these situations, connective tissue grows into the area of damage or exudate, converting it into a mass of fibrous tissue, a process also called *organization.*

- Progression of the response to **chronic inflammation** (discussed later). Acute to chronic transition occurs when the acute inflammatory response cannot be resolved, as a result of either the persistence of the injurious agent or some interference with the normal process of healing.

Summary of Acute Inflammation

Now that we have described the components, mediators, and pathologic manifestations of acute inflammatory responses, it is useful to summarize the main features of a typical response of this type. When a host encounters an injurious agent, such as an infectious microbe or dead cells, phagocytes that reside in all tissues try to eliminate these agents. At the same time, phagocytes and other host cells react to the presence of the foreign or abnormal substance by liberating cytokines, lipid messengers, and other mediators of inflammation. Some of these mediators act on small blood vessels in the vicinity and promote the efflux of plasma and the recruitment of circulating leukocytes to the site where the offending agent is located. The recruited leukocytes are activated by the injurious agent and by locally produced mediators, and the activated leukocytes try to remove the offending agent by phagocytosis. As the injurious agent is eliminated and anti-inflammatory mechanisms become active, the process subsides and the host returns to a normal state of health. If the injurious agent cannot be quickly eliminated, the result may be chronic inflammation.

The vascular and cellular reactions account for the signs and symptoms of the inflammatory response. The increased blood flow to the injured area and increased vascular permeability lead to the accumulation of extravascular fluid rich in plasma proteins, known as *edema*. The redness *(rubor)*, warmth *(calor)*, and swelling *(tumor)* of acute inflammation are caused by the increased blood flow and edema. Circulating leukocytes, initially predominantly neutrophils, adhere to the endothelium via adhesion molecules, traverse the endothelium, and migrate to the site of injury under the influence of chemotactic agents. Leukocytes that are activated by the offending agent and by endogenous mediators may release toxic metabolites and proteases extracellularly, causing tissue damage. During the damage, and in part as a result of the liberation of prostaglandins, neuropeptides, and cytokines, one of the local symptoms is pain *(dolor).*

Chronic Inflammation

Chronic inflammation is a response of prolonged duration (weeks or months) in which inflammation, tissue injury and attempts at repair coexist, in varying combinations. It may follow acute inflammation, as described earlier, or chronic inflammation may begin insidiously, as a low-grade, smoldering response without any manifestations of a preceding acute reaction.

Causes of Chronic Inflammation

Chronic inflammation arises in the following settings:

- **Persistent infections** by microorganisms that are difficult to eradicate, such as mycobacteria and certain viruses, fungi, and parasites. These organisms often evoke an immune reaction called *delayed-type hypersensitivity* (Chapter 6). The inflammatory response sometimes takes a specific pattern called a *granulomatous reaction* (discussed later). In other cases, an unresolved acute inflammation may evolve into chronic inflammation, as may occur in acute bacterial infection of the lung that progresses to a chronic lung abscess.
- **Hypersensitivity diseases.** Chronic inflammation plays an important role in a group of diseases that are caused by excessive and inappropriate activation of the immune system. Under certain conditions immune reactions develop against the individual's own tissues, leading to *autoimmune diseases* (Chapter 6). In these diseases, autoantigens evoke a self-perpetuating immune reaction that results in chronic tissue damage and inflammation; examples of such diseases are rheumatoid arthritis and multiple sclerosis. In other cases, chronic inflammation is the result of unregulated immune responses against microbes, as in inflammatory bowel disease. Immune responses against common environmental substances are the cause of *allergic diseases*, such as bronchial asthma (Chapter 6). Because these autoimmune and allergic reactions are inappropriately triggered against antigens that are normally harmless, the reactions serve no useful purpose and only cause disease. Such diseases may show morphologic patterns of mixed acute and chronic inflammation because they are characterized by repeated bouts of inflammation. Fibrosis may dominate the late stages.
- **Prolonged exposure to potentially toxic agents, either exogenous or endogenous.** An example of an exogenous agent is particulate silica, a nondegradable inanimate material that, when inhaled for prolonged periods, results in an inflammatory lung disease called *silicosis* (Chapter 15). *Atherosclerosis* (Chapter 11) is thought to be a chronic inflammatory process of the arterial wall induced, at least in part, by excessive production and tissue deposition of endogenous cholesterol and other lipids.
- Some forms of chronic inflammation may be important in the pathogenesis of diseases that are not conventionally thought of as inflammatory disorders. These include neurodegenerative diseases such as Alzheimer disease, metabolic syndrome and the associated type 2 diabetes, and certain cancers in which inflammatory reactions promote tumor development. The role of inflammation in these conditions is discussed in the relevant chapters.

Morphologic Features

In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, **chronic inflammation is characterized by:**

- **Infiltration with mononuclear cells,** which include macrophages, lymphocytes, and plasma cells (Fig. 3-18)