Transplantation of solid organs has become the treatment of choice for end-stage renal, hepatic, cardiac, and pulmonary disease. The field has progressed rapidly in the past 5 decades, primarily because of the development of safer and more effective immunosuppressive agents. After Carrel described a reliable technique for vascular anastomoses in the early 1900s, the technical problems confronting surgeons seeking to replace diseased kidneys or other solid organs were largely resolved. However, the crucial advance that made clinical organ transplantation feasible between unrelated individuals was the development of immunosuppressive drugs to prevent or control rejection. The combination of azathioprine with corticosteroids, introduced in 1962, was the first effective clinical immunosuppressive regimen. It is still used in many patients today. The introduction of cyclosporine in 1978, a specific and nonmyelotoxic immunosuppressant, changed heart and liver transplantation from research to service procedures and dramatically increased the success rates of renal transplantation. Continued improvements in the control of rejection at both the cellular and molecular levels have been possible, owing to increased understanding of the complexity of the immune system and of the events that constitute the rejection process. Because outcomes may vary with the type of graft and the patient’s clinical history, the choice of immunosuppression depends on a complete understanding of the interrelationship between host and graft. In the past decade a diverse armamentarium of immunosuppressive agents targeting various aspects of the immune system has emerged.
CONCEPTUAL APPROACHES TO IMMUNOSUPPRESSIVE THERAPY

Lymphocytes have an essential, central role in the immune response and mediate its specificity. The rejection reaction begins when T lymphocytes recognize foreign histocompatibility antigens on cells of the transplanted tissue. The foreign antigen is thought to be presented directly to host lymphocytes by antigen-presenting cells (APCs), most notably dendritic cells and macrophages, which phagocytose and then display the processed antigenic epitope on their surface. Whatever the APC, the ability to differentiate self from nonself resides with the lymphocytes. Early in the development of the body’s immune system, groups or clones of lymphocytes are formed that have discrete target specificity. A lymphocyte, therefore, can recognize only one or a few closely related antigens. The range of possible antigen configurations is matched by a panoply of lymphocyte clones arrayed against them. Immune specificity is acquired during early development, and it is postulated that fully competent clones of small resting lymphocytes await immunologic stimulation by foreign tissue antigens. Among the vast variety of antigens that can be recognized are the foreign antigens, which are governed by the major histocompatibility complex (MHC).

Stimulation of a resting lymphocyte by the antigen for which it is specific causes it to transform into a large active cell that secretes chemical communicators called cytokines. These are soluble proteins or glycoproteins that are effective across short distances and that, in turn, amplify the response and activate other cells. Before the antigen is disposed of, however, myriad cellular and subcellular events ensue. Interference with this complex series of events at one or more stages offers many opportunities for therapeutic intervention to suppress the rejection response. For the transplant patient, the encounter of the APC and the T lymphocyte is generally considered to be the first point of possible immunosuppressive attack.

Once the lymphocyte has responded to foreign antigen and become activated, immunosuppressive therapy is less effective. Many cells and molecules are involved. Specific effectors, such as preformed antibodies and activated killer (cytotoxic) lymphocytes as well as nonspecific agents such as platelets, neutrophils, complement, and coagulation factors, are difficult to suppress. The suppression of only one or two effectors is ineffective.

In the early days of organ transplantation, the major problem was suppression of allograft rejection. Even though this can be achieved, its consequences and potential dangers are apparent. Immunosuppressive agents that are in widespread use today act largely in a broad, nonspecific manner to suppress the entire immune response. As a result, there is increased risk of opportunistic infections and malignancy. Effective general immunosuppression can cripple the host response to infections or suppress other proliferating cells (e.g., bone marrow and intestinal mucosal cells). Infections with agents such as cytomegalovirus (CMV) and Pneumocystis carinii, which are not life threatening to normal individuals, frequently become lethal to the transplant recipient.

At present, clinical immunosuppression relies on three general approaches. The first is to simply deplete circulating lymphocytes by destroying them. The second is to use an inhibitor of lymphocyte activation (cyclosporine or tacrolimus) to interrupt the early events of antigen-induced T-lymphocyte
activation and cytokine production crucial for the subsequent cascade of immunologic events leading to graft rejection. The third is to use various metabolic inhibitors (e.g., azathioprine, mycophenolate mofetil) to interfere with lymphocyte proliferation essential to amplify the response. These agents are biochemically specific but do not distinguish between dividing lymphocytes and other proliferating cells.

