INFLAMMATION & REPAIR

Lectures 2 & 3
Classifying Inflammation
Winter 2013

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Special thanks to Drs. Hanna and Forzan
Course Outline

i. Inflammation: Introduction and generalities (lecture 1, pp.1-2)

ii. Classification of inflammation (lectures 2 and 3, pp. 2-8)

iii. Acute Inflammation
   i. Vascular events / permeability (lecture 4, pp. 9-11)
   ii. Inflammatory cell types (lecture 5, pp. 12-14)
   iii. Sequence of events (lecture 6, pp. 15-20)
   iv. Chemical mediators (lecture 7, pp. 20-26)

iv. Chronic Inflammation (lecture 8, pp. 27-30)
   i. Granulomatous inflammation

v. Repair and wound healing (lecture 9, pp. 31-35)

vi. Healing in specific tissues (lecture 9, cont., pp. 35-37)
Morphologic Diagnosis

1. Anatomic modifier: ‘Organ’-itis (+/- anatomic subtypes)
   a) Nephritis (vs nephrosis / nephropathy → non-inflammatory)
   b) subtype, eg glomerulonephritis, interstitial nephritis, etc

2. Exudate - purulent, fibrinous, necrotizing, etc

3. Distribution - focal, multifocal (coalescing), locally extensive, diffuse

4. Duration - peracute, acute, subacute, chronic, chronic-active

5. Extent (Severity) - mild, moderate, marked /severe
<table>
<thead>
<tr>
<th>Inflammation of the:</th>
<th>Modifier:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
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<tr>
<td>Liver</td>
<td></td>
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<tr>
<td>Lymph node</td>
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<tr>
<td>Large Intestine</td>
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<td>Cecum</td>
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<td>Heart muscle</td>
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<tr>
<td>Skeletal Muscle</td>
<td></td>
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<tr>
<td>Cholecystitis</td>
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<tr>
<td>Pneumonia</td>
<td></td>
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<tr>
<td>Blepharitis</td>
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</table>
### Anatomic Modifiers

**Not on your list are:**

<table>
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<tr>
<th>Inflammation of:</th>
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<tr>
<td>Adipose tissue</td>
<td>Steatitis / panniculitis (subQ)</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Epididymitis</td>
</tr>
<tr>
<td>Air sac</td>
<td>Air sacculitis</td>
</tr>
<tr>
<td>Gland (any)</td>
<td>Adenitis</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>Sialoadenitis</td>
</tr>
<tr>
<td>Sinus</td>
<td>Sinusitis</td>
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</table>
Anatomic Modifiers: Subtypes

Nephritis, interstitial (inflammation/damage in the interstitium)

Tubulonephritis (inflammation/damage in the tubules)

Glomerulonephritis (inflammation/damage in glomeruli)

Nephritis (inflamed kidney)
Anatomic Modifiers: *Subtypes*

- Bronchitis
- Tracheitis
- Bronchopneumonia
- Tracheobronchitis

Subtypes:

- Lung pneumonia
- Interstitial pneumonia
EXUDATE
(type of inflammation)

Exudate classified by predominant type of inflammatory cells, protein content &/or type of fluid present.

Types of exudate:
- Fibrinous
- Necrotizing
- Suppurative (= purulent)
- Granulomatous
- Pyogranulomatous
- Hemorrhagic
- Serous / Mucoid / Catarrhal
- Eosinophilic
- Non-suppurative / Lymphoplasmacytic
FIBRINOUS EXUDATE

Can be in tissue or body cavities

1. Increased vascular permeability (inflammatory edema)
2. Leakage of fibrinogen
3. Fibrinogen turns into fibrin
4. Fibrin clots

Gross Appearance
FIBRINOUS EXUDATE

- acute process - can form in minutes
- **histo:** thread-like eosinophilic meshwork or solid amorphous eosionophilic material (few neutrophils)
- **outcome:** small amounts removed.
  - larger amounts provide the support for the eventual growth of fibroblasts and new capillaries (granulation)
Fibrous adhesions are common sequelae of fibrinous exudate.
NECROTIC INFLAMMATION

