unless the recipient's immune system is adequately suppressed by immunosuppressant drugs.

Rejection reactions are designated as hyperacute, acute, or chronic, depending on the time elapsed between transplantation and rejection. *Hyperacute* reactions occur within 24 hours. This rare type of reaction occurs in recipients who have previously formed antibodies against antigens in the graft. The antibodies bind to the graft and induce intense inflammation with extensive infiltration of neutrophils into the grafted tissue. The inflammatory reaction causes massive blood clots within the capillaries and prevents vascularization and function of the graft. *Acute* reactions, which may occur from 10 days to a few months after transplantation, mainly involve a cellular response with the proliferation of T lymphocytes. Characteristics include signs of organ failure and vasculitis lesions that often lead to arterial narrowing or obliteration. Treatment with immunosuppressant drugs is usually effective in ensuring short-term survival of the transplant, but does not prevent chronic rejection. *Chronic* reactions, which may occur after months or years of normal function, are caused by both cellular and humoral immunity and do not respond to increased immunosuppressive drug therapy. Characteristics include fibrosis of blood vessels and progressive failure of the transplanted organ.

Rejection reactions produce general manifestations of inflammation and specific manifestations depending on the organ involved. With renal transplantation, for example, acute rejection reactions produce fever, flank tenderness over the graft organ site, and symptoms of renal failure (eg, increased serum creatinine, decreased urine output, edema, weight gain, hypertension). Chronic rejection reactions are characterized by a gradual increase in serum creatinine levels over approximately 4 to 6 months.

Bone Marrow Transplantation and Graft-Versus-Host Disease

With bone marrow transplantation, the donor bone marrow mounts an immune response (mainly by stimulating T lymphocytes) against antigens on the host's tissues, producing GVHD. Tissue damage is produced directly by the action of cytotoxic T cells or indirectly through the release of inflammatory mediators such as complement and cytokines such as tumor necrosis factor (TNF)-alpha and interleukins.

Acute GVHD occurs in 30% to 50% of clients, usually within 6 weeks. Signs and symptoms include delayed recovery of blood cell production in the bone marrow, skin rash, liver dysfunction (indicated by increased alkaline phosphatase, aminotransferases, and bilirubin), and diarrhea. The skin reaction is usually a pruritic maculopapular rash that begins on the palms and soles and may extend over the entire body. Liver involvement can lead to bleeding disorders and coma.

Chronic GVHD occurs when symptoms persist or occur 100 days or more after transplantation. It is characterized by abnormal humoral and cellular immunity, severe skin disorders, and liver disease. Chronic GVHD appears to be an autoimmune disorder in which activated T cells perceive autoantigens as foreign antigens.

IMMUNOSUPPRESSANT DRUGS

Drugs used as immunosuppressants are diverse agents with often overlapping mechanisms of actions and effects. Older drugs generally depress the immune system (ie, suppress the immune response to all antigens). This greatly increases risks of serious infections with bacteria, viruses, fungi, or protozoa, at any time during the immunosuppressed state. In addition, many immunosuppressant drugs slow the proliferation of activated lymphocytes and damage rapidly dividing nonimmune cells (eg, mucosal, intestinal, and bone marrow hematopoietic stem cells). As a result, serious or life-threatening complications can occur. For example, patients on long-term immunosuppressant drug therapy (eg, with autoimmune disorders and organ transplantation) are at increased risk of cancer (especially lymphoma), hypertension, and metabolic bone disease.

For many reasons, including adverse effects of older drugs and the efforts to develop more effective agents, extensive research has been done to develop drugs that modify the immune response (often called immunomodulators or biologic response modifiers). As a result, several drugs with more specific immunosuppressive actions have been approved in recent years. Most are used in combination with older immunosuppressants for synergistic effects.

Immunosuppressants are discussed here as corticosteroids, cytotoxic antiproliferative agents, conventional antirejection agents, antibody preparations, and miscellaneous drugs. This grouping is rather arbitrary because most of the drugs could also fit in one or more other categories (eg, the cytotoxic drugs and most of the antibody preparations are also antirejection drugs; some of the drugs can also be called anticytokines because they block the actions of cytokines such as interleukin-2 [IL-2] and TNF). It is hoped that the chosen groupings will assist the reader in differentiating drug sources, effects, and clinical uses.

Corticosteroids

Corticosteroids are potent anti-inflammatory drugs that act to suppress the immune response at many levels. In many disorders, they relieve signs and symptoms by decreasing the accumulation of lymphocytes and macrophages and the production of cell-damaging cytokines at sites of inflammatory reactions. Because inflammation is a common response to chemical mediators or antigens that cause tissue injury, the anti-inflammatory and immunosuppressive actions of corticosteroids often overlap and are indistinguishable. Despite this somewhat arbitrary separation, corticosteroid effects on the immune response are emphasized here. In general, the drugs suppress growth of all lymphoid tissue and therefore decrease formation and function of antibodies and T cells. For patients with transplanted tissues, a corticosteroid is usually given with