INFLAMMATION

NEW YORK INSTITUTE OF TECHNOLOGY

College of Osteopathic Medicine

FOUNDATIONS OF OSTEOPATHIC MEDICINE

Maria M. Plummer, M.D.

Associate Professor
Dept. of Clinical Specialties
Rockefeller Room #306
mplummer@nyit.edu

Do.
Make.
Heal.
Innovate.
Reinvent the Future.

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.

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

J. Minarcik, MD

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

INFLAMMATION

- Early, transient response to cell injury
- Purpose - to localize and eliminate cause of cell injury and to restore tissue normality
- Involves release of chemical mediators, vascular changes, leukocyte responses
- Acute: Fast, minute – hours, neutrophils
- Chronic: Slow, days or longer, monocytes, macrophages, lymphocytes
- “-itis”

Cardinal signs of inflammation

- Rubor (redness)
- Calor (warmth)
- Tumor (swelling)
- Dolor (pain)
- Functio Laesa (loss of function)

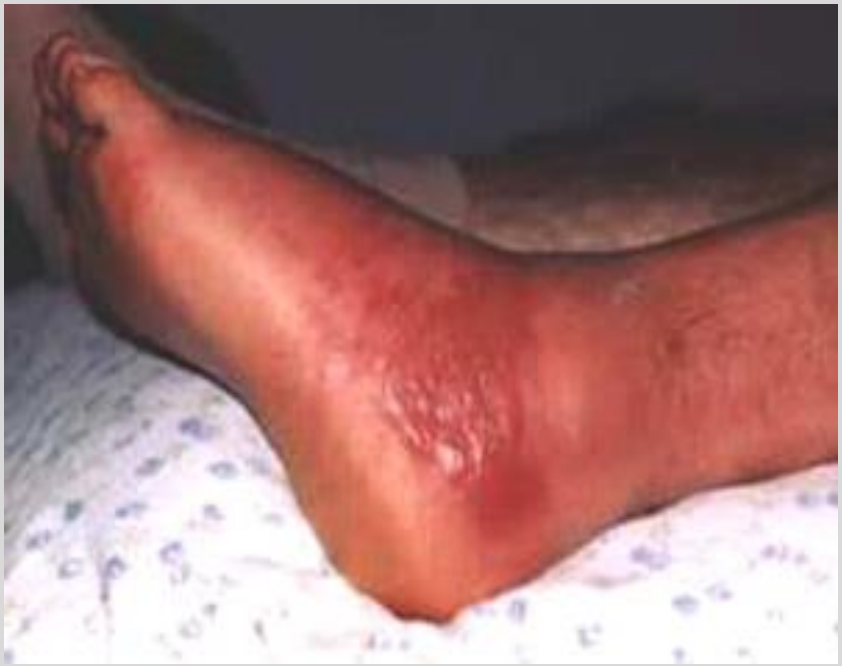
Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3

Causes/Stimuli: Inflammation

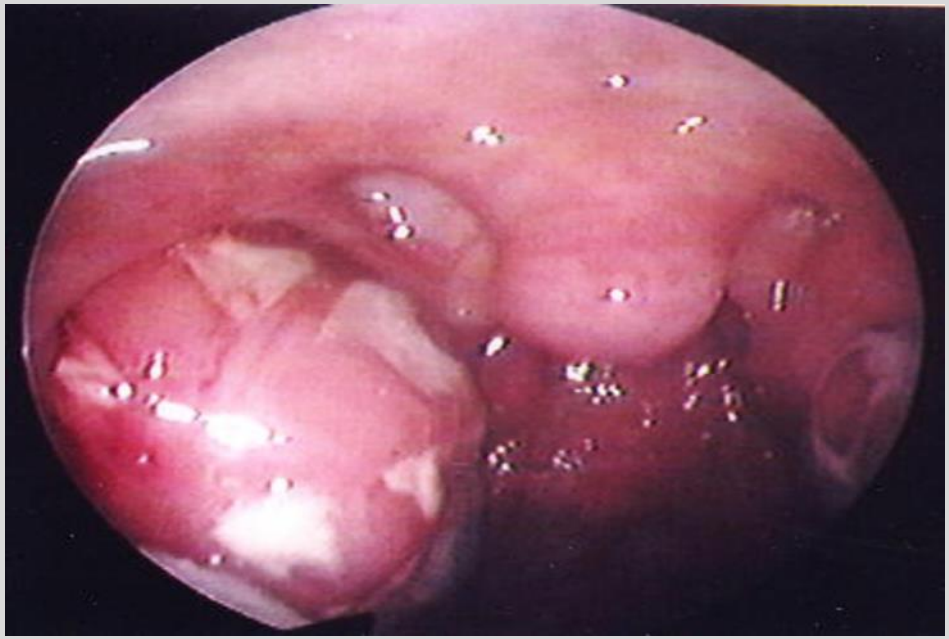
- Infection
- Immune reaction
- Tissue necrosis
- Foreign bodies
- Trauma
- Radiation
- Burns

