Inflammation: Chronic

Secondary article

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Chronic inflammation may result from failure to eliminate an acute inflammatory irritant, from an autoimmune response to a self antigen, or may be caused by an innately chronic irritant of low intensity that persists. It is characterized by simultaneous inflammation and repair, with recruitment and activation of macrophages, lymphocytes and other cells triggered by the coordinated action of cytokines and growth factors.

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Introduction

Inflammation is a pattern of response to injury, in which cells and exudate accumulate in irritated tissues and tend to protect from further damage. It may be classified as acute or chronic. Chronic inflammation may result from failure of the recovery phase of acute inflammation, or may occur as a distinct process from the outset, because of the nature of the irritant. Although it shares many characteristics of the acute inflammatory response, chronic inflammation is a biologically distinct pattern of response to an irritant. It may be divided into nongranulomatous and granulomatous chronic inflammation; the term granuloma refers to a localized collection of activated macrophages and their derivatives. Many common and clinically important disease states, such as rheumatoid arthritis, asthma, tuberculosis, leprosy, schistosomiasis, chronic hepatitis, thyroiditis and multiple sclerosis, are examples of chronic inflammation and its consequences.

Definition

Chronic inflammation is most appropriately defined in terms of the process, in which continuing inflammation and attempted tissue healing by repair occur simultaneously. Although it is often defined simply in terms of time course, with lesions of over 6 weeks' duration traditionally being regarded as chronic, any such definition is entirely arbitrary. At a microscopic level, chronic inflammation is sometimes defined in terms of the pattern of cellular response, although this is variable and not altogether reliable.

Characteristics

The distinctive features of this process are best appreciated by comparing it with the acute inflammatory response. In contrast to acute inflammation, where the host response leads to elimination of the irritant, followed by recovery involving tissue regeneration or repair, chronic inflammation is characterized by inflammation and repair occurring concurrently, rather than consecutively. Note that repair is always a feature of chronic inflammation because it is associated with irritants that cause destruction of tissue architecture. Repair is typically achieved by ingrowth of granulation tissue, which includes macrophages, fibroblasts and new blood vessels.

Because the irritant fails to be eliminated in chronic inflammation (either because of its innate characteristics or because of an ineffective host response) it may cause continuing tissue damage in its own right. In addition, most persistent irritants are recognized as foreign antigens by the host immune response, which contributes to the chronic inflammatory process and may add to the tissue destruction. This is well illustrated in diseases such as tuberculosis and hepatitis B, where the inciting agents persist in the host and continue to evoke a chronic inflammatory response.

Other important distinctions between acute and chronic inflammation relate to the relative balance between exudation and cellular recruitment, as well as the types of cells that predominate in the inflammatory response. In chronic inflammation there is typically a less pronounced exudative response (although this is still in evidence) and increased inflammatory cellular recruitment, which may be accompanied by local cellular proliferation. In contrast to acute inflammation, which is usually characterized by recruitment of large numbers of neutrophil leucocytes, the dominant infiltrating cell in all forms of chronic inflammation is the macrophage. Depending on the nature of the irritant, different profiles of inflammatory mediators and growth factors (collectively referred to as cytokines) are generated locally, giving rise to different morphological patterns of chronic inflammation (see below).

The systemic effects of inflammation are more pronounced in chronic inflammatory diseases and may contribute significantly to the clinical consequences. These systemic effects are largely mediated by cytokines. Whereas the most prominent systemic effects of acute inflammation

are fever and leucocytosis, chronic inflammation is usually associated with fatigue, sleepiness, weight loss and wasting.

Role of Persistent Irritant

Chronic inflammation may be caused by:

1. an irritant that usually evokes an acute inflammatory response, which fails to be eliminated or continues to be generated locally; or
2. self antigens that induce an autoimmune response; or
3. an irritant of low intensity but long persistence, which does not evoke a significant acute inflammatory reaction.

