INFLAMMATION

8.1 AN OVERVIEW

Remember, injury occurring at the tissue level cannot be separated from alterations at the cellular and subcellular levels (refer to discussions in previous sections). As the concepts of inflammation evolve, the student should not allow attention to specific detail cloud his/her general overview of the inflammatory process. Even though inflammation and repair occur together, the latter is considered in section 9 of this syllabus.

8.2 TERMINAL OBJECTIVES

8.3 KEY WORDS

8.4 GENERAL CONSIDERATIONS

Inflammation can best be defined as the vascular and cellular response of living tissue to injury. However, the reaction of blood vessels is its identifying feature. The inflammatory process serves to destroy, dilute or wall-off the injurious agent as well as the tissue cells that may have been destroyed. In other words, a complex series of events are initiated which, as far as possible, heal and reconstitute the damaged tissue. Repair is the process by which lost or destroyed cells are replaced by vital cells. Sometimes, repair is accomplished by regeneration of native parenchymal cells, but more often it occurs by fibroblastic scar formation. On the whole, inflammation and repair are beneficial to the host. In their absence, infections would go unchecked, burns would not heal, and wounds would remain festering open sores. However, under certain circumstances, inflammation and repair may become aberrant and harmful.

As discussed in section 1 of this syllabus, inflammation has a rich and ancient history that is intimately linked to the history of wars and the resulting wounds and infections.

- -- Cornelius Celsus (**30 B.C. - 38 A.D.**) - described the four cardinal signs of inflammation as rubor **(redness),** tumor (**swelling**), calor (**heat)** and dolar (**pain).** Galen added a fifth: "**loss of function."**
- -- Julius Cohnheim (**1839-1884)** - revealed the vascular alterations that are the basis of the inflammatory response.
- -- Elie Metchnikoff **(1845-1916**) - discovered the process of phagocytosis and concluded that the purpose of inflammation was to bring phagocytic cells to the injured area to engulf invading bacteria.

(The interested students should review the "*Historical Aspect of Pathology"* as discussed in *section 1 of this syllabus*).

As the discussion of inflammation unfolds, the student should be reminded of the following pertinent points:

- 1. The causes of inflammation are the same as those listed for cell injury in section 1 of this syllabus **(bacteria, viruses, chemicals, trauma, etc.).**
- 2. The host reaction to an injurious agent will influence the manner in which inflammation is expressed.
- 3. Specific chemical substances **(histamines, etc.)** mediate the inflammatory response **(even though it is precipitated by injury).**
- 4. Many nonspecific biochemical factors in the blood serum aid in the destruction of the injurious agents associated with inflammation **(i.e., edematous fluid dilutes the effects of the irritant; fibrin acts as a physical barrier to spreading and confines the irritant; phagocytosis by neutrophils and macrophages aids in the destruction and removal of the irritant; etc.**).
- 5. An exudate is the fluid and cellular debris associated with the inflammatory response.
- 6. Inflammation in an organ or tissue is identified by the suffix **"itis" (nephritis, enteritis, hepatitis, etc.)**.

8.5 DURATION OF INFLAMMATION

Traditionally, inflammation has been divided into acute and chronic forms, depending on its duration **(subacute is an intermediate form).**

Acute inflammation is one of relative short duration, lasting for a few minutes, several hours, or one to two days. It is characterized by the exudation of fluids and plasma proteins **(inflammatory edema)** and by the emigration of leukocytes **(predominantly neutrophils**). In general, the acute inflammatory response is basically the same regardless of the location or nature of the injurious agent.

Subacute inflammation usually is characterized by a decline in the vascular contribution **(edema and hyperemia**) and often by a change in the character of infiltrating leukocytes. although neutrophilic may be prominent at the inflammatory site, the infiltrate becomes mixed with mononuclear cells **(lymphocytes, macrophages and maybe plasma cells)** in reasonable numbers. It represents an intermediate time frame that can vary from a few days to a few weeks depending on the nature of the inciting stimulus.

Chronic inflammation is less uniform than acute inflammation. It is generally of longer duration and is associated with the presence of lymphocytes, macrophages and the proliferation of small blood vessels and fibroblasts. However, many factors may modify the course and histologic appearance of chronic inflammation **(which will become apparent later in this section)**.

NOTE: Clinically, an acute disease is one that arises suddenly, often within a few hours, and progresses rather promptly within a matter of days or a few weeks to recovery or death.

Remember, an acute clinical disease may have the pathologic features of chronicity. Clinically, a chronic disease begins slowly and insidiously and it may not be possible to determine just when the patient passed from a healthy to a diseased state. The chronic disease then continues indefinitely or for a prolonged period of time.

In the following discussions, the acute inflammatory response is considered first, the the chronic response, and finally, repair. However, the student should remember that these phases of the inflammatory response occur together **(even though they are discussed separately)**. For example, repair actually begins soon after the inflammatory process is initiated.

8.6 ACUTE INFLAMMATORY RESPONSE

The events in the acute inflammatory reaction are conveniently divided into:

- (1) hemodynamic or changes in vascular flow and caliber,
- (2) vascular permeability changes and
- (3) leukocytic exudation.

Remember, there is chronologic overlap among the three reactions and they may share common mediator mechanisms. However, since the structural and biochemical basis of each of these responses is sufficiently different, they are best discussed separately.

8.6.1 HEMODYNAMIC CHANGES

Hemodynamic changes or changes in vascular flow and caliber begin very early after injury, but develop at varying rates, depending on the severity of the injury. These changes consist of an integrated chain of events activated by chemical mediators, but perhaps transiently initiated by neurogenic mechanisms.

Remember, hemodynamic changes are important in determining blood flow to the injured area and, therefore, the amount of exudate that may eventually form. The observable vascular changes are manifested in the following order:

8.6.1.1 Transient Vasoconstriction of Arterioles

Vasoconstriction of arterioles occurs immediately following injury. However, this is an inconstant finding. With mild forms of injury, it disappears within three to five seconds. With more severe injury, it may remain for several minutes. The mechanism of this vasoconstriction is unknown, but is probably neurogenic or adrenergic in origin.

8.6.1.2 Vasodilatation of Arterioles resulting in Increased Blood Flow

Vasodilatation is a constant and fundamental event in the inflammatory process. Initially, it involves arterioles which result in opening of new capillaries and venular beds in the area. Subsequent to vasodilatation, there is increased blood flow to the affected areas **(this is the hallmark of the early hemodynamic changes in acute inflammation).**

Remember, active hyperemia is the first stage of inflammation.

Vasodilatation is induced in part by an axon reflex arc which occurs immediately after tissue injury. Following stimulation of sensory nerve endings at the site of injury, a nerve impulse passes centrally along the axon to its division and then peripherally to the arteriole supplying the injured area. Synaptic vesicles within the adrenergic synapse liberate adrenalin which dilates the peripheral arterioles resulting in increased blood flow to the affected area. The vasomotor nerves are not necessary to the development of dilation or any other aspect of the inflammatory response. Chemical mediators are of more importance in causing vasodilation and are of greater significance in altering vascular permeability.

8.6.1.3 Retardation of Blood Flow

Slowing of the blood flow to the injured area is brought about by increased permeability of the microvasculature (**to be discussed later).** The slowing and/or stasis of blood disrupts the laminar flow pattern of the blood and results in the displacement of the cellular elements to the periphery of the microvessels. The leukocytes appear to fall out of the central column of flow and assume positions in contact with the endothelium. When numerous cells adhere to and virtually line the endothelium, the process is referred to as pavementing. These marginated leukocytes stick to the vascular endothelium and eventually migrate through the vascular wall into the extravascular space by a process called emigration which is an active process since leukocytes are motile.

