INFLAMMATION AND REPAIR

"Inflammation is one of the most important and most useful of our host defense mechanisms, and without an adequate inflammatory response none of us or our patients would be living. Ironically it is also one of the most common means whereby our own tissues are injured." (Slauson and Cooper, page 142, 2002)

GOALS OF GENERAL PATHOLOGY:

1. Develop the ability to recognize and describe morphologic changes
2. Develop the ability to identify the cause and etiology of a particular lesion
3. Learn the mechanisms or pathogenesis of the disease process.

By the end of these lectures and laboratories the learner will (hopefully) understand the mechanisms of inflammation and repair. Students will gain an appreciation for the intricacies involved in the inflammatory process and understand general mechanisms.

Recommended Text:


Additional Resources:
- Basic Pathology 7th ed, V Kumar, R Cotran and SL Robbins, 2003 Chapter 2 (33-59), Chapter 3, (61-77)
- Introduction to Veterinary Pathology, 2nd ed, NF Cheville, 1999, (105-152)
- Essential Pathology 2nd ed, E Rubin, JL Farber, 1995, Chapters 2 & 3 (23-63)
- Videodiscs and programs

Lecture Outline: Page
1. Inflammation – generalities .................................................. 2
2. Classification of inflammation .................................................. 3-9
3. Acute inflammation .............................................................. 10-34
   - Vascular events/permeability 10-12
   - Inflammatory Cell Types 13-17
   - Sequence of events 18-27
   - Chemical Mediators 28-36
4. Chronic Inflammation and Granulomatous Inflammation .......... 37-42
5. Repair ................................................................. 42-45
6. Wound Healing .............................................................. 45-47
7. Healing in Specific Tissues .................................................. 47-50
General Information

Definition: Inflammation is the reaction of vascularized living tissues to local injury. Inflammation comprises a series of changes in the terminal vascular bed, in blood and in connective tissues with the purpose of eliminating the offending irritant and to repair the damaged tissue.

Roles of Inflammation:
- Protection
  - Contain and isolate the injury
  - Destroy invading organisms and inactive toxins
- Achieve healing and repair

1. Under ideal conditions the source of the tissue injury is eliminated, the inflammatory response resolves and normal tissue architecture and physiologic functions are restored.
2. The nature of the acute inflammatory reaction is intense and the affected area is walled-off by the collection of inflammatory cells. This process results in destruction of tissue by products of polymorphonuclear leucocytes and formation of an abscess.
3. Failure to eliminate the pathologic insult results in persistence of the inflammatory reaction.
4. Chronic inflammation often leads to scar formation.

Signs of Inflammation:
- Heat (calor)
- Redness (rubor)
- Swelling (tumour)
- Pain (dolor)
- Loss of Function (functio laesa)

These signs are due to the movement of plasma fluids, proteins, and inflammatory cells from the lumen of the vascular system out into the tissues.

10 Generalities Regarding the Inflammatory Response: (adapted from Slauson and Cooper)

1. Inflammation is a process involving multiple participants.
2. Inflammation occurs only in living tissue.
3. It is a series of events which overlap and form a continuum.
4. It is a response to an initiating event.
5. It can be harmful.
6. It is primarily a defensive reaction, (Survival oriented).
7. The inflammatory reaction is fairly stereotypical.
8. Many components are found in the blood stream.
9. There are multiple overlapping pathways in the inflammatory response. - Multiple ways to initiate a pathway, feedback and dampen or accelerate to control, (ie. redundant)
10. Much of the inflammatory response is a “surface phenomenon” - cell membrane perturbations are important.

It requires an initiating stimulus. There are many causes of inflammation, including infectious agents (bacteria, viruses, parasites), chemical agents, physical agents (trauma, radiation, burns) and immunologic reactions.
CLASSIFICATION OF INFLAMMATION

Purpose: Using specific criteria, it is possible to provide a brief description evaluation, also known as morphologic diagnosis, for each type of inflammatory response.

CLASSIFICATION OF INFLAMMATORY REACTIONS

<table>
<thead>
<tr>
<th>EXTENT</th>
<th>DURATION</th>
<th>DISTRIBUTION</th>
<th>EXUDATE</th>
<th>ANATOMIC MODIFIERS</th>
<th>ORGAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Peracute</td>
<td>Focal</td>
<td>Suppurative</td>
<td>Interstitial</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Moderate</td>
<td>Acute</td>
<td>Multifocal</td>
<td>Fibrinous</td>
<td>Broncho-interstitial</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Severe</td>
<td>Subacute</td>
<td>Coalescent</td>
<td>Serofibrinous</td>
<td>Glomerulonephritis</td>
<td>Enteritis</td>
</tr>
<tr>
<td>Chronic</td>
<td>Locally</td>
<td>Extensive</td>
<td>Fibrino-</td>
<td></td>
<td>Etc</td>
</tr>
<tr>
<td></td>
<td>Diffuse</td>
<td></td>
<td>Purulent</td>
<td>Submandibular</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>active</td>
<td></td>
<td>Necrotizing,</td>
<td></td>
<td>Granulomatous, Etc</td>
</tr>
</tbody>
</table>

EXTENT/SEVERITY - The severity of the process must be evaluated. However, it is important to recognize that determining the degree of severity is often very subjective.

