- **Inflammation.** *C3a*, *C5a*, and, to a lesser extent, *C4a* are cleavage products of the corresponding complement components that stimulate histamine release from mast cells and thereby increase vascular permeability and cause vasodilation. They are called *anaphylatoxins* because they have effects similar to those of mast cell mediators that are involved in the reaction called *anaphylaxis* (Chapter 6). C5a is also a chemotactic agent for neutrophils, monocytes, eosinophils, and basophils. In addition, C5a activates the lipoxygenase pathway of AA metabolism in neutrophils and monocytes, causing further release of inflammatory mediators.
- **Opsonization and phagocytosis.** *C3b* and its cleavage product *iC3b* (inactive C3b), when fixed to a microbial cell wall, act as opsonins and promote phagocytosis by neutrophils and macrophages, which bear cell surface receptors for the complement fragments.
- **Cell lysis.** The deposition of the MAC on cells makes these cells permeable to water and ions and results in death (lysis) of the cells. This role of complement is important mainly for the killing of microbes with thin cell walls, such as *Neisseria* bacteria, and deficiency of the terminal components of complement predisposes to *Neisseria* infections.

The activation of complement is tightly controlled by cell-associated and circulating regulatory proteins. Different regulatory proteins inhibit the production of active complement fragments or remove fragments that deposit on cells. These regulators are expressed on normal host cells and are thus designed to prevent healthy tissues from being injured at sites of complement activation. Regulatory proteins can be overwhelmed when large amounts of complement are deposited on host cells and in tissues, as happens in autoimmune diseases, in which individuals produce complement-fixing antibodies against their own cell and tissue antigens (Chapter 6). The most important of these regulatory proteins are the following:

- **C1 inhibitor (C1 INH)** blocks the activation of C1, the first protein of the classical complement pathway. Inherited deficiency of this inhibitor is the cause of *hereditary angioedema*.
- **Decay accelerating factor (DAF)** and **CD59** are two proteins that are linked to plasma membranes by a glycophosphatidyl (GPI) anchor. DAF prevents formation of C3 convertases and CD59 inhibits formation of the membrane attack complex. An acquired deficiency of the enzyme that creates GPI anchors leads to deficiency of these regulators and excessive complement activation and lysis of red cells (which are sensitive to complement-mediated cell lysis) in the disease called *paroxysmal nocturnal hemoglobinuria (PNH)* (Chapter 14).
- Other complement regulatory proteins proteolytically cleave active complement components.

The complement system contributes to disease in several ways. The activation of complement by antibodies or antigen-antibody complexes deposited on host cells and tissues is an important mechanism of cell and tissue injury (Chapter 6). Inherited deficiencies of complement proteins cause increased susceptibility to infections (Chapter 6), and, as mentioned earlier, deficiencies of regulatory proteins cause a variety of disorders, such as macular degeneration and hemolytic uremic syndrome, resulting from excessive complement activation.

Other Mediators of Inflammation

Platelet-Activating Factor (PAF)

PAF is a phospholipid-derived mediator that was discovered as a factor that caused platelet aggregation, but it is now known to have multiple inflammatory effects. A variety of cell types, including platelets themselves, basophils, mast cells, neutrophils, macrophages, and endothelial cells, can elaborate PAF, in both secreted and cell-bound forms. In addition to platelet aggregation, PAF causes vasoconstriction and bronchoconstriction, and at low concentrations it induces vasodilation and increased venular permeability. In the 1990s there was great interest in PAF as a mediator of inflammation, but trials of PAF antagonists in various inflammatory diseases have been disappointing.

Products of Coagulation

Studies done more than 50 years ago suggested that inhibiting coagulation reduced the inflammatory reaction to some microbes, leading to the idea that coagulation and inflammation are linked processes. This concept was supported by the discovery of protease-activated receptors (PARs), which are activated by thrombin (the protease that cleaves fibrinogen to produce fibrin, which forms the clot), and are expressed on platelets and leukocytes. It is, however, likely that the major role of the PARs is in platelet activation during clotting (Chapter 4). In fact, it is difficult to dissociate clotting and inflammation, since virtually all forms of tissue injury that lead to clotting also induce inflammation, and inflammation causes changes in endothelial cells that increase the likelihood of abnormal clotting (thrombosis, described in Chapter 4). However, whether the products of coagulation, per se, have a key role in stimulating inflammation is still not established.

Kinins

Kinins are vasoactive peptides derived from plasma proteins, called *kininogens*, by the action of specific proteases called kallikreins. The enzyme kallikrein cleaves a plasma glycoprotein precursor, high-molecular-weight kininogen, to produce *bradykinin*. **Bradykinin increases vascular permeability and causes contraction of smooth muscle, dilation of blood vessels, and pain when injected into the skin.** These effects are similar to those of histamine. The action of bradykinin is short-lived, because it is quickly inactivated by an enzyme called kininase. Bradykinin has been implicated as a mediator in some forms of allergic reaction, such as anaphylaxis (Chapter 6).

Neuropeptides

Neuropeptides are secreted by sensory nerves and various leukocytes, and may play a role in the initiation and regulation of inflammatory responses. These small peptides, such as substance P and neurokinin A, are produced in the central and peripheral nervous systems. Nerve fibers containing substance P are prominent in the lung and gastrointestinal tract. Substance P has many biologic functions, including the transmission of pain signals, regulation of