CHAPTER THREE
INFLAMMATION

General Features
Inflammation is defined as "the response of living vascularized tissues to harmful agents." It consists principally of vascular changes associated with leukocytes infiltration and systemic reactions." Inflammation is a fundamental and common pathologic process seen in many disease states. It is essentially a protective response, the aim of which is to get rid of the injurious agents (e.g., microbes, toxins) as well as its consequences (e.g., necrotic cells and tissues). Inflammation is concurrently tangled with another process (repair) that tries to mend the damaged tissues resulting from the battle between the offending agent and the host. Without inflammation, infections would go uninhibited, wounds would never heal, and injured organs might remain permanently damaged. Some times, however, inflammation and its associated repair may be potentially harmful. For this reason, pharmacies flourish with anti-inflammatory drugs, which ideally control the harmful sequelae of inflammation yet do not interfere with its beneficial effects.

Many tissues and cells are involved in the inflammatory reaction, including plasma fluid proteins, circulating leukocytes, blood vessels, and cellular and extracellular constituents of connective tissues. The circulating leukocytes include neutrophils, monocytes, eosinophils, lymphocytes, basophils, in addition to platelets. The connective tissue cells are mast cells, fibroblasts, macrophages, and lymphocytes. The extracellular matrix consists of structural proteins (collagen, elastin), adhesive glycoproteins (fibronectin, laminin), and proteoglycans.

Inflammation is divided into acute or chronic. The latter includes also a specific form called granulomatous inflammation.

Acute inflammation is rapid in onset (seconds or minutes), of relatively short duration (minutes, hours, or at most a few days), characterized by the exudation of fluid and plasma proteins, & the emigration of leukocytes, predominantly neutrophils.

Chronic inflammation, in contradistinction, is of insidious onset, of longer duration, and is associated histologically with the presence of lymphocytes, macrophages, plasma cells, proliferation of blood vessels and fibroblasts.

In both forms tissue necrosis of varying extent occurs. The vascular and cellular reactions of both acute and chronic inflammation are mediated by chemical substances (chemical mediators) that are derived from plasma proteins or cells. Such substances, acting singly, in combinations, or in sequence, amplify the inflammatory response and influence its evolution.

The five cardinal signs of inflammation are rubor (redness), tumor (swelling), calor (heat), dolor (pain), and loss of function (functio laesa). The first four signs are typically more prominent in acute inflammations than in chronic ones.

ACUTE INFLAMMATION
Stimuli of acute inflammation
Acute inflammatory reactions are triggered by a variety of stimuli that include
1. Infections: bacterial, viral, parasitic and microbial toxins
2. Physical and chemical agents (trauma, thermal injuries, irradiation, toxins, strong acids, etc.)
3. Tissue necrosis (of any from or cause)
4. Foreign bodies (splinters, dirt, sutures)
5. Immune reactions (hypersensitivity and autoimmune reactions)

Exudation is the escape of fluid, proteins, and blood cells from the vascular system into the interstitial tissue. An exudate is an extravascular fluid that has a high protein concentration and a specific gravity above 1.020. It involves significant alteration in the normal permeability of small blood vessels in the area of injury. In contrast, a transudate is a fluid with low protein content (most of which is albumin) and a specific gravity of less than 1.012.
It is essentially an ultrafiltrate of blood plasma that results from osmotic or hydrostatic imbalance across the vessel wall without an increase in vascular permeability. Edema refers to an excess of fluid in the interstitial tissues or body cavities; the accumulated fluid can be either an exudate or a transudate. Pur (purulent exudate) is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells and, in many cases, microbes (pyogenic bacteria).

Acute inflammation has three major components: (Fig. 3-1)

A. Vasodilation associated with increased blood flow
B. Increased vascular permeability associated with decreased blood flow
C. Emigration and activation of leukocytes and phagocytosis

A. Vasodilation and increased blood flow

This is, sometimes, preceded by a transient constriction of arterioles, lasting a few seconds. Vasodilation first involves the arterioles, which leads to an increase in blood flow; this in turn leads to opening of new capillary beds in the area with subsequent dilation of capillaries & venules. This process allows more blood to flow into the area, a process known as “active hyperemia” (hyper- = increased; -emia = blood). These changes explain the clinically noted heat and redness. Vasodilation is induced by the action of several mediators (such as histamine) on vascular smooth muscles. It is possible that autonomic nerve impulses may also play a role in relaxation of arteriolar smooth muscle leading to their dilation.

B. Increased Vascular Permeability and decreased blood flow

Increased vascular permeability leads to the escape of exudates into the extravascular tissue. This is driven by the increased hydrostatic pressure owing to increased blood flow through the dilated vessels and is perpetuated through the loss of proteins from the plasma that reduces the intravascular osmotic pressure and increases the osmotic pressure of the interstitial fluid.

Several mechanisms have been proposed for the increased vascular permeability, that include

1. Formation of endothelial gaps in venules due to endothelial cells contraction. This is the most common mechanism & is elicited by several mediators e.g. histamine, bradykinin, and leukotrienes. Binding of these mediators to receptors on endothelial cells leads to stimulation of contractile proteins (such as myosin). The result is contraction of the endothelial cells and separation of intercellular junctions that eventuate in intercellular gaps formation.
2. Junctional retraction caused by chemical mediators such as TNF and IL-1; these induce structural reorganization of the cytoskeleton of the cells.
3. Direct endothelial cell injury as by burns or infections. Because of endothelial damage and exposure of the subendothelial thrombogenic collagen, this type is frequently associated with platelets adhesion with subsequent thrombosis.
4. Leukocyte-dependant injury due to accumulation of leukocytes and their activation products (such as toxic oxygen radicals and proteolytic enzymes) during the inflammatory response. These lead to endothelial cell damage.

According to the above mechanisms, there are three basic patterns of increased permeability

1. Immediate transient response lasting for 30 minutes or less, mediated mainly by the actions of histamine and leukotrienes on endothelium
2. Delayed response starting at about 2 hours and lasting for about 8 hours, mediated principally by kinins, complement products.
3. Prolonged response that is most noticeable after direct endothelial injury, e.g. after burns.

The inflammatory exudate, in addition to leukocytes, is composed of plasma proteins; of these, two play a particularly important role

1. Immunoglobulins; a group of antibodies that have the ability to react with certain antigens, making them vulnerable to the actions of neutrophils and macrophages (opsonization)
1. Binding of leukocytes to the endothelial cells. Normally, the vascular endothelium does not bind circulating cells or impede their passage. In inflammation, however, the endothelium becomes activated to permit binding of leukocytes to its surface. This is followed by
2. Transmigration of leukocytes across the endothelium (diapedesis)
3. Migration of leukocytes within the interstitial tissues toward the focus of tissue injury.
Because blood flow slows down in inflammation, more white cells assume a peripheral position along the endothelial surface. This process is called margination. Subsequently, leukocytes tumble and roll over slowly along the endothelium and eventually come to rest through firm adhesions with the endothelial cells. In time, the endothelium becomes virtually lined by white cells, an appearance called pavementing. After firm adhesion, leukocytes insert pseudopods into the junctions between the endothelial cells, squeeze through interendothelial junctions, and eventually, traverse the basement membrane and escape into the extravascular space. Neutrophils, monocytes, lymphocytes, eosinophils, and basophils, all use the same pathway to migrate from the blood into tissues. Leukocyte adhesion and transmigration are achieved by the binding of complementary adhesion molecules on the leukocyte and endothelial cells, a process regulated by chemical mediators. The adhesion receptors involved belong to several molecular families including selectins and integrins. The next step in the process is migration of the leukocytes through the endothelium, called transmigration or diapedesis. Chemokines (chemoattractants) act on the adherent leukocytes and stimulate the cells to migrate toward the site of injury or infection. Certain adhesion molecules, present in the intercellular junction of endothelium, are involved in the migration of leukocytes. Leukocyte diapedesis, similar to increased vascular permeability, occurs predominantly in the venules. After traversing the endothelium, leukocytes eventually pierce the basement membrane, probably by secreting degrading enzymes such as collagenases & elastases. Once leukocytes enter the extravascular connective tissue, they are able to adhere to the extracellular matrix by virtue of integrins and CD44. Thus, the leukocytes are retained at the site where they are needed. (Fig. 3-3) The type of emigrating leukocyte varies with the age of the inflammatory response and with the type of stimulus. In most forms of acute inflammation, neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours, and then are replaced by monocytes in 24 to 48 hours. After entering tissues, neutrophils are short-lived; they undergo apoptosis (self destruction) and disappear after 24 to 48 hours, whereas monocytes (by now called macrophages: macro- = large and phage = eater) survive longer and thus outlive neutrophils and become more apparent. There are, however, exceptions to this pattern of cellular exudation. In certain infections—for example, those produced by Pseudomonas organisms—neutrophils predominate over 2 to 4 days; in viral infections, lymphocytes may be the first cells to arrive; in some hypersensitivity reactions and parasitic infestations, eosinophils may be the main cell type.