Examples in the first category include persisting infections by pyogenic bacteria, e.g. in anatomical locations such as bone (osteomyelitis) where elimination of the organism may be inefficient. In these cases, the microscopic appearance of the inflammatory reaction is typically diffuse, with a mixture of neutrophils (which continue to be recruited by the triggering acute irritant) as well as numerous macrophages and lymphocytes (**Figure 1a**). There may be recrudescences of acute inflammation superimposed on the background of chronic inflammation. Frequently, B lymphocytes exhibit local differentiation to plasma cells, which generate antibodies at the site of inflammation and thus contribute to the host response. The entire inflammatory lesion is bounded by a zone of granulation tissue. Under the influence of cytokine stimulation, granulation tissue fibroblasts synthesize collagen and thus the irritant may be 'walled off' by scar tissue.

The arthritis of rheumatoid disease is a typical example of the acute-on-chronic inflammation seen in some autoimmune diseases. Microscopically, the response is very similar to that associated with persisting acute infections, although accumulation of lymphocytes and plasma cells in the synovium of affected joints is often striking (**Figure 1b**). The ongoing acute inflammation is evident in the synovial fluid, which contains numerous neutrophils. These are recruited in response to activation of the complement cascade by the local formation of immune complexes, which consist of immunoglobulin molecules and anti-immunoglobulin antibodies (known as rheumatoid factors) produced by synovial plasma cells.

Innately chronic irritants include relatively inert foreign bodies, some microorganisms (e.g. tuberculosis and other mycobacteria, some fungi, helminths and protozoa) and immunological inflammatory lesions characterized by delayed type hypersensitivity reactions (e.g. sarcoidosis). Except during a transient acute phase, the microscopic appearance of such lesions typically includes few neutrophils. Instead, there is a predominance of lymphocytes, macrophages and their derivatives, with the formation of multiple focal aggregates of these cells referred to as granulomas. If the irritant is inert and not recognized as antigenic by the immune system (e.g. a foreign body such as suture material), then the granulomas tend to be relatively small and the only important macrophage derivatives observed are multinucleate giant cells formed by fusion. However, most persistent irritants are capable of eliciting an immune response. The morphology of immunologically driven granulomas is more complex. Typically, they consist of an aggregation of modified macrophages with abundant cytoplasm and poorly demarcated cell boundaries, referred to as 'epithelioid cells', together with numerous multinucleate giant cells of different morphology to those observed in foreign body granulomas (McNally and Anderson, 1995). This may be surrounded by a zone of lymphocytes (predominantly T lymphocytes) and there is usually a peripheral zone of healing by collagenous connective tissue (**Figure 2a**). In some forms of granulomatous inflammation, there may be necrosis in the

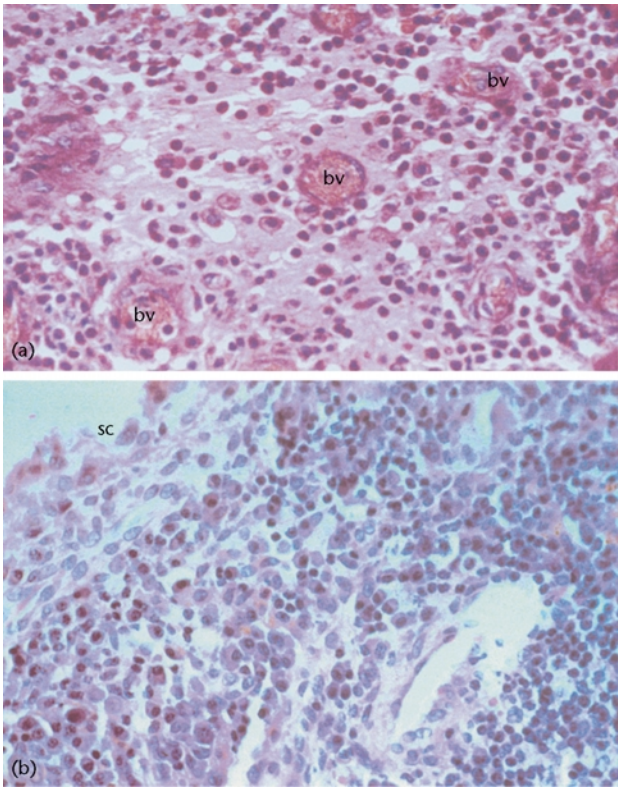

Figure 1 (a) Diffuse pattern of chronic inflammation in the wall of a chronic abscess of bone, with numerous dilated blood vessels (bv) surrounded by a mixture of inflammatory cells including neutrophils, macrophages and lymphocytes.

