



Inflammation and Leukocyte Migration

Immunology Lecture 5

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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





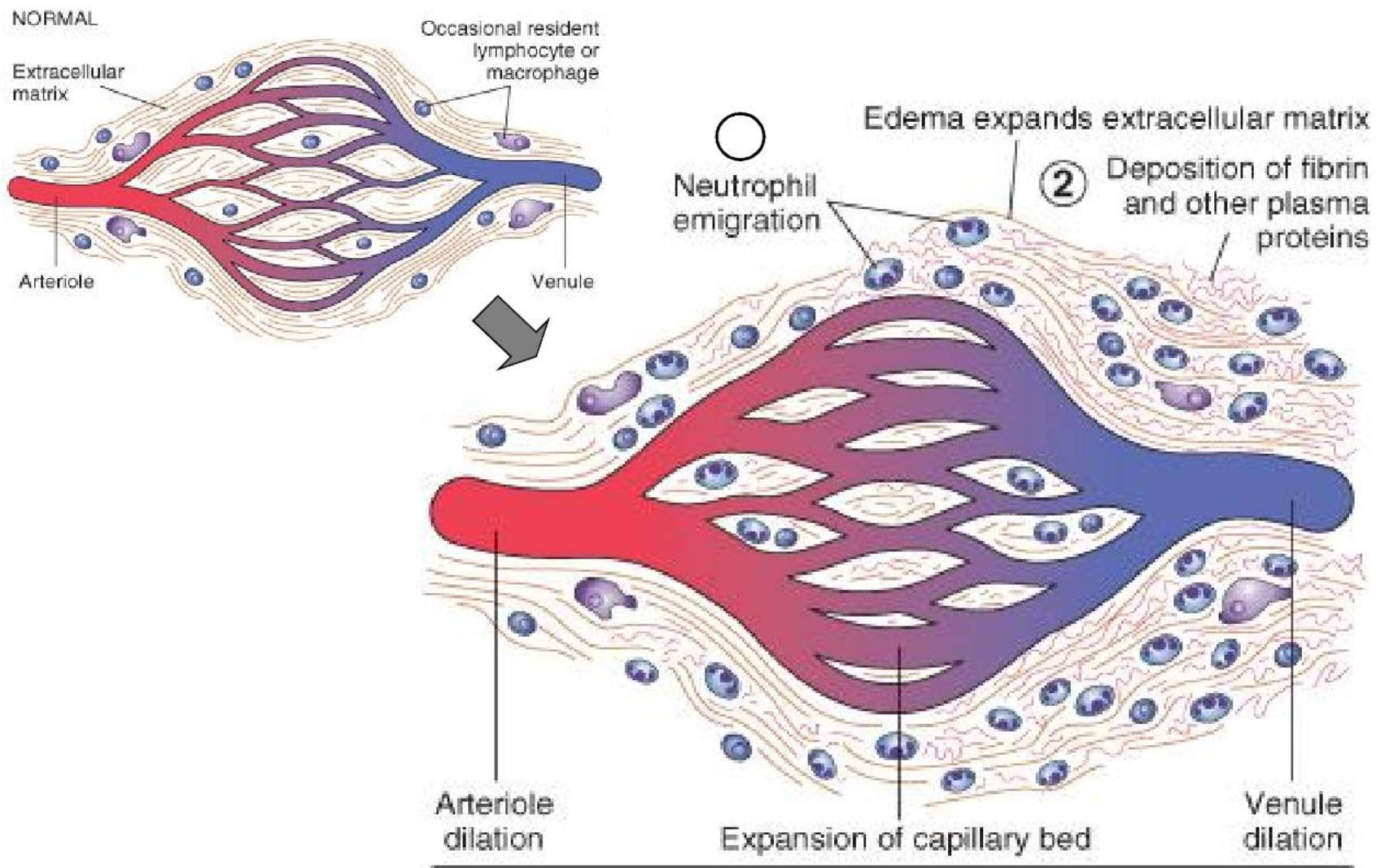
Pathogenesis

- 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.





