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 3-2: Features of Acute and Chronic Inflammation |
|-----------------|------------------|------------------|
| Feature         | Acute            | Chronic          |
| Onset           | Fast: minutes or hours | Slow: days       |
| Cellular infiltrate | Mostly neutrophils | Macrophages/macrophages and lymphocytes |
| Tissue injury, involvement | Usually mild and self-limited | Often severe and progressive |
| Local and systemic signs | Prominent | Less |
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 a central area of caseous necrosis (C), activated epithelioid macrophages (M), giant cells (G), and a peripheral accumulation of lymphocytes (L).

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 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 leucocyte 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 levels of inflammation
  - when normal can exclude significant inflammation being present
- Obesity is the 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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Questions?
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