Chronic Inflammation

- Prolonged tissue reaction characterized by:
  - Accumulation of lymphocytes and macrophages
  - Proliferating blood vessels
  - Formation of connective tissue
- Clinically, the process is of longer duration
  - Days, weeks or months

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>Onset</td>
<td>Fast: minutes or hours</td>
<td>Slow: days</td>
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<tr>
<td>Cellular infiltrate</td>
<td>Mostly neutrophils</td>
<td>Mononuclear/macrophages and lymphocytes</td>
</tr>
<tr>
<td>Tissue injury, color</td>
<td>Usually mild and self-limited</td>
<td>Often severe and progressive</td>
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<tr>
<td>Local and systemic</td>
<td>Prominent</td>
<td>Less</td>
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<td>signs</td>
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Chronic Inflammation

- Predominated by macrophages, lymphocytes and plasma cells
- Significant collateral damage
- Repair processes occurring in parallel with persistent inflammation
Chronic Inflammation - Fundamentals

- Persistence of the stimulus of acute inflammation
- The lack of resolution may be secondary to:
  - Inability to get rid of the pathogen
  - Pathogen resistance to antimicrobials
  - Degradation resistant foreign body
  - Persistent exposure to an autoantigen
  - Genetic inability of the host to mount the appropriate response to the pathogen

'Signature cell' of chronic inflammation

- Activated macrophages
- M1 macrophages are associated with high levels of pro-inflammatory cytokines
- The innate immune system senses the persistent threat and increases innate protein and cell production to thwart it
- Chronic high levels of inflammatory cytokines cause:
  - Increased rates of hepatic production of defense proteins
  - Increased hepcidin production - the innate system wants to sequester Fe++ which is a growth factor for many microbes
  - Increased growth factors for platelets, monocytes and platelets
Granulomatous Inflammation

- Distinct form associated with persistent T-cell activation
- Common with persistent intracellular microbial infection
- Common with macrophage uptake of poorly degradable foreign bodies
- Found in several disease of unknown etiology
  - Sarcoidosis
  - Inflammatory bowel disease (IBD)

Unique morphology

- Central portion is necrotic debris
  - "caseous" or "necrotizing" granuloma, commonly in TB
- Activated macrophages and multinucleated giant cells in periphery
- Cuff of T-cells, the vast majority of which are CD3+/CD4+
- The entire granuloma is rimmed by proliferating fibroblasts
A typical granuloma resulting from infection with Mycobacterium tuberculosis showing an area of central necrosis (C), activated epithelioid macrophages (M), giant cells (G), and a peripheral accumulation of lymphocytes (L).

Figure 3-23: Typical tuberculous granuloma showing an area of central necrosis surrounded by multiple Langhans-type giant cells, epithelioid cells, and lymphocytes.
Foreign body granuloma

The logic of the granuloma appears to walling off the infecting organism
Is that logic sound?

- Yes and No
- The organism is indeed ‘walled off’, BUT
  - Collateral damage caused by progressive tissue
c necrosis and fibrosis can be extensive

Local and systemic effects and how the physician can exploit them for diagnosis and treatment...

- Pathophysiological effects of inflammation based on macrophage activation
  and release of pro-inflammatory cytokine and inflammation provoked growth
  factors
- Clinical differences are based solely upon intensity and duration of the
  stimulus
- The biochemical changes are “acute phase reactants” and reflect hepatic
  adjustments to inflammation

Biochemical Changes in Inflammation

- Increased hepatic production of:
  - Fibrinogen
  - Ceruloplasmin
  - Complement components (C3)
- Reciprocal decrease in albumin synthesis
  - Rough correlation between decrease and duration of inflammatory process
- Increased hepatic production of hepcidin
  - Anemia
- Growth factors stimulate marrow
  - Increase leukocyte production
  - Increase platelet production
  (leukocytosis and thrombocytosis can be present)
C-Reactive protein (CRP)
• CRP production is stimulated by inflammation and is tightly linked to IL-6 levels
• Can be measured rapidly, reliably and relatively low cost
• Can be used in semi-quantitative fashion for level of inflammation when normal can exclude significant inflammation being present
• Obesity is one morbidity that can cause a "false" elevation of CRP

Erythrocyte Sedimentation Rate (ESR)
• Chronic inflammation causes clinically detectable antibody synthesis expressed as polyclonal increase in IgG
• IgG and fibrinogen coat erythrocytes and the red cells then fall more rapidly through a column of plasma: this rate is the ESR.
• False elevations can occur when there is increased IgG present for non-inflammatory reason - eg., myeloma, age
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<tr>
<th>Subject</th>
<th>Principal Causes</th>
<th>Principal Aetia of Inflammation</th>
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<tbody>
<tr>
<td>Chlamydia, gonorrhea, syphilis</td>
<td>Transmission of infection through sexual contact with an infected person.</td>
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<tr>
<td>HIV, hepatitis B, and C</td>
<td>Transmission of infection through exposure to blood or other body fluids.</td>
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<tr>
<td>Tuberculosis</td>
<td>Transmission of infection through respiratory droplets.</td>
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**Figure 8.10.** Major roles of cytokines in acute inflammation. FSG, Feeder stromal growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor.

**Figure 8.11.** Pathways of immune response and inflammation. Mφ, Macrophage; T, T lymphocyte; B, B lymphocyte; NK, Natural killer cell; DC, Dendritic cell. 

**Figure 8.12.** The role of inflammation in scarring. SCAR, Scarring.
Questions?
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