ACUTE INFLAMMATION

I. INTRODUCTION:

A. DEFINITION: Inflammation is the reaction of vascularized tissue to injury.

1. Inflammation is the culmination of a tightly regulated, complex series of interactions between a pathogen/injury and host inflammatory cells, the complement and coagulation cascades, chemokines and cytokines that generate changes in blood vessels, blood flow and connective tissue matrix.

2. An inflammatory response neutralizes the injurious agent and removes dead tissue. Thus, inflammation is an integral component of healing, because it prepares the damaged organ for the process of repair (healing).

3. Inflammation and repair can be a "double edged sword." On one hand, inflammation is a biologic defense mechanism which protects the multicellular organism and leads to healing. On the other hand, inflammation "out of control" may lead to extensive tissue damage, deleterious fibrosis, or even death of the organism.

B. ACUTE VERSUS CHRONIC INFLAMMATION

1. Acute inflammation is an immediate tissue reaction characterized by the accumulation of fluid, plasma proteins and leukocytes, predominantly neutrophils, at the site of injury. Clinically, the process is of short duration, lasting hours or several days. The symptoms and signs are sudden in onset and rapidly progressive.

2. Chronic inflammation (next lecture) is a prolonged tissue reaction characterized by the accumulation of lymphocytes and macrophages, the presence of proliferating blood vessels and the formation of connective tissue at the site of injury. Clinically, the process is of longer duration, lasting days, weeks or months. Symptoms and signs may be slow to appear.
3. The intensity of the inflammatory response depends on:
   - the duration of the stimulus, e.g. bacteria or foreign body
   - type of injury
   - genetics of the host response
   - local factors, such as blood supply
   - physician interventions.

II. ACUTE INFLAMMATION: GENERAL

A. COMPONENTS.

   1. Vascular Events- regulated by cytokines, chemokines & other inflammatory mediators
   2. White Cell (leukocyte) events-- regulated by cytokines, chemokines & other inflammatory mediators

B. CLINICAL MANIFESTATIONS: How does a physician recognize an acute inflammation? More on this in next lecture.
   1. Local: redness (rubor), swelling (tumor), heat (calor), pain (dolor)
   2. Systemic: fever, shaking chills, malaise, leukocytosis

III. ACUTE INFLAMMATION: VASCULAR EVENTS

A. STRUCTURAL CHANGE OF BLOOD VESSELS, ALTERED BLOOD FLOW & INCREASED VASCULAR PERMEABILITY..

   1. The logic is to prepare the site for efficient delivery of innate inflammatory cells and expedite disposal of pathologic organisms and damaged tissue.

   2. Initial vasodilatation (arteriole, then capillaries), induced by the cytokine driven local release of nitric oxide, causes increased blood flow. Increased blood flow causes increased hydrostatic pressure that, in combination with increased vascular permeability, leads to leakage of plasma proteins and decreased colloid osmotic pressure. Both mechanisms work in concert to cause increased extravascular fluid or
3 Simultaneously, chemokine/cytokine induced changes in the endothelium allow protein-rich fluid containing antibodies, complement proteins and many other innate immune molecules to access the interstitial space at the site of inflammation.

4. Clinically these changes are manifest by local swelling and warmth; systemically they can cause increased cardiac output and a decrease in peripheral vascular resistance if the inflammatory stimulus is severe.

IV. CHEMICAL MEDIATION OF ACUTE INFLAMMATION

A. The mediators are predominantly cytokines and chemokines that arise though activation of the innate immune system.

1. Recognition that an inflammatory response is needed is mediated by DAMPS (danger associated molecular patterns) and PAMPS (pathogen associated molecular patterns) which you remember from Host Defense!

2. DAMP AND PAMP activation of TLRs on M1 macrophages and monocytes lead to the intracellular formation of an inflammasome.

3. The inflammasome is a multi-protein complex characterized by activation of CASPASE1 which then leads to activation and release of IL-1, 6, 8 and TNF-\(\alpha\) from activated macrophages and monocytes.

B. White cell events during acute inflammation

1. Rheologic changes: increased blood flow delivers more innate cells/unit time and increases the potential for leukocytes to respond to cytokine/chemokine signals and congregate along the endothelium or margin of the vessel lumen.

2. Margination, rolling adhesion and transmigration. The logic here is that in order to eliminate an inflammatory stimulus like infection, the innate
immune system activates cells that release signals that will recruit neutrophils— the ultimate destroyer and scavenger—from the vascular compartment to the site.

a. Inflammatory cytokines upregulate a family of receptors on the endothelium that induce leukocytes to the periphery of the lumen (margination). The marginated cells roll along the endothelium and finally “stick” to it (adhesion).

3. The process of leukocyte movement, which includes rolling, adhesion and transmigration, requires the interaction of complimentary adhesion molecules on the cell membranes of the leukocyte and endothelial cell.

4. Responding leukocytes, the vast majority of which are neutrophils, then extend pseudopods between adjacent endothelial cells and migrate through the vessel wall (transmigration).

C. Neutrophils—also known as polymorphonuclear leucocytes (PMN).

1. The neutrophil is the most numerous leucocyte in the circulation and is the signature cell of acute inflammation.

2. The bone marrow is capable of rapid production and release of neutrophils during acute inflammation.

3. In the peripheral blood, the neutrophil has a life of about 12’, once it has been directed to a site of inflammation, it’s half life is about 1-2’

4. Circulating neutrophils circulate in two compartments- 50% in the core of blood flow and the other 50% much closer to the endothelium. There is a rapid shift from core to the margin during acute inflammation.

5. Growth factors and inflammatory cytokines, especially IL-8 (and also IL-17 in some cases), produced by innate immune cells at the site of acute inflammation stimulate the bone marrow to accelerate maturation, proliferation and release of highly mobile PMNs to the
peripheral blood.

D. How Do Leukocytes (neutrophils) move from a blood vessel to the point of injury? The process is called **chemotaxis**.

1. Chemotaxis is the unidirectional movement of leukocytes along a chemical gradient to a site of tissue injury. The key processes here are unidirectional and gradient. Chemical substances released at the site of injury attract the leukocytes, especially granulocytes and monocytes. Powerful chemotactic attractants include: peptides released by bacteria, components of the complement system, especially C5a, arachidonic metabolites (leukotriene B₄) and the tetrad of inflammatory cytokines (IL 1,6,8 & TNF-α),

2. Activation of membrane receptors by chemotactic substances lead to changes in the cytoskeleton that enable the cell to move along a gradient to the site of inflammation.

E. What Does The Leukocyte Do At The Site Of Injury?

1. **Phagocytosis** is a complex process that includes leukocyte recognition of an injurious agent, attachment to and engulfment, and then killing or degrading the agent. Granulocytes, monocytes and tissue macrophages are the major phagocytes.

2. **Recognition and attachment**: Although phagocytosis can occur without innate immune system help, phagocytosis of pathogenic microorganisms occurs more efficiently if the microbes are coated with serum proteins called opsonins. A typical example of an opsonin would be IgG antibody to a bacterial capsular polysaccharide complexed with C3b that undergoes subsequent binding to a C3b receptor on a neutrophil, or an antibody complexed with a bacterial antigen that binds to the FcR on a neutrophil. Either process will then prompt the neutrophil to phagocytose the complex.

3. **Engulfment/degranulation**: Engulfment begins with the extension of pseudopods around the microbe. This amoeboid movement involves
microfilaments, actin and myosin, and requires energy and intracellular calcium. Before the pocket closes, lysosomal granules fuse with the portion of the cell membrane that lines the pocket. At this time, some lysosomes may release their contents into the unclosed pocket, intensifying the tissue injury. When the tips of the pseudopods fuse, the microbe is enclosed in an intracellular vacuole called a PHAGOLYSOSOME.

4. **Lyosomal granules** that are attached to the wall of the phagosome release their contents into the vacuole, a process known as degranulation.

5. **Killing/degradation**: As the neutrophil degranulates, a series of chemical reactions is initiated by the activation of an oxidative (respiratory) burst that generates microbiocidal agents. The most important ones are:

   a. **Reactive Oxygen Species (ROS)**. Activation of NADPH converts oxygen to superoxide ion, which is then converted to H2O2 and free oxygen radicals.

   b. **Lysosomal Enzymes**. These are sequestered in azurophilic granules of neutrophils. Myeloperoxidase is a major enzyme in the granule and, in the presence of a halide like chloride, generates the powerful oxidant HOCl that kills by halogenation and peroxidation. The H2O2-Halide-Myeloperoxidase System is the major mechanism used by the phagocyte to destroy bacteria.

6. An uncontrolled inflammatory process is dangerous to the host. The powerful oxidants released during inflammation, including products of arachidonic acid metabolism, can cause collateral tissue damage and disease if not regulated.

7. “NETS” (neutrophil extracellular nets). PMNs sacrifices its nucleus to cast out its chromatin loaded with granules and other anti-microbial molecules to trap bacteria and fungi. One picture is worth a thousand words on this defense mechanism. (See powerpoint for this lecture)
F. Control of Acute Inflammation

1. Control is highly dependent on monocytes/macrophages.
   a. Macs are derived from circulating monocytes. The latter cell is the
      largest of the circulating leukocytes, has a large indented nucleus,
      abundant lysosomes, a large golgi apparatus and circulates for ~16’
      before leaving the blood.
   b. They also have a rich display of MHC-II that enables them to function
      as antigen presenting cells.
   c. When a circulating monocyte exits the blood and enters tissue it
      becomes a tissue macrophage.
   d. They acquire regional phenotypic modifiers depending upon their final
      residence-examples would be alveolar if in lung or fixed macrophage in
      liver sinusoids.

2. When the stimulus to inflammation is destroyed or neutralized, acute
   inflammation begins to subside because of decreased PAMP/DAMP
   presence

3. Decreased PAMP/DAMP presence decreases TLR stimulation which
   then leads to sharply reduced inflammatory mediator production and
   release by M1 macrophages

4. Apoptotic neutrophils release inhibitors of neutrophil influx from blood
   vessels while enhancing monocyte traffic to the inflammatory site

5. Diminished TLR activation signals M1 macrophages to convert to M2
   macrophage phenotype and upregulate their synthesis of TGF-β and IL-
   10.

6. The latter 2 cytokines establish an anti-inflammatory milieu which sets
   the stage for appropriate healing and wound repair

G. Outcomes of acute inflammation.

1. Resolution and repair with restoration of normal architecture
2. Transition to chronic inflammation (next lecture)

H. Morphology of acute inflammation-pathologic classification based on severity that comes in handy during clinical assessment.

1. Least severe: **serous**. Protein poor transudate from capillary to a space-pleural, pericardial or peritoneal- or between epidermis and dermis (aka-blisters)

2. Intermediate severity: **fibrinous**. Fluid with larger molecules than a serous one and dominated by fibrinogen which then converts to fibrin. The latter provides a scaffold for scar formation

3. Most severe: **suppurative /abscess**. Protein rich fluid collection containing inflammatory cells, alive and dead, and cellular debris (aka “pus”). When the fluid collection is walled off by proliferating fibroblasts it’s an abscess.

4. Special category: **Ulcerative**. Underlying inflammation causes excavation of a mucosal or skin surface.