Chemotaxis
After extravasation, leukocytes emigrate in tissues toward the site of injury; this is achieved by a process called chemotaxis. Chemotaxis is defined as locomotion oriented along a chemical gradient of chemoattractants. All granulocytes, monocytes and, to a lesser extent, lymphocytes respond to chemoattractants (chemotactic stimuli) with varying rates of speed. Both exogenous and endogenous substances can act as chemoattractants. The former is exemplified by bacterial products. Endogenous chemoattractants, however, include several chemical mediators:
1. Components of the complement system, particularly C5a
2. Products of the lipoxygenase pathway, mainly leukotriene B4 (LTB4)
3. Cytokines (secreted from cells) e.g., IL-8
All the chemoattractants mentioned above bind to specific receptors on the surface of leukocytes. Signals initiated from these receptors result in recruitment & activation of specific leukocytic proteins including tyrosine kinases. These changes eventuate in polymerization of actin that results in increased amounts of this contractile protein at the leading edge of the cell. The leukocyte moves by extending filopodia that pull the back of the cell in the direction of extension, much as a car with front-wheel drive is pulled by the wheels in front.

Leukocyte Activation
This refers to induction of a number of responses within leukocytes, which are mediated by microbes, products of necrotic cells, antigen-antibody complexes, and cytokines. These mediators trigger several
signaling pathways in leukocytes that result in an increase in cytoplasmic Ca\(^{++}\) and activation of enzymes. 

**The activation of leukocytes is reflected functionally as follows:**

1. Production of arachidonic acid (AA) metabolites
2. Secretion of lysosomal enzymes and other microbicidal substances
3. Modulation of leukocyte adhesion molecules allowing firm adhesion to endothelium
4. Activation of macrophages: through the release of IFN-\(\gamma\) (major macrophage-activating cytokine), which is secreted by natural killer (NK) cells.
5. Activation of phagocytosis through stimulation of opsonins-receptors. The process of coating a particle, such as a microbe, to make it vulnerable for phagocytosis is called opsonization; substances that do this are opsonins.

**Phagocytosis (Fig. 3-4)**

Phagocytosis is one of the major functions of the accumulated neutrophils and macrophages at the inflammatory focus, being responsible for eliminating the injurious agents.

Phagocytosis involves three distinct but interrelated steps:

1. Recognition and attachment of the particle to be ingested by the leukocyte
2. Its engulfment, with subsequent formation of a phagocytic vacuole
3. Killing and degradation of the ingested material.

**Recognition and Attachment**

Although neutrophils and macrophages can engulf bacteria without attachment to specific receptors, typically the phagocytosis of microbes and dead cells is initiated by recognition of these particles by receptors expressed on the leukocyte surface. The efficiency of phagocytosis is greatly enhanced when microbes are opsonized by specific proteins (opsonins) for which the phagocytes express high-affinity receptors. The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins.

**Engulfment**

Binding of a particle to phagocytic leukocyte receptors initiates the process of active phagocytosis. During engulfment, extensions of the cytoplasm (pseudopods) flow around the particle to be engulfed, eventually resulting in complete enclosure of the particle within a phagosome created by the plasma membrane of the cell. The limiting membrane of this phagocytic vacuole then fuses with the limiting membrane of a lysosomal granule forming phagolysosome. This fusion results in discharge of lysosomal contents into the phagolysosome.

**Killing and Degradation**

The ultimate step in the elimination of infectious agents and necrotic cells is their killing and degradation within neutrophils and macrophages, which occur most efficiently after activation of these phagocytes.

**Microbial killing is accomplished largely by oxygen-dependent mechanisms, which depends on the production of reactive oxygen species, particularly H2O2. The latter is generally not able to efficiently kill microbes by itself. However, the azurophilic granules of neutrophils contain the enzyme myeloperoxidase (MPO), which, in the presence of Cl\(^{-}\), converts H2O2 to hypochlorite (HOCl). The latter is a potent antimicrobial agent that destroys microbes by halogenation or by oxidation of proteins and lipids (lipid peroxidation). The H2O2-MPO-halide system is the most efficient bactericidal system in neutrophils.**

**Oxygen-independent degradation depends on the release of granules, containing proteolytic enzymes such as defensins (antibacterial peptide attacking bacterial cell membrane), proteolytic enzymes such as elastases, lysozymes, and cationic proteins. The major basic protein of eosinophils has limited bactericidal activity but is cytotoxic to many parasites. After killing, acid hydrolases, which are normally stored in lysosomes, degrade the microbes within phagolysosomes. Macrophages are excellent phagocytes and are particularly good at engulfing and processing antigenic substances and presenting altered antigens to other cells (lymphocytes) for ultimate destruction.**

**Release of leukocyte products and leukocyte-induced Tissue Injury**

During activation and phagocytosis, leukocytes release microbicidal and other products not only within the phagolysosome but also into the extracellular space. The most important of these substances are lysosomal enzymes, reactive oxygen radicals, and products of AA metabolism (including prostaglandins and leukotrienes). These products are capable of causing injuries of the host endothelium and tissues, and may thus amplify the effects of the initial injurious agent. Products of monocytes/macrophages and other
leukocyte types have additional potentially harmful products (see chronic inflammation). Thus, if persistent and unchecked, the leukocyte infiltrate itself becomes harmful. Leukocyte-dependent tissue injury underlies many acute and chronic human diseases as listed in the following table.

Clinical Examples of Leukocyte-Induced Injury

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Acute transplant rejection</td>
<td>Asthma</td>
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<tr>
<td>Asthma</td>
<td>Atherosclerosis</td>
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<tr>
<td>Glomerulonephritis</td>
<td>Chronic lung disease</td>
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<tr>
<td>Reperfusion injury</td>
<td>Chronic rejection</td>
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<tr>
<td>Septic shock</td>
<td></td>
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<tr>
<td>Vasculitis</td>
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Defects in Leukocyte Function
Leukocytes play a central role in host defense. Not surprisingly, therefore, defects in leukocyte function, genetic or acquired, lead to increased vulnerability to infections. Impairments of virtually every phase of leukocyte function—from adherence to vascular endothelium to microbicidal activity—have been identified, and the existence of clinical genetic deficiencies in each step in the process has been described. These defects are manifested clinically by recurrent bacterial infections and impaired wound healing. In practice, the most frequent cause of leukocyte defects is bone marrow suppression, leading to reduced production of leukocytes. This is seen following therapies for cancer (radiation and chemotherapy) and when the marrow space is replaced and destroyed by metastatic cancers to bone.

Contribution of tissue cells to the inflammatory process
There are in addition to leukocytes other cells that are resident in tissues. These also serve important functions in initiating acute inflammation. The two most important of these cell types are mast cells and tissue macrophages. Mast cells react to physical trauma, breakdown products of complement, microbial products, etc. The cells release histamine, leukotrienes, enzymes, and many cytokines (including TNF, IL-1, and chemokines), all of which contribute to inflammation. Macrophages recognize microbial products and secrete most of the cytokines important in acute inflammation. These cells are stationed in tissues to rapidly recognize potentially injurious stimuli and initiate the host defense reaction.

CHEMICAL MEDIATORS OF INFLAMMATION
Chemical mediators are substances that are responsible for many of the inflammatory events. According to their origin, they are either

1. **Plasma-derived** (e.g., complements & kinins): these are present in plasma in precursor forms and need to be activated to function.
2. **Cell-derived:** either
   a. ready-made within intracellular granules (e.g., histamine in mast cell granules) or
   b. synthesized when needed (e.g., prostaglandins, cytokines) in response to a stimulus.

The major cellular sources are platelets, neutrophils, monocytes/macrophages, and mast cells. Most mediators perform their job by binding to specific receptors on target cells. Most mediators have the potential to cause harmful effects that is why their biological actions are short-lived or they are inactivated or degraded rapidly by other substances. One mediator can stimulate the release of other mediators. These secondary mediators may be have identical or similar action to the initial mediators but may also have opposing activities.

The more important mediators of acute inflammation are

1. **Vasoactive amines**
   - Histamine
   - Serotonin

Histamine and serotonin are stored in cells and are therefore among the first mediators to be released during inflammation.

a. Histamine
The richest source of this amine is the mast cells that are normally present in the connective tissue adjacent to blood vessels. It is also found basophils and platelets. Histamine causes dilation of the arterioles and increases the permeability of veins by binding to receptors on endothelial cells.

b. Serotonin (5-hydroxytryptamine) is present in platelets (and enterochromaffin cells). It has actions similar to those of histamine.

Release of serotonin and histamine from platelets (platelet release reaction) occurs when platelets aggregate after contact for e.g. with collagen, thrombin, and antigen-antibody complexes and platelet activating factors (PAF). They are released by mast cells during IgE-mediated immune reactions.

2. Plasma proteins
These belong to three interrelated systems, the complement, kinin, and clotting systems.

a. The complement System is composed of specific proteins found in greatest concentration in plasma. In the process of complement activation, a number of complement components are elaborated to mediate a variety of phenomena in acute inflammation:

i. Vascular phenomena: C3a, C5a stimulate histamine release from mast cells and thereby increase vascular permeability and cause vasodilation.

ii. Chemoattractants: for e.g. C5a is a powerful chemotactic agent for neutrophils, monocytes, eosinophils, and basophils.

iii. Opsonins: when fixed to the bacterial cell wall, C3b acts as an opsonin and favor phagocytosis by neutrophils and macrophages.

b. The kinin System
Initial activation of the kinin system is through the action of XIIa on prekallikrein that lead to the formation of kallikrein. This occurs following the exposure of blood plasma to vascular basement membrane collagen after injury to endothelial cells. Kallikrein has a chemotactic activity, and also directly converts C5 to the chemoattractant C5a. One of the important kinins is the vasoactive bradykinin, which has actions similar to those of histamine.

c. Clotting System
Activation of the clotting system results in the formation of thrombin. Thrombin generates insoluble fibrin clot. It also binds to specific receptors expressed on platelets, endothelial and smooth muscle cells, triggering recruitment of leukocytes. Factor XIIa has two opposing actions; induces clotting and activating the fibrinolytic system through generation of plasmin, which is important in lysing fibrin clots. Such degradation, leads to the formation fibrin degradation (split) products (FDP), which may increase vascular permeability. It is evident from the preceding that coagulation and inflammation are tightly linked. Acute inflammation, by activating or damaging the endothelium, can trigger coagulation and induce thrombus formation. Conversely, the coagulation cascade induces inflammation, primarily via the actions of thrombin.

