failure. These patients are also at increased risk for developing EBV-induced lymphomas, human papillomavirus-induced squamous cell carcinomas, and Kaposi sarcoma (Chapter 11), all probably the result of reactivation of latent viral infections because of diminished host defenses. To circumvent the untoward effects of immunosuppression, much effort is being devoted to induce donor-specific tolerance in graft recipients. For instance, giving donor cells to graft recipients may prevent reactions to the graft, perhaps because the donor inoculum contains cells, such as immature dendritic cells, that induce tolerance to the donor alloantigens. This approach may result in long-term *mixed chimerism*, in which the recipient lives with the injected donor cells. Other strategies being tested include injecting regulatory T cells, and blocking the costimulatory signals that are required for lymphocyte activation, as mentioned above.

Transplantation of Other Solid Organs

In addition to the kidney, a variety of organs, such as the liver (Chapter 18), heart (Chapter 12), lungs, and pancreas, are also transplanted. The rejection reaction against liver transplants is not as vigorous as might be expected from the degree of HLA disparity. The molecular basis of this "privilege" is not understood.

Transplantation of Hematopoietic Stem Cells

Use of hematopoietic stem cell (HSC) transplants for hematologic malignancies, bone marrow failure syndromes (such as aplastic anemia), and disorders caused by inherited HSC defects (such as sickle cell anemia, thalassemia, and immunodeficiency states) is increasing in number each year. Transplantation of genetically "reengineered" hematopoietic stem cells obtained from affected patients may also be useful for somatic cell gene therapy, and is being evaluated in some immunodeficiencies. Historically, HSCs were obtained from the bone marrow, but now they usually are harvested from peripheral blood after they are mobilized from the bone marrow by administration of hematopoietic growth factors, or from the umbilical cord blood of newborn infants, a rich source of HSCs. In most of the conditions in which HSC transplantation is indicated, the recipient is irradiated or treated with high doses of chemotherapy to destroy the immune system (and sometimes, cancer cells) and to "open up" niches in the microenvironment of the marrow that nurture HSCs, thus allowing the transplanted HSCs to engraft. Several features distinguish HSC transplants from solid-organ transplants. Two problems that are unique to HSC transplantation are graft-versus-host disease (GVHD) and immunodeficiency.

GVHD occurs when immunologically competent cells or their precursors are transplanted into immunologically crippled recipients, and the transferred cells recognize alloantigens in the host and attack host tissues. It is seen most commonly in the setting of HSC transplantation but, rarely, may occur following transplantation of solid organs rich in lymphoid cells (e.g., the liver) or transfusion of unirradiated blood. When immune-compromised recipients receive HSC preparations from allogeneic donors, the immunocompetent T cells present in the donor inoculum recognize the recipient's HLA antigens as foreign and react against them. To try to minimize GVHD, HSC transplants are done between donor and recipient that are HLA-matched using precise DNA sequencing-based methods for molecular typing of HLA alleles.

- **Acute GVHD** occurs within days to weeks after allogeneic bone marrow transplantation. Although any organ may be affected, the major clinical manifestations result from involvement of the immune system and epithelia of the skin, liver, and intestines. Involvement of skin in GVHD is manifested by a generalized rash that may lead to desquamation in severe cases. Destruction of small bile ducts gives rise to jaundice, and mucosal ulceration of the gut results in bloody diarrhea. Although tissue injury may be severe, the affected tissues are usually not heavily infiltrated by lymphocytes. It is believed that in addition to direct cytotoxicity by CD8+ T cells, considerable damage is inflicted by cytokines released by the sensitized donor T cells.
- **Chronic GVHD** may follow the acute syndrome or may occur insidiously. These patients have extensive cutaneous injury, with destruction of skin appendages and fibrosis of the dermis. The changes may resemble systemic sclerosis (discussed earlier). Chronic liver disease manifested by cholestatic jaundice is also frequent. Damage to the gastrointestinal tract may cause esophageal strictures. The immune system is devastated, with involution of the thymus and depletion of lymphocytes in the lymph nodes. Not surprisingly, the patients experience recurrent and life-threatening infections. Some patients develop manifestations of autoimmunity, postulated to result from the grafted CD4+ helper T cells reacting with host B cells and stimulating these cells, some of which may be capable of producing autoantibodies.

Because GVHD is mediated by T lymphocytes contained in the transplanted donor cells, depletion of donor T cells before transfusion virtually eliminates the disease. This protocol, however, has proved to be a mixed blessing: GVHD is ameliorated, but the recurrence of tumor in leukemic patients as well as the incidence of graft failures and EBV-related B-cell lymphoma increase. It seems that the multifaceted T cells not only mediate GVHD but also are required for engraftment of the transplanted HSCs, suppression of EBV-infected B-cell clones, and control of leukemia cells. The latter *graft-versus-leukemia* effect can be quite dramatic. In fact, deliberate induction of graft-versus-leukemia effect by infusion of allogeneic T cells is used to treat chronic myelogenous leukemia that has relapsed after HSC transplantation.

Immunodeficiency is a frequent complication of HSC transplantation. The immunodeficiency may be a result of prior treatment, myeloablative preparation for the graft, a delay in repopulation of the recipient's immune system, and attack on the host's immune cells by grafted lymphocytes. Affected individuals are profoundly immunosuppressed and are easy prey to infections. Although many different types of organisms may infect patients, infection with cytomegalovirus is particularly important. This usually results from activation of previously silent infection. Cytomegalovirus-induced pneumonitis can be a fatal complication.