Remember, erythrocytes have no power of movement and their passages through the vascular wall is passive or via diapedesis.

8.6.2 The hemodynamic changes can be summarized as follows:

Immediately after an injury, there is arteriolar dilatation which may be preceded by a transient vasoconstriction. Pre-capillary sphincters open which leads to increased blood flow in previously functioning capillaries as well as opening of inactive capillary beds. Also, the postcapillary venules dilate and fill with the rapidly flowing blood. Thus, the microvasculature at the site of injury becomes hyperemic **(active hyperemia)**. The hyperemia is followed by slowing of blood (**which may progress to stasis)**. Concomitant with the development of hyperemia, the venules and capillaries become abnormally permeable, resulting in the escape of fluid. Thus, the viscosity of blood is increased leading to increased frictional resistance to flow. Subsequently, the outflow from the injured site is impeded which contributes to the stasis of blood **(there is increased hydrostatic pressure in venules and**

capillaries). Along with the slowing and/or stasis of blood, the laminar flow pattern is disrupted and cellular elements are displaced to the periphery of microvessels **(margination**). Soon after margination becomes evident, leukocytes escape from their vascular confinement (**via emigration)** and appear in the perivascular tissue.

8.6.3 VASCULAR PERMEABILITY CHANGES

Increased vascular permeability with the escape of plasma fluid (**including plasma proteins**) and leukocytes is known as exudation. This is a major and constant feature of all acute inflammatory reactions.

Remember, in the earliest stages of inflammation, vasodilatation, stasis and the resulting increased hydrostatic pressure may result in some degree of transudation (loss of fluid with low protein content). However, with the appearance of increased vascular permeability, there is exudation of large amounts of plasma proteins.

By employing special techniques, three general patterns of increased permeability responses can be recognized. These patterns are dependent on the severity of various types of injury and include

- (1) the immediate-transient response,
- (2) the immediate-prolonged response and
- (3) the delayed-prolonged response.

Immediate-Transient Permeability Response: begins immediately after mild injury, reaches it peak by 5 to 10 minutes and phase out within 15 to 30 minutes. The response is elicited by histamine and histamine-like chemical mediators. The venules are the site of increased permeability and leakage **(the capillaries are not affected)**. Vascular leakage result from contraction of endothelial cells which leads to the formation of intercellular gaps.

Intermediate-Prolonged Permeability Response: begins immediately after injury, is sustained at a high peak for several hours and continues for one to several days until the damaged vessels are thrombosed or repaired. The response is encountered with severe injury (**usually associated with necrosis of endothelial cells)**. Increased permeability and vascular leakage occur at all levels of the microcirculation, including venules, capillaries and arterioles. The mechanism for increased permeability appear to be **"direct damage"** to the vascular endothelium.

Delayed-Prolonged Permeability Response: occurs after a period of delay (**latent period of 6-12 hours**) and lasts for several hours or days (t**he duration of the latent period and the time of peak permeability vary with the form of injury)**. This response occurs after mild to moderate thermal injury, or x-ray or ultraviolet irradiation, with certain bacterial toxins and in delayed hypersensitivity reaction. It is believed that the delayed leakage is largely due to direct injury to the endothelium by the injurious agent. However, electron microscopy studies show the leakage to occur between endothelial cells, somewhat similar to that produced by histamine, but there is no endothelial cell contraction. Why intercellular gaps form with this type of direct

injury and why the leakage is delayed is unknown. Increased permeability and leakage occur in both venules and capillaries.

8.6.4 LEUKOCYTIC EXUDATION

Leukocytic exudation refers to the massing of leukocytes, principally neutrophils and monocytes (macrophages), in sites of inflammation. The phagocytic leukocytes engulf and destroy or, at least, weaken foreign invaders.

Remember, neutrophils play a dominant role in the acute inflammatory process, whereas, lymphocytes and monocytes (macrophages) are more prominent in chronic inflammation.

The sequence of events by which leukocytes aggregate and act at the inflammatory site can be considered under the following headings:

- (1) margination and pavementing,
- (2) emigration,
- (3) chemotaxis and
- (4) phagocytosis.

8.6.4.1 Margination and Pavementing of Leukocytes:

Margination or the peripheral orientation of leukocytes in the slow-moving bloodstream was mentioned in the discussion of **"hemodynamic changes."** Basically, slowing or stagnation of blood disrupts the normal laminar pattern of flow and cellular elements fall out of the central column to assume positions in contact with the endothelium. Subsequently, leukocytes adhere to the endothelial wall **(pavementing)**. This displacement of leukocytes toward the periphery of the bloodstream is apparently governed by the laws of physics.

8.6.4.2 Emigration of Leukocytes:

Emigration refers to the process by which motile leukocytes escape from the blood vessel lumen into the perivascular tissues **(neutrophils, basophils, monocytes and lymphocytes all use the same pathway).**

NOTE: After leukocytes adhere to the endothelial wall, they move slightly along the surface and insert large pseudopods into the junctions between the endothelial cells. Subsequently, they crawl through widened interendothelial junctions and eventually assume a position between endothelial cells and the basement membrane. Ultimately, they transverse the basement membrane and escape into the perivascular tissues. Remember, the movement of leukocytes between endothelial cells is an active process since these cells are motile.

It is now apparent that the route of leukocytic emigration along intercellular junctions is the same as that described for vascular leakage of fluids and proteins. However, leukocytic emigration and increased vascular permeability are two separate phenomena that may or may not occur concurrently.

- -- Emigrating leukocytes adhere so tightly to the endothelial membrane in their passage across the endothelium that no gaps are formed and vascular leakage may not occur.
- -- Widening of the intercellular junctions that allows for leukocytic emigration is not due to contraction of the endothelial cells (**as is the case for vascular leakage induced by histamine).**

In addition to leukocytes, erythrocytes may also leave blood vessels and enter the perivascular tissues (**especially in severe injuries**). These cells are non-motile and are passively pushed through the vessel walls by increased hydrostatic pressure. Erythrocytes are not active components of the inflammatory process.

The cell type found in the inflammatory response varies with the duration of the lesion and with the type of injurious agent. Neutrophils predominate in most types of acute inflammatory reactions for the first 6 to 24 hours. After this time, monocytes are most prominent. However, there are many exceptions to this pattern (**i.e., in viral infections, lymphocytes predominate during the acute stages. In some hypersensitivity reactions, eosinophils may be the main cell type).**

8.6.4.3 Chemotaxis:

Chemotaxis may be defined as the unidirectional migration of leukocytes toward an attractant. Thus, leukocytes are drawn to the site of injury by chemotactic influences which may be exogenous or endogenous. All granulocytes, monocytes and, to a lesser extent, lymphocytes respond to such chemoattractants.

Neutrophils are attracted primarily by two chemotactic agents:

- (1) bacterial products and
- (2) products of the complement system. Soluble bacterial factors with chemotactic activity can be isolated from filtrates of a variety of organisms ***(E. coli, Staphylococcus aureus, etc.)***. Also, bacterial proteases can generate chemotactic activity by cleaving the C3 and C5 fragments, C3 fragment and C5,6,7 fragments.

Recent evidence suggest that neutrophils respond to chemotactic influences by converting an inert cytoplasmic precursor (**proesterase I)** to the active enzyme **"serine esterase"** upon exposure to the chemotactic factor(s). Activation of serine esterase makes it possible for neutrophils to move toward the attractant.