3. PHOSPHOLIPIDS-DERIVED MEDIATORS
A. Arachidonic acid metabolites: prostaglandins, leukotriens, & lipoxins
On cell activation, arachidonic acid (AA), which is a fatty acid, is released from membrane phospholipids through the action of cellular phospholipase A2 (activated by C5a). AA metabolites are synthesized by two major classes of enzymes:

1. Cyclooxygenases (COX) leading to the generation of prostaglandins (PGs) including thromboxane (TxA2)
2. Lipooxygenases that generate leukotrienes and lipoxins

AA metabolites bind to specific receptors on many cell types and can mediate virtually every step of inflammation. Suppressors of cyclooxygenase activity (aspirin, nonsteroidal anti-inflammatory drugs, and COX-2 inhibitors [coxib]) reduce inflammation in vivo.

Several PGs are important in inflammation including PGI2 (prostacyclin), and thromboxane (TxA2).
Platelets contain the enzyme thromboxane synthetase, and hence TxA2 is the major product in these cells. TxA2 is a potent platelet-aggregating agent and a vasoconstrictor. Vascular endothelium (unlike platelets) lacks thromboxane synthetase but possesses prostacyclin synthetase, which leads to the formation of
prostacyclin. Prostacyclin, has actions opposing that of TxA2 in that it is a vasodilator, a potent inhibitor of platelet aggregation. The prostaglandins are also involved in the pathogenesis of pain and fever in inflammation. PGD2 is the major metabolite of the cyclooxygenase (COX) pathway in mast cells; along with PGE2, it causes vasodilation and increases the permeability of postcapillary venules, thus potentiating edema formation.

In the lipoxygenase pathway, the main products are a family of compounds collectively called leukotrienes. LTB4 is a potent chemotactic agent and activator of neutrophils. Lipoxins are a recent addition to the family of bioactive products generated from AA. Leukocytes, particularly neutrophils, produce lipoxins through their interaction with platelets. The principal actions of lipoxins are to inhibit neutrophil chemotaxis and adhesion to endothelium.

B. Platelet-activating factor (PAF) is another bioactive phospholipid-derived mediator. A variety of cell types, including platelets, basophils (and mast cells), neutrophils, monocytes/macrophages, and endothelial cells, can elaborate PAF. In addition to platelet stimulation, PAF causes vasoconstriction (and bronchospasm), and at extremely low concentrations it induces vasodilation and increased venular permeability with a potency 100 to 10,000 times greater than that of histamine. PAF also causes increased leukocyte adhesion to endothelium (by enhancing integrin-mediated leukocyte binding), chemotaxis, and leukocytes activation. Thus, PAF can elicit most of the cardinal features of inflammation.

4. CYTOKINES AND CHEMOKINES

Cytokines are proteins produced principally activated lymphocytes and macrophages. In addition to being involved in cellular immune responses, they also play important roles in both acute and chronic inflammation. Those relevant to the inflammatory response include Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1), which are the major cytokines that mediate inflammation. The secretion of TNF and IL-1 can be stimulated by endotoxin and other microbial products, immune complexes, and physical injury. Their most important actions in inflammation are:

a. Induce the synthesis of endothelial adhesion molecules and chemical mediators
b. Increase the surface thrombogenicity of the endothelium.
c. Induce the systemic acute-phase responses associated with infection or injury (e.g. fever, loss of appetite, release of neutrophils into the circulation, the release of corticosteroids).

Chemokines are a family of small proteins that act primarily as chemoattractants for specific types of leukocytes, for e.g. IL-8 acts primarily on neutrophils. It is secreted by activated macrophages, endothelial cells, and other cell types and causes activation and chemotaxis of neutrophils, with limited activity on monocytes and eosinophils. Its most important inducers are microbial products and other cytokines, mainly IL-1 and TNF.

5. NITRIC OXIDE (NO)

NO is a soluble gas that is produced by endothelial cells & macrophages (and some neurons in the brain). Since the in vivo half-life of NO is only seconds, the gas acts only on cells in close proximity to where it is produced. NO is a potent vasodilator by virtue of its actions on vascular smooth muscle. In addition, NO reduces platelet aggregation and adhesion & other inflammatory responses. Thus, production of NO reduces many inflammatory responses. Abnormalities in endothelial production of NO occur in atherosclerosis, diabetes, and hypertension. NO and its derivatives are microbicidal, and thus NO is also a mediator of host defense against infection.

6. LYSOSOMAL CONSTITUENTS OF LEUKOCYTES

Neutrophils and monocytes/macrophages contain lysosomal granules, which when released may contribute to the inflammatory response. Neutrophils have two main types of granules

1. The smaller specific (or secondary) granules that contain lysozyme, collagenase, gelatinase, lactoferrin, plasminogen activator, etc.

2. The large azurophil (or primary) granules that contain myeloperoxidase, bactericidal factors (lysozyme, defensins), acid hydrolases, and neutral proteases (e.g. collagenases, proteinase 3).

Both types of granules can empty into phagocytic vacuoles that form around engulfed material, or the granule contents can be released into the extracellular space. Different granule enzymes serve different
functions. Acid proteases degrade bacteria and debris within the phagolysosomes, in which a low (acid) pH is readily reached. Neutral proteases are capable of degrading various extracellular components. These enzymes can attack collagen, basement membrane, fibrin, elastin, and cartilage, resulting in the tissue destruction that accompanies inflammatory processes. Neutrophil elastase has been shown to degrade virulence factors of bacteria and thus combat bacterial infections. Monocytes and macrophages also contain acid hydrolases, collagenase, elastase, phospholipase, and plasminogen activator. These may be particularly active in chronic inflammatory reactions.

Because of the destructive effects of lysosomal enzymes, the initial leukocytic infiltration, if unchecked, can potentiate further increases in vascular permeability and tissue damage. These harmful proteases, however, are held in check by a system of antiproteases in the serum and tissue fluids. Foremost among these is α1-antitrypsin, which is the major inhibitor of neutrophil elastase. A deficiency of these inhibitors may lead to sustained action of leukocyte proteases (progressive tissue damage), as is the case in patients with α1-antitrypsin deficiency.

7. OXYGEN-DERIVED FREE RADICALS

Oxygen-derived free radicals may be released extracellularly from leukocytes after exposure to microbes, chemokines, and immune complexes. Superoxide anion (O2−) hydrogen peroxide (H2O2), and hydroxyl radical (OH) are the major species produced within the cell. Extracellular release of low levels of these potent mediators can amplify the inflammatory response. The physiologic function of these reactive oxygen intermediates is to destroy phagocytosed microbes. At higher levels, release of these potent mediators can damage the tissues. Serum, tissue fluids, and host cells possess antioxidant mechanisms that protect against these potentially harmful oxygen-derived radicals. The influence of oxygen-derived free radicals in any given inflammatory reaction depends on the balance between the production and the inactivation of these metabolites by cells and tissues.

8. NEUROPEPTIDES

Neuropeptides, similar to the vasoactive amines and the AA metabolites, play a role in the initiation and propagation of an inflammatory response. They include substance P, which has many biologic functions, including the transmission of pain signals, regulation of blood pressure, and increasing vascular permeability.

9. OTHER MEDIATORS

The mediators described above account for inflammatory reactions to microbes, toxins, and many types of injury, but may not explain why inflammation develops in some specific situations. Recent studies are providing clues about the mechanisms of inflammation in two frequently encountered pathologic conditions.

a. Response to hypoxia

It is known that hypoxia causes cell injury and necrosis. However, it is also an inducer of the inflammatory response. The latter is mediated by a protein called hypoxia-induced factor 1α, which is produced by cells deprived of oxygen and activates many genes involved in inflammation; one of these leads to the production of vascular endothelium growth factor (VEGF), which increases vascular permeability.

b. Response to necrotic cells

It is well known that necrotic cells elicit inflammatory reactions that serve to eliminate these cells. One participant may be uric acid, which is a product of necrotic cell’s DNA breakdown. Uric acid crystallizes when present at sufficiently high concentrations in extracellular tissues. Uric acid crystals stimulate inflammation and subsequent immune response. This inflammatory action of uric acid is the basis of the disease gout, in which excessive amounts of uric acid are produced and crystals deposit in joints and other tissues.

MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

Many variables may modify the basic inflammatory response; these include

1. The nature and intensity of the injury
2. The site and tissues affected
3. The responsiveness of the host

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Several types of inflammation are recognized, which vary in their morphology and clinical correlates. **Serous inflammation** is characterized by the outpouring of a thin fluid that is derived from either the plasma or the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. In these serous cavities the accumulated fluid is called effusion. (Fig. 3-5) The skin blister resulting from a burn or viral infection represents a large accumulation of serous fluid, either within or immediately beneath the epidermis of the skin.

