Acute and Chronic Inflammation

(Lecture)

OBJECTIVES

Acute inflammation

- Describe the components of the inflammatory response, particularly the reactions of blood vessels and leukocytes during inflammation.
- Identify, with illustrative examples, the beneficial and harmful consequences of inflammation.
- Recognize where the mediators of inflammation are produced and what their main actions are.
- Define the common morphologic patterns of inflammation.
- Explain the local and systemic manifestations of inflammation.

Chronic inflammation

- Compare and contrast acute vs. chronic inflammation in terms of: etiology (causes), time course, pathogenesis, and morphologic changes.
- Summarize the components of the mononuclear phagocyte system, including how macrophages are activated and what functions are performed by activated macrophages.
- Identify the features of a granuloma, and list the major diseases in which granulomatous inflammation is a prominent feature.
- Interpret the relationships between immune responses and acute and chronic inflammation.

KEYWORDS

abscess	hypersensitivity reactions	purulent inflammation
acute phase response	inflammasome	pus
cellulitis	left-shift	septic shock
cytokine storm	leukotrienes	serous inflammation
cytokines	lymphocyte	tissue necrosis
edema	macrophage	transcytosis
exudate	mediators	transudate
fibrinous inflammation	mononuclear phagocyte system	tumor
granuloma	neutrophil	ulcer
histamine	prostaglandins	vasodilation

REQUIRED READING

Robbins and Cotran Pathologic Basis of Disease (8th ed). Chapter 2, selected text, tables, and figures, see individual sections below.

I. OVERVIEW AND HISTORY

Inflammation is a complex tissue reaction composed of changes in blood vessels, leukocytes (neutrophils and monocytes/macrophages), and plasma proteins. Triggers include microbial infection, cell necrosis, and hypoxia. In this lecture, we will cover *acute* and *chronic inflammation*. Historically, the four *cardinal signs of inflammation* were identified by the Roman writer Celsus:

1. *rubor* redness
2. *tumor* swelling – a confusing term. Think of the word *tumescent,* which doesn't just apply to cancer. *Tumors* (neoplasms) can be benign (such as

hepatic adenoma) or malignant (such as hepatocellular carcinoma) and are growths due to proliferating cells.

3. *calor* heat
4. *dolor* pain

and the fifth sign was added by eminent German pathologist Rudolf Virchow in the 19th century:

5. *functio laesa* loss of function

II. ACUTE INFLAMMATION

As stated in Robbins, *acute inflammation* is a rapid host response that serves to deliver leukocytes and plasma proteins, such as antibodies, to sites of infection or tissue injury so these cells and antibodies can combat the external stimulus and rid the body of the harmful agent (microbe or toxin) and dead tissues. The components of the inflammatory response are:

1. Change in vascular caliber → increased blood flow.
2. Structural changes in vessels → leukocytes and plasma proteins leave the circulation.
3. Leukocytes (white blood cells, WBCs) exit the circulation → leukocytes accumulate at the site of injury and are activated to eliminate the culprit (see Figure 2-1).

THE BIG QUESTIONS TO KEEP IN MIND:

1. What is recognized to trigger inflammation?
2. Who does the recognizing?
3. What are the responses of host cells and molecules?
4. What is the outcome of acute inflammation?
5. What are the pathological consequences?

A. Stimuli And Recognition Mechanisms

- *Infections* – bacterial, viral, fungal, parasitic and microbial toxins. Leukocytes have *pattern recognition receptors* including *Toll-like receptors (TLRs)* homologous to the *Drosophila* protein Toll. Cell surface and endosomal TLRs recognize extracellular and ingested microbes and respond appropriately.

*Clinical example: Preterm placentas with chorioamnionitis have increased TLR-4 expression. TLR-4 signalling may deregulate prostaglandin expression → uterine smooth muscle contraction.

