Inflammation

HST.035

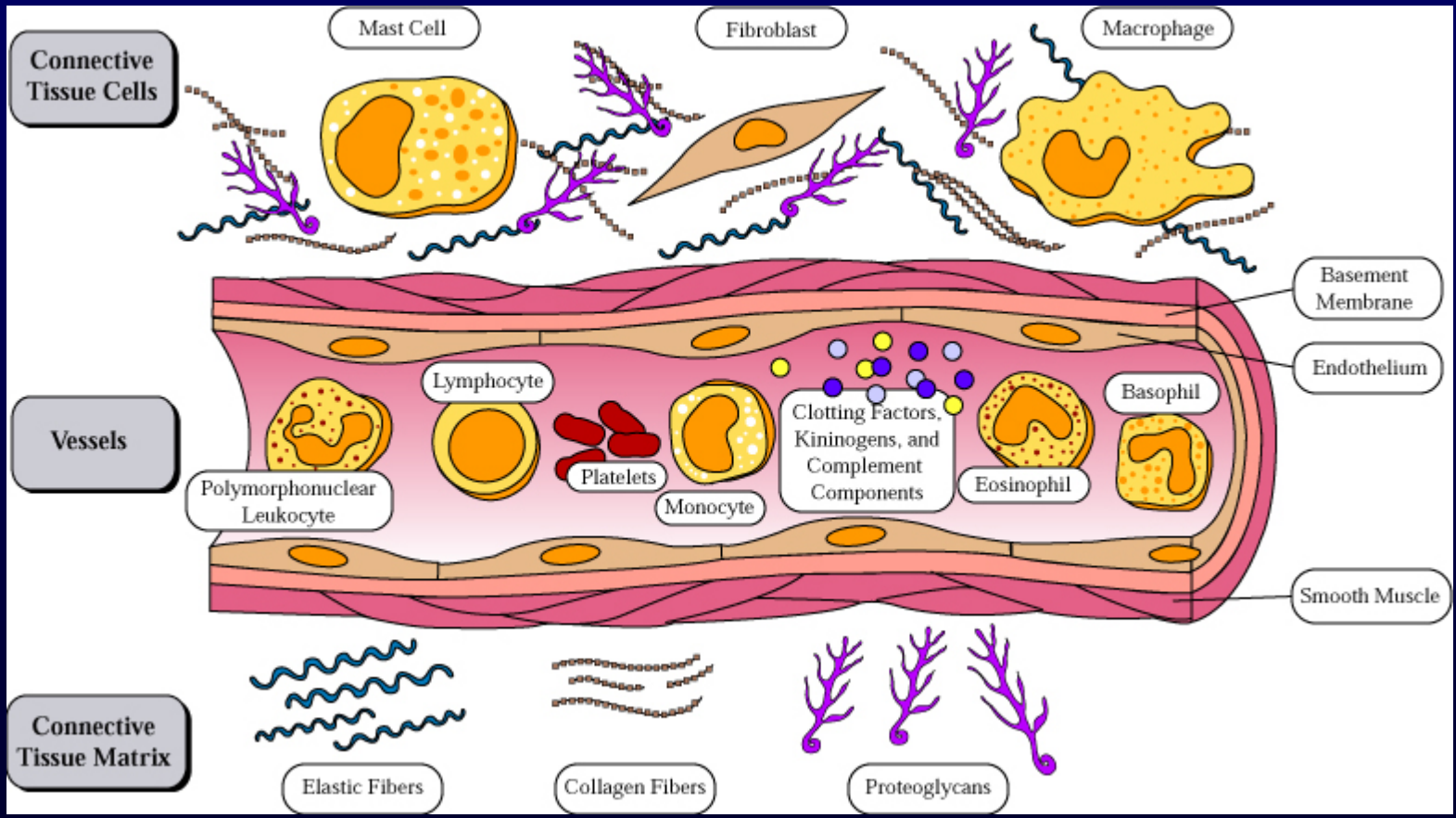
Spring 2003

The stimuli that cause cell injury also elicit a complex *inflammatory* reaction designed to (1) eliminate the cause of injury and (2) clean up the dead and the dying cells and tissues.

Inflammation and Repair

- Inflammation accomplishes its missions by trying to dilute, destroy or otherwise neutralize the offending agents.
- The inflammatory response is followed by a set of repair processes designed to regenerate the damaged tissue and/or fill the gaps with fibrous tissue (scar).
- Both the initial inflammatory reaction and the subsequent repair reactions can potentially cause harm.