Future progress in immunosuppressive therapy concerns the successful implementation of an antigen-specific approach in which the goal is to induce long-lasting donor-specific unresponsiveness (immunologic tolerance) in the host while preserving general immunocompetence. The full promise of transplantation will not be fulfilled until graft rejection can be specifically and safely prevented while the integrity of the immune system as a whole is maintained. Such tolerance of the recipient to allografted organs without the requirement for nonspecific immunosuppression is the ultimate goal in clinical transplantation.

Table 26-1 -- Summary of Cytokines and Their Associated Functions:

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell Source</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-1</td>
<td>IL-1 Mononuclear phagocytes; T and B cells; NK cells; fibroblasts; neutrophils; smooth muscle cells</td>
<td>Proliferation of T and B cells; fever, inflammation; endothelial cell activation; increases liver protein synthesis. Binds to CD121</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>IL-2 Activated T cells</td>
<td>T-cell growth factor, cytotoxic T-cell generation; B-cell proliferation/differentiation; growth/activation of NK cells. Binds to CD122</td>
</tr>
<tr>
<td>Interleukin-4</td>
<td>IL-4 CD4+ T cells; mast cells</td>
<td>B-cell activation/differentiation; T and mast cells growth factor. Binds to CDw124</td>
</tr>
<tr>
<td>Interleukin-5</td>
<td>IL-5 T cells</td>
<td>Eosinophil proliferation/activation. Binds to CD125</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>IL-6 Mononuclear phagocytes; T cells; endothelial cells</td>
<td>B-cell proliferation/differentiation; T-cell activation; increases liver acute phase reactants; fever, inflammation. Binds to CD126</td>
</tr>
<tr>
<td>Interleukin-7</td>
<td>IL-7 Bone marrow, thymic stromal cells, and spleen cells</td>
<td>Stimulates growth of progenitor B and T cells and mature T cells</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>IL-8 Lymphocytes, monocytes, and multiple other cell types</td>
<td>Stimulates granulocyte activity, chemotactic activity; potent angiogenic factor</td>
</tr>
<tr>
<td>Interleukin-9</td>
<td>IL-9 Activated Tα2 lymphocytes</td>
<td>Enhances proliferation of T cells, mast cell lines, erythroid precursors, and megakaryoblastic cell lines</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>IL-10 Mononuclear phagocytes; T cells</td>
<td>B-cell activation/differentiation; inhibition; mononuclear phagocyte</td>
</tr>
<tr>
<td>Interleukin-11</td>
<td>IL-11 Fibroblasts, bone marrow stromal cell lines</td>
<td>Stimulates growth of hematopoietic multipotential and committed megakaryocytic and macrophage progenitors; stimulates growth of plasmacytomas; inhibits adipogenesis</td>
</tr>
<tr>
<td>Interleukin-12</td>
<td>IL-12 Mononuclear phagocytes; dendritic cells</td>
<td>INF-γ synthesis; T-cell cytolytic function; CD4+ T-cell differentiation</td>
</tr>
<tr>
<td>Interleukin-13</td>
<td>IL-13 Activated T cells</td>
<td>Inhibits cytokine and nitric oxide production by activated macrophages; induces B-cell proliferation; stimulates IgE and IgG isotype switching</td>
</tr>
<tr>
<td>Interleukin-14</td>
<td>IL-14 T cells and some B cell tumors</td>
<td>Enhances proliferation of activated B cells; inhibits immunoglobulin synthesis</td>
</tr>
<tr>
<td>Interleukin-15</td>
<td>IL-15 Mononuclear phagocytes; others</td>
<td>NK-cell and T-cell proliferation</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>IFN-γ NK and T cells</td>
<td>Increased expression of class I and class II MHC; activates macrophages and endothelial cells; augments NK-cell activity; antiviral. Binds to CDw119</td>
</tr>
<tr>
<td>Interferon alfa and beta</td>
<td>IFN-α, -β Mononuclear phagocyte-α; fibroblast-β</td>
<td>Mononuclear phagocyte increases class I MHC expression; antiviral; NK-cell activation. Binds to CD118</td>
</tr>
<tr>
<td>Tumor necrosis factor-alpha and beta</td>
<td>TNF-α, -β NK and T cells; mononuclear phagocytes</td>
<td>B-cell growth/differentiation; enhances T-cell function; macrophage activator; neutrophil activator. Binds to CD120</td>
</tr>
<tr>
<td>Transforming growth factor-beta</td>
<td>TGF-β T cells; mononuclear phagocytes</td>
<td>T-cell inhibition</td>
</tr>
<tr>
<td>Lymphotoxin</td>
<td>T cell</td>
<td>Neutrophil activator; endothelial activation</td>
</tr>
</tbody>
</table>

MHC, major histocompatibility complex; NK, natural killer.


