Inflammation: 'itis' (defense / protective response)

→ response of vascularized connective tissue to injurious stimuli

→ Injurious stimuli – infections
– immune reaction
– foreign bodies
– tissue injury

Inflammation

ACUTE	(> 6 weeks) CHRONIC
→ shorter duration	→ longer duration
→ sudden onset	→ insidious onset
→ local signs & symptoms are more prominent	→ less prominent
→ less prominent	→ tissue healing & fibrosis is more prominent
→ NEUTROPHIL	→ MONOCYTE / MACROPHAGE / (mononuclear cells) LYMPHOCYTES / PLASMA CELLS

Purpose of Inflammation: 3 D's – Destroy
– Dilute
– Dam-off

Desired result of inflammation: – Regeneration
– Fibrosis

Inflammation is a double edged sword.

- It is protective, but in some cases it has -ve effect
- -ve effects – rheumatoid arthritis
  – atherosclerosis
  – lung febrosis

Steps of Inflammation: 5 R's

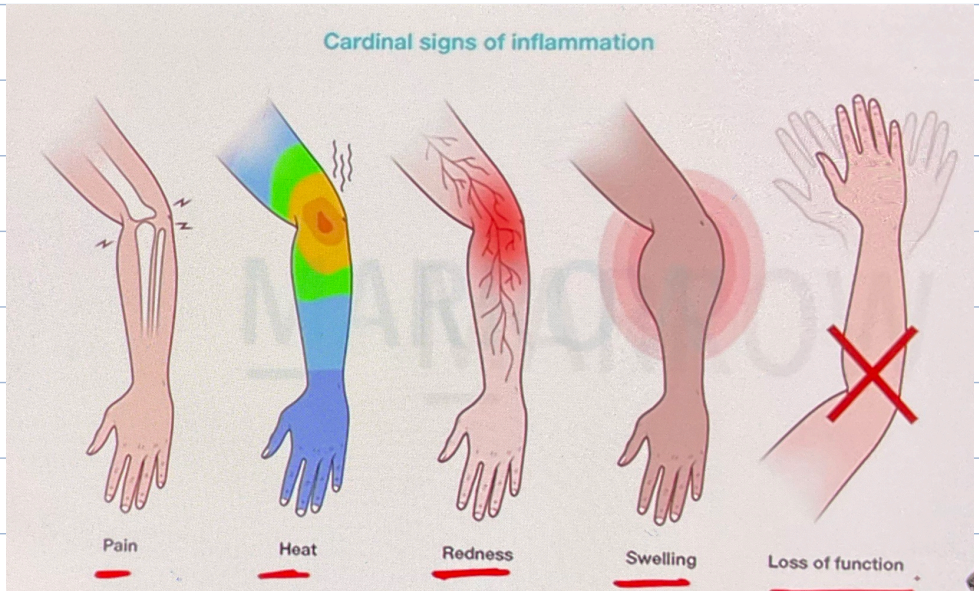
- Recognition of injurious events
- Recruitment of leukocytes
- Removal of agent
- Regulation of response
- Resolution

Signs of Inflammation:

i. Redness / rubour
ii. Swelling / tumor
iii. Heat / calor
iv. Pain / dolor

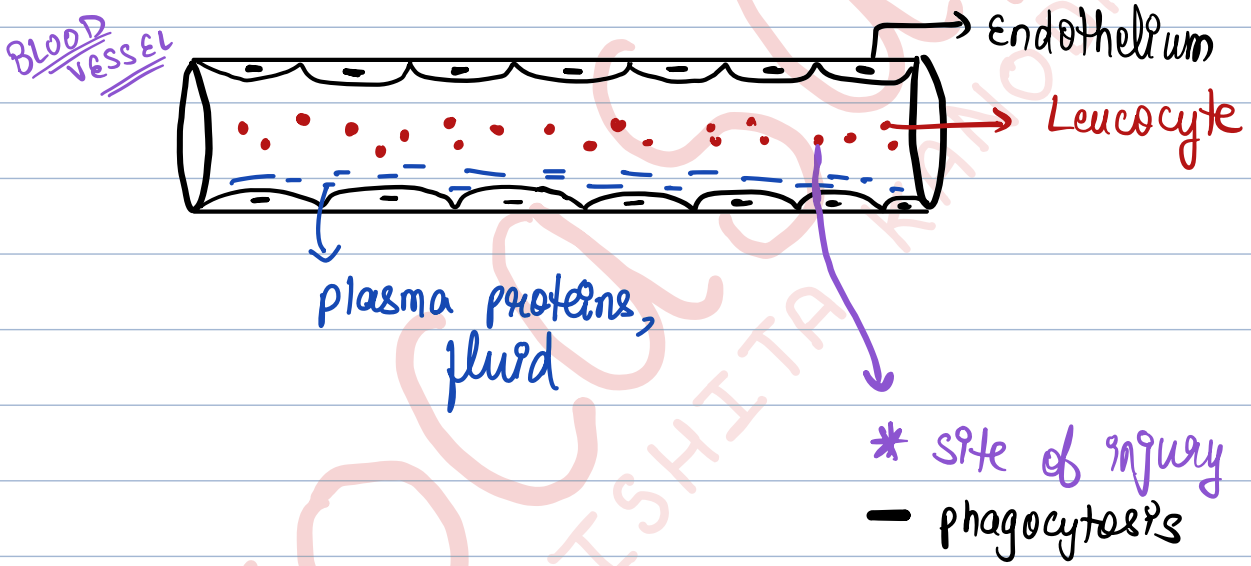
} 4 cardinal signs of inflammation (given by Celsus)

Virchow = Father of modern Pathology
↳ gave 5th sign of inflammation: Functio Laesa (loss of function)



Mechanism of Acute Inflammation: vascular response + cellular response

- Marker for endothelium: CD 34



Vascular events

Early transient arteriolar vasoconstriction (few seconds)

↓

Vasodilation

↓

Increased vascular permeability — Hallmark of inflammation

↓

Stasis / Slowing

Cellular events

Margination

↓

Rolling

↓

Adhesion

↓

Transmigration / Diapedesis

↓

Chemotaxis

↓

Opsonisation

↓

Phagocytosis

Early Transient Arteriolar Vasoconstriction:

→ lasts for a few seconds
→ mediators — nerve reflex
— endothelins

Vasodilation: usually involves arterioles

→ mediator : - histamine
→ causes increased blood flow ⇒ Redness (Rubor)
⇒ Heat (calor)

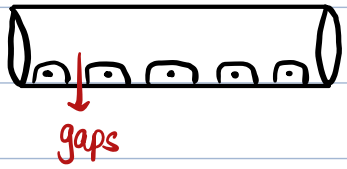
Increased Vascular Permeability:

→ usually affects the venules
→ mediator : - histamine
→ Hallmark of acute inflammation
→ causes leakage of proteins & fluids from the blood vessel leading to extravascular accumulation ⇒ SWELLING / TUMOR
(protein rich fluid = exudate)

EXUDATE	TRANSUDATE
• specific gravity > 1.020	• < 1.020
• responsible for inflammatory edema	• responsible for non-inflammatory edema
• rich in proteins & cells	• poor in proteins & cells
• increased LDH	• decreased LDH

Mechanism of Increased Vascular Permeability:

i. Endothelial Cell Contraction / Retraction [formation of endothelial gaps]



→ usually affects the post capillary venules

→ mediators : – histamine
– leukotrienes

→ this is an immediate transient response

ii. Direct Endothelial Injury:

MILD

→ burns

→ responsible for delayed prolonged response

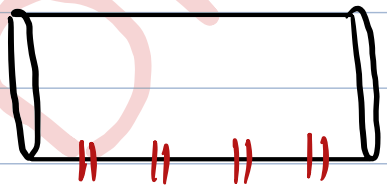
SEVERE

→ sepsis

→ responsible for immediate sustained response.

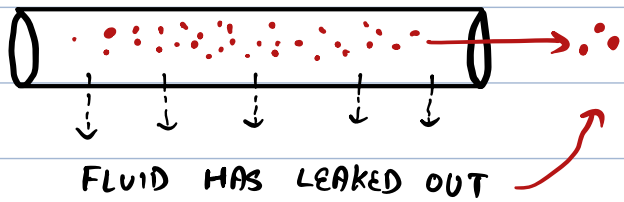
iii. Leucocyte Mediated Endothelial Injury

iv. Increased transcytosis:



→ formation of tunnels in blood vessel which cause leakage

Stasis / Slowing of blood flow:



∴ RBC's accumulate inside

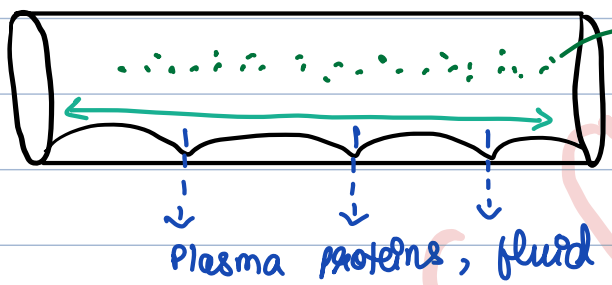
↓

hyperviscosity

↓

slowing of flow

CELLULAR EVENTS:



∴ margin is free & stasis has occured

↓

PAVEMENTING / MARGINATION

Pavementing / Margination:

→ process of redistribution of leucocytes to the margins of blood vessel

Rolling: Leucocytes roll over the endothelium

↳ process of attachment, detachment & reattachment to endothelium [LOOSE ATTACHMENT]

→ mediators: – Selectins

- E selectin: endothelium
- P " : platelets, endothelium
- L " : leucocytes

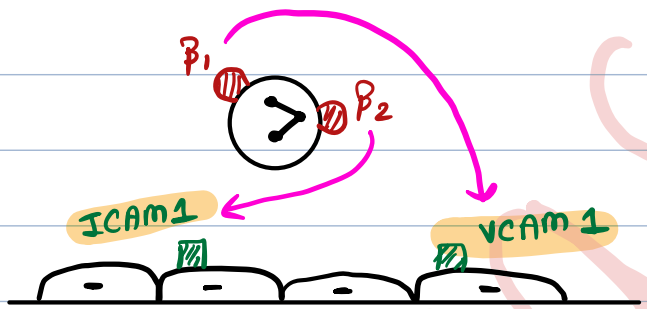
Endothelial surface	Lymphocyte surface
P- selectin	Sialyl Lewis X modified glycoprotein
E- selectin	Sialyl Lewis X modified glycoprotein
Glycam1 - CD34	L - selectin

→ expressions of selectins overall in induced by IL-1, TNF.

→ Redistribution of p-selectins from the Weibel Palade bodies inside endothelial cells is mediated by — Histamine
— Thrombin.

Adhesion: firm attachment of leucocytes to endothelial cells.

→ Mediators: INTEGRINS → β1 / VLA 4
→ β2 / LFA 1 / MAC 1
} present on leucocytes



→ Chemokines & chemoattractants cause leukocyte activation & conversion of low affinity integrins on leukocytes to high affinity state resulting in firm adhesion of leukocytes to endothelium.

Transmigration (Diapedesis): movement of leucocytes across the endothelium or basement membrane.

→ Mediators: PECAM 1 or CD 31

↓

Causes synthesis of collagenases or MMP's (matrix metalo proteinases)

↓

digests the endothelium / basement membrane.

Chemotaxis: movement of leucocyte in the direction of a chemical stimulus towards the site of injury.

→ Unidirectional & targetted movement

Chemotactic Mediators:

EXOGENOUS	ENDOGENOUS
• Bacterial cell wall products like - N-formyl methionine	• L - LTB4 • I - IL 8 • C - C5a

Mechanism of Chemotaxis:

Ligand binds to the 7 transmembrane g-protein coupled receptor

↓

increased cytosolic Ca^{2+}

↓

polymerization of actin

↓

Chemotaxis

Opsonization: (does not happen every time)

→ coating of microbe so that, it is easily phagocytosed ['to make tasty']

OPSONINS

- Fc fragment of IgG (best opsonin)
- (best) C3b, C4b, C5b
- serum proteins
- fibrinogen
- CRP

→ discovered by Elie Mechnikoff.

Phagocytosis: (killing of microbe)

1. Recognition & attachment
   - Scavenger receptors
   - Mannose receptors
   - Receptors for opsonins
2. Engulfment
3. Killing

Phagocytosis (cell eating)

→ refers to process of engulfment & destruction of solid particulate material by the cells

Steps:

(I) Chemotaxis: process of migration of neutrophils to the site of infection

→ chemical factors that are released from the site of infection/inflammation attracts the neutrophils & are called chemotaxins (eg- complement proteins)

→ neutrophils change their shape to become highly amoeboid.

→ bone marrow is stimulated to produce more neutrophils.

(II) Diapedesis: process of neutrophils passing through the capillary endothelial cell to reach the site of invasion in tissue

→ neutrophils first marginate (margination & pavementing) & adhere tightly to endothelial lining (rolling & adhesion) with the help of L-selectins

(III) Opsonization & Adherence: process by which bacteria are made tasty to the phagocyte

→ chemicals that promote opsonisation (opsonins) — IgG antibody, complement proteins (C5a, C3b)

→ opsonized bacteria bind to the receptor on the neutrophil membrane by a process called adherence.

(IV) Ingestion (Endocytosis): membrane of phagocyte extends projections (pseudopodia) from both sides to engulf the microbe.

→ The pseudopodia unite to form phagocytic vesicle around the microbe

→ phagocytic vesicle fuses with lysosome to form phagolysosome.

(pseudopodia formation ⇒ actin polymerization)

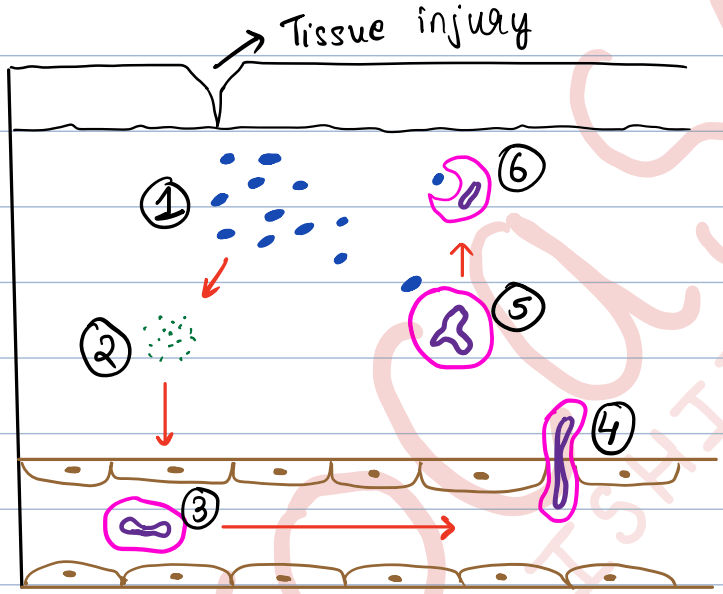
⑤ Killing: non-oxidative / oxidative

→ **Non-oxidative**

- Lysosome hydrolyzes the cell wall of bacteria & lactoferrin sequesters iron which is required for bacterial growth.
- Defensins released from azurophil granules have unusual cyclic structure & kill bacteria by disrupting their outer membrane & breaking single-strand DNA

→ **Oxidative** – by oxygen metabolites like $OH^{\cdot}$, O_2^-, H_2O_2

- these metabolites are generated by NADPH oxidase
- Activation of NADPH oxidase is associated with increased oxygen intake of neutrophil called respiratory burst.



① = Invasion
② = Release of chemotaxins
③ = Chemotaxis
④ = Diapedesis
⑤ = Opsonization
⑥ = Ingestion & Killing.

Frustrated Phagocytosis:

→ occurs when the cell encounters material which cannot be phagocytosed.
eg: immune complexes bound to basement membrane

→ leucocytes starts releasing lysosomal enzymes outside through which phagocytosis occurs.

Leucocyte Function Defects:

- LAD 1 (Leucocyte Adhesion deficiency)
- LAD 2

→ autosomal recessive
→ Presentation: — recurrent infections

Pathogenesis:

LAD 1: defect in synthesis of β2 integrin (CD11/CD18).
LAD 2: " " " " sialyl Lewis x modified glycoprotein.

→ delayed separation of umbilical stump in LAD 1.
→ LAD 2 is sometimes associated with Bombay Blood Group.

- Chronic Granulomatous Disorder [CGD]:

→ 75% cases ⇒ X-linked recessive (∴ more common in males)
25% cases ⇒ Autosomal recessive

Pathogenesis:

→ defect in NADPH oxidase (required for oxidative killing)

Clinical Presentation: — increased risk of infections with catalase positive organisms

→ Nitro Blue Tetrazolium (NBT) Test ⇒ screening test for CGD
Confirmatory Test ⇒ DHR [Dihydro Rhodamine] Test

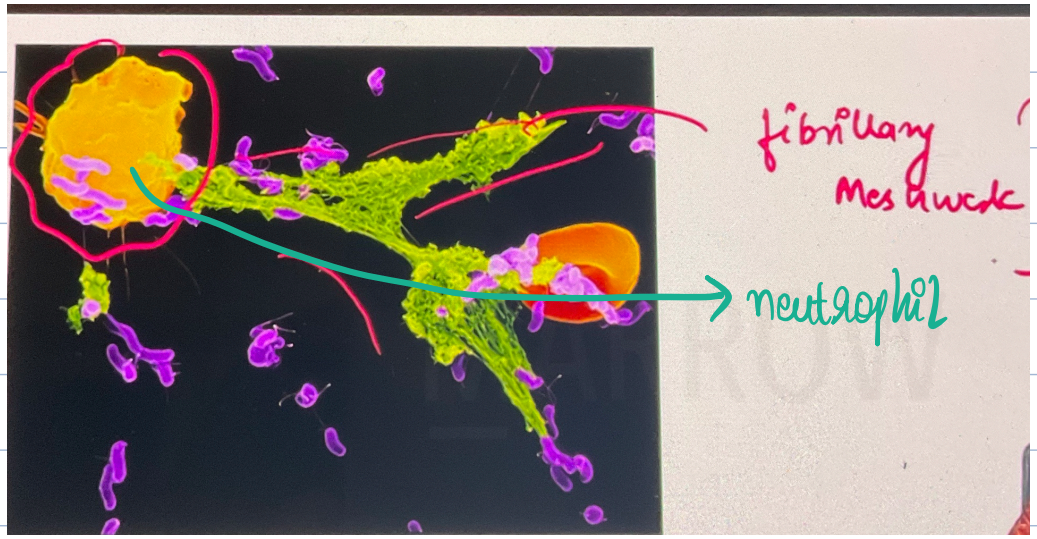
• **Chediak Higashi Syndrome:**

→ autosomal recessive
→ defect in LYST protein which is required for phagolysosome fusion.
→ Presentation: — fever
— recurrent infections
— albinism
— Nerve defects / deafness
— thrombocytopenia.
— silver gray hair

H&E: presence of giant granules in neutrophils in P/s.