Components of the Inflammatory Response



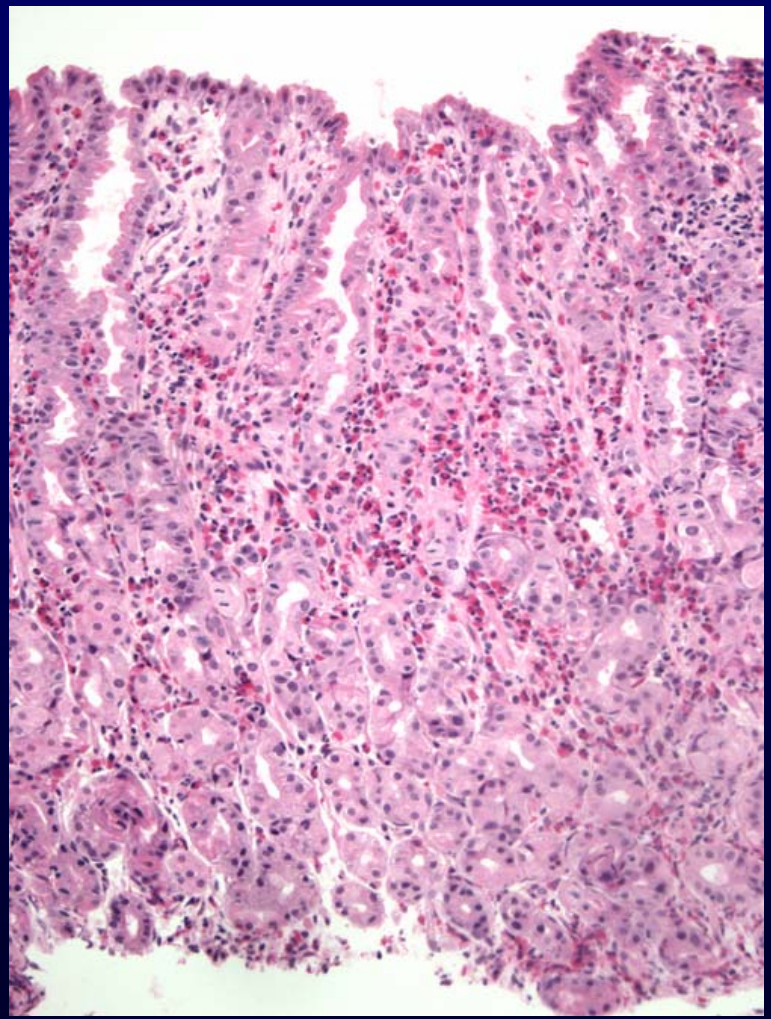
Basic Patterns of Inflammation

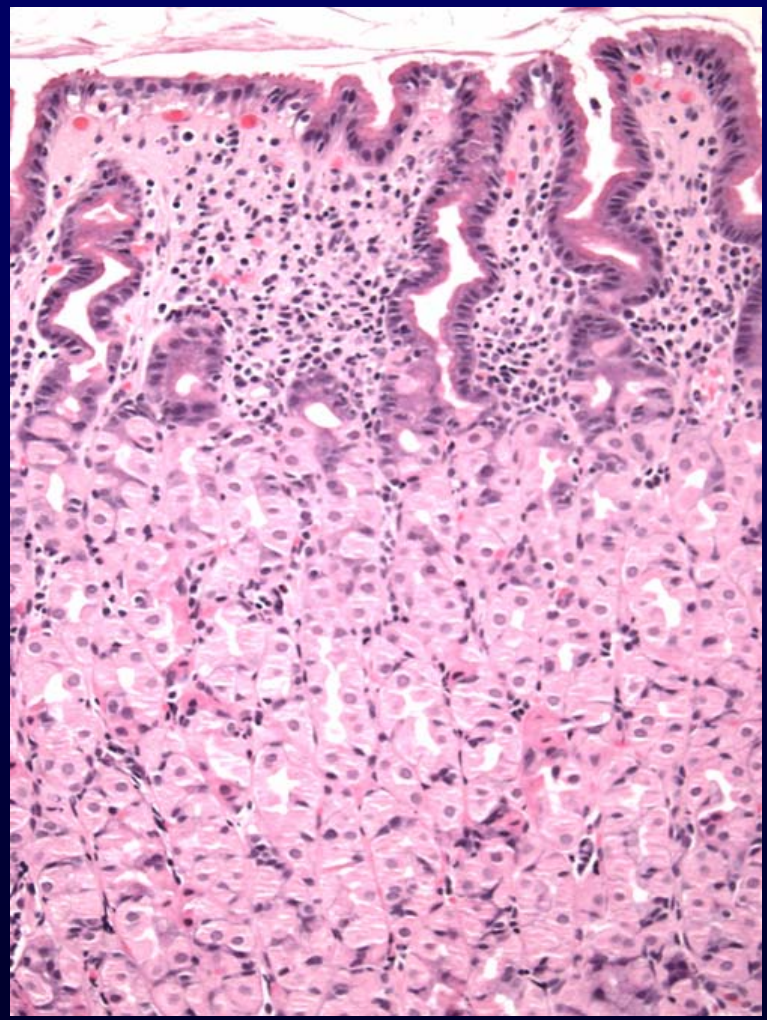
- *Acute inflammation* is of relatively short duration (hours to days) and is primarily characterized by exudation of fluid and plasma proteins, as well as a neutrophilic infiltration.

- *Chronic inflammation* is of longer duration (days to years) and is characterized by mononuclear infiltration, vascular proliferation and scarring.

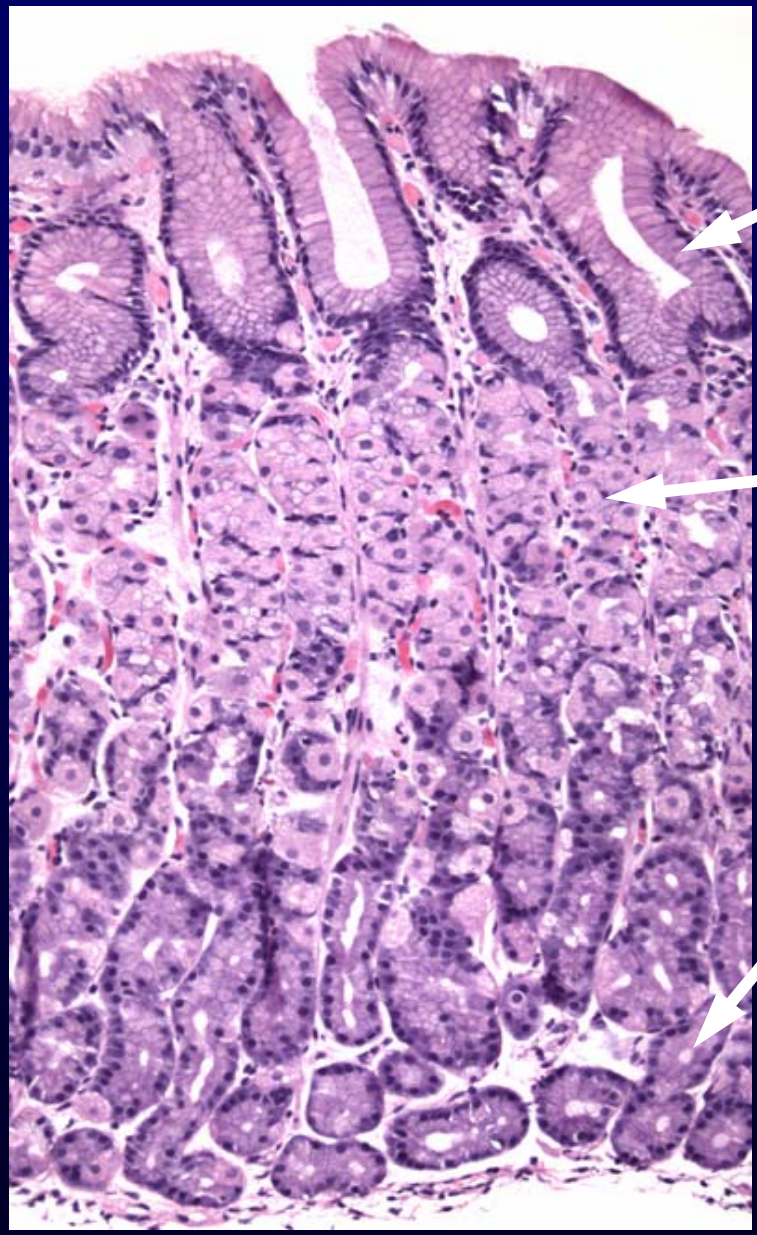
- In practice, these two patterns of inflammation often overlap.

