Inflammation and Leukocyte Migration

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Objectives

- Overview of the inflammatory process: initiation, inflammation, resolution, benefits and liabilities
- Major constituents
- Clinically relevant inflammatory processes
- Control of inflammation

Introduction

- “Inflame” – to set fire
- Inflammation is “A dynamic response of vascularised tissue to injury.”
- Inflammation: Local defense and protective response against cell injury or irritation or local vascular and cellular reaction, against an irritant.
- It is a protective response.
- It serves to bring defense & healing mechanisms to the site of injury.
- Inflammation is designated by adding the suffix (itis) to the end of the name of the inflamed organ or tissue.

Etiology

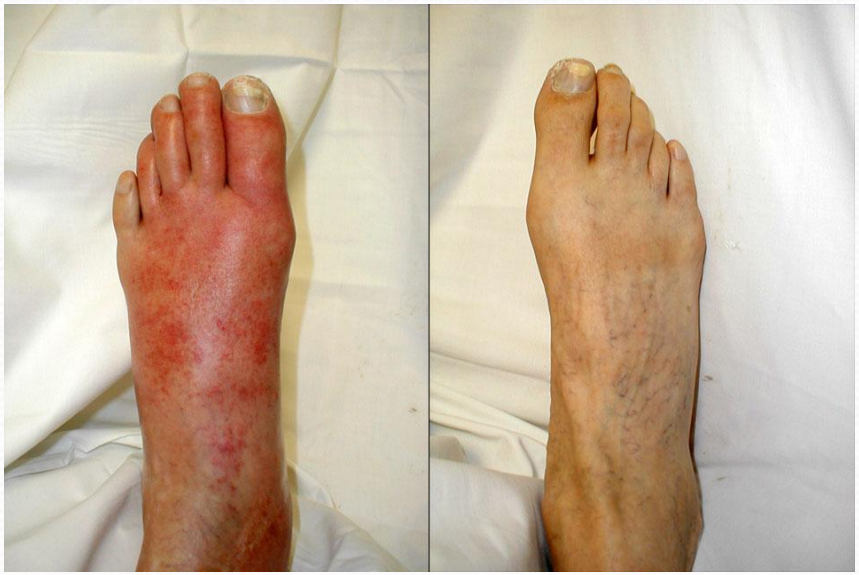
- Microbial infections: bacterial, viral, fungal, etc.
- Physical agents: burns, trauma--like cuts, radiation
- Chemicals: drugs, toxins, or caustic substances like battery acid.
- Immunologic reactions: rheumatoid arthritis.

Types

- Time course
  - Acute inflammation: Less than 48 hours
  - Chronic inflammation: Greater than 48 hours (weeks, months, years)
- Cell type
  - Acute inflammation: Neutrophils
  - Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).

Cardinal Signs of Inflammation

- Redness : Hyperemia.
- Warm : Hyperemia.
- Pain : Nerve, Chemical mediators.
- Swelling : Exudation
- Loss of Function: Pain



