KING SAUD UNIVERSITY

COLLEGE OF MEDICINE

INFLAMMATION AND REPAIR FOR MEDICAL STUDENTS

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INFLAMMATION AND REPAIR

5 Lectures

OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:

Upon completion of these lectures, the student should:

1. Define inflammation.
2. Recognize the cardinal signs of inflammation.
3. List cells & molecules that play important roles in inflammation
4. Compare between acute and chronic inflammation
5. Describe the sequence of vascular changes in acute inflammation (vasodilation, increased permeability) and their purpose.
6. Know the mechanisms of increased vascular permeability.
7. Define the terms edema, transudate, and exudate.
8. Describe the steps involved in extravasation of leukocytes from the blood to the tissues. Know the steps at which selectins and integrins act.
9. Describe the meaning and utility of chemotaxis. Understand the role that chemokines play in inflammation.
10. Describe the steps involved in phagocytosis and the role of IgG and C3b as opsonins and receptors.
11. Know various defect in leukocyte function.
12. Chemical mediators of inflammation are numerous). You should learn the cellular sources and major effects of the mediators and, conversely, list the most likely mediators of each of the steps of inflammation.
13. Compare and contrast acute vs chronic inflammation with respect to causes, nature of the inflammatory response, and tissue changes.
14. Compare and contrast the clinical settings in which different types of inflammatory cells (eg, neutrophils, eosinophils, monocyte-macrophages, and lymphocytes) accumulate in tissues. Compare and contrast the contents of neutrophil and eosinophil granules.
15. Distinguish between fibrinous, purulent, and serous inflammation. Define an abscess.
16. Describe the systemic manifestations of inflammation and their general physiology, including fever, leukocyte left shift, and acute phase reactants.
17. Describe the differences between the various cell types (ie, labile, stable, and permanent cells) in terms of their regeneration potential. List examples of each cell type.
18. Know the factors that are most important in determining whether regeneration will restore normal tissue architecture.
19. List the three main phases of cutaneous wound healing.
20. Compare and contrast the difference between healing by primary intention and healing by secondary intention.
21. List factors which are associated with delayed wound healing.
22. List complication of wound healing.

TAKE HOME MESSAGES:

1. Inflammation, the local response of the vascularised living tissue to injury.
2. Could be acute or chronic.
3. Several cells & molecules that play important roles in inflammation.
4. Inflammation has vascular and cellular events to eliminate the cause.
5. Vascular events include vasodilation and increased permeability to deliver a protein rich fluid to site of inflammation.
6. Several steps are involved in extravasation of leukocytes from the blood to the tissues.
7. Phagocytosis is important step to get rid of necrotic material and bacteria.
8. Various defect in leukocyte function are present.
9. Chemical mediators are important in many events in inflammation. Their action should be under control to prevent excessive tissue damage
10. Paterns of acute inflammation include fibrinous, purulent, and serous inflammation.
11. The systemic manifestations of inflammation include fever, leukocyte left shift, and acute phase reactants.
12. the various cell types (ie, labile, stable, and permanent cells) affect the outcome of healing.
13. Three main phases of cutaneous wound healing: formation of granulation tissue, fibrosis and contraction.
14. Healing by primary intention occur in surgical clean wound and healing by secondary intention occur when excessive tissue damage is present.
15. Several factors are associated with delayed wound healing.
16. Complication of wound healing include failure of healing, contracture and excessive scar formation.

FURTHER READING:

- Kumar, Cotran and Robbins: Basic pathology, 8th edition.

Keywords:

inflammation, acute, chronic, vasodilation, increased , permeability, edema, transudate, and exudates, chemotaxis, phagocytosis, chronic granulomatous disease chemical mediators, fibrinous inflammation, purulent inflammation, serous inflammation, abscess, ulcer, fistula, fever, leukocyte left shift, and acute phase reactants, healing, repair, fibrosis, labile cells, stable cells, permanent cells, granulation tissue, fibrosis, contraction, healing by primary intention, healing by scondary intention, complication of wound healing. Scar, resolution, anorexia leucocytosis purulent, collagen, interferons, macrophages, regeneration, replacement.