Patterns of Inflammation





Normal Gastric Corpus



Acute Inflammation

- Acute inflammation has two major components:
  1. Vascular component
  2. Cellular (leukocytes) component
- Which result in the classic clinical triad of:
  1. Calor
  2. Rubor
  3. Tumor

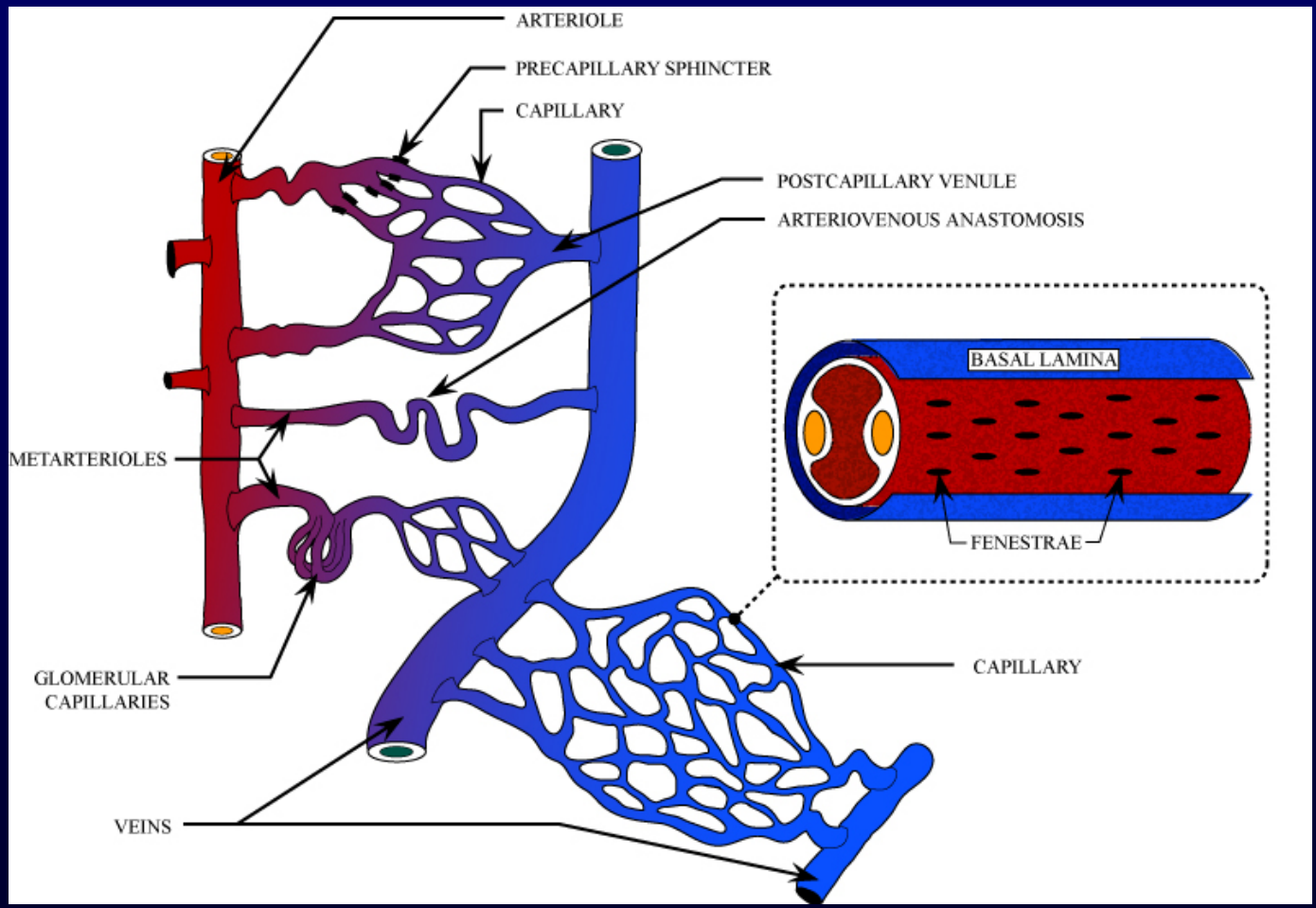
Summary of Events in Acute Inflammation

- Arteriolar vasodilation results in locally increased blood flow, engorgement of the capillary bed, and increased *transudation*
- *Exudation* of protein-rich fluid from the lumen into the extracellular space results in
  - Outflow of water and ions into the interstitial space ("*edema*")
  - Increased blood viscosity and decreased flow ("*stasis*")
- Stasis helps leukocytes escape the flow and attach to the vascular endothelium ("*margination*")
- Margination leads to *transmigration* of leukocytes out of the vessel into the interstitial space