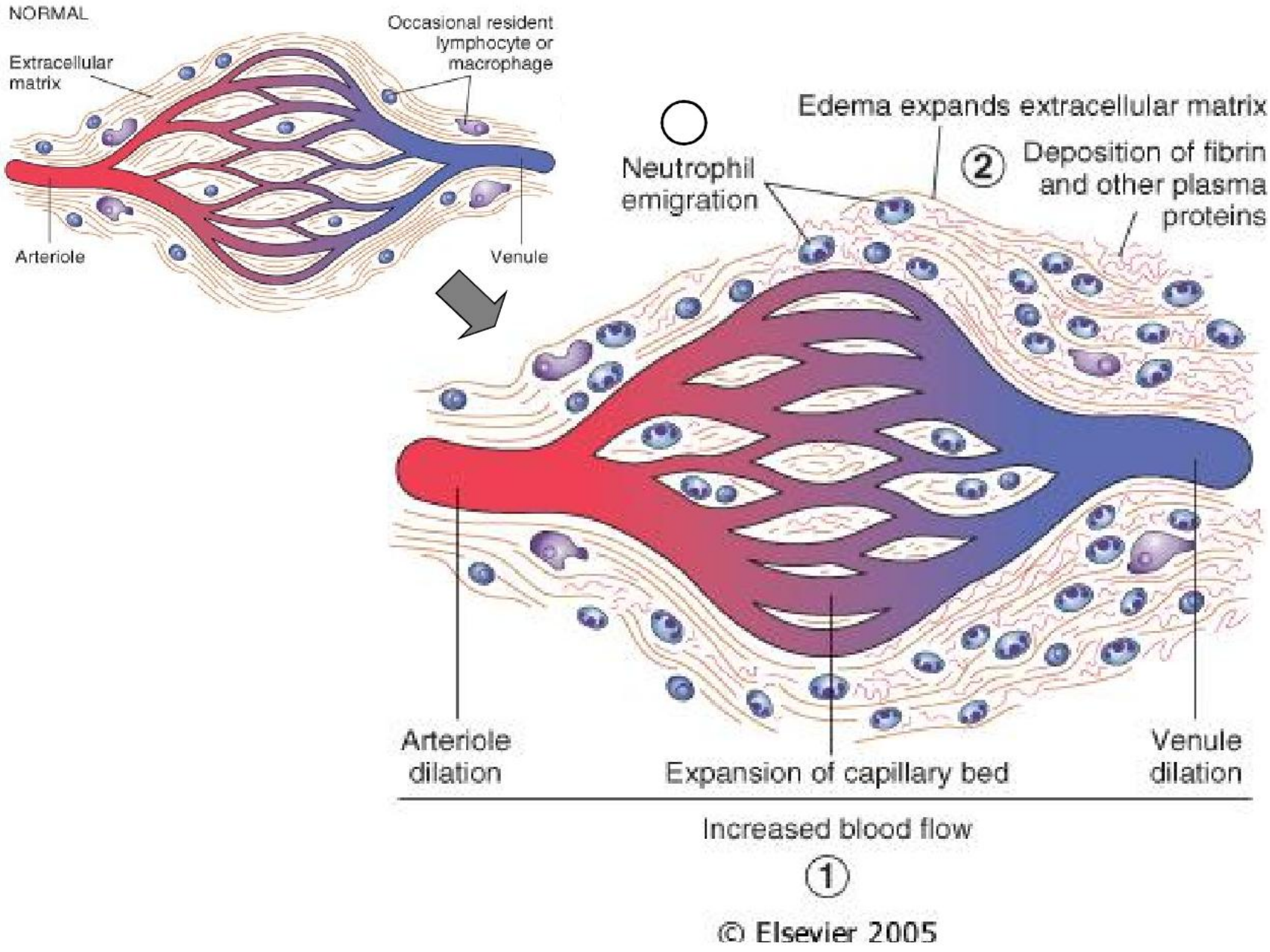
Pathogenesis

- The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.
- Three main processes occur at the site of inflammation, due to the release of chemical mediators :

1. Increased blood flow (redness and warmth).
2. Increased vascular permeability (swelling, pain & loss of function).
3. Leukocytic Infiltration.

1. Local Vascular Changes

- Initial temporary vasoconstriction for few seconds.
- Active vasodilatation of arterioles and capillaries by chemical mediators like histamine and passive dilatation of venules.
- Slowing of the circulation: outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood (stasis).
- Pavmentation: the margination of leukocytes. Neutrophils become oriented at the periphery of vessels and start to stick.


