30.9.24

INFLAMMATION AND TISSUE REPAIR

⇒ Inflammation : is a protective response involving host cells, blood vessels and proteins and other mediators that is intended to eliminate the initial cause of cell injury as well as necrotic cells and tissues resulting from the original insult, and to initiate the process of repair.

- It is a component of innate immunity

→ although inflammation helps clear infections and other noxious stimuli & initiates repair, the inflammatory reactions and the subsequent repair process can themselves cause considerable harm.

→ the components of the inflammatory rxn that destroy and eliminate microbes & dead tissues are also capable of injuring normal tissues.

Cardinal signs - Celsus

① Calor - heat
② rubor - redness
③ tumor - swelling
④ dolor - pain
⑤ functio laesa - loss of function (Clubs added by galen)

Types - acute
chronic.

5R's

" Sequence of events in inflammatory reaction " → { flow chart in Ibsun Ab }

Rubor - due to ↑ blood flow & stasis

Calor - ↑ blood flow

Tumor - increased vascular permeability causing escape of a protein-rich fluid from blood vessels

Dolor - Chemical mediators: prostaglandins & kinins.

Types → acute
→ chronic.

UQ what are 3 major components? ✓

Acute Inflammation

The initial, rapid response to infection and tissue damage is called acute inflammation. It is of short duration - develops within min/hours lasting for several hours/days.

→ It is a type of innate immunity.

The main feature are:

① Exudation of fluid and plasma proteins (edema).
② emigration of leukocyte - neutrophils
③ Intravascular activation predominantly of platelets.

Severe acute inflammation → fulminant.

Inflammation is a response of vascularized tissues to infections and damaged tissues that brings cells and molecules of host defense from the circulation to the sites where they are needed, in order to eliminate the offending agents.

S. No.	Date	Title	Page No.	Teacher's Sign / Remarks

(1) Cardinal signs {External signs}. Celsus

① RUBOR – Redness. } due to vasodilation, which results in
② CALOR – warmth } increased blood flow.

- occurs via relaxation of arteriolar smooth muscle
- Key mediators → histamine, prostaglandins, bradykinin. I2, D2, E2

③ TUMOR – swelling → due to leakage of fluid from post capillary venule into interstitial space.

- Key mediators: ① histamine.
② tissue damage

④ DOLOR Pain → Bradykinin
PGE_2
by sensitizing sensory nerve endings.

Fever → pyrogens cause macrophages to release IL-1 & TNF.

↑ Cyclooxygenase activity in perivascular cells of hypothalamus

↑ PGE_2

↓

fever

(2)

	Acute.	Chronic
onset :	rapid onset (min/hours)	Slow onset (days), may follow acute inflammation.
duration:	short (hours/days)	longer duration, may be months
predominant cells:	Neutrophils.	lymphocytes, monocytes/macrophages, plasma cells
Character:	exudation of fluid & plasma proteins emigration of leukocytes	• inflammatory cell associated with the proliferation of blood vessels, tissue destruction & fibroblast proliferation.
injury/ damage (stimuli & fibrosis)	• usually mild & self limited. and can progress to a chronic phase.	• Usually severe and progressive with fibrosis & scar formation.
Signs: local & systemic	prominent	less prominent.

Stimuli for acute inflammation

① **Infections** – bacterial, viral, fungal & parasitic and microbial toxins.

② **Tissue necrosis** – • ischaemia – MI.
• physical agents.
Mechanical trauma – eg crush injury
Thermal injury – burns/frostbite.
radiation.
Electric shock
sudden change in atmospheric pressure.
• Chemical injury.
strong acids, alkali, insecticides, herbicides.

③ **Foreign bodies** – Sutures

④ **Immune reactions**
– hypersensitivity reactions.
– Autoimmune disease.