Mechanisms of Increase in Vascular Permeability

1. Endothelial gap formation
    - Endothelial cell contraction
    - Cytoskeletal reorganization
2. Endothelial cell injury
    - Direct
    - Leukocyte-mediated
3. Increased transcytosis (vesicular trafficking)
4. Angiogenesis

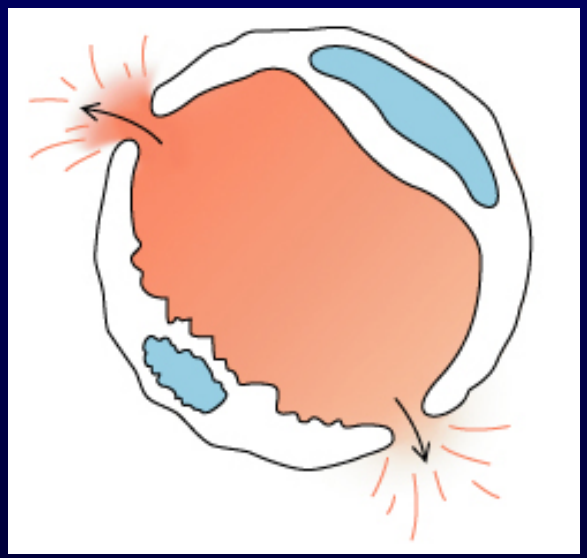
Overview of the Microcirculation



Arterioles and Venules

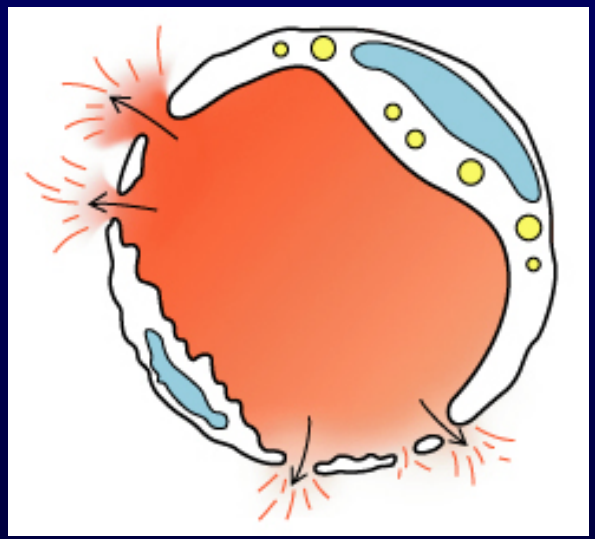
Please see Junqueira & Carneiro. *Basic Histology: Text and Atlas*. 10th edition. McGraw Hill. 2003. ISBN: 0071378294.

Gaps Due to Endothelial Cell Contraction



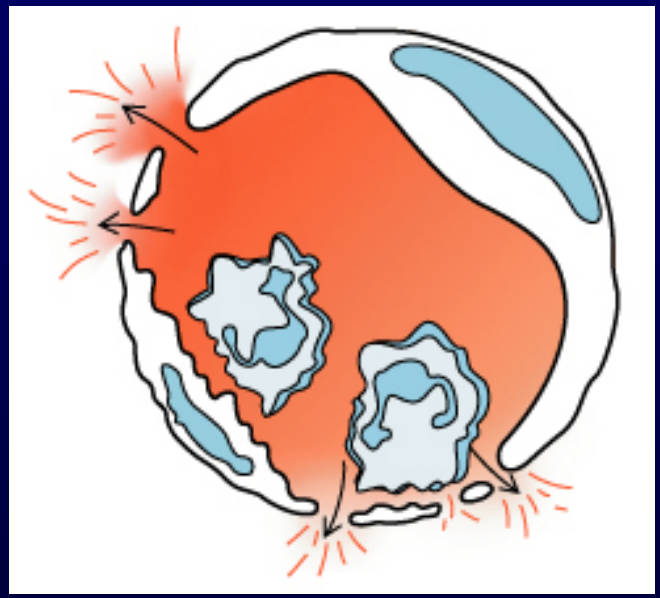
- The most common form of increased vascular permeability
- Limited to post-capillary venules
- Reversible process elicited by histamine, bradykinin, leukotrienes, and many other chemical mediators
- Rapid and short-lived reaction (minutes), hence *immediate transient response*
- ? Relationship to gaps due to “cytoskeletal reorganization” (which takes longer and lasts longer)

Direct Endothelial Injury



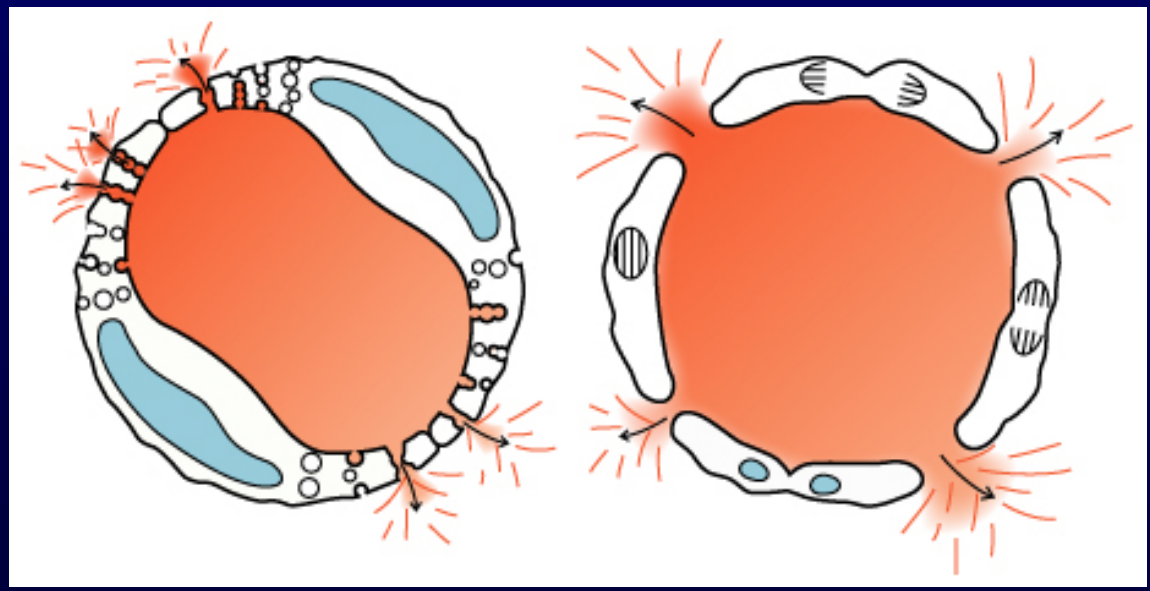
- Non-specific damage to vessels due to burns, infections, etc.
- Affects all small vessels
- Severe injury results in immediate increase in permeability and lasts until vessels are thrombosed or repaired, hence *immediate sustained response*
- Mild direct injury may result in a *delayed prolonged* leakage as endothelial injury evolves after exposure (e.g., sunburn)

