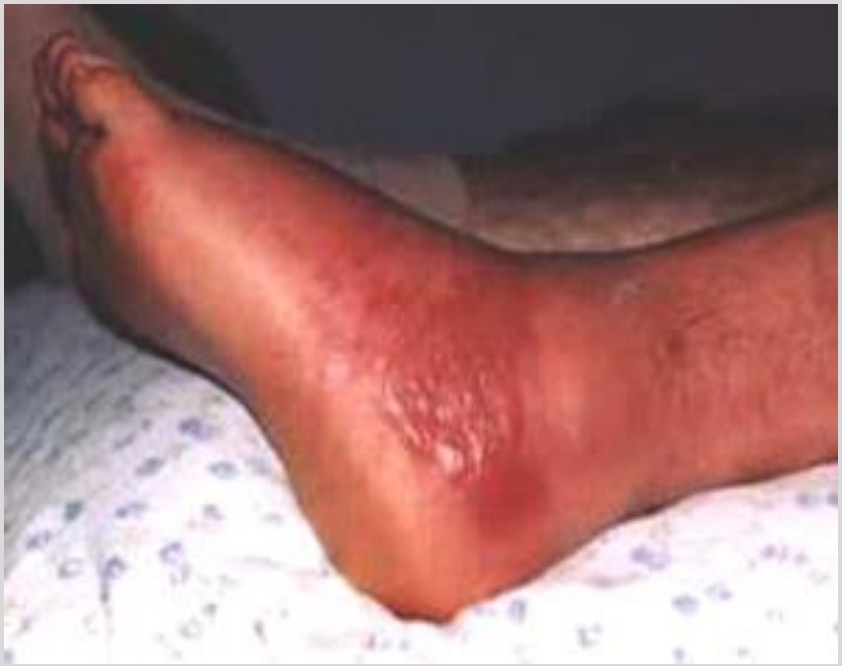
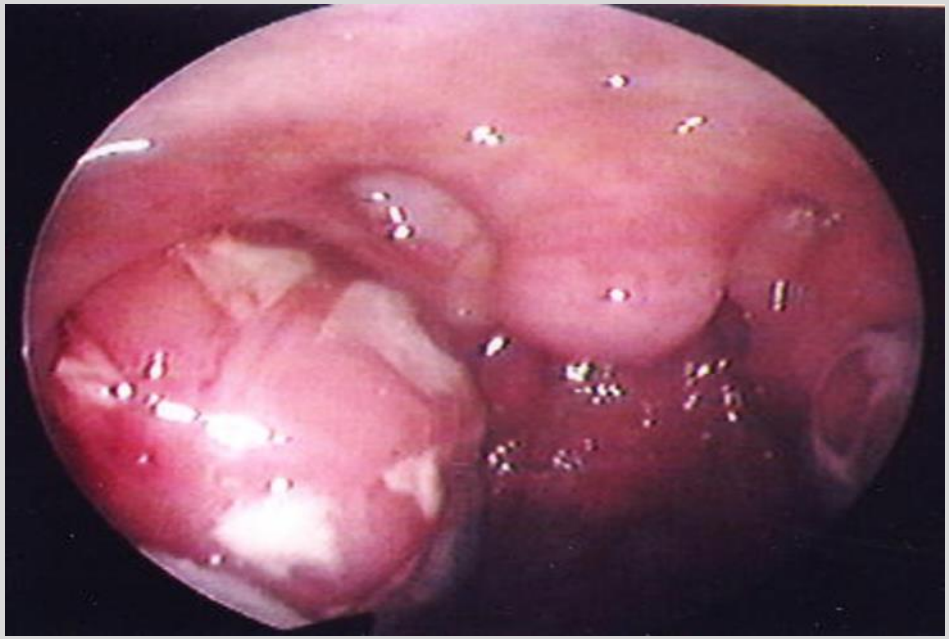
Session Objectives

1. Explain the vascular and cellular changes in acute inflammation and discuss important mediators, their origins, their roles in the inflammatory response, and how they contribute to the cardinal signs of inflammation.
2. Describe the sequential steps of phagocytosis and its end result.
3. Discuss and compare the different types of acute inflammation (e.g., serous, fibrinous, suppurative).
4. Describe and explain the function, role, and morphology of monocytes, macrophages, lymphocytes, and eosinophils in chronic inflammation and compare chronic to acute inflammation.
5. Discuss and describe granulomatous inflammation, its formation and significance.