Monocytes are attracted by chemotactic factors which include:

- (1) C3 and C5 fragments of complement,
- (2) soluble bacterial factors,
- (3) a factor present in lysates of neutrophils,
- (4) a factor formed in serum by interaction with antigen-antibody complexes (**but not related to the complement system)** and
- (5) a factor liberated by sensitized lymphocytes when exposed to specific antigens.

Eosinophil chemotactic substances include

- (1) eosinophilic chemotactic factor of anaphylaxis (**from IgE-sensitized basophils or mast cells),**
- (2) factors released by sensitized lymphocytes and
- (3) C5 fragment of complement.

8.6.4.4 Phagocytosis:

Phagocytosis refers to the engulfment of foreign particulate matter by phagocytic cells, particularly by neutrophils and macrophages. Once particulate matter is engulfed, the phagocytic cells release powerful enzymes which kills or degrades. Phagocytosis involves three distinct but interrelated steps:

- (1) recognition,
- (2) engulfment and
- (3) killing and/or degradation.

Recognition of foreign particulate matter by leukocytes is the initial step. Once a foreign particulate matter is recognized, it becomes attached to the surface of the leukocytes. Most organisms are not attached to leukocytes **(recognized)** until they are coated with serum factors called opsonins. IgG and the opsonic fragment of C3 (**generated by activation of complement by immune or non-immune mechanisms)** are well characterized opsonins.

Engulfment occurs once the phagocyte recognizes a foreign particle. Extensions of the cytoplasm (**pseudopods**) flow around the particle to be engulfed. Eventually, the particle is completely surrounded by the cytoplasmic membrane **(phagosome**). Subsequently, the limiting membrane of the phagosome fuses with the limiting membrane of the enzyme-rich lysosomal granule of leukocytes, resulting in discharge of the granule's content into the phagolysosome.

Remember, the process of phagocytosis is an energy-dependent phenomenon that stimulates numerous intracellular events, including

(1) increased oxygen consumption,

(2) glycogenolysis,

(3) increased glucose oxidation via the hexose-monphosphate shunt and (4) hydrogen peroxide production.

Killing and/or Degradation is the ultimate step in the process of phagocytosis. There are a number of antimicrobial mechanisms or degradative enzymes to account for these events, at least in neutrophils. The two categories of bactericidal mechanisms recognized in neutrophils are:

- (1) oxygen-dependent bactericidal mechanisms and
- (2) oxygen-independent bactericidal mechanisms.

Oxygen-dependent Bactericidal Mechanisms are initiated by a burst of oxidative activity during phagocytosis. This results from activation of a plasma membrane linked oxidase that converts oxygen (**O2**) to hydrogen peroxide **(H2O2**). It is now believed that various toxic byproducts of such oxygen are the killers of ingested bacteria. The toxic products that have been most widely studied are hydrogen peroxide and superoxide ions.

Hydrogen-Peroxide-Myeloperoxidase-Halide System is effective in killing bacteria, fungi, viruses and mycoplasma. During phagocytosis, reduced pyridine nucleotide oxidase is activated, resulting in the liberation of hydrogen peroxide within the phagolysosome. This hydrogen peroxide in the presence of myeloperoxidase (**an enzyme found in lysosomes of neutrophils**) and a halide ion (**such as chloride, iodide or bromide**) is effective in killing phagocytized organisms.

Remember, hydrogen peroxide is microbicidal for most organisms but is most effective in the presence of myeloperoxidase and a halide ion.

(Note: myelo-peroxidase is present in large amounts in phagolysosomes and it is responsible for the green color of pus).

Superoxide anion is a free radical generated during the conversion of oxygen to hydrogen peroxide in the phagosomes. There is evidence that this reactive radical alone is toxic to microorganisms.

Oxygen-Independent Bactericidal Mechanisms include the following:

- (1) hydrogen ions derived from increased production of lactate or from the action of carbonic anhydrase result in a marked reduction of pH within phagolysosomes (few bacteria can continue to grow at a pH of 4.0 or less and many are actually killed by lactic acid).
- (2) lysozyme action which attacks bacterial cell walls, especially those of gram-positive cocci, by hydrolyzing the muramic acid-N-acetyl glucosamine bond which is found in the glycopeptide coat of all bacteria.

- (3) Arginine-rich cationic proteins found in neutrophils can lyse bacterial membranes. Although most organisms are killed by phagocytes (**neutrophils and monocytes**), some are virulent enough to destroy such cells. Also, there are organisms (**tubercle bacilli, etc.**) which survive within phagocytes.

8.7 CHEMICAL MEDIATORS OF INFLAMMATION

At this point in the discussion of the acute inflammatory process, the chemical mediators **(histamine, etc**.) eluded to earlier should be considered in more detail. The student should be reminded that the inflammatory response is precipitated by injury, but it is mediated by chemicals derived from plasma, cells or damaged tissue.

The chemical mediators of inflammation are usually present within the body in an inactive form that is activated by injury. In general, the mediators dilate vessels, alter permeability and attract leukocytes into the following groups:

- (1) amines (**histamine and serotonin**),
- (2) plasma proteases (**kinin, complement system, etc.**),
- (3) prostaglandins,
- (4) neutrophil products,
- (5) lymphocyte factors and
- (6) others (**slow-reacting substances, etc.**).

8.7.1 HISTAMINE:

is contained within and released from granules of mast cells **(also released from basophils and platelets)**. It induces dilatation of arterioles and increased permeability of venules and capillaries. Histamine exerts its effect almost exclusively in early inflammatory responses. Its action is relatively brief and occurs primarily during the intermediate-transient response induced by mild injury. There are a number of agents that act to release histamine from mast cells, these include

- (1) immunologic reactions (**through binding with IgE**),
- (2) physical agents (**trauma, heat, etc.**),
- (3) C3 and C5 fragments of complement and
- (4) cationic proteins (**derived from lysosomes of neutrophils)**.

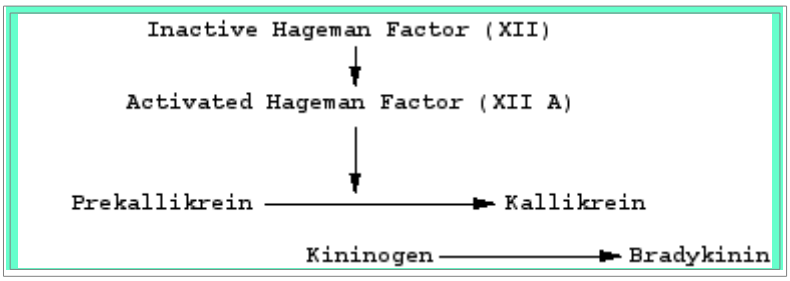
8.7.2 SEROTONIN

Has actions similar to those of histamine in some species **(rodents**). It is also released from mast cell granules.

8.7.3 KININS

Are polypeptides in circulating blood that arise from alpha 2-globulin. Lysis of cells in the injured area (**especially leukocytes**) releases enzymes which generate kinins. Once generated, the kinins sustain and enhance the early transitory vascular alterations begun by histamine **(arteriolar vasodilatation and increased capillary permeability**). In addition, kinins are potent mediators of pain and smooth muscle

contraction (**arterioles and venules).** The formation of the vasoactive bradykinin occurs as outlined below:



8.7.4 COMPLEMENT

Is a self-assembling, extracellular system of serum enzymes that occur in body fluids in association with membranes. The complement sequence is activated by antigen-antibody complexes and by some other large molecules. The components of the system that have biologic activity in inflammation are as follows:

- -- C3 component increases vascular permeability. It can be cleaved directly by plasmin, trypsin, bacterial proteases, as well as produced by the classic and alternate pathways.
- -- C5 component increases vascular permeability (**being more potent than C3**). It is also chemotactic to neutrophils and macrophages.
- -- C5,6,7 complex is chemotactic for neutrophils and macrophages, but it has no permeability effect.