NET (Neutrophil Extracellular Traps):

→ extracellular fibrillar meshwork produced by neutrophils in response to severe infections
→ helps to limit the spread of infections
→ produces a lot of anti-microbial substances
→ Arginine helps in formation of NETs
→ excess NETs can lead to increased risk of autoimmune disorders like SLE (Systemic Lupus Erythematosus)

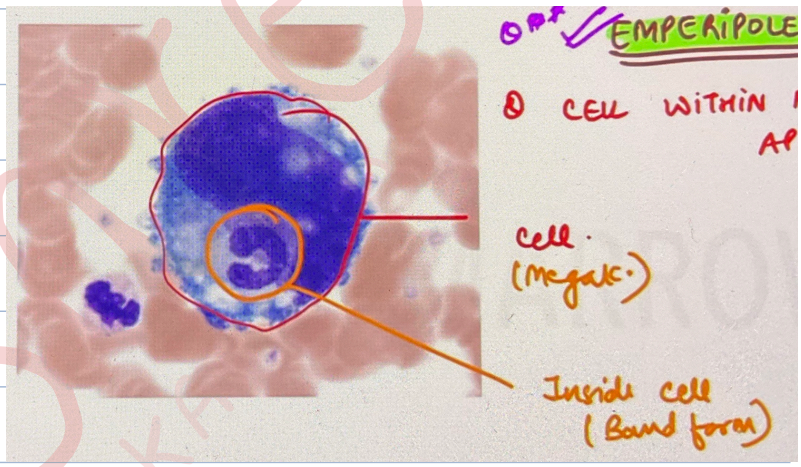


Emperipolesis :

→ cell within a cell appearance

→ ~~differential diagnosis~~: phagocytosis (but in phagocytosis, the cell inside is dead).

→ but in emperipolesis, the cell inside can be extruded without any abnormality.



→ Seen in:
- Rosai Dorfman Syndrome
- CLL [chronic lymphocytic leukemia]
- Hematolymphoid disorders
- Myelodisplastic Syndrome (MDS)

Acute appendicitis - H & E

→ Neutrophil (infiltrate) in muscle layer (HALLMARK)

→ Mucosa : ulceration / erosion

[acute inflammatory exudate in the appendicular lumen]

→ Submucosa : hyperplastic lymphoid follicles (reactive germinal centres)

→ Serosa : consistent blood vessels

GROSS :

→ dull colour (not shiny) externally

→ some exudate is seen covering it

→ Cut surface : patent / non-patent lumen (haemorrhage, faecoliths)

VIVA QUESTIONS

1) Clinical features
2) H & E
3) gross features
4) Complications - appendicular abscess, mass, perforation, pseudomyxoma peritonii, mucinous carcinoma of ovary
5) Etiology

(Consolidation)

Lobar Pneumonia: heavy, firm lungs

(Normally: lungs are spongy)

→ acute bacterial infection of lung tissue of a partial / complete lobe

[Bronchopneumonia: bilateral, patchy]

(Atypical pneumonia)

→ Cough, fever

Microscopy:

- Stage of Congestion
- Stage of Red hepatization - consistency of liver; RBC & inflammatory cells in lumen.
- Stage of Gray hepatization - fibrino purrulent exudate in lumen; clearing / retraction space
- Stage of Consolidation

Complications - empyema, resolution, lung abscess, meningitis, systemic spread, valvular diseases, etc. (pleural effusion)

Chronic Inflammation:

- granulomatous (specific)
- non-specific

→ longer duration
→ insidious onset
→ Cell of chronic inflammation : Mononuclear cells (Monocyte / macrophage).

- Infiltration of tissue with lymphocytes, monocytes or plasma cells.
- Tissue destruction/injury ⇒ hallmark of chronic inflammation
- Attempts at healing / repair

Cells of Chronic Inflammation:

- **Monocyte / Macrophage:**

- monocyte present in blood
- in tissue, it is called macrophage.

Brain	⟹	Microglia
Lymph Node	⟹	Sinus histiocytes
Bone	⟹	Osteoclasts
Lung	⟹	Pulmonary alveolar macrophages / Dust cells
Liver	⟹	Kupffer Cells
Spleen	⟹	Littoral cells
Placenta	⟹	Haufbauer cells
Kidney	⟹	Mesangial Cells

Macrophage:

CLASSICALLY ACTIVATED
M_1

→ pro inflammatory

→ activated by IFN-γ or TLR (Toll like receptor)

→ leads to:

- production of ROS (to kill microbes) or
- production of IL-1, IL-12, IL-23 which cause inflammation.