(b) Diffuse pattern of chronic inflammation in the synovial membrane in rheumatoid arthritis; large numbers of lymphocytes and plasma cells (recognizable by their abundant dark pink cytoplasm) are visible beneath the layer of synovial cells (sc).

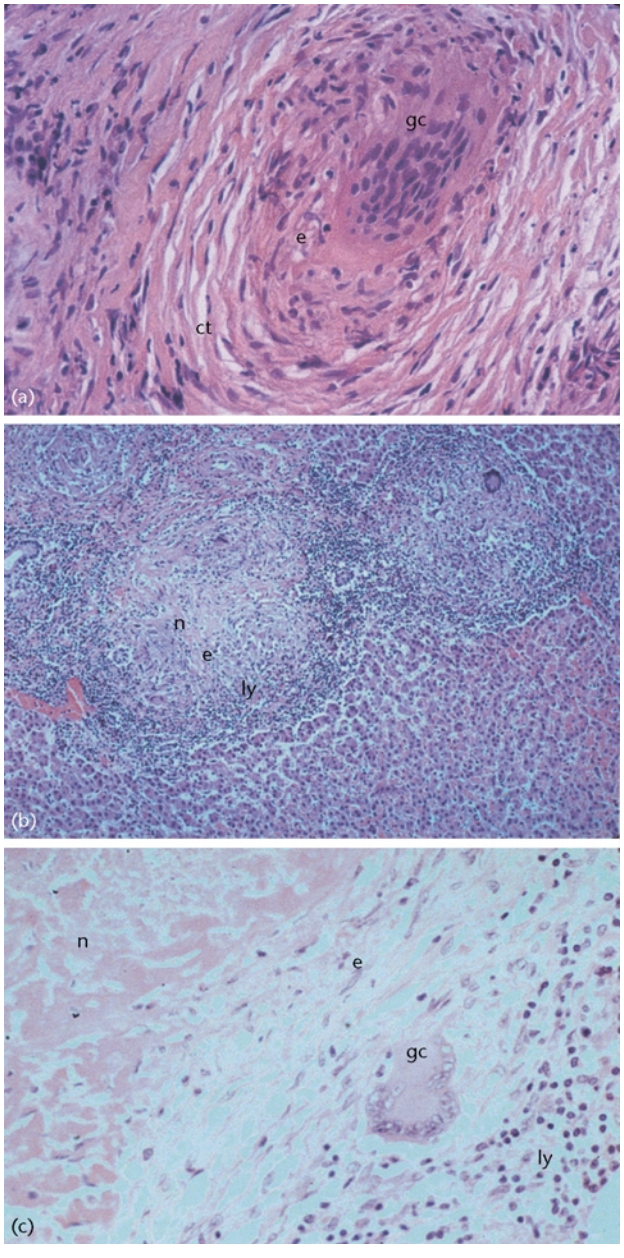

Figure 2 (a) Immunologically driven granuloma of sarcoidosis, with a prominent multinucleated giant cell (gc) surrounded by epithelioid cells (e) and a peripheral zone of collagenous connective tissue (ct).

(b) Two tuberculous granulomas at low magnification, demonstrating central necrosis (n) surrounded by epithelioid cells (e), multinucleated giant cells and a cuff of lymphocytes (ly).

(c) High magnification of the edge of tuberculous granuloma, showing caseous necrosis (n), epithelioid cells (e) and a multinucleate giant cell (gc), as well as a zone of lymphocytes (ly).

centre of such lesions; this is especially characteristic of tuberculous granulomas (**Figures 2b** and **2c**).

Note that although usually distinct, the diffuse and granulomatous patterns of chronic inflammation are not mutually exclusive. Fungal infections may be associated with lesions that exhibit mixed features, e.g. epithelioid cell granulomas accompanied by continuing recruitment of neutrophils and local accumulation of plasma cells.

Inflammatory Mediators

As is the case in acute inflammation, the ordered process of cellular accumulation and activation in chronic inflammation is dependent upon the sequential release of chemical mediators of inflammation. Some of these are preformed and stored in the granules of platelets and mast cells; some, such as complement components, are generated by activation of plasma enzyme cascades; but the majority are newly synthesized by cells of the tissue or by previously recruited inflammatory cells. Prominent among the latter group are relatively small protein molecules, collectively referred to as cytokines, which act as potent biological signals for cellular migration and activation (Wakefield and Lloyd, 1992).

In chronic inflammation, cytokines play critical roles in macrophage and T-cell recruitment, activation and local replication; in the survival of inflammatory cells by inhibition of apoptosis of an immune response; and in the induction of granulation tissue and fibrosis (Jackson *et al*., 1997). Cytokines exert their effects by binding to cell membrane receptors on the same cell (autocrine action), adjacent cells (paracrine action) or remote cells (acting as a hormone). These mediators are characterized by redundancy (with different cytokines having overlapping effects) and pleiotropism (in which one particular cytokine has multiple effects). The families of cytokines include molecules referred to as chemokines, interleukins, interferons, colony-stimulating factors and growth factors, many of which are important in chronic inflammation.

Chemokines regulate leucocyte migration by modifying the expression and affinity of adhesion molecules on the leucocyte surface (Adams and Lloyd, 1997). During inflammation, circulating cells attach to the vascular endothelium and migrate between endothelial cells. When stimulated by cytokines, endothelial cells regulate the recruitment of leucocytes via sets of surface adhesion molecules that tether the two cells together. Activation of the endothelial cells induces a variety of cytokines, as well as adhesion molecules. **Figure 3** illustrates the role of chemokines in leucocyte migration.

The ability of chemokines to attract and activate specific leucocyte subsets at sites of inflammation appears to be an important determinant of the nature of the inflammatory cellular infiltrate, as well as of the subsequent evolution of the inflammatory response. Acute inflammation is initially characterized by recruitment of neutrophils, in part mediated by the activity of the so-called α chemokines such as interleukin 8. This is followed by T-cell and

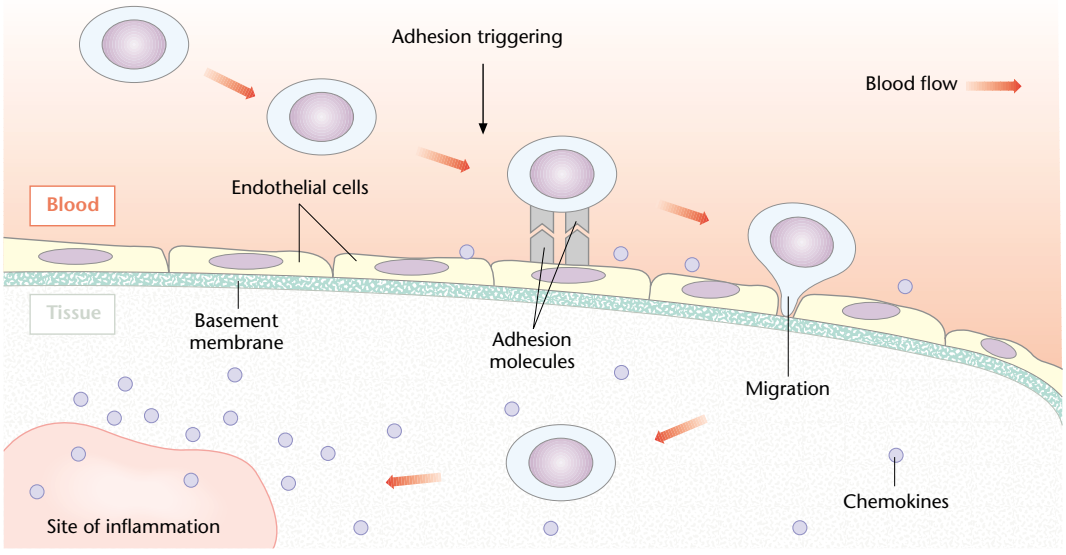

Figure 3 Diagrammatic representation of the role of chemokines, generated at a site of inflammation, in promoting leucocyte activation and recruitment.

monocyte accumulation, believed to be mediated by other chemokines (Rand *et al*., 1996). Additional chemokines exhibit relative specificity for eosinophils or basophils, which are frequently associated with allergic disorders (Adams and Lloyd, 1997).

Proinflammatory cytokines such as interleukin 1, tumour necrosis factor α and interleukin 6, which are primarily produced by macrophages, play multiple roles in inflammation. These include: (1) activation of vascular endothelium, resulting in enhanced expression of leucocyte adhesion molecules; (2) induction of chemokine synthesis; (3) activation of the effector cells of inflammation, notably neutrophils and macrophages; (4) induction of fever; (5) synthesis by the liver of 'acute-phase proteins' such as fibrinogen, amyloid A and C-reactive protein; and (6) subsequent induction of other systemic manifestations of chronic inflammation such as fever, night sweats, tiredness, anorexia and weight loss.

Cytokines secreted by macrophages are critical to the development of the repair response that parallels chronic inflammation, because of their role in the induction of granulation tissue. The names of many of these cytokines are confusing, as they are usually based on the first biological activity or source identified experimentally, rather than on the dominant activity. Mediators that are considered to be especially important inducers of fibroblast proliferation and collagen synthesis include the platelet-derived growth factor and insulin-like growth factor families, the epidermal growth factor family, which includes transforming growth factor α as well as several related molecules, and the transforming growth factor β family. Basic fibroblast growth factor and the vascular endothelial growth factor family appear to be the most important mediators of angiogenesis.

Cytokines secreted by CD4 + T cells, the predominant lymphocyte subset involved in most autoimmune and chronic inflammatory disorders, have been extensively investigated. Animal research suggests that CD4 cells can be divided into T-helper cells T_H0, T_H1 and T_H2 based on their profile of cytokine production and immunological activities. T_H0 cells exhibit an unrestricted cytokine profile. T_H1 cells, which secrete tumour necrosis factor α, interleukin 2 and interferon γ, are believed to mediate predominantly cell-mediated immunity and protection from intracellular infection. T_H2 cells mainly secrete interleukins 4, 5, 10 and 13, mediate humoral immunity and type I (IgE) hypersensitivity, and protect the host from many extracellular pathogens. Although the paradigm of protective or harmful responses biased towards T_H1 or T_H2 responses in infection, autoimmunity or transplantation is not fully explanatory of these processes, this is a helpful way of analysing and understanding complex immune responses.

In granulomatous inflammation, T cell-derived cytokines promote the formation of multinucleated giant cells by fusion of macrophages. Different patterns of cytokine secretion may account for the morphologically distinct giant cells of foreign body and immunologically driven granulomas. Experimentally, foreign body giant cells develop following exposure to interleukin 4 in an environment containing either granulocyte–macrophage colony-stimulating factor or interleukin 3. In contrast, larger multinucleated cells with peripherally arranged nuclei, resembling the so-called Langhans giant cells seen in tuberculosis, develop in the presence of interferon γ and

either granulocyte–macrophage colony-stimulating factor or interleukin 3 (McNally and Anderson, 1995).

While infiltrating macrophages and T cells are particularly important in cytokine-mediated activities in chronic inflammation, they are certainly not the only cells involved. Neutrophil polymorphonuclear leucocytes (PMNs) and various resident cells of the involved tissue also contribute. Such cells are able to synthesize and release cytokines such as interleukin 1, an interleukin 1 receptor antagonist, tumour necrosis factor α, as well as interleukins 6 and 8. Thus they may modulate the activity of other cells of the chronic inflammatory response, by induction of adhesion molecules, chemotaxis and enhancement of effector mechanisms including phagocytosis and microbial killing (the latter are stimulated by interleukins 1 and 8 as well as tumour necrosis factor α).

Clinical Consequences

The effects of chronic inflammation may be the result of: (1) the continuing effects of acute inflammation; (2) the associated tissue destruction; (3) scarring resulting from healing by repair; or (4) systemic effects of chronic inflammation such as fever, wasting and weight loss. In the longer term, chronic inflammation may also be associated with the development of anaemia of chronic disease (Jurado, 1997) and with amyloidosis.

Some important chronic inflammatory diseases and the pathogenesis of their clinical effects are described below.

Asthma

Asthma is an acute-on-chronic inflammation of the airways, often associated with type I IgE-mediated hypersensitivity. Other trigger factors include viral infections, drugs such as salicylates, exercise and exposure to occupational irritants such as toluene and epoxy resins. Bronchial biopsy has established that chronic inflammation of the airways is present even in mild, controlled asthma; whether this is responsible for the nonspecific airway hyperresponsiveness to stimuli is unclear. Recurrent episodes of airflow obstruction are primarily a consequence of the acute inflammatory exacerbations, which are associated with increased secretion of mucus, inflammatory oedema of the airway wall and contraction of the hypertrophied bronchial smooth muscle.

Chronic peptic ulcer

This disease is characterized by remitting–relapsing ulceration, usually in the stomach or duodenum, associated with exposure to the action of acid and pepsin in gastric juice. The development of peptic ulcers is usually preceded by mucosal inflammation due to microbial infection by *Helicobacter pylori*. Clinical features largely result from ongoing destruction of tissue and accompanying acute-on-chronic inflammation (e.g. pain, acute haemorrhage, anaemia, perforation and penetration), but are sometimes also related to the effects of healing by repair (e.g. recurrent vomiting secondary to obstruction).

Chronic periodontitis

Chronic periodontitis is a diffuse acute-on-chronic inflammation of the supporting connective tissues of the teeth, triggered by a mixture of aerobic and microaerophilic bacteria, which is associated with loss of integrity of the gingival epithelial attachment to the tooth and the development of an inflamed cleft or pocket. Clinical features primarily result from deepening of the periodontal pocket and destruction of connective tissues, eventually leading to loss of the tooth. In addition, periodontitis may cause seeding of bacteria into the bloodstream, which may give rise to complicating infections elsewhere.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by acute-on-chronic inflammation of synovial joints, often associated with inflammation in other organs and tissues. Clinical features are partly related to acute inflammation of the joints (e.g. pain, swelling, tenderness and loss of function); partly to long-term effects of tissue destruction and associated healing by repair, which have serious functional consequences (e.g. rupture of tendons, dislocation and deformity); and partly to the systemic effects of chronic inflammation (e.g. fever, weight loss, anaemia of chronic disease).

Tuberculosis

Tuberculosis is the infectious disease caused by *Mycobacterium tuberculosis*. It is characterized by immunologically driven necrotizing granulomatous inflammation primarily involving the lung, but less commonly also affecting lymph nodes, bones, central nervous system, gut and genitourinary system. Clinical effects are related to acute-on-chronic inflammation (e.g. cough, breathlessness), to ongoing tissue destruction (e.g. haemoptysis), to the resultant scarring (e.g. urinary tract obstruction) and to the prominent systemic effects of inflammation (e.g. fever, anorexia, weight loss, anaemia of chronic disease and amyloidosis). The prominent weight loss and wasting associated with tuberculosis gave rise to the old term 'consumption', as patients appeared to be consumed by the illness.

Ulcerative colitis and Crohn disease

These are chronic inflammatory bowel disorders of uncertain aetiology, the former characterized by diffuse mucosal inflammation with ulceration and the latter by nonnecrotizing granulomatous lesions. Clinical features of both diseases include intermittent diarrhoea, abdominal pain and fever, often with visible blood loss, especially with ulcerative colitis. They may be complicated by bowel obstruction or fistula formation, especially with Crohn disease.

Chronic active hepatitis

This is the name given to infective (e.g. hepatitis B and C) or immunologically mediated (so-called lupoid hepatitis) chronic inflammation of the liver parenchyma, characterized by destruction of the hepatic architecture and associated scarring leading to functional impairment (jaundice, portal hypertension, liver failure) and eventually to cirrhosis.

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