Acute inflammation has 2 components
① vascular events
② cellular events

Vascular changes/reactions of blood vessels/ hemodynamic changes.

purpose → to deliver circulating cells, fluids and plasma proteins from the circulation to site of infection or tissue injury.

vascular changes consists of
① Changes in vascular flow & caliber
② Increased vascular permeability.

① Changes in vascular flow & caliber

→ vasodilation → (arteriole).
results in increased blood flow.
↓
local heat & redness (cardinal sign).
• mediator → Histamine
PG – D_2, I_2, E_2.
platelet activating factor
kinins, Nitric oxide.

→ increased permeability of microvasculature.
histamine, LT, platelet activating factor, kinins.
protein rich fluid → circulation → Extravascular tissue.
↓
↑ concentration of red cell in blood
↓
↑ viscosity. → slowed circulation.
→ Stasis ✓
→ margination ✓

→ leads to TUMOR.

② Increased vascular permeability

(vascular leakage) (post capillary venules). capt-lung.

- Increasing vascular permeability leads to movement of protein-rich fluid and even blood cells into the extravascular tissue.

↓

The resulting protein rich fluid accumulation is called Exudate

Exudation: process of escape of fluid, proteins and circulating blood cells from vessels into interstitial tissue or body cavities.

(Learn differences btw exudate & transudate)

Mechanism of Increased vascular permeability:

several mechanisms:

① Contraction of endothelial cells:

- most common mechanism of vascular leakage.
- Chemical mediators: histamine, bradykinin, LT, neuropeptide substance P.

Binds to endothelial cell receptors → contraction.

"immediate transient response"

② Direct Endothelial injury →

eg: burns or infection by microbes.

③ → accumulation of activated leukocytes that release toxic mediators.

↓

cause endothelial injury or detachment.

"Immediate sustained response"

③ Leukocyte-mediated vascular injury.

leukocytes (neutrophils mainly) that adhere to endothelium during inflammation may themselves injure endothelial cells.

{write same as before}

④ Increased Transcytosis

of proteins by intracellular vesicular pathway → ↑ permeability.

⑤ Leakage from new blood vessels.

new blood vessels formed during repair (angiogenesis) are leaky till endothelial cells mature.

Cellular Events.

- Leukocyte recruitment.
- Activation.

Leukocyte recruitment/ Extravasation

the process of migration of leukocytes from the lumen of the vessel to site of injury in the extravascular tissue

Steps

① margination and rolling along vessel wall

② adhesion - to endothelium

③ transmigration → btw endothelial cells.

④ migration in interstitial tissues towards a chemotactic stimulus.

① margination → when blood flow slows down (stasis) WBC (neutrophils) move towards peripheral column & accumulate along or endothelial surface of vessels.

Vascular Events.

1. Changes in Vascular flow & Caliber.
2. Increased vascular permeability.

Vascular events.

(a) transient vasoconstriction. (QQ).

↓

(b) vasodilation: {↑ blood flow}

↓

(c) ↑ vascular permeability {exudation}

↓

(d) Stasis. (slower blood flow)

↓

{↑ conc. of RBC and WBC along endothelium}

Vasodilation.

(I) Changes in Vascular flow and caliber.

→ 1st involves the arterioles

→ occurs due to action of several mediators, particularly

Histamine (2) on **vascular smooth muscles** → vasodilation

(3) ↑ Blood flow → leads to → Heat and redness {erythema}.

(4) → leads to increased hydrostatic pressure.

(1) **Mediators:** Histamine.
PGs - D_2, E_2, I_2.
Kinins
NO.

(LH BNs)

(II) Increased Vascular permiability.
{vascular leakage} (4) → diff @ next page

* mainly affects post capillary venules

Mechanism.

1. Contraction of endothelial cells.
2. direct endothelial injury.
3. mild endothelial damage.
4. Leukocyte mediated endothelial injury.
5. Increased transcytosis
6. Leakage from new vessels

(1) **Contraction of endothelial cells**
It is an.
→ **Immediate, transient response**
lasts only 15-30 min, rapid onset.
• most common mechanism of increased vascular permeability.