Fibrinous inflammation
With more severe injuries and the resulting greater vascular permeability, larger molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and deposited in the extracellular space. A fibrinous exudate develops in such cases. The latter also occurs when there is a stimulus for coagulation in the interstitial (e.g., cancer cells). A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium, and pleura. (Fig. 3-6) **Microscopically**, fibrin appears as an eosinophilic meshwork of threads or amorphous coagulated mass. Fibrinous exudates may be removed by fibrinolysis and clearing of other debris by macrophages. However, when the fibrin is not removed, it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue is called organization. When this occurs within the pericardial sac it leads either to opaque fibrous thickening of the pericardium or, more often, to the development of fibrous strands that reduce and may even obliterate the pericardial space.

Suppurative (purulent) inflammation
This is characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid. Certain bacteria (e.g., staph. aureus, St. pyogenes, Pneumococci, gonococci, meningococci and E. coli) produce this localized suppuration and are therefore called pyogenic (pus-producing) bacteria. A common example of an acute suppurative inflammation is **acute (suppurative) appendicitis**. (Fig. 3-7)

An **abscess** is a localized collection of purulent inflammatory fluid (pus) caused by suppuration buried in a tissue, an organ, or a confined space. Pus is a thick creamy yellow or blood-stained fluid. Abscesses are produced by deep seeding of pyogenic bacteria into a tissue. They have a central region that appears as a mass of necrotic leukocytes and tissue cells. There is usually a zone of preserved neutrophils around this necrotic focus, and outside this region vascular dilation and fibroplastic proliferation occur, indicating the beginning of repair. In time, the abscess may become walled off and ultimately replaced by connective tissue. A common example of an abscess is the skin furuncle. (Fig. 3-8)

**Ulcers**

An ulcer is a local defect, or excavation of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue. Ulceration occurs only when tissue necrosis and resultant inflammation exist on or near a surface. It is most commonly encountered in:

1. Inflammatory necrosis of mucosa-lined cavities e.g. mouth, larynx, stomach, intestines, or genitourinary tract. (Fig. 3-9)
2. Subcutaneous inflammation of the lower extremities in older persons who have circulatory disturbances that predispose to extensive necrosis.

Ulcerations are best exemplified by peptic ulcer of the stomach or duodenum, in which acute and chronic inflammation coexist.

Pseudomembranous inflammation of mucous membranes
Severe injury may be associated with extensive epithelial necrosis with sloughing. This creates large shallow ulcers. Fibrin, dead epithelium, neutrophils, red cells and bacteria mix together to produce a white or cream-colored false (pseudo-) membrane covering the affected mucosa. Diphtheria and pseudomembranous colitis are typical examples. (Fig. 3-10)

**EFFECTS OF ACUTE INFLAMMATION**

**Beneficial Effects**

1. Dilution of Toxins by the edema fluid
2. Production of protective Antibodies & promotion of immunity
3. Fibrin meshwork formation that forms a scaffold for inflammatory cell migration & also limits the spread of infections

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4. Cell Nutrition

Harmful Effects
1. Swelling & edema that can be detrimental for e.g. acute epiglottitis that may be life threatening (Fig. 3-11)
2. Rise in tissue pressure that contributes to tissue necrosis
3. Digestion of adjacent viable tissue
4. Severe damaging allergic reaction
5. Generalized increase in vascular permeability can cause shock as seen in anaphylactic reactions.

OUTCOMES OF ACUTE INFLAMMATION
In general, acute inflammation may have one of three outcomes
1. Complete resolution
   The battle between the injurious agent and the host may end with restoration of the site of acute inflammation to normal. This is called resolution and is the usual outcome when
   a. the injury is limited or short-lived
   b. there has been little tissue destruction
   c. the damaged parenchymal cells can regenerate
2. Healing by fibrosis
   This occurs
   a. after extensive tissue destruction
   b. when the inflammatory injury involves tissues that are incapable of regeneration
   c. when there is abundant fibrin exudation.

When the fibrinous exudate in tissue or serous cavities (pleural, peritoneal, synovial) cannot be adequately cleared, connective tissue grows into the area of exudate, converting it into a mass of fibrous tissue—a process also called organization.
3. Progression to chronic inflammation
   Acute to chronic transition occurs when the acute inflammatory response persists, owing either to the perseverance of the injurious agent or to some interference with the normal process of healing. For example, failure of acute bacterial pneumonia to resolve may lead to extensive tissue destruction and formation of a cavity in which the inflammation continues to smolder, leading eventually to a chronic lung abscess.

CHRONIC INFLAMMATION
Although it may follow acute inflammation, it frequently begins from the outset as a chronic (chronic inflammation ab initio), insidious, and low-grade, smoldering response. Chronic inflammation is the cause of tissue damage in some of the most common and disabling human diseases, such as rheumatoid arthritis, atherosclerosis, tuberculosis, and chronic lung diseases.

Chronic Inflammation may complicate acute inflammation. The latter is almost always a suppurative type of inflammation that presents as a purulent discharge (pus) as seen in abscess. The cause is either a delay in the evacuation of an abscess, or presence of foreign body within inflamed area (dirt, wood, metal or a sequestrated bone).

Causes of chronic inflammation ab initio include
1. Persistent infections by certain microorganisms such as tubercle bacilli, Treponema pallidum, certain viruses, fungi, and parasites. These organisms are of low toxicity and evoke delayed type hypersensitivity reaction.
2. Prolonged exposure to toxic agents either endogenous as inhaled silica particles, or endogenous such as toxic plasma lipids that are thought to be responsible for atherosclerosis. The latter is thought to be a chronic inflammatory process of the arterial wall.
3. Autoimmunity
   Under certain conditions, immune reactions develop against the individual's own tissues, leading to autoimmune diseases. In these diseases, autoantigens activate a self-perpetuating immune reaction that
results in chronic inflammation with associated tissue damage. Examples of this type include several common chronic inflammatory diseases, such as rheumatoid arthritis and lupus erythematosus. Morphologic features of chronic inflammation
In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, chronic inflammation is characterized by:
1. Infiltration with mononuclear cells including macrophages, lymphocytes, and plasma cells.
2. Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.
3. Attempts at healing by fibrosis of the damaged tissue, achieved by proliferation of small blood vessels (angiogenesis) & fibroblasts. (Fig. 3-12)
Mononuclear cell infiltration
The macrophage is the dominant cells in chronic inflammation. The mononuclear phagocyte system (reticuloendothelial system) consists of closely related cells of bone marrow origin, including blood monocytes and tissue macrophages. The latter are diffusely scattered in connective tissues or located in organs such as the liver (Kupffer cells), spleen and lymph nodes (sinus histiocytes), and lungs (alveolar macrophages). From the blood, monocytes migrate into various tissues and differentiate into macrophages. The half-life of blood monocytes is about 1 day, whereas the life span of tissue macrophages is several months or years. When the monocyte reaches the extravascular tissue, it undergoes transformation into a larger phagocytic cell, the macrophage. Macrophages may be activated by a variety of stimuli, including cytokines (e.g., IFN-γ) secreted by sensitized T lymphocytes, NK cells, bacterial endotoxins, and other chemical mediators. Activation results in increased cell size, and greater ability to phagocytose and kill ingested microbes. Activated macrophages secrete a wide variety of biologically active products that result in the tissue injury and fibrosis. In short-lived acute inflammation, if the irritant is eliminated, macrophages eventually disappear (dying off or travel through lymphatics to lymph nodes). In chronic inflammation, macrophage accumulation persists, and this is mediated by the following:
1. Recruitment from circulating monocytes, a process fundamentally similar to that of neutrophils.
2. Local proliferation of macrophages after their emigration from the bloodstream. This is now known to occur prominently in some chronic inflammatory lesions, such as atheromatous plaques.
3. Immobilization of macrophages within the site of inflammation. Certain cytokines and oxidized lipids can cause such immobilization (migration inhibiting factors).
The products of activated macrophages serve to eliminate injurious agents such as microbes and to initiate the process of repair, but are also responsible for much of the tissue injury in chronic inflammation; these products include
1. Toxic substances to microbes and host cells (e.g., toxic O2 species, NO, and proteases)
2. Chemoattractants to other inflammatory cells
3. Growth factors the cause of fibroblast proliferation, collagen deposition, and angiogenesis.
Other cells in chronic inflammation
Other cell types present in chronic inflammation include lymphocytes, plasma cells, eosinophils, and mast cells:
Lympocytes are mobilized in immune and nonimmune inflammation. Antigen-stimulated T and B-cells use various adhesion molecules (predominantly the integrins) and chemokines to migrate into inflammatory sites. Lymphocytes and macrophages interact in a bidirectional way and these reactions play an important role in chronic inflammation. Macrophages display antigens to T cells that stimulate them. Activated T lymphocytes produce cytokines, and one of these, IFN-γ, which is a major activator of macrophages.
Plasma cells develop from activated B lymphocytes and produce antibody directed against persistent antigen in the inflammatory site.
Eosinophils are abundant in immune reactions mediated by IgE and in parasitic infections. The recruitment of eosinophils involves extravasation from the blood and their migration into tissue by processes similar to those for other leukocytes. One of the chemokines that is especially important for eosinophil recruitment is eotaxin. Eosinophils have granules that contain major basic protein that is toxic to parasites.
Mast cells are widely distributed in connective tissues and participate in both acute and persistent inflammatory reactions. Mast cells express on their surface the receptor that binds the Fc portion of IgE antibody. In acute reactions, IgE antibodies bound to the cells' Fc receptors specifically recognize antigen,
and the cells degranulate and release mediators, such as histamine and products of AA oxidation. Mast cells are also present in chronic inflammatory reactions, and may produce cytokines that contribute to fibrosis. 