Inflammation

Inflammation, the local response of the vascularised living tissue to injury. It is fundamentally a vascular phenomenon. Inflammation is a protective response intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult. Inflammation accomplishes its protective mission by diluting, destroying, or neutralizing harmful agents (e.g., microbes and toxins). It then sets into motion the events that eventually heal and repair the sites of injury.
The suffix "itis" is added to the base word to state the condition as in appendix/appendicitis and spleen/splenitis.
The 5 ancient cardinal signs of inflammation are:

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

Causes of tissue injury are those physical and chemical agents; they range from simple mechanical tissue disruption to the effects of irradiation. The inflammation can be caused by bacteria, viruses, parasites, fungi, thermal injuries, immunological injuries, foreign bodies and toxic substances.
Although inflammation helps clear infections and other noxious stimuli and initiates repair, the inflammatory reaction and the subsequent repair process can cause considerable harm. The components of the inflammatory reaction that destroy and eliminate microbes and dead tissues are capable of also injuring normal tissues. Therefore, inflammation is terminated when the offending agent is eliminated and the secreted mediators are broken down or dissipated. There are active anti-inflammatory mechanisms that serve to control the response and prevent it from causing excessive damage to the host.

Cells of the inflammatory process: **Neutrophils** phagocytize a foreign material (e.g. bacteria) and then attempt to oxidize and digest it through oxidase and proteases. These are the first inflammatory cells on the scene after tissue injury. **Eosinophils** are also phagocytic and possess many of the enzymes of the neutrophil. In addition, they can dispense antihistamine in an area of histamine release. The **eosinophil** is also associated with allergic responses. It is seen in both acute and chronic inflammation and become increased in parasitic infestations.

Lymphocytes are simple-appearing cells with varied and complex functions. Briefly, some lymphocytes are in the T-cell system and produce various type of lymphokines, which have local effects. Immunoglobulins or antibodies can also be produced by this cell as a B cell. The lymphocyte characterizes chronic inflammation. Antibody production is the function of **the plasma cell**, a specialized B cell, which is also found in chronic inflammation. It is especially prominent in chronic inflammation involving mucosal surfaces.

Cells of Inflammation

Cell	Activity	Phagocytosis	Inflammation
Neutrophil	Proteases, oxidases	+	Acute
Eosinophil	Antihistamine	+	Acute, chronic
Macrophage (modified monocytes)	Antigen processing, digestion	+	Late acute, chronic
Lymphocyte	Lymphokines	-	Chronic
Plasma cell	Antibody production	-	Chronic

There are other components that play important roles in inflammation including plasma proteins (mediators of inflammation), cells of vascular walls (source of mediators), extracellular matrix (ECM) proteins and cells of the surrounding connective tissue (for repair).

Types of Inflammation

Classically, inflammation has been divided into acute (immediate, short duration) and chronic (protracted) varieties. Granulomatous inflammation is also regarded as a type of chronic inflammation.

Acute inflammation	Chronic inflammation
▣ rapid in onset (seconds or minutes) ▣ relatively short duration, lasting for minutes, several hours, or a few days ▣ its main characteristics: ▪ the exudation of fluid and plasma proteins (edema) ▪ the emigration of leukocytes, predominantly neutrophils.	▣ is of longer duration ▣ associated histologically with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis, and tissue necrosis. ▣ Less uniform.

Acute inflammation

Systemically, acute inflammation may be accompanied by fever. There may be a peripheral blood leukocytosis, especially of neutrophils, along with increased number of immature forms of neutrophils ("left shift").

