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INFLAMMATION

→ "The response of vascular connective tissue towards injury——."

Purpose OF Inflammation :

* To destroy / wall-off the cause of injury.
* To remove necrotic cell so that to open the way for tissue repair.

Types :

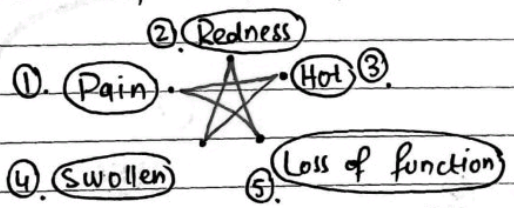
① Acute Inflammation

→ Tissue response to the injury Rapidly & Transiently (short-duration)

② Chronic Inflammation

→ Response for long duration.

→ ⑤ Cardinal signs of Inflammation:



* Pain → Dolar
* Redness → Rubor
* Hot → calor
* Swollen → Tumor
* Loss of func. → Functiono Losia

Paranchymal cells :

→ "Functional cells of any tissue——." ↑↑↑

e.g: → Hepatocytes in liver
→ Neurons in CNS

Stromal cells :

→ "Supporting cells w/c supports Paranchymal cells——."

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ACUTE INFLAMMATION

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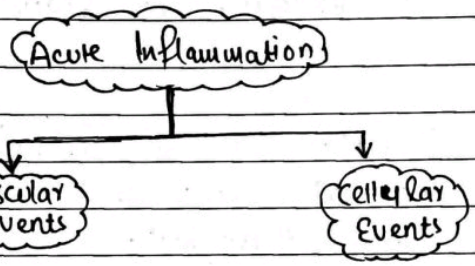
→ When a tissue is injured by any means → Paranchymal & Stromal cells release mediators of Inflammation like Prostaglandin, Leukotriens, tumor Necrotic factor etc.

→ Mast cells are present all over body but they are specially concentrated around the Blood vessels, around the nerves, Around all External & Internal lining of the body.



Vascular Events :

① Vasodialation OF Arterioles :

→ Histamines, PG-E_2, NO etc have receptors on vascular Smooth muscle → due to w/c vasodialation occurs.

② Exudation : ↑↑ Permeability :

→ Loss of Protien-rich fluid from micro circulation to Interstitial fluid of injured tissue → (Exudate) compartment

→ Initially there is Neurogenic vasoconstriction w/c is followed by Prolonged vasodialation.

* Exudate has high Specific gravity.

→ Occurs due to Disturbed starling forces, + Disturbed vascular Permeability.

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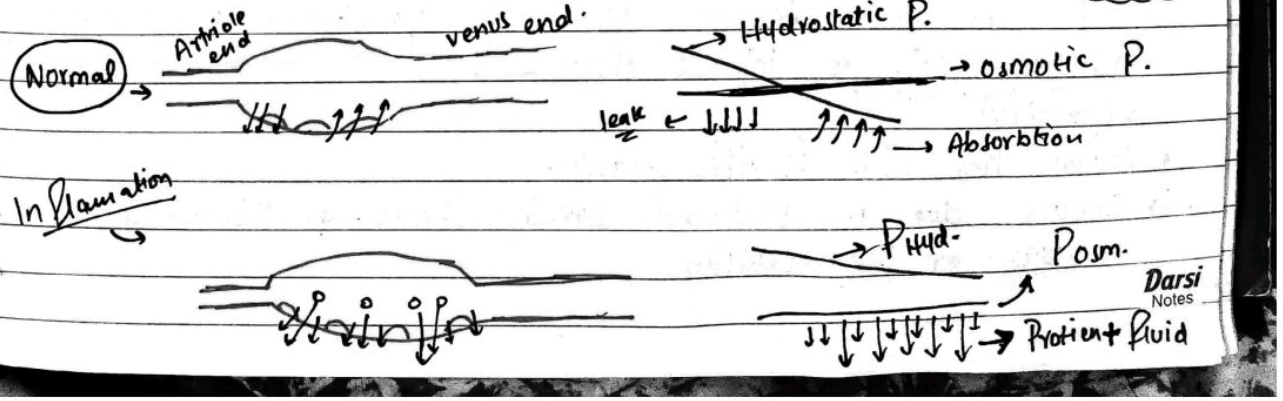
⊛ **Transudate** → Loss of Protien-Poor fluid from vasculature to Interstitial fluid.
→ occurs due to Disturbed starling forces only.
→ have low specific gravity.