Inflammation - *response to cell injury*

Cellulitis (Erysipelas) of the foot



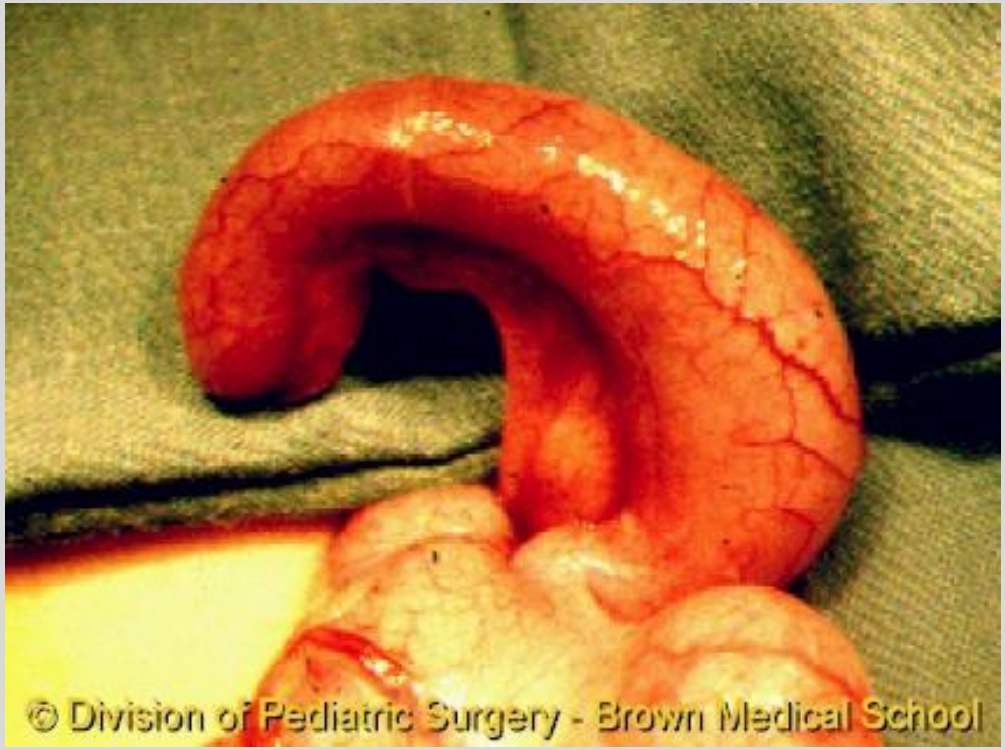
Inflamed tonsil

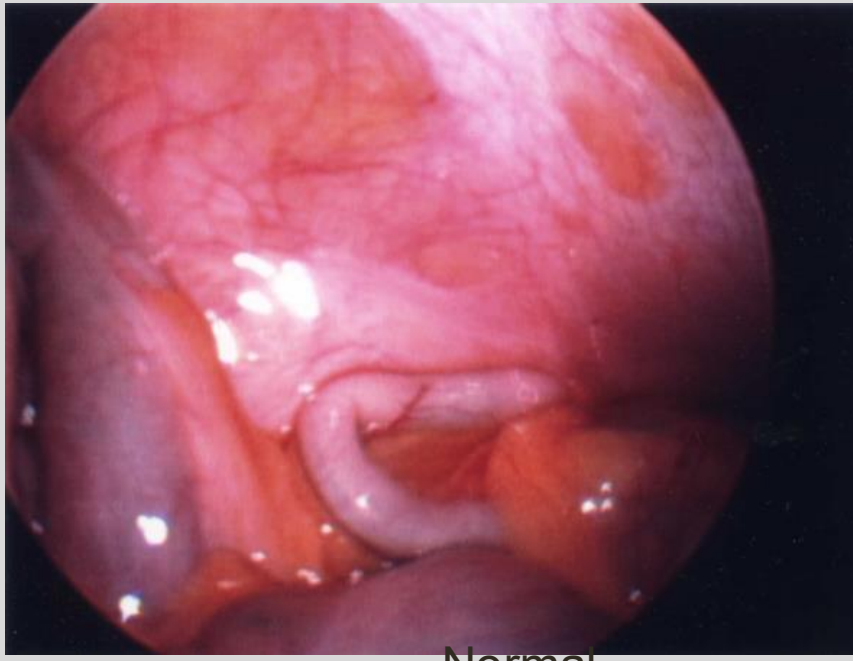


http://www.gradydoctor.com/2010/06/reflection-on-friday-sockin-it-to-me.html

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

Inflamed appendix





Normal

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

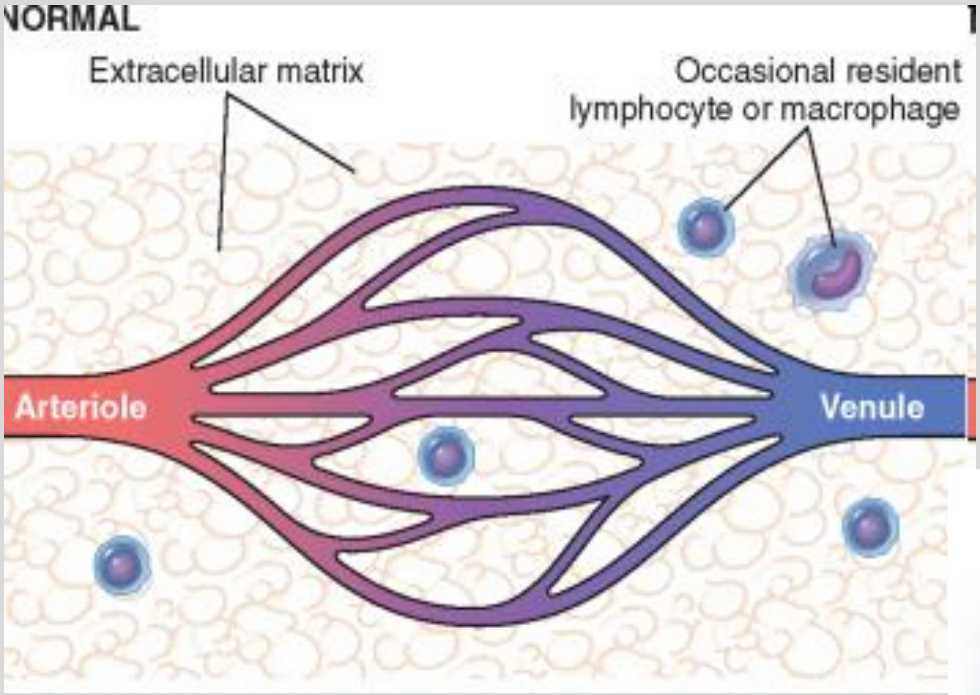
How does acute inflammation happen? (overview)

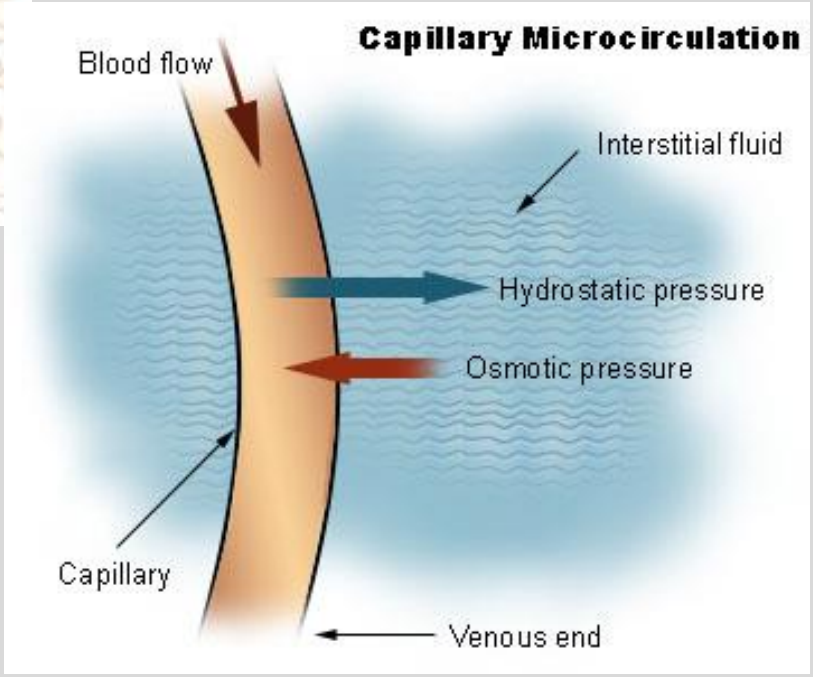
- Stimuli for inflammation
- Sequence of vascular events
- Sequence of cellular events
- Phagocytosis
- Termination of acute inflammation
- Consequences of acute inflammation

Inflammatory Response (in general)

- Recognition of Injurious agent
- Recruitment of leukocytes
- Removal of agent
- Regulation (control) of response
- Resolution (repair)

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



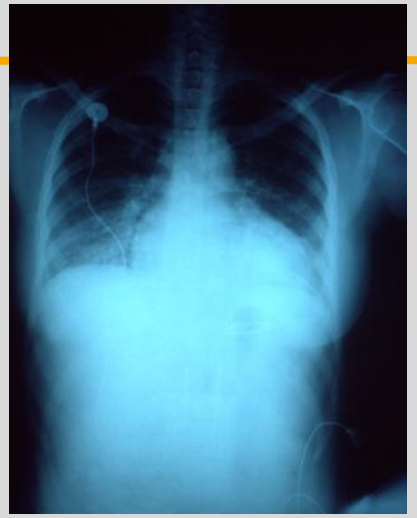


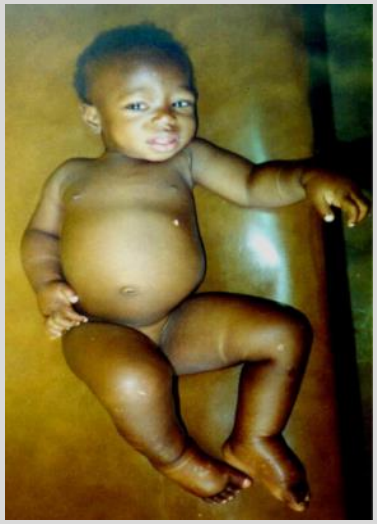
Hydrostatic pressure – pushes fluid out
Oncotic (osmotic) pressure – keeps fluid in

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

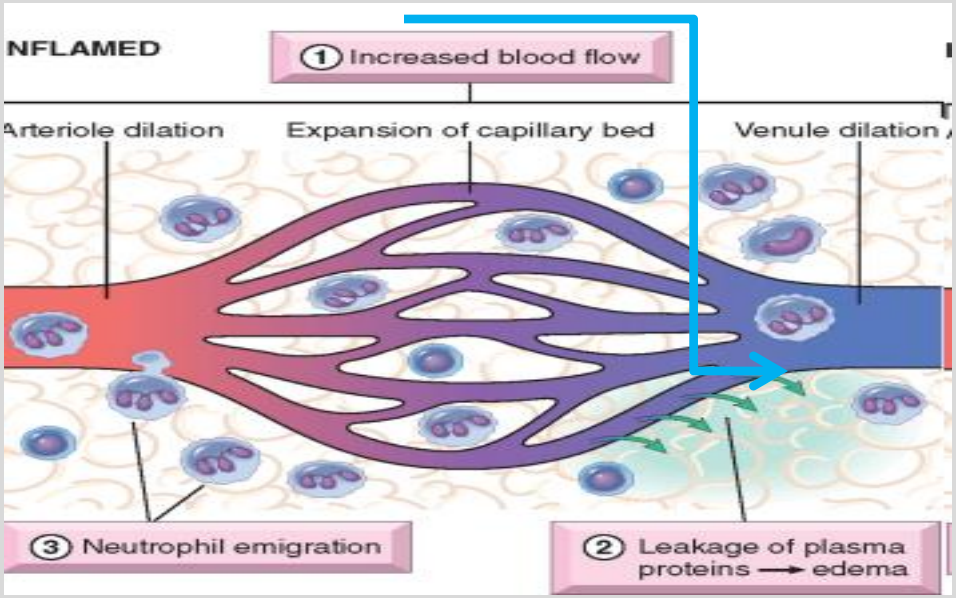




Kwashiorkor disease: severe protein malnutrition; usually affects infants and children, seen in very severe cases of starvation and poverty-stricken regions worldwide

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

Histamine and NO

Histamine

- Made and stored in mast cells
- Physical trauma
  - binding of Abs to mast cells (allergic rxns)
  - anaphylatoxins (proteins of complement system C3a and C5a, neuropeptides, cytokines, etc.)
- Relaxes vascular smooth muscle and causes increased vascular permeability

Nitric Oxide

- Produced by endothelial cells
- Dissolved gas that acts as signaling molecule
- Relaxes vascular smooth muscle

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

Table 3.8
Role of Mediators in Different Reactions of Inflammation

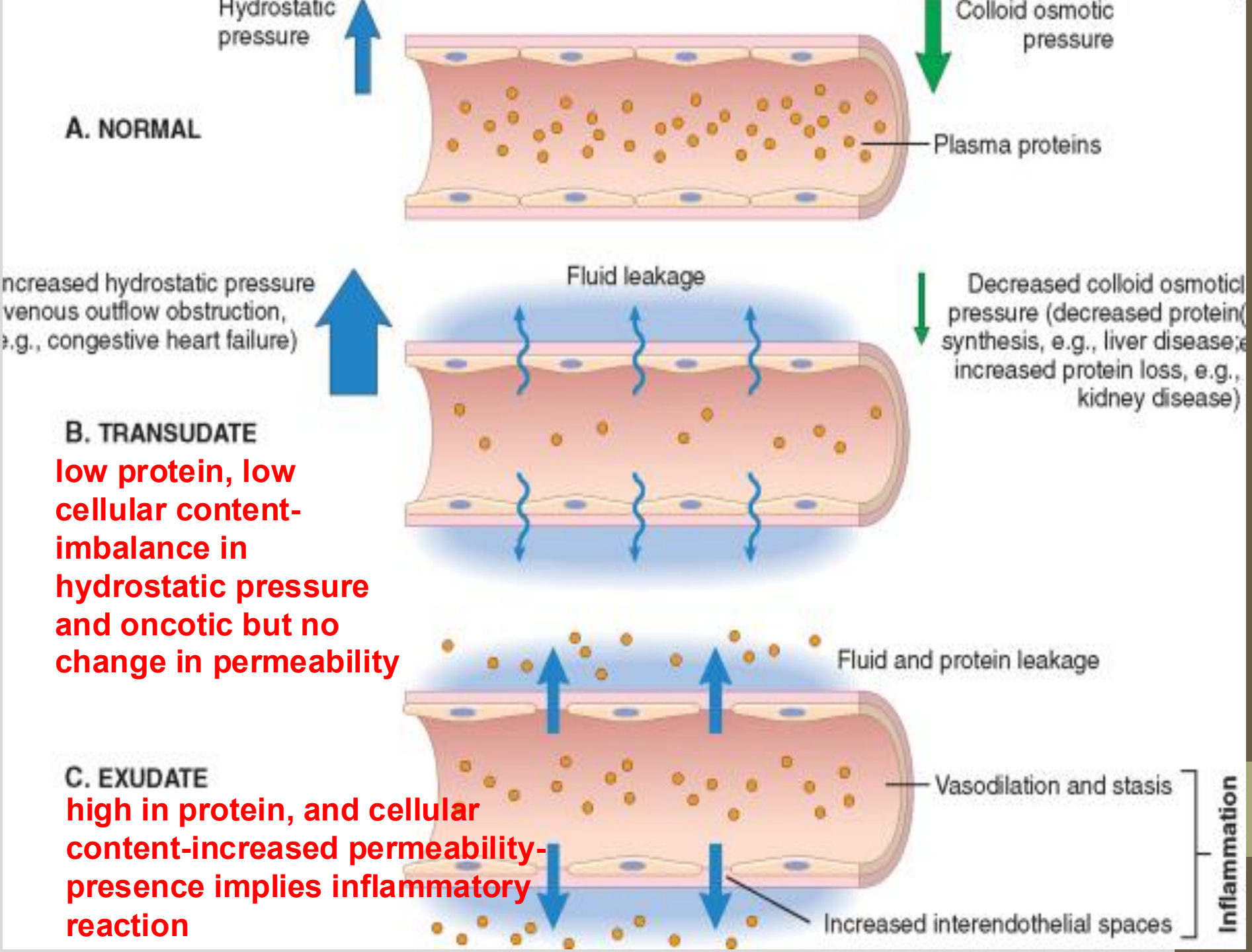
Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine
	Prostaglandins
Increased vascular permeability	Histamine and serotonin
	C3a and C5a (by liberating vasoactive amines from mast cells, other cells)
	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1
	Chemokines
	C3a, C5a
	Leukotriene B_4
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
	Substance P
Tissue damage	Lysosomal enzymes of leukocytes
	Reactive oxygen species