Acute inflammation has three main events:

(1) Hemodynamic changes

(alterations in vascular caliber that lead to an increase in blood flow)

(2) Increased vascular permeability

(structural changes in the microvasculature that permit plasma proteins and leukocytes to leave the circulation)

(3) Emigration of the leukocytes from the microcirculation

(their accumulation in the focus of injury, *and their activation* to eliminate the offending agent)

Locally, it is **the vascular response** to tissue injury that is fundamental. The initial response to tissue injury is an episode lasting from seconds to 5 minutes of arteriolar **vasoconstriction**, probably as a direct effect on the vessels. In several minutes, the precapillary arterioles dilate, resulting in greater blood flow to the area. This lasts as long as the acute inflammation persists. The injured area reddens from **increased blood flow**. This is accompanied by **increased vascular permeability** lead to outpouring of protein-rich fluid in the extravascular tissues. As a consequence, **interstitial edema** (swelling) occurs owing to the escape of intravascular fluid, called an exudate. As a result, there will be slowing of the circulation due to increased permeability of the microvasculature. This will leads to stasis (slow circulation due to dilated small vessels packed with red cells). The purpose is to allow neutrophil to move toward the endothelium then to cross the blood vessel to the site of injury.

Transudate, exudate and pus. A **transudate** results when increased intravascular fluid escapes into the interstitial tissues related **to increased hydrostatic pressure** in the vessels. A good example is the pedal (ankle) edema seen in congestive heart failure. This fluid has low protein content and specific gravity (< 1.020). In acute inflammation, the edema is caused by the escape of fluid into the interstitial tissues related to increased vascular permeability. This fluid is called an **exudate**. Because more protein escapes with the fluid compared with that which occurs with a transudate, an exudate has a higher protein content and specific gravity (> 1.020). **Pus** consists mostly of neutrophils and necrotic derbis, being high in protein content with a specific gravity greater than 1.020.

Characteristics of transudate, exudate and pus

Fluid type	Condition	Content	Specific gravity
Transudate	Increased hydrostatic pressure	Low protein	< 1.020
Exudate	Acute inflammation	High protein	> 1.020

Mechanisms lead to increased vascular permeability:

1. Endothelial cell contraction, most common mechanism forming gap between enotheluim within 15-30 min, occur in venules and mediated mainly by the actions of histamine and leukotrienes on endothelium.
2. Endothelial injury
    a. immediate sustained response, 6-24 hours.
    b. delayed prolonged leakage, 12 hours- days.
3. Leukocyte-mediated endothelial injury.
4. Transcytosis (occurs via channels formed by fusion of intracellular vesicles).
5. Leakage from new blood vessels.

Then, the lymphatic vessels admit the escaped fluid into the lymphatic system and after several days the swelling subsides.

Cellular events in acute inflammation. Cellular events begin soon after vasodilatation. Leukocytes (especially polymorphouclear leukocytes) move from the center of the blood column in a vessel to the periphery (margination) and begin to adhere to the endothelium (pavementing). There are three stages to this process mediated by different cell adhesion mechanisms (**Rolling** - neutrophils roll along the endothelium in close contact, **Adhesion** - neutrophils adhere firmly to the endothelium and **Aggregation** - adjacent neutrophils adhere to each other and undergo shape changes).

Later, the leukocytes move from the vessels into the interstitial tisues (transendothelial emigration). Neutrophils actively emigrate from vessels into tissues down a concentration gradient of chemotactic factors (C5a, LTB4, bacterial components, chemokines). Initially, it is the neutrophils that emigrate in the greatest number, whereas lymphocytes, macrophages and eosinophils also take part in this process, initially in fewer numbers. As the inflammation regresses, decreasing numbers of neutrophils emigrate, whereas more lymphocytes and macrophages make the trip and finally predominate when the process becomes chronic with the disappearance of the neutrophils.

At site of injury, phagocytosis of offending agent occurs by neutrophils. Neutrophils have membrane receptors for the Fc portion of antibodies, complement factors bound to foreign particles, and bacterial polysaccharides. Neutrophils do not phagocytose material to which they do not bind. Steps of phagocytosis include: (1) The neutrophil binds to the abnormal particle by its specific receptors. The cell pushes out pseudopodia to surround the particle, driven by assembly and disassembly of actin filaments. (2) The pseudopodia fuse to enclose the abnormal particle completely, forming an endocytic vesicle. Special proteins probably allow final sealing of the membrane. (3) The internalized particle in the endocytic vesicle is called a phagosome. (4) The phagosome fuses with neutrophil granules, particularly primary granules, which discharge their contents, exposing the particle to a potent mixture of **lysosomal enzymes**. If the particle is a bacterium, killing is enhanced by hydrogen peroxide, superoxide and halide, which are generated by the enzymatic reduction of oxygen by respiratory burst oxidases (Oxygen dependent pathway).

