SEQUENCE OF EVENTS

- NORMAL HISTOLOGY →
- VASODILATATION →
- INCREASED VASCULAR PERMEABILITY →
- LEAKAGE OF EXUDATE →
- MARGINATION, ROLLING, ADHESION →
- TRANSMIGRATION (DIAPEDESIS) →
- CHEMOTAXIS →
- PMN ACTIVATION →
- PHAGOCYTOSIS: Recognition, Attachment, Engulfment, Killing (degradation or digestion) →
- TERMINATION →
- 100% RESOLUTION, SCAR, or CHRONIC inflammation

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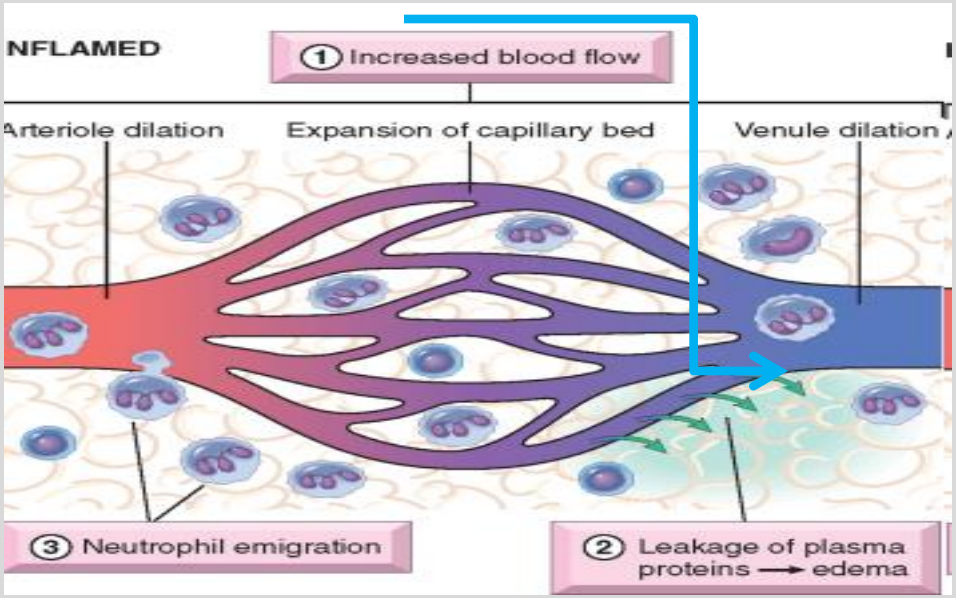
Step 1 of vascular changes in inflammation: vasodilation



Mechanism:
Inflammatory trigger ->Histamine -> Relaxation of vascular smooth muscle
Increases hydrostatic pressure; Causes transudate
Increased blood flow: heat and edema – Rubor (erythema)