Vascular permeability

Permeability (leakiness) of the vessel affects hemodynamics:

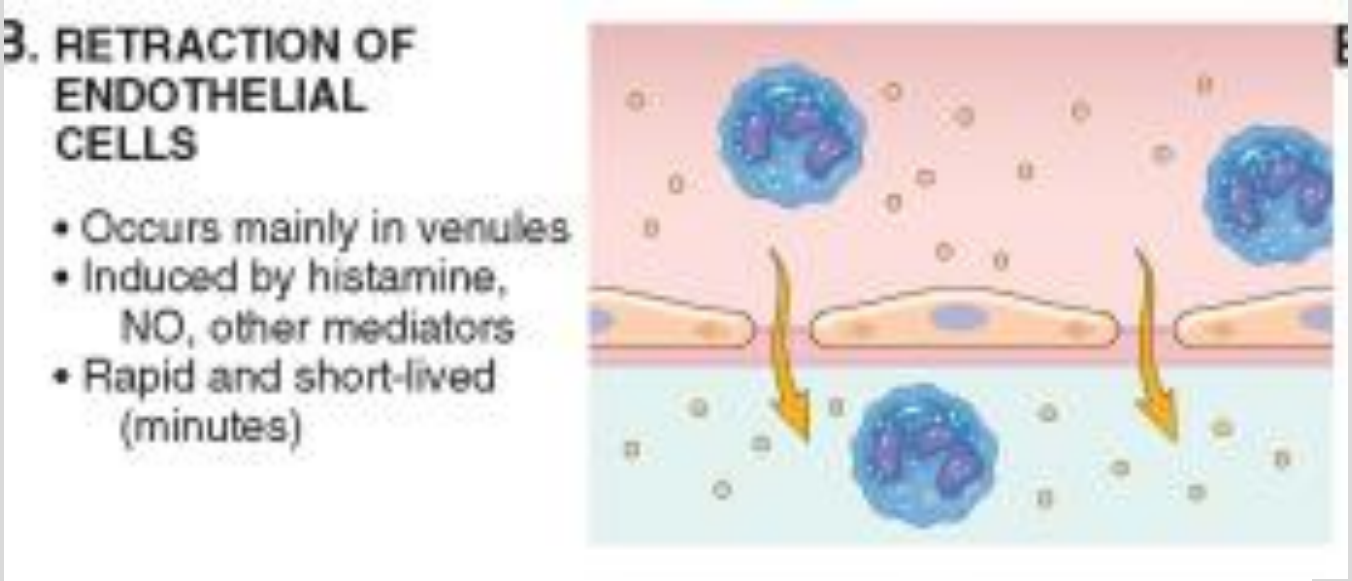
- Increased permeability (more leaky)—exudate results (high cellular and protein content fluid, high specific gravity)
- Pus - example of exudate: purulent exudate or inflammatory exudate rich in leukocytes, debris of dead cells and often microbes

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)

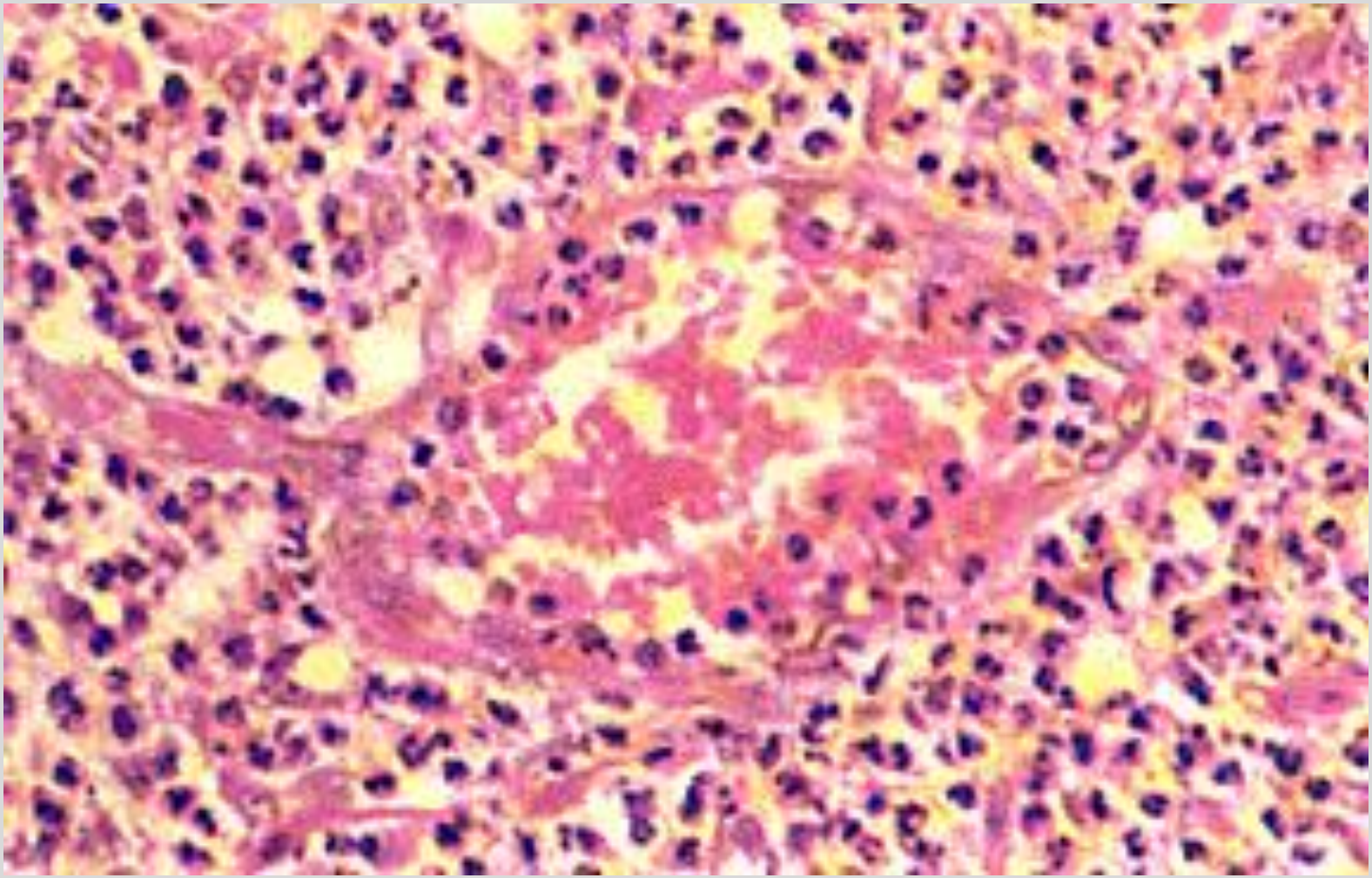
Mechanism:

- 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

Margination



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

Cardinal signs of inflammation

- Histamine (and nitric oxide) mediated vasodilation, increased blood flow and vascular permeablity
- Prostaglandins (PGE2) sensitize nerve endings to effects of bradykinin

- Rubor (redness)
- Calor (warmth)
- Tumor (swelling-edema)
- Dolor (pain)
- Functio Laesa (loss of function)

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

Bradykinin (kinins – vasoactive peptides)

- Bradykinin (as well as prostaglandins and histamine) mediates **vasodilation**
  - causes arterioles to dilate by releasing nitric oxide, prostacyclin, and other factors, increasing blood flow
  - arteriolar smooth muscle relaxes, increasing blood flow **(rubor and calor)**
- Bradykinin, along with prostaglandin E2 (PGE2), helps sensitize sensory nerve endings, causing **pain** (dolor)
- Bradykinin causes veins to vasoconstrict by releasing prostaglandin F2 : increased pressure in capillaries can lead to leakage into capillary beds (**increase in vascular permeability**)

- Note: Bradykinin causes vasodilation at low concentrations and vasoconstriction at higher concentration