8.7.5 PROSTAGLANDINS

Are 20-carbon chain unsaturated fatty acids that exert enhancing or depressant effects on numerous biological processes **(including inflammation).** The inflammatory stimuli induce prostaglandin synthesis and release. In inflammation, prostaglandins contribute to the genesis of vasodilatation, increased permeability, fever and pain.

8.7.6 LYSOSOMAL ENZYMES

Of neutrophils (**cationic proteins, acid proteases, neutral proteases**) have numerous and profound effects on the inflammatory process. They may serve to increase vascular permeability and chemotaxis.

8.7.7 LYMPHOCYTE FACTORS

Are referred to as lymphokines and they are produced by the sensitized T-lymphocytes associated with cell-mediated immunity. The lymphokines induce a variety of activities, including chemotaxis of macrophages, neutrophils and basophils as well as inhibition of macrophage migration.

8.8 CELLS IN THE INFLAMMATORY RESPONSE

At this point, it is appropriate to consider the various cell types that participate in the inflammatory reaction. All of these cells play fairly distinctive roles in inflammatory reaction. All of these cells play fairly distinctive roles in inflammation and enter into the inflammatory response in a definite, though overlapping, sequence. Therefore, for convenience, those cells associated with acute and/or chronic reactions are discussed. In the following brief discussion, an attempt is made to summarize the morphologic appearance and origin of inflammatory cells, as well as the conditions under which these cells are encountered and their functions.

8.8.1 .Neutrophils (Polymorphonuclear neutrophilic granulocytes, heterophils, pus cells)

Morphology: Neutrophils are 10-12 microns in diameter and have nuclei which are band-shaped or have three to five lobes. In tissue sections, the nuclei usually stain intensely with hematoxylin. The cytoplasm is irregular and may not be seen with H & E. If observable, the cytoplasm tends to be eosinophilic. In blood smears, the cytoplasm of neutrophils contains granules which are lavender. These granules **(which are not usually apparent in tissue sections**), correspond to the lysosomes and they are rich in proteolytic enzymes. Neutrophils are actively motile and phagocytic.

Origin:

Neutrophils originate from myeloid tissue of the bone marrow. They are attracted to injured areas by chemotactic substances and do not reproduce at the inflamed sites.

Conditions Encountered:

Neutrophils constitute the **"first line of cellular defense"** against invading organisms and particulate material. They are the first to gather in acute inflammation. Neutrophils are seen in response to pyogenic organisms and are the principal constituent of pus. Remember, the number of neutrophils in the circulation increases greatly in the early stages of inflammation.

Function:

All of the neutrophil's characteristic cell activities participate in the inflammatory response. These include

- (1) phagocytosis,
- (2) production of proteolytic and lipolytic enzymes to digest bacteria, dead cells, etc.,
- (3) they may produce substances which neutralize the toxic products of bacteria and
- (4) they may act as an energy source for other cells **(there is evidence that neutrophils shed their cytoplasm which is then transferred to "mononuclear cells" as an energy source).**

8.8.2 Eosinophils

Morphology:

The eosinophil is 10-15 microns in diameter. In tissue sections, it has a nucleus which is usually bilobed and does not stain as intensely as the nucleus of the neutrophil. The cytoplasmic granules are larger and more eosinophilic than those of neutrophils. The eosinophil of the horse has the largest granules among domestic animals. This cell is motile, phagocytic and attracted by chemotactic substances.

Origin:

The eosinophil originates in the myeloid tissue of bone marrow and does no reproduce at the site of inflammation.

Conditions Encountered:

The eosinophil may appear early and/or late in inflammation. It is most prominent in conditions where there is no immune response (**hay fever and asthma in man, parasitic conditions, etc.)**. The eosinophil is especially prominent in

- (1) the secondary invasion of parasites in a tissue,
- (2) in the brain of pigs with salt poisoning and
- (3) in so-called eosinophilic myositis of cattle.

Function:

The true functions of the eosinophil are unknown. Their biologic activities resembles, to some degree, those of neutrophils. They are motile, respond to chemotactic agents and are also phagocytic **(although to a much lesser degree than are neutrophils).** In hypersensitivity reactions, it has been suggested that eosinophils serve to degrade chemical mediators (**especially histamine**) and terminate the allergic reactions (i**.e., eosinophil granules contain histinase**). The phagocytic function may be of importance, especially the phagocytosis of antigen-antibody complexes. Another possible function is the production of fibrinolysin.

8.8.3 Basophils and Mast Cells

Morphology: In blood smears, the basophil is 10-12 microns in diameter and contains blue granules (**with Giemsa or Wright stain)**. The cell is slowly motile and not phagocytic. Basophils are present in blood in very small numbers and they are seldom seen as a prominent part of the inflammatory reaction. Morphologically, basophils have large lobulated nuclei and their granules contain heparin and histamine but no acid hydrolases. There remains no convincing evidence that the mature circulating basophil represents a precursor of mature tissue mast cells.

Mast cells are granular connective tissue cells found throughout the connective tissues in virtually every organ, principally in perivascular sites. They have mononuclear nuclei, are slightly larger, and have somewhat more abundant cytoplasm than the basophil. Their granules contain heparin, histamine and other proteolytic enzymes. In some animals they also are rich in serotonin.

Function:

The true functions of basophils are unknown. However, both basophils and mast cells release pharmacologically active compounds (**heparin/histamine)** in response to antigen-antibody complexes (**as well as trauma and drugs**). The immunoglobulin IgE binds selectively to the surfaces of mast cells and basophils and interaction of this antibody with specific antigens trigger degranulation and the release of histamines and other mediators. Mast cells are intimately involved in the pathogenesis of acute inflammation since it is their release of histamine which triggers many of the manifestations arising from smooth muscle contraction and edema formation.

8.8.4 .Lymphocytes

Morphology:

The mature lymphocyte is 7 10 12 microns in diameter, but larger lymphocytes may range up to 16 microns or more in diameter. The nucleus is round to somewhat oval and the nuclear membrane is thinner than that of the other inflammatory cells. Heavy chromatin granules are present within the nucleus and these often tend to be marginated just under the nuclear membrane. Their nucleoli usually are masked by the heavy clumps of chromatin. In tissue sections, the cytoplasm, if visible, consists of a narrow rim which may or may not completely surround the nucleus. The cytoplasm is homogeneous, pale blue and may contain a few azurophilic granules. Larger lymphocytes have more cytoplasm. Lymphocytes are slightly ameboid, but they are not phagocytic.

Origin:

Lymphocytes originate in lymphoid tissue, such as lymph nodes, spleen and thymus, and are carried to the site of inflammation by the blood. In addition, some lymphocytes are produced in bone marrow and there is some reproduction at the site of inflammation. Circulating small lymphocytes represent at least two different functional populations of lymphoid cells (**however, they cannot be distinguished structurally**). These thymic-derived lymphocytes (**T-lymphocytes**) and bone marrow-derived lymphocytes (**B-lymphocytes)** are differentiated on the basis of life-span, their response to mitosis-inducing drugs and the reactivity of their cell membranes in immunologic reactions. B-lymphocytes represent the precursors of plasma cells which form antibody. Following contact with an appropriate antigen, these lymphocytes become transformed into large **"blast"** cells (**plasmablasts**). The T-lymphocytes are associated with cell-mediated reactions involving the direct interaction of small lymphocytes and foreign proteins. The immunologic reaction is represented in tissues as lymphocytic **"exudate"** (**lymphocytic perivascular cuffing**). The small T-lymphocyte may transform into large lymphocytes (**activated T-lymphocytes that act by secreting lymphotoxins and lymphokines)**.