Cellulitis (Erysipelas) of the foot



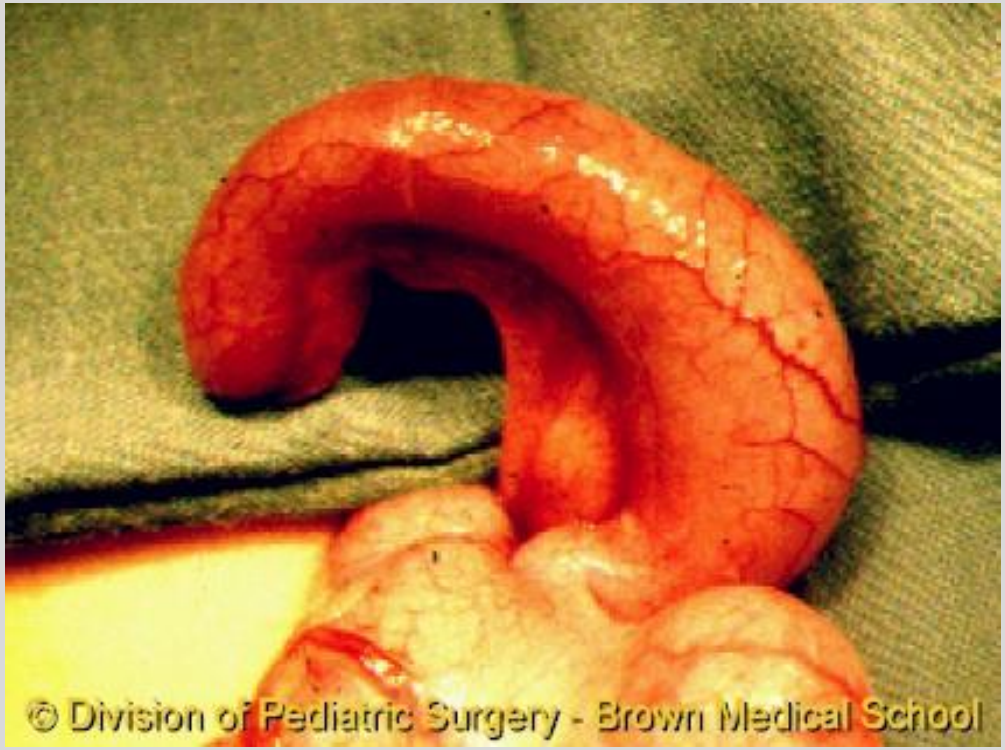
Inflamed tonsil

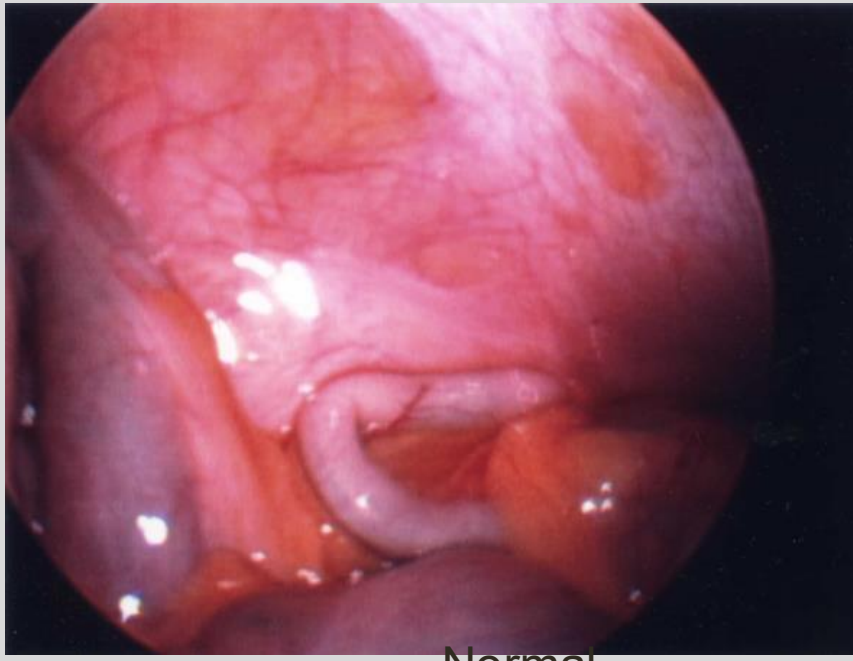


http://www.gradydoctor.com/2010/06/reflection-on-friday-sockin-it-to-me.html

http://tonsillitispictures.org/Infected-Tonsils.php

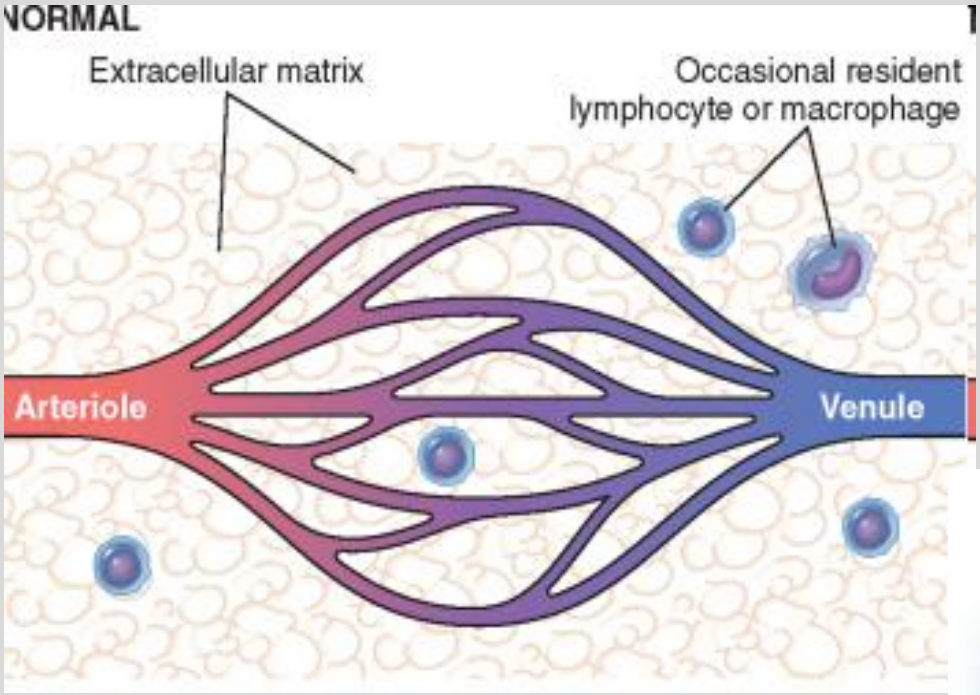
Inflamed appendix

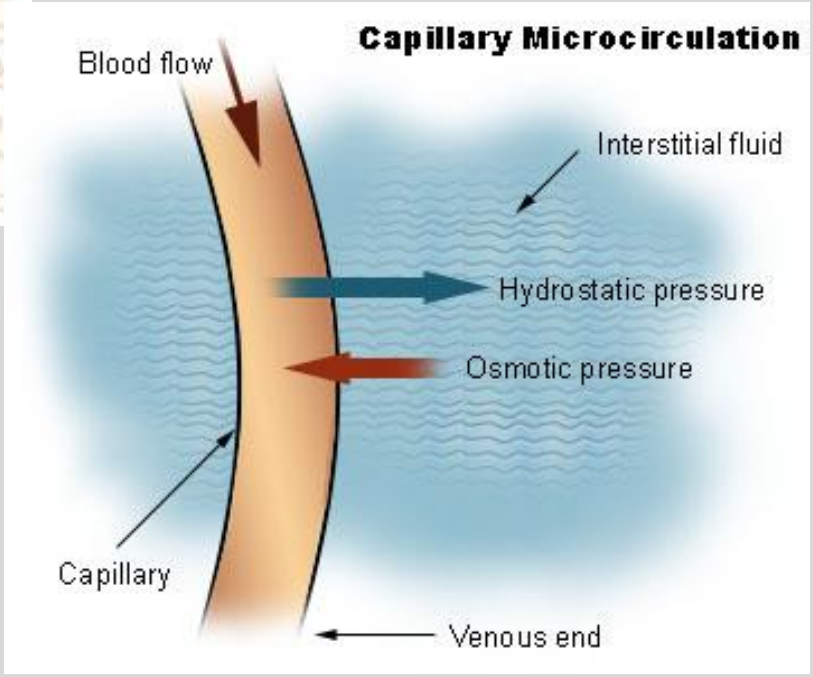




Normal

http://www.ucsfcme.com/2008/slides/MDM08Q05/15-Vissers.pdf



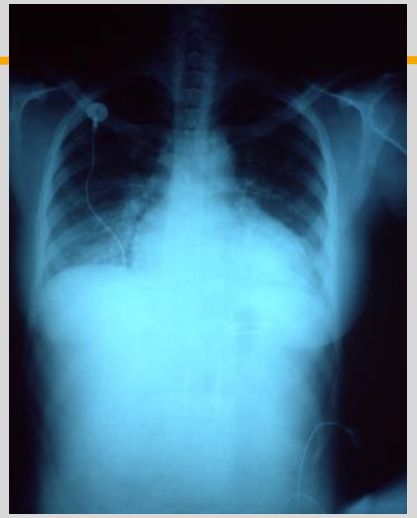


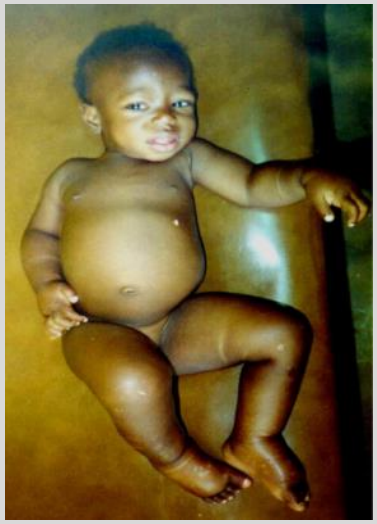
Hydrostatic pressure – pushes fluid out
Oncotic (osmotic) pressure – keeps fluid in

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

Forces acting on blood vessel

- If hydrostatic and oncotic pressures not in equilibrium→ transudate
  - protein content low, little cellular material, low specific gravity
- **If hydrostatic pressure increased (e.g., CHF), then localized edema**
- **If oncotic pressure decreased (e.g, liver, kidney disease), then generalized edema (anasarca)**
- Edema- excessive fluid in the extravascular space

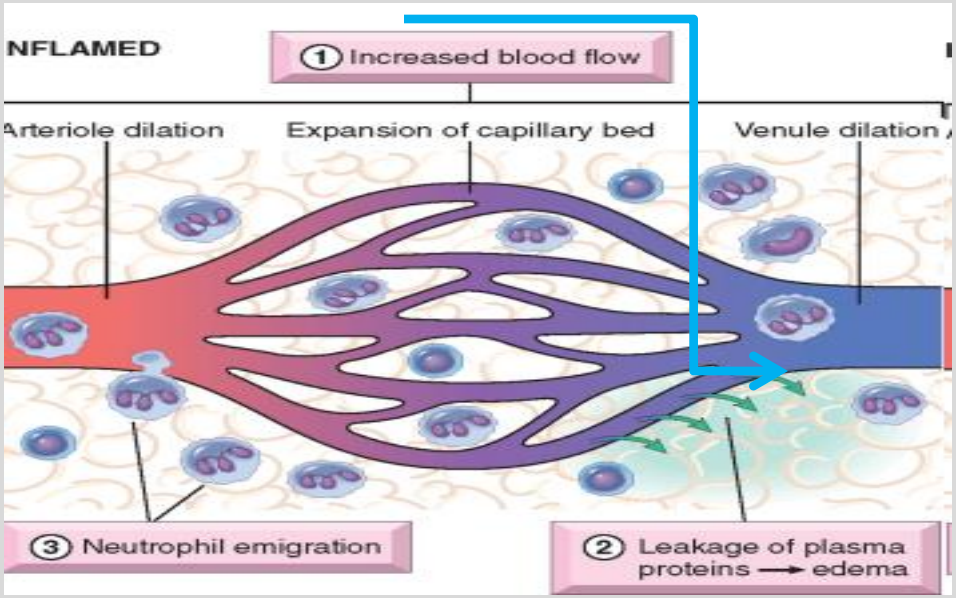




Kwashiorkor disease: severe protein malnutrition; usually affects infants and children, seen in very severe cases of starvation and poverty-stricken regions worldwide