- *Tissue necrosis* – can be caused by *ischemia* (myocardial infarct), *trauma* (blunt injury), or *physical/chemical injury* (burns, frostbite). Molecular triggers of inflammation include uric acid, ATP, and even cytoplasmic DNA. *Hypoxia* is another trigger; for example, hypoxia-induced factor-1α (HIF-1α) is produced by cells in a hypoxic environment and is a transcriptional activator of genes involved in the inflammatory response, such as vascular endothelial growth factor (VEGF).
- *Foreign bodies* – even therapeutic foreign bodies like sutures or prosthetic implants can trigger inflammation via trauma to local tissues.
- *Immune reactions (hypersensitivity reactions)* – not just for the allergy sufferers, protective immune mechanisms can damage your own tissues by excessive responses to environmental triggers or by targeting self-antigens

to cause *autoimmune diseases*. Collectively, this category is called *immune-mediated inflammatory disease.*

- *The "inflammasome"* – recognition of products of dead cells by components of high-molecular weight, multi-protein complexes called *inflammasomes*. Inflammasomes control the maturation and secretion of interleukins such as IL-1β, thereby controlling proinflammatory activity in an infected/injured host. See pp. 61-62 for more.

B. Reactions of Blood Vessels

Exudate vs transudate (see Figure 2-2)

An *exudate* is extravascular fluid that has high protein, cellular debris, and specific gravity. It indicates a change in vascular permeability near a site of injury…suggesting inflammation.

A *transudate* has low protein (mostly albumin), cellular material, and specific gravity. It is a plasma ultrafiltrate caused by osmotic or hydrostatic changes WITHOUT changes in vascular permeability.

Edema = excess fluid in the interstitium or serous cavities, either a transudate or an exudate.

Pus = *purulent* inflammatory exudate with lots of leukocytes (mostly neutrophils aka polymorphonuclear leukocytes aka polys aka PMNs), cell debris, and often microbes.

1. Changes in vascular flow and caliber include
   Vasodilation mediated by histamine and nitric oxide (NO) acting on vascular smooth muscle.

   Increased permeability of the microvasculature with resulting exudate flow
   Slower blood flow, more red cells in small vessels, increased blood viscosity → *stasis* and *vascular congestion,* seen as redness.

   Leukocytes, mostly neutrophils, accumulate near and adhere to the endothelium. You will learn about vascular migration later in your Pathology curriculum.

2. Increased vascular permeability (vascular leakage, see Figure 2-3)
   Responsible mechanisms include:
   - *Endothelial cell contraction* → *increased inter-endothelial spaces* (effect of histamine, bradykinin, leukotrienes, neuropeptide substance P, et al). This is the *immediate transient response* (rapid onset, lasts 15-30 minutes). May also see *delayed prolonged leakage* in cases of burns, x-rays, UV rays, some bacterial toxins (vascular leakage after a delay of 2-12 hours, lasts for several hours to days).

   *Clinical example: late-appearing sunburn.

- *Endothelial injury* → *endothelial cell necrosis,* *achment* (rapid onset, lasts several hours till vascular repair is complete).
- *Transcytosis* (increased fluid and protein transported through endothelial cell). May involve the *vesiculovacuolar organelle,* a network of uncoated vesicles and vacuoles, many of which are close to intercellular junctions.

Vascular leakage can cause severe fluid loss.
*Clinical example: severe burns.

3. Changes in lymphatic vessels
   Lymphatics normally drain extravascular fluid that has left capillaries. Lymphatics proliferate during inflammatory reactions and may become secondarily inflamed = *lymphangitis.* Draining lymph nodes may become inflamed = *phadenitis.* Enlarged lymph node with follicular hyperplasia = *reactive/inflammatory lymphadenitis.*
   *Clinical example: red streaks near a skin puncture.

C. Reactions Of Leukocytes

Leukocytes become involved via these steps:
1. Recruitment
2. Activation
3. Function – eliminating the insult
4. Return to baseline

ailed descriptions and illustrations of these steps are in Robbins (text on pp. 48-56, Figures 2-4 through 2-9, Table 2-1) ~~for~~. Two subsets of activated macrophages (a type of activated leukocyte) are involved in fighting infection/ inflammation and in wound repair. They are the *classically activated macrophage (M1)* and the *alternatively activated macrophage (M2).* See Figure 2-10.

The release of leukocyte products (such as *lysosomal enzymes* in neutrophil granules) can itself induce tissue injury. This is outlined in Table 2-2.

Defects in leukocyte function play an important role in some human diseases. See Table 2-3.

nical example: Chédiak-Higashi syndrome: autosomal recessive, with
- defective fusion of phagosomes and lysosomes in phagocytes → susceptible to infections
- abnormalities in melanocytes → albinism
- abnormalities in nervous system → nerve defects
- platelet abnormalities → bleeding
- patients are neutropenic with defective neutrophil degranulation and delayed microbial killing. Leukocytes have *giant granules* likely due to aberrant phagolysosome fusion. Associated gene = LYST, encodes a large cytosolic protein believed to regulate lysosomal trafficking.

