Chronic Inflammation

I. Introduction.
   A. Definition: Chronic inflammation is a prolonged tissue reaction characterized by the accumulation of lymphocytes and macrophages, the presence of proliferating blood vessels and the formation of connective tissue at the site of injury. Clinically, the process is of longer duration, lasting days, weeks or months and the acute changes of local: redness (rubor), swelling (tumor), heat (calor), pain (dolor) become less dramatic.

II. Chronic inflammation is characterized by:
   A. Predominance of M1 macrophages, lymphocytes and plasma cells.
   B. Collateral tissue damage
   C. Repair processes occurring in parallel with persistent inflammation

III. Chronic inflammation is caused by persistence of the cause of the initial episode of acute inflammation.
   A. A lack of resolution by acute inflammation may be secondary to:
      1. Inability to eradicate microbial pathogen
      2. Drug resistance
      3. Intracellular pathogens
      4. Persistent or degradation resistant antigen
   B. Persistent exposure to an autoantigen which is an integral component of self and cannot be eradicated. Example: DNA in systemic lupus erythematosus
   C. Genetic inability of the host to mount the correct immune response that would eliminate the pathogen in the “normal” population

IV. In contrast to the signature neutrophil of acute inflammation- macrophages are the dominant cell of chronic inflammation.
   A. Persistent presence and stimulation of M1 macrophages is associated with high levels of inflammatory cytokines especially IL-1, 6, and TNF-α. IL-8 (and possibly IL-17) is also present and accounts for the neutrophils found in chronic inflammation but, over time, IL-1, 6 and TNF α are present in greater amounts leading to dominance of macrophages in chronic inflammatory lesions
   B. The logic is that the innate system senses that there is a persistent inflammatory stimulus that needs eradication and therefore continues to increase recruitment of proteins and cells to combat the threat. Since neutrophils didn’t succeed, the innate system switches to a different cell type.
C. Chronic inflammatory cytokine stimulation causes increases in synthetic rates of liver proteins associated with innate immune responses to inflammation with a reciprocal decrease in albumin synthesis.

D. Hepatic hepcidin production is increased. Hepcidin is a peptide hormone that is the master regulator of iron. It controls iron metabolism by regulating the rate of iron absorption in the gut and its release when stored in marrow macrophages. Increased hepcidin causes decreased iron availability in the bone marrow (and also decreases availability to bacteria that could use it as a growth factor).

E. Chronic inflammatory cytokine stimulation causes increases in synthetic rates of critical growth factors for platelets, neutrophils and monocytes.

V. Granulomatous Inflammation.

A. A very distinctive form of chronic inflammation associated with persistent T-cell activation. In the parlance of HD, frustrated T cell mediated macrophage immunity.

1. Characteristic of microbial intracellular infection of macrophages with organisms that are resistant to antimicrobials/intracellular killing mechanisms. M. tuberculosis is the prototype infection but many fungi and some bacteria are also associated with granulomas.

2. Macrophage ingestion of non-degradable foreign bodies can also cause granuloma formation or..

3. Diseases of unknown etiology, sarcoidosis or inflammatory bowel disease are examples that most likely represent persistent antigen presentation by the macrophage.

B. Granuloma morphology is unique. The typical granuloma has a central area of necrosis, termed caseous or necrotizing, when TB infection is present, surrounded by activated macrophages, multinucleated giant cells and then peripheral cuff of predominantly CD3, 4 helper T cells. The giant cells are
the ultimate expression of a frustrated macrophage response. They are formed by the fusion of up to a 100 activated macrophages and can function as a huge phagocytic cell. Finally, the entire granuloma is rimmed by proliferating fibroblasts.

C. The logic appears to be a mechanism to “wall off” an infecting organism but the collateral damage caused by progressive tissue necrosis and fibrosis can be extensive.

VI. The systemic effects of acute and chronic inflammation and how they can be exploited by the physician for diagnosis and treatment

A. The systemic effects of both acute and chronic inflammation are based on neutrophil and macrophage activation and release of pro-inflammatory cytokines and inflammation provoked growth factors.

B. The biochemical, immunologic and clinical differences between the two are based on intensity and duration of the stimulus- the longer it lasts, the greater the changes in constitutional symptoms like fever, chills, sweats and fatigue will be present.

C. The biochemical changes are termed “acute phase reactants” (really bad term but we are stuck with it) and these are the reflection of hepatic protein production adjustments to inflammation.

1. Examples would be increased production of fibrinogen, ceruloplasmin and complement components, especially C3.

2. The liver has to shunt energy for production to the reactants and there is a reciprocal decrease in albumin synthesis. A decreased serum albumin is characteristic of ongoing inflammation and there is a rough correlation between its decrease and the intensity and duration of the inflammatory process.

3. Hepcidin is increased and this leads to anemia because the marrow cannot utilize iron trapped in macrophages.

D. The cytokine driven growth factors stimulate the marrow to increase leucocyte production and platelet production. Leucocytosis and thrombocytosis are characteristic of inflammation. The former more so with acute inflammation, the latter with chronic inflammation.

E. The inflammatory cytokines are elevated in the plasma and can be measured directly, but it is simpler to use a proxy measurement like C-reactive protein (CRP). This liver produced factor is closely linked to IL-6 levels and can be measured rapidly and at low cost. CRP is an invaluable
clinical tool. It can be used in semi-quantitative fashion to assess the intensity of inflammation, or conversely, when it is normal can rule out significant inflammation. The only cause of a “false positive” CRP is marked obesity—presumably M1 macrophages in the obese white adipose tissue are stimulating higher baseline amounts that are detected in plasma.

F. If the duration of inflammation is longer than acute, increased antibody synthesis becomes detectable and this is reflected in increased IgG levels in blood. Increased IgG and fibrinogen will cause erythrocytes to fall rapidly through a column of plasma and the rate of fall can be measured as the erythrocyte sedimentation rate (ESR). The ESR, until recently, was used as an index of inflammation but is rapidly becoming obsolescent because of “false elevations” that can be cause by increasing age, gender and presence of serum proteins that are not related to inflammation—myeloma proteins for example.

(modified from original handout by John Robinson, MD)