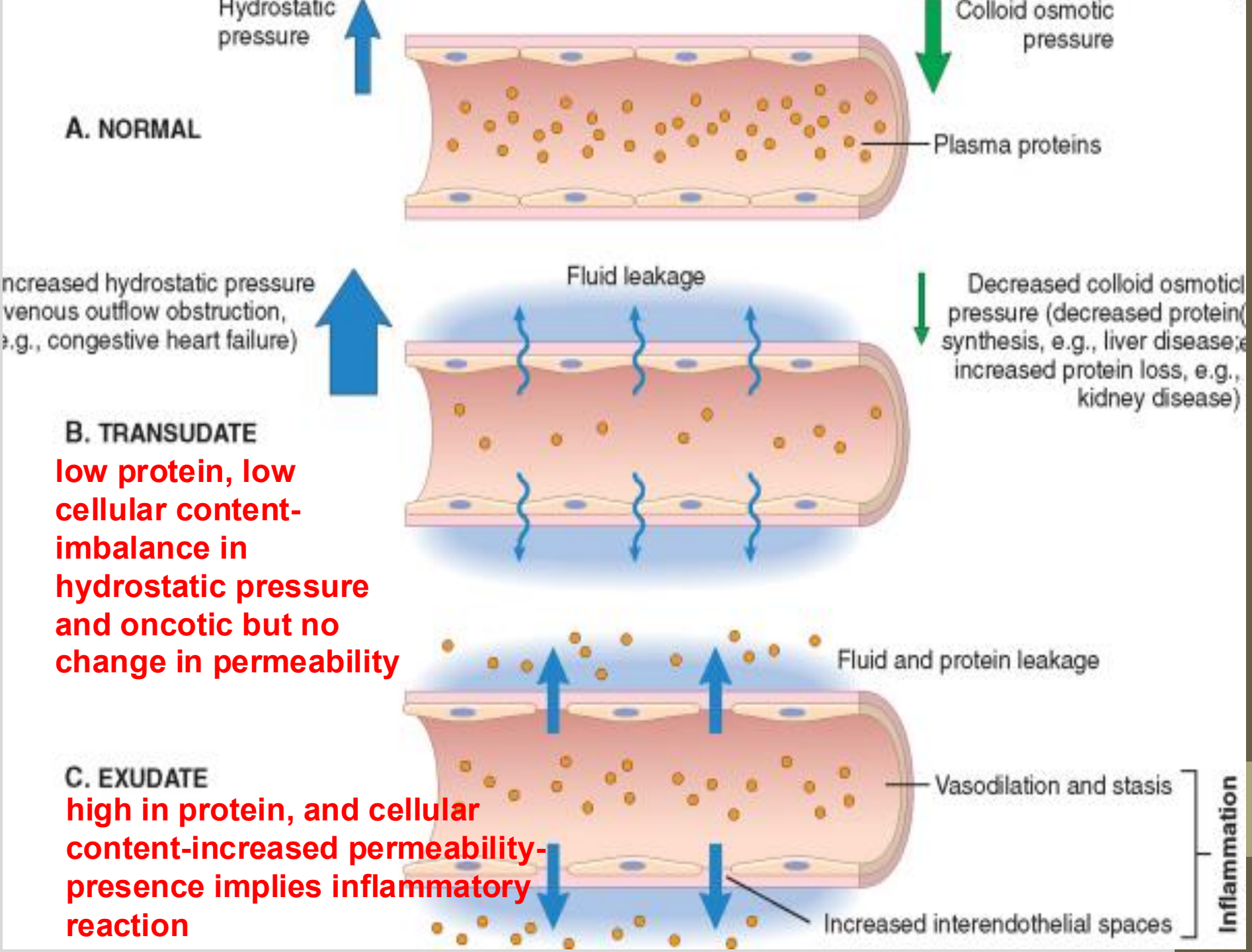
Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3
https://www.ncbi.nlm.nih.gov/books/NBK507876/#:~:text=Introduction,and%20poverty%2Dstricken%20regions%20worldwide.

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


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

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

Stasis = slowing of blood flow (vascular congestion)

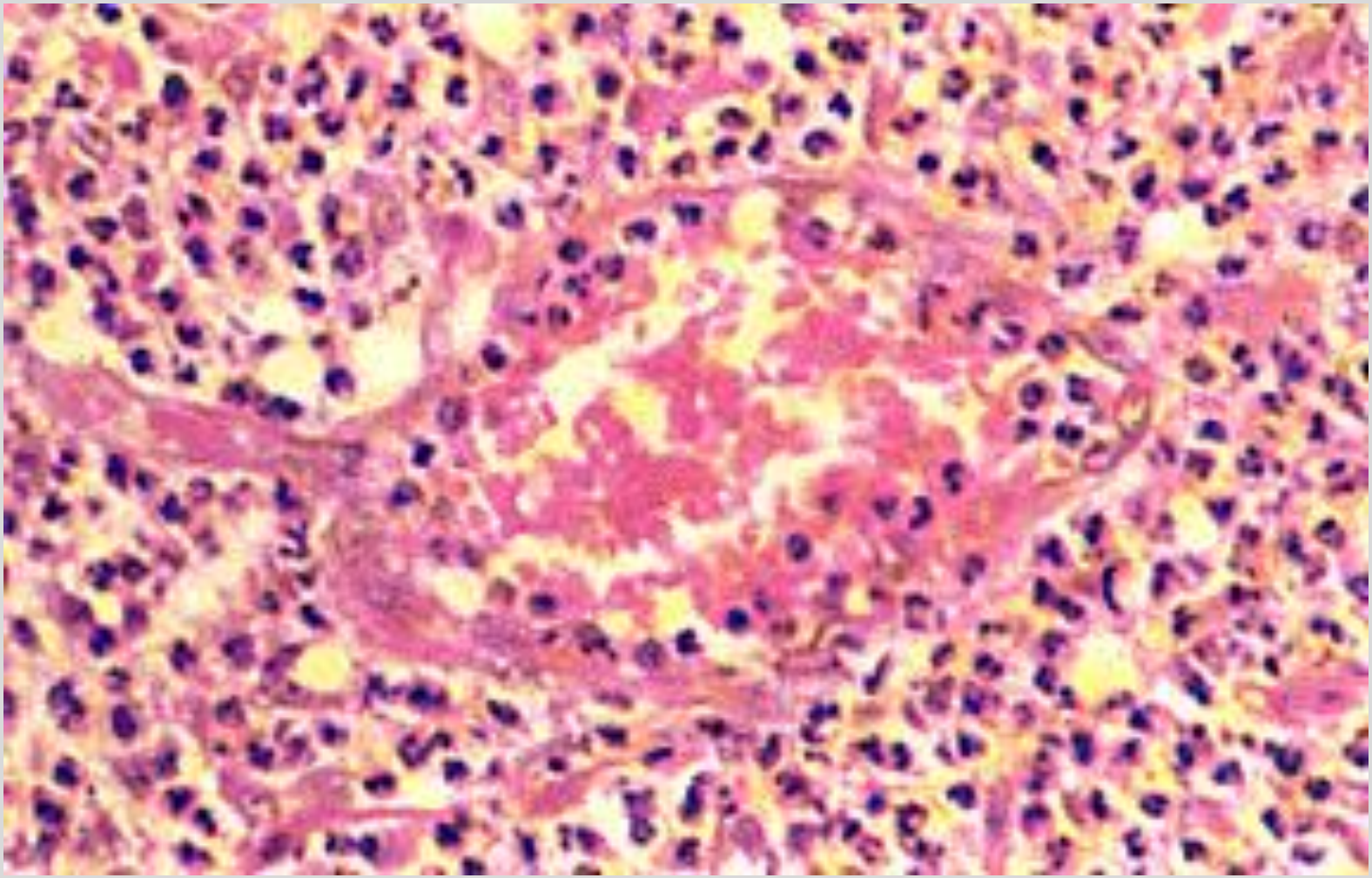
Mechanism:

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

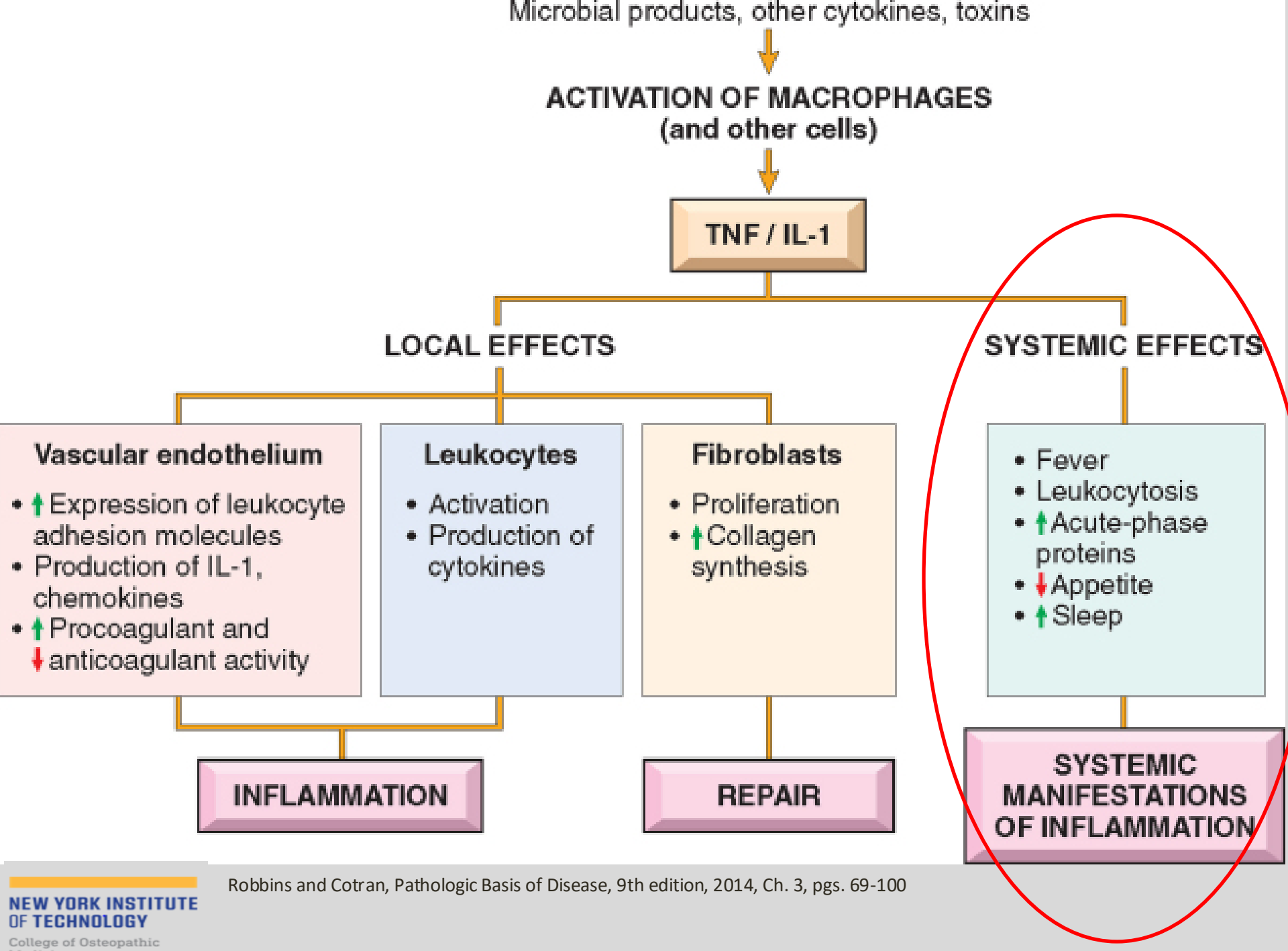
Hemodynamic changes→ accumulation of neutrophils along vascular epithelium, i.e., peripheral displacement — ***margination***

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

Margination



http://courses.washington.edu/conj/inflammation/acuteinflam.htm



Robbins and Cotran, Pathologic Basis of Disease, 9th edition, 2014, Ch. 3, pgs. 69-100

Step 2 of cellular response: Rolling

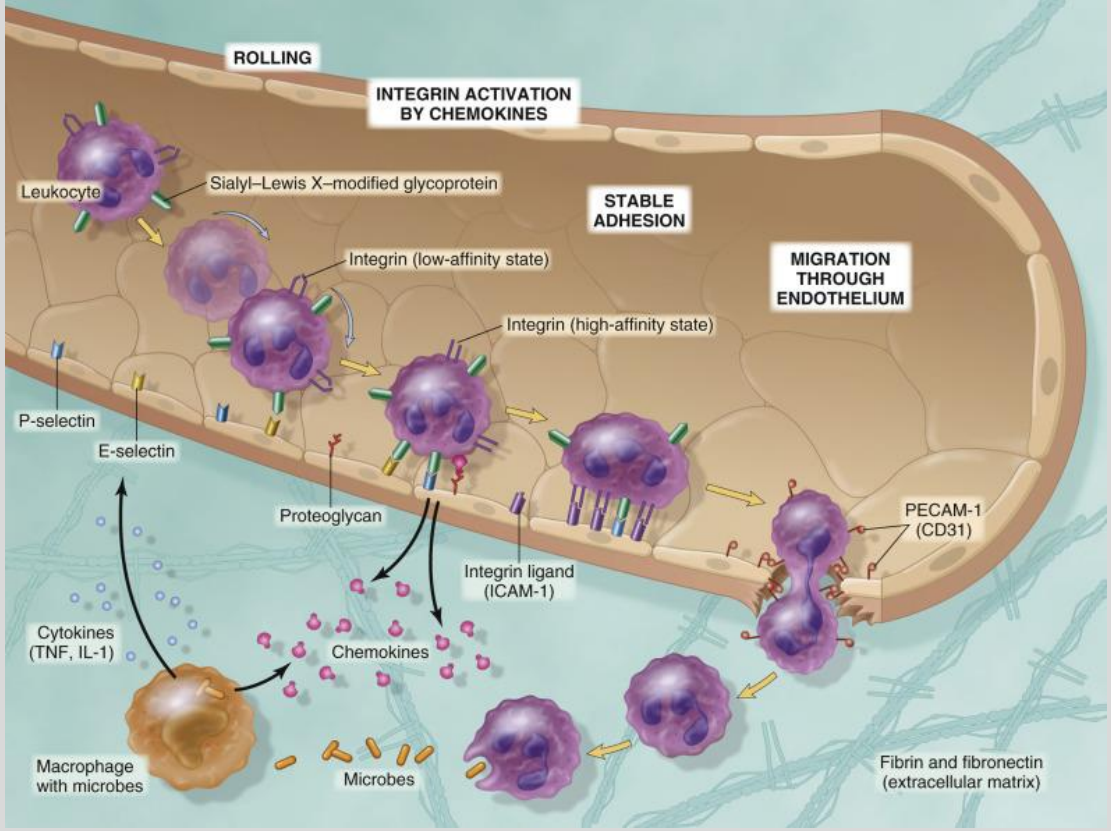
- Purpose: SLOW down leukocytes
- Mechanism: Expression of selectins on endothelial cells
  - Selectins – low affinity adhesion molecules on neutrophils (L-selectins) and endothelial cells (E-selectins
  - Neutrophils naturally express selectins
  - Endothelial cells require stimulation to express selectins
  - 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

Step 3 of cellular response: adhesion

- Purpose: STOP the leukocytes
- Mechanism: Activity of high affinity integrins on leukocytes and endothelial cells
  - Integrin molecules expressed on neutrophils in low affinity state. Need C5a and leukotriene B4 (metabolite of AA) to be activated and become high affinity.
  - TNF and IL-1 (from macrophages), will stimulate expression of integrin molecules on endothelial cells