ALTERNATELY ACTIVATED
M_2

→ anti-inflammatory

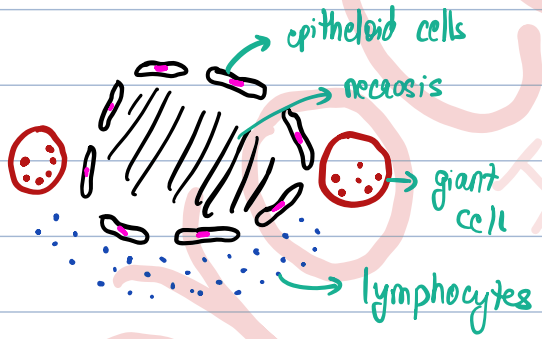
→ activated by IL-4, IL-13

→ leads to production of IL-10 & TGF-β

⇓

Cause fibrosis

Granuloma: Type of chronic inflammation



→ collection of modified macrophages called epithelioid cells

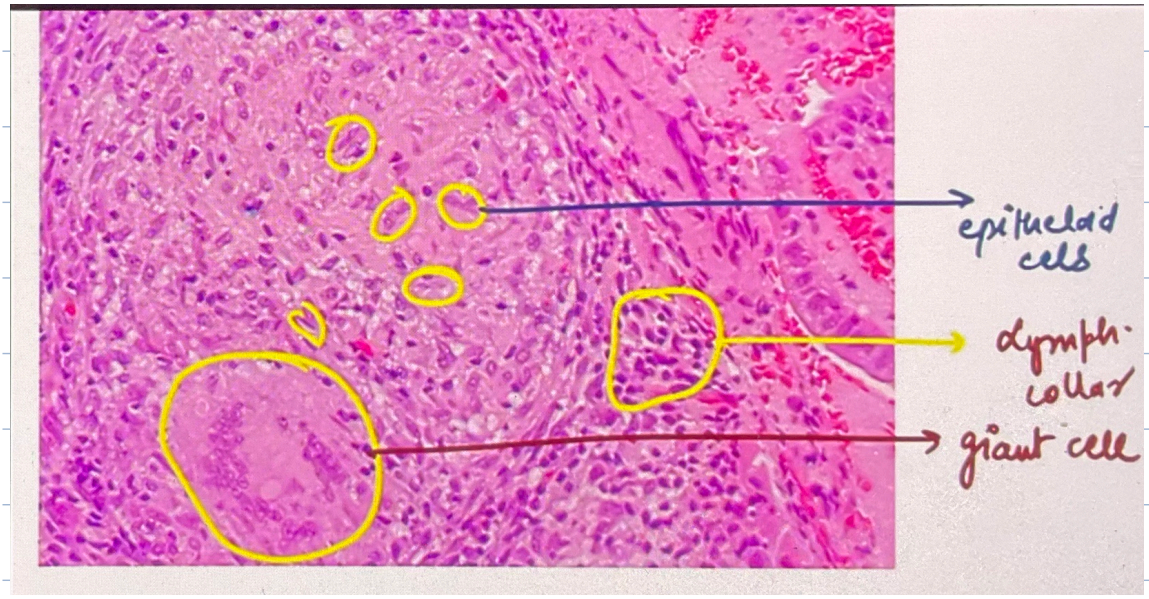
→ surrounded by a collar of lymphocytes

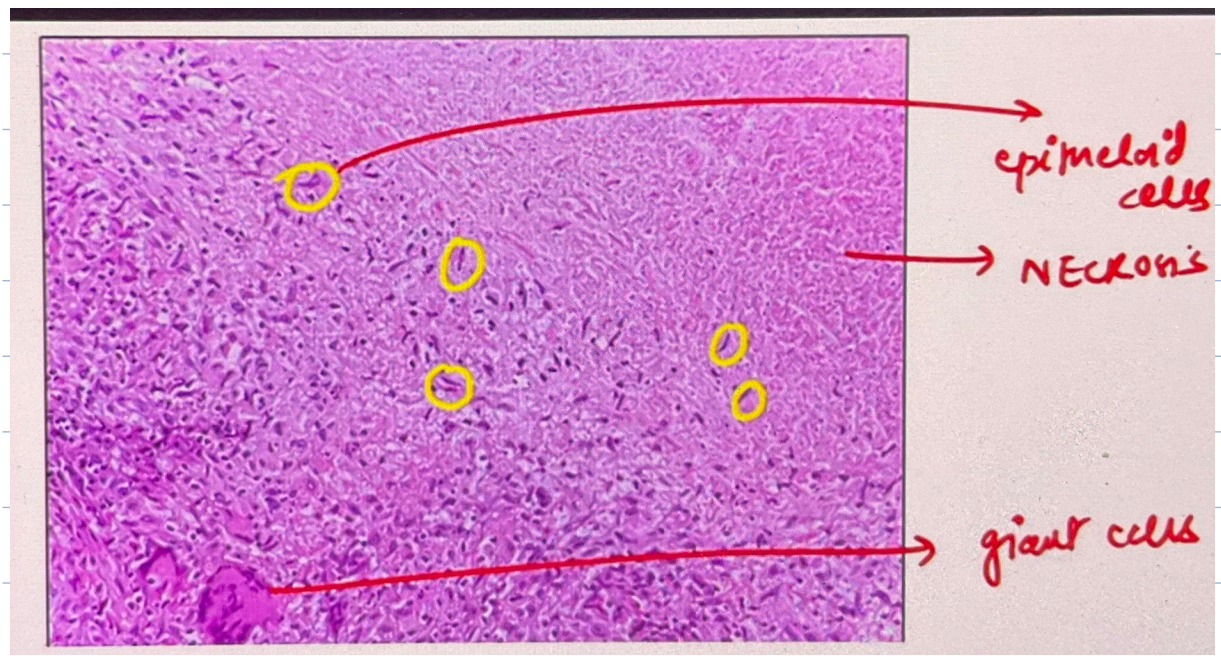
→ presence of giant cells

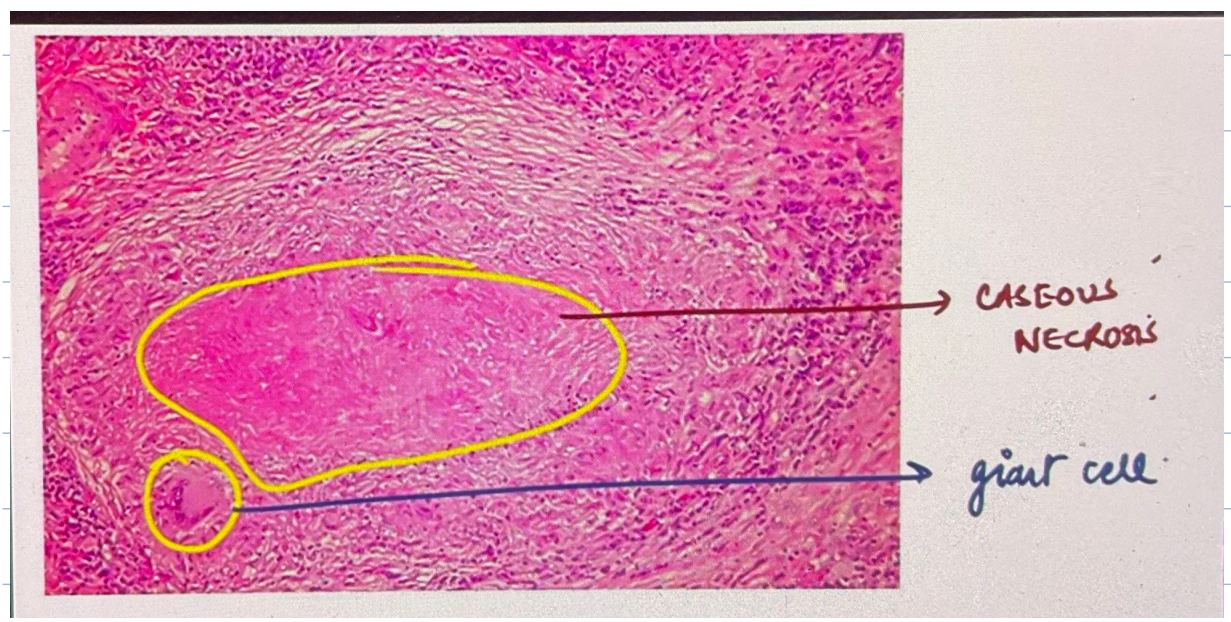
→ centre shows caseous necrosis in case of caseating granuloma

→ epithelioid cells: epithelium like appearance with a slipper shaped nucleus

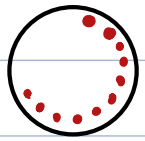
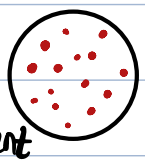
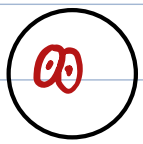
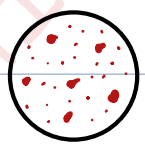
→ giant cell: formed by the fusion of a large number of epitheloid cells







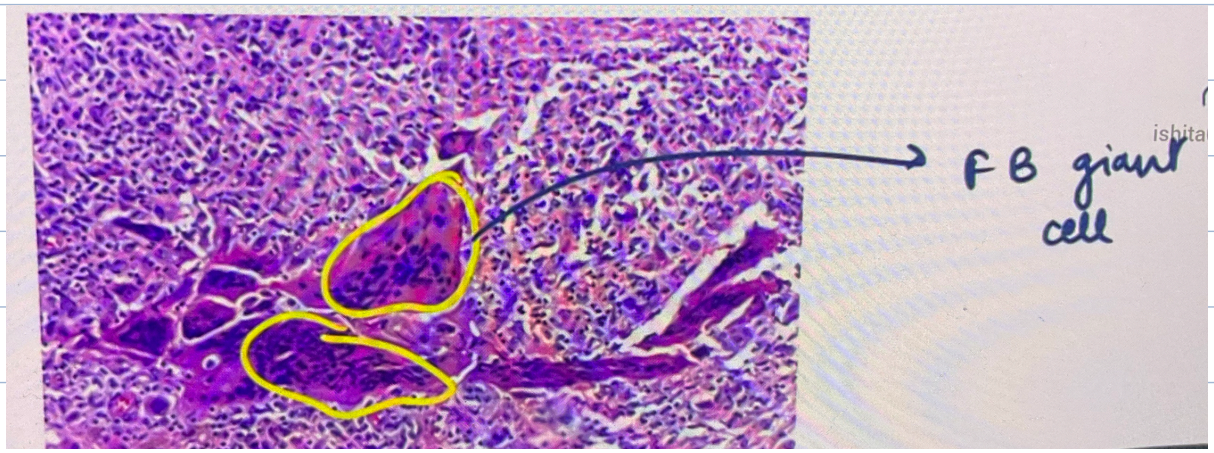
Types of Giant Cells:

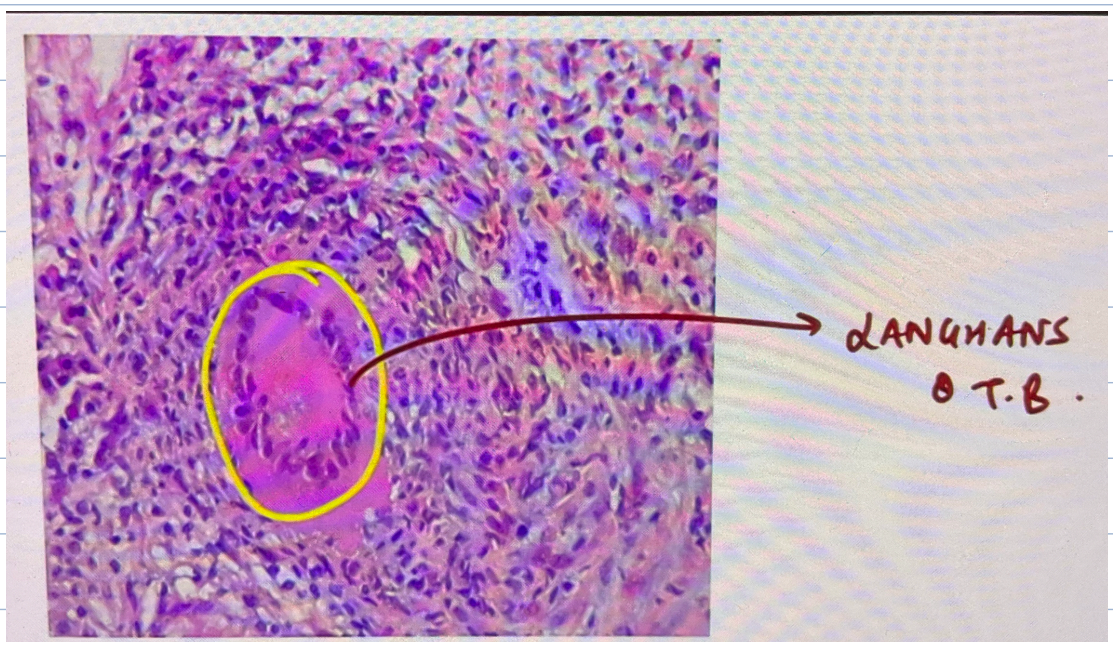
- **LANGHANS GIANT CELLS**  → horse-shoe / necklace arrangement of nuclei
  → seen in TB
- **FOREIGN BODY**  → seen with foreign bodies like Talc / sutures
  → haphazard arrangement of nuclei
- **TUMOR GIANT CELLS / RS CELL (Reed Sternberg Cells)**  → Seen in Hodgkin's lymphoma
  → owl's eye appearance
- **TOUTON GIANT CELL**  → xanthoma
  → foamy cytoplasm / vacuolated cytoplasm
- **ASCOFF GIANT CELL**
  → seen in rheumatic heart disease
- **WARTHIN FINKELDEY CELL**  → seen in measles
  → intracytoplasmic / intranuclear inclusions.