• characterized primarily by necrosis, with usually minimal exudate

Multifocal necrotizing hepatitis, lamb. The cause of the abortion in this case was *Campylobacter fetus*. Note the numerous large (up to 1 cm diameter) pale foci scattered throughout the liver; these represent areas of necrosis and inflammation.
• necrosis of well-vascularized epithelial surface = necrosis + fibrin exudation

• eg, pseudomembranes (diphtheric membranes) where the fibrinonecrotic exudate forms a membrane like structure on the luminal surface (fibrin + necrotic mucosa)

Fibrinonecrotic tracheitis, Bison.
Note the pseudomembrane on the luminal surface of the trachea.
FIBRINONECROTIC EXUDATE

• in the gut “casts” of friable material (fibrin & necrotic mucosa) can fill the lumen.

Morph Dx: Enteritis, fibrinonecrotizing
Etiology: Lawsonia intracellularis
Differ Dx: Salmonellosis
SUPPURATIVE EXUDATE

- aka purulent exudate
- composed of many neutrophils, necrotic cells and debris
- formation of *pus* due to proteolytic enzymes (esp myeloperoxidase)
• avian species, amphibians, fish, reptiles & some mammals have *heterophils*, instead of neutrophils
  
  ♦ lack myeloperoxidase → caseous exudate (no liquefaction)
ABSCESS:

- localized form of suppurative inflammation that is walled off by a connective tissue capsule (i.e., chronic)
- suppurative lesions are often of bacterial origin!
SUPPURATIVE EXUDATE

Pyothorax (pleural empyema): pus in the thoracic cavity

Note large numbers of neutrophils & a few fibrin strands
FIBRINOSUPPURATIVE EXUDATE

- inflammatory process rich in both neutrophils and fibrin
GRANULOMATOUS INFLAMMATION
(aka granulomatous exudate)

Definition:

- where macrophages predominate; often with some lymphocytes & plasma cells.
- macrophages can be clustered around the causative agent and are often in the form of “epithelioid” or “multinucleated giant cells”.

multinucleated giant cells
epithelioid macrophages
TIME: always chronic

ETIOLOGY:
- typically non-digestible organism or particles
  - eg:
    - Fungus
    - some bacteria (eg Mycobacteria)
    - Plant material
    - Mineral crystals
    - Suture material
    - Sperm
    - Keratin, etc.
- delayed-type HS often required
GRANULOMATOUS INFLAMMATION

Example: Johne’s disease (paratuberculosis)

Morph. dx: Enteritis, granulomatous
Etio. dx: Mycobacterial enteritis
Etiology: Mycobacterium avium spp. paratuberculosis
**Definition:** neutrophilic + granulomatous inflammation

**Morph. dx:**
Lymphadenitis, pyogranulomatous

**Name dz:**
Rhodococcosis

**Etiologic agent:**
*Rhodococcus equi*
Example:
Morph. dx: Dermatitis, pyogranulomatous
Etiologic agent: Actinobacillus spp
HEMORRHAGIC INFLAMMATION

• hemorrhage predominates
• severe injury to blood vessels:
  o thrombosis / vascular obstruction
  o bacterial toxins
  o proteolytic enzymes
• most often acute or peracute
• often accompanied by necrosis (necrohemorrhagic)
SEROUS EXUDATE

Definition
- fluid rich in protein, few cells (inflammatory edema)
- on body surface or mucosa

Time
- usually acute

Causes
- often dominant pattern of exudation for a wide variety of mild injuries.
- eg, trauma, cold, blisters, sunburn

Gross Appearance
- straw-yellow or clear fluid

Morph. dx: Dermatitis, vesicular
Etio. dx: Viral dermatitis
Etiology: Vesicular exanthema virus
MUCOID EXUDATE

- **Mucoid exudate:** predominately mucus with few inflammatory cells
- **Mucopurulent exudate:** combination of mucus and neutrophilic exudate

Example (rabbit):
Morph. Dx: **Enteritis, mucoid**
Disease name: **Mucoid Enteritis**
Etiology: **Unknown**
CATARRHAL EXUDATE

- inflammation of a mucous membrane with marked increase in flow of exudate (typically mucoid or mucopurulent exudate)
Exudate classified by predominant type of inflammatory cells, protein content &/or type of fluid present.