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

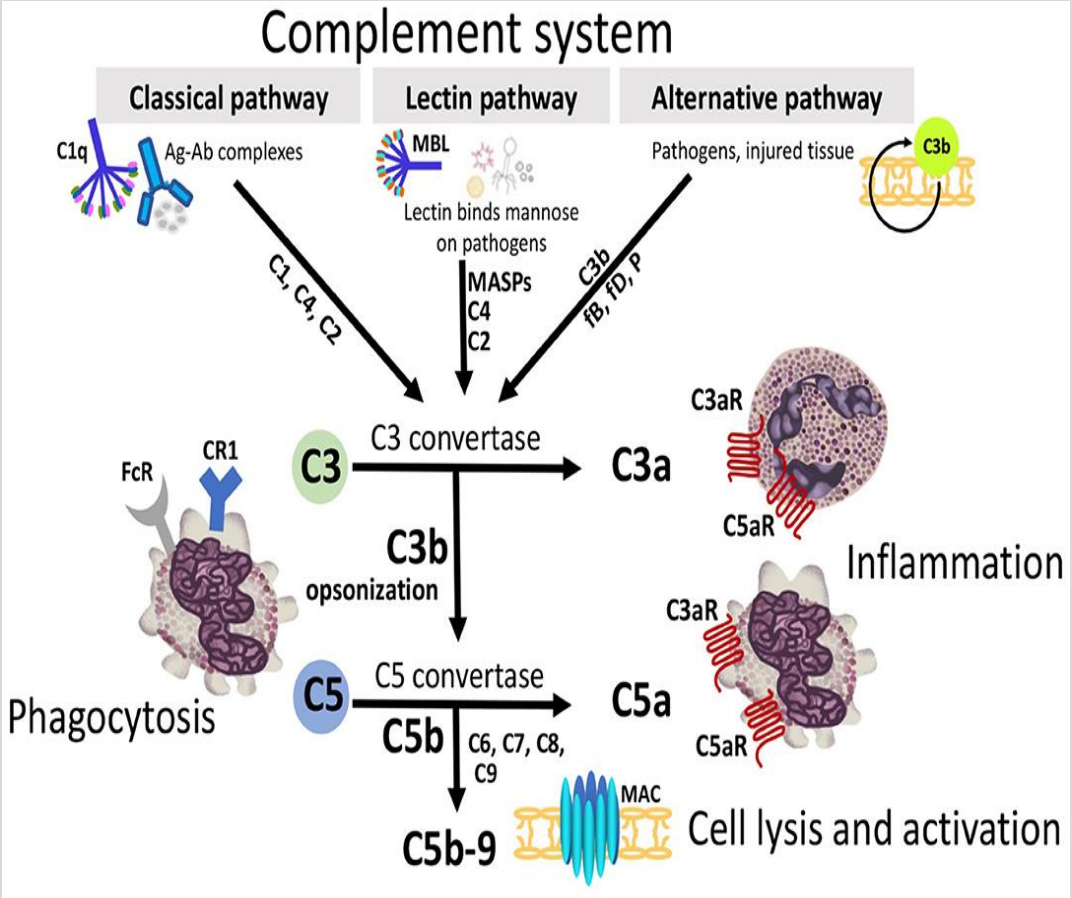
COMPLEMENT SYSTEM

- **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

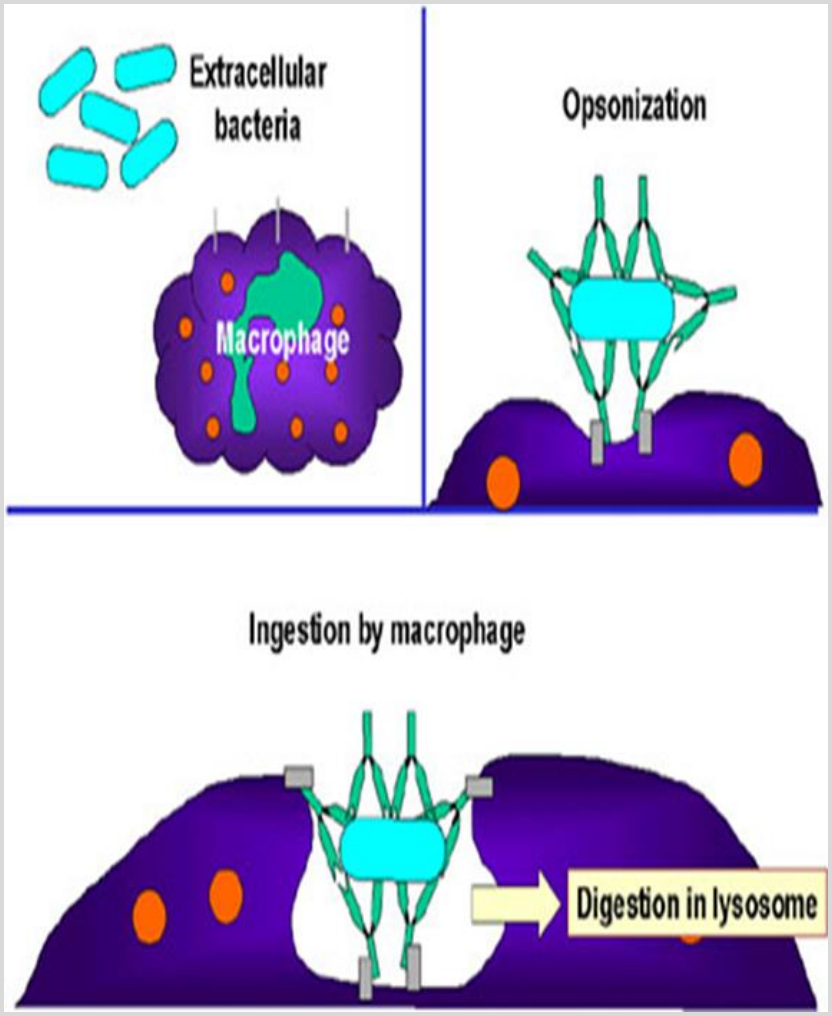
- **ALL PATHWAYS LEAD TO C3 CONVERTASE ENZYME FORMATION WHICH SPLITS C3 INTO C3A AND C3B**



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

Phagocytosis 1: Opsonization

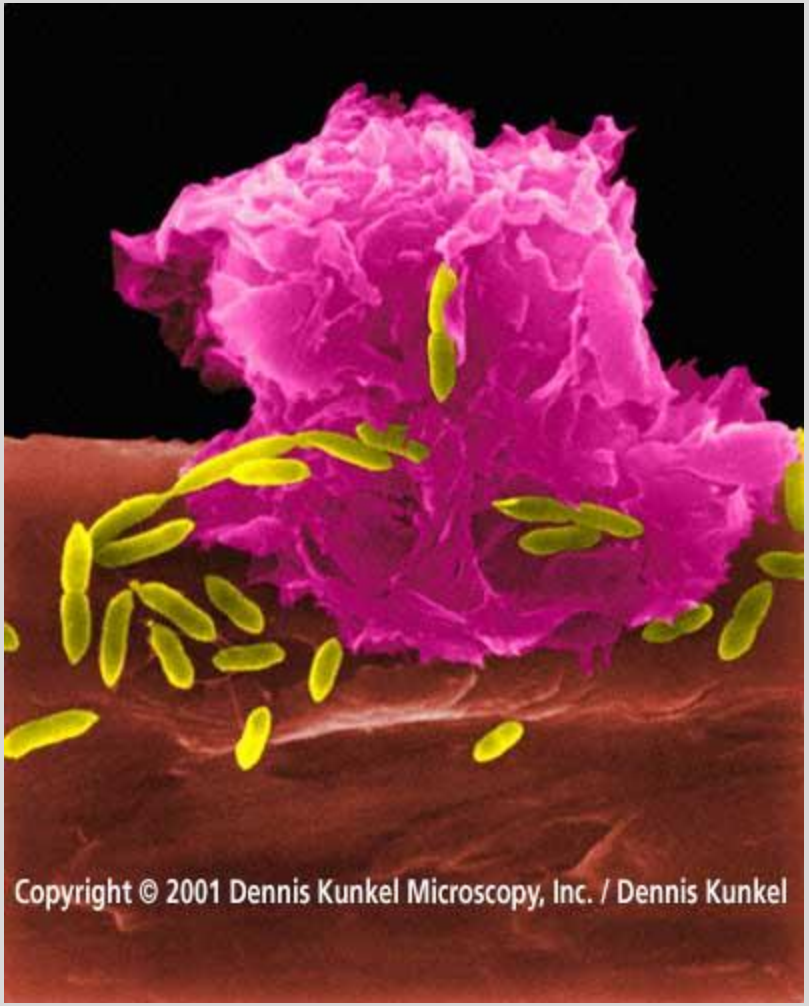


- Opsonization – opsonins attached to microbes (coating them) which helps wbcs better recognize microbes to destroy them
- Neutrophils have membrane receptors for opsonins
- Major opsonins: C3b (complement system), IgG (an antibody), mannose binding lectin
  - Path- Bruton's agammaglobulinemia- an opsin defect

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

Phagocytosis 2: engulfment (ingestion)

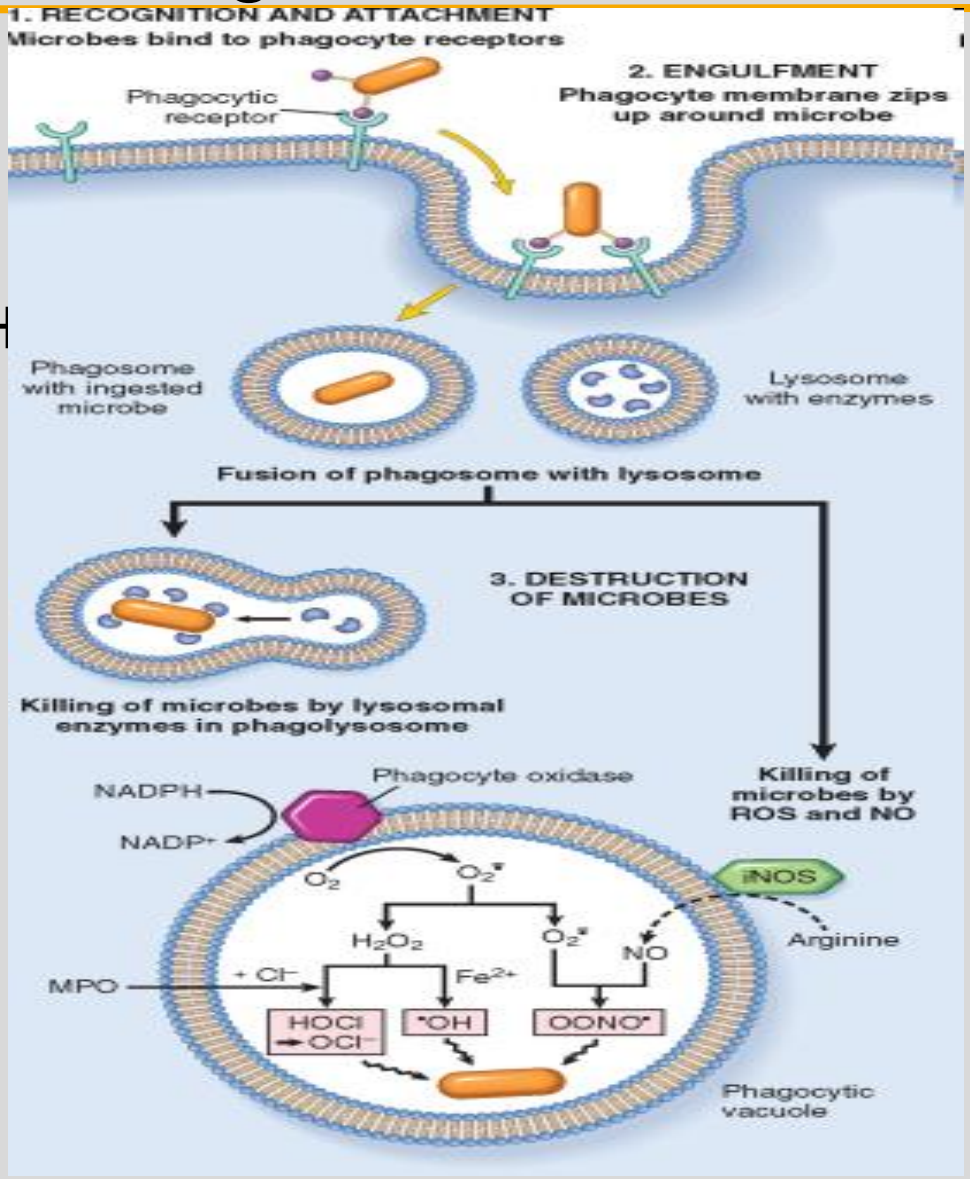
- Ingestion – engulfed microbes form phagosomes which fuse with lysosomes: phagolysosomes
  - Dependent on polymerization of actin
- Path- Chediak-Higashi syndrome- defect in microtubule function – impaired phagolysosome formation