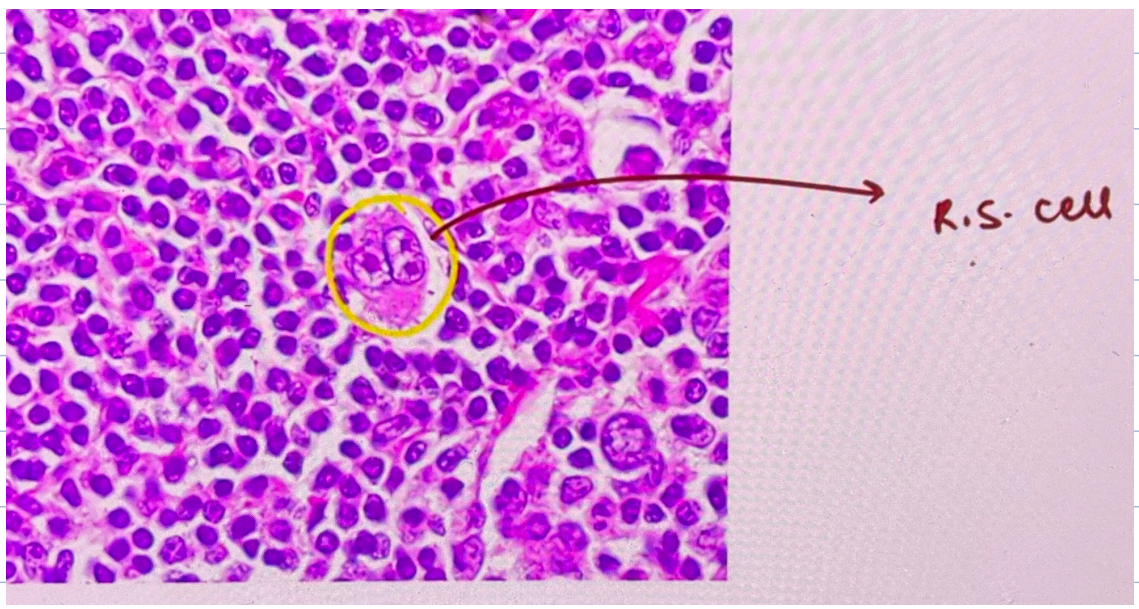
Inclusions in giant cells
- Asteroid body
- Schauman body

} seen in sarcoidosis

↓
composed of Ca^{2+}.
∴ densely basophilic







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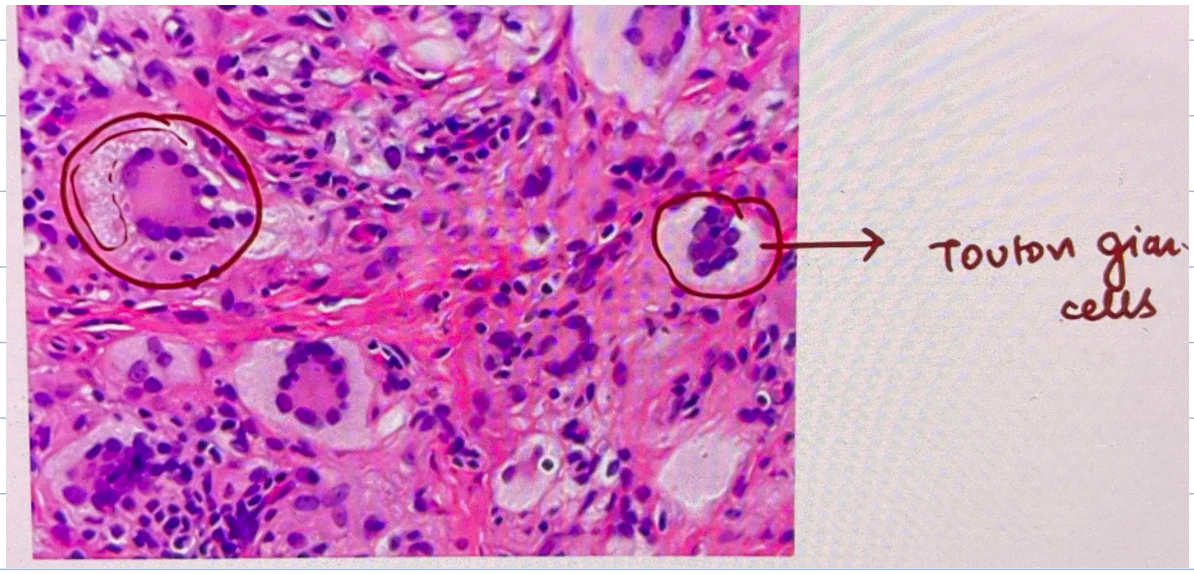
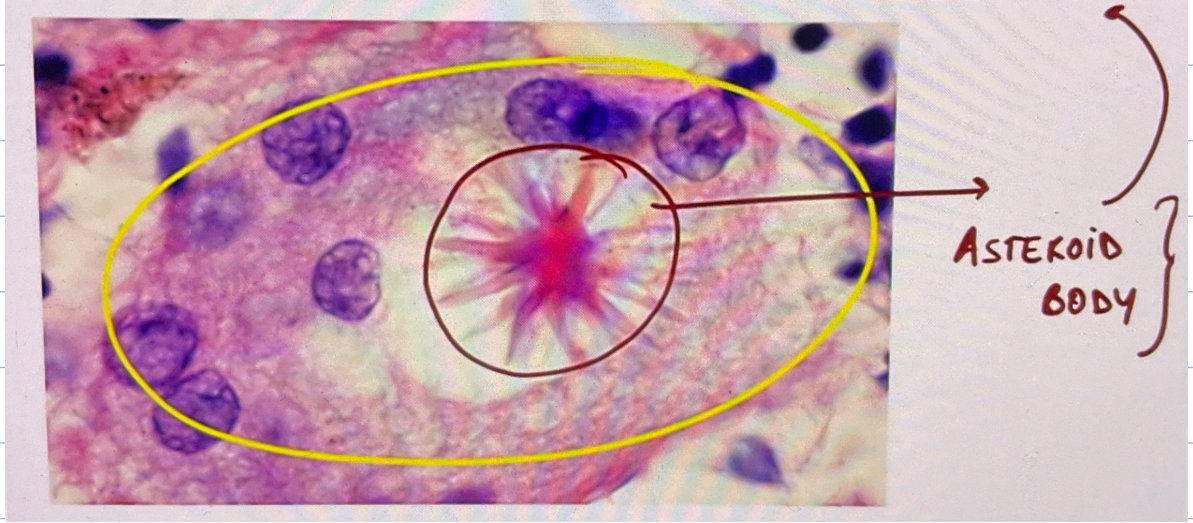
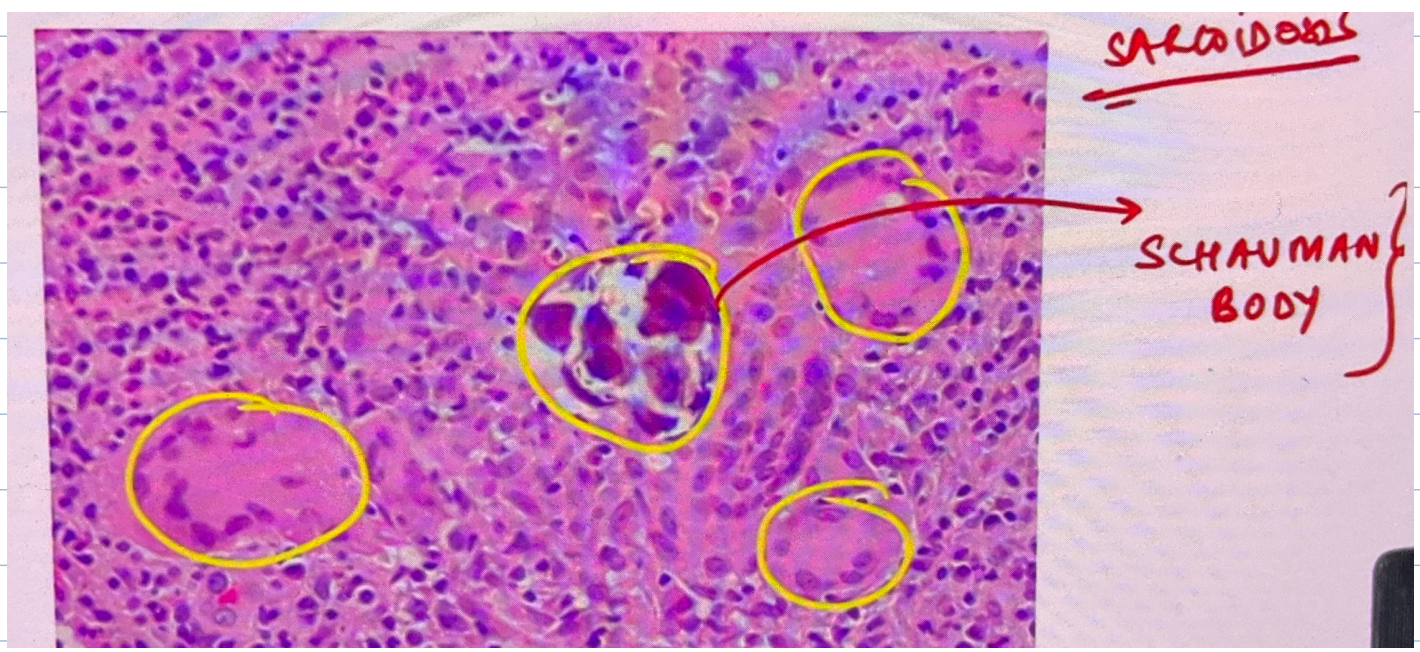