**Neutrophils** although characteristic of acute inflammation, many forms of chronic inflammation continue to show large numbers of neutrophils, induced either by persistent microbes or by mediators produced by macrophages and T lymphocytes. In chronic bacterial infection of bone (osteomyelitis), a neutrophilic exudate can persist for many months. Neutrophils are also important in the chronic damage induced in lungs by smoking and other irritant stimuli.

Mediators of chronic inflammation (Fig. 3-13)

Examples of chronic inflammation

**Chronic Cholecystitis** may be the sequel to repeated bouts of acute cholecystitis, but in most instances it develops de novo. **Like acute cholecystitis it is almost always associated with gallstones** but these do not seem to have a direct role in the initiation of inflammation. Rather, supersaturation of bile predisposes to both chronic inflammation and, in most instances, stone formation. Microorganisms, usually E. coli and enterococci, can be cultured from the bile in only about one-third of cases. The gallbladder may be contracted, of normal size, or enlarged. The submucosa and subserosa are often thickened from fibrosis. In the absence of superimposed acute cholecystitis, mural lymphocytes are the only feature of inflammation. (Fig. 3-14)

**GRANULOMATOUS INFLAMMATION**

This is a distinctive pattern of chronic inflammatory reaction characterized by focal accumulations of activated macrophages, which often develop an epithelioid (epithelial-like) appearance.

**Causes**

Granulomatous inflammation is encountered in a number of immunologically mediated infectious and some noninfectious conditions, these include

1. Tuberculosis
2. Sarcoïdosis
3. Cat-scratch disease
4. Lymphogranuloma inguinale
5. Leprosy
6. Brucellosis
7. Syphilis
8. Some fungal infections
9. Berylliosis
10. Reactions of irritant lipids

Recognition of granulomas in a biopsy specimen is important because it shortens the list of the differential diagnosis. A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelioid cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells. The epithelioid cells have a pale pink granular cytoplasm with indistinct cell borders and a vesicular nucleus that is oval or elongate. Older granulomas develop an enclosing rim of fibroblasts and connective tissue. Frequently, epithelioid cells fuse to form giant cells in the periphery or sometimes in the center of granulomas. These **giant cells** may attain diameters of 40 to 50 µm. (Fig. 3-15) They have a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (foreign body-type giant cell).

There are two types of granulomas, which differ in their pathogenesis.

1. **Foreign body granulomas**, which are provoked by foreign bodies. Typically, foreign body granulomas form when material such as talc (associated with intravenous drug abuse), sutures, or other fibers are large enough to preclude phagocytosis by a single macrophage and do not incite any specific inflammatory or immune response. Epithelioid cells and giant cells form and are apposed to the surface of the foreign body and/or actually include it. The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it appears refractile. (Fig. 3-16)

2. **Immune granulomas**; these are caused by insoluble, poorly degradable or particulate particles, typically microbes that are capable of inducing a cell-mediated immune response. In these responses, macrophages engulf the inciting agent, process it, and present some of it to appropriate T lymphocytes, causing them to become activated. The responding T cells produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which is important in activating macrophages and transforming them into epithelioid cells and multinucleate giant cells.
The typical example of an immune granuloma is that caused \(M.\) tuberculosis. In tuberculosis, the granulomatous reaction is referred to as a tubercle and is classically characterized by the presence of central caseous necrosis, whereas caseation is rare in other granulomatous diseases. (Fig. 3-17) It is always necessary to identify the specific etiologic agent by special stains for organisms (e.g., acid-fast stains for tubercle bacilli), by culture methods (e.g., in tuberculosis and fungal diseases), by molecular techniques (e.g., the polymerase chain reaction in tuberculosis), and by serologic studies (e.g., in syphilis). In sarcoidosis, the etiologic agent is unknown and the diagnosis is that of exclusion. (Fig. 3-18)

LYMPHATICS IN INFLAMMATION

Lymph nodes filters the extravascular fluids brought to them by lymphatic vessels. They represent a secondary line of defense that operates whenever a local inflammatory reaction fails to contain and neutralize an external agent, such as a microbe. Lymphatics are delicate channels that are difficult to visualize in ordinary tissue sections because they readily collapse. In inflammation lymph flow is increased and helps drain the edema fluid from the extravascular space. Not only fluid, but also leukocytes and cell debris may find their way into lymph. The drainage may transport the offending agent (chemical or microbial). The lymphatics may become secondarily inflamed (lymphangitis), as may the draining lymph nodes (lymphadenitis). Therefore, it is not uncommon in infections of the hand, for example, to observe red streaks along the entire arm up to the axilla following the course of the lymphatics (lymphangitis), accompanied by painful enlargement of the axillary lymph nodes (lymphadenitis). The nodal enlargement is usually caused by hyperplasia of the lymphoid follicles as well as by hyperplasia of the phagocytic cells lining the sinuses of the lymph nodes (reactive or inflammatory lymphadenitis). In severe infections, the lymph nodes may be overwhelmed and fail to halt the spread of infection. The organisms gain access to the vascular circulation, thus inducing a bacteremia. The phagocytic cells of the liver, spleen, and bone marrow constitute the next line of defense, but in massive infections, bacteria seed distant tissues of the body. The heart valves, meninges, kidneys, and joints are favored sites of implantation for blood-borne organisms, and when this happens; endocarditis, meningitis, renal abscesses, and septic arthritis may develop.

SYSTEMIC EFFECTS OF INFLAMMATION

The systemic changes associated with inflammation, especially infections, are collectively called the acute phase response (Systemic inflammatory response syndrome [SIRS]). These changes are reactions to cytokines produced in response to bacterial infections and other inflammatory stimuli. The acute phase response consists of several clinical and pathologic changes:

1. Fever is a prominent manifestation; it is produced in response to pyrogens that act by stimulating PG synthesis in the vascular and perivascular cells of the hypothalamus.
2. Acute-phase proteins are plasma proteins, mostly synthesized in the liver, and whose plasma concentrations may increase several hundred times in inflammation. The best-known of these are
   a. C-reactive protein (CRP)
   b. Fibrinogen
   c. Serum amyloid A protein (SAA).

   CRP and SAA, bind to microbial cell walls acting as opsonins and fixing complement. The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly than individual erythrocytes. This is the basis for the elevation of the ESR. Prolonged production of SAA causes secondary amyloidosis in destructive chronic inflammations (e.g., rheumatoid arthritis). Elevated serum levels of CRP are now used as a marker for increased risk of myocardial infarction in patients with atherosclerotic coronary artery disease. The inflammation involving atherosclerotic plaques in the coronary arteries may predispose to thrombosis and subsequent infarction, and CRP is produced during inflammation. On this basis, anti-inflammatory agents are being tested in patients to reduce the risk of myocardial infarction.
3. Leukocytosis is a common feature of the acute phase response, especially those induced by bacterial infection. The leukocyte count usually rises to 15,000 or 20,000 cells/\(\mu\)l, but sometimes it may reach very high levels of 40,000 to 100,000 cells/\(\mu\)l. These extreme elevations are referred to as leukemoid reactions because they are similar to the white cell counts obtained in leukemia. The leukocytosis occurs initially because of accelerated release of cells from the bone marrow reserve pool (induced by cytokines, including
IL-1 and TNF) and is therefore associated with a rise in the number of more immature neutrophils in the blood (shift to the left). Prolonged infection also induces proliferation of precursors in the bone marrow, caused by increased production of colony stimulating factors (CSFs). Neutrophilia refers to an increase in the blood neutrophil count. Most bacterial infections induce neutrophilia. Viral infections such as infectious mononucleosis, mumps, and German measles produce a leukocytosis due to absolute lymphocytosis. In bronchial asthma, hay fever, and parasitic infestations, there is an absolute increase in the number of eosinophils, creating an eosinophilia. Certain infections (typhoid fever and infections caused by viruses, rickettsiae, and certain protozoa) are associated with a decreased number of circulating white cells (leukopenia). Leukopenia is also encountered in infections that overwhelm patients debilitated by disseminated cancer or uncontrolled tuberculosis.

4. Other manifestations of the acute phase response include increased pulse and blood pressure; decreased sweating; rigors, and anorexia.

5. Disseminated intravascular coagulation (DIC) & septic shock: in severe bacterial infections (sepsis), the large amounts of organisms and lipopolysaccharides (LPS) in the blood stimulate the production of enormous quantities of TNF and IL-1. High levels of TNF cause DIC. LPS and TNF induce tissue factor (TF) expression on endothelial cells, which initiates coagulation; the same agents inhibit natural anticoagulation mechanisms. Cytokines cause liver injury and impaired liver function, resulting in a failure to maintain normal blood glucose levels due to a lack of gluconeogenesis from stored glycogen. Overproduction of NO by cytokine-activated cardiac myocytes and vascular smooth muscle cells leads to heart failure and loss of perfusion pressure, respectively, resulting in cardiogenic shock. The clinical triad of DIC, hypoglycemia, and cardiovascular failure is described as septic shock. Multiple organs show inflammation and intravascular thrombosis, which can produce organ failure. Lung damage (adult respiratory distress syndrome [ARDS]) results when neutrophil-mediated endothelial injury allows fluid to escape from the blood into the airspaces. The kidney and the bowel are also injured, largely due to reduced perfusion. Septic shock is often fatal.

CONSEQUENCES OF DEFECTIVE OR EXCESSIVE INFLAMMATION

Defective inflammation typically results in
1. Increased susceptibility to infections
2. Delayed healing or repair of wounds
3. Tissue damage

Delayed repair is due to the fact that the inflammatory response provides the necessary stimulus to get the repair process started.