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

Phagocytosis - Killing

- **ROS (reactive oxygen species):**
  - Activation of NADPH oxidase oxidizes NADPH and reduces oxygen to superoxide anion
  - Superoxide dismutase reduces to H2O2
  - Myeloperoxidase in neutrophils combines with Cl- and converts H2O2 to hypochlorite (bleach) which kills



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

Phagocytosis - Killing

- Reactive Oxygen Species made within lysosome - phagolysosome can ingest particles without damage to host cells
- ROS damage cells via membrane lipid peroxidation, protein modification, and DNA breakage
- Nitric oxide synthetase: also nitrogen derived free radicals
- Lysosomal enzymes: can also cause tissue damage, controlled by anti-proteases such as alpha-antitrypsin

- Chronic granulomatous disease: absent NADPH oxidase (example)
  - Genetic
  - Catalase positive organisms ingested but not killed (S. aureus,eg)
  - Catalase negative organisms are killed (MPO converts peroxide made by the organism)

MPO deficiency – defective conversion of H2O2 to HOCl – increased risk for Candida infections

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

Types of acute inflammation

Serous

- cell-poor fluid build up (effusion)
- blisters, viral pleuritis

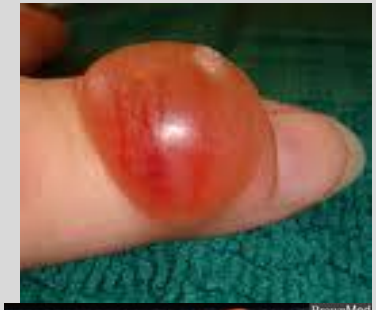
Fibrinous

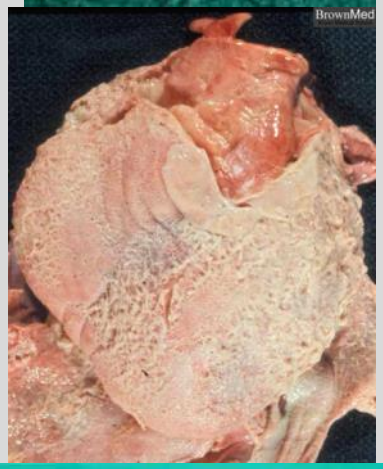
- increased permeability→ exudative-type fluid→increased fibrin deposition
- fibrinous pericarditis

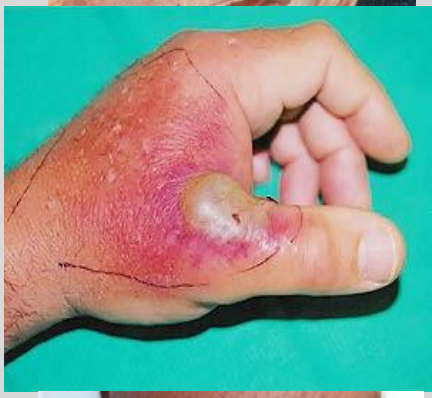
Suppurative (purulent)

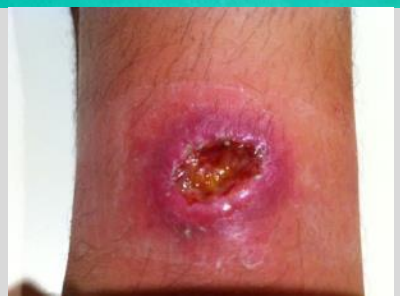
- exudative type fluid with cells→pus
- pyogenic bacteria (staph), abcesses (localized collections of purulent inflammatory tissue)

Ulcer – excavation of surface of tissue because of shedding of inflammed necrotic tissue