Leukocyte-Mediated Endothelial Injury



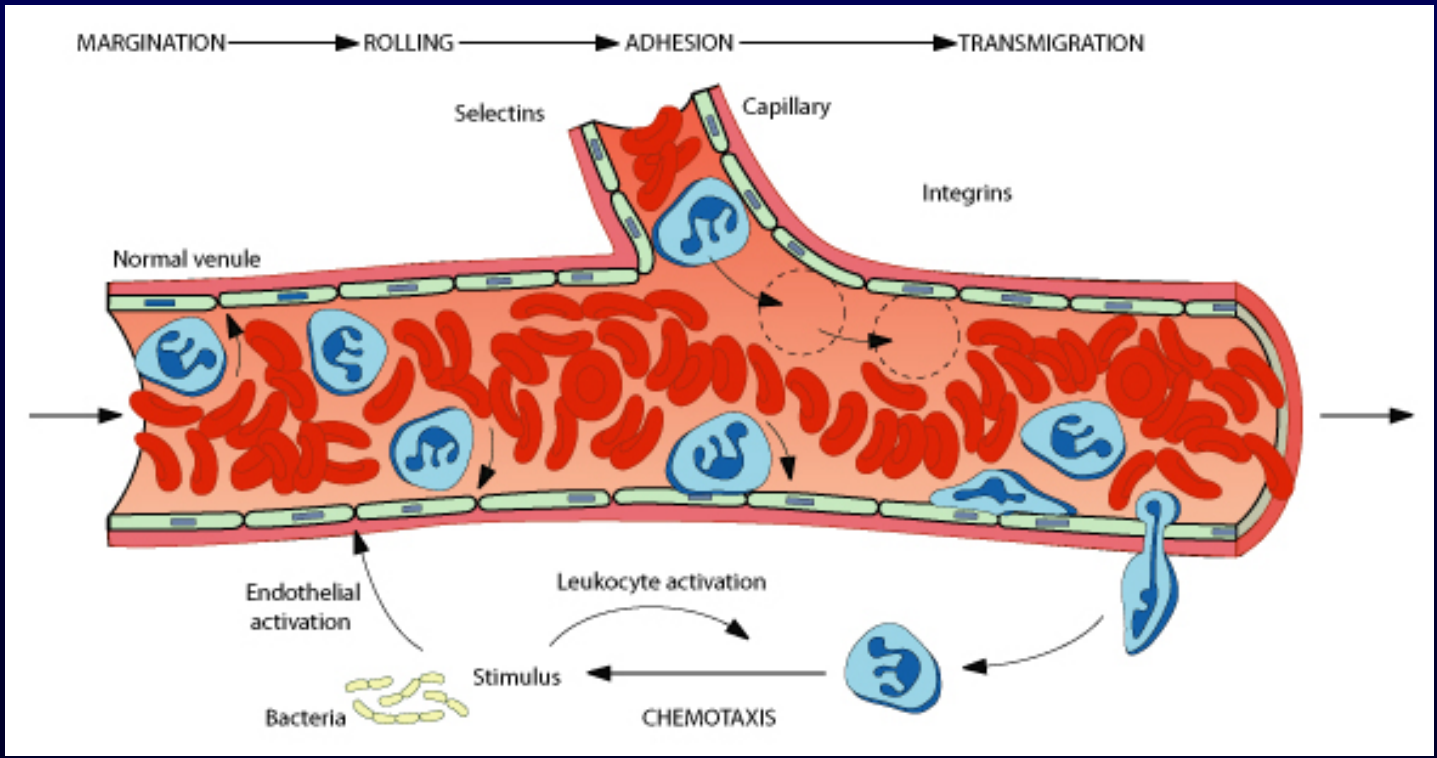
- Endothelial damage resulting from the action of activated leukocytes
- Primarily restricted to the sites of leukocyte adhesion (venules)