Termination of the acute inflammatory response is tightly controlled. The *mediators* of inflammation (see below) are produced in rapid, short bursts and

are degraded quickly. Neutrophils have short half-lives in tissue after exiting the circulation, and they die by apoptosis within hours. Termination signals include:

- switches in type of arachidonic acid (AA) metabolite produced, from pro-inflammatory leukotriene to anti-inflammatory lipoxins
- macrophage release of anti-inflammatory cytokines such as transforming growth factor-β (TGF- β) and interleukin (IL)-10

D. Mediators Of Inflammation

The basic sequence in inflammation is: stimulus (see causes above) → production of chemical mediators → reactions of vessels and leukocytes. Therefore, in order to understand the reactions of inflammation, you have to appreciate the mediators. *In your daily medical practice, you will be prescribing and administering drugs that inhibit one or more of these mediators.* The list of inflammatory mediators can be overwhelming (as is the list of anti-inflammatory medications occupying pharmacy shelves). The problem of understanding (and remembering) this long list is compounded by the fact that many mediators have overlapping actions. Descriptions of the individual mediators are in the Robbins Pathology textbook (pp. 56-66, including Tables 2-4 through 2-7, Figures 2-11 through 2-15). It is important to remember the general properties of these mediators:

- Mediators of inflammation are either *produced by various host cells* or *are derived from plasma proteins.*
- Biologically active mediators are produced only when needed, i.e., in response to external stimuli. Cell-derived mediators are either pre-formed and secreted rapidly (histamine), or newly synthesized and secreted (prostaglandins and leukotrienes; cytokines). Plasma-derived mediators circulate in an inactive form and need to be activated to do their job.
- Most of the mediators act briefly and close to where they are produced.

Three classes of mediators that you will hear about in the 1st year are discussed below. Drugs that antagonize these mediators will be discussed in some detail in the I-3 course.

- *Histamine* is a major vasoactive amine (has an effect on blood vessels). It is stored as a preformed molecule in mast cells present in connective tissue next to blood vessels and is released by mast cell degranulation.
- *Prostaglandins* and *leukotrienes* are metabolites of arachidonic acid. Prostaglandins are produced by mast cells and other leukocytes via the constitutively expressed cyclooxgenases COX-1 and COX-2; prostaglandins affect inflammation and hemostasis. Leukotrienes are produced via lipoxygenases and have vascular effects such as neutrophil aggregation.
- *Cytokines* are produced by cells such as activated lymphocytes and macrophages and also by endothelial, epithelial, and connective tissue cells. Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are two major

cytokines that mediate inflammation and induce the *acute-phase response* of infection/injury (more later).

The principal mediators of inflammation, their sources, and their actions are summarized in Table 1.

Table 1. *Summary of the major mediators of inflammation (courtesy Abul K. Abbas, MD)*

Mediator	Source	Action
Cell-Derived		
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)	Macrophages, endothelial cells, mast cells, T-lymphocytes	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, hypotension (shock), weight loss (chronic exposure).
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Reactive Oxygen Species	Leukocytes	Killing of microbes, tissue damage
Nitric Oxide	Endothelial cells, macrophages	Vascular smooth muscle relaxation; killing of microbes
Plasma Protein-Derived		
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (MAC), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

E. Outcomes Of Acute Inflammation

Despite the complexity of the process, the outcomes must be one of the three following (see Figure 2-16):

- *Complete resolution* = site of acute inflammation returns to normal. This is usually the case with limited, short-lived tissue injury. Macrophages remove cellular debris and microbes, lymphatics resorb edema fluid.
- *Healing by connective tissue replacement = fibrosis = scarring.* Substantial tissue destruction, incomplete tissue regeneration, abundant fibrin deposition in tissues or serous cavities (pleura, peritoneum).
- *Progression to chronic inflammation.* Persistent injury or inability of normal healing process to act properly.

*Clinical example of progression to chronic inflammation: Acute bacterial pneumonia (acute inflammation) → fails to resolve → extensive tissue damage → recurrent damage → chronic lung abscess.

F. Morphologic Patterns Of Acute Inflammation

Common features: vasodilation, edema, leukocyte (mostly neutrophil) infiltration in tissues.