NORMAL
Occasional resident lymphocyte or macrophage
Extracellular matrix
Arteriole
Venule
Edema expands extracellular matrix
Neutrophil emigration
2
Deposition of fibrin and other plasma proteins
Arteriole dilation
Expansion of capillary bed
Venule dilation
Increased blood flow
1
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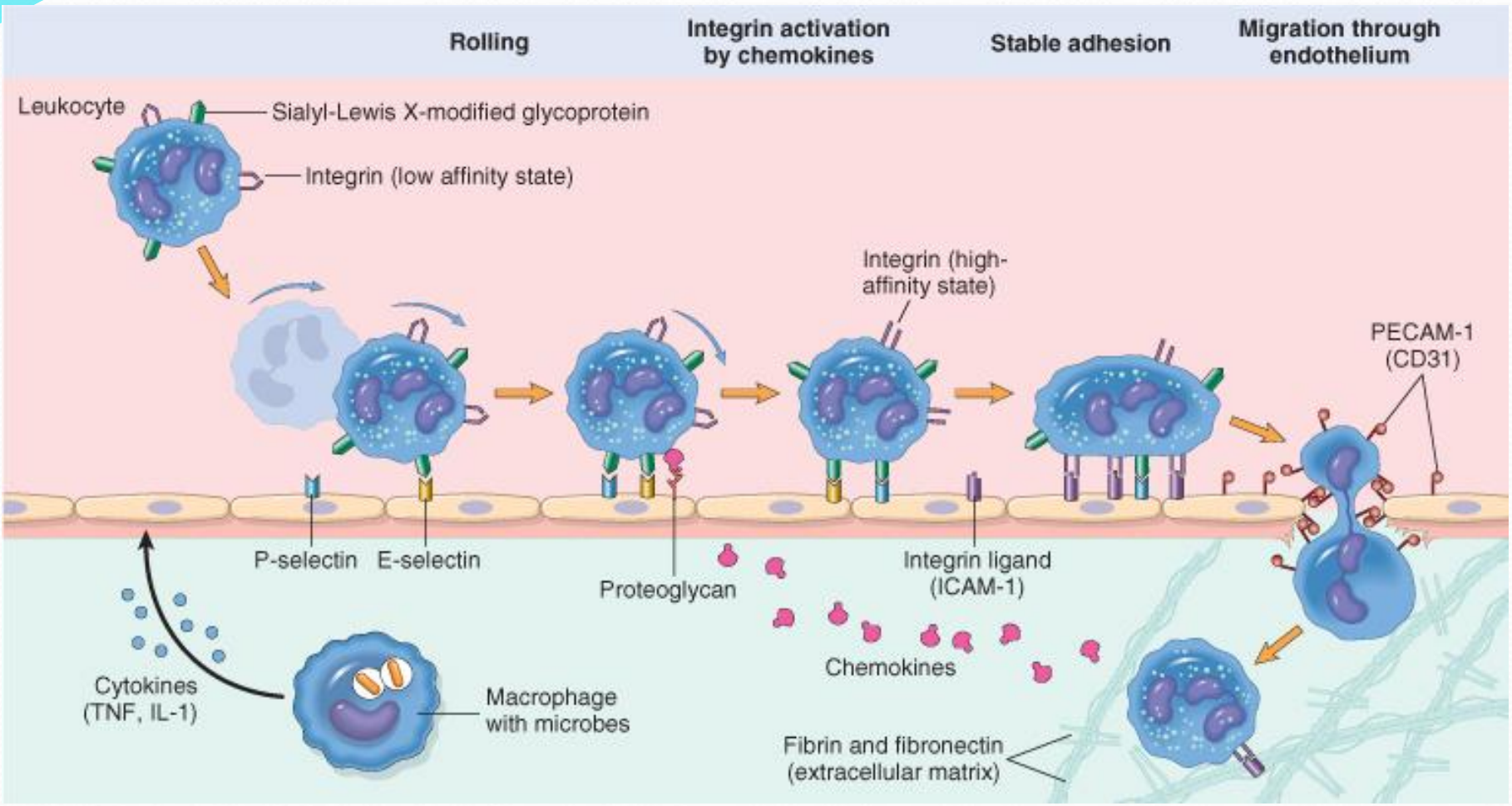
2. Leukocyte Exudation

- Leukocytes (PMN's , Mphages, lymphocytes, mainly T) circulate in the blood, but often do their work in tissues.
- For T and B cells, circulation increases the chances that you'll meet your antigen.
- For both to do their jobs, however, you often have to leave the blood to enter either the lymph node or the site of damage.
- Once at the site of damage, you want to kill microbes, control the damage, and repair it.

Leukocytes Extravasation

- Neutrophils are usually the first cells to move to site of infections or inflammations
- Neutrophils extravasation involves 4 main stages:

1. Rolling: mediated by selectines
2. Activation by chemoattractant stimulus
3. Arrest and adhesion mediated by Integrins binding to Ig-family members
4. Transendothelial migration


Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Sialyl-Lewis X-modified glycoprotein
Integrin (low affinity state)
Integrin (high-affinity state)
PECAM-1 (CD31)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
Chemokines
Cytokines (TNF, IL-1)
Macrophage with microbes
Fibrin and fibronectin (extracellular matrix)

