In all these situations, **the mechanisms by which leukocytes damage normal tissues are the same as the mechanisms involved in antimicrobial defense**, because once the leukocytes are activated, their effector mechanisms do not distinguish between offender and host. During activation and phagocytosis, neutrophils and macrophages produce microbicidal substances (ROS, NO, and lysosomal enzymes) within the phagolysosome; these substances are also released into the extracellular space. These released substances are capable of damaging normal cells and vascular endothelium, and may thus amplify the effects of the initial injurious agent. If unchecked or inappropriately directed against host tissues, the leukocyte infiltrate itself becomes the offender, and indeed leukocyte-dependent tissue injury underlies many acute and chronic human diseases (Table 3-1). This fact becomes evident in the discussion of specific disorders throughout the book.

The contents of lysosomal granules are secreted by leukocytes into the extracellular milieu by several mechanisms. Controlled secretion of granule contents is a normal response of activated leukocytes. If phagocytes encounter materials that cannot be easily ingested, such as immune complexes deposited on immovable flat surfaces (e.g., glomerular basement membrane), the inability of the leukocytes to surround and ingest these substances *(frustrated phagocytosis)* triggers strong activation, and the release of large amounts of lysosomal enzymes into the extracellular environment. Some phagocytosed substances, such as urate crystals, may damage the membrane of the phagolysosome and also lead to the release of lysosomal granule contents.

Other Functional Responses of Activated Leukocytes

In addition to eliminating microbes and dead cells, activated leukocytes play several other roles in host defense. Importantly, these cells, especially macrophages, produce cytokines that can either amplify or limit inflammatory reactions, growth factors that stimulate the proliferation of endothelial cells and fibroblasts and the synthesis of collagen, and enzymes that remodel connective tissues. Because of these activities, macrophages are also critical cells of chronic inflammation and tissue repair, after the inflammation has subsided. These functions of macrophages are discussed later in the chapter.

In this discussion of acute inflammation, we emphasize the importance of neutrophils and macrophages. However, it has recently become clear that some T lymphocytes, which are cells of adaptive immunity, also contribute to acute inflammation. The most important of these cells are those that produce the cytokine IL-17 (so-called T_H17 cells), which are discussed in more detail in Chapter 6. IL-17 induces the secretion of chemokines that recruit other leukocytes. In the absence of effective T_H17 responses, individuals are susceptible to fungal and bacterial infections, and the skin abscesses that develop are "cold abscesses," lacking the classic features of acute inflammation, such as warmth and redness.

Termination of the Acute Inflammatory Response

Such a powerful system of host defense, with its inherent capacity to cause tissue injury, needs tight controls to minimize damage. In part, inflammation declines after the offending agents are removed simply because the mediators of inflammation are produced in rapid bursts, only as long as the stimulus persists, have short half-lives, and are degraded after their release. Neutrophils also have short half-lives in tissues and die by apoptosis within a few hours after leaving the blood. In addition, as inflammation develops, the process itself triggers a variety of stop signals that actively terminate the reaction. These active termination mechanisms include a switch in the type of arachidonic acid metabolite produced, from proinflammatory leukotrienes to antiinflammatory lipoxins (described later), and the liberation of antiinflammatory cytokines, including transforming growth factor-β (TGF-β) and IL-10, from macrophages and other cells. Other control mechanisms that have been demonstrated experimentally include neural impulses (cholinergic discharge) that inhibit the production of TNF in macrophages.

KEY CONCEPTS

Leukocyte Activation and Removal of Offending Agents

- Leukocytes can eliminate microbes and dead cells by phagocytosis, followed by their destruction in phagolysosomes.
- Destruction is caused by free radicals (ROS, NO) generated in activated leukocytes and lysosomal enzymes.
- Neutrophils can extrude their nuclear contents to form extracellular nets that trap and destroy microbes.
- Enzymes and ROS may be released into the extracellular environment.
- The mechanisms that function to eliminate microbes and dead cells (the physiologic role of inflammation) are also capable of damaging normal tissues (the pathologic consequences of inflammation).
- Antiinflammatory mediators terminate the acute inflammatory reaction when it is no longer needed.

Mediators of Inflammation

The mediators of inflammation are the substances that initiate and regulate inflammatory reactions. Many mediators have been identified and targeted therapeutically to limit inflammation. In this discussion, we review their shared properties and the general principles of their production and actions.

- **The most important mediators of acute inflammation are vasoactive amines, lipid products (prostaglandins and leukotrienes), cytokines (including chemokines), and products of complement activation** (Table 3-4). These mediators induce various components of the inflammatory response typically by distinct mechanisms, which is why inhibiting each has been therapeutically beneficial. However, there is also some overlap (redundancy) in the actions of the mediators.
- **Mediators are either secreted by cells or generated from plasma proteins.** *Cell-derived mediators* are normally sequestered in intracellular granules and can be rapidly secreted by granule exocytosis (e.g., histamine in mast cell granules) or are synthesized de novo (e.g., prostaglandins and leukotrienes, cytokines) in response