<table>
<thead>
<tr>
<th>EXTENT OF INJURY</th>
<th>TISSUE DAMAGE</th>
<th>INFLAMMATORY CELLS</th>
<th>VASCULAR INVOLVEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Absent to Minimal</td>
<td>Few</td>
<td>Slight</td>
</tr>
<tr>
<td>Moderate</td>
<td>Some Present</td>
<td>Inflammatory cells</td>
<td>Moderate Edema and Evidence of Haemorrhage</td>
</tr>
<tr>
<td>Severe</td>
<td>Substantial</td>
<td>Inflammatory cells</td>
<td>Massive Edema and Haemorrhage may be seen</td>
</tr>
</tbody>
</table>

NOTE: In addition to mild, moderate, severe; other modifiers can also be used, eg, extensive, minimal, etc.

DURATION - How long has the process been underway? Determination of duration can also be very subjective and the morphologic changes associated with an inflammatory process may not correlate with the onset of clinical signs. For example, due to the high functional reserve of the liver and kidney it is common to find severe chronic lesions in these organs in animals that die suddenly.

PERACUTE INFLAMMATION:
* Definition: very acute
* Usually caused by a potent stimulus
* Usually the animal has no time to respond morphologically to a disease process
  * Less common than acute disease processes
General Features: Eg: Bee Sting
* Time: 0-4 hours
* Vascular Involvement: Hyperaemia, Slight edema, Haemorrhage
* Inflammatory cells: Not usually numerous, Few leucocytes
* Clinical Signs: Shock, sudden death

ACUTE INFLAMMATION:
* Definition: having a short and relatively severe course
* Time: It begins within 4-6 hours can last for 3-5 days
* Vascular Involvement:
  - Active Hyperaemia
  - Edema (due to endothelial damage-lymphatics and small blood vessels)
  - Occasional fibrin thrombi within vessels
* Inflammatory cells - Leukocyte infiltration is variable. In general neutrophils usually predominate, but sometimes-mononuclear cells (lymphocytes and plasma cells) can also be present.
* Clinical Signs - Most associated to the vascular changes: warm, red, swollen, painful, loss of function.
* Lymphatics - Lymphatic vessels have a role in moving away the exudate. The transportation of the exudate (i.e., inflammatory cells and necrotic debris) can lead to acute regional lymphadenitis.

Definitions:
- Acute regional lymphadenitis - Inflammation of regional lymph nodes
- Lymphangitis: Inflammation of a lymphatic vessel or vessels.

SUBACUTE INFLAMMATION:
Definition: Transition period separating acute and chronic inflammation. Evidence of hyperaemia and edema is regressing but evidence of repair such as fibroplasia and angiogenesis is lacking.
Time: varies from a few days to a few weeks.
Vascular involvement: There is a decline in the magnitude of vascular changes, compared to acute inflammation (less haemorrhage, hyperaemia and edema).
Inflammatory Cells: Characterised by a "mixed" or "pleocellular" inflammatory infiltrate. This means that the inflammatory cell type still may be primarily neutrophilic but usually it is also associated with an infiltration by lymphocytes, macrophages and plasma cells. Fibrosis and neovascularization is not a feature of subacute inflammation.
Lymphatics: 8 lymphatic drainage
  Endothelial damage repaired
**CHRONIC INFLAMMATION:**

**Definition:** Inflammation which persists over a period of time.

**Features:**
- Chronic inflammation is often the result of a persistent inflammatory stimulus in which the host has failed to completely eliminate the causative agent.
- Inflammatory response usually is accompanied by an immune response.
- Chronic inflammation is characterized by evidence of host tissue response in terms of repair - formation of scar and regeneration of damaged tissue.

**Histology:** mononuclear inflammatory cells, fibroblasts and collagen with proliferating vasculature.

**Cause:** May follow an acute inflammatory phase. May develop as an insidious, low-grade, subclinical process without history of a prior acute episode.

**Time:** Variable

**Vascular involvement:** Proliferations of capillaries and small blood vessels (angiogenesis/neovascularization) resulting in edema, haemorrhage and congestion.