1. Rolling

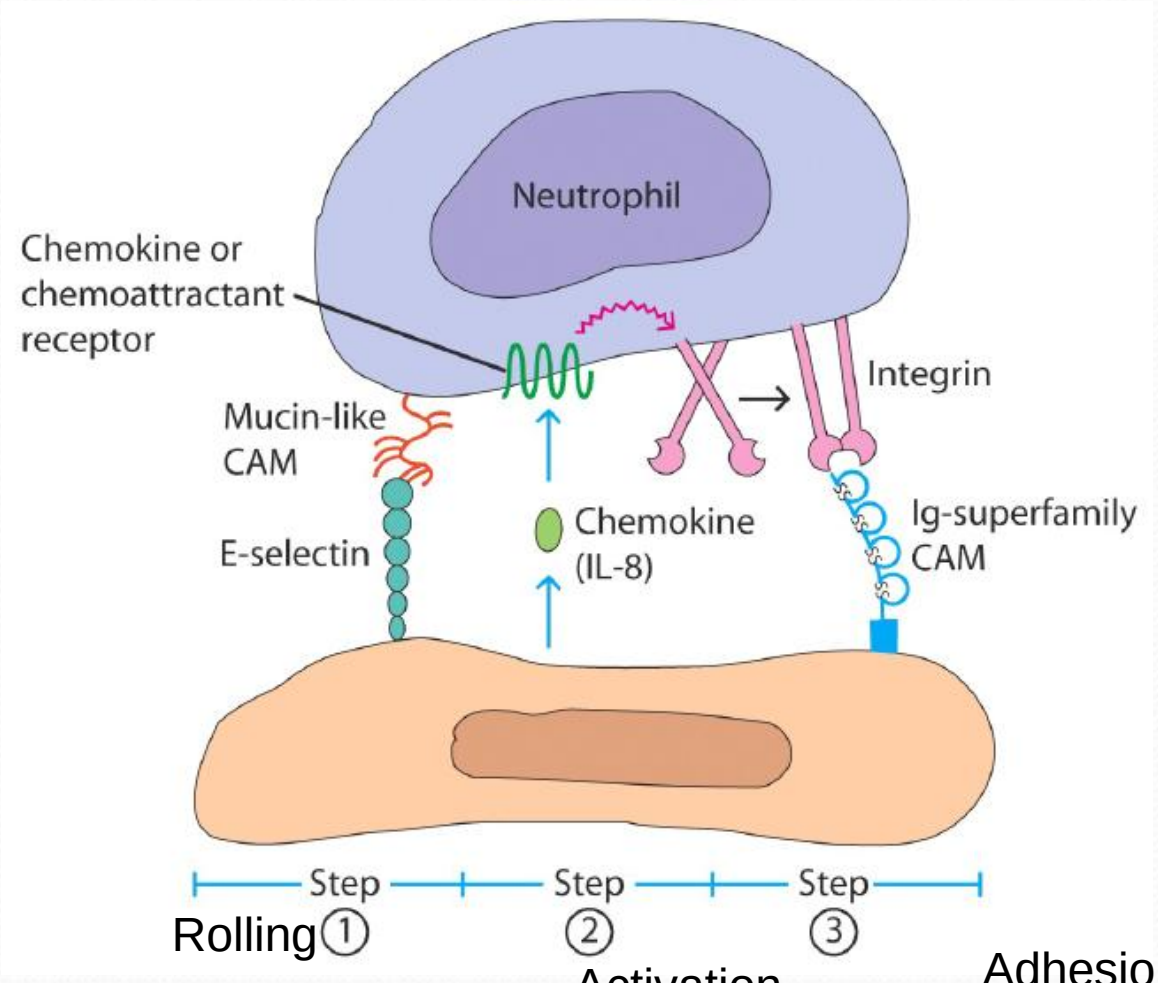
- In this step leukocytes attached loosely to the endothelium by low affinity selectines-carbohydrate interaction
- This interaction tether the leukocyte briefly to endothelium but the shearing force of blood flow detached the cells soon
- Selectine molecules on another endothelial cells tether the leukocytes again, this process is repeated so the cells trumble over the endothelium “rolling”

2. Activation

- The process of rolling slow the cells enough to allow interactions between chmokines on the endothelium surface and receptors on leukocytes
- This binding leads to signal transduction events results in change in confirmation and clustering of integrins on leukocytes

3. Firm Adhesion

- Binding of leukocytes to endothelium and slowing down of leukocytes allow binding of other adhesion molecules including integrins which leads to firm adhesion
- This allowed the leukocytes to binds more tightly to endothelium and it become less likely that blood force will detach them