* Cytokines are secreted polypeptides that mediate autocrine (act on self) and paracrine (nearby) cellular communication but do not bind antigen. They include those compounds previously termed interleukins and lymphokines.

fulfilled until graft rejection can be specifically and safely prevented while the integrity of the immune system as a whole is maintained. Such tolerance of the recipient to allografted organs without the requirement for nonspecific immunosuppression is the ultimate goal in clinical transplantation. Approaches to achieve this state are discussed later. Finally, because the number of individuals who can benefit from a transplant far exceed the number of donors available, xenotransplantation is considered by some to hold promise for the future.
<table>
<thead>
<tr>
<th>Marker</th>
<th>Main Cellular Expression</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-CELL ASSOCIATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td>T cells, thymocytes</td>
<td>Cell surface expression and signal transduction with TCR; ε is required for both expression and signal transduction</td>
</tr>
<tr>
<td>CD4</td>
<td>Class II restricted T cells, thymocyte subsets, monocytes, and macrophages</td>
<td>Adhesion molecule, binds to class II MHC; signal transduction; thymocyte development; primary receptor for HIV retroviruses</td>
</tr>
<tr>
<td>CD5</td>
<td>T cells, B-cell subset</td>
<td>Ligand for CD72</td>
</tr>
<tr>
<td>CD8</td>
<td>Class I restricted T cells, thymocyte subsets</td>
<td>Adhesion molecule, binds to class I MHC; signal transduction, thymocyte development</td>
</tr>
<tr>
<td>CD28</td>
<td>T cells (most CD4⁺, some CD8⁺)</td>
<td>T-cell receptor for co-stimulatory molecules CD80 (B7-1) and CD86 (B7-2)</td>
</tr>
<tr>
<td>CD152</td>
<td>Activated T lymphocytes</td>
<td>Inhibitory signaling in T cells, binds CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells</td>
</tr>
<tr>
<td>CD154</td>
<td>Activated CD4⁺ T cells</td>
<td>Activates B cells, macrophages, and endothelial cells; ligand for CD40</td>
</tr>
<tr>
<td><strong>B-CELL ASSOCIATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD10</td>
<td>Immature and some mature B cells, granulocytes</td>
<td>Cell surface metalloprotease</td>
</tr>
<tr>
<td>CD19</td>
<td>Most B cells</td>
<td>B-cell activation, forms co-receptor with CD21 and CD81 to synergize with signals from B-cell antigen receptor complexes</td>
</tr>
<tr>
<td>CD20</td>
<td>Most or all B cells</td>
<td>? B cell activation or regulation, calcium ion channel</td>
</tr>
<tr>
<td>CD21</td>
<td>Mature B cells, follicular dendritic cells</td>
<td>B-cell activation; receptor for C3d, forms a co-receptor with CD19 and CD81 to deliver activated signals in B cells; EBV receptor</td>
</tr>
<tr>
<td>CD40</td>
