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INFLAMMATION AND REPAIR

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Objectives that should be achieved through teaching the concepts and principles of inflammation.

Inflammation is a central area in general pathology. The medical student should be able to:

A] Identify the cardinal signs of inflammation.

B] Understand the underlying mechanisms that produce these signs.

C] Appreciate the vascular and microvascular response of the tissue to any injury.

D] Understand the importance of fluid accumulation during inflammation and the differentiation between exudates and transudate fluids.

E] Acquire a basic knowledge of the chemical mediators of inflammation and their link with complement and coagulation factors.

F] Know the types and functions of the various inflammatory cells.

G] Become aware of the complications resulting from the inflammatory response.

H] Understand the mechanisms of resolution of the inflammatory response and the process of healing and repair.

I] Appreciate the relationship between acute inflammation, healing and repair and chronic inflammation.

Chapters and paragraphs that should be read from Robbins Basic Pathology - International 8th Edition:

1) Figure 2-1 in page 32 and the general features of inflammation.

2) Figure 2-2 in page 33 - major local manifestations of acute inflammation.

3) Figures 2-3 and 2-4 in pages 34 and 36.

4) Figures 2-5 and 2-7, pages 38 and 40.

5) Table on sequence of events in acute inflammation page 42.

6) Figures 2-8 and 2-9 in page 43.

7) Morphologic patterns of acute inflammation, pages 43-44 and figures 2-12 and 2-13 in page 45.

8) Table 2-4 page 46 (the actions of principal mediators of inflammation).

9) Page 50 - Summary of major cell derived mediators of inflammation.

10) Page 54 - chronic inflammatory cells and mediators.

11) Summary of features of chronic inflammation, page 57.

12) Systemic effects of inflammation, pages 57-58.

13) Figure 3-1, page 60.

14) Figure 3-11, page 71.

15) Figure 3-15,16 and 17, pages 75, 76 and 77.

INFLAMMATION AND REPAIR

Inflammation

Inflammation, the local response of tissue to injury, is fundamentally a vascular phenomenon. 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
Systemic manifestations of inflammation include: fever, chills, increased sedimentation rate and increased levels of C reactive protein.

Causes of tissue injury leading to inflammation 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. The inflammatory process consists of: cellular events, vascular changes and effects of chemical mediators.

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 and digestion	+	Late acute, chronic
Lymphocyte	Lymphokines	-	Chronic
Plasma cell	Antibody production	-	Chronic

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

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 occurring 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**. As a consequence, **interstitial edema** (swelling) occurs owing to the escape of intravascular fluid, called an exudate. Then, the lymphatic vessels admit the escaped fluid into the lymphatic system and after several days the swelling subsides.

A. 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.

B. 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). At the same time, the leukocytes move from the vessels into the interstitial tissues (emigration). 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.

C. Chemical mediators of the acute inflammatory response. Attraction of the interstitial leukocytes to the area of tissue injury occurs through **chemotaxis** or attraction by chemical agents. Numerous chemical mediators are responsible for the vascular events surrounding the acute inflammatory process.

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
Pus	Acute inflammation	High protein plus neutrophils	> 1.020

The Actions of the Principal Mediators of Inflammation

Mediators	Source	Principal Actions
Cell-Derived		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation.
Serotonin	Platelets	Vasodilatation, increased vascular permeability.
Prostaglandins	Mast cells, leukocytes	Vasodilatation, pain, fever.
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation.
Platelet-activating factor	Leukocytes, endothelial cells	Vasodilatation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst.
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage.
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes.
Cytokines (e.g. TNF, IL-)	Macrophages, lymphocytes, Endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules), systemic acute-phase response in severe infections, septic shock.

- Bradykinin is a metabolite of the Kinin system which is activated by the action of Hageman's factor (factor 12 of coagulation).

Mediators	Source	Principal Actions
Plasma Protein-Derived		
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, opsonization, vasolidalation (mast cell stimulation).
Kinis	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilatation, pain.
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruirmenr.

- IL-1, interleukin-1, TNF- tumor necrosis factor.

Role of Mediators in Different Reactions of Inflammation

Vasodilatation	Prostaglandins Nitric oxide Histamine
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Bradykinin Leukotrines C4, D4, E4 Platelets activating factor Substance P
Leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotrienes B4 (Bacterial products, eg., *N*-formyl methyl peptides)
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin Neuropeptides
Tissue damage	Lysomal enzymes of leukocytes Reactive oxygen species Nitric oxide

- IL-1, Interleukin-1, PAF, Platelet activating factor, TNF, tumor necrosis factor.
- Prostaglandins and Leukotrienes are arachidonic add metabolites.

Chronic inflammation. The preponderance of lymphocytes, plasma cells and macrophages in acute inflammation indicates 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.

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**. 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.

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. The laying down of excessive collagen results in **keloid and fibrous adhesions formation. 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 **Wound contractures** is related to the action of myofibroblasts. **This is seen especially following burns.**