Defects in Leukocyte Function

Since leukocytes play a central role in host defense, it is not surprising that defects in leukocyte function, both acquired and inherited, lead to increased susceptibility to infections, which may be recurrent and life-threatening. The most common causes of defective inflammation are bone marrow suppression caused by tumors and chemotherapy or radiation (resulting in decreased leukocyte numbers), and metabolic diseases such as diabetes.

The genetic disorders are rare, examples:

Defects in leukocyte adhesion: defective synthesis of the CD18 β subunit of the leukocyte integrins or the absence of sialyl-Lewis X. This leads to impaired leukocyte adhesion to and migration through endothelium, and defective phagocytosis and generation of an oxidative burst.

Defects in microbicidal activity: An example is chronic granulomatous disease, a genetic deficiency in one of the several components of the phagocyte oxidase responsible for generating ROS. In these patients, engulfment of bacteria does not

result in activation of oxygen-dependent killing mechanisms. In an attempt to control these infections, the microbes are surrounded by activated macrophages, forming the "granulomas" that give the disease its distinctive pathology and its name.

Defects in phagolysosome formation: One such disorder, Chédiak-Higashi syndrome, is an autosomal recessive disease that results from disordered intracellular trafficking of organelles, ultimately impairing the fusion of lysosomes with phagosomes.

Mediators of acute inflammation

Many factors that mediate the events of acute inflammation have been documented. These chemical mediators of inflammation are important, as the process can be modified by drug therapy to minimize unwanted and potentially damaging effects. The mediators either come from cells or are plasma derived. Plasma-derived mediators gain entry to the damaged area via the inflammatory exudate. They are mostly precursor proteins, which are activated by proteolytic enzymes and, once activated, generally have short half-lives. Once in tissues, they are rapidly inactivated by a variety of enzymatic or scavenging systems.

Histamine is the main preformed mediator of inflammation. Released from mast cells, basophils and platelets, it causes transient dilatation of arterioles, increases permeability in venules, and is the primary cause of increased vascular permeability in the first hour after injury.

Both prostaglandins and leukotrienes are derived by local synthesis from arachidonic acid. This long-chain fatty acid is liberated from cell membranes by activation of the enzyme, phospholipase A_2. There are two main pathways in arachidonic acid metabolism:

1. The **cyclo-oxygenase pathway** produces: thromboxane A_2 (TXA_2), which aggregates platelets and causes vascular constriction; prostacyclin (PGI_2), which inhibits platelet aggregation and dilates vessels; and stable prostaglandins (PGE_2, $PGF_{2\alpha}$, PGD_2), which cause vasodilatation and increase vascular permeability. PGE_2 also causes pain.
2. The **lipoxygenase pathway** produces leukotrienes (LTC_4, LTD_4, LTE_4), which cause vasoconstriction and increase permeability in venules. Leukotriene LTB_4 stimulates leukocyte adhesion to endothelium.

Platelet-activating factor (PAF) is synthesized by mast cells/basophilsl, platelets, neutrophils, monocytes, and endothelium, it is a specialized phospholipid compound that causes vasoconstriction, increased vascular permeability, and platelet aggregation, and is at least 1000 times more potent than histamine. It also stimulates the synthesis of arachidonic acid metabolites.

Cytokines are polypeptide products of activated lymphocytes and monocytes. The main cytokines participating in acute inflammation are interleukin (IL)-1, IL-8, and tumor necrosis factor α (TNFα). These are responsible for:

- Induction of cell adhesion molecules on endothelium.
- Induction of PGI_2 (prostacyclin) synthesis.
- Induction of PAF synthesis.
- Fever, anorexia, and stimulation of acute-phase protein synthesis by the liver.
- Stimulation of fibroblast proliferation and secretory activity.