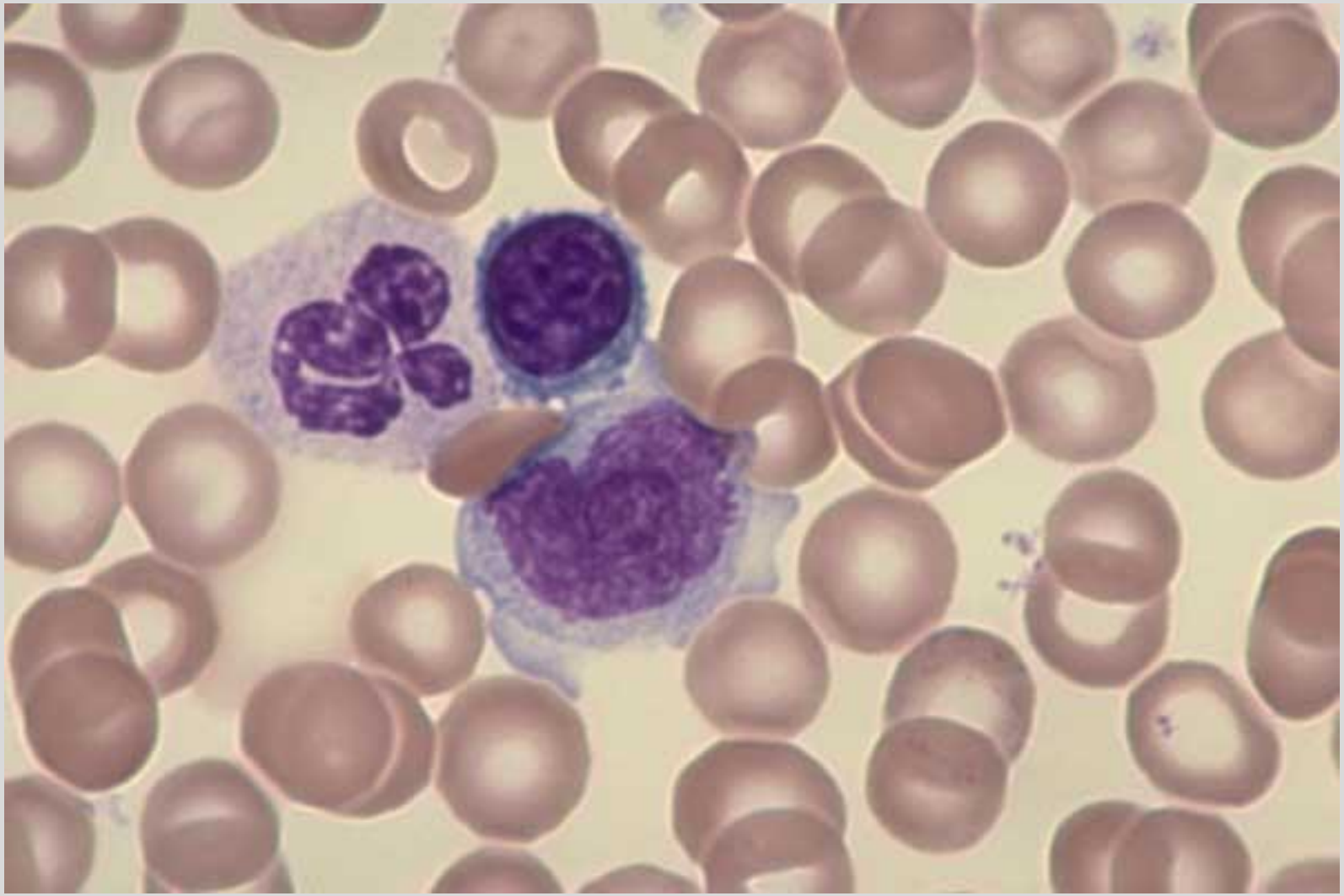




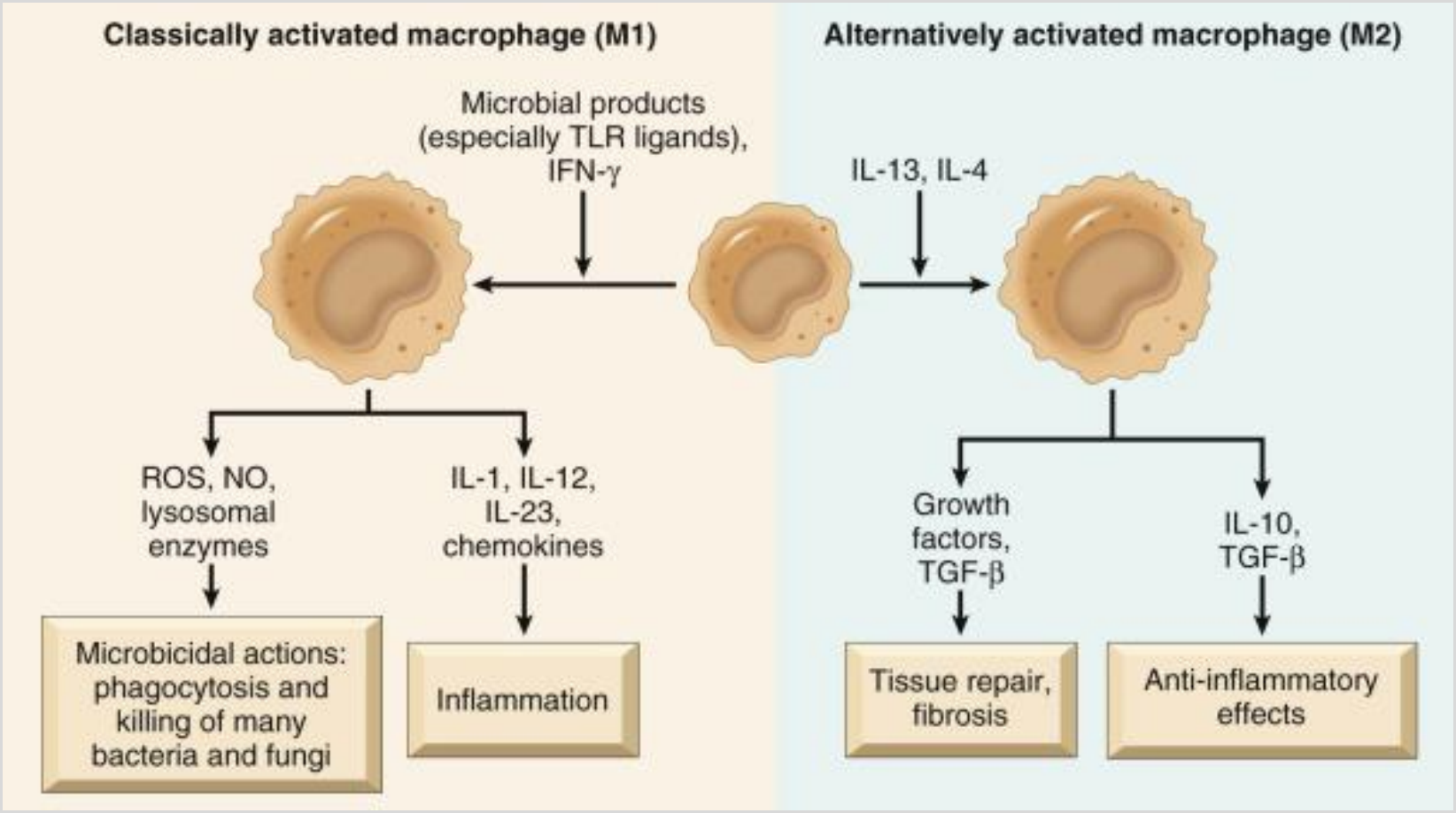




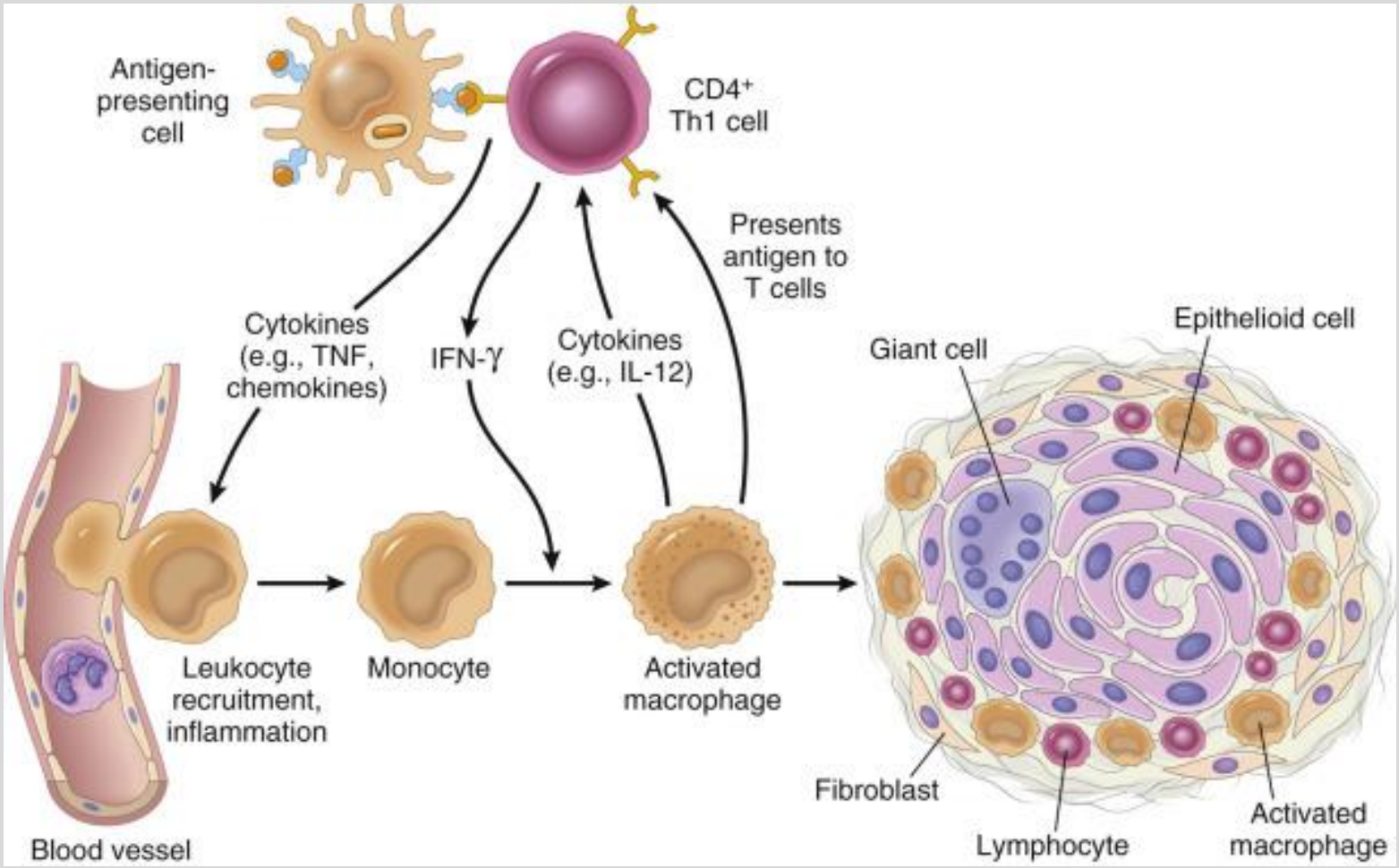
Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3