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

https://www.ncbi.nlm.nih.gov/books/NBK537187/

Arachidonic Acid Metabolites

- Derived from essential fatty acid linoleic acid: **Prostaglandins and leukotrienes**
- Released from membrane phospholipids mainly by action of phospholipase A2
- PROSTAGLANDINS – AA mediators generated by COX1 and COX2 enzymes: vasodilation, vascular permeability, **pain, fever (note: aspirin blocks)**
- LEUKOTRIENES – AA mediatiors generated by lipoxygynases: vasoconstriction, bronchospasm, vascular permeability

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

- Vascular changes in inflammation results: stasis, edema, and margination

- To mobilize immune cells to the site of injury (outside the vessel lumen)

- Cellular response follows…

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

Cellular response in inflammation - overview

Purpose: mobilize immune cells out of the circulation to site of cellular injury

Mediated and controlled by adhesion molecules and cytokines

- Step 1: margination
- Step 2: rolling
- Step 3: adhesion
- Step 4: transmigration
- Step 5: chemotaxis

} Within the vessel lumen

} Through the lumen and to the site of injury

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

How did we signal rolling to begin? An intro to cytokines

Cytokines

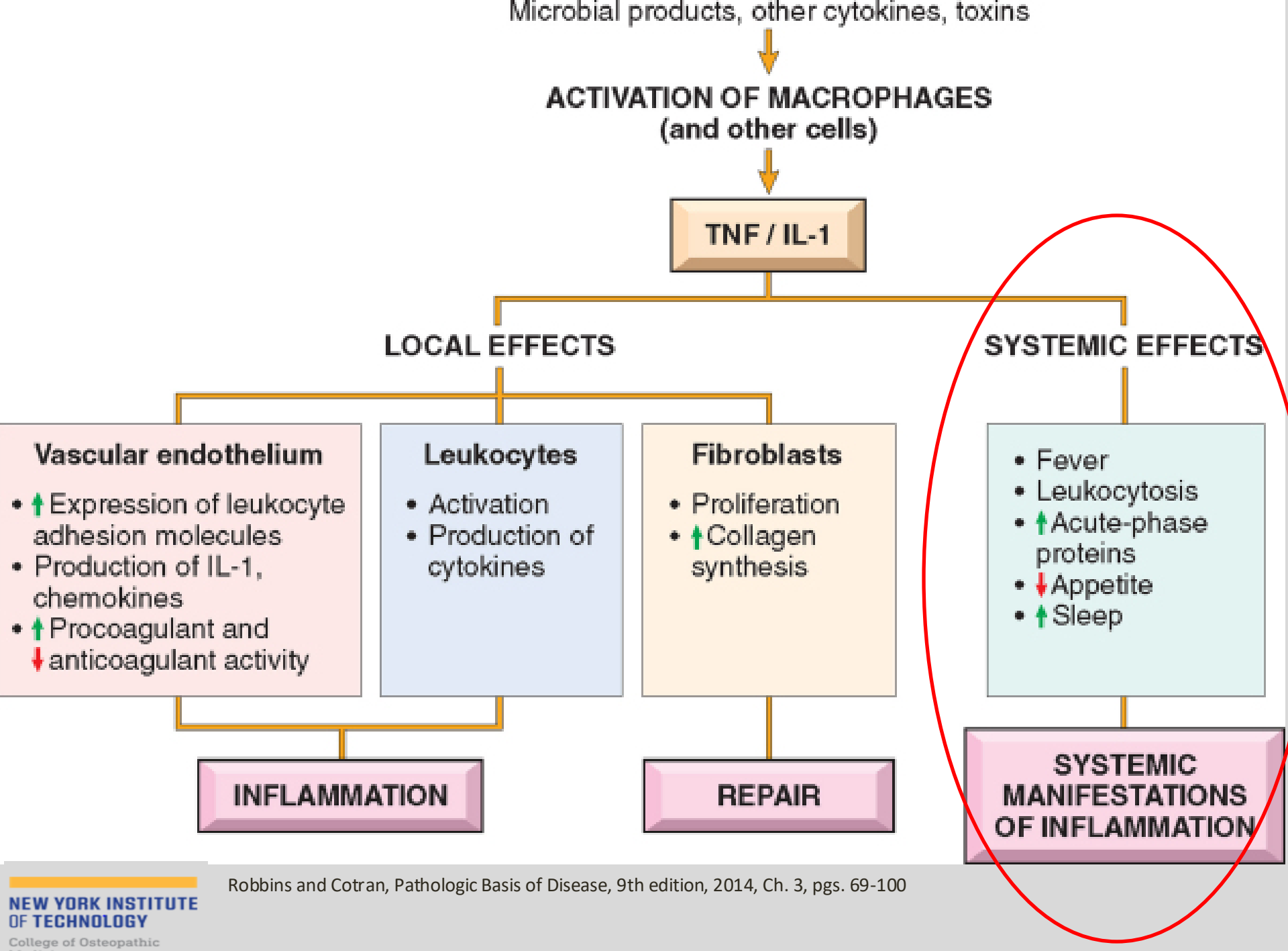
- signaling molecules (proteins) made by cells (e.g activated lymphs and macrophages) in response to injurious agents
- modulate functions of other cells

TNF and IL-1

- two major cytokines that mediate inflammation
- produced by activated macrophages, lymphocytes
- stimulated by microbrial products, immune complexes, physical injury, etc.
- TNF, tumor necrosis factor, or cachectin, is destructive of human tissues, “cachexia”
- Interleukin-1: first discovered; propagates inflammatory response at many levels and also has a significant effect on T-cells

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

Cytokine	Principal source	Principal Actions in Inflammation
In acute inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute-phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells to normal tissues
IN CHRONIC INFLAMMATION		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes



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

Step 2 of cellular response: Rolling

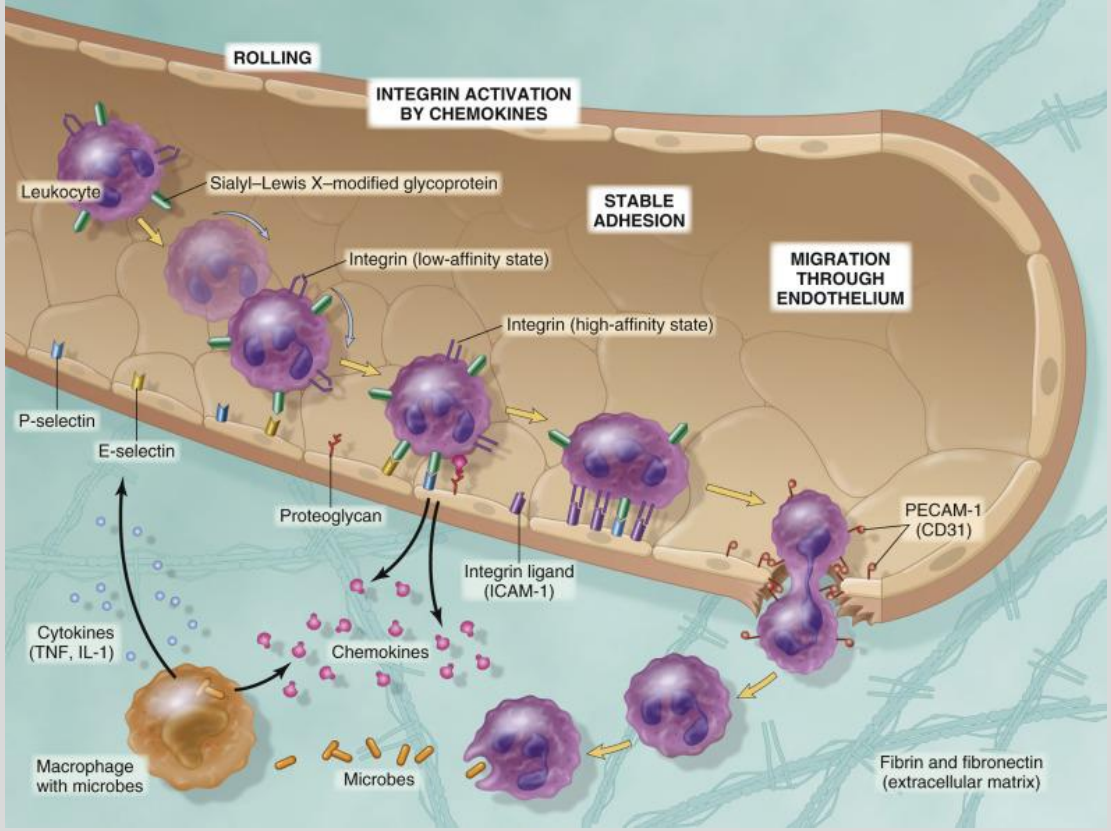
- Purpose: SLOW down leukocytes
- Mechanism: Expression of selectins on endothelial cells
  - Selectins – low affinity adhesion molecules on neutrophils (L-selectins) and endothelial cells (E-selectins
  - Neutrophils naturally express selectins
  - Endothelial cells require stimulation to express selectins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

Step 4 of cellular response: Transmigration (diapedesis)

- Purpose: migration of leukocytes through vessel wall
- Mechanism: endothelial cells retracted, leukocytes travel between them
  - Mainly in post-capillary venules
  - Chemokines stimulate adherent neutrophils to migrate through gaps toward chemical concentration gradient (site of injury)
  - After crossing endothelium, leukocytes pierce basement membrane probably by secreting collagenases and enter extravascular tissue

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

Step 5 cellular response: Chemotaxis – locomotion along chemical gradient

- WBCs follow chemical gradient to where stimuli for inflammation started:
  - Chemotactic agents* bind to specific seven membrane G protein coupled receptors on surface of wbcs
  - Signals from receptors cause 2nd messengers to increase cytosolic Ca+2 active enzymes (e.g. kinases) that polymerize actin and localize myosin filaments causing migration

  - *Include: C5a-from complement system , Leukotriene B4- arachadonic acid metabolite, IL-8- cytokine, N-Formylmethionine- bacterial product