Conditions Encountered:

Lymphocytes appear late in inflammation. The arbitrary time of 48 to 72 hours is usually given as the time of appearance. They are seen as a prominent part of long-standing inflammatory reactions. Viral infections, particularly those of the central nervous system, are often associated with lymphocytes. In the brain and spinal cord, lymphocytes tend to accumulate around blood vessels (**perivascular cuffing**). The number of lymphocytes is under the control of endocrine secretions from the pituitary and adrenal cortex. Some of the glucocorticoids cause a decrease in the circulating lymphocytes and eosinophils. They also have an anti-inflammatory effect by decreasing the accumulation of lymphocytes and other inflammatory cells in the tissue.

Function:

It is generally agreed that lymphocytes function primarily in the immune response (**including both the humoral and cell-mediated immunity)**. The T-lymphocytes form the major portion of circulating lymphocytes. They have the capability of recirculating from lymphoid tissue to the thoracic duct, to the circulating blood and back to lymphoid tissue. These cells are involved in cell-mediated immunity. The B-lymphocytes are found in the blood, but do not recirculate. They are found in lymphoid tissues and are responsible for antibody synthesis (**along with plasma cells**). Other less well-defined functions have also been attributed to lymphocytes.

8.8.5 Plasma Cells

Morphology:

The plasma cell is about 12 to 15 microns in its greatest diameter. The nucleus is similar to that of lymphocytes, although the arrangement of the chromatin tends to resemble more nearly the typical **"cartwheel"** of **"clock-face" (with the large chromatin mass in the center of the nucleus surrounded by other masses just beneath the nuclear membrane).** The nucleus is usually eccentrically located in the cell. The cytoplasm is more abundant than in lymphocytes and tends to be more basophilic. There is usually a clear space or halo near the nucleus which corresponds to the Golgi complex. The plasma cell is said to be slightly ameboid and slightly phagocytic.

Origin:

Plasma cells originate from lymphocytes. Under an appropriate antigenic stimulus, small lymphocytes **(B-cells)** transform into larger **"blast"** cells which, in turn, develop into plasma cells. Once the plasma cell is formed, there is no evidence of reproduction.

Function:

Plasma cells are committed to antibody production. Following excretion of globulin, most lyse and die.

8.8.6 Macrophages

Morphology:

Macrophages vary in size (f**rom 12 to 20 microns or more in diameter)**. The nucleus is round to oval and the nuclear membrane is relatively thin. There are fine to medium chromatin granules in the nucleus. One to two nucleoli can usually be seen. There is abundant homogeneous, eosinophilic cytoplasm. Macrophages may **"bunch"** together and resemble epithelium, thus the term **"epithelioid cells."** The macrophage is actively ameboid and actively phagocytic.

Origin:

There is evidence that macrophages originate from blood monocytes. Monocytes emigrate from the blood into the inflammatory lesions and immediately transform into macrophages. Even though some macrophages may originate from lymphocytes, the majority of those that accumulate in inflammation are derived from blood monocytes.

Remember, macrophages have the capability of reproducing at the site of inflammation. Macrophages found in various body sites are referred to by the following terms:

- **a.Histiocytes - connective tissue macrophages**
- **b.Kupffer cells - liver macrophages**
- **c.Inflammatory macrophages - macrophages in inflammatory lesions**
- **d.Microglial cells - nervous system macrophages**
- **e.Fixed and free macrophages - macrophages in spleen and lymph nodes**
- **f.Pleural and peritoneal macrophages - macrophages in serous cavities**
- **g.Alveolar macrophages - lung macrophages**

Monocytes and macrophages belong to the reticuloendothelial system or the mononuclear-phagocytic system.

Conditions Encountered: In inflammatory processes, macrophages appear in large numbers late (**48 to 72 hours**). Actually, they enter an inflammatory lesion simultaneously with neutrophils. However, they do not appear in large numbers in the early stages of acute inflammation because:

- (1) they are not as aggressively ameboid as neutrophils,
- (2) their number in circulating blood (**monocytes**) are much lower than neutrophils and
-

- (3) their reproduction is stimulated at a much slower rate. In general, macrophages are most prominent in subacute to chronic reactions.

Function:

The primary function of macrophages is phagocytosis and they are termed the **"second line of cellular defense."** They are also capable of pinocytosis of soluble molecules. Thus, the function of macrophages in the inflammatory process include the following:

- a.Phagocytosis and digestion of invading organisms or foreign particles.
- b.Release potent enzymes that may degrade connective tissue.
- c.Release chemotactic and permeability factors that may prolong inflammation.
- d.Release substances responsible for leukocytosis and fever **(prostaglandins, endogenous pyrogens).**
- e.Release factors that aid in wound healing.
- f.Secrete proteins that are important in defense mechanisms **(lysozymes, interferon).**
- gServe to process antigens in cell-mediated immune reactions.

8.8.7 Giant Cells

Inflammatory giant cells are multinucleated cells that result from the fusion of monocytes and/or macrophages. However, giant cells may form by mitotic division of the nuclei without division of the cytoplasm. In giant cells, the nuclei may be clustered in the center of the cell or arranged in a "ring" fashion around the periphery. The finding of giant cells in lesions usually suggest the possibility of diseases involving fungi, mycobacteria or some foreign body **(they are associated with large amounts of indigestible material**).

8.9 EXUDATES IN ACUTE INFLAMMATION

The exudates associated with inflammatory reactions vary in their fluid, plasma protein and cell content. In general, the nature of the exudate is dictated by the severity of the reaction and its specific cause. (***Please refer to pages 184-190 of your textbook***).

8.9.1 SEROUS EXUDATION:

Serous exudation is characterized by the outpouring of a low-protein fluid. (**This is so-called inflammatory edema and the protein content is higher than that of non-inflammatory edema).** A serous exudate is composed primarily of a slightly cloudy fluid. Its presence usually indicates mild injury. However, this type of exudate is seen in the early stages of most acute inflammatory reactions. Microscopically, serous exudation appears as a homogeneous, slightly eosinophilic material. It functions to dilute the irritant and to bring antibodies into the inflamed area. The skin

blister that results from a burn is a simple example of a serous exudate. Serous exudation along with hyperemia represents the "first" stage of pneumonia.

8.9.2 FIBRINOUS EXUDATION:

Fibrinous exudation is characterized by the presence of fibrin as the major constituent. It occurs in the more severe inflammations which permit the escape of large fibrinogen molecules from the blood vessels **(a fibrinous exudation is indicative of severe vascular damage).** Fibrinous exudation occurs chiefly on mucous and serous membranes, including the alveolar surfaces of the lungs. Masses of fibrin on an epithelial surface are referred to as follows:

- --Croupous membrane **(pseudomembrane**) refers to masses or layers of fibrin which can be peeled away from the surface quite easily, leaving an intact epithelial membrane.
- --Diphtheritic membrane refers to masses or layers of fibrin which are quite firmly attached to the underlying tissue **(when removed, the underlying tissue torn**).

Microscopically, fibrin appears as fine threads or filaments. These threads may fuse to form a solid eosinophilic mass. Neutrophils are usually present. Grossly, fibrin appears as thin strands or layers of white to yellowish elastic-like material.