- Attraction of neutrophils into damaged area (IL-8).

Interferon-γ INF- γ & Interleukin (IL-12) activate lymphocytes and macrophages in chronic Inflammation.

The chemokines are a family of factors secreted by leukocytes and endothelial cells in response to tissue damage and to other inflammatory mediators. They are locally bound to the extracellular matrix and heparin-sulphate proteoglycans of cells, and establish a concentration gradient away from the focus of inflammation. Neutrophil rolling causes neutrophils to encounter chemokines bound to proteoglycans on endothelial cells. Specific chemokine receptors are activated, and this signals for activation of leukocyte integrins, mediating adhesion and emigration.

Nitric oxide is a small molecule that is locally synthesized by endothelium and macrophages through the activity of the enzyme nitric oxide synthase. It is a powerful cause of vascular dilatation, and increases vascular permeability. As an important reactive oxygen intermediary it can also mediate cell and bacterial killing.

The complement system comprises a set of plasma proteins with important roles in immunity and inflammation. There is a cascade of activation, with production of numerous intermediary activated peptides. The main products with roles in acute inflammation are as follows:

- C3a increases vascular permeability by liberating histamine from mast cells/platelets.
- C5a increases vascular permeability by liberating histamine from mast cells/platelets, is chemotactic to neutrophils, and induces endothelial cell adhesion molecules.
- C345 complex is chemoattractive to neutrophils.
- C3b opsonizes bacteria and facilitates neutrophil phagocytosis.

The **kinins** are small peptides derived from plasma precursors by proteolytic cleavage. The system is activated by one of the coagulation proteins, activated **Hageman factor** (**Factor XII**); this cleaves the peptide prekallikrein to kallikrein. Kallikrein stimulates a high molecular weight kininogen to form bradykinin, which is a powerful mediator of increased vascular permeability, causes pain, and activates the complement system.

The **clotting pathway** is responsible for coagulation of blood by formation of fibrin from fibrinogen. Factor XII (Hageman factor) is activated in the inflammatory exudate when it comes into contact with collagen outside the vessel. It then stimulates the deposition of fibrin, activates the kinin system, and also stimulates the thrombolytic system. When fibrinogen is converted to fibrin, fibrinopeptides are formed. These cause increased vascular permeability, as well as being chemotactic for neutrophils.

The **thrombolytic pathway.** The enzyme plasmin (generated by plasminogen activator derived from endothelium by the action of bradykinin) is a proteolytic enzyme with several roles in inflammation.

Plasmin:

- activates the complement system.
- activates Hageman factor.
- lyses fibrin to form fibrin degradation products, which increase the permeability of vessels.

In acute inflammation these factors act in concert to bring about the structural and functional changes.

Vasodilation	Prostaglandins Histamine Nitric oxide
Increased vascular permeability	Vasoactive amines (histamine & serotonin) Bradykinin Leukotrienes C4, D4, E4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	C5a Leukotriene B4 Chemokines IL-1, TNF Bacterial products
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes Oxygen metabolites Nitric oxide

The outcome of acute inflammation may be removal of the exudate with restoration of normal tissue architecture (resolution); transition to chronic inflammation; or extensive destruction of the tissue resulting in scarring.

Chronic inflammation

The preponderance of lymphocytes, plasma cells and macrophages in acute inflammation heralds the transition from acute to chronic inflammation. **Chronic inflammation may also arise de novo**. Whereas acute inflammation lasts days to weeks, chronic inflammation lasts months to years. Chronic inflammation is seen following acute inflammation when tissue injury persists. De novo chronic inflammation may be due to low-pathogenicity bacteria or chemical and physical agents that produce lower levels of tissue damage. Macrophages, lymphocytes, plasma cells, occasionally eosinophils, and even a few neutrophils are seen in chronic inflammation.