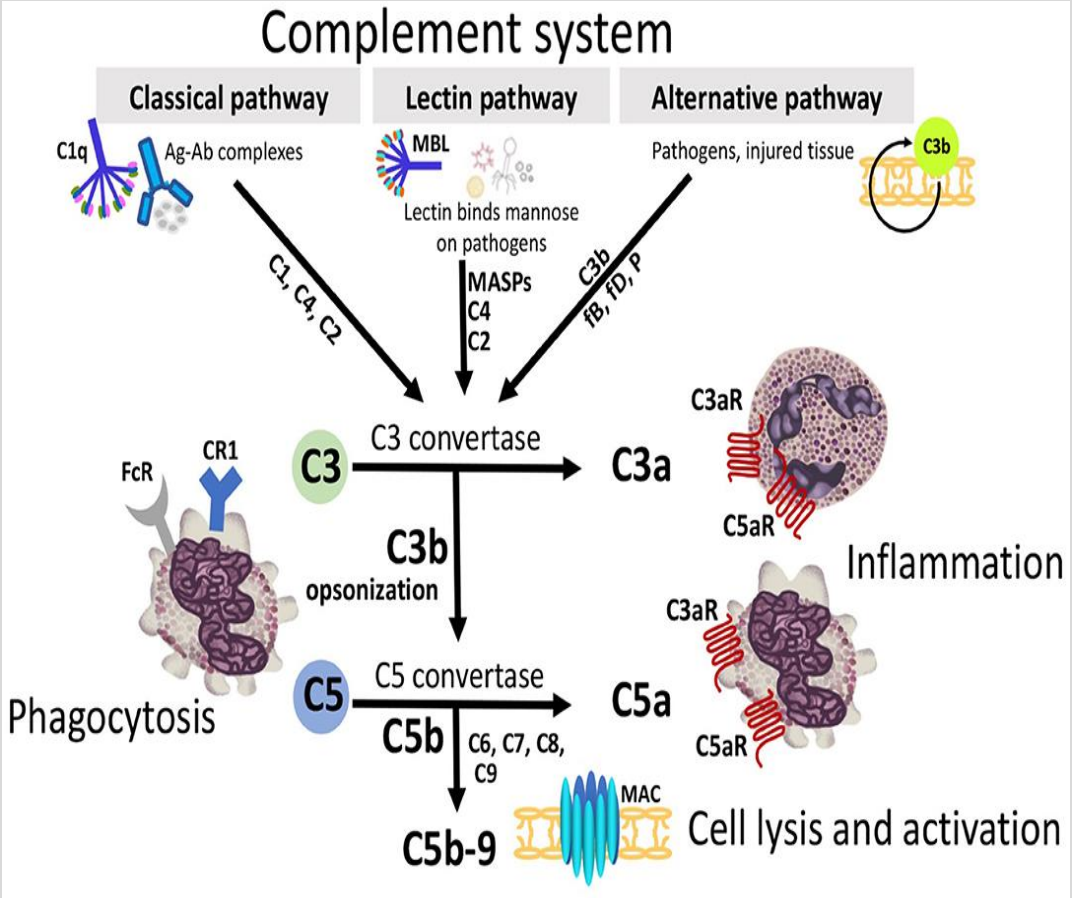
COMPLEMENT SYSTEM

- **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

Complement Cleavage Products

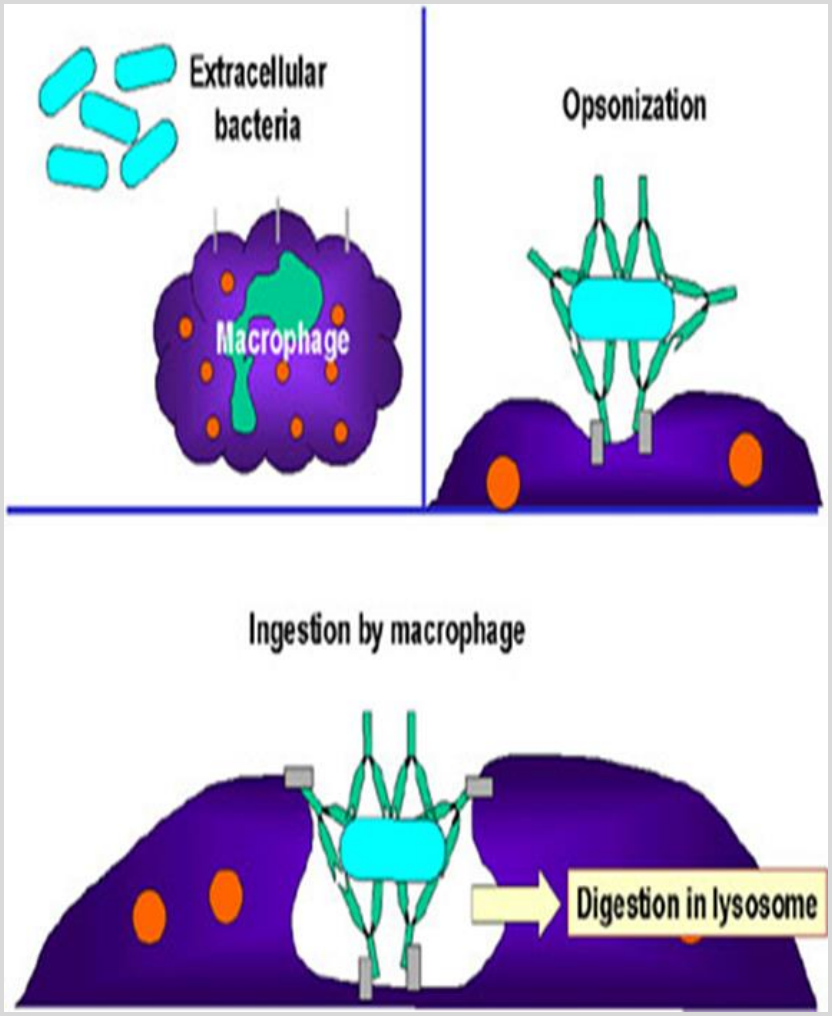
- C3a, C5a, (and C4a) : stimulate histamine and cause increased vascular permeability and vasodilation - known as anaphylatoxins
- C3b : opsonization and phagocytosis
- C5b-9: formation of MAC (membrane attack complex), lysis of microbe

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**

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

Phagocytosis 1: Opsonization

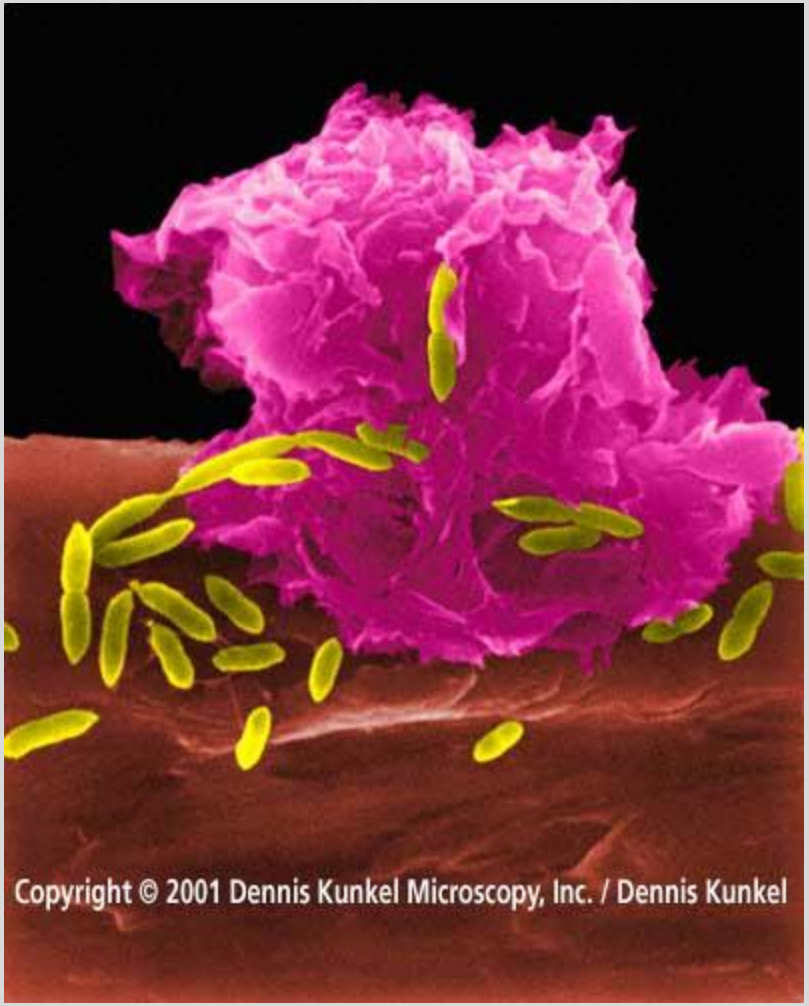


- Opsonization – opsonins attached to microbes (coating them) which helps wbcs better recognize microbes to destroy them
- Neutrophils have membrane receptors for opsonins
- Major opsonins: C3b (complement system), IgG (an antibody), mannose binding lectin
  - Path- Bruton's agammaglobulinemia- an opsin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

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

Phagocytosis 2: engulfment (ingestion)