Excessive inflammation is the basis of many categories of human disease that include allergies and autoimmune diseases.

Recent studies, however, are pointing to an important role of inflammation in a wide variety of human diseases that are not primarily disorders of the immune system. These include
1. Cancer
2. Atherosclerosis
3. Ischemic heart disease
4. Some neurodegenerative diseases such as Alzheimer disease.

In addition, prolonged inflammation and the fibrosis that accompanies it are responsible for much of the pathology in many chronic infectious, metabolic and other diseases. Since these disorders are some of the major curses of mankind, it is not surprising that the normally protective inflammatory response is being called the "silent killer".
CHAPTER FOUR
TISSUE REPAIR

REGENERATION & HEALING BY FIBROSIS
Critical to survival is the ability to repair the damage caused by injurious agents & inflammation. Repair refers to the restoration of tissue architecture and function after an injury. This occurs by regeneration &/or healing.

Regeneration: complete reinstitution of the damaged components of the affected tissue i.e. the tissue essentially returns to a normal state.

Healing is a reparative process characterized by laying down of connective (fibrous) tissue that results in scar formation. This mode occurs when
1. The injured tissues are incapable of complete regeneration, or
2. The supporting structures of the tissue are severely damaged
Although the resulting fibrous scar is not normal, it provides enough structural stability that allows the injured tissue to function. Both regeneration and healing by fibrosis contribute in varying degrees to the ultimate repair.

Repair involves
a. The proliferation of various cells, and
b. Close interactions between cells and the extracellular matrix (ECM).

Therefore, an understanding of the process of repair requires some knowledge of the control of cell proliferation and the functions of the ECM.

THE CONTROL OF CELL PROLIFERATION
Several cell types proliferate during tissue repair. These include
1. The remnants of the injured tissue (which attempt to restore normal structure)
2. Vascular endothelial cells (to create new vessels that provide the nutrients for the repair process)
3. Fibroblasts (the source of the fibrous tissue that fills defects).

The proliferation of the above cell types is driven by growth factors. The production of polypeptide growth factors, responses of cells to these factors, and the ability of these cells to divide and expand in numbers are all important determinants of the adequacy of the repair process.

The normal size of cell populations in any given tissue is determined by a balance of cell proliferation, cell death by apoptosis, and emergence of new differentiated cells from stem cells (Fig. 4-1).

THE CELL CYCLE
The cell cycle represents the sequence of events that control DNA replication & mitosis in the proliferation of cells. It consists of a series of steps at which the cell checks for the accuracy of the process and instructs itself to proceed to the next step (Fig. 4-2). The cycle consists of the presynthetic growth phase 1 (G₁), the DNA synthesis phase (S), the premitotic growth phase 2 (G₂), and the mitotic phase (M). Non-dividing cells are either in cell cycle arrest in G₁ or they exit the cycle to enter a phase called G₀. Any stimulus that initiates cell proliferation, such as exposure to growth factors, needs to promote the G₀/G₁ transition and the entry of cells into the G₁. Further progression is determined by the ability of the cell to pass through an intrinsic quality control mechanism for cell integrity, known as checkpoint control. Checkpoint controls prevent DNA replication or mitosis of damaged cells and either transiently stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells by apoptosis. Progression through the cell cycle from G₁ is regulated by proteins called cyclins, which form complexes with enzymes called cyclin-dependent kinases (CDKs). These complexes regulate the phosphorylation of proteins involved in cell cycle progression leading to DNA replication and mitosis, and thus are required for cell cycle progression.

A major action of growth factors is to overcome the checkpoint controls by liberating the suppression of CDK activity. Once cells enter the S phase, the DNA is replicated and the cell progresses through G₂ and mitosis.
Proliferative Capacities of Tissues
Tissue repair is critically influenced by the intrinsic proliferative capacity of the constituent cells. Based on this criterion, the tissues of the body are divided into three groups:

1. Continuously Dividing Tissues (labile tissues): cells of these tissues are continuously being lost and replaced by maturation from stem cells and by proliferation of mature cells. Labile cells include hematopoietic cells in the bone marrow and the majority of surface epithelia. These tissues can readily regenerate after injury provided the pool of stem cells is preserved.

2. Stable Tissues: cells of these tissues are quiescent (in the G0 stage of the cell cycle) and have only minimal replicative activity in their normal state. However, these cells are capable of proliferating in response to injury or loss of tissue mass. Stable cells constitute the parenchyma of most solid tissues, such as liver & kidney. They also include endothelial cells, fibroblasts, and smooth muscle cells; the proliferation of these cells is particularly important in wound healing. With the exception of liver, stable tissues have a limited capacity to regenerate after injury.

3. Permanent Tissues: cells of these tissues are terminally differentiated and nonproliferative in postnatal life. The majority of neurons and cardiac muscle cells belong to this category. Accordingly, injury to brain or heart is irreversible and results in a scar. Skeletal muscle is usually classified as a permanent tissue, but satellite cells attached to the endomysial sheath provide some regenerative capacity for this tissue.

Stem Cells
In most continuously dividing tissues the mature cells are terminally differentiated and short-lived. As mature cells die they are compensated for by identical differentiated cells generated from stem cells. Thus, in these tissues there is a homeostatic equilibrium between the replication and differentiation of stem cells and the death of the mature, fully differentiated cells. Such relationships are particularly evident in the multilayered epithelium of the skin and the gastrointestinal tract, in which stem cell positions have been identified near the basal layer of the epithelium. Cells differentiate progressively as they migrate to the upper layers of the epithelium; they ultimately die and are shed from the surface of the tissue.

Stem cells are characterized by two important properties:
1. Self-renewal capacity
2. Asymmetric replication.

Asymmetric replication of stem cells means that after each cell division, some progeny enter a differentiation pathway, while others remain undifferentiated, retaining their self-renewal capacity. Stem cells with the capacity to generate multiple cell lineages (pluripotent stem cells) can be isolated from embryos and are called embryonic stem (ES) cells. As mentioned above, stem cells are normally present in proliferative tissues and generate cell lineages specific for the tissue. However, it is now recognized that stem cells with the capacity to generate multiple lineages are present in the bone marrow and several other tissues of adult individuals. These cells are called tissue stem cells or adult stem cells. Whether tissue stem cells have similar differentiation capacity (differentiation plasticity) as ES cells remains the subject of active research and much dispute. Bone marrow stem cells have the ability to generate fat, cartilage, bone, endothelium, and muscle.

The new field of regenerative medicine has a main objective of regeneration and repopulation of damaged organs using ES or adult stem cells. One of the most exciting prospects in this field is the type of stem cell therapy known as therapeutic cloning. The main steps of this procedure are illustrated in (Figure 4-3)

Other potential therapeutic strategies using stem cells involve transplanting stem cells into areas of injury, mobilization of stem cells from the bone marrow into injured tissue, and the use of stem cell culture systems to produce large amounts of differentiated cells for transplantation into injured tissue.

GROWTH FACTORS
Cell proliferation can be triggered by
1. Growth factors
2. Hormones
3. Cytokines

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4. Signals from the ECM

The polypeptide growth factors have a major role of promoting cell survival and proliferation, which are important in regeneration and healing. Thus, these proteins expand cell populations by stimulating cell division as well as by promoting cell survival through protection from apoptotic death. Most growth factors also stimulate migration, differentiation, & the synthesis of specialized proteins (such as collagen in fibroblasts).

They induce cell proliferation by binding to specific receptors and by doing so affect the expression of genes through
1. Relieving blocks on cell cycle progression (thus promoting replication),
2. Preventing apoptosis
3. Enhancing the synthesis of cellular proteins in preparation for mitosis

A major activity of growth factors is to stimulate the function of growth control genes, many of which are protooncogenes (so named because mutations in them lead to unrestrained cell proliferation characteristic of neoplasia (oncogenesis). Many of the growth factors that are involved in repair are produced by leukocytes that are recruited & activated at the site of injury, as part of the inflammatory process. Other growth factors are produced by the specialized tissue (parenchymal) cells or the stromal (connective tissue) cells in response to cell injury or loss.

Signaling Mechanisms of Growth Factor Receptors
The major intracellular signaling pathways induced by growth factor receptors are similar to those of many other cellular receptors that recognize extracellular ligands. The binding of a ligand to its receptor triggers a series of events by which extracellular signals are transduced into the cell, leading to the stimulation or repression of gene expression. Signaling may occur directly in the same cell (autocrine signaling e.g. lymphocyte proliferation induced by cytokines in some immune responses), between adjacent cells (paracrine signaling e.g. recruiting inflammatory cells to the site of infection & in wound healing), or over greater distances (endocrine signaling e.g. a hormone, is released into the bloodstream and acts on target cells at a distance) (Fig. 4-4).

The binding of a ligand to its cell surface receptor leads to a cascade of secondary intracellular events that culminate in transcription factor activation or repression, leading to cellular responses. Transcription factors bind to gene promoters and enhancers to trigger or inhibit transcription.

EXTRACELLULAR MATRIX (ECM) AND CELL-MATRIX INTERACTIONS

Tissue repair depends not only on growth factor activity but also on interactions between cells and ECM components. The ECM is a dynamic, constantly remodeling macromolecular complex synthesized locally, which assembles into a network that surrounds cells. It constitutes a significant proportion of any tissue. By supplying a substrate for cell adhesion and serving as a reservoir for growth factors, ECM regulates the proliferation, movement, and differentiation of the cells living within it. Synthesis and degradation of ECM accompanies wound healing & chronic fibrotic processes.