<td>B cells, macrophages, dendritic cells, endothelial cells, epithelial cells</td>
<td>Role in B-cell activation by T-cell contact; receptor for CD154 (CD40 ligand); macrophage, dendritic cell, and endothelial cell activation</td>
</tr>
<tr>
<td>CD80 (B7-1)</td>
<td>Dendritic cells, activated B cells, macrophages</td>
<td>Co-stimulator for T-cell activation; ligand for CD28 and CD152 (CTLA-4)</td>
</tr>
<tr>
<td>CD86 (B7-2)</td>
<td>B cells, monocytes</td>
<td>Co-stimulator for T-cell activation; ligand for CD28 and CD152 (CTLA-4)</td>
</tr>
<tr>
<td><strong>MYELOID-CELL ASSOCIATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD11a</td>
<td>Leukocytes</td>
<td>Adhesion, binds to CD54 (ICAM-1), CD102 (ICAM-2), CD50 (ICAM-3)</td>
</tr>
<tr>
<td>CD11b</td>
<td>Granulocytes, monocytes, NK cells</td>
<td>Adhesion; phagocytosis of iC3b-coated particles</td>
</tr>
<tr>
<td>CD11c</td>
<td>Granulocytes, monocytes, NK cells, dendritic cells</td>
<td>Similar to CD11b; major CD11, CD18 integrin on macrophages and dendritic cells</td>
</tr>
<tr>
<td><strong>NK-CELL ASSOCIATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD16a</td>
<td>Macrophages, NK cells</td>
<td>Low-affinity Fc receptor; activation of NK cells, ADCC</td>
</tr>
<tr>
<td>CD16b</td>
<td>Neutrophils</td>
<td>Immune complex–mediated neutrophil activation</td>
</tr>
<tr>
<td>CD57</td>
<td>NK cells, subset of T cells</td>
<td>? Adhesion</td>
</tr>
<tr>
<td><strong>PLATELET ASSOCIATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD31</td>
<td>Platelets, monocytes, granulocytes, B cells, endothelial cells, T cells</td>
<td>Adhesion molecule in leukocyte diapedesis</td>
</tr>
<tr>
<td>CD41</td>
<td>Platelets, megakaryocytes</td>
<td>Platelet aggregation and activation; binds to fibrinogen</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD25</td>
<td>Activated T cells and B cells</td>
<td>Complexes with IL-2R, high-affinity IL-2 receptor</td>
</tr>
<tr>
<td>CD34</td>
<td>Precursors of hematopoietic cells</td>
<td>Ligand for L-selectin; cell-to-cell adhesion</td>
</tr>
<tr>
<td>CD55</td>
<td>Broad</td>
<td>Regulation of complement activation; binds C3b, C4b</td>
</tr>
<tr>
<td>CD58</td>
<td>Broad</td>
<td>Adhesion; ligand for CD2</td>
</tr>
<tr>
<td>CD59</td>
<td>Broad</td>
<td>Inhibits formation of complement MAC</td>
</tr>
<tr>
<td>CDw70</td>
<td>Activated T and B cells, macrophages</td>
<td>Binds CD27, co-stimulatory signals</td>
</tr>
<tr>
<td>CD95</td>
<td>Multiple cell types</td>
<td>Binds Fas ligand, mediates activation-induced cell death</td>
</tr>
<tr>
<td>CD102 (ICAM-2)</td>
<td>Endothelial cells, monocytes, other leukocytes</td>
<td>Ligand for CD11a; CD18 (LFA-1), cell-cell adhesion</td>
</tr>
<tr>
<td>CD105</td>
<td>Endothelial cells, activated macrophages</td>
<td>Binds TGF-β, modulates cell response to TGF-β</td>
</tr>
</tbody>
</table>