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

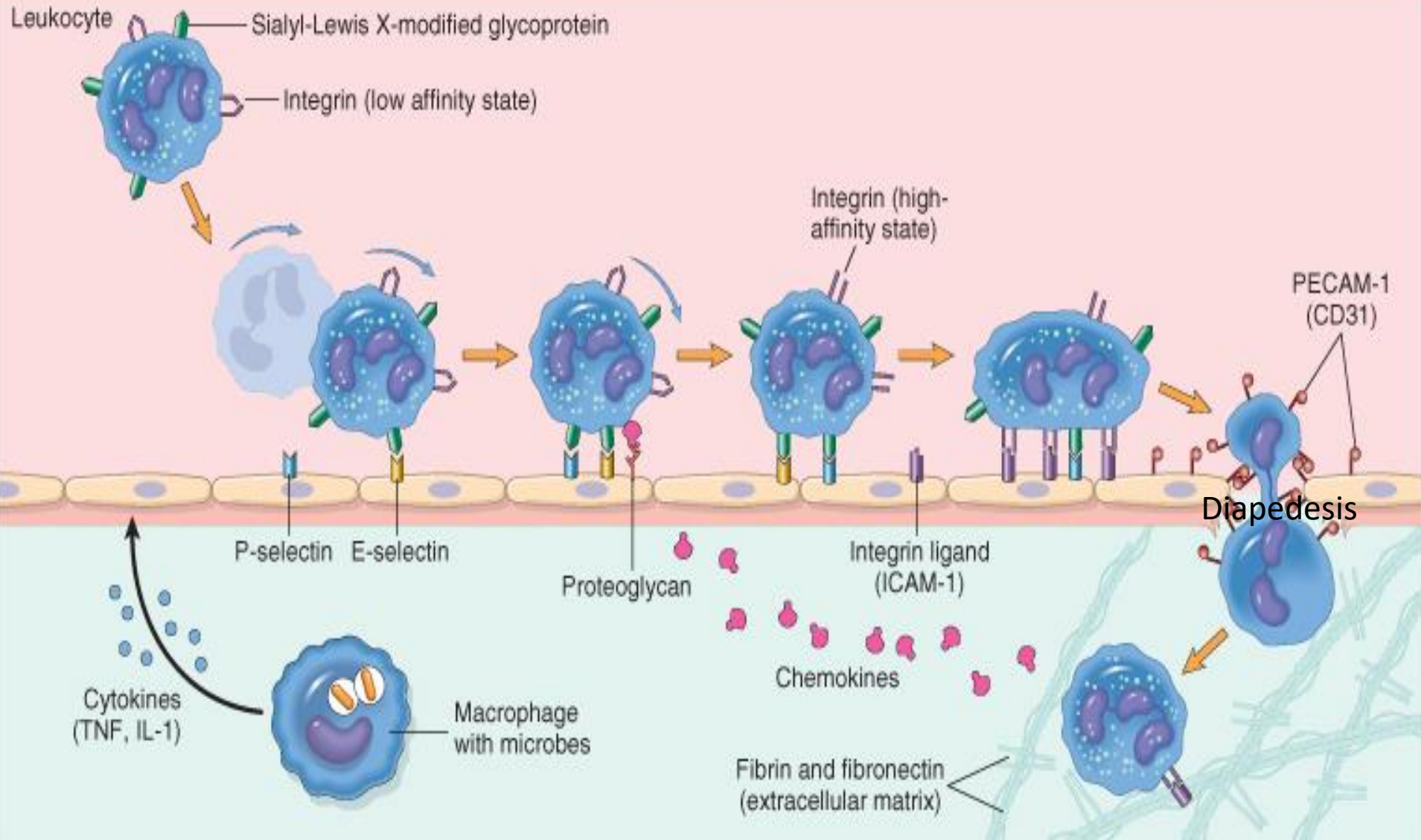


Rolling

Integrin activation
by chemokines

Stable adhesion

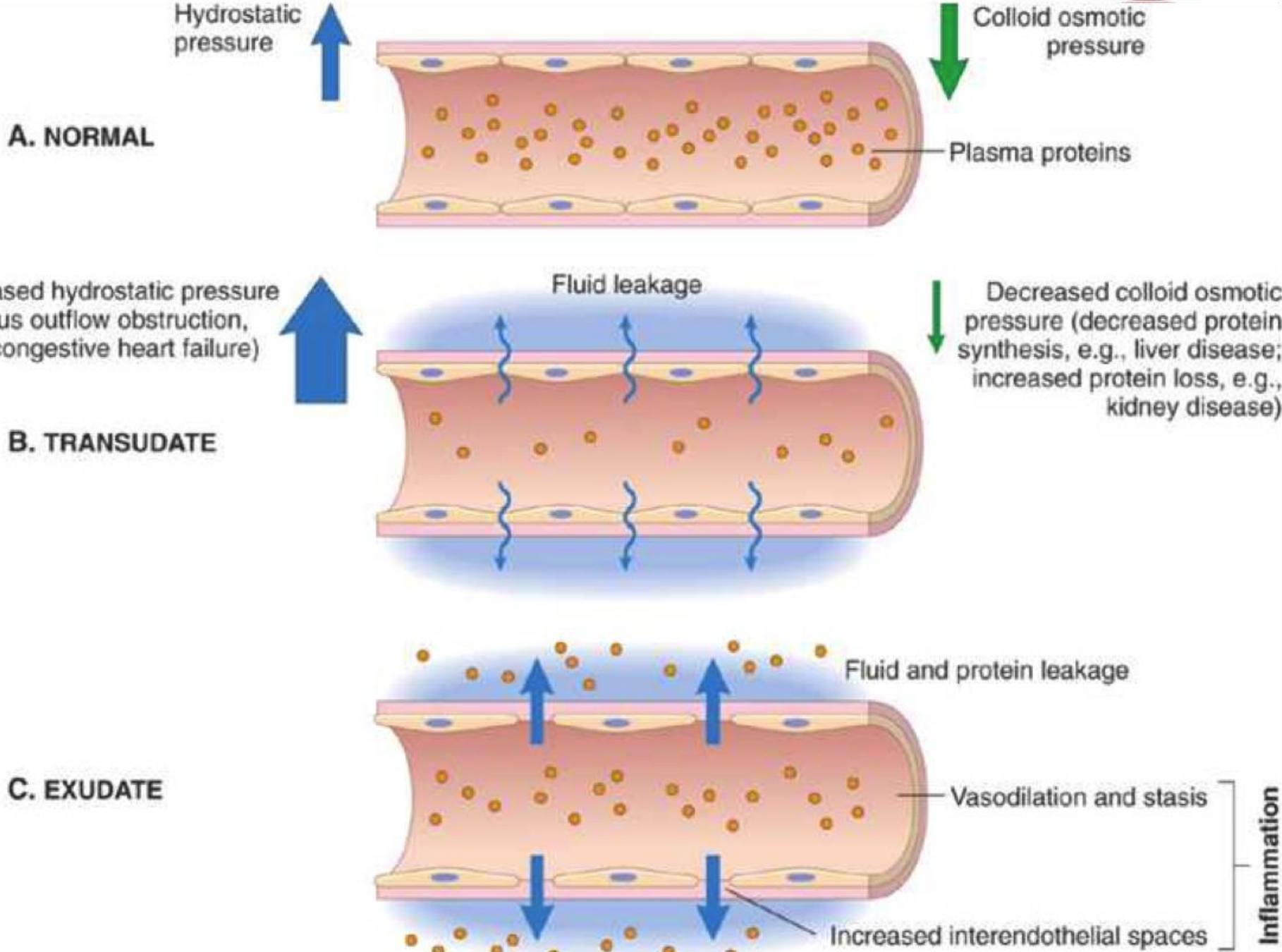
Migration through
endothelium





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 – vasodilation, fever, and pain.
 3. Bradykinin - induce vasodilation, increase vascular permeability, cause smooth muscle contraction, and induce 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 fever and 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)



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 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.



Photo Credit: Gregory Moran, M.D.

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)