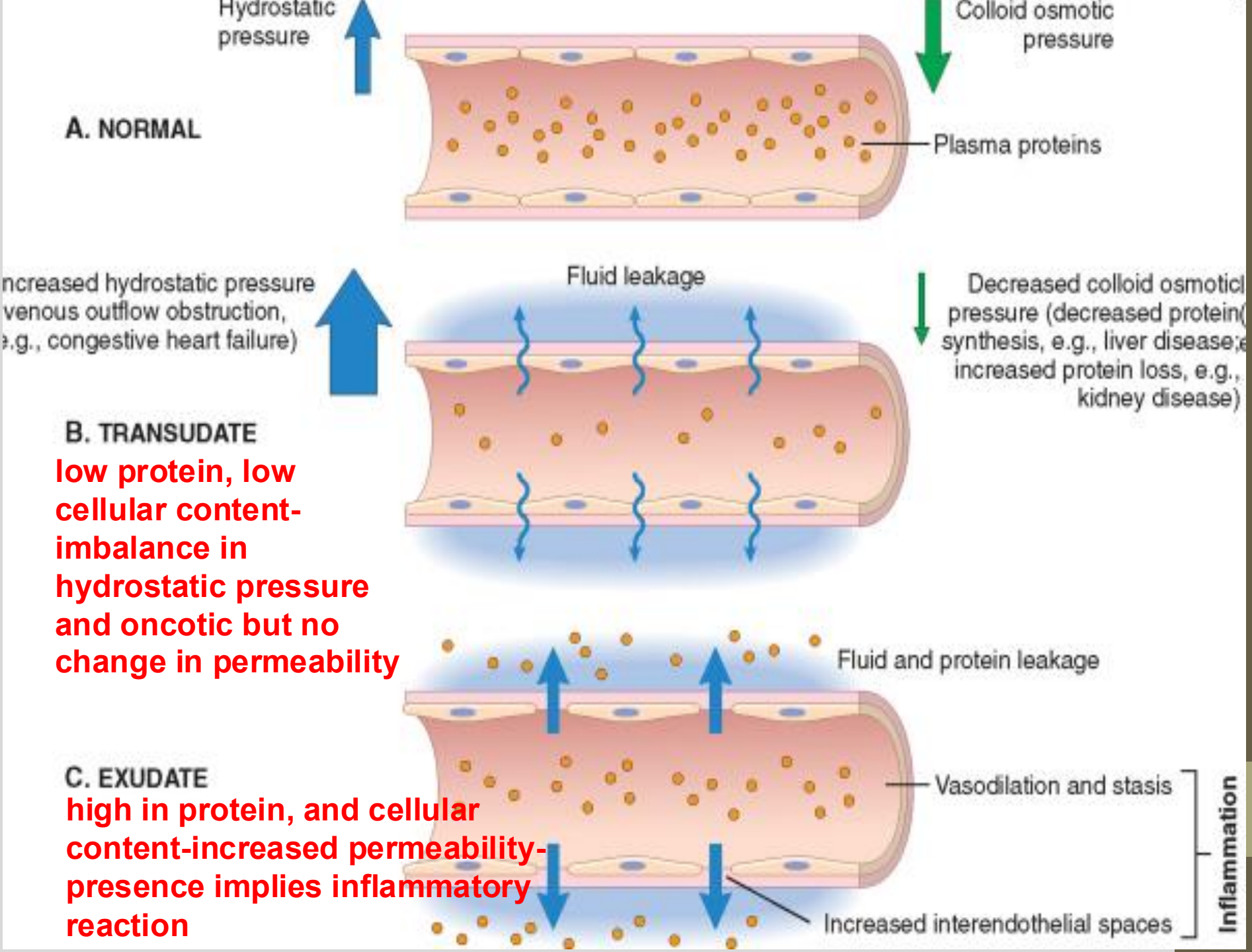
Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Vascular permeability

Permeability (leakiness) of the vessel affects hemodynamics:

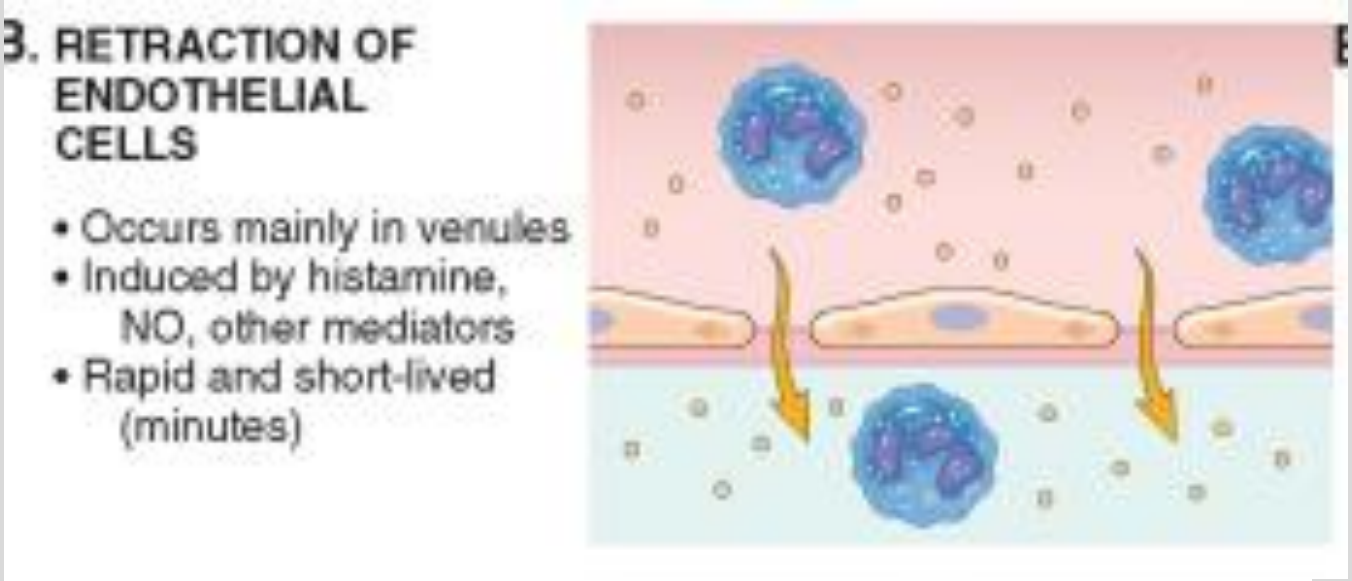
- Increased permeability (more leaky)—exudate results (high cellular and protein content fluid, high specific gravity)
- Pus - example of exudate: purulent exudate or inflammatory exudate rich in leukocytes, debris of dead cells and often microbes