⊛ **Edema**:
↑↑↑ fluid in insterstital fluid ——.
May be due to Exudate or Transudate.

→ Normally at Artriolar side of capillaries → Hydrostatic press. is high & low at venus end But Osmotic colloidal Press. remain Same throughout.
so at Artriolar side → Hyd-P. is greater than Osm-P. → so fluid come out of Capillaries but oppasite occur at venous end → fluid absorbed into Capillaries.
→ In Inflammation → due to vasodialation → $P_{Hyd.}$ → ↑↑ more and also due to mediators of Inflammation → Permeability of endothelial C-Tissue ↓↓ → ~~then~~ thus large amount of fluid & protiens are last from capillaries to Int-fluid Compartment → (Exudate).

* When Permeability → Same → Only fluid last → (Transudate)



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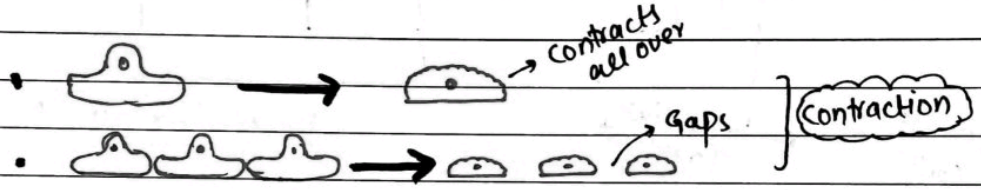
How Permeability of Endothelial Cells Increases ?

* Histamine → By mast cell.
* Bradykinine → By Plasma Protiens.
* Leukotriene → By Injured tissue cell memb.

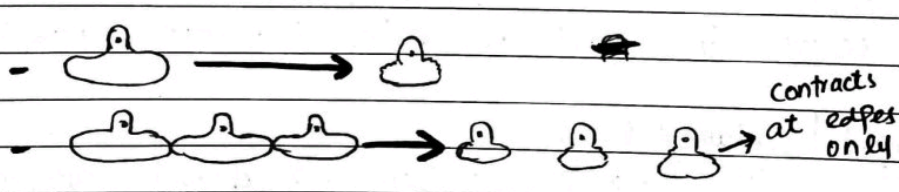
] Vasoactive substance

→ All of them have receptors on Endo-cells → they cause (Contraction) of endoth-cells → inter-endoth-gaps are produced.



→ These mediators are Pre-formed / released rapidly.

→ As Inflammation continues → Cytokines (TNF, IL-2) are produced after some time → w/c cause (Retraction) of end-cell → same gaps are produced.



* Actually These substances binds wd Receptors on endo-cells → w/c activate Intracellular Protien kinases → → Contraction/Retraction occurs.

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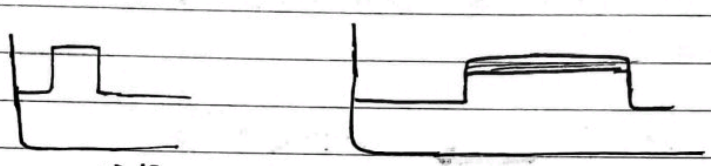
Immediate Transient Response : Increased permeability initially due to Histamine, Brady. L-T → for short Interval.

Prolonged | Delayed Response : ↑ permeability after Transient response → due to Cytokines → for long time



Due to contraction ← Immediate Transient

Delayed → due to Retraction

* ↑ permeability occurs more on venous side of Capillaries | venules → Bcz they have more receptors for chemical mediators of Inflammation.

(Physical Trauma) :

★★★ Injury to tissue → Also directly disrupts endoth. linings → ↑↑↑ vascular permeability.
→ occurs in part of microCirculation equally.

Much
Prolonged | Delayed :
→ In sun burn → delayed cytokines release →
→ affect appear after many hours.

★★★ ↑ permeability also occurs sometimes when WBCs gets attached to endo-cell & start destroying them.

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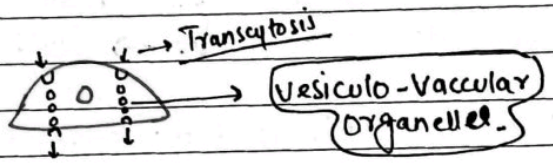
★★★ Leukocytes Mediated Endothelial cells Injury :

→ Commonly occurs in Pulmonry & Glumerular micro-circulation → bcz these ② loves to hold the Leukocytes for Longer duration.

→ Leukocytes cause injury by ①. Oxygen derived free radicals
②. Lysosomal Degradation.