ADCC, antibody-dependent cellular cytotoxicity; EBV, Epstein-Barr virus; INF, interferon; ICAM, intracellular adhesion molecule; IL, interleukin; LFA, leukocyte function-associated; MAC, membrane attack complex; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

THE CELLS INVOLVED IN ALLOGRAFT REACTIVITY

The key components of the immune system—T cells, B cells, and APCs—are produced by the hematopoietic stem cell. The development of the lymphoid system begins with pluripotential stem cells in the liver and bone marrow of the fetus. As the fetus matures, the bone marrow becomes the primary site for lymphopoiesis. The pre-T cells migrate to the thymus, which becomes the primary lymphoid organ wherein CD3+ T lymphocytes mature and become “educated” to self. The mature T cells are then released to populate the peripheral lymphoid tissues, including lymph nodes, spleen, and gut. It is in the thymus that T cells acquire their cell surface antigen-specific receptors (T-cell receptors [TCRs]) (Table 26–2), which, in turn, confer specificity to the immune system.

and immune responses. Another lymphocyte subpopulation produced by the hematopoietic stem cell is the B cell. B cells derive their name from the primary lymphoid organ that produces B cells in birds, the bursa of Fabricius. In the human and other mammals, the bone marrow is the primary site of B-cell development.

The T cells, B cells, and APCs have unique roles in orchestrating the immune response. It is a very tightly controlled network, with most communication mediated by cytokines. B cells have the unique capacity to synthesize antibody. A behavioral difference between B and T cells reflects their functional abilities. B cells are specialized to respond to whole antigen and synthesize and secrete antibody that can interact with antigen at distant sites. The T cells that are responsible for cell-mediated immunity are of necessity more peripatetic and must migrate to the periphery to neutralize or eliminate foreign antigens. From the peripheral blood, T cells enter the lymph nodes or spleen through highly specialized regions in the postcapillary venules. After exiting the lymphoid tissue through the efferent lymph, they percolate through the thoracic duct and return to the blood to begin recirculation in quest of antigen. When an organ is transplanted, responsive clones of T cells are activated in the organ itself. In addition, donor dendritic cells leave the graft, home to host lymph nodes, and stimulate both host T and B cells therein. Activated T cells leave the lymph nodes and can augment the cellular response in the graft. B cells send out antibody molecules that bind to antigens in the graft within a few days, mediating destructive reactions.

Considerable progress has been made in dissecting the mechanisms of T-cell maturation in the thymus. Precursor T cells migrate to the thymus where they undergo matutational changes. All T cells express on their surface an antigen-specific TCR, which is the site for antigen binding. The majority of T cells are αβ-TCR+. A smaller subpopulation, which primarily resides in the gut, is γδ-TCR+. There are also transmembrane proteins (CD3) with the TCR. Collectively, these complexes compose the TCR complex and provide the signaling molecules needed to respond to foreign antigens.

The thymic stromal cells produce two types of molecules that are important for T-cell maturation. The first type is thymic hormones (e.g., thyroperoxidase and thymosin) and the cytokine interleukin-7 (IL-7), which regulate the functional differentiation of the peripheral T-cell system. The second type is MHC molecules that are important for selection of the T-cell repertoire. Fundamental properties of a mature T-cell repertoire include (1) restriction to self-MHC and (2) tolerance to self-antigens.

The development of self-tolerance occurs through both central and peripheral mechanisms. Each of these mechanisms is vital for the discrimination of self/nonself. Central tolerance is achieved through clonal deletion occurring in the thymus. The acquisition of the TCR complex takes place through a series of genetically programmed matutational steps. Pre-T cells, not expressing CD4 or CD8 molecules, enter the thymus and proliferate to an intermediate stage of development where they become double positive (CD4+ and CD8+) cells. These cells are educated by self-MHC class I or class II (present on host stromal cells). T cells expressing TCR molecules that interact at an intermediate affinity with self-MHC survive whereas those with too low or too high affinities for MHC do not. This phenomenon is termed positive selection. Cells that do not bind to class I or class II undergo programmed cell death or death by neglect. After positive selection occurs, the developing T cells are exposed to self-antigens. If they react too strongly to self-antigen MHC complexes, they are deleted from the immune repertoire, a phenomenon termed negative selection (Fig. 26–2).

Programmed Cell Death

Not all progeny of stimulated T cells proliferate but instead die by a process called apoptosis. Apoptosis is a form of regulated cell death. In apoptosis, the nucleus of the cell condenses and becomes fragmented, the plasma membrane becomes vesiculated, and the dead cell is rapidly phagocytosed. There is subsequently no release of the cellular contents, and an inflammatory response does not occur. This programmed cell death is an important homeostatic mechanism that limits the lymphoid pool, allowing it to remain relatively constant throughout a lifetime.

Activation-induced cell death (AICD) is an apoptotic pathway that is important in the maintenance of self-tolerance in the periphery. The hallmark of this system is Fas(CD95)/FasL(CD95 ligand) interactions. The physiologic importance of this system is to prevent uncontrolled T-cell activation and resulting autoimmune disease. The importance of Fas/FasL to peripheral tolerance was first discovered in two mouse strains: lpr and gld. The lpr mutation occurs in the gene that encodes Fas and results in a lack of Fas expression. The gld mutation results in a defective FasL protein that lacks the ability to bind to the Fas receptor. Either of these mutations results in severe, accelerated autoimmune diseases.

Fas is a surface receptor expressed on activated T cells. The expression of FasL occurs in response to increased levels of IL-2 secreted by activated T cells. This expression of Fas and FasL leads to cell death through apoptosis. The Fas/FasL system is believed to be one mechanism to control immune responses from being too robust. Binding of Fasl to Fas results in the activation of intracellular cysteine proteases, which ultimately results in the fragmentation of nucleoproteins and apoptotic cell death. CD4+ T cells appear to be more sensitive to the Fas/FasL interaction than CD8+ T cells.