INCLUSIONS IN GIANT CELLS

SARCOIDOSIS





Granuloma Formation:

→ Type IV hypersensitivity reaction

→ IFN-γ ⇒ most important in granuloma formation

APC + CD4 + TH1 lymphocyte

↓

production of IFN-γ

↓

activation of macrophage

↓

now called epitheloid cell

↓

fusion of epitheloid cells to form giant cell

} granuloma

[APC = antigen presenting cell]

Types of Granulomas:

Foreign body granuloma

→ seen when there are foreign bodies like talc, suture, etc.

→ No immune reaction

→ Foreign body giant cells

Best microscopy to visualise:

Polarising microscopy

Immune granuloma

→ Immune reaction

→ Type IV hypersensitivity reaction

Granulomatous Disorders:

Infective Cause

- → TB ⇒ caseating granuloma (may show non-caseating)
- → Leprosy
- → Syphilis (tertiary / gumma stage)
  - ↳ presence of a lot of plasma cells
- → Dark's granuloma in malaria
- → Cat scratch disease
- → Lymphogranuloma venerum (LGV) } stellate granuloma
- → Q - fever ⇒ Dough nut / Fibrin-ring granuloma
  (allopurinol causes ↗)

Non-infective Cause

- → Sarcoidosis ⇒ non caseating or naked granuloma (may show caseation) due to absence of lymphocytic collar.
- → Crohn's disease
- → Giant Cell / granulomatous Arteritis
- → Churg Strauss Syndrome (eosinophilic granuloma)
- → Berylliosis

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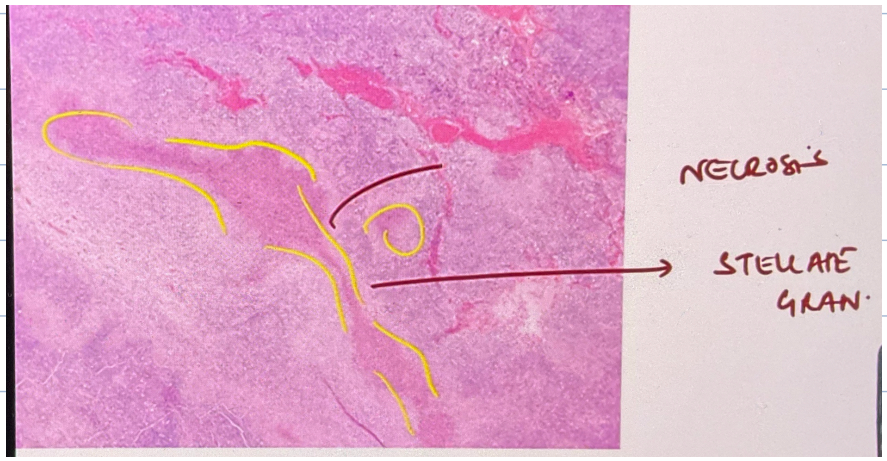
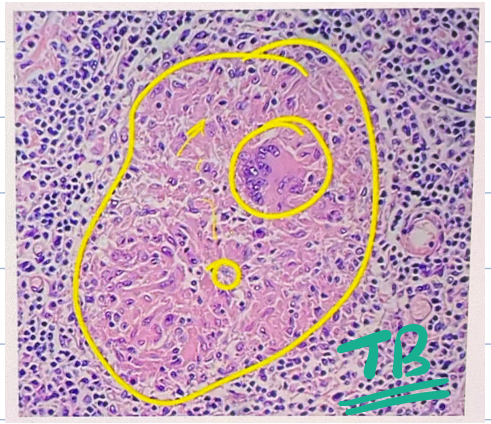
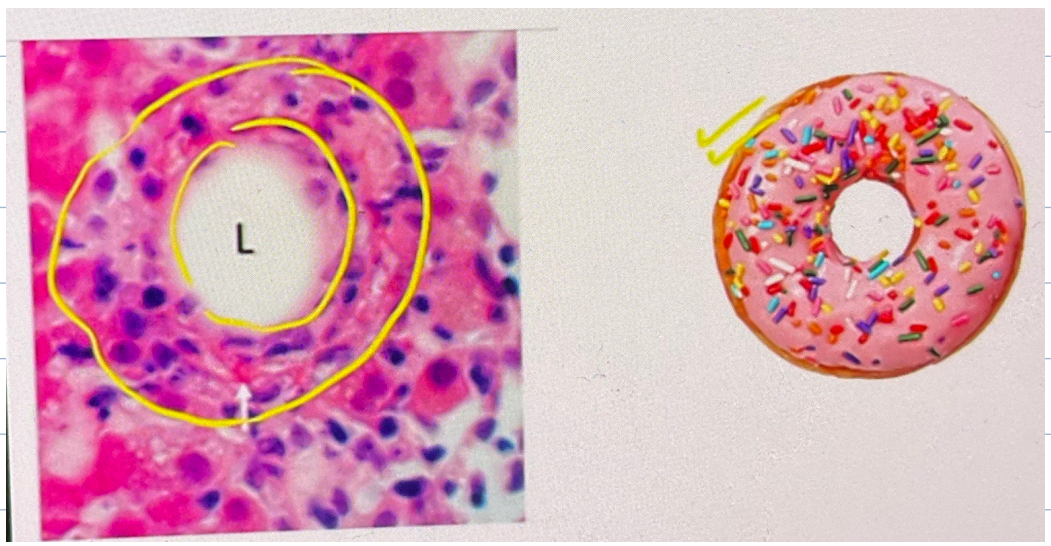






Examples of Acute Inflammation:

- pyogenic abscess
- Cellulitis
- Bacterial Pneumonia
- Pyaemia

Chronic Inflammation:

- granuloma formation
- tuberculous leprosy
- chronic osteomyeletis.

Systemic Effects of Inflammation:

- Fever: IL-1, IL-6, TNF-α

Acute phase reactants:

Positive

→ increase during inflammation

- CRP
- Fibrinogen
- IL-6
- Hepcidin
- Ferritin
- Haptoglobin
- Ceruloplasmin
- factor VIII
- Von willebrand factor

Negative

→ decrease during inflammation

- transferrin
- albumin
- transcortin

→ systemic changes in acute inflammation are collectively known as acute phase response or SIRS [systemic inflammatory response syndrome]

- Cause: due to cytokines produced by leukocytes in response to infection & immune reaction.

Changes: — Fever
— Raised plasma levels of acute phase proteins
— changes in leukocytes
— other features

Fever: caused by pyrogens

→ exogenous pyrogens (bacterial products like LPS) stimulate endogenous pyrogens (IL-1, TNF) to be released from leukocytes.

→ these cytokines increase the enzymes cyclooxygenases resulting in conversion of arachidonic acid into prostaglandins

→ pyrogens & prostaglandins act on hypothalamic thermoregulatory center causing fever

Raised Plasma Levels of Acute-Phase Proteins:

→ synthesized in the liver

→ synthesis of these proteins by hepatocytes is increased by cytokines (IL-6, IL-1, TNF)

Functions of Acute Phase Proteins:

(i) CRP & SAA bind to microbial cell walls & may act as opsonins

(ii) Fibrinogen binds to red cells to form rouleaux & is responsible for raised erythrocyte sedimentation rate (ESR)

(iii) During acute inflammation, acute phase proteins have beneficial effects, but prolonged production (especially SAA) like in chronic inflammation cause secondary amyloidosis.

(iv) CRP levels when increased in plasma, serves as a marker for necrosis & disease activity.

Changes in Leukocytes:

Leukocytosis: TLC > 11,000 / μL

Causes: due to increased release of leukocytes from the bone marrow caused by cytokines including CSF's [colony stimulating factors], TNF, IL-1.

→ Bacterial infections: Neutrophilia

Viral infections: Lymphocytosis

Parasitic infestations: Eosinophilia.