Mediators: Histamine,
Leukotrienes
Bradykinin.
Neuropeptides
Substance P.

② Direct Endothelial injury.

- Immediate and prolonged.

→ due to severe physical injury.
eg: thermal burns ✓
microbial toxins ✓

→ due to Endothelial (cell necrosis) and detachment.

③ mild endothelial damage. {no need to worry}
{sunburn}.

→ affects venules.

→ delayed prolonged response.
eg: Sunburns

③ Leukocyte mediated endothelial injury.

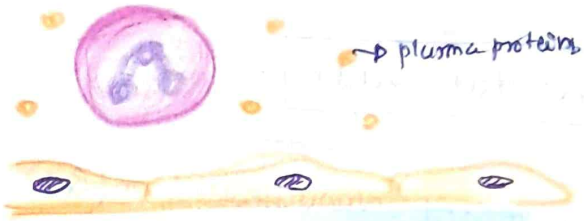
- delayed prolonged.

→ due to activated WBC at site of inflammation. / binding to endothelium and themselves injuring the endothelial cell).

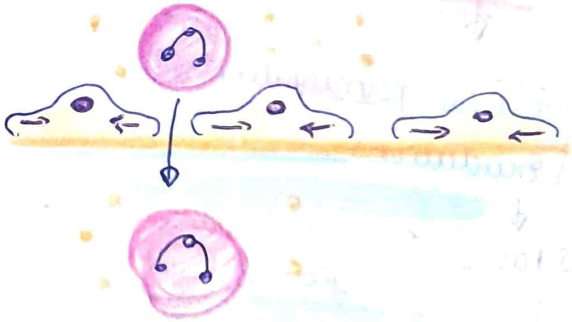
1 ↑ vascular permeability
↓
movement of protein-rich fluid & WBC into extravascular tissue.

Figure – Robbins.

Normal.



Retraction of Endothelial cells
(▷ Induced by histamine + other mediators).