Patterns of chronic inflammation include:

A. **Granulation tissue and chronic inflammation**. **Granulation tissue** is often associated with chronic inflammation. It represents a healing phase following acute inflammation. **Endothelial proliferation** is prominent. At first, the interstitial tissue is edematous with an admixture of acute and chronic inflammatory cells; later, it is dominated by chronic inflammatory cells. Eventually, fibroblasts dominate in the interstitial tissues. Externally,

granulation tissue has a red granular appearance due to endothelial proliferation.

B. **Granulomatous inflammation**: a type of chronic inflammation: Substances present in the inflammatory response that are not digestible by neutrophils may evoke granlomatous inflammation. Characteristic of this type of chronic inflammation are granulomas, which form 0.5 to 2.0 mm aggregations of epithelioid macrophages surrounded by a rim of lymphocytes. Epithelioid macrophages have an appearance suggestive of squamous epithelial cells due to their abundant pink cytoplasm. Granulomatous inflammation may be caused by foreign bodies, mycobacterial infection (e.g. tuberculosis, leprosy, Schistosomiasis, the gumma of tertiary syphilis, cat-scratch disease, lymphogranuloma venereum, tularemia and others). **At times, the granuloma contains caseous (cheese-like) necrosis as in tuberculosis.** Multinucleated giant cells form from the cytoplasmic fusion of macrophages. A variation of the multinucleated or foreign body giant cell is the Langhan's giant cell which has nuclei arranged peripherally.

Gross configurations of acute and chronic inflammation.

Acute and chronic inflammation conform themselves into several appearances. **Fibrinous inflammation** consists of neutrophils admixed with fibrin (e.g., fibrinous pericarditis). An effusion of fluid under acute inflammatory conditions from a surface (often mesothelial) is called **serous inflammation**. **Suppurative inflammation** exudes pus, a mixture of neutrophils and necrotic debris. An enclosed collection of pus is called an **abscess.** It may open to the surface with draining of pus, forming a **sinus** (blind tract open to the surface). **Fistula** occurs as a complication, which is a formation of inflammatory tract between two surfaces. Mucosa-lined surfaces may exhibit **catarrhal inflammation** with the outpouring of **watery mucus**. Any **ulcer** is a focal defect usually on an epithelial surface where the epithelium is entirely lacking; the exposed tissue is covered by a fibrinopurulent exudate (mixture of fibrin and neutrophils). Finally, the term **cellulitis** denotes a spreading acute inflammation through interstitial tissues.

Systemic Effects of Inflammation

Fever: cytokines (TNF, IL-1) stimulate production of prostaglandins in hypothalamus.
Production of acute-phase proteins: C-reactive protein, others; synthesis stimulated by cytokines (IL-6, others) acting on liver cells
Leukocytosis: cytokines (colony-stimulating factors) stimulate production of leukocytes from precursors in the bone marrow with formation of immature band neutrophils, *shift to the left*).
Others: In some severe infections, septic shock (fall in blood pressure), disseminated intravascular coagulation, metabolic abnormalities can occur and are induced by high levels of TNF.

Regeneration and repair

Regeneration and repair of a damage tissue occur through the reproduction of the normal, parent tissue or fibrosis (scar). Whether regeneration or repair or both occurs depends on the regenerative capacity of the original damaged cells. **Labile cells** are rapidly regenerating cells (short life span), which can be readily regenerated. Epidermis is an example. **Stable cells** are longer-lived cells with a slower mitotic rate, but given proper conditions, these cells can regenerate to some extent. Liver and renal tubular cells are an example. Lastly, **permanent cells** have a long life span with no mitotic activity in post natal life. The neurons of the central nervous system are an example.

Supporting tissues. **The collagens**, a series of complex polypeptides, bind epithelial and the various connective tissues to themselves and each other where appropriate, thus providing tensile strength. **Fibroblasts** secrete collagen.

Basement membranes lie at the interface of cells and stroma. They support the overlying cells. Materials found in basement membranes include entactin, heparin sulfate, laminin, proteoglycan and type IV collagen.