Leukopenia: decreased number of circulating white cells is associated with few infections like typhoid fever & some viruses like rickettsia & certain protozoa.

Other Features:

→ increased pulse & BP

→ anorexia & malaise

→ production of large quantities of cytokines which can result in DIC [disseminated intravascular coagulation] & cardiovascular failure.

Chemical mediators of Inflammation:

Steps of Inflammation	Mediators
① Early transient arteriolar vaso constriction	– nerve reflex – endothelins
② Vasodilation & increased vascular permeability	– Histamine – leukotrienes
③ Rolling	– Selectins
④ Adhesion	– Integrins
⑤ Transmigration	– PECAM 1 or CD 31
⑥ Exogenous chemotactic mediators	– Bacterial cell wall products (like N-formyl methionine)
⑦ Endogenous chemotactic mediators	– LTB_4 – C5a – IL 8
⑧ Opsonization	– Fc fragment of IgG – C3b, C4b, C5b – Serum protins, CRP.

Histamine:

Source: mast cell, basophil, platelets

Function: – vasodilation
– increased vascular permeability
– broncho constriction

Prostaglandins & Leukotrienes:

→ 20 carbon poly-unsaturated fatty acids [PUFA]

→ derivatives of arachidonic acid derived from membrane phospolipids.

Cytokines: soluble polypeptides

Function	Cytokine
Pro-inflammatory	– IL 1, 2, 4, 6, 8
	– IFN γ
	– TNF α
Anti-inflammatory	– IL 4, 6, 10
	– TGF β
Cancer cachexia	– IL 4, 6
	– TNF α
Angiogenesis	– VEGF
Fever	→ IL 1
Eosinophil activation	→ IL 5

Complement Proteins:

→ series of 20 proteins present in plasma

→ synthesized by liver

Functions:	
– Anaphylatoxins	C3a, C5a
– Chemotactic	C5a
– Opsonin	C3b
– MAC	C5b-9

Selectins: cell surface lectins (family of Cell Adhesion Molecules)

→ single chain transmembrane glycoprotein

Types of selectin	Site
E selectin	– Endothelium
P selectin	– Platelets, endothelium
L selectin	– Leukocytes

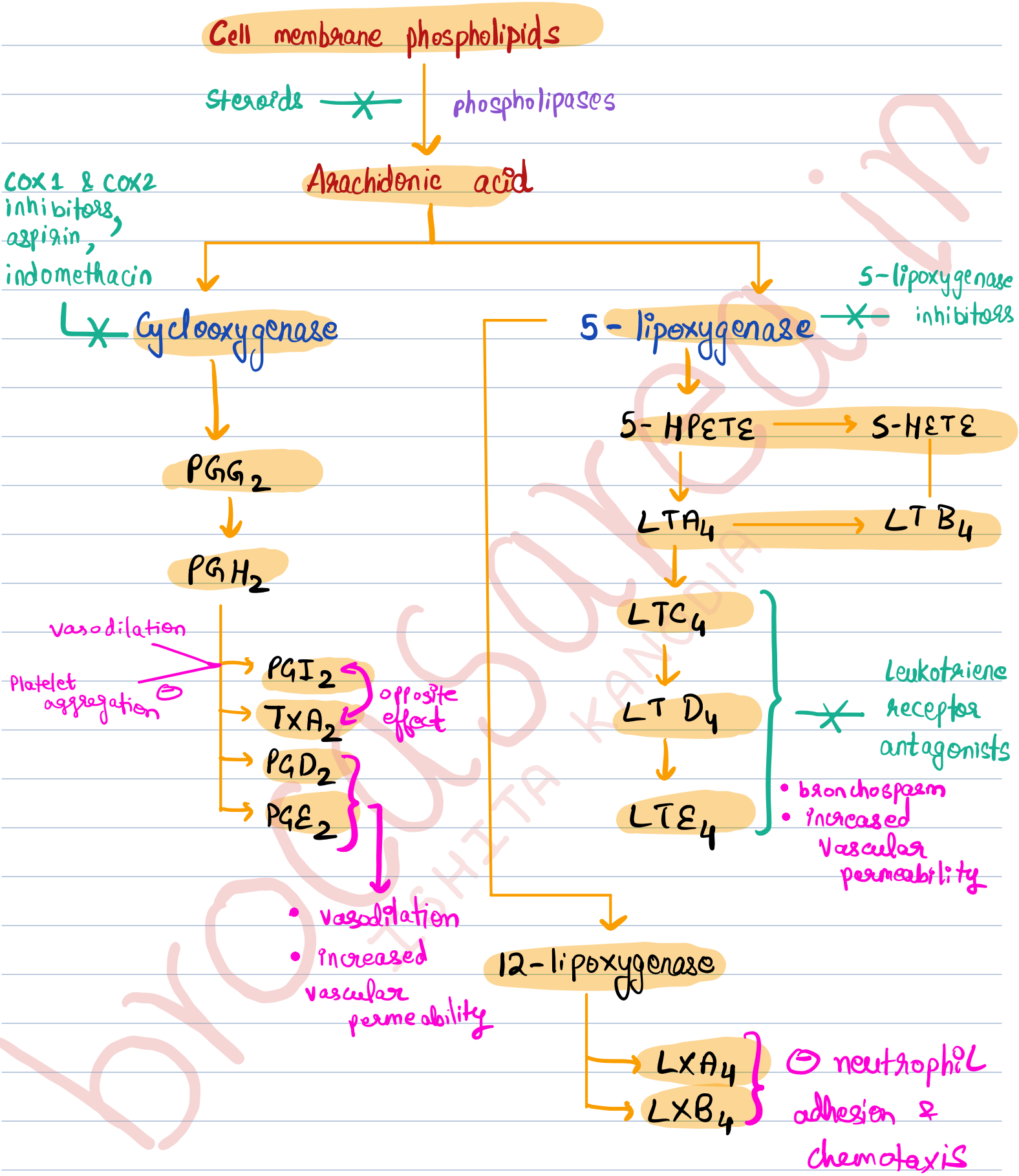
Endothelial surface	Lymphocyte
P selectin	Sialyl Lewis x modified glycoprotein
E selectin	" " " " "
Glycam 1 - CD 34	E selectin

→ Expression of selectins is induced by IL-1, TNF.

Integrins:

Integrin on Leucocyte	Receptor on Endothelium
β1 or VLA 4	VCAM 1
β2 or LFA 1 or MAC 1	ICAM 1

PECAM 1 or CD31: cause synthesis of collagenases & MMPs (matrix metalloproteinases) which digest endothelium / basement membrane & promote diapedesis.


Cell membrane phospholipids
Steroids
phospholipases
Arachidonic acid
COX1 & COX2 inhibitors, aspirin, indomethacin
Cyclooxygenase
5-lipoxygenase
5-lipoxygenase inhibitors
PGG2
PGH2
vasodilation
Platelet aggregation
PGI2
TxA2
opposite effect
PGD2
PGE2
• vasodilation
• increased vascular permeability
5-HPETE
5-HETE
LTA4
LTB4
LTC4
LTD4
LTE4
Leukotriene receptor antagonists
• bronchospasm
• increased Vascular permeability
12-lipoxygenase
LXA4
LXB4
neutrophil adhesion & chemotaxis

PGI_2 : - vasodilation
- inhibits platelet aggregation

TXA_2 : - vasoconstriction
- promotes platelet aggregation

PGD_2, PGE_2 - vasodilation
- increased vascular permeability
- leukocyte chemotaxis

LTC_4, LTD_4, LTE_4 - bronchospasm
- increased vascular permeability

LXA_4, LXB_4 - inhibit neutrophil adhesion
- inhibit chemotaxis

Wound Healing & Tissue Repair :

Regeneration: dead cells are replaced by same parenchymal cells.

Repair: dead cells are replaced by fibrous connective tissue.

Types of Cells:

Permanent

→ never divide
→ do not enter the cell cycle
→ remain in G0 phase.
- Neurons
- Skeletal muscle
- Cardiac muscle

→ can adapt only by hypertrophy, not hyperplasia

Stable

→ divide when needed
→ low replicative potential
- Liver
- PCT, DCT
- Endothelial cells
- osteoblasts

Labile

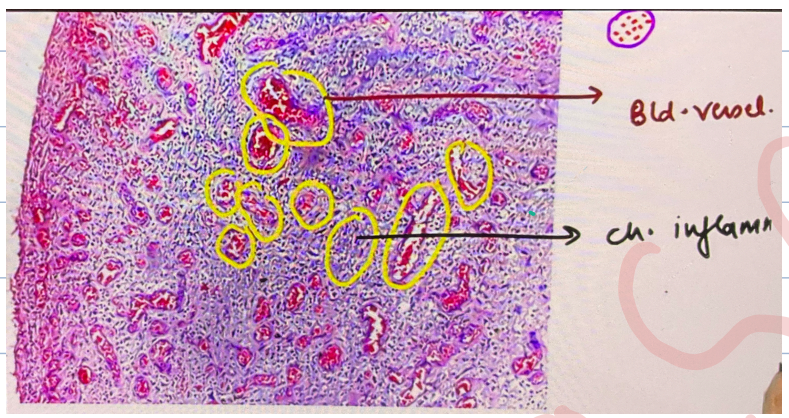
→ continuously dividing
→ high replicative potential
- Epithelium
- Skin
- Bone marrow
- GIT

Repair:

- Infiltration with chronic inflammatory cells like lymphocytes.
- Fibrosis
- Neo-vascularisation
  - by VEGF (vascular endothelial growth factor)

→ Hallmark of repair: formation of granulation tissue.