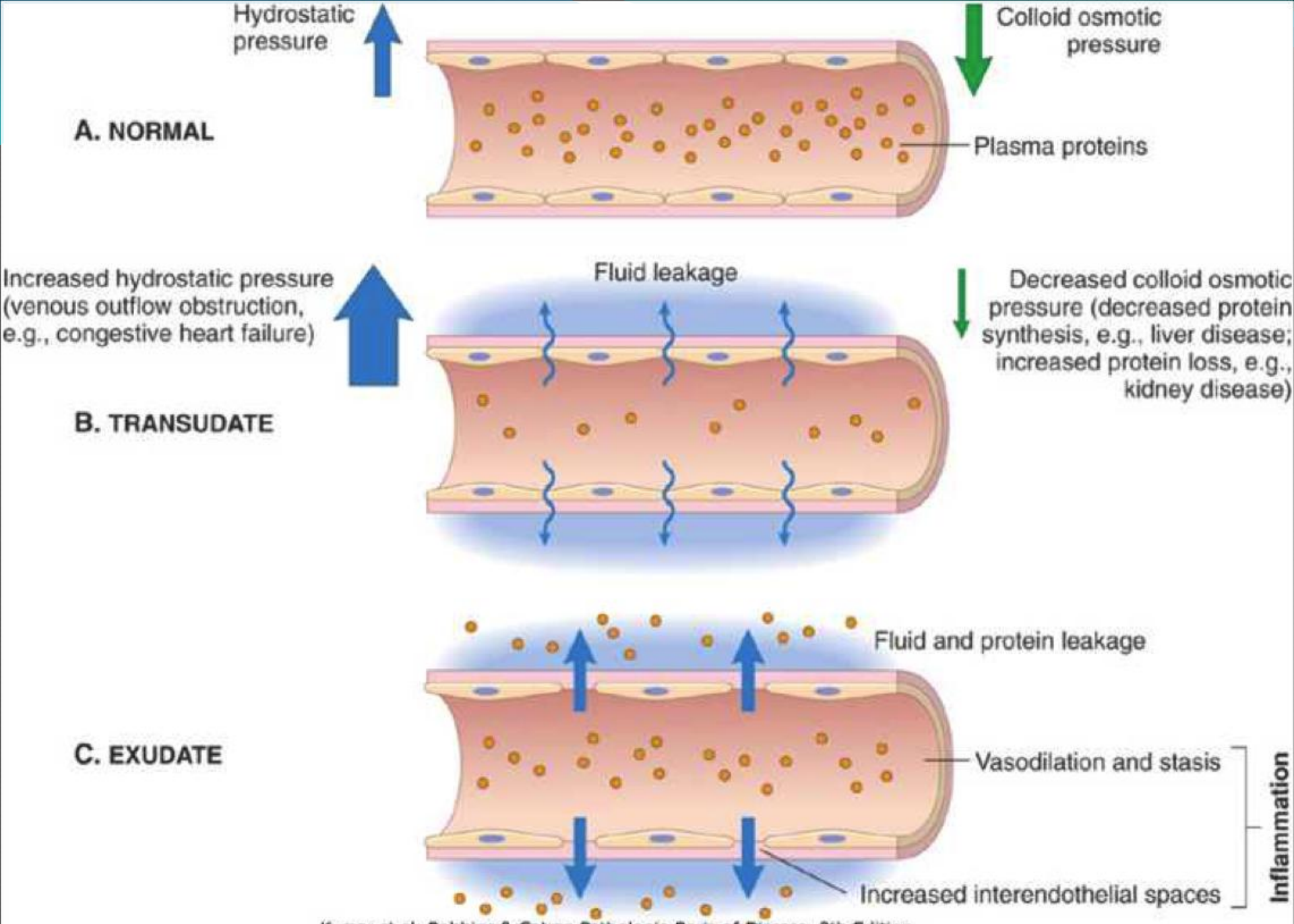

Neutrophil
Chemokine or
chemoattractant
receptor
Integrin
Mucin-like
CAM
Chemokine
(IL-8)
Ig-superfamily
CAM
E-selectin
Step
1
Step
2
Step
3
Rolling
Activation
Adhesion