★★★ Transcytosis

→ Histamine & VEGF → ↑↑ transcytosis → can cause endo- injury.



★★★ Excessive leakage of fluid from Newly formed vessels :

→ During Tissue repair → new capillaries are formed → → w/c are immature → don't have tight Junctions b/w endo- cell → leaky → Large Gaps.

→ lethal → in Excessive burns → to much fluid exudate → → Hypo volumic shock.

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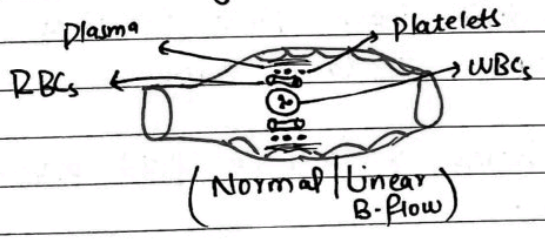
Cellular Events (WBCs Events)

→ The normal blood flow thru B-vessels → Linear Blood Flow → in w/c Big cells i.e WBCs are in center then outer to it are RBCs and outermost are platelets.

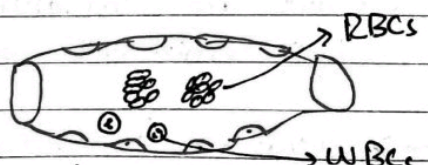
→ outer to platelets → cells free → Plasma → Plasmatic Zone.

→ When there is severe Inflammation → due to vasodialation → → B-flow increases to microcirculation of Inflammed area → → &p also due to ↑ permeability → Protien rich fluid escapes out of circulation → the blood in vessels become concentrated due to fluid leakage → (Hemo Concentration) → Its flow doesn't remain Linear → Its viscosity ↑↑ &p its velocity ↓↓ → fluid exit → ↓↓↓ → (Stasis) occ. uvs.

→ Due to stasis &p Hemo conc. → RBCs starts to clump together → &p their group is bigger than individual WBCs → &p they take central position &p WBCs are pushed to Periphery → to the margins → this process → **Margination**



(Normal Linear B-flow)



(Inflammation)

→ Now chemical mediators Histamine, L-T etc acts on vascular Endo-cell &p activate them → i.e → they have pre-formed granules (Weible Palate Bodies) w/c contain (P-T-O)

Darsi Notes

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→ Adhesion molecule → these granules fuses wd membrane → & sticky / molecular Hooks → (P-Selectins) are expressed on endoth- cells.

→ Also wBCs have Adhesive molec. → all the times present on their surface → (Sialated Sugars / sialy Lewis x- oliposacchride)

→ These wBCs adheres to endo- cell due to Complementry Adhesion of sialated sugar wd P-selectin.

→ Then of due to high B-flow → Adhesion B/w wBCs & Endo-cell breaks & wBC bcf become free.

→ These selectins are first discovered in platelets → so called → P-selectin.

→ Then after some time → Another mediators (IL-1, TNF etc) acts on Endo- cell → & beside P-selectins they also Expresses E-Selectins due to w/c Endo-cell become more sticky & wBCs adhere to it. But again due to high B-flow the bond break & wBCs keep on rolling i.e. attaching & detaching & moving forward → This process → (Rolling).

→ Then another mediators (IL-8) → chemokines → & w/c have Receptors on endo-cells → attached wd Endo-cell w/c hold the wBCs strongly → strong Adhesion.
wBCs have Integrins on its surface but they are not active → when Binds wd chemokines on endo-cell surface → → Integrins → Activated & make strong Adhesion wd I-CAM / V-CAM w/c are expressed on endo. cell surface.
(Intercellular Adhesion molecule / Vascular cell Ad. mol.)

(P-T-O)