Healing by first intention (primary union). Healing by first intention occurs when wound edges are approximated and the wound is quickly covered with epithelium and bound together by collagen. At first, the surface epithelial gap and apposed edges of the connective tissue contain blood clot and debris. Epithelium is regenerated from the edges of the wound. Capillaries, neutrophils, macrophages and fibrocytes migrate into the clot. Within a few days, the scab (patch of dried, clotted blood) at the surface falls revealing re-epithelialization and the blood clot in the apposed tissues is removed by macrophages. Endothelial cells proliferate with the laying down of collagen by fibroblasts, **producing granulation tissue**. The phagocytic neutrophils progressively decrease in number as macrophages increase. As collagen in the gap increases, the blood vessels in the area decrease in number, and the scar begins to contract. Healing by first intention is best exemplified by the healing of an apposed surgical incision.

Healing by second intention (secondary union). Edges of the wound cannot be apposed in healing by second intention, leaving a defect containing blood clot and debris.

The process of wound healing is similar to that of first intention, but it takes much longer. The same cells take part in this process. Granulation tissue is much more pronounced.

In both types of healing, the wound contracts in the later stages due to the presence of the **myofibroblast,** a contractile cell that has properties of both fibroblasts and smooth muscle cells. Tensile strength of the wound in both kinds of healing gradually increases with more fibroblast activity and the laying down of collagen.

Abnormal repair. Wound repair does not always go well. **Bacterial infection of the wound,** the presence of **foreign bodies, poor blood supply**, and **lack of mobility** may retard healing. Deficient scar formation may result from **deficiencies of vitamin C or severe protein deficiencies.** Retarded wound healing and deficient scar formation may cause wound separation at wound margin: a **wound dehiscence.** If a large wound cannot be totally covered by epithelium, the resulting ulcer may require a skin graft. The laying down of excessive collagen results in **keloid and fibrous adhesions formation. Wound contractures** is related to the action of myofibroblasts. **This is seen especially following burns.**

Questions: Inflammation and Repair

Choose one answer to complete the following statements.

Q.1 Pain in acute inflammation is mediated by:

A] Bradykinin.
B] Histamine.
C] Protaglandins.
D] Leukotrienes.
E] Oxygen radicals.

Q.2 All of the following are true of neutrophils except:

A] Phagocytize bacteria.
B] Contain oxidases and proteases.
C] First on scene after tissue injury.
D] Release histamine.
E] Release complement C3b.

Q.3 The vascular response in acute inflammation.

A] Is initially a vasodilatation followed by vasoconstriction.
B] Involves the emigration of neutrophils into the interstitial tissues before other inflammatory cells.
C] Allows leukocytes to move from the periphery to the center of the column of blood in a vessel.
D] Results in a transudate.
E] Results in leukocyte pavementing the adventitia of blood vessels.

Q.4 An exudate is best described as:

A] A fluid low in protein content with a specific gravity of less than 1.020.
B] A fluid high in protein content with a specific gravity of less than 1.020.
C] A fluid high in protein content with a specific gravity of more than 1.020.
D] A fluid with large amounts of neutrophils and necrotic material.
E] A clear yellowish fluid rich in monocytes.

Q.5 The cardinal (principal) sign of swelling associated with acute inflammation results from:

A] Arteriolar constriction.
B] Arteriolar dilatation.
C] Veinous obstruction.
D] Outpouring of protein-rich fluid into tissues.
E] Proliferation of fibroblasts.

Q.6 Which one of the following is responsible for the pain in acute inflammation?

A] Hageman factor.
B] Adenosine disphosphate (ADP).
C] Platelet factor III.
D] Histamine.
E] Bradykinin.

Q.7 After severe inflammation with necrosis of cells, which of the following is (are) most likely to regenerate most completely?

A] Neurons of the central nervous system (CNS).
B] Liver parenchymal cells.
C] Skeletal muscle.
D] Heart muscle.
E] Neurons of the retina.