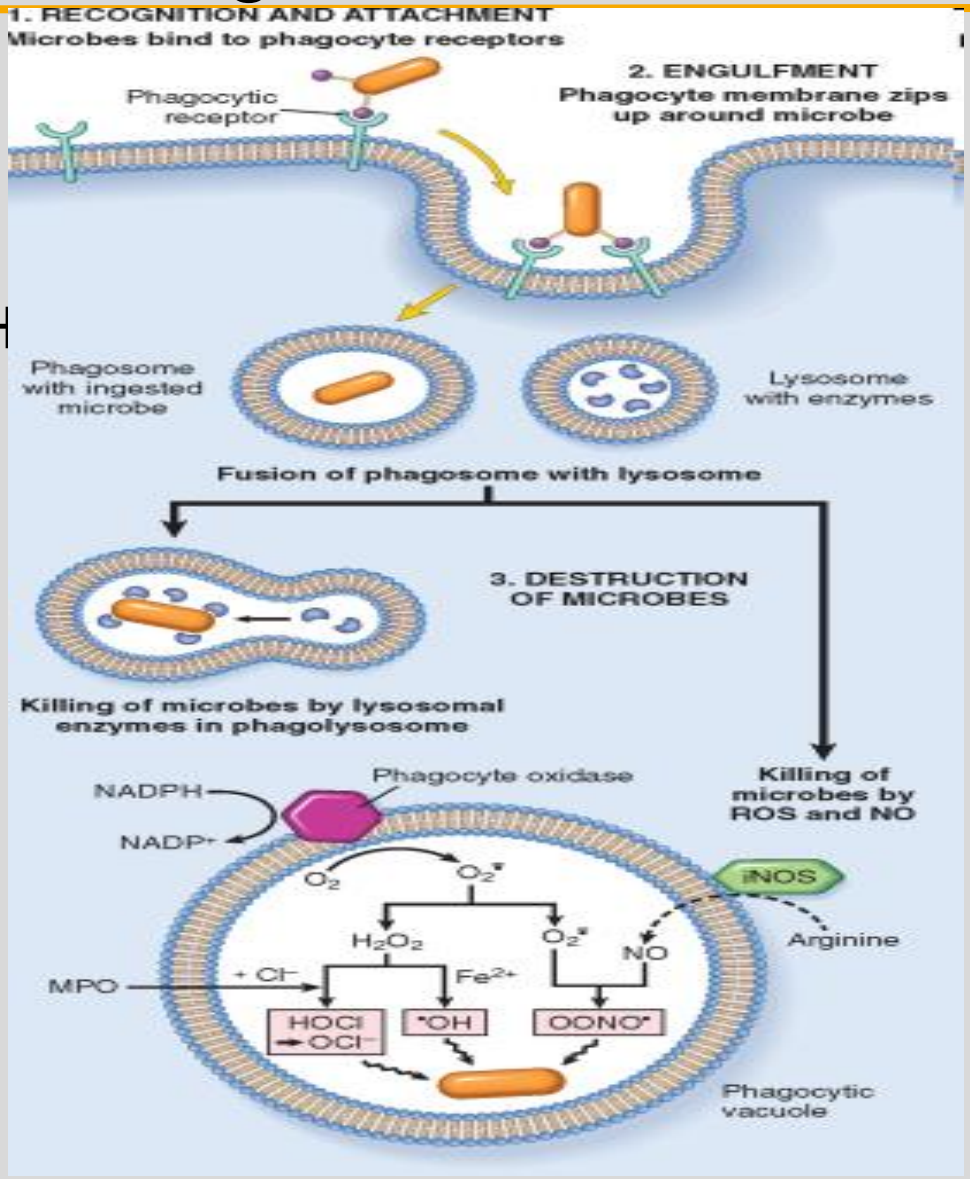
- Ingestion – engulfed microbes form phagosomes which fuse with lysosomes: phagolysosomes
  - Dependent on polymerization of actin
- Path- Chediak-Higashi syndrome- defect in microtubule function – impaired phagolysosome formation



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

Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules) Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3, Table 3-5

Types of acute inflammation

Serous

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

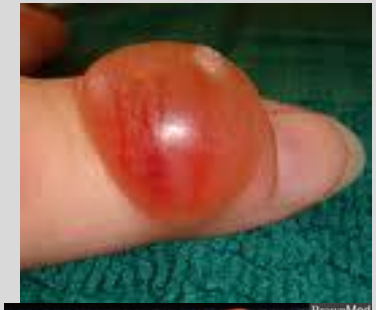
Fibrinous

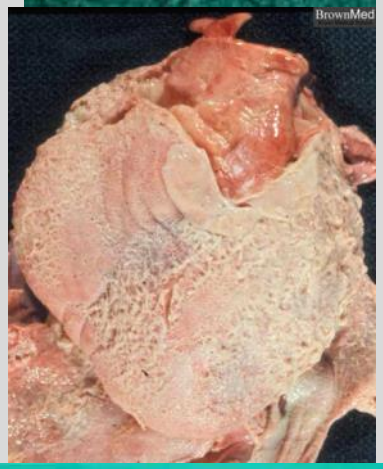
- increased permeability→ exudative-type fluid→increased fibrin deposition
- fibrinous pericarditis

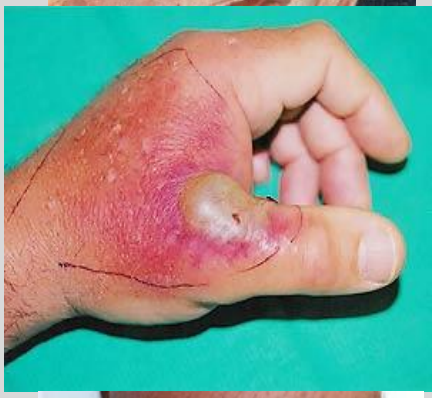
Suppurative (purulent)

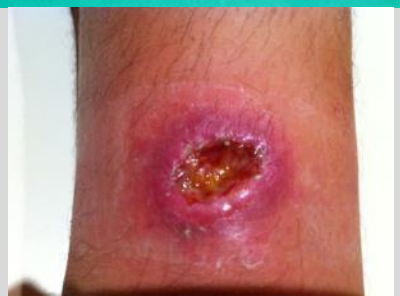
- exudative type fluid with cells→pus
- pyogenic bacteria (staph), abcesses (localized collections of purulent inflammatory tissue)

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

Termination of Acute Inflammation

- Decrease in mediators of acute inflammation
- Outcomes:
  1. Complete resolution- minor injury, labile and stable cells
  2. Tissue destruction and extensive injury – fibrosis, organization, healing by scar

     (abscess formation – organization)
  3. Progression to chronic inflammation

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

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**

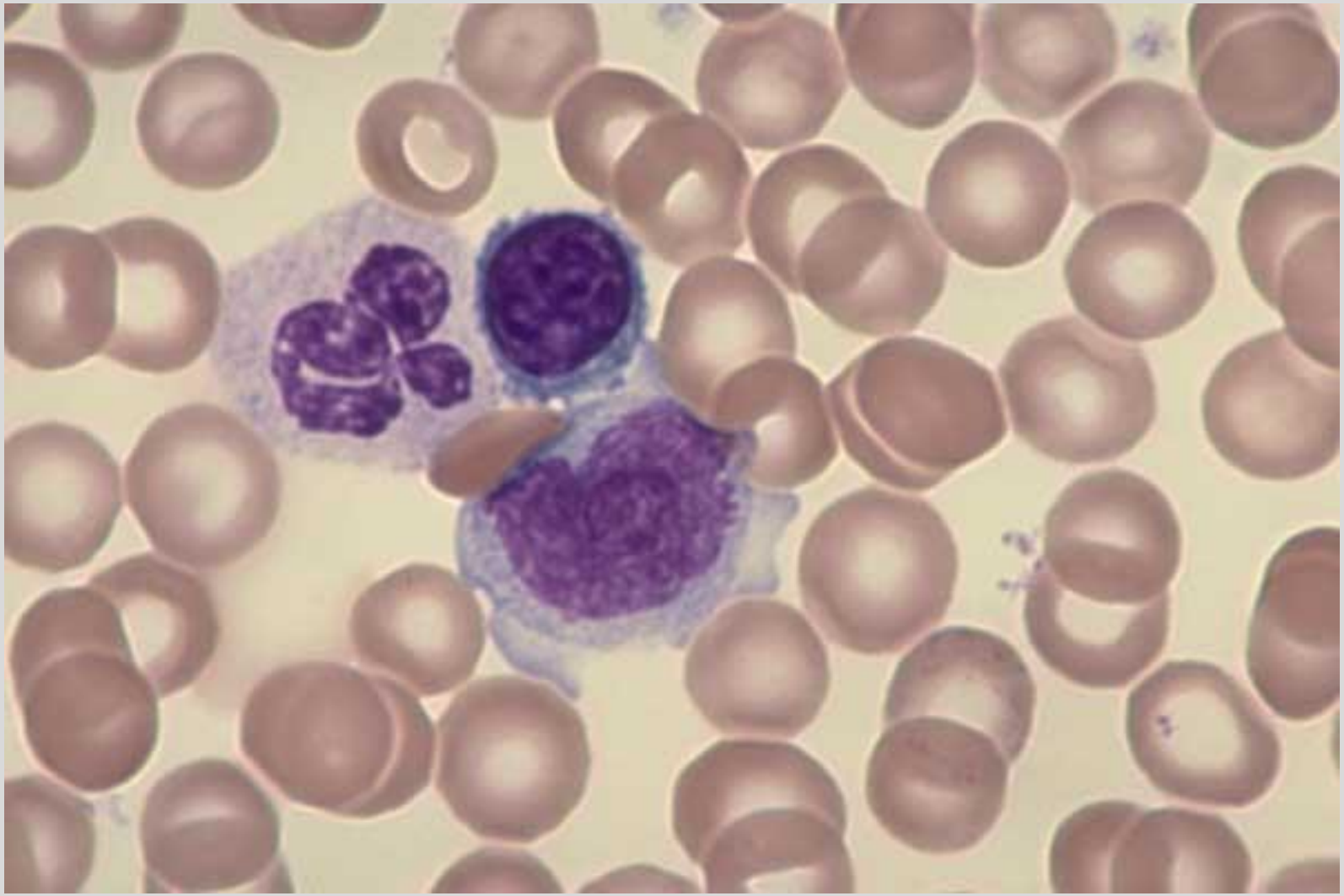
- In **acute infections, especially bacterial, neutrophils predominate:**
  - More numerous in general
  - Respond quicker to chemokines; arrive within 6 to 24 hours
  - Attach more firmly to adhesion molecules
  - Are short-lived and undergo apoptosis within 24 to 48 hours