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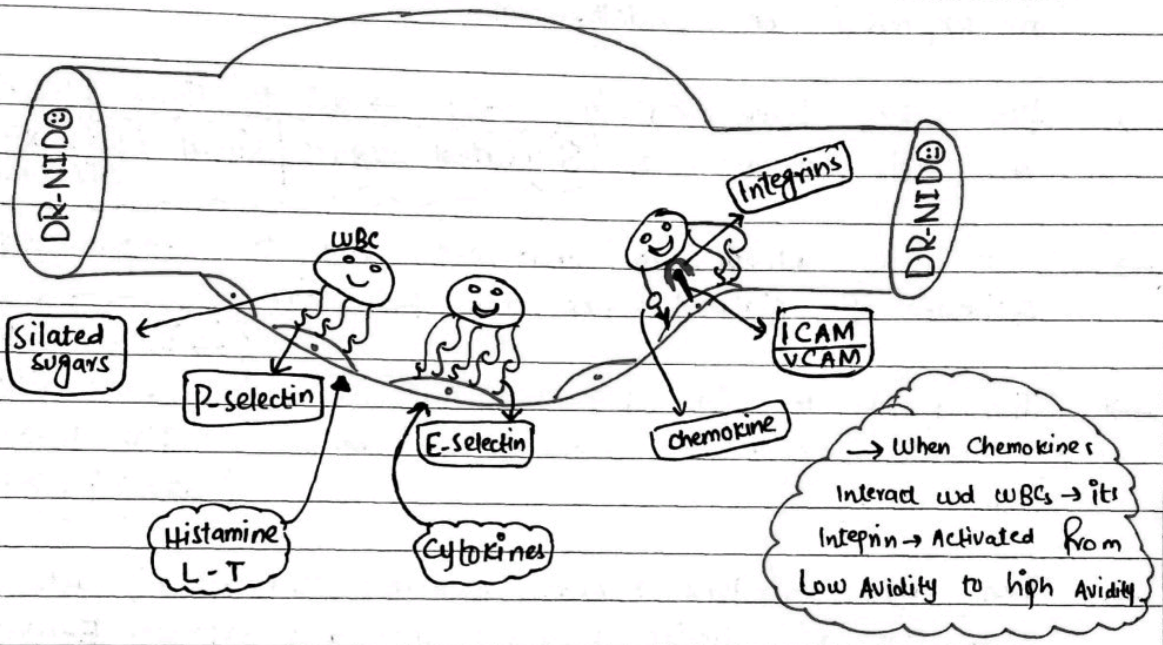
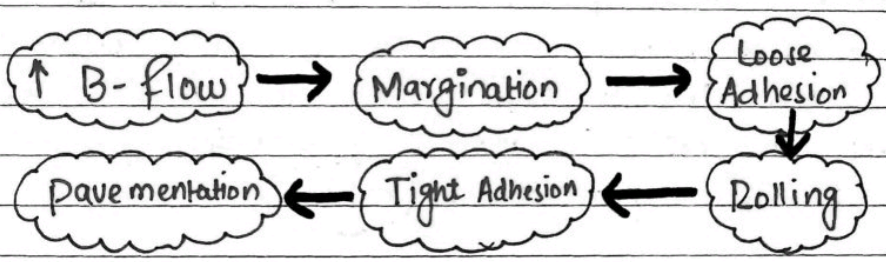
→ Now WBCs are spread over Endo-cell → as Pavement of WBCs is made over Endo-cell → Process → (Pavementation).





How WBCs get out of Vascular Compartment to Extra-Vascular Comp.

→ Also called "Emigration or Extravasation or Diapedisis."

→ While WBCs are sticked to Endo-cell → other cytokines → → acts on Both WBCs & Endo-cell → & both expresses another adhesion molecules of same type →

(P-T-O)

Darsi Notes

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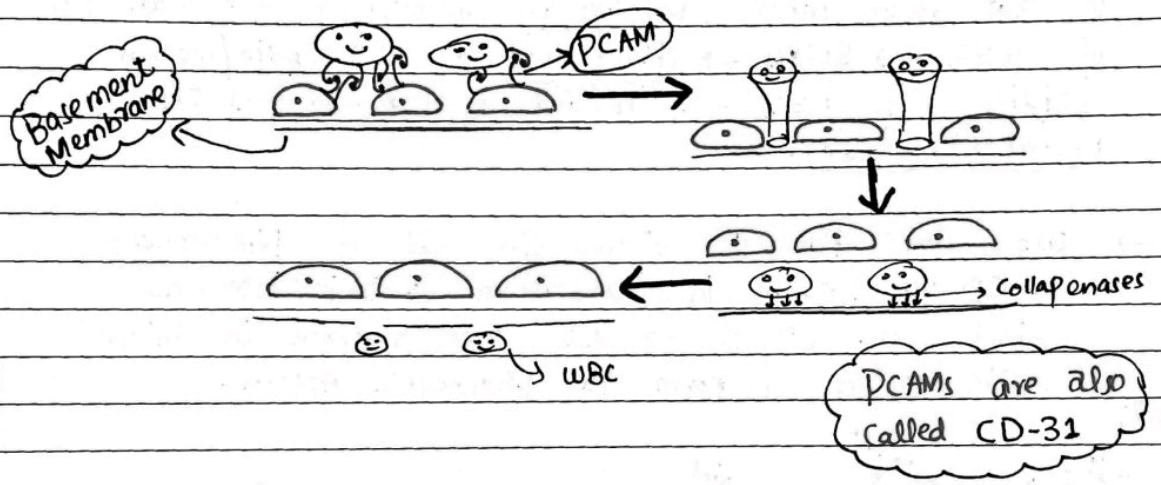
→ Homophilic Adhesion molecule → Platelets cell Adhesion molecules (PCAMs)
→ through w/c WBCs starts interacting wd adjacent Endo- cells → &p finally WBC squeezes out through gaps b/w Endo cell &p then WBCs releases Collapenases enzymes w/c digest Collapen of Basement memb- → &p WBCs are extravasated out to Extra Vascular space.