Types of exudate:
- Fibrinous
- Necrotizing
- Suppurative (= purulent)
- Granulomatous
- Pyogranulomatous
- Hemorrhagic
- **Serous / Mucoid / Catarrhal**
- Eosinophilic
- Non-suppurative / Lymphoplasmacytic
EOSINOPHILIC INFLAMMATION

- eosinophils predominate
- grossly may be green
- usually associated with:
  - parasites
  - allergies
  - sometimes with foreign bodies
Example (cow):
Morph. Dx: **Myositis, eosinophilic**
Dz. name: **Eosinophilic myositis**
Etiology: **Sarcocystis** infection
Etiologic Dx: **Parasitic myositis**
NON-SUPPURATIVE INFLAMMATION

• microscopic diagnosis
• mononuclear cells predominate, esp lymphocytes & plasma cells

Non-suppurative is often used instead of lymphocytic or lymphoplasmacytic, particularly in viral disease of the brain.
LYMPHOCYTIC INFLAMMATION

- lymphocytes predominate

Example (dog):
Morph. Dx: **Thyroiditis, lymphocytic**
Etiology: **autoimmune**
Fibrin (yellow/clotted) → Fibrin (pink strands/clumps) → Fibrin (yellow/clotted)

Necrotic/Bloody → Necrosis/hemorrhage → Necrotic/Bloody

Edema, few neutrophils → Edema, few neutrophils → Edema, few neutrophils

MØ/giant cells LØ’s/PC’s → MØ/giant cells LØ’s/PC’s → MØ/giant cells LØ’s/PC’s

Caseous (dry) → Caseous (dry) → Caseous (dry)

Clear/pale → Clear/pale → Clear/pale

Suppurative/Purulent → Fibrinous → Suppurative/Purulent

Serous → Granulomatous (mostly) → Serous

Exudate
Why is exudate type important?

- **Fibrinous**
  - Bacteria - ACUTE

- **Suppurative**
  - Bacteria

- **Granulomatous**
  - specific bacteria, many fungi

- **Hemorrhagic**
  - Toxin (bacterial or otherwise)
  - Ischemia

- **Eosinophilic**
  - esp parasites & allergies
### Classification of Inflammation

To make a morphologic diagnosis of an inflammatory response

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<td>(severe)</td>
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Adapted from: Mechanisms of Disease 3rd ed, Slauson and Cooper, Figure 4-3 page 149
DISTRIBUTION

- location of the lesion within an organ
- usually a gross classification but ALSO used microscopically

And, again, our kidney
Definition
• single abnormality or inflamed area within a tissue

Size
• from 1 mm to several cm in diameter / length

Example (turkey):

**Morphologic Dx:**
Typhlitis, fibrinonecrotic, **focal**

**Etiologic Dx:**
Protozoan Typhlitis (*H. meleagris*idae)

**Name of disease:**
Histomoniasis / Black head
Example

Morph. Dx:
Pnemonia, granulomatous, focal

Etiol. Dx:
Mycobacterial pneumonia

Name of disease:
Mycobacteriosis
DISTRIBUTION – Multifocal

**Definition**

- arising from or pertaining to many foci
- size is variable
- each focus of inflammation is separated from other inflamed foci by an intervening zone of relatively normal tissue.

**Example (dog):**

**Morph. Dx:** Pneumonia, granulomatous, **multifocal**

**Etiol. Dx:** Pulmonary blastomycosis

**Etiology:** *Blastomyces dermatitidis*
DISTRIBUTION – Multifocal to coalescing

Multifocal to coalescing lesions start as multiple foci, but as they grow, they merge into fewer larger nodules.