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

FEATURE	ACUTE INFLAMMATION	CHRONIC INFLAMMATION
Pathogenesis	Microbial pathogens, trauma, burns	Persistent acute inflammation, foreign bodies (e.g., silicone, glass), autoimmune disease, certain types of infection (e.g., tuberculosis, leprosy)
Primary cells involved	Neutrophils	Monocytes/macrophages (key cells), B and T lymphocytes, plasma cells, fibroblasts
Primary mediators	Histamine (key mediator), prostaglandins, leukotrienes	Cytokines (e.g., IL-1), growth factors
Necrosis	Present	Less prominent
Scar tissue	Absent	Present
Onset	Immediate	Delayed
Duration	Few days	Weeks, months, years
Outcome	Complete resolution, progression to chronic inflammation, abscess formation	Scar tissue formation, disability, amyloidosis
Main immunoglobulin	IgM	IgG
Peripheral blood leukocyte response	Neutrophilic leukocytosis	Monocytosis

Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 3, Table 3-7



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

T lymphocytes and B lymphocytes

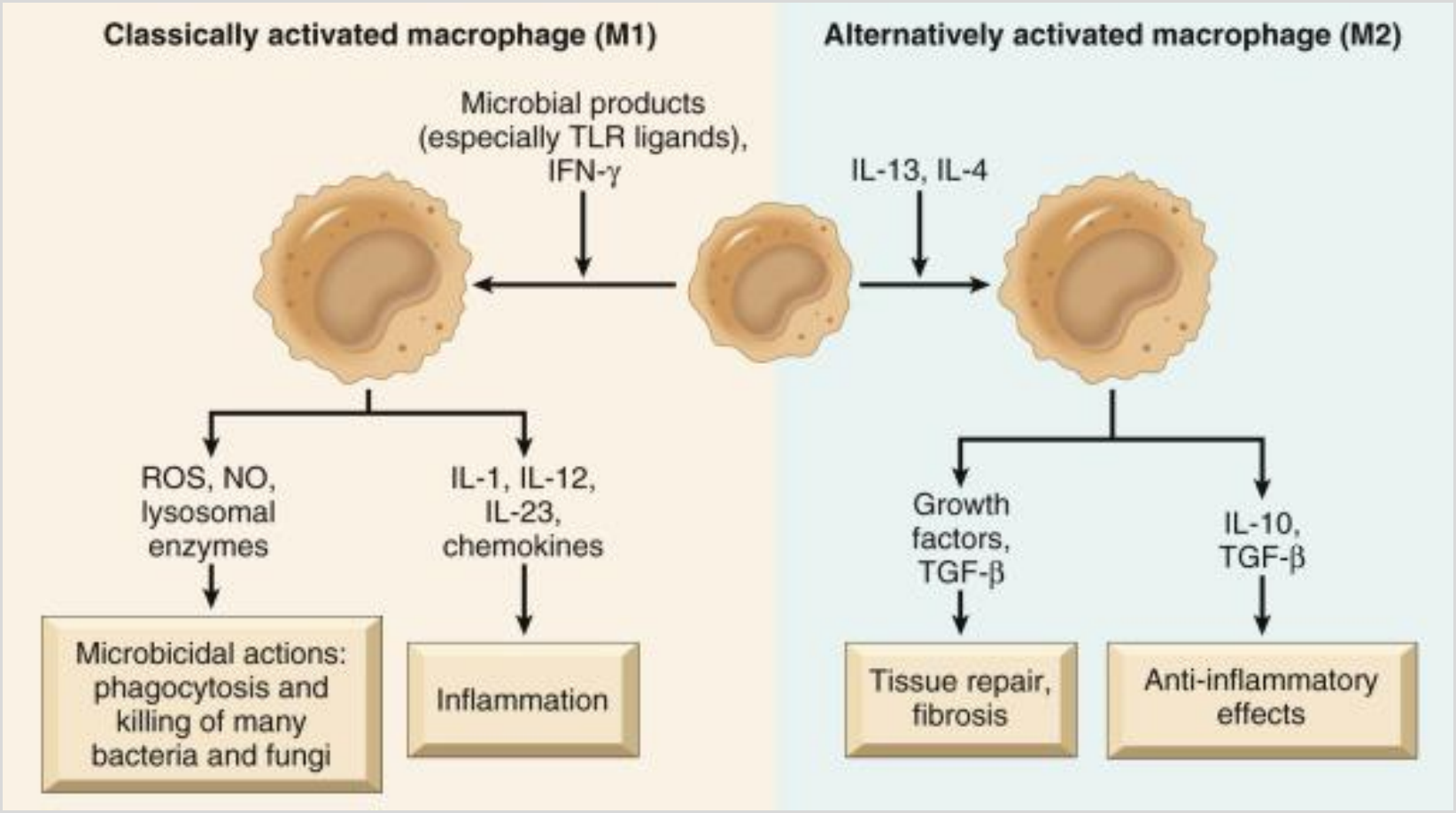
- Progenitor T cells in bone marrow
- Further developed in thymus where TCR undergoes rearrangement and cells become CD4+ helper T cells and CD8+ cytotoxic T cells
- Immature B cells produced in bone marrow undergo Ig rearrangements to become naïve B cells which express IgM and IgD
- More specifics to follow in heme/immune system

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

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



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

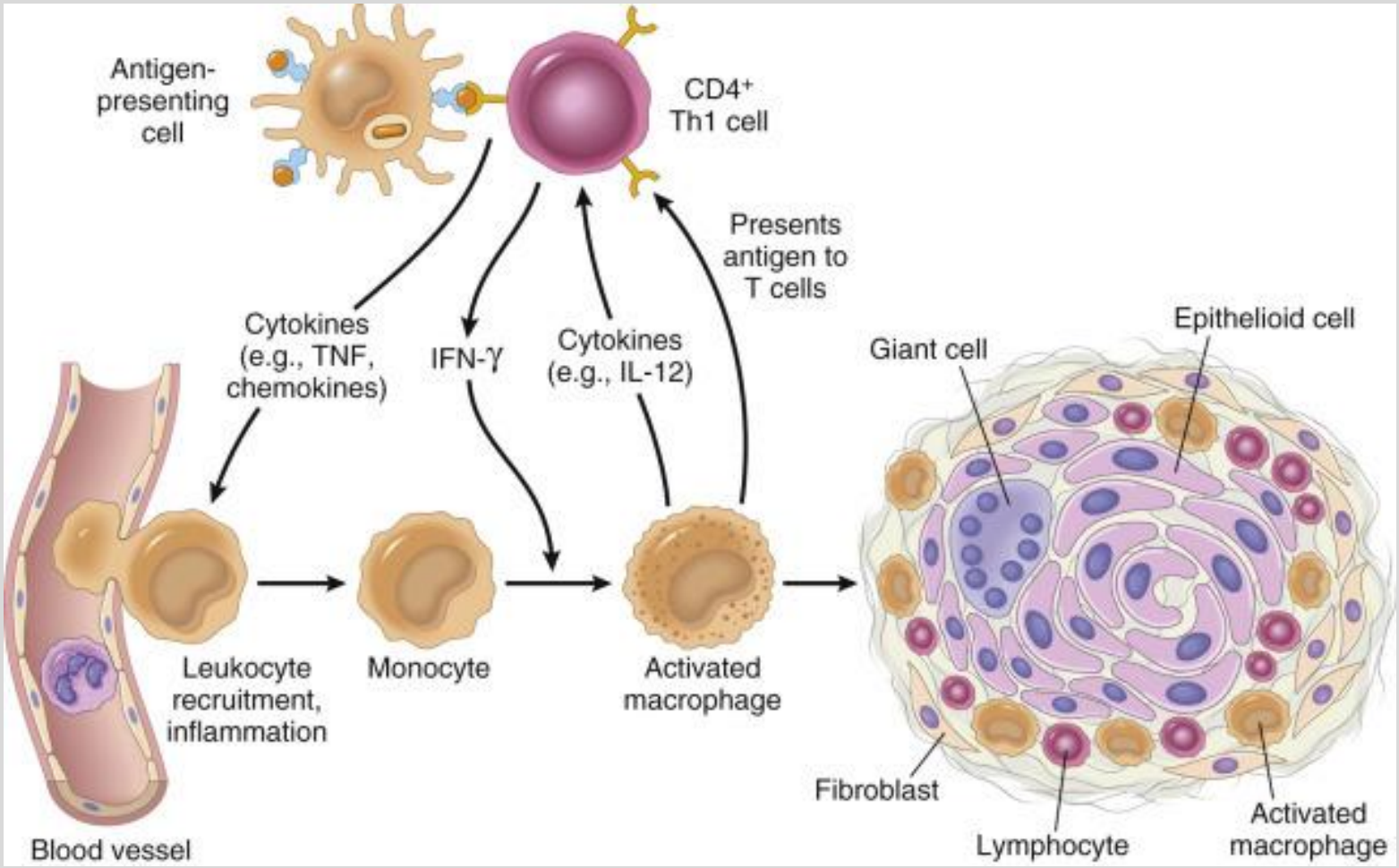
T lymphocytes

- Cytokines (TNF, IL-1, etc.) from activated macrophage recruit lymphocytes and CD4+ T lymphocytes secrete cytokines depending on subset:

1. TH1 produce IFN gamma - activates macrophages via classical pathway
2. TH2 produce IL-4, IL-5, IL-13 - activate eosinophils and responsible for the alternative macrophage pathway
3. TH17 secrete IL-17 and other cytokines which induce chemokines responsible for recruiting neutrophils (and monocytes)

Lymphocytes and Macrophages act bidirectionally.