PCAMs are also called CD-31

How WBCs move in a Specific direction toward Injury?

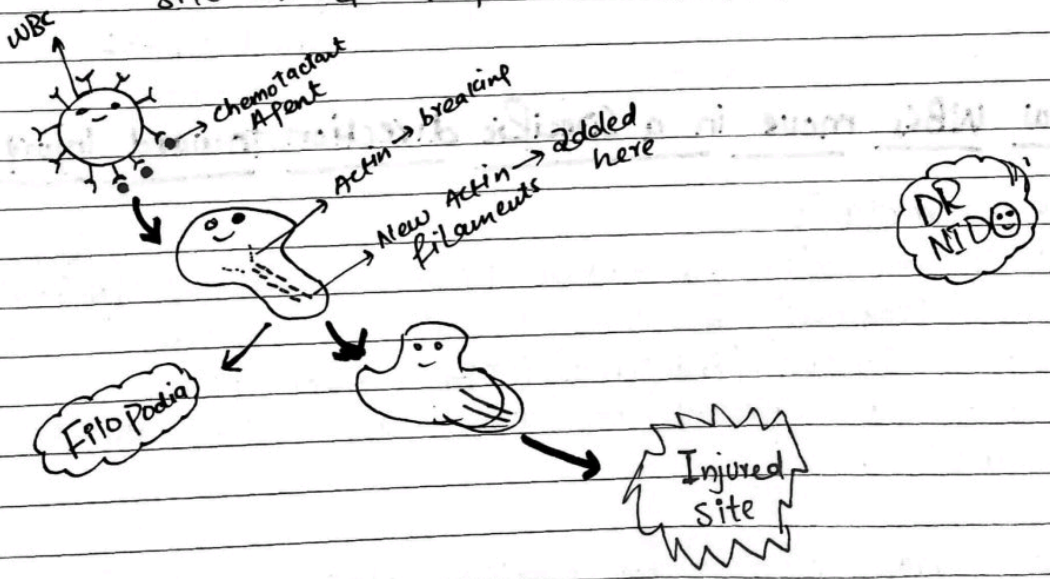
→ Chemotaxis
→ At site of injury → Bacteria produces chemotactic Substances (Exogenous) &p also Injured cells produce Chemotactic Substances (Endogenous) (LT-B4) → for w/c receptors are present on WBCs → so they attract WBCs. (Methionine N-formyl)

→ WBCs have receptor for chemotactic agents all over its surface → But only those receptors are stimulated w/c

(P-T-O)

→ are present toward injured site. These receptors are 7-Pass $G_{q\alpha}$ (R) → Phospholipase-C → final IP_3 → formed → w/c cause phosphorylation of Proteins → Actin Filaments are forming in that region where Receptors are stimulated → That Part of WBCs → Bulges → Filopodia → due to Actin/myosin sliding → WBCs → toward injured site → like Front wheel Car.

→ WBCs don't Pass the injured site b/c of Foot Stones → → CD-44 present in interstitium → Their integrins bind wd CD-44 → Thus they remain in injured site → & Perform its Phagocytic Action.



Sr. No.	Date	Topic

Leukocyte Adhesion Difficiency (LAD-2) :

* The disease in w/c WBCs don't have Sialated sugars → so they don't interact wd selectins → don't roll properly → don't helps in inflammation.

Neutrophilic Leukocytosis :

Normally some Neutrophils are sticked to endothelial cells all the time

* When Blood level of Catecholamines, Corticosteroids & Lithium is high → they inhabits endo-cells to express selectins → thus WBCs / Neutrophils → don't stick to endo-cells → → & Apparantly Neutrophils level in Blood → high → although total Count may be normal.

Neutropenia :

* Endotoxins → over express selectins → Ntphils → stick → more → in Blood → less.