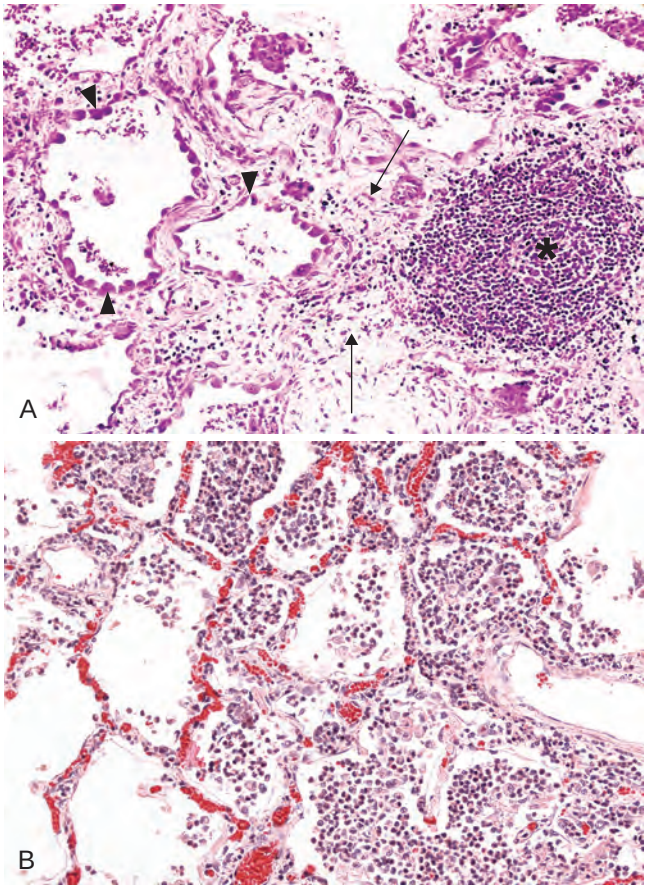

Figure 3-18 A, Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, *arrowheads*), and (3) replacement by connective tissue (fibrosis, *arrows*). **B,** In contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.

- **Tissue destruction,** induced by the persistent offending agent or by the inflammatory cells
- **Attempts at healing** by connective tissue replacement of damaged tissue, accomplished by *angiogenesis* (proliferation of small blood vessels) and, in particular, *fibrosis*

Because angiogenesis and fibrosis are also components of wound healing and repair, they are discussed later, in the context of tissue repair.

Cells and Mediators of Chronic Inflammation

The combination of leukocyte infiltration, tissue damage, and fibrosis that characterize chronic inflammation is the result of the local activation of several cell types and the production of mediators.

Role of Macrophages

The dominant cells in most chronic inflammatory reactions are macrophages, which contribute to the reaction by secreting cytokines and growth factors that act on various cells, by destroying foreign invaders and tissues, and by activating other cells, notably T lymphocytes. Macrophages are professional phagocytes that act as filters for particulate matter, microbes, and senescent cells. They also function as effector cells that eliminate microbes in cellular and humoral immune responses (Chapter 6). But they serve many other roles in inflammation and repair. Here we review the basic biology of macrophages, including their development and functional responses.

Macrophages are tissue cells derived from hematopoietic stem cells in the bone marrow and from progenitors in the embryonic yolk sac and fetal liver during early development (Fig. 3-19). Circulating cells of this lineage are known as *monocytes*. Macrophages are normally diffusely scattered in most connective tissues. In addition, they are found in specific locations in organs such as the liver (where they are called Kupffer cells), spleen and lymph nodes (called sinus histiocytes), central nervous system (microglial cells), and lungs (alveolar macrophages). Together these cells comprise the *mononuclear phagocyte system*, also known by the older (and inaccurate) name of reticuloendothelial system.

Committed progenitors in the bone marrow give rise to monocytes, which enter the blood, migrate into various tissues and differentiate into macrophages. This is typical of macrophages at sites of inflammation and in some tissues such as the skin and intestinal tract. The half-life of blood monocytes is about 1 day, whereas the life span of tissue macrophages is several months or years. Most tissue resident macrophages, such as microglia, Kupffer cells, alveolar macrophages and macrophages in the spleen and connective tissues, may arise from yolk sac or fetal liver very early in embryogenesis, populate the tissues, stay for long periods in the steady state, and are replenished mainly by proliferation of resident cells. As discussed earlier, in inflammatory reactions, monocytes begin to emigrate into extravascular tissues quite early, and within 48 hours they may constitute the predominant cell type. Extravasation of monocytes is governed by the same factors that are involved in neutrophil emigration, that is, adhesion molecules and chemical mediators with chemotactic and activating properties.

There are two major pathways of macrophage activation, called *classical* and *alternative* (Fig. 3-20). The stimuli that activate macrophages by these pathways, and the functions of the activated cells, are quite different.

- **Classical macrophage activation** may be induced by microbial products such as endotoxin, which engage TLRs and other sensors; by T cell–derived signals, importantly the cytokine IFN-γ, in immune responses; or by foreign substances including crystals and particulate matter. Classically activated (also called M1) macrophages produce NO and ROS and upregulate lysosomal enzymes, all of which enhance their ability to kill ingested organisms, and secrete cytokines that stimulate inflammation. These macrophages are important in host defense against microbes and in many inflammatory reactions. As discussed earlier in the context of acute inflammation and leukocyte activation, the same activated cells are capable of injuring normal tissues.
- **Alternative macrophage activation** is induced by cytokines other than IFN-γ, such as IL-4 and IL-13, produced by T lymphocytes and other cells. These macrophages