Example (cat):
Morph. Dx: Nephritis, (pyo)granulomatous, **multifocal to coalescing**
Name of Disease: **Feline infectious peritonitis**
DISTRIBUTION – Locally (focally) extensive

Definition
- involvement of considerable area within an organ
- often use segmental for tubular organ

Possible origins
- severe local reactions that spread into adjacent tissue

Example:
Morph. Dx: Bronchopneumonia, suppurative, **locally extensive**

Etiol. Dx: Pasteurella pneumonia
Etiology: Pasteurella multocida
DISTRIBUTION - Diffuse

- involves entire organ or tissue
- can vary in severity
- etiology often viral or toxic

Example:
Morph. Dx: Pneumonia, interstitial, **diffuse**
Etiol. Dx: Toxic pneumonia
Etiology: Paraquat
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DURATION – Peracute Inflammation

Features

• hyperemia / hemorrhage, slight edema

• few inflammatory cells

• if highly pathogenic agent, often few clinical signs ➞ shock / sudden death
Peracute Inflammation

**Definition:** very acute

- usually due to a potent stimulus (eg virus, bee sting)
- few gross or histo lesions: as little time for a tissue response.

**Time:** 0-4 hours

Example (mute swan):

**Morph. Dx:** Pericarditis (includes epicarditis), hemorrhagic, multifocal, **peracute**

**Etiology:** Avian Influenza (highly pathogenic H5N1)
DURATION – Acute Inflammation

**Time**
- 4-6 hours to 3-5 days

**Vascular Involvement**
- active hyperemia + edema
- fibrin on tissue surfaces/cavities

**Inflammatory cells**
- neutrophils predominate

**Lymphatics**
- remove exudate

**Cardinal Signs**
- rubor, calor, tumor, dolor

Example:
Morph. Dx:
Peritonitis, fibrinous, diffuse, acute
DURATION – Acute Inflammation

Example (pig):
Morph. Dx: Bronchitis, suppurative, multifocal, **acute**
DURATION – Subacute Inflammation

**Definition:**
- transition between acute & chronic

**Time**
- few days to ~1 week

**Inflammatory cells**
- mix of LØ’s / PC’s (often predominate) & MØ’s, PMN’s

**Vascular involvement**
- less hemorrhage, hyperemia & edema than in acute
- no evidence of repair

**Example:**

Morph. Dx:
Colitis, lymphoplasmacytic, segmental, **subacute**
DURATION – Subacute Inflammation

• we often see primarily lymphocytic accumulation in viral infections
• these are often referred to as subacute (regardless of actual duration)

Example (horse):

Morph. Dx: Arteritis, lymphoplasmacytic, focal, subacute
Etiol. Dx: Equine Viral Arteritis
DURATION – Subacute Inflammation

- we often see primarily lymphocytic accumulation in viral infections
- these are often referred to as subacute (regardless of actual duration)

Example:

**Morph. Dx:** Encephalitis, non-suppurative, focal, subacute

**Etiol. Dx:** Viral disease (several)
DURATION – Chronic Inflammation

Definition:
• inflammation that persists over a long period of time.
• result of a persistent inflammatory stimulus (failure to completely eliminate agent)
• usually some degree of repair (regeneration & fibrosis)

Time:
• weeks to years
DURATION – Chronic Inflammation

May be an insidious, low-grade, subclinical process with no evidence of an acute episode

Morph. dx: Enteritis, granulomatous, segmental, chronic
Etiology: Mycobacterium avium spp paratuberculosis
May be an insidious, low-grade, subclinical process with no evidence of an acute episode

Morph. dx: Enteritis, granulomatous, segmental, **chronic**

Etiology: Mycobacterium avium spp paratuberculosis

**DURATION – Chronic Inflammation**

- Epithelioid macrophage
- Multinucleated giant cell
DURATION – Chronic Inflammation

Histo

- mononuclear inflammatory cells – MØ’s (EM’s / MGC’s), LØ’s, PC’s
- see fibrosis (fibroblasts / collagen) and angiogenesis / neovascularization (proliferating small vessels)

Morph. dx:
Dermatitis, granulomatous, multifocal, chronic

Etiol. dx:
Fungal dermatitis

Etiology:
Blastomyces sp
DURATION – Chronic Inflammation

- lesions due to larva migrans are sometimes granulomatous

Morph. Dx: Nephritis, granulomatous, focal, chronic, with intralesional ascarid larva
Name of disease: Visceral larva migrans
DURATION – Chronic Inflammation