Fibrinous exudate serves to help localize bacteria and to act as a scaffold or framework for repair processes. In serous cavities, the strands of fibrin connecting the parietal and visceral layers are called fibrinous adhesions. If during the repair process the fibrinous adhesions are replaced by connective tissue, they are called fibrous adhesions.

8.9.3 SUPPURATIVE OR PURULENT EXUDATION:

A suppurative or purulent exudation is characterized by the presence of pus (**neutrophils mixed with cellular debris**).

Remember, most inflammatory reactions begin as a suppurative process when the "first line of cellular defense" (neutrophils) accumulate in the area. Classically, there are three requisites of suppuration:

(1) presence of neutrophils that release proteolytic enzymes,

(2) necrosis of some type and

(3) liquefaction.

Suppurative exudation is usually caused by pyogenic or pus-forming bacteria **(Corynebacterium pyogenes, Pseudomonas aeruginosa, etc.)**. The following are some terms applied to different forms of suppurative reactions:

- --Abscess refers to a focal or circumscribed collection of pus. When well-developed, it has a wall or capsule of fibrous connective tissue separating it from the surrounding tissue. Metastatic abscesses are multiple collections of pus scattered throughout the body. These usually result from the spread of pyogenic organisms by way of the bloodstream or lymphatics. A pustule is a circumscribed collection of pus within or beneath the epidermis. A furuncle (**boil)** is a suppurative reaction involving the hair follicles or sebaceous glands.
- --Phlegmon (**cellulitis**) refers to a diffuse suppurative process, especially one involving the subcutis. A phlegmon tends to spread indefinitely, whereas an abscess is usually confined.
- --Empyema refers to the presence of pus in preformed body cavities, usually serous cavities **(pyothorax, pyoperitoneum, etc.).**
- --Pyometria refers to pus in the uterus.
- --Pyoderma refers to any suppurative skin condition.
- --Pyocephalus refers to pus in the cerebral ventricles.
- --Pyemia refers to a condition in which pyogenic organisms travel from one part of the body to another by way of the bloodstream and set up secondary sites of suppuration (**metastasis).**

8.9.4 HEMORRHAGIC EXUDATION:

Hemorrhagic exudation occurs whenever some form of severe injury causes rupture of vessels or diapedesis of erythrocytes.

NOTE:A hemorrhagic exudate is not a distinctive form of exudation. It is almost always a basic fibrinous or suppurative exudation accompanied by the extravasation of large numbers of erythrocytes.

The gross and microscopic appearances are similar to those of hemorrhage except that fibrin or excessive numbers of leukocytes usually accompany the erythrocytes.

8.9.5 CATARRHAL EXUDATION:

A catarrhal exudate is characterized by excessive mucin

(NOTE: although excess mucus is included as an inflammatory exudate, it is questionable if this truly represents an exudative change since the material comes from goblet cells rather than from the blood vascular system).

Catarrhal exudation is limited to mucous membranes since it is secreted by goblet cells. Grossly, catarrhal exudate appears as a clear or cloudy tenacious fluid on the mucosal surfaces. The increased mucin serves to protect damaged mucosal surfaces.

In summary, serous, fibrinous, purulent, hemorrhagic and catarrhal exudation are associated with acute inflammatory processes. Although the various types of exudative reactions were described separately, mixed patterns develop in many inflammations **(serofibrinous, fibrinopurulent, etc.).** Also, the exudation may begin as a serous response in any single inflammatory reaction and, with extension and increasing severity of the reaction, it may become predominantly fibrinous and ultimately change into a suppurative exudate. The acute exudates may change to chronic forms in which connective tissue is a prominent feature.

Remember, the type of exudate encountered may be a useful clue as to the cause of the condition.

In addition to the five exudative inflammations listed above, some inflammations are recognized by the presence of numerous lymphocytes (**lymphocytic exudation)**. Such lymphocytic accumulations are usually associated with viral infections in the central nervous system and visceral organs **(perivascular cuffing).** So-called lymphocytic exudate is observed on microscopic examination only.

8.10 CLINICAL SIGNS OF ACUTE INFLAMMATION

The local clinical signs of acute inflammation are heat, redness, swelling, pain and loss of function. The heat and redness result from dilation of the microcirculation and increased blood flow into the injured area. Swelling is produced largely by the escape of fluid, plasma proteins and cells from the blood into the perivascular tissue. The origin of pain is somewhat obscure, but the best evidence suggests that overt pain can be induced by the prostaglandins as well as bradykinin. Also, pain may be caused by increased tissue pressure due to the inflammatory exudate.

8.11 CHRONIC INFLAMMATION

To this point, the acute inflammatory response as well as inflammatory cells and exudates associated with acute and prolonged responses have been discusses.

Remember, an acute inflammation is usually seen when the etiologic agent is more or less transient (an allergic wheal, a mild burn, an avirulent infection). The responsible agent is rapidly cleared by the host response. Some of these acute reactions disappear completely, while others are repaired by processes to be discussed later. However, some etiologic agents may remain active for weeks, months or even years. Such persistent etiologic agents lead to chronic inflammation. Actually, the transition from acute to chronic is often difficult to determine.

Clinically, chronic inflammation may occur in three ways:

- --Chronic inflammation may follow acute inflammation because of the persistence of the etiologic agent.

- --Chronic inflammation may be due to repeated bouts of acute inflammation, with the animal exhibiting successive attacks of fever, pain, swelling, etc. (**Microscopically, acute inflammatory changes and healing that occurred between attacks are seen.)**
- --Chronic inflammation may begin insidiously as a low-grade, smoldering response that never acquires the classical features of acute inflammation.

Microscopically, chronic inflammation is characterized by:

- 1) an infiltration by mononuclear cells (**principally macrophages but also lymphocytes and plasma cells)** and
- (2) proliferation of fibroblasts (a**s well as small blood vessels**).

Infiltration by macrophages is a particularly important component of chronic inflammation. As discussed earlier in this section, monocytes begin to emigrate rather early in acute inflammation and, within 48 to 72 hours, they constitute the predominate cell type. Remember, when the monocyte reaches the extravascular tissue it undergoes transformation into a macrophage. Macrophages may persist for prolonged periods of time in inflamed areas. Other types of cells found in chronic inflammation are plasma cells, lymphocytes and eosinophils.

Plasma cells produce antibody in response to antigens in the inflamed area. Lymphocytes play a role in antibody production and in cell-mediated immunologic reactions. However, they occur in non-immunologic inflammation. Eosinophils are characteristic of immunologic reactions mediated by IgE and in parasitic infections. However, they may be associated with inflammation for obscure reasons. The student should be reminded of the following pertinent points.

- --Although neutrophils are usually considered to be the **"hallmark"** of acute inflammation, many forms of chronic inflammation may continue to show large numbers of neutrophils and to form pus **(chronic and acute responses are superimposed).**
- --The presence of lymphocytes does not always mean that a chronic inflammation is present. This is especially true with viral infections **(perivascular cuffing**).

The mechanisms that lead to fibroblastic and vascular proliferation (the other two characteristic features of chronic inflammation) are obscure. However, factors derived from activated macrophages have been implicated in both fibroblast and new vessel growth. Regardless of the mechanism, continued fibroblast proliferation results in increased deposition of collagen. Therefore, chronic inflammation is often followed by considerable scarring with resultant deformities.