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3


Hydrostatic pressure
Colloid osmotic pressure
A. NORMAL
Plasma proteins
ncreased hydrostatic pressure
venous outflow obstruction,
.g., congestive heart failure)
Fluid leakage
Decreased colloid osmotic
pressure (decreased protein(
synthesis, e.g., liver disease;
increased protein loss, e.g.,
kidney disease)
B. TRANSUDATE
low protein, low cellular content-imbalance in hydrostatic pressure and oncotic but no change in permeability
Fluid and protein leakage
C. EXUDATE
high in protein, and cellular content-increased permeability-presence implies inflammatory reaction
Vasodilation and stasis
Increased interendothelial spaces
Inflammation

Step 2 of vascular changes in inflammation: Vascular permeability increase

- **Mechanism (most significant): histamine retraction of endothelial cells: openings within the lining of venules (increased vascular permeability), fluid, proteins, and cells leak out→ exudate**
- **Exudate – high protein content, high cellular content, high Specifc Gravity**



Immediate transient response
15 – 30 minutes

If severe, endothelial injury (e.g burns, microbial toxins), may be long lived

Vasodilation + permeability→ Step 3 of vascular changes: Vascular congestion/Stasis

Stasis = slowing of blood flow (vascular congestion)

Mechanism:

- Vasodilation→ increased diameter (hemodynamics)
- Transudation→ decreased fluid→ higher concentration of RBCs→ higher viscosity of blood (leads to stasis)
- Permeability→ loss of fluid (decreased flow)

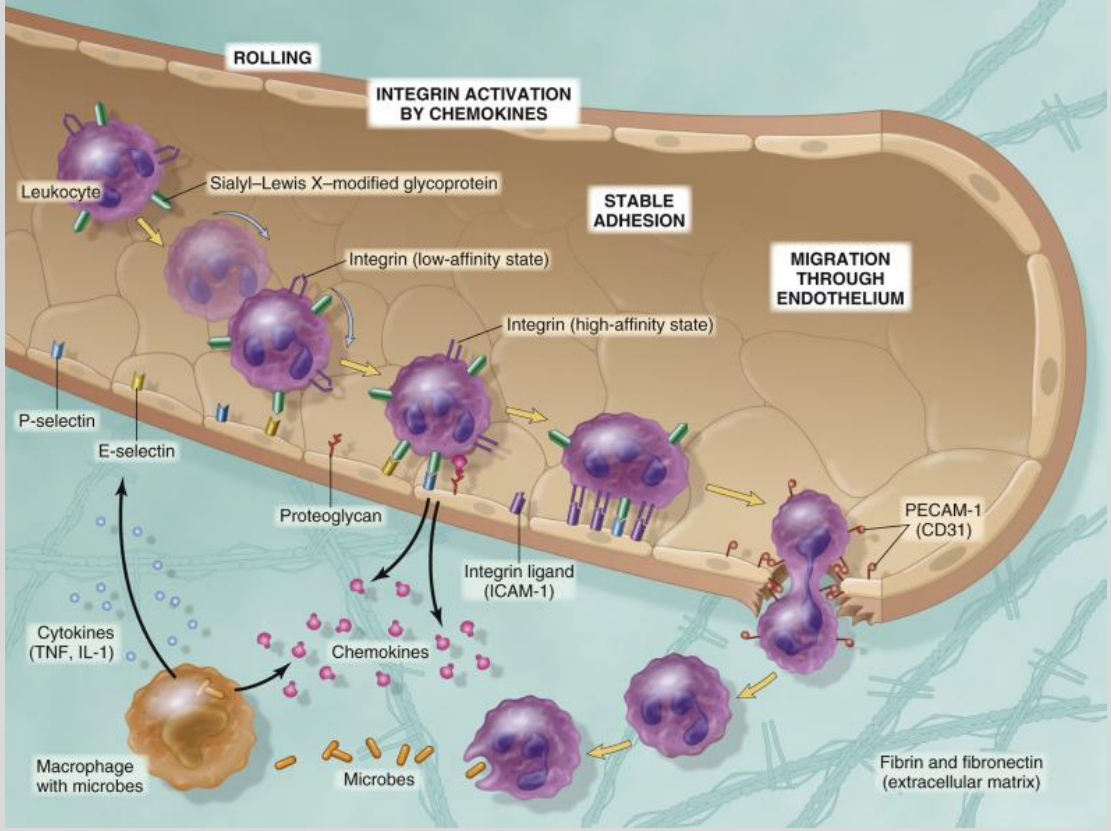
Hemodynamic changes→ accumulation of neutrophils along vascular epithelium, i.e., peripheral displacement — ***margination***