Granulation tissue (REPAIR):
• neovascularization and fibrous tissue proliferation
# DURATION – Chronic-active Inflammation

<table>
<thead>
<tr>
<th>Definition</th>
<th>Time</th>
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<tbody>
<tr>
<td>• usual characteristics of chronicity, with superimposed features of acute inflammation</td>
<td>• chronic time frame (with overlapping acute features)</td>
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<td>• usually host has failed to adequately contain the inciting agent</td>
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Morph. Dx: Pericarditis (epicarditis), fibrinosuppurative, diffuse, chronic (chronic-active)

Name of condition: Traumatic reticulo-pericarditis (hardware disease)
Chronic-active Inflammation

Morph. Dx (horse):
Pericarditis (epicarditis), fibrinous, diffuse, chronic (chronic-active), severe, with abundant fibrosis
DURATION - Review of Time Frame

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<th>Type</th>
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<td>4-6 hours to 3-5 days</td>
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<tr>
<td>Subacute</td>
<td>Few to several days</td>
</tr>
<tr>
<td>Chronic</td>
<td>Weeks / Months / Years</td>
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DURATION

FIBRIN & OR NEUTROPHILS (pus) = ACUTE

GRANULOMATOUS INFLAMMATION & OR FIBROSIS = CHRONIC

FIBROSIS + NEUTROPHILS and/or FIBRIN = CHRONIC- ACTIVE
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Adapted from: Mechanisms of Disease 3rd ed, Slauson and Cooper, Figure 4-3 page 149
EXTENT- How severe is it?

Mild - not too bad

- Tissue damage
  - absent or minimal
- Inflammatory cells
  - few
- Vascular involvement
  - little edema &/or congestion

Morph. Dx:
Myocarditis, suppurative (neutrophilic), multifocal, acute, mild
Example (cow):

**Morph. Dx:**
Myocarditis, suppurative (neutrophilic), multifocal, acute, **moderate**
EXTENT - How severe is it?

Mild
Moderate
Marked (severe) - really bad

- ↑ Tissue damage
- ↑ Inflammatory cells
- ↑ Vascular involvement
  - lots of edema &/or hemorrhage

Example (cow):

Morph. Dx:
Myocarditis, suppurative, multifocal to coalescing, acute to subacute, severe
HISTORY AND SIGNALMENT:

3-month-old feeder pig with history of weight loss for several weeks. Given antibiotics yesterday, but dead today.
1. Description:
The inner surface of the pericardial sac and the epicardium of the heart are diffusely covered by abundant white, stringy, friable / elastic material (fibrin), loosely attached. The pericardial sac is moderately to markedly thickened. [A small amount of turbid gray fluid escaped when the pericardium was opened]
2. On low power the epicardium is thickened with a rough surface.
2. The deeper part of the epicardium is thickened by loose connective tissue with edema (clear spaces), several small blood vessels and moderate numbers of inflammatory cells.
Surface of Epicardium.

3. Fibrin
4. Degenerated neutrophils and other cellular debris
Heart:
The epicardium (& pericardium) is diffusely thickened and infiltrated by inflammatory cells. The thickening is due to increased numbers of fibroblasts and capillaries, with moderate edema and infiltration of inflammatory cells, mostly macrophages and lymphocytes (mononuclear inflammatory cells)

Many degenerated neutrophils are present on the surface, admixed with very abundant eosinophilic material (fibrin) and necrotic debris.
7. MORPHOLOGIC DIAGNOSIS

Anatomic Modifiers: Pericarditis (includes epicarditis)

Exudate: Fibrinous or fibrinosuppurative

Distribution: Diffuse

Duration: Chronic-active

Extent: Severe

Etiologic Diagnosis: Bacterial infection
PATHOGENESIS:

Bacteria gained entrance into the pericardial sac - likely localized from blood stream during sepsis (ie hematogenious spread during bacteremia). The fibrosis nearest the heart and fibrinous inflammation on the surface suggests failure to clear the agent (bacteria) with continuous acute inflammation on the surface with on-going healing (chronic) underneath.