8.12 CHRONIC GRANULOMATOUS INFLAMMATION:

Granulomatous T a distinctive pattern of chronic inflammation evoked by certain etiologic agents **(fungi, mycobacteria, some foreign bodies, etc.**). Granulomas consist of collections of modified macrophages (**epithelioid cells)** usually surrounded by a rim of lymphocytes.

NOTE:The characteristic cell of the granuloma is a modified macrophage which is referred to as an "epithelioid cell" because of its abundant, pale-pink cytoplasm and plumpness (resembling an epithelial cell).

Remember, epithelioid cells are derived from blood monocytes (like all macrophages).

However, the reason for their transformation into this peculiar cell type is poorly understood. In general, epithelioid cells and granulomas are associated with materials that macrophage lysosomes cannot adequately process. The initial phagocytosis of such substances is followed by **"digestive failure,"** and death of the macrophages. Subsequently, more blood monocytes emigrate to the location, transform into macrophages, and rephagocytize the substance and its associated cellular debris. New populations of macrophages collect in progressively enlarging foci called granulomas. Although the material may not be destroyed, granulomas provide an effective means of localizing it and allowing other inflammatory and immunologic mechanisms to act for longer periods of time. The presence of Langhan's or foreign body giant cells (f**ormed from the coalescent and fusion of macrophages)** is another feature of granulomas. Also, fibroblasts, lymphocytes, plasma cells and, at times, neutrophils can be seen in granulomas. However, the presence of the characteristic cell **("epithelioid cell")** is required for the diagnosis of granulomatous inflammation.

Two factors appear to determine the formation of granulomas:

- (1) the presence of indigestible organisms or particles (**tubercle bacillus, mineral oil, etc.**) and/or
- (2) the presence of cell-mediated immunity to the inciting agents.

8.13 SYSTEMIC EFFECTS OF INFLAMMATION

Systemic manifestations may be evoked by acute or chronic inflammation. Fever and leukocytosis are two of the most prominent systemic manifestations, especially when the inflammation is associated with bacteremia.

8.13.1 .FEVER:

The cause of fever has not been completely elucidated. However, evidence suggests that endogenous pyrogens and prostaglandins play dominant roles in fever production.

NOTE:Normal body temperature is maintained by hypothalmic regulation of the production and dissipation of heat.

Endogenous pyrogens are basic proteins of low molecular weight which act on the thermoregulatory centers in the hypothalamus, leading to elevation of the "thermostat" and the development of fever. Endogenous pyrogens exist in an inactive form in monocytes, macrophages, neutrophils and possibly eosinophils. They are

activated and released by phagocytosis, endotoxin, viruses, bacteria, fungi, immune complexes, lymphocyte products, etc. Aspirin, a common antipyretic substance, antagonizes the action of endogenous pyrogens within the hypothalamus. Prostaglandins are also involved in fever production. However, the exact mechanism has not been elucidated.

The following sequence of events are believed to account for the pathogenesis of fever:

Endogenous pyrogens are produced by phagocytic leukocytes in response to infections, toxins, immunologic reactions, etc. These pyogens are released into the bloodstream where they interact with receptors on or near the thermosensitive neurons in the thermoregulatory center of the anterior hypothalamus. Either through the local action of endogenous pyrogens or through the local production of prostaglandins, information is transmitted from the anterior hypothalamus through the posterior hypothalamus to the vasomotor centers, resulting in sympathetic nerve stimulation, vasoconstriction of skin vessels, decrease in heat dissipation and fever.

8.13.2 LEUKOCYTOSIS:

Leukocytosis or an increased number of leukocytes in the circulating blood is a common feature of the inflammatory reaction (**especially those induced by bacterial agents)**.

"Under normal conditions, the number of leukocytes in the circulating bloodstream ranges from 4,000 to 12,000 per cubic millimeter, depending on the species of animal. In most animals, neutrophils constitute approximately 60 to 75% of the total number of leukocytes (however, in a few species (cattle, sheep) neutrophils comprise only 40-50% of the total leukocytes)."

In inflammation, the leukocyte count usually increases to **12,000 - 20,000**, but sometimes may reach extraordinary high levels of **40,000 - 100,000.** These extreme elevations are referred to as Leukemoid reactions since they are similar to the leukocyte counts obtained in cases of leukemia. The leukocytosis of acute inflammation is usually due to an absolute increase in the number of neutrophils. The leukocytosis apparently initially occurs because of accelerated release of cells from the bone marrow reserve pool **(there is often a rise in the number of more immature neutrophils in the blood - shift to the left).** However, prolonged infections stimulate proliferation of precursors in the bone marrow. Mediators for the accelerated release from the bone marrow or the proliferation of precursors have not been well elucidated. However, C3 fraction of complement augments neutrophil release.

Remember, certain systemic inflammatory states decrease the number of circulating leukocytes (leukopenia). These include viral infections, rickettsial infections, certain protozoan infections and maelevations are referred to as Leukemoid reactions since they are similar to the leukocyte counts obtained in cases of leukemia. The leukocytosis of acute inflammation is usually due to an absolute

increase in the number of neutrophils. The leukocytosis apparently initially occurs because of accelerated release of cells from the bone marrow reserve pool (there is often a rise in the number of more immature neutrophils in the blood - shift to the left). However, prolonged infections stimulate proliferation of precursors in the bone marrow. Mediators for the accelerated release from the bone marrow or the proliferation of precursors have not been well elucidated. However, C3 fraction of complement augments neutrophil release.

Remember, certain systemic inflammatory states decrease the number of circulating leukocytes (leukopenia). These include viral infections, rickettsial infections, certain protozoan infections and many infections which overwhelm the animal defense system.

8.14 CONCLUSION

The discussion of systemic manifestations of inflammation climaxes the basic description of the acute and chronic inflammatory processes. Even though the basic inflammatory changes were described sequentially and may occur in this order in the fully evolved reaction to injury, all of the phenomena usually occur more or less concurrently in a seemingly chaotic but remarkably organized manner.

8.15 POST-INSTRUCTIONAL SELF-EXAMINATION

After completing this section, each student should be in a position to provide appropriate answers for the following questions.

- **1.List the primary functions of the inflammatory process.**
- **2.How would you define inflammation?**
- **3.What is the most prominent identifying feature of inflammation?**
- **4.What is the interrelationship between inflammation and repair?**
- **5.Outline the outstanding contributions made by the following individuals relative to inflammation and repair:**
- **6.List and describe the mechanisms responsible for the five cardinal signs of acute local inflammation.**
- **7.List at least two systemic manifestations of inflammation.**
- **8.How would you define and/or describe the following terms (relative to the inflammatory process)?**
  - **--Calor --Tumor**
  - **--Dolar --Rubor**
- **9.How would you distinguish between an acute, subacute and chronic inflammation on the basis of microscopic findings?**
- **10.How would you distinguish between an acute and a chronic inflammation on the basis of clinical findings in the live dog?**
- **11.What cell type(s) would you expect to dominate in the early stages of an acute inflammation?**
- **12.Distinguish an exudate from a transudate.**
- **13.What cell type(s) would you expect to dominate in a chronic**

inflammatory process?