→ Hallmark of granulation tissue: Neo-vascularisation.



→ granulation tissue is red due to neo-vascularisation
- It is edematous due to leakage of plasma proteins from the new leaky blood vessels

Types of Wound Healing:

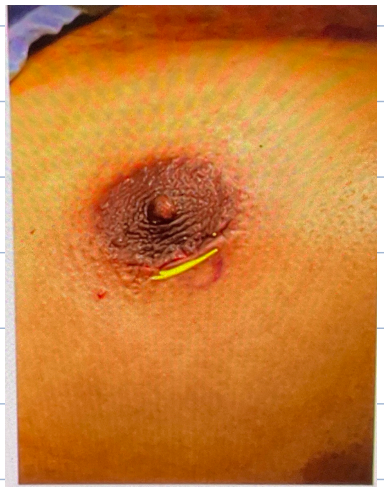
Healing by Primary Intention

→ clean, uninfected wounds

→ apposed margins

→ no tissue loss

eg: surgical incision



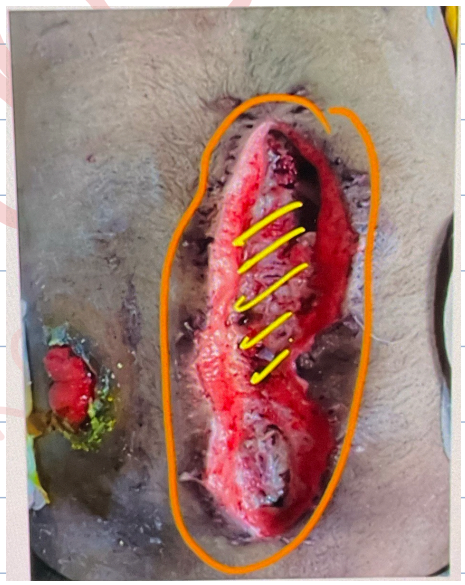
Healing by Secondary Intention

→ lacerated, infected wounds

→ tissue loss

→ irregular margins

eg: after RTAs



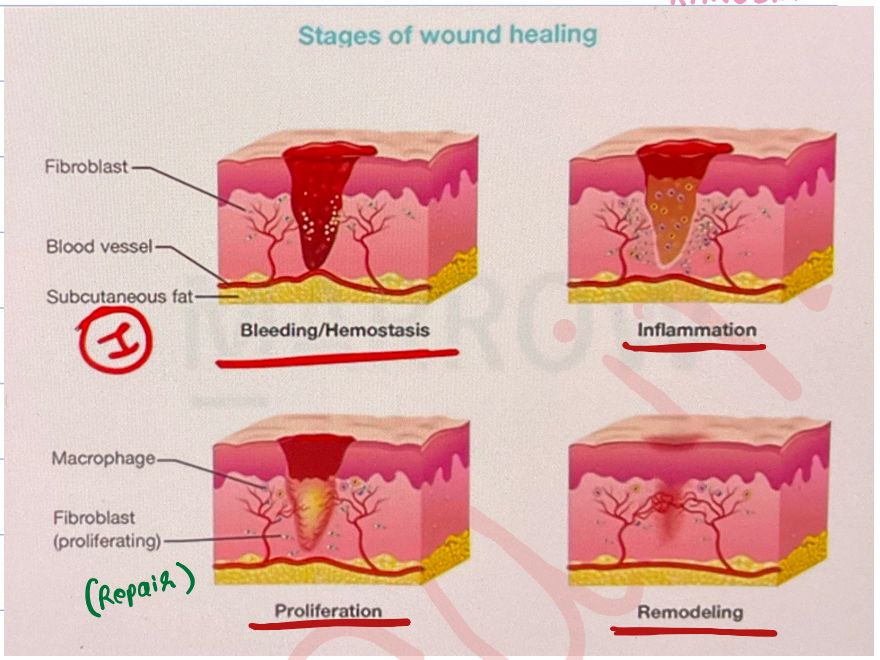
Feature	Primary Intention	Secondary Intention
Nature of wound	clean surgical wound	Unclean
Margins	surgical clean margin	Irregular
Sutures	used for apposition of margins	Cannot be used
Infection	Absent	May be infected
Amount of granulation tissue	Scanty ; at the incision gap & along suture track	Abundant & fill the gap
Outcome	Neat linear Scar	Irregular contracted scar
Complications	Rare	Infection & suppuration

Features of Secondary Union:

- shows more exudate & necrotic tissue
- clot or scab formed at the surface of wound is large
- Severe inflammatory reaction
- Larger defects require more amount of granulation tissue.
- extensive deposition of collagen with substantial scar formation
- **Wound Contraction:** generally occurs in large surface wounds & is an important feature in healing by secondary union.
  - myofibroblasts of granulation tissue have ultrastructural features of smooth muscle cells
  - they contract in the wound ⇒ wound contraction

Steps in Wound Healing:

- Hemostasis
- Inflammation
- Proliferation
- Maturation / Remodelling



0 hrs (immediate)	• hemostasis
within 24 hrs	• Neutrophils from margins start coming towards the clot • mitosis begins in the basal layer of epidermis
24 - 48 hrs	• dense neutrophilic infiltrate • thin continuous epithelial layer is formed
Day 3	• neutrophils are replaced by macrophages • early granulation tissue (neovascularisation) • collagen fibres are evident at margins
Day 5	• Maximum granulation tissue • maximum neovascularisation • collagen fibres bridge the incision
3rd week	• decreased inflammation, edema & neovascularization • increased fibroblastic proliferation • maximum collagen
Day 28	• Scar

In secondary intention healing:

- more inflammatory cells
- bigger clot
- more granulation tissue
- Wound contraction mediated by myofibroblasts occur (doesn't occur in primary intention)

→ After 1 week ⇒ wound regains 10% of its tensile strength

→ After 3 months ⇒ " " 70-80% " " " "

[a wound never regains its original (100%) tensile strength].

Initial Collagen Type III ⟶ Type I collagen
- more abundant
- has highest tensile strength.

at the end, ratio of type I : type III = 4:1.

Factors Affecting Wound Healing:

LOCAL

- type of injury
- site of injury
- blood supply
- presence of foreign body
- infection ⇒ most common cause of delayed wound healing.

SYSTEMIC

- presence of diabetes mellitus
- steroids
- malnutrition
- vitamin C deficiency
  ⇓
  required for cross-linking of collagen
- Zn deficiency

Collagen:

→ triple helical
→ 33% glycine
→ 4 types

Type 1 :- most abundant
- maximum tensile strength.
- skin, bone, tendons.

Type 2 : - vitreous humor, cartilage

Type 3 : - keloid, uterus, granulation tissue.

Type 4 : present in basement membrane.

Disorders Due to Defective Wound Healing:

Excess granulation tissue
[aka proud flesh]

→ red
→ edematous
→ treatment: cautery

Excess collagen / Scar

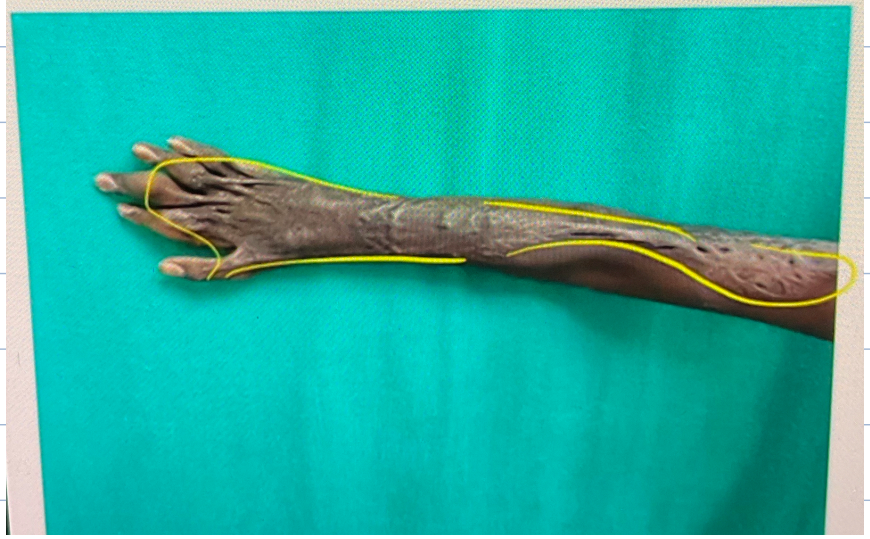
- KELOID
- HYPERTROPHIC SCAR

KELOID	HYPERTROPHIC SCAR
→ Scar crosses the wound margins	→ Scar which is raised just above the surface
→ do not regress spontaneously	→ spontaneous regression
→ thick haphazard collagen bundles	→ thin orderly arrangement of collagen.

Stain for collagen: Masson's trichrome

Desmoid: excessive proliferation of fibroblasts.

Hypertrophic scars



Keloid