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Step 2 of cellular response: Rolling

- Purpose: SLOW down leukocytes
- Mechanism: Expression of selectins on endothelial cells
  - Selectins – low affinity adhesion molecules on neutrophils (L-selectins) and endothelial cells (E-selectins
  - Neutrophils naturally express selectins
  - Endothelial cells require stimulation to express selectins
  - Expression is stimulated/regulated by TNF and IL-1
  - Selectins bind sialyl Lewis X on wbcs

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3



Multistep process of leukocyte (white blood cell) migration through blood vessels, for neutrophils:

- **After margination, leukocytes first roll,**
- **then become activated and adhere to endothelium,**
- **then transmigrate across the endothelium (by piercing the basement membrane),**
- **and migrate toward chemoattractants coming from source of injury**

DIFFERENT MOLECULES PLAY ROLES IN DIFFERENT STEPS OF PROCESS:
-**SELECTINS, IN ROLLING**;
-**CHEMOKINES**, IN ACTIVATING NEUTROPHILS TO INCREASE AVIDITY OF **INTEGRINS**;
-**INTEGRINS, IN FIRM ADHESION;**
-CD31 (PECAM-1), IN TRANSMIGRATION

ICAM-1, Intercellular adhesion molecule 1; IL-1, interleukin-1; PECAM-1, platelet endothelial cell adhesion molecule (also known as CD31); TNF, tumor necrosis factor