**Host involvement:** Parenchymal regeneration or repair by fibrosis (scarring).

**Inflammatory Cells:**
- Lymphocytes
- Macrophages - Cells responsible for phagocytosis and tissue debridement
- Plasma cells
- Fibroblasts

**Lymphatics:** involvement variable - +/- proliferation and activation

**Clinical Signs:** Primary dependent upon duration of the illness and inflammatory lesions

**NOTE:** Many changes represented in chronic inflammation are also seen in areas of REPAIR.

**CHRONIC-ACTIVE INFLAMMATION:**

**Definition:** Chronic inflammation accompanied by acute exacerbations in which the tissues exhibit all of the usual characteristics of chronicity, with superimposed features of acute inflammation.

**Time:** Long period with exacerbations

**Vascular Involvement:** Same as with acute

**Inflammatory cells:** Neutrophils and cells associated with chronic inflammatory cells associated with chronic inflammation and host responses such as fibroplasia and angiogenesis

**Lymphatics:** May be inflamed

**Clinical Signs:** Variable

**Origin:**
1. Repeated episodes of inflammation have occurred and overlapped
2. Host has failed to adequately contain the invaders acute condition
DISTRIBUTION: What is the location of the lesion within an organ? [Usually a gross classification but can be used microscopically]

FOCAL:
Definition: Single abnormality or inflamed area within a tissue
Size: Varies from 1 mm to several centimetres in diameter

MULTIFOCAL:
Definition: Arising from or pertaining to many foci (several foci separated from one another)
Size: Variable.
Note: Each focus of inflammation is separated from other inflamed foci by an intervening zone of relatively normal tissue.

LOCALLY EXTENSIVE:
Definition: Involvement of considerable area within an organ.
AKA: Focally extensive
Possible origin:
1. Severe local reactions that spread into adjacent tissue
2. Coalescence of foci in a multifocal reaction
EXAMPLE: Pulmonary lesion of pneumonic Mannheimiosis in cattle. The cranioventral aspects of the lungs are involved while the dorsal portions usually are spared. Often bacterial in nature.

DIFFUSE:
Involve all the tissue or organ in which the inflammation is present
- Variations in severity may exist
EXAMPLE: Interstitial pneumonia. Diffuse lesions are often viral or toxic in etiology.

EXUDATE: The inflammatory process can be classified according to the predominant type of inflammatory cells, plasma protein content, and amount of fluid present.

SUPPURATIVE EXUDATION composed of large numbers of neutrophils along with dead cells.
Synonym: Purulent Exudation
Definition of purulent - predominant feature is the formation of pus.
Suppuration - process of forming pus
- implies that neutrophils and their proteolytic enzymes are present and that necrosis of host tissue cells has occurred
Gross Appearance: yellow-white to gray-white and varies from watery to viscous

**ABSCESS**: Localized form of suppurative exudative inflammation which is often walled off by a connective tissue capsule.

**Note**: Suppurative lesions are often bacterial in origin

**FIBRINOUS EXUDATION**

Pathogenesis: Increased vascular permeability (inflammatory edema) due to injury of endothelium and basement membranes results in leakage of plasma proteins including fibrinogen, which polymerizes perivascularly to fibrin - can be within inflamed tissue or body cavities.

Gross Appearance: yellow-white, or pale tan, stringy, shaggy meshwork (or fibrillar material) which gives a rough irregular appearance to the tissue surfaces. Casts of this friable material may form in the lumen of tubular organs. Can easily be broken apart and pulled from the underlying tissue.

**Time**: Acute process - can form in seconds

Histo and Outcome - composed of thread-like eosinophilic meshwork that can form masses of solid amorphous material. Fibrin provides the support for the eventual ingrowth of fibroblasts and new capillaries. The transformation of the fibrinous exudate (acute process) into well-vascularized connective tissue (chronic process), is known as organization of the exudate. However, fibrin can also be dissolved by enzymatic fibrinolysis or by phagocytosis by macrophages.

**IMPORTANT NOTE**: Do not confuse fibrinous exudation with fibrosis. Presence of a fibrinous exudate involves an acute process. In contrast, fibrosis is a chronic process and occurs when fibroblasts synthesize and secrete collagen.

**FIBRINOPURULENT EXUDATE**: Term used to classify an inflammatory process in which neutrophils and fibrin are abundant.

**SEROUS EXUDATION**

Definition: Inflammatory process characterized by accumulation of fluid relatively rich in protein on body surfaces with little cellular infiltrate.

Time: Usually acute

Causes: May be a dominant pattern of exudation for a wide variety of mild injuries.