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



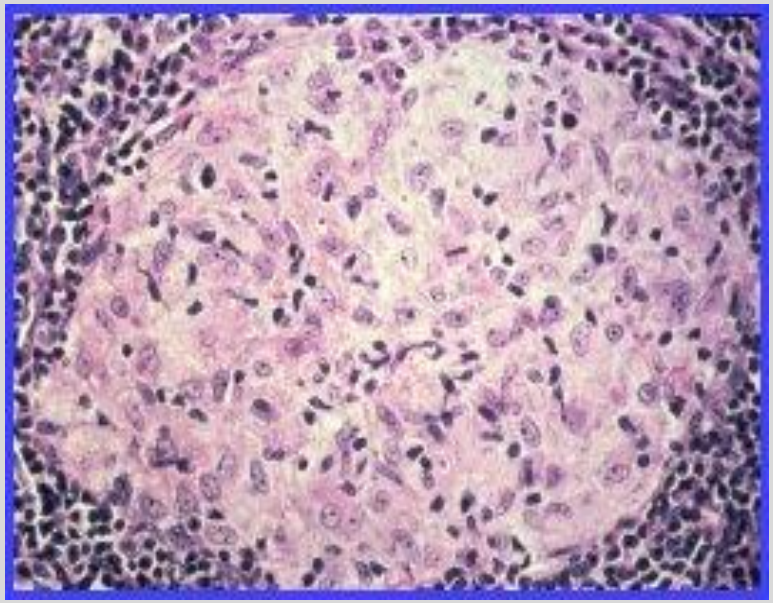
Macrophage–lymphocyte interactions in chronic inflammation.
Activated T cells produce cytokines that recruit macrophages (tumor necrosis factor [TNF], interleukin-17 [IL-17], chemokines) and others that activate macrophages (interferon-γ [IFN-γ]). Activated macrophages in turn stimulate T cells by presenting 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

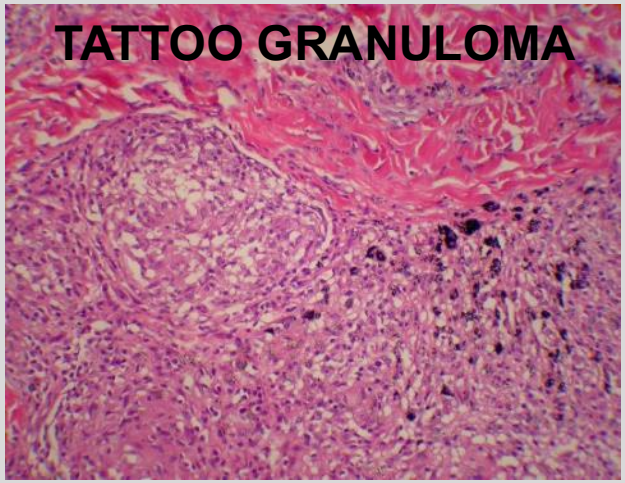
Granulomatous inflammation

- Chronic inflammation - attempt to contain offending agent difficult to eradicate, e.g. Mycobacteria tuberculosis
- Macrophages process and present antigen to helper T cells.
- This interaction produces cytokines like IL-2 which activate other T cells (TH1 subtype) **perpetuating response by causing secretion of IFN gamma**
- IFN gamma leads to macrophage activation, converting macrophages to epithelioid histiocytes and giant cells
- Necrotizing (caseating) v. non-necrotizing (non-caseating)

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



SARCOID GRANULOMA



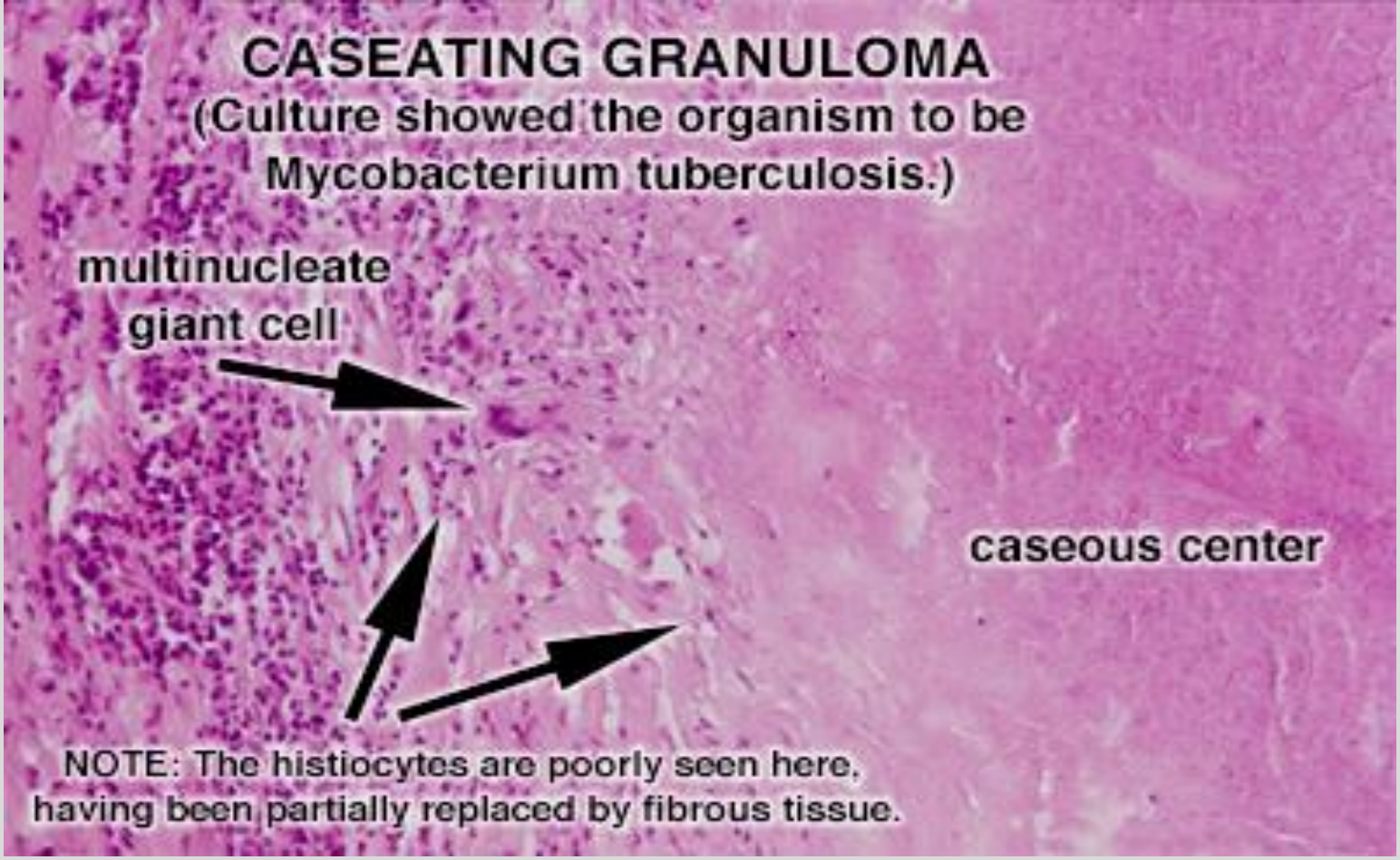
GRANULOMA:

- 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



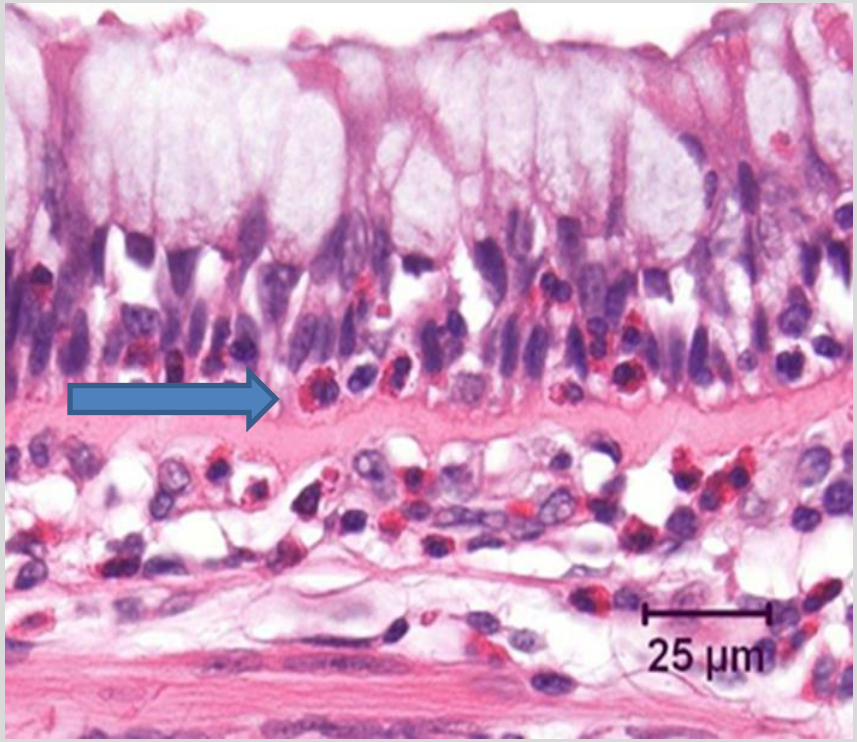
Caseating = necrotizing

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

Case Question

- A 7-year-old falls from his scooter and injures his ankle. He ankle becomes swollen, red, and is painful. Which of the following is most responsible for all three of these consequences?
- A. Histamine
- B. Nitric oxide
- C. Selectins
- D. Bradykinin
- E. Integrins

Summary Slide

- Cardinal signs, causes, and overview of inflammation
- Vascular changes of inflammation (vasodilation, vascular permeability, edema, stasis, margination)
- Major mediators involved in inflammation (histamine, NO, bradykinin, prostaglandins, leukotrienes, cytokines, complement)
- Cellular response in inflammation (margination, rolling, adhesion, transmigration, chemotaxis) including roles of adhesion selectins and integrins
- Phagocytosis – Recognition (Opsonization), Engulfment, Killing
- Termination of acute inflammation
- Types of acute inflammation – serous, fibrinous, suppurative
- Chronic inflammation including cell types – macrophages, lymphocytes, eosinophils, granulomas
- Acute v. Chronic inflammation

Lecture Feedback Form:

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