Increased Transcytosis and Angiogenesis

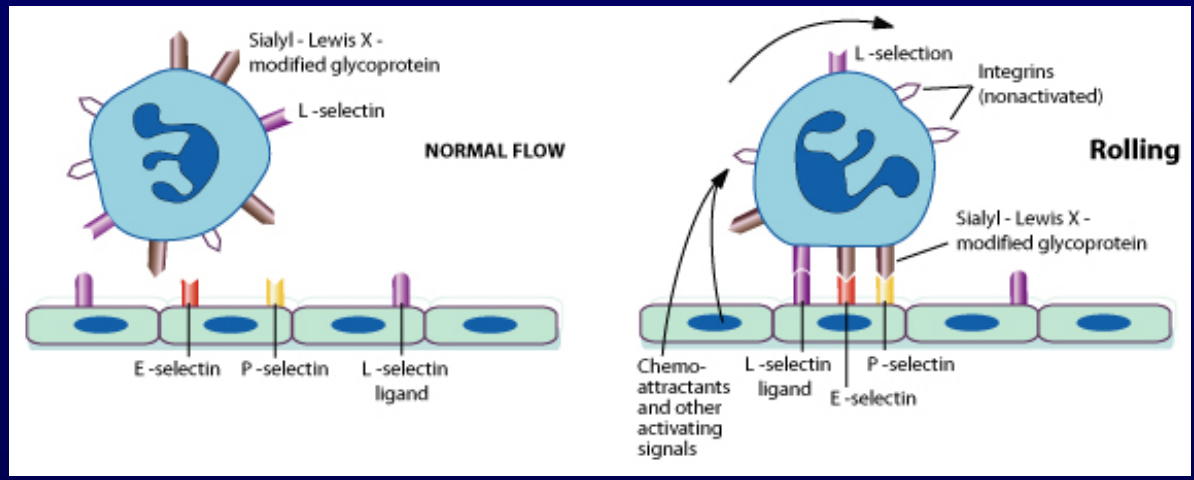


The Sequence of Cellular Events

- Margination and rolling
- Adhesion and transmigration
- Migration in the interstitial space

