cramps, diarrhea, and laryngeal obstruction follow, and the patient may go into shock and even die within the hour. The risk of anaphylaxis must be borne in mind when certain therapeutic agents are administered. Although patients at risk can generally be identified by a previous history of some form of allergy, the absence of such a history does not preclude the possibility of an anaphylactic reaction.

Local Immediate Hypersensitivity Reactions

About 10% to 20% of the population suffers from allergies involving localized reactions to common environmental allergens, such as pollen, animal dander, house dust, foods, and the like. Specific diseases include urticaria, allergic rhinitis (hay fever), bronchial asthma, and food allergies; these are discussed elsewhere in this text.

KEY CONCEPTS

Immediate (Type I) Hypersensitivity

- These are also called allergic reactions, or allergies
- They are induced by environmental antigens (allergens) that stimulate strong T_H2 responses and IgE production in genetically susceptible individuals
- IgE coats mast cells by binding to Fcε receptors; reexposure to the allergen leads to cross-linking of the IgE and FcεRI, activation of mast cells, and release of mediators.
- The principal mediators are histamine, proteases, and other granule contents, prostaglandins and leukotrienes, and cytokines.
- The mediators are responsible for the immediate vascular and smooth muscle reactions and the late-phase reaction (inflammation).
- The clinical manifestations may be local or systemic, and range from mildly annoying rhinitis to fatal anaphylaxis.

Antibody-Mediated (Type II) Hypersensitivity

Antibodies that react with antigens present on cell surfaces or in the extracellular matrix cause disease by destroying these cells, triggering inflammation, or interfering with normal functions. The antibodies may be specific for normal cell or tissue antigens (*autoantibodies*) or for exogenous antigens, such as chemical or microbial proteins, that bind to a cell surface or tissue matrix. The antibody-dependent mechanisms that cause tissue injury and disease are illustrated in Figure 6-16 and described next. These reactions are the cause of several important diseases (Table 6-3).

Opsonization and Phagocytosis

Phagocytosis is largely responsible for depletion of cells coated with antibodies. Cells opsonized by IgG antibodies are recognized by phagocyte Fc receptors, which are specific for the Fc portions of some IgG subclasses. In addition, when IgM or IgG antibodies are deposited on the surfaces of cells, they may activate the complement system by the classical pathway. Complement activation generates by-products, mainly C3b and C4b, which are deposited on the surfaces of the cells and recognized by phagocytes that express receptors for these proteins. The net result is phagocytosis of the opsonized cells and their destruction (Fig. 6-16*A*). Complement activation on cells also leads to the formation of the membrane attack complex, which disrupts membrane integrity by "drilling holes" through the lipid bilayer, thereby causing osmotic lysis of the cells. This mechanism of killing is probably effective only with cells that have thin cell walls, such as *Neisseria* bacteria.

Antibody-mediated destruction of cells may occur by another process called *antibody-dependent cellular cytotoxicity (ADCC)*. Cells that are coated with IgG antibody are killed by a variety of effector cells, mainly NK cells and macrophages, which bind to the target by their receptors for the Fc fragment of IgG, and cell lysis proceeds without phagocytosis. The contribution of ADCC to common hypersensitivity diseases is uncertain.

Clinically, antibody-mediated cell destruction and phagocytosis occur in the following situations: (1) transfusion reactions, in which cells from an incompatible donor react with and are opsonized by preformed antibody in the host (Chapter 14); (2) hemolytic disease of the newborn (erythroblastosis fetalis), in which there is an antigenic difference between the mother and the fetus, and IgG antierythrocyte antibodies from the mother cross the placenta and cause destruction of fetal red cells (Chapter 10); (3) autoimmune hemolytic anemia, agranulocytosis, and thrombocytopenia, in which individuals produce antibodies to their own blood cells, which are then destroyed (Chapter 14); and (4) certain drug reactions, in which a drug acts as a "hapten" by attaching to plasma membrane proteins of red cells and antibodies are produced against the drug-protein complex.

Inflammation

When antibodies deposit in fixed tissues, such as basement membranes and extracellular matrix, the resultant injury is due to inflammation. The deposited antibodies activate complement, generating by-products, including chemotactic agents (mainly C5a), which direct the migration of polymorphonuclear leukocytes and monocytes, and anaphylatoxins (C3a and C5a), which increase vascular permeability (Fig. 6-16*B*). The leukocytes are activated by engagement of their C3b and Fc receptors. This results in the production of other substances that damage tissues, such as lysosomal enzymes, including proteases capable of digesting basement membrane, collagen, elastin, and cartilage, and reactive oxygen species.

Antibody-mediated inflammation is the mechanism responsible for tissue injury in some forms of *glomerulonephritis*, *vascular rejection* in organ grafts, and other disorders (Table 6-3).

Cellular Dysfunction

In some cases, antibodies directed against cell surface receptors impair or dysregulate function without causing cell injury or inflammation (Fig. 6-16C). For example, in *myasthenia gravis*, antibodies reactive with acetylcholine receptors in the motor end plates of skeletal muscles block neuromuscular transmission and therefore cause muscle weakness. The converse (i.e., antibody-mediated stimulation of cell function) is the basis of *Graves disease*. In this disorder, antibodies against the thyroid-stimulating hormone receptor on thyroid epithelial cells stimulate the cells, resulting in hyperthyroidism.