ECM occurs in two basic forms:
1. Interstitial matrix, which is present in the spaces between mesenchymal (connective tissue) cells, and between epithelium and supportive vascular and smooth muscle structures; it is synthesized by the mesenchymal cells (e.g., fibroblasts). Its major constituents are fibrillar and nonfibrillar collagens, as well as fibronectin, elastin, proteoglycans, hyaluronate, and other elements.
2. Basement membrane, which lies beneath the epithelium and is synthesized by overlying epithelium and underlying mesenchymal cells; it tends to form a platelike "chicken wire" mesh. Its major constituents are amorphous nonfibrillar type IV collagen and laminin.

Functions of the ECM
1. Mechanical support for cell anchorage and migration, and maintenance of cell polarity
2. Control of cell growth by signaling through cellular receptors of the integrin family.
3. Maintenance of cell differentiation through the type of ECM proteins, also acting largely via cell surface integrins.

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4. Scaffolding for tissue renewal: the maintenance of normal tissue structure requires a basement membrane or stromal scaffold. The integrity of the basement membrane or the stroma of the parenchymal cells is critical for the organized regeneration of tissues. It is particularly noteworthy that although labile and stable cells are capable of regeneration, injury to these tissues results in restitution of the normal structure only if the ECM is not damaged. Disruption of these structures leads to collagen deposition and scar formation.
5. Establishment of tissue microenvironments: basement membrane acts as a boundary between epithelium and underlying connective tissue and also forms part of the filtration apparatus in the kidney.
6. Storage and presentation of regulatory molecules. For example, growth factors like FGF is excreted and stored in the ECM in some tissues. This allows the rapid deployment of growth factors after local injury, or during regeneration.

Components of the Extracellular Matrix
There are three basic components of ECM:
1. Fibrous structural proteins (collagens and elastins) that confer tensile strength and recoil.
2. Water-hydrated gels (proteoglycans and hyaluronan), which permit resilience and lubrication
3. Adhesive glycoproteins that connect the matrix elements to one another and to cells.

Collagen
The collagens are fibrous structural proteins that confer tensile strength; without them human beings would be reduced to a clump of cells connected by neurons. Collagens are composed of three separate polypeptide chains braided into a ropelike triple helix. About 30 collagen types have been identified. Some collagen types (e.g., types I, II, III, and V) form fibrils. The fibrillar collagens form a major proportion of the connective tissue in healing wounds and particularly in scars. The tensile strength of the fibrillar collagens derives from their cross-linking. This process is dependent on vitamin C; therefore, children with ascorbate deficiency have skeletal deformities, bleed easily because of weak vascular wall basement membrane, and heal poorly. Genetic defects in these collagens cause diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome. Other collagens are nonfibrillar and may form basement membrane (type IV), or be a component of intervertebral discs (type IX) or dermal-epidermal junctions (type VII).

Elastin
The ability of tissues to recoil and return to a baseline structure after physical stress is conferred by elastic tissue. This is especially important in the walls of large vessels (which must accommodate recurrent pulsatile flow of blood), as well as in the uterus, skin, and ligaments. Elastic fibers differ from collagen by having fewer cross-links. The fibrillin meshwork serves as a scaffold for the deposition of elastin and assembly of elastic fibers; defects in fibrillin synthesis lead to skeletal abnormalities and weakened aortic walls (Marfan syndrome).

Proteoglycans and Hyaluronan
Proteoglycans form highly hydrated compressible gels conferring resilience and lubrication (such as in the cartilage in joints). They consist of long polysaccharides called glycosaminoglycans linked to a protein backbone. Hyaluronan, a huge molecule composed of many disaccharide repeats without a protein core, is also an important constituent of the ECM. Because of its ability to bind water, it forms a viscous, gelatin-like matrix. Besides providing compressibility to a tissue, proteoglycans also serve as reservoirs for growth factors secreted into the ECM (e.g., FGF). Proteoglycans can also be integral cell membrane proteins and have roles in cell proliferation, migration, and adhesion.

Adhesive Glycoproteins and Adhesion Receptors
Adhesive glycoproteins and adhesion receptors are structurally diverse molecules involved in cell-to-cell adhesion, the linkage between cells and ECM, and binding between ECM components. The adhesive glycoproteins include fibronectin (major component of the interstitial ECM) and laminin (major constituent of basement membrane). The adhesion receptors, also known as cell adhesion molecules (CAMs), are grouped into four families:
1. Immunoglobulins
2. Cadherins
3. Selectins
4. Integrins

Fibronectin is synthesized by a variety of cells, including fibroblasts, monocytes, and endothelium. Fibronectins have specific domains that bind to a wide spectrum of ECM components. Tissue fibronectin
forms fibrillar aggregates at wound healing sites; plasma fibronectin binds to fibrin to form the provisional blood clot of a wound, which serves as a background for ECM deposition and re-epithelialization. **Laminin** is the most abundant glycoprotein in basement membrane that connects cells to underlying ECM components such as type IV collagen and heparan sulfate. Besides mediating attachment to basement membrane, laminin can also modulate cell proliferation, differentiation, and motility. **Integrins** are a family of transmembrane glycoproteins composed of α and β chains that are the main cellular receptors for ECM components, such as fibronectins and laminins. Some integrins are leukocyte surface molecules that mediate firm adhesion and transmigration across endothelium at sites of inflammation, and also play a role in platelet aggregation. Integrins are present in the plasma membrane of most animal cells, with the exception of red blood cells. They bind to many ECM components initiating signaling cascades that can affect cell locomotion, proliferation, and differentiation. Integrin signal transduction utilizes the same intracellular signaling pathways used by growth factor receptors. In this manner, extracellular mechanical forces can be coupled to intracellular synthetic and transcriptional pathways.

**CELL AND TISSUE REGENERATION**

Cell renewal occurs continuously in labile tissues, such as the bone marrow, gut epithelium, and the skin. Damage to epithelia or an increased loss of blood cells can be corrected by the proliferation and differentiation of stem cells and, in the bone marrow, by proliferation of more differentiated progenitors. The renewal of hematopoietic cells is driven by growth factors called colony-stimulative factors (CSFs), which are produced in response to increased consumption or loss of blood cells. Tissue regeneration can occur in parenchymal organs with stable cell populations, but with the exception of the liver, this is usually a limited process. The surgical removal of a kidney elicits in the contralateral kidney a compensatory response that consists of both hypertrophy and hyperplasia of proximal duct cells. The regenerative response of the liver that occurs after surgical removal of hepatic tissue is striking. Up to 60% of the liver may be removed in a procedure called living-donor transplantation, in which a portion of the liver is resected from a normal individual and is transplanted into a recipient with end-stage liver disease (Fig. 4-5), or after partial hepatectomies performed for tumor removal. In such cases, the tissue resection triggers proliferation of the remaining hepatocytes (normally quiescent). Experimentally, hepatocyte replication after partial hepatectomy is initiated by cytokines (e.g., tumor necrosis factor [TNF] and interleukin 6 [IL-6]).

EGF (epidermal growth factor receptor, or EGFR) with intrinsic tyrosine kinase activity, is mitogenic for hepatocytes and most epithelial cells, including keratinocytes. In cutaneous wound healing EGF is produced by keratinocytes, macrophages, and other inflammatory cells. The main EGFR (referred to as EGFR1) is frequently overexpressed in lung and some brain tumors and is an important therapeutic target for the treatment of these conditions. ERB B2 (also known as HER-2/NEU) has received great attention because of its overexpression in breast cancers, in which it is a target for effective cancer control. It should be emphasized that extensive regeneration or compensatory hyperplasia can occur only if the residual tissue is structurally and functionally intact, as after partial surgical resection. By contrast, if the tissue is damaged by infection or inflammation, regeneration is incomplete and is accompanied by scarring.

**REPAIR BY CONNECTIVE TISSUE**

Healing or repair by connective tissue is encountered if:

1. A severe or persistent (chronic) tissue injury that result in damage to parenchymal cells as well as the stromal framework
2. Injury affects nondividing cells

Under these conditions, repair occurs by replacement of the nonrenewed cells with connective tissue, or by a combination of regeneration of some cells and scar formation.

Repair begins within 24 hours of injury by the emigration of fibroblasts and the induction of fibroblast and endothelial cell proliferation. By 3 to 5 days, a specialized type of tissue that is characteristic of healing, called **granulation tissue** is apparent. The term granulation tissue derives from the pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound. Its microscopic appearance is characterized by proliferation of fibroblasts and new thin-walled, delicate capillaries (angiogenesis), in a loose ECM.
Granulation tissue then progressively accumulates connective tissue matrix, eventually resulting in the formation of a scar (Fig. 4-6), which may remodel over time.

Repair by connective tissue deposition consists of four sequential processes:

1. Formation of new blood vessels (angiogenesis)
2. Migration and proliferation of fibroblasts
3. Deposition of ECM (scar formation)
4. Maturation and reorganization of the fibrous tissue (remodeling)

Angiogenesis (neoangiogenesis)

The preexisting vessels send out capillary sprouts to produce new vessels. Angiogenesis is a critical process in healing at sites of injury, in the development of collateral circulations at sites of ischemia, and in allowing tumors to increase in size beyond the limits of their original blood supply. It has recently been found that endothelial precursor cells may migrate from the bone marrow to areas of injury and participate in angiogenesis at these sites. Much work has been done to understand the mechanisms underlying angiogenesis, and therapies to either enhance the process (e.g., to improve blood flow to a heart ruined by coronary atherosclerosis) or inhibit it (to interfere with tumor growth) are being developed.