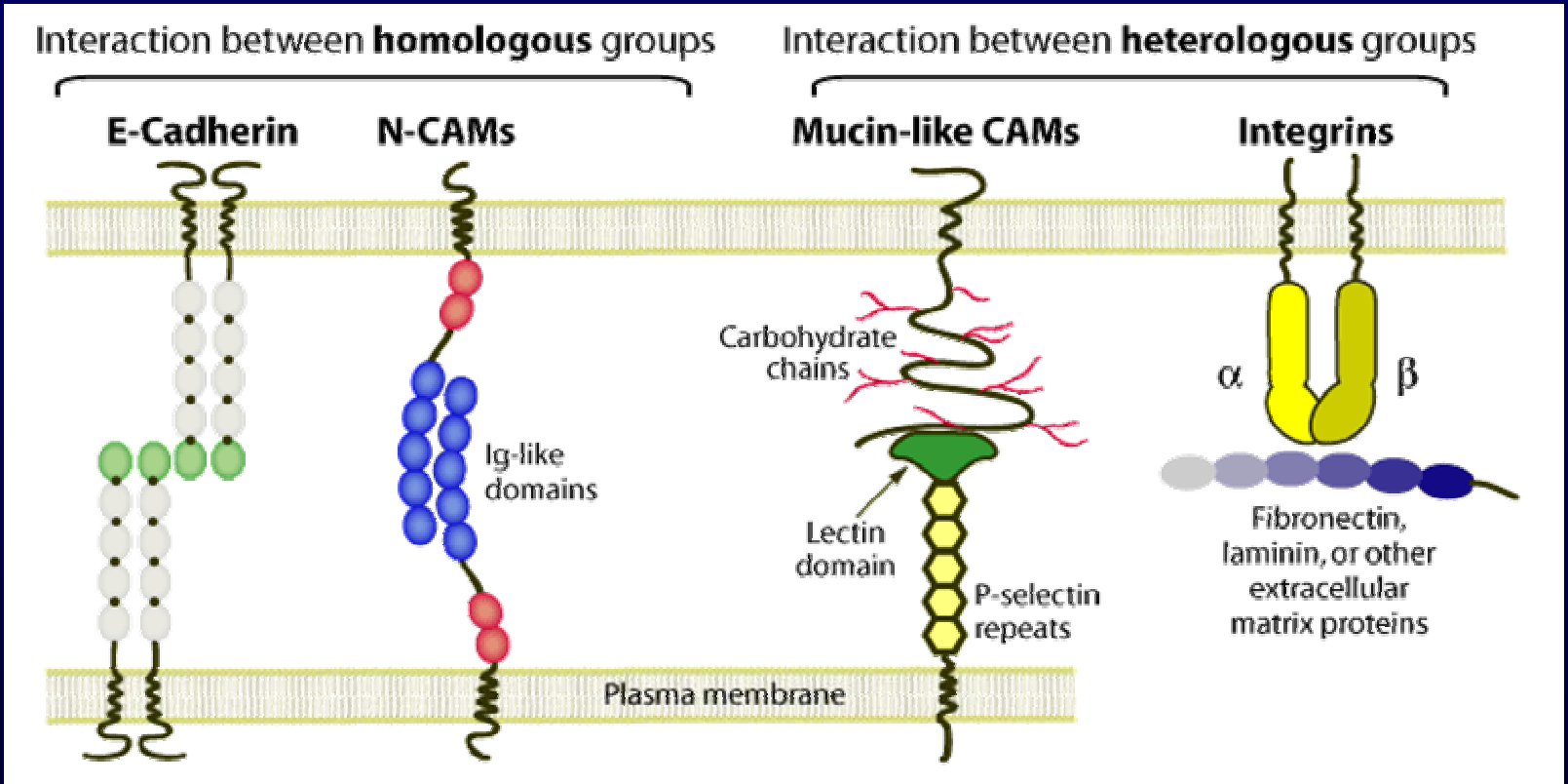


Margination and Rolling



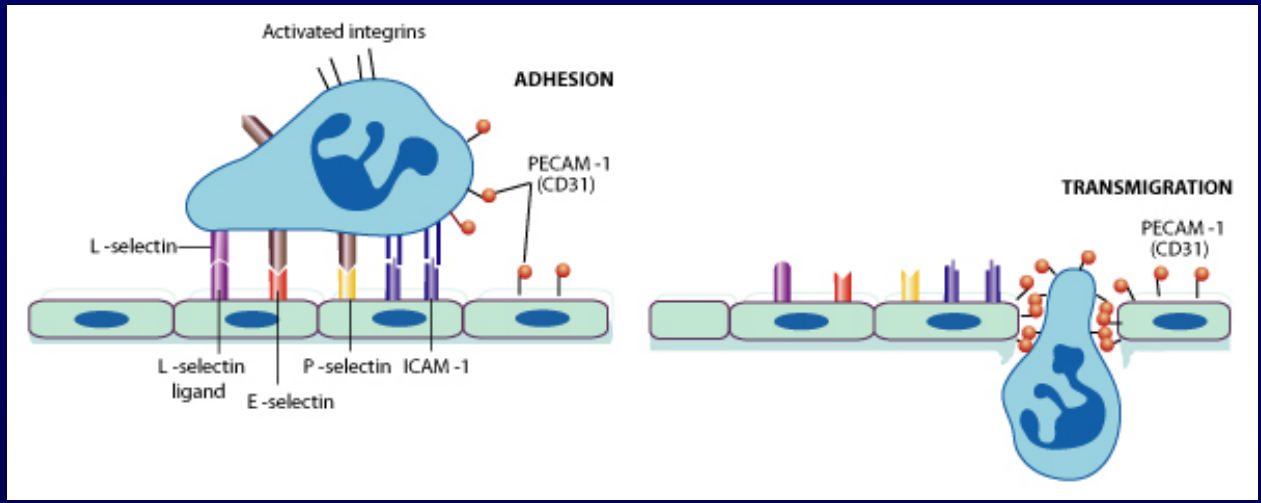
- Margination is a consequence of flow characteristics in small vessels
- Marginated leukocytes begin to roll on the endothelial surface by forming transient adhesions via the selectin family of proteins:
  - E-selectin on endothelial cells
  - P-selectin on endothelial cells and platelets
  - L-selectin on most leukocytes
- Selectins bind oligosaccharides that decorate mucin-like glycoproteins

Cell Adhesion Molecules



Redrawn from Molecular Cell Biology, Freeman, 1999.

Adhesion and Transmigration

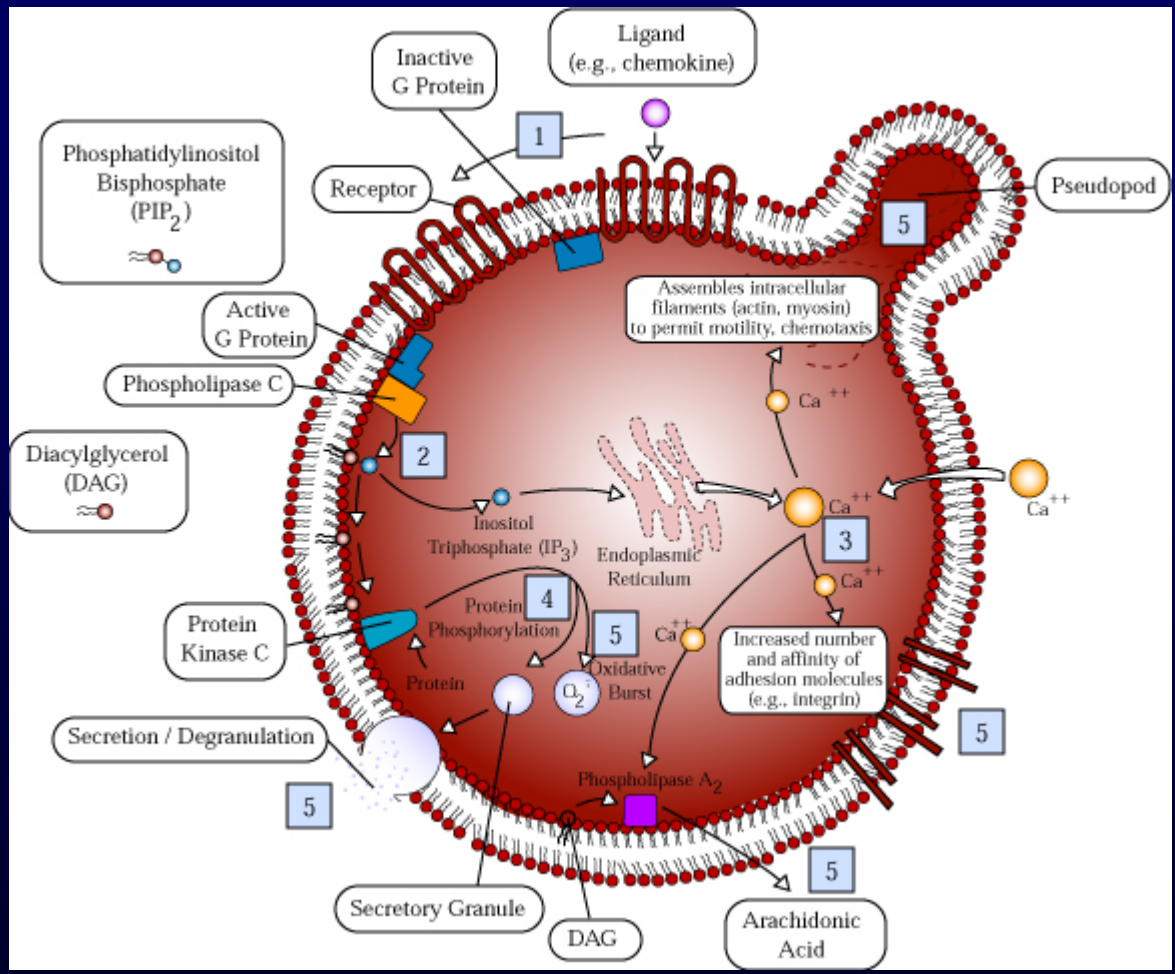


- Leukocytes firmly adhere to endothelial cells before diapedesis
- Adhesion is mediated by members of Ig superfamily on endothelial cells (ICAM-1, VCAM-1) that interact with leukocyte integrins (VLA-4, LFA-1)
- Diapedesis typically occurs in venules and is mediated by PECAM-1 (CD31), also of Ig superfamily