- **14.What is the identifying feature of granulomatous inflammation?**
- **15.List the major events that occur in acute inflammatory responses.**
- **16.What factor(s) is usually responsible for activating hemodynamic changes in acute inflammation?**
- **17.What are chemical mediators?**
- **18.In approximate sequential order, list the major hemodynamic changes that occur in acute inflammation.**
- **19.Please answer the following as they relate to the hemodynamic changes of acute inflammation:**
  - **_____is the most likely mechanism for the transient vasoconstriction of arterioles.**
  - **_____is the "hallmark" of early hemodynamic changes in acute inflammation.**
  - **_____is induced by an axon reflex arc.**
  - **_____are cellular elements that pass through the vascular wall by passive means.**
- **20.Briefly explain the mechanism(s) whereby vasodilatation of arterioles occurs in acute inflammation.**
- **21.Distinguish margination of neutrophils from pavementing and emigration.**
- **22.What is permeability? What is a semipermeable membrane?**
- **23.What is an exudate? What is exudation?**
- **24.What are the usual components of an exudate?**
- **25.List the 3 patterns of increased vascular permeability.**
- **26.What pattern(s) of increased permeability is characterized by each of the following:**
  - **_____leakage from venules only.**
  - **_____elicited by histamine.**
  - **_____associated with severe injury with necrosis of endothelial cells.**
  - **_____vascular leakage occurs in venules, arterioles and capillaries.**
  - **_____occurs only after a latent period.**
  - **_____associated with injuries caused by irradiation.**
  - **_____increased permeability due to direct damage to the vascular endothelium.**
  - **_____associated with mild injuries.**
  - **_____vascular leakage results from contraction of endothelial cells.**
- **27.What portion of the microvasculature is usually affected first by increased permeability and leakage?**
- **28.What are leukocytes?**
- **29.Outline the sequence of events by which leukocytes aggregate and act at the inflammatory site.**
- **30.What leukocytes have the major responsibility for phagocytosis in an injured area?**
- **31.Briefly explain how the slow-moving bloodstream predisposes an animal to:**

  - **(1) venous stasis,**
  - **(2) transudation,**
  - **(3) exudation,**
  - **(4) thrombosis and**
  - **(5) margination of leukocytes.**
- **32.Briefly explain how marginated neutrophils are able to make their way from the blood vessel lumen into the perivascular tissues.**
- **33.Since leukocytic exudation and vascular leakage of fluid occur along interendothelial junctions, why are they considered to be two separate phenomenon?**
- **34.Explain the mechanisms responsible for the movement of erythrocytes from the blood vessel lumen into the perivascular tissues.**
- **35.What is chemotaxis?**
- **36.Briefly explain how leukocytes are drawn to a site of injury.**
  - **-- List the chemotactic agent for neutrophils, monocytes, macrophages and eosinophils.**
- **37.What fractions of the complement system are chemotactic for neutrophils? for macrophages?**
- **38.What is the role of serine esterase in chemotaxis?**
- **39.Based on chemotactic forces and/or agents, would you expect neutrophils to move into an injured area more rapidly than macrophages?**
- **40.what three important events are involved in phagocytosis?**
- **41.What cellular element is responsible for the "first line of cellular defense?"**
- **42.What cell type is responsible for the "second line of cellular defense?"**
- **43.Briefly explain how leukocytes are able to recognize foreign particulate matter.**
- **44.What are opsonins?**
- **45.Briefly outline the sequence of events involved in phagocytosis of bacteria by a neutrophil, beginning with recognition and ending with exposure of the organisms to lysosomal enzymes.**
- **46.Explain how bacterial agents are exposed to hydrogen peroxide and superoxide ions during phagocytosis.**
- **47.What is a phagosome?**
- **48.What is a phagolysosome?**
- **49.What is the role of the hydrogen peroxide-myeloperoxidase-halide system in phagocytosis?**
- **50.What is responsible for the green color of pus?**
- **51.What is pus?**
- **52.What are the major functions of chemical mediators in acute inflammation?**
- **53.What is the major role of histamine in inflammation?**
- **54.What cell(s) is responsible for releasing histamine within an inflamed area?**
- **55.What are the major contributions of kinins in the inflammatory process?**
- **56.What is complement? What are the major functions of complement in inflammation?**
- **57.What fragment(s) of complement is responsible for both increased permeability and chemotaxis?**

- **58.List the cell type(s) usually associated with an acute inflammatory process.**
- **59.What cell types are usually associated with granulomas?**
- **60.What cell types are usually associated with chronic inflammation?**
- **61.What cell types are both motile and phagocytic?**
- **62.What cell types originate from myeloid tissue of bone marrow?**
- **63.What cell type is transformed into macrophages within perivascular tissues?**
- **64.What cell type(s) have the capability of reproducing in the inflamed area?**
- **65.What cell type(s) accumulate in response to pyogenic agents?**
- **66.What cell type(s) is usually associated with liquefactive necrosis in the liver?**
- **67.What are heterophils?**
- **68.What is the interrelationship between basophils and mast cells?**
- **69.What immunoglobulin is oftentimes associated with the release of histamine from mast cells?**
- **70.Briefly discuss the origin of lymphocytes.**
- **71.What are the major functions of B- and T-lymphocytes?**
- **72.What is the interrelationship between lymphocytes and plasma cells:**
- **73.What are Russell bodies?**
- **74.What is the interrelationship between lymphocytes and antibody production?**
- **75.What is "perivascular cuffing?"**
- **76.What is the role of glucocorticoids in inflammation?**
- **77.What is the role of epinephrine in inflammation?**
- **78.Discuss the functions of lymphocytes and mast cells in inflammation.**
- **79.Discuss the functions of plasma cells in inflammation.**
- **80.What are macrophages?**
- **81.What are giant cells?**
- **82.What are epithelioid cells?**
- **83.What is the interrelationship between monocytes and giant cells?**
- **84.Give an appropriate name for macrophages found in the following body sites:**
  - **--Central nervous system**
  - **--Lung**
  - **--Liver**
  - **--Connective tissue**
- **85.Discuss the important functions of macrophages in inflammation.**
- **86.Explain how giant cells are formed.**
- **87.What are Langhan's giant cells?**
- **88.What are so-called foreign body giant cells?**
- **89.Under what circumstances would you expect to observe giant cells and epithelioid cells at an inflamed site?**
- **90.What exudates are usually associated with acute inflammatory processes?**
- **91.Under what circumstances would you expect to find neutrophils in a chronic inflammatory reaction?**
- **92.Under what circumstances would you expect to observe the following exudates:**

- **--Catarrhal --Hemorrhagic**
- **--Purulent --Lymphocytic**
- **--Fibrinous --Serous**

- **93.How would you characterize the following exudates:**
- **--purulent --Hemorrhagic**
- **--Fibrinous --Serous**
- **94.What exudate(s) occurs chiefly on mucous and serous membranes?**
- **95.Distinguish a croupous membrane from a diphtheritic membrane?**
- **96.What are the advantages and disadvantages of a fibrinous exudate?**
- **97.Distinguish fibrous adhesions from fibrinous adhesions.**
- **98.Describe and/or define the following terms:**
  - **--Abscesses --Pustule**
  - **--Cellulitis --Furuncle**
  - **--Phlegmon --Empyemia**
  - **--Metastasis --Pyemia**
- **99.Briefly discuss the occurrence of a hemorrhagic exudate in an inflamed area.**
- **100.What are the cardinal signs of acute inflammation? What factors are responsible for these signs?**
- **101.What is a chronic inflammation?**
- **102.Briefly explain how a chronic inflammatory process may develop.**
- **103.what are the identifying features of a chronic inflammation?**
- **104.What are "activated macrophages?"**
- **105.Why would you expect epithelioid cells to accumulate in an inflamed area?**
- **106.What is fever? What are pyrogens?**
- **107.Explain how fever develops in an animal with a bacteremia.**
- **108.What is a leukemoid reaction?**
- **109.What effect would an acute viral infection have on the number of circulating neutrophils?**

- **110.Briefly explain how granulomas are formed.**