New vessels formed during angiogenesis are leaky. This leakiness explains why granulation tissue is often edematous, and accounts in part for the edema that may persist in healing wounds long after the acute inflammatory response has resolved. Several factors induce angiogenesis, but the most important are VEGF and basic fibroblast growth factor (FGF-2). VEGF stimulates both proliferation and motility of endothelial cells, thus initiating the process of capillary sprouting. In angiogenesis involving endothelial cell precursors from the bone marrow, VEGF acts through VEGFR-2 to mobilize these cells from the bone marrow and to induce proliferation and motility of these cells at the sites of angiogenesis.

Migration of Fibroblasts and ECM Deposition (Scar Formation)

Scar formation builds on the granulation tissue framework of new vessels and loose ECM that develop early at the repair site. It occurs in two steps:

1. Migration and proliferation of fibroblasts into the site of injury and
2. Deposition of ECM by these cells.

The recruitment and stimulation of fibroblasts is driven by many growth factors, including PDGF. One source of this factor is the activated endothelium, but more importantly, growth factors are also elaborated by inflammatory cells. Macrophages, in particular, are important cellular constituents of granulation tissue, and besides clearing extracellular debris and fibrin at the site of injury, they elaborate a host of mediators that induce fibroblast proliferation and ECM production. Mast cells and lymphocytes can contribute directly or indirectly to fibroblast proliferation and activation.

As healing progresses, the number of proliferating fibroblasts and new vessels decreases; however, the fibroblasts progressively become more synthetic, and hence there is increased deposition of ECM. Collagen synthesis, in particular, is critical to the development of strength in a healing wound site. Collagen synthesis by fibroblasts begins early in wound healing (days 3 to 5) and continues for several weeks, depending on the size of the wound. The same growth factors that regulate fibroblast proliferation also participate in stimulating ECM synthesis. Net collagen accumulation, however, depends not only on increased synthesis but also on diminished collagen degradation. Ultimately, the granulation tissue scaffold evolves into a scar composed of largely inactive, spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components. As the scar matures, there is progressive vascular regression, which eventually transforms the highly vascularized granulation tissue into a pale, largely avascular scar. Many growth factors are involved in the above processes, including TGF-β, PDGF, and FGF as well as cytokines (IL-1 & TNF).

ECM and Tissue Remodeling

The transition from granulation tissue to scar involves shifts in the composition of the ECM; even after its synthesis and deposition, scar ECM continues to be modified and remodeled. The outcome of the repair process is, in part, a balance between ECM synthesis and degradation. The degradation of collagens and other ECM components is accomplished by a family of matrix metalloproteinases (MMPs), which are dependent on zinc ions for their activity. MMPs include interstitial enzymes that degrade collagen, fibronectin, proteoglycans, & laminin. MMPs are produced by a variety of cell types (fibroblasts, macrophages, neutrophils, synovial cells), and their synthesis and secretion are regulated by growth factors, cytokines, and other agents. Their synthesis may be suppressed pharmacologically with steroids.
CUTANEOUS WOUND HEALING
This is a process that involves both epithelial regeneration and the formation of connective tissue scar and is thus illustrative of the general principles that apply to wound healing in all tissues. The events are orchestrated by interplay of growth factors and ECM.
Cutaneous wound healing has three main phases:
inflammation
formation of granulation tissue
ECM deposition and remodeling
Larger wounds also contract during the healing process. Events in wound healing overlap to a great extent and cannot be completely separated from each other.
Based on the nature of the wound, the healing of cutaneous wounds can occur by first or second intention.
Healing by First Intention
One of the simplest examples of wound repair is the healing of a clean, uninjured surgical incision approximated by surgical sutures. This is referred to as primary union or healing by first intention. The incision causes only focal disruption of epithelial basement membrane continuity and death of a relatively few epithelial and connective tissue cells. As a result, epithelial regeneration predominates over fibrosis. A small scar is formed, but there is minimal wound contraction.
The narrow incisional space first fills with fibrin-clotted blood. Within 24 hours, neutrophils are seen at the incision margin, migrating toward the fibrin clot. Within 24 to 48 hours, epithelial cells from both edges have begun to migrate and proliferate along the dermis. The cells meet in the midline beneath the surface scab, yielding a thin but continuous epithelial layer.
By day 3, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Epithelial cell proliferation continues, yielding a thickened epidermal covering layer.
By day 5, neovascularization reaches its peak as granulation tissue fills the incisional space. The epidermis recovers its normal thickness as differentiation of surface cells yields a mature epidermal architecture with surface keratinization.
During the second week, there is continued collagen accumulation and fibroblast proliferation that bridge the incision. The leukocyte infiltrate, edema, and increased vascularity are diminished. The long process of “blanching” begins, accomplished by increasing collagen deposition within the incisional scar and the regression of vascular channels.
By the end of the first month, the scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis. The tensile strength of the wound increases with time. However, the dermal appendages destroyed in the line of the incision are permanently lost (Fig. 4-7)
Healing by Second Intention (healing by secondary union)
When cell or tissue loss is more extensive, the repair process is more complex, the inflammatory reaction is more intense, there is abundant development of granulation tissue, and the wound contracts by the action of myofibroblasts. This is followed by accumulation of ECM and formation of a large scar. This mode of healing occurs in .Large wounds, Abscesses, Ulcerations, and After infarction in parenchymal organs. (Fig. 4-7 & 4-8)
Secondary healing differs from primary healing in several respects:
A larger clot or scab rich in fibrin and fibronectin forms at the surface of the wound. Inflammation is more intense because large tissue defects have a greater volume of necrotic debris, exudate, and fibrin that must be removed.
Much larger amounts of granulation tissue are formed. A greater volume of granulation tissue generally results in a greater mass of scar tissue.
Secondary healing involves wound contraction. Within 6 weeks, for example, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction. This process has been ascribed to the presence of myofibroblasts, which are modified fibroblasts exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells.
Wound Strength
Carefully sutured wounds have approximately 70% of the strength of unwounded skin, largely because of the placement of the sutures. When sutures are removed, usually at 1 week, wound strength is approximately 10% of that of unwounded skin, but this increases rapidly over the next 4 weeks. The recovery of tensile strength results from collagen synthesis exceeding degradation during the first 2 months, and from structural modifications of collagen (e.g., cross-linking and increased fiber size) when synthesis declines at later times. Wound strength reaches approximately 70% to 80% of normal by 3 months but usually does not substantially improve beyond that point.

PATHOLOGIC ASPECTS OF REPAIR
Wound healing may be affected by several external or internal influences that reduce the quality or adequacy of the reparative process. Particularly important are infections and diabetes. These adverse influences include
1. Infection is the single most important cause of delay in healing; it prolongs the inflammation phase of the process and potentially increases the local tissue injury.
2. Nutrition has profound effects on wound healing; protein deficiency & vitamin C deficiency, inhibits collagen synthesis and retards healing.
3. Glucocorticoids (steroids) have anti-inflammatory effects, and their administration may result in poor wound strength due to diminished fibrosis. In some instances, however, the anti-inflammatory effects of glucocorticoids are desirable. For example, in corneal infections, glucocorticoids are sometimes prescribed (along with antibiotics) to reduce the likelihood of opacity that may result from collagen deposition.
4. Mechanical variables such as increased local pressure or torsion may cause wounds to pull apart, or dehiscence i.e. open out or gape.
5. Poor perfusion, due either to arteriosclerosis and diabetes or to obstructed venous drainage (e.g. in varicose veins), also impairs healing
6. Foreign bodies such as fragments of steel, glass, or even bone impede healing.
7. The type (and volume) of tissue injured is critical. Complete restoration can occur only in tissues composed of stable and labile cells; even then, extensive injury will probably result in incomplete tissue regeneration and at least partial loss of function. Injury to tissues composed of permanent cells must inevitably result in scarring with, at most, attempts at functional compensation by the remaining viable elements. Such is the case with healing of a myocardial infarct.
8. The location of the injury and the character of the tissue in which the injury occurs are also important. For example, inflammation arising in tissue spaces (e.g., pleural, peritoneal, synovial cavities) develops extensive exudates. Subsequent repair may occur by digestion of the exudate, initiated by the proteolytic enzymes of leukocytes and resorption of the liquefied exudate. This is called resolution, and in the absence of cellular necrosis, normal tissue architecture is generally restored. However, in the setting of larger accumulations, the exudate undergoes organization: granulation tissue grows into the exudate, and a fibrous scar ultimately forms.
Aberrations of cell growth and ECM production
This may occur even in what begins as normal wound healing.
1. Keloid refers to the accumulation of exuberant amounts of collagen that give rise to prominent, raised scars. (Fig. 4-9). There appears to be a heritable predisposition to keloid formation, and the condition is more common in blacks.
2. Exuberant granulation: healing wounds may also generate excessive granulation tissue that protrudes above the level of the surrounding skin and hinders re-epithelialization. The restoration of epithelial continuity requires cautery or surgical resection of the granulation tissue.
3. Disabling fibrosis associated with chronic inflammatory diseases such as rheumatoid arthritis, pulmonary fibrosis, and cirrhosis have many similarities to those involved in normal wound healing. In these diseases, however, persistent stimulation of fibrogenesis results from chronic immune reactions that sustain the synthesis and secretion of growth factors, fibrogenic cytokines, and proteases. Collagen degradation by collagenases, normally important in wound remodeling, is responsible for much of the joint destruction seen in rheumatoid arthritis. (Fig. 4-10)