**Example**: Traumatic blisters, sunburn.

Gross Appearance: Yellow, straw-like colour fluid, commonly seen in very early stages of many kinds of inflammatory responses.
GRANULOMATOUS INFLAMMATION
Definition: Granulomatous refers to an inflammatory response characterized by the presence of lymphocytes, macrophages, and plasma cells with the predominant cell being the macrophage. Macrophages are clustered in a characteristic elliptical formation around the causative etiologic agent, or around a central necrotic area, or simply as organized nodules. Large cells with abundant cytoplasm, referred to as "epithelioid cells," and "multinucleated giant cells" are also commonly present in this type of inflammatory response.

TIME: always chronic
Etiology: Usually some non-digestible organism or particle which serves as a chronic inflammatory stimulus, delayed-type hypersensitivity is often required.
Organisms: Mycobacterium sp, Actinomyces bovis, Blastomyces dermatitidis, Coccidioides immitis
Noninfectious agents: Mineral oil, Complex polysaccharides, Foreign bodies

OTHER TYPES OF EXUDATE AND INFLAMMATION

NECROTIZING INFLAMMATION:
Definition: Inflammation characterized primarily by necrosis (variable amounts of vascular and leukocyte contributions)

-Necrotizing inflammation is often associated with the interruption of blood flow, such as in mycotic diseases of the gastrointestinal tract that result in arterial thrombosis.
-It is also seen in association with toxin-producing bacterial infections such as blackleg (Clostridium chauvoei).
Histologically, there is only scant evidence of vascular or leucocytic contributions.

Fibrinonecrotic Inflammation: Inflammation on a well-vascularized epithelial surface (eg: trachea, intestine, nasal passages), characterized by necrosis of the surface epithelium and presence of fibrin.

Pseudomembranes/ Diphtheritic Membranes: This is a form of fibrinonecrotic exudate. The fibrin and necrotic surface epithelium forms a structure which resembles the lumenal surface of the tissue (looks like a the affected tissue is covered by a membrane (eg: small intestine).
Haemorrhagic Inflammation: Haemorrhage is the predominant feature of inflammation. It occurs due to severe injury to blood vessel or marked diapedesis. Haemorrhagic inflammation is most commonly

Mucoid Exudate: Consists of mucus as well as variable amounts of inflammatory cells. Mucopurulent Exudate: an exudate containing both mucus and pus (large numbers of neutrophils and neutrophil debris).

Catarrhal inflammation - Synonym for mucopurulent inflammation.

Eosinophilic Inflammation: Eosinophils are the primary inflammatory cell type present. In some cases it is possible to diagnose macroscopically because eosinophils possess granules which give the affected tissue a green tinge. Example: Eosinophilic myositis in cattle.

Nonsuppurative Inflammation: This a microscopic diagnosis as mononuclear cells (lymphocytes and plasma cells) are the primary inflammatory cell type present.

Lymphocytic Inflammation: Lymphocytes are the predominant inflammatory cell type.

ANATOMIC MODIFIERS: Uses: Terms used to describe a specific area within an organ that may be affected by inflammation or degenerative conditions.

Example: Cardiac Inflammation
   Endocardium - Endocardiosis/endoendocardiitis
      valvular/mural
   Myocardium - Cardiomyopathy/myocarditis
   Pericardium - Pericardial effusion, hydropericardium/pericarditis
   Pancarditis - Involves all layers

NOTE: Additional study help can be found in the following programs available in the Noah’s Ark laser-disk (Room 217S)

<table>
<thead>
<tr>
<th>LESSON</th>
<th>NAME</th>
<th>CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIAG2</td>
<td>Morphologic diagnosis</td>
<td></td>
</tr>
<tr>
<td>DIAG3</td>
<td>Morphologic diagnosis-2</td>
<td></td>
</tr>
<tr>
<td>INFLAMN</td>
<td>Classification of inflammation</td>
<td></td>
</tr>
<tr>
<td>INFLAMQ5S</td>
<td>Descriptions/classifications</td>
<td></td>
</tr>
<tr>
<td>INFLCELL</td>
<td>Cells in inflammation</td>
<td></td>
</tr>
<tr>
<td>INJURY</td>
<td>Cell degeneration</td>
<td></td>
</tr>
<tr>
<td>MEDQUIZ</td>
<td>Mediators quiz</td>
<td></td>
</tr>
<tr>
<td>INFLAQUIZ</td>
<td>Quiz</td>
<td></td>
</tr>
<tr>
<td>INFLA1</td>
<td>Histopath Lab Exercise</td>
<td></td>
</tr>
<tr>
<td>INFLA2</td>
<td>Histopath Lab Exercise</td>
<td></td>
</tr>
</tbody>
</table>