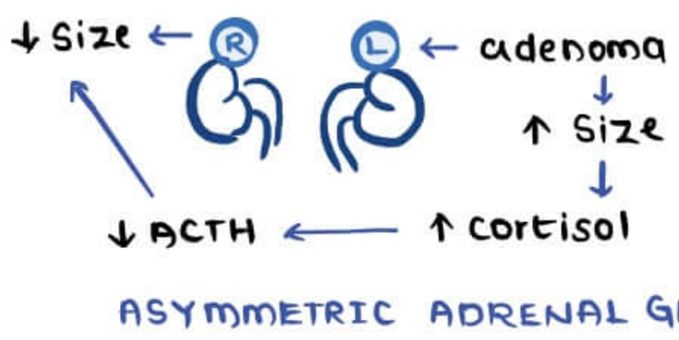
→ a/w small cell cancer of lung
medullary thyroid cancer

→ ↑ ACTH by tumor cells → BIL Adrenal hyperplasia

→ DEXA METHASONE SUPPRESSION TEST
↳ high dose → ⊖ pituitary
→ ⊗ Ectopic ACTH

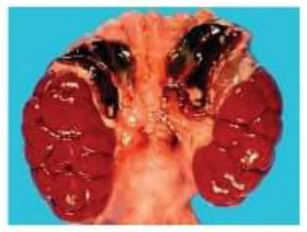
iii ADRENAL CAUSE

→ dlt hyperplasia | adenoma [mc] | cancer



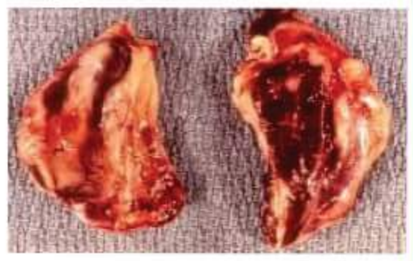
ASYMMETRIC ADRENAL GLAND

ADRENO - CORTICAL DISORDERS



1° DISEASE

1. ACUTE DISEASE [ADRENAL CRISIS]



ETIOLOGY

1. abrupt withdrawal of steroids [mc]
2. Stress (Chronic adrenal Insufficiency]
3. Adrenal hemorrhage
   - ↳ Anti coagulant therapy
   - ↳ DIC
   - ↳ meningococcus infection [WATERHOUSE - FREDRICKSON SYNDROME]
   - ↳ difficult delivery

2. CHRONIC ADRENO CORTICAL INSUFFICIENCY [ADDISON'S DISEASE]

ETIOLOGY

1. AUTO IMMUNE DISORDERS
   - → mc cause of addison's disease in developed countries
   - → APS 1
     - → Auto Ab against IL-17
     - → hypoparathyroidism ⊕
     - → addison's disease ⊕
     - → muco cutaneous candidiasis ⊕
   - → APS 2 = SCHIMDT SYNDROME
     - → addison's ⊕
     - → Thyroiditis ⊕
     - → Type 1 DM ⊕

2. INFECTIONS
   - → TB [mc cause of addison's disease in developing countries]
   - → Histoplasmosis
   - → AIDS
3. METASTASIS
   - → Lung cancer [mc]
   - → Breast cancer
4. GENETIC → ADRENO GENITAL SYNDROME
   - → mcc of addison's disease in a child

CIF → Progressive Weakness → HTN
→ ↑ Fatigue → ↓ Na^+ / ↑ K^+

POMC [Proopiomelanocortin] →
- ↑ ACTH
- ↑ MSH [melanocyte stimulating Hormone]
  - ↳ Hyperpigmentation ⊕
    - → Sun exposed areas [neck]
    - → Knuckles / Elbows / Knees

2° ADRENAL INSUFFICIENCY

→ dlt Hypothalamus or Pituitary defects

ETIOLOGY → metastasis → Infarction
→ Infection → post - Radiation

CIF
→ ↓ ACTH → No pigmentation
→ ↓ cortisol / ↓ Androgens
→ Nearly Normal Aldosterone → no hyponatremia or hyperkalemia

ADRENAL MEDULLA

→ composed OF CHROMAFFIN CELLS [derived from Neural crest]
→ NEURAL CREST CELLS
→ Secretes Adrenaline & Nor adrenaline
→ Located at
↳ Adrenal gland
↳ mediastinum
↳ Bladder
↳ ORGAN OF ZUCKEKANDL [Aortic bifurcation]

→ at Adrenal medulla & Organ of zuckekandl

Adrenaline $\xrightarrow{\text{N-methyl Transferase}}$ ~~Nor~~ Adrenaline

PHEOCHROMOCYTOMA

→ Adrenal medullary tumor
→ Adult
→ a/w VHL Syndrome
NF-1 gene mutation
MEN 2A & 2B
Sturge weber Syndrome
Succinyl dehydrogenase mutations

→ aka RULE OF TEN TUMOR
↳ 10% → BIL
↳ 10% → Extra adrenal location [PARAGANGLIOMA]
↳ 10% → Children
↳ 10% → no HTN
↳ 10% → malignant [metastasis is the differentiating feature [vs Benign]
↳ 25% → Familial [previously it was 10%.]