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3, Fig. 3.4

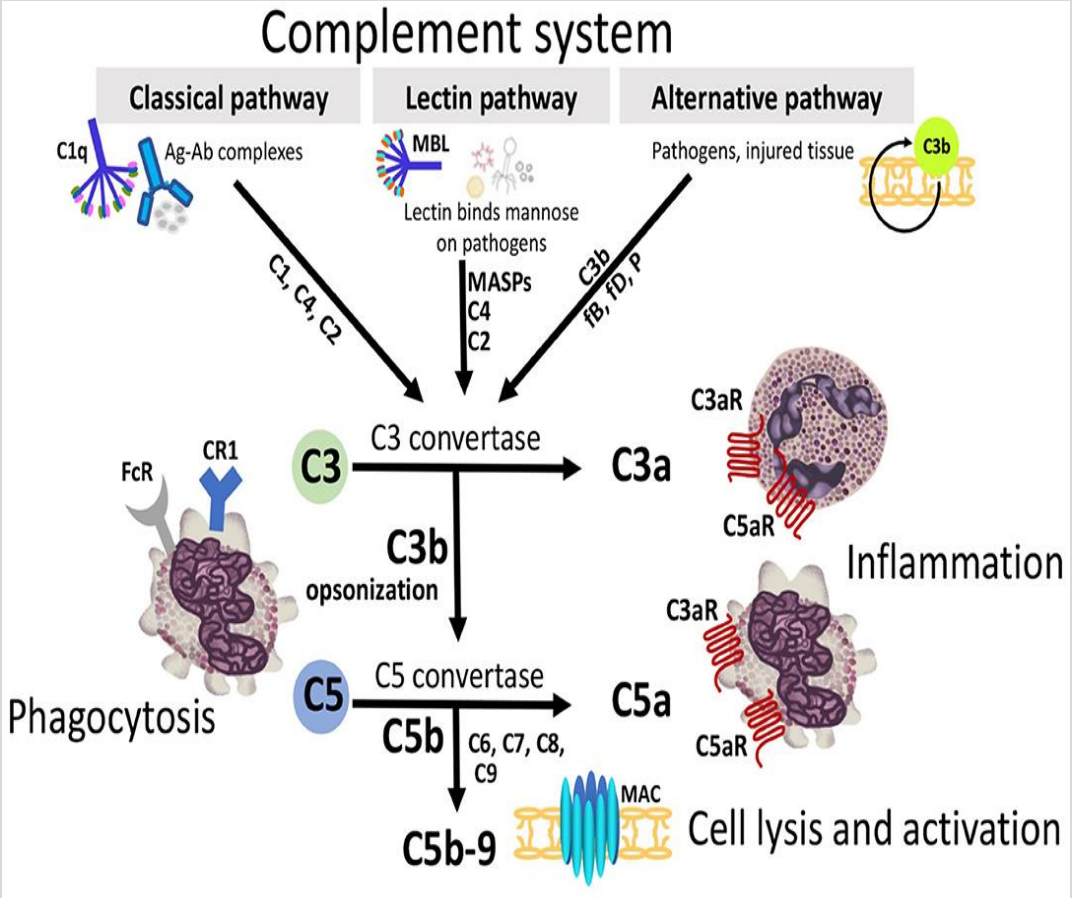
COMPLEMENT SYSTEM

- **More than 20 soluble proteins, host defense against microbes**
- Multiple sites of action, ultimately result in **LYSIS**
- **Activated,** become proteolytic enzymes that degrade other complement proteins **- enzymatic cascade**
- **Cleavage products cause increased vascular permeability, chemotaxis, and opsonization**

Critical step is proteolysis of C3; cleavage of C3 can occur via:

- **Classical pathway** - triggered by fixation of C1 to IgM or IgG which has combined with Ag
- **Alternative pathway:** no Ab
- **Lectin pathway:** directly activates C1

- **ALL PATHWAYS LEAD TO C3 CONVERTASE ENZYME FORMATION WHICH SPLITS C3 INTO C3A AND C3B**



https://www.frontiersin.org/articles/10.3389/fimmu.2020.01681/full

Complement fixation is the end stage of a cascade of multiple chemical events, which **ultimately results in lysis of cell membranes**, for example, of microorganisms

Recognition of Microbes and Dead Tissue

- Activation results from signaling pathways triggered in wbcs that result in increased cytosolic Ca+2, activation of protein kinase C, phospholipase A2
  - Receptors for microbial products: TLR's
  - N-Formylmethionyl receptors
  - Receptors for opsins (Ab's and comlement proteins)
  - Receptors for cytokines
- **After recognition comes removal, by phagocytosis**
  - **3 steps: 1-Recognition, 2-Engulfment, 3-Killing**

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Chronic inflammation

- **Persistent infections**; response of prolonged duration (weeks/months) - inflammation, tissue injury, attempts at repair occurring at same time
- **Tissue destruction with attempts at healing** by connective tissue replacement of damaged tissue (angiogenesis and fibrosis)
- **Infiltration by mononuclear cells** – lymphocytes, macrophages (aka histiocytes), plasma cell, eosinophils
- **Immune-mediated inflammatory diseases** – examples multiple sclerosis, asthma, Rheumatoid arthritis (autoimmune disease)
- **Prolonged exposure to toxins** (exogenous and endogenous) – silicosis, atherosclerosis

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Monocytes and Macrophages

Monocytes extravasate into connective tissue - transform into macrophages

- Become dominant cell by 48 hours
  - **Macrophages appear after neutrophils, though some neutrophils may still be present with macrophages**
- Tissue macrophages can live months to years
- Help eliminate injurious agents and induce tissue repair

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Acute and chronic inflammation