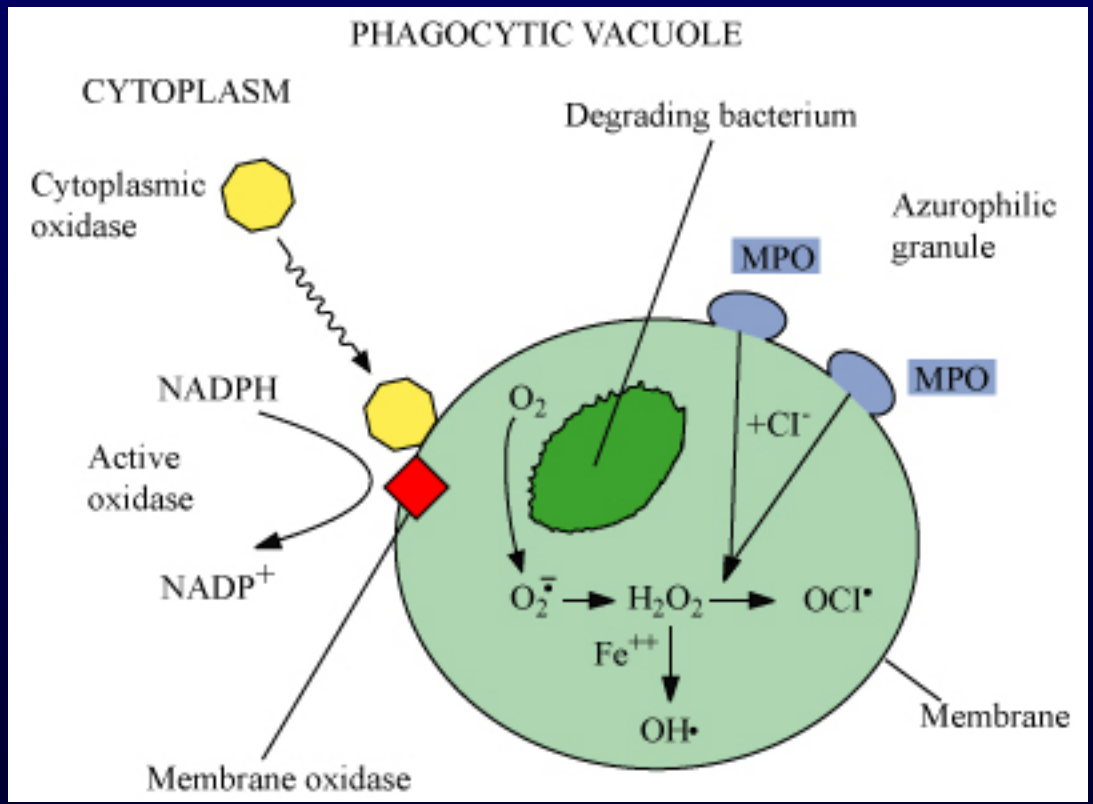
Chemotaxis and Activation

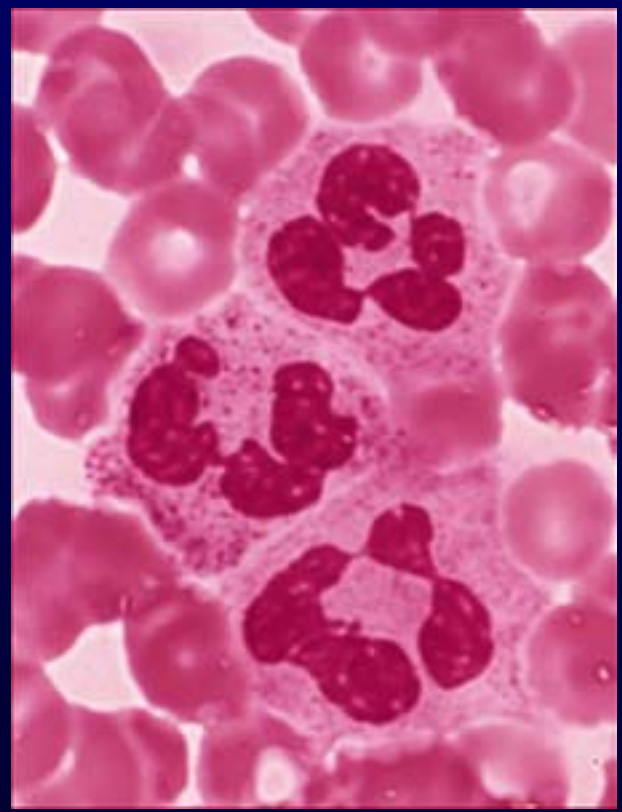
- Transmigrated leukocytes move to the site of injury along chemical gradients of chemotactic agents
- Chemotactic agent can be:
  - Soluble bacterial products (N-formylmethionine termini)
  - Components of the complement system (C5a)
  - Products of lipoxygenase pathway of arachidonic acid metabolism (leukotriene B4)
  - Cytokines (chemokines such as IL-8)
- Chemotactic molecules bind cell-surface receptors, resulting in activation of phospholipase C

Leukocyte Activation



Phagocytosis, Degranulation, and Oxygen-Dependent Antimicrobial Activity





Oxygen-Independent Antimicrobial Activity

- *Bactericidal permeability increasing protein (BPI)* causes phospholipase activation, phospholipid degradation and increased membrane permeability
- *Lysozyme* causes degradation of bacterial coat oliggosaccharides
- *Major basic protein (MBP)* is cytotoxic component of eosinophil granules
- *Defensins* are pore-forming antibacterial peptides

Defects in Leukocyte Function

Category	*Disease*	*Defect*
Defective adhesion	Leukocyte adhesion deficiency 1	β-chain of CD11/CD18
	Leukocyte adhesion deficiency 2	Sialylated oligosaccharide
Defective activation	Chronic granulomatous disease (X-linked)	NADPH oxidase membrane subunit
	Chronic granulomatous disease (AR)	NADPH oxidase cytoplasmic subunit
Defective phagocytosis	Chédiak-Higashi disease	Organelle docking and fusion