*Figures 2-17 through 2-21 include gross photos of tissue and microscopic images of cells. These are typical clinical cases you will see in pathology practice. The cells are stained with H&E, hematoxylin (purple, stains acids, hence DNA-rich nuclei are purple) and eosin (pink, stains bases, hence protein-rich cytoplasm is pink).

In different tissues, and in response to different external stimuli, the reaction assumes particular forms that often suggest the underlying pathophysiology.

- *Serous inflammation:* outpouring of clear fluid in a confined space, e.g. a blister; also in cavities like the pleural cavity.
- *Fibrinous inflammation:* rich in fibrin (acellular, proteinaceous material); often seen on serosal surfaces (pericardium, peritoneum, pleura)
- *Purulent (suppurative) inflammation:* abundant pus (thick, usually yellowish, fluid consisting of dead neutrophils, cellular debris and microbes); indicates infection.
- *Cellulitis:* dense infiltrate of leukocytes through tissue, usually subcutaneous, accompanied by erythema (redness); strongly suggestive of infection.
- *Ulcer:* discontinuity in epithelium with underlying inflammation and repair; acute or chronic.
- *Abscess:* focus of inflammation walled off by leukocytes and fibrosis; acute or chronic.

III. CHRONIC INFLAMMATION

A. Overview

In many respects, chronic inflammation represents a failure of the initial (acute) response to deal with the offending agent. As the offending agent persists, the adaptive immune system kicks in. Therefore, chronic inflammation often has a large component of adaptive immunity (hypersensitivity). Not surprisingly, the causes of chronic inflammation are agents that are difficult to eradicate, the most important being:

1. Microbes that resist clearance (mycobacteria, some viruses and fungi); and
2. Self-antigens**,** the targets of autoimmune diseases (such antigens obviously being impossible to get rid of). We have referred previously to the category of *immune-mediated inflammatory diseases;* most of these diseases are characterized by chronic inflammation.
3. Some environmental substances, such as proteins that cause allergies, some dietary lipids. Although traditionally one thinks of persistent infections and immunological diseases as prototypes of chronic inflammatory disorders, this process now is implicated in a wide variety of diseases, including atherosclerosis and heart disease (in which cholesterol crystals elicit chronic inflammation in arteries) and obesity-associated type 2 diabetes (in which lipids trigger chronic inflammation, which causes insulin resistance). You will hear more about this later in the first year.

Chronic inflammation is largely a cellular response, with a minor (if any) role of vascular dilation and permeability.

See Figure 2-22 for a good contrast of acute and chronic inflammation. *When it comes to histology, acute = neutrophils and chronic = macrophages and lymphocytes.*

B. The Cellular Players In Chronic Inflammation

Persistent stimuli recruit circulating cells by the same mechanisms as those described in the previous lecture. The **principal cells** involved in chronic inflammation are illustrated in Figures 2-23 through 2-25. They are:

- Blood monocytes and their tissue counterpart, macrophages (the cells of the mononuclear phagocyte system), the body's most powerful phagocytes
- Lymphocytes, including effector T-lymphocytes ($CD4^+$ helper and $CD8^+$ CTLs), which enhance recruitment and activation of macrophages and neutrophils, and antibody-secreting cells (plasma cells)
- In cial cases, eosinophils
- Fibroblasts and blood vessels involved in the repair reaction (discussed in the lecture on Tissue Repair)

1. The Mononuclear Phagocyte System
   - The **mononuclear phagocyte system** (still sometimes – and erroneously – called the reticuloendothelial system) consists of circulating monocytes and tissue macrophages, cells whose primary function is to ingest (phagocytose) and destroy foreign invaders (i.e., microbes) and dead cells. Macrophages recognize microbes by many receptors, and phagocytosis is accompanied by activation of the phagocytes. Activated macrophages produce microbicidal substances, cytokines and other mediators of inflammation, and molecules that stimulate lymphocytes (the adaptive immune response). *The products of activated macrophages are responsible for tissue injury.*

   Because the products of activated macrophages amplify the inflammatory reaction and enhance T-cell responses, and T cells, in turn, activate

macrophages, once the cycle starts it is difficult to stop. This is why the cellular reaction in chronic inflammation is often severe and persists for long periods.