- Chronic inflammation sometimes shows neutrophils induced by persistent microbes or mediators produced by activated macrophages and T lymphocytes
- **Lymphocytes usually predominate in viral infections - may be first cells to arrive**

- In **acute infections, especially bacterial, neutrophils predominate:**
  - More numerous in general
  - Respond quicker to chemokines; arrive within 6 to 24 hours
  - Attach more firmly to adhesion molecules
  - Are short-lived and undergo apoptosis within 24 to 48 hours

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Activated Macrophages in Chronic Inflammation

- **Classically activated (M1)**
  - from interferon-gamma or microbial products, etc.
  - kill via ROS, NOS, lysosomal enzymes in acute inflammation
  - In chronic inflammation, secrete IL-1, IL-12, and IL23 and potentiate inflammatory reaction
- **Alternatively activated (M2)**
  - from IL-13, IL-4, possibly T cells
  - promote growth factors, especially TGF-beta, important in tissue repair and fibrosis
  - also induce IL-10 which has anti-inflammatory effects

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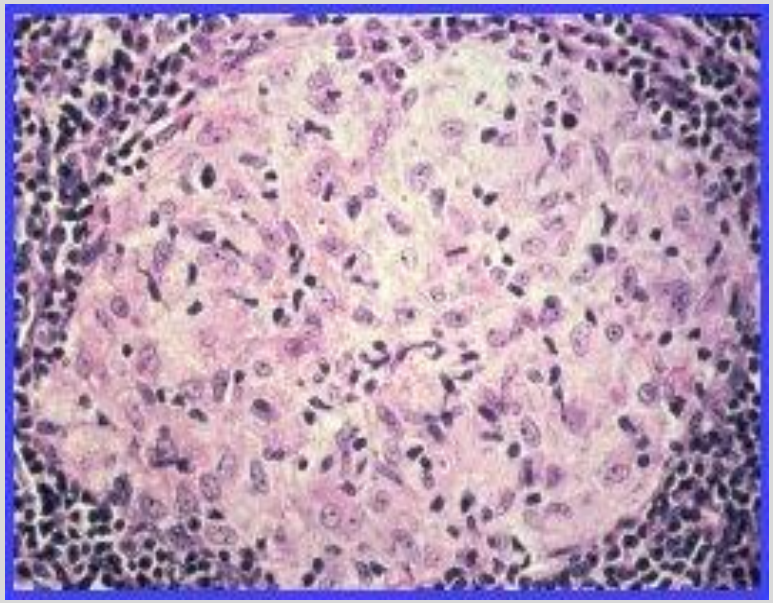
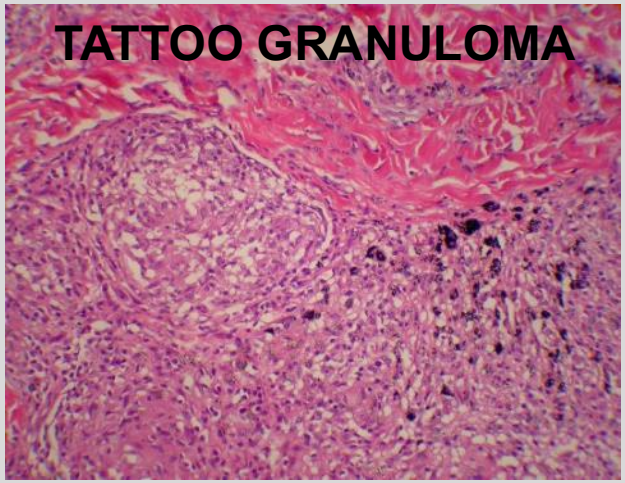


SARCOID GRANULOMA



GRANULOMA:

- Focus of chronic inflammation showing **aggregate of macrophages** (may fuse), transformed into epithelial-like cells, surrounded by rim of mononuclear wbcs, especially lymphocytes and some plasma cells
- Giant cells may be present (see next slide)

- Occurs when immune system attempts to isolate foreign substances. unable to eliminate, including infectious organisms (**e.g tuberculosis and fungi)**, as well as foreign objects, keratin, and suture fragments, etc.

Foreign body granuloma v. Immune granuloma (e.g sarcoidosis – persistent T cell immune response)

http://granuloma.homestead.com/Tatoo3_SP0302250.jpg