Not all apoptosis is the direct result of activation; some forms occur when activated cells are exposed to an environment without needed growth factors or cytokines necessary for T-cell function; this is termed growth factor withdrawal.
CELL-TO-CELL INTERACTIONS

Once confronted with an antigen, the response of the lymphocytes is complex. Multiple cell-to-cell interactions are required to produce the immune response. T cells, B cells,

![Diagram of cell-to-cell interactions](image)

**Figure 26-3** Lineage relationships of maturing T cells. γδ-T-cell receptor (TCR) and αβ-TCR-expressing cells are separate lineages that develop from a common precursor. In the αβ lineage, the majority of thymocytes express both CD4 and CD8. TCR expression commences in this double-positive stage, beginning with low numbers of receptors on each cell and increasing as maturation proceeds. Single-positive (i.e., CD4 or CD8 αβ-TCR–expressing mature cells) are selected from this population. Some αβ cells express CD4 or CD8. (From Abbas AK, Lichtman AH, Pober JS: T cell maturation in the thymus. In Cellular and Molecular Immunology, 3rd ed. Philadelphia, WB Saunders, 1997.)

APCs, and cytokines all play a role. Critical to this response are the professional APCs—dendritic cells and macrophages—that bind antigen and present it to T and B cells. Protein antigens need to be digested by phagocytic cells before the antigenic information can be presented to the lymphocyte for self and nonself recognition by MHC. In addition, activated macrophages produce and secrete IL-1, a cytokine that further amplifies the response and stimulates T- and B-cell activation.

For a productive immune response to be generated, the TCR complex must bind to the MHC on the APC, be stabilized by co-stimulatory molecules, and cause intracellular signaling, resulting in activation of the lymphocyte and production of cytokines.

**T-Lymphocyte Activation**

T-cell activation is an elegant series of events that are still in the process of full delineation (Fig. 26-4). Antigen recognition by T cells is the initiating stimulus for their activation, proliferation, cytokine production, and performance of regulatory or cytolytic effector functions. The TCR is composed of membrane proteins expressed only on T lymphocytes. The TCR does not recognize soluble antigens; rather, it must recognize antigen in the context of peptide (6-13 amino acids in length)/MHC complexes on the surface of APCs. Associated with the TCR is the CD3 molecule. Together they constitute the TCR complex.

Most TCRs are heterodimers, consisting of two transmembrane polypeptide chains designated α and β, which are bonded covalently. All TCRs have a variable region that confers antigen specificity. The αβ-TCR is noncovalently associated with CD3. This highly conserved complex of proteins is responsible for providing the signaling components to the antigen-binding TCR heterodimer, which binds the antigen. Binding of a foreign antigen results in the conformational change in the complex. The associated CD3 molecules transduce the intracellular signals after antigen binding occurs. The development of monoclonal antibodies directed against CD3, such as OKT3, which interfere with T-cell function by altering or inhibiting the intracellular signaling, have played a significant clinical role in organ transplantation.

Both MHC molecules and αβ-TCR are expressed on resting T cells; however, the IL-2 receptor (IL-2R) is expressed at only very low levels. When T-cell activation
Figure 26-4 Overview of intracellular signaling events during T-cell activation. Immediately after the T-cell receptor (TCR) binds antigen on an antigen-presenting cell (APC), several protein tyrosine kinases are activated, and these enzymes phosphorylate substrates, which leads to activation of guanosine triphosphate (GTP)-binding proteins such as Ras and activation of enzymes that break down membrane phospholipids. (From Abbas AK, Lichtman AH, Pober JS: Intracellular signaling events during T-cell activation. In Cellular and Molecular Immunology, 4th ed. Philadelphia, WB Saunders, 2000.)

occurs, there is a decrease in the number of TCRs expressed on the T cell, accompanied by an increase in IL-2R expression. Activated T cells produce and secrete IL-2, exerting an autocrine and paracrine response. Only those T cells that have been activated by their specific antigen and express the high-affinity IL-2R can respond to IL-2. After IL-2R bind IL-2, T-cell proliferation begins. After the antigenic stimulus is removed, the number of surface IL-2R starts to decrease, and the TCR complex is re-expressed on the cell surface. This inverse relationship between the TCR and IL-2R suggests a negative feedback mechanism. This is an elegant system, which is reactive only in the presence of an antigen and ceases to function as the antigen is removed.

Molecular signaling via the TCR/CD3 complex and its relationship with IL-2 production and IL-2R expression have been characterized. