chronic reactions that cause extensive tissue injury. The outcomes are determined largely by the type of pathogen and, to some extent, by characteristics of the host that remain poorly defined.

- **Tissue necrosis** elicits inflammation regardless of the cause of cell death, which may include *ischemia* (reduced blood flow, the cause of myocardial infarction), *trauma*, and *physical and chemical injury* (e.g., thermal injury, as in burns or frostbite; irradiation; exposure to some environmental chemicals). Several molecules released from necrotic cells are known to trigger inflammation; some of these are described below.
- **Foreign bodies** (splinters, dirt, sutures) may elicit inflammation by themselves or because they cause traumatic tissue injury or carry microbes. Even some endogenous substances can be considered potentially harmful if large amounts are deposited in tissues; such substances include urate crystals (in the disease gout), cholesterol crystals (in atherosclerosis), and lipids (in obesity-associated metabolic syndrome).
- **Immune reactions** (also called *hypersensitivity*) are reactions in which the normally protective immune system damages the individual's own tissues. The injurious immune responses may be directed against self antigens, causing *autoimmune diseases*, or may be inappropriate reactions against environmental substances, as in *allergies*, or against microbes. Inflammation is a major cause of tissue injury in these diseases (Chapter 6). Because the stimuli for the inflammatory responses (e.g., self and environmental antigens) cannot be eliminated, autoimmune and allergic reactions tend to be persistent and difficult to cure, are often associated with chronic inflammation, and are important causes of morbidity and mortality. The inflammation is induced by cytokines produced by T lymphocytes and other cells of the immune system (Chapter 6).

Recognition of Microbes and Damaged Cells

Recognition of offending agents is the first step in all inflammatory reactions. The cells and receptors that perform this function of recognizing invaders evolved as adaptation of multicellular organisms to the presence of microbes in the environment, and the responses they trigger are critical for the survival of the organisms. Several cellular receptors and circulating proteins are capable of recognizing microbes and products of cell damage and triggering inflammation.

- **Cellular receptors for microbes.** Cells express receptors in the plasma membrane (for extracellular microbes), the endosomes (for ingested microbes), and the cytosol (for intracellular microbes) that enable the cells to sense the presence of foreign invaders in any cellular compartment. The best defined of these receptors belong to the family of *Toll-like receptors (TLRs)*; these and other cellular receptors of innate immunity are described in Chapter 6. The receptors are expressed on many cell types, including epithelial cells (through which microbes enter from the external environment), dendritic cells, macrophages, and other leukocytes (which may encounter microbes in various tissues). Engagement of these receptors triggers production of molecules involved in inflammation, including adhesion molecules on endothelial cells, cytokines, and other mediators.
- **Sensors of cell damage.** All cells have cytosolic receptors that recognize a diverse set of molecules that are liberated or altered as a consequence of cell damage. These molecules include uric acid (a product of DNA breakdown), ATP (released from damaged mitochondria), reduced intracellular K+ concentrations (reflecting loss of ions because of plasma membrane injury), even DNA when it is released into the cytoplasm and not sequestered in nuclei, as it should be normally, and many others. These receptors activate a multiprotein cytosolic complex called the *inflammasome* (Chapter 6), which induces the production of the cytokine interleukin-1 (IL-1). IL-1 recruits leukocytes and thus induces inflammation (see later). Gain-of-function mutations in the sensor are the cause of rare diseases known as *autoinflammatory syndromes* that are characterized by spontaneous inflammation; IL-1 antagonists are effective treatments for these disorders. The inflammasome has also been implicated in inflammatory reactions to urate crystals (the cause of *gout*), lipids (in metabolic syndrome), cholesterol crystals (in atherosclerosis), and even amyloid deposits in the brain (in Alzheimer disease). These disorders are discussed later in this and other chapters.
- **Other cellular receptors involved in inflammation.** In addition to directly recognizing microbes, many leukocytes express receptors for the Fc tails of antibodies and for complement proteins. These receptors recognize microbes coated with antibodies and complement (the coating process is called *opsonization*) and promote ingestion and destruction of the microbes as well as inflammation.
- **Circulating proteins.** The *complement system* reacts against microbes and produces mediators of inflammation (discussed later). A circulating protein called *mannose-binding lectin* recognizes microbial sugars and promotes ingestion of the microbes and the activation of the complement system. Other proteins called *collectins* also bind to and combat microbes.

KEY CONCEPTS

General Features and Causes of Inflammation

- Inflammation is a beneficial host response to foreign invaders and necrotic tissue, but it may also cause tissue damage.
- The main components of inflammation are a vascular reaction and a cellular response; both are activated by mediators that are derived from plasma proteins and various cells.
- The steps of the inflammatory response can be remembered as the five Rs: (1) recognition of the injurious agent, (2) recruitment of leukocytes, (3) removal of the agent, (4) regulation (control) of the response, and (5) resolution (repair).
- The causes of inflammation include infections, tissue necrosis, foreign bodies, trauma, and immune responses.