Endothelial Injury.
- burns, microbial toxins, WBC binding

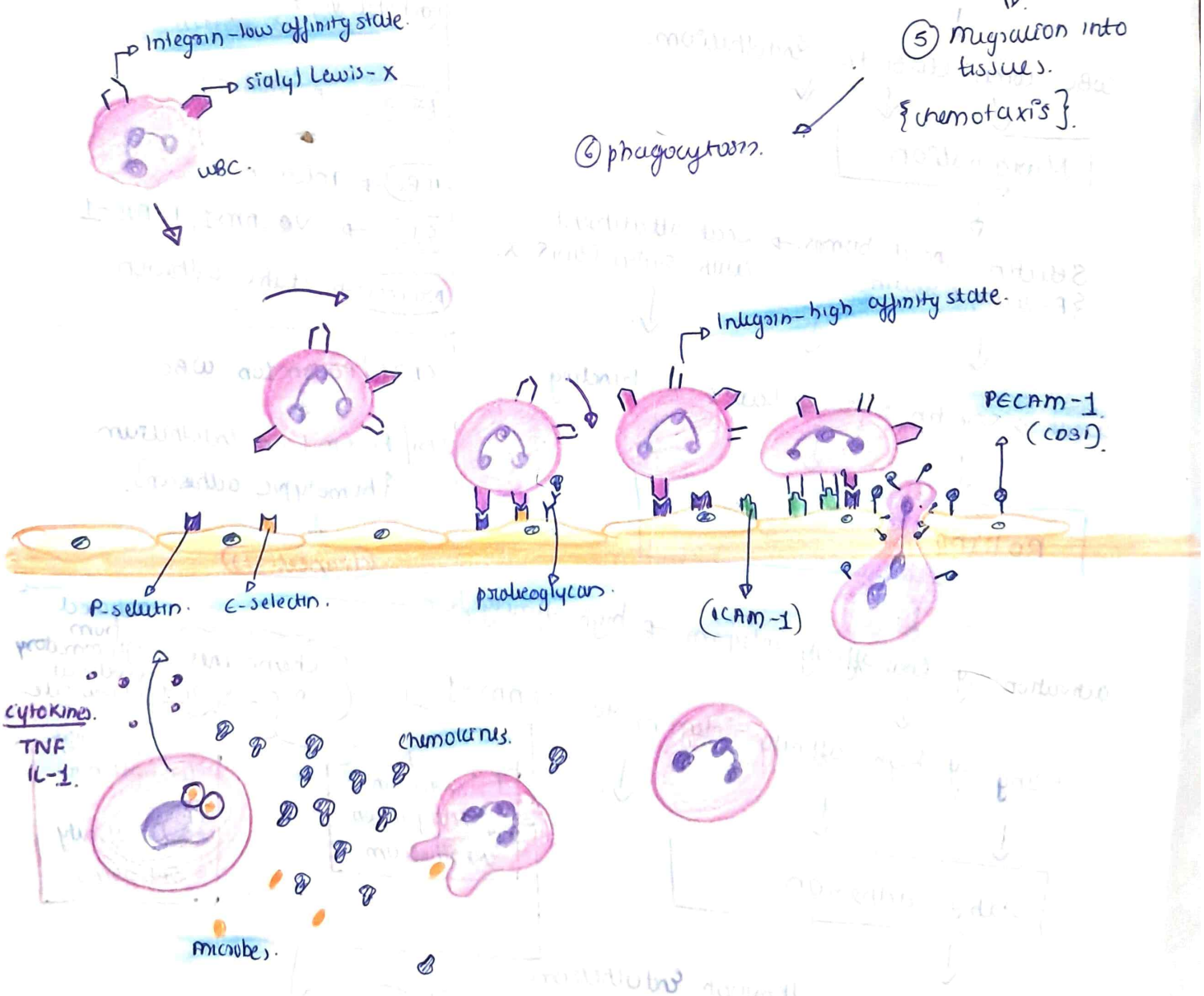
Cellular Events

- Multistep process that involves journey of leukocytes from vessel lumen to the tissues, that is mediated by adhesion molecules and cytokines called chemokines.

⇓

① Margination → ② rolling → ③ Interaction with low affinity Integrin → ④ Interaction with high affinity Integrins → ⑤ Migration across endothelium {diapedesis} → ⑥ Migration into tissues {chemotaxis}.

③ Stable adhesion.



Sequential phases

Leukocyte recruitment

① In lumen → margination, rolling and adhesion to endothelium.

② migration across the endothelium and vessel wall

③ migration in the tissue towards a chemotactic stimulus

Leukocyte recruitment

Due to changes in blood flow {dilation}

↓

Stasis.

↓

WBC comes closer to Endothelium.

↓

Margination

↓

Selectin speed bumps → weak attachment with sialyl Lewis X.
{P selectin, E selectin}

↓

weak → selectin : sialyl Lewis X binding.

↓

Rolling

↓

activation of low affinity integrins → high affinity form.

↓

Binding of high affinity Integrins to ICAM-1.

↓

Stable adhesion

↓

Leukocyte migration through Endothelium.

↓

Transmigration / diapedesis → By PECAM1 / CD31 & collagenases.

Interactions during adhesion

WBC	sialyl Lewis X
Endothelium	P selectin, E selectin
process	rolling.
WBC	Integrins
Edo	VCAM1, ICAM-1
process	stable adhesion
CD31 / PECAM1 on WBC → CD31 / PECAM1 on endothelium {homotypic adhesion} → diapedesis	

Chemokines TNF-α IL1 (released from inflammatory cells at injury site)

↑ Expression of Integrins on Endothelium

convert low affinity → high affinity Integrins.