4. Transendothelial Migration

- Leukocyte then squeeze in between two neighboring endothelial cells without disrupting the integriity of these cells
- This is accomplished by binding of platelet endothelial cell adhesion molecule 1 (PECAM-1) on leukocyte with PECAM-1 on endothelial cels

Lymphatics in Inflammation:

- Lymphatics are responsible for draining edema.
- Edema: An excess of fluid in the interstitial tissue or serous cavities; either a transudate or an exudate
- Transudate: An ultrafiltrate of blood plasma
  - permeability of endothelium is usually normal.
  - low protein content (mostly albumin)
- Exudate: A filtrate of blood plasma mixed with inflammatory cells and cellular debris.
  - permeability of endothelium is usually altered
  - high protein content.
- Pus: A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.



Function of Inflammatory Exudates

- Dilute the invading microorganism and its toxins.
- Bring antibodies through the plasma to the inflamed area.
- Bring leukocytes that engulf the invading microorganisms.
- Bring fibrinogen through the plasma, which is converted, to fibrin mesh, helping in trapping the microorganism and localize the infection

Inflammatory Mediators:

- Chemical substances synthesised or released and mediate the changes in inflammation.
  1. Histamine by mast cells - vasodilatation.
  2. Prostaglandins – Cause pain & fever.
  3. Bradykinin - Causes pain.
- Cytokines including TNF, IL1, IL6, IL8
- Lipid mediators: prostaglandins, leukotirns, and platelet activation factor

Cytokines and Inflammation

- Macrophages or DCs stimulated via innate immune receptors make pro-inflammatory cytokines, especially TNF (Tumor necrosis factor), IL-1, and IL-6
- TNF and IL-1 signal to endothelial cells to make them:
  - Leaky to fluid (influx of plasma; containing antibodies, complement components, etc.)
  - Sticky for leukocytes, leading to influx of first neutrophils, later monocytes, lymphocytes
  - IL-6 promotes adaptive immune responses and has systemic effects ("acute phase response" of liver, including C-reactive protein or CRP; levels used clinically as an indication of systemic inflammation)

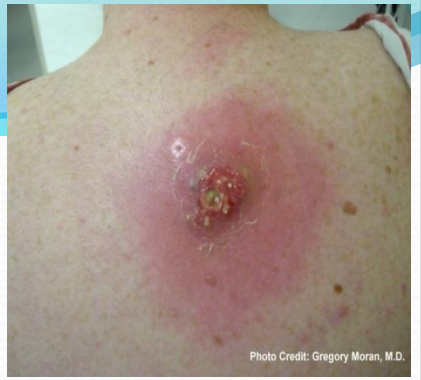
Negative Regulation of Inflammation

- Cells responding to innate stimuli stop making inflammatory mediators after short time period and convert to making anti-inflammatory lipids
- Killing the infectious agent and removal of the dead cells, debris, crystals, will stop stimulation of incoming inflammatory cells
- Systemic elevation of inflammatory cytokines (esp. IL-1) induce production of glucocorticoids, which are anti-inflammatory
- Regulatory T cells are also anti-inflammatory, both by blocking effector T cells and by inhibiting innate cells

Inflammation Outcomes

1. Abscess formation
2. Progression to chronic inflammation
3. Resolution--tissue goes back to normal
4. Repair--healing by scarring or fibrosis
5. Spread through lymphatics or blood or stream

Suppurative or Purulent Inflammation



- Pus: thick fluid containing viable and necrotic polymorph and necrotic tissue
- 1. Localized: ex. Abscess: Abscess is the localized collection of pus, commonly seen solid block of tissue - Example: dermis, liver, kidney, brain etc. Pus consists of partly or completely liquefied dead tissue mixed with dead or dying neutrophils and living or dead bacteria, formed of 3 zones
  - Small abscess is called boil or furuncle
  - Large one carbuncle
  - Fistula
- 2. Diffused: Spreading of pus to adjacent areas e.g. cellulites occurring in subcutaneous tissue . Usually caused by streptococci.

Anti-Inflammatory Therapeutics

- NSAIDs: inhibitors of inflammation and fever (block prostaglandin synthesis)
- Glucocorticoids are also potent anti-inflammatory drugs
- Agents that block TNF are effective in treating rheumatoid arthritis, Crohn's disease, etc.
- Agents that block IL-1 are less effective for these diseases but are useful for some genetic inflammatory diseases (and are currently in clinical trials for more common conditions)