http://image.bloodline.net/stories/storyReader$1640.html

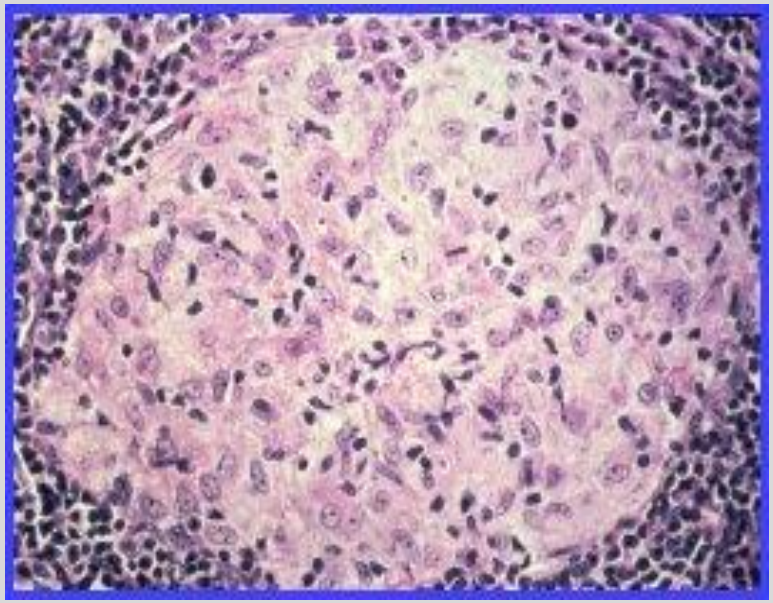


Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3, Fig 3-20

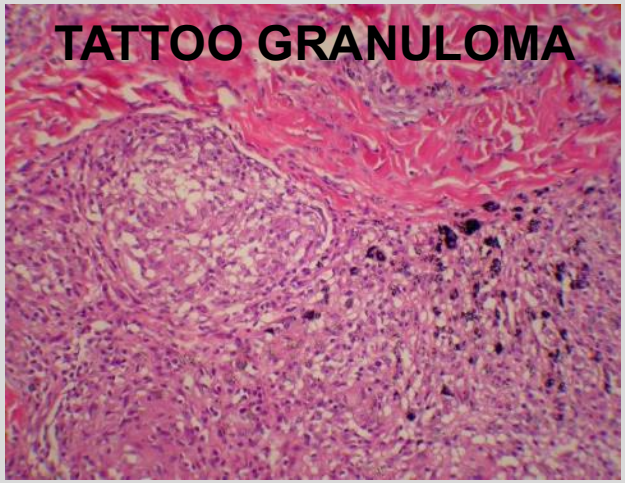


Macrophage–lymphocyte interactions in chronic inflammation.
Activated T cells produce cytokines that recruit macrophages (tumor necrosis factor [TNF], interleukin-17 [IL-17], chemokines) and others that activate macrophages (interferon-γ [IFN-γ]). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12. Prolonged reactions involving T cells and macrophages may result in granuloma formation.

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3, F[g. 3-21



SARCOID GRANULOMA



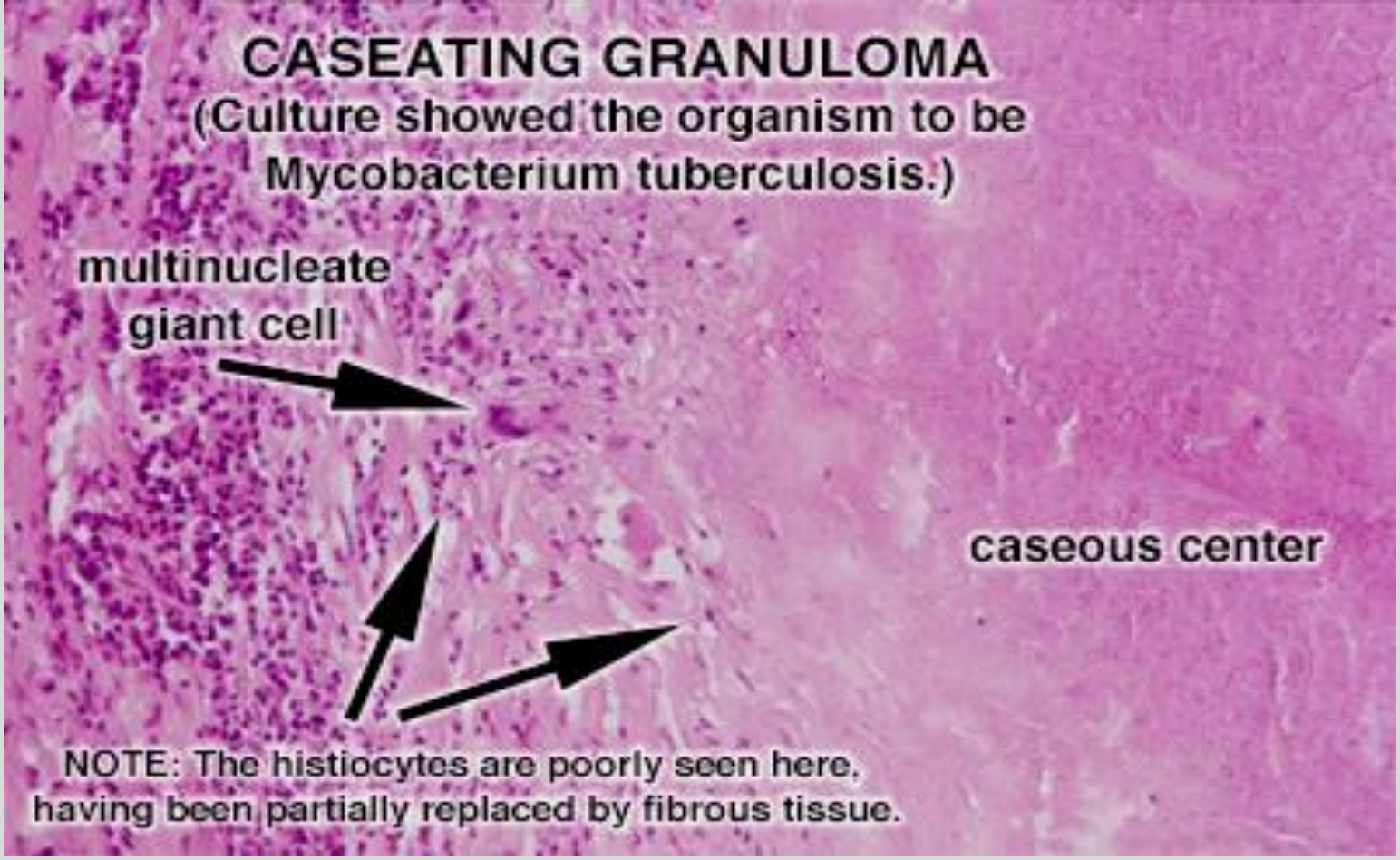
GRANULOMA:

- 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



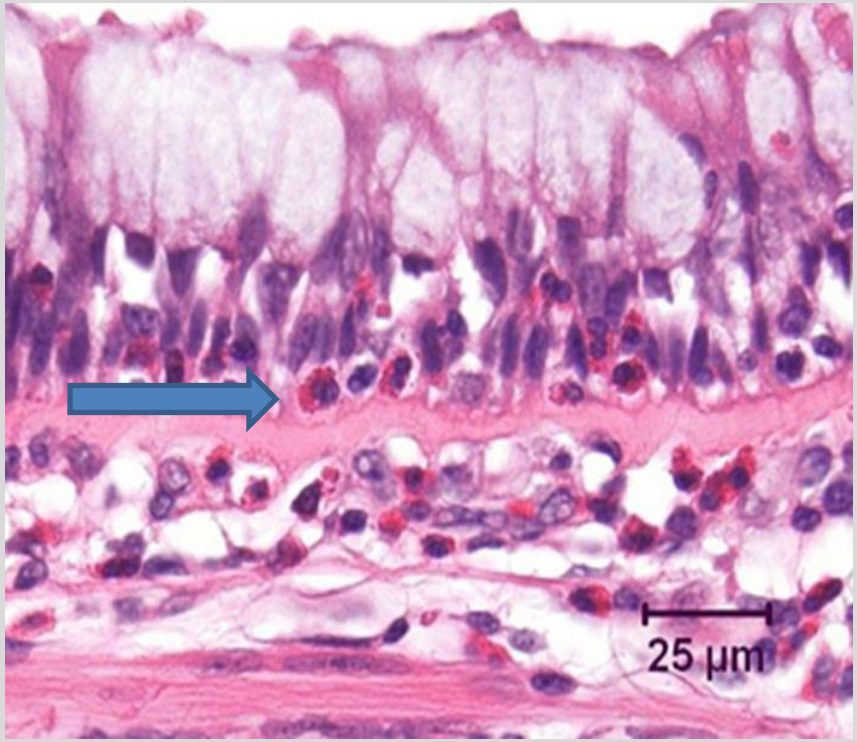
Caseating = necrotizing

Caseating e.g **tuberculosis**
Non-caseating/non-necrotizing: e.g sarcoidosis (previous slide)

http://blog.daum.net/_blog/photoImage.do?blogid=0BoNU&imgurl=http://cfile206.uf.daum.net/original/205823214C0A4E2C6B4143

Eosinophils - allergies, asthma, parasites

- Immune/allergic rxns mediated by IgE; parasitic infections
- Contain granules with major basic protein, toxic to parasites
- causes lysis of mammalian epithelial cells
- kills parasites but also contributes to tissue damage in allergies and asthma



BRONCHUS, HIGH POWER

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

Case question

- A 24 year old woman who is nursing her newborn baby develops a tender erythematous area around the nipple of her left breast. Thick, yellow fluid is observed to drain from an open fissure. Examination of the yellow breast fluid under the light microscope will most likely reveal an abundance of which inflammatory cells?
- A. B lymphocytes
- B. T lymphocytes
- C. Mast cells
- D. Neutrophils
- E. Eosinophils

Case question

- A 19 year old woman presents with a 5 day history of fever up to 101 degrees F and sore throat. She reports that she has felt fatigued for the past week and has difficulty swallowing. A physical exam reveals generalized lymphadenopathy. If this patient has a viral infection, a CBC will most likely show which of the following hematological findings?

- A. leukopenia
- B. leukocytosis
- C. eosinophilia
- D. lymphocytosis
- E. anemia

Lecture Feedback Form:

https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R