2. Lymphocytes and Other Cells
   - T lymphocytes: $CD4^+$ helper cells (usually of the Th1 subset, may be Th17 cells*) and $CD8^+$ CTLs, responding to peptides derived from microbial or self-antigens. Both Th1 cells and CTLs secrete the cytokine IFN-γ, which activates macrophages. It is easy to understand how this reaction can become a vicious cycle – macrophages display peptide antigens to T-cells and secrete the T-cell-activating cytokine IL-12 – T-cells develop into Th1 cells and secrete the macrophage-activating cytokine IFN-γ – and so on. This *cross-talk* between macrophages and T-lymphocytes sets up an internal amplification (positive feedback) loop, because of which chronic inflammatory diseases are often persistent, progressive, and difficult to treat.

*Th17 cells secrete cytokines that recruit more leukocytes, thus propagating the inflammatory reaction. You will learn more about T-cells and their role in chronic inflammation in the I-3 course.

   - B-lymphocytes and plasma cells
   - In special circumstances, other cells such as *eosinophils* (e.g. in persistent allergies and infection by helminthic parasites). See Figure 2-26.

C. Granulomatous Inflammation

It is key to be able to identify a granuloma in a tissue section in order to form your differential diagnosis. It is a focus of chronic inflammation composed of epithelioid macrophages surrounded by mononuclear leukocytes, mostly lymphocytes with some plasma cells. Table 2-8 lists some granulomatous diseases (tuberculosis, leprosy, syphilis, cat-scratch disease, sarcoidosis, and Crohn disease). Figure 2-27 shows a classic granuloma of tuberculosis.

In usual clinical practice, the presence of granulomas (especially with central necrosis) is suggestive of tuberculosis and stains and culture for mycobacteria should be done to rule the infection in or out.

D. Systemic Effects Of Inflammation

1. Fever (mediated by cytokines, prostaglandins)
2. *Acute-phase response:* change in levels of several plasma proteins; proteins affected include some that increase rouleaux formation of RBCs (measured as increased erythrocyte sedimentation rate), elevated serum C-reactive protein.
3. Leukocytosis: increased numbers of WBCs in the blood; in severe reactions, incompletely differentiated (immature) neutrophils may spill

out of the marrow into the blood (because the nuclei are not multilobed, these are called *band* forms) -- this phenomenon is called *-shift.*

Inflammation is the cause of clinical problems in many diseases. Sometimes, it is a minor nuisance (e.g. a sore throat); sometimes it causes chronic and debilitating diseases (e.g. rheumatoid arthritis); and at other times it is acute and life-threatening. An example of the last group is *septic shock,* seen in some severe disseminated bacterial infections. In this syndrome, massive leukocyte activation leads to a *cytokine storm* (TNF et al), causing low blood pressure, disseminated intravascular coagulation, and metabolic disturbances.

IV. CLINICAL CORRELATION

The goal of therapy for inflammation is to reduce the pathologic consequences without interfering with its role in host defense. The development of these drugs has relied on defining the mediators of inflammation. Many different types of drugs are used.

- Anti-inflammatory drugs that reduce acute inflammation: include anti-histamines; drugs that block prostaglandin synthesis (the largest group includes aspirin, ibuprofen, COX-2 inhibitors); more recently, antagonists of leukotrienes. These drugs are grouped under *non-steroidal anti-inflammatory drugs (NSAIDs).*
- Corticosteroids: often the mainstay of treatment for immune-mediated chronic inflammatory diseases; work by inhibiting production of cytokines and other mediators in macrophages and T lymphocytes.
- Cytokine antagonists: Since cytokines were recognized as key players in the positive feedback (amplification) loop of chronic inflammation, there has been great interest in blocking these cytokines and interrupting the cycle. A remarkable success story is that of TNF antagonists; recall that TNF is an important mediator of leukocyte recruitment to sites of inflammation. This class of drugs has changed the lives of many patients with immune-mediated inflammatory diseases (most notably rheumatoid arthritis, Crohn disease, and psoriasis). In fact, for the first time in the history of rheumatoid arthritis, physicians can tell their patients that the disease can be controlled and will go into remission – largely because of TNF antagonists! You will hear more about these drugs in future courses, and especially in I-3.

As we said at the outset, the same inflammatory reaction that causes disease is responsible for defense against infection. It is, therefore, not surprising that potent anti-inflammatory drugs (particularly steroids and cytokine antagonists) reduce normal defenses and make individuals susceptible to infection.

We have now concluded your introduction to some of the most important processes in normal physiology and disease – host defense mechanisms and how these normally beneficial reactions can be the cause of serious illness. The concepts we have discussed in this introductory lecture will recur throughout medical school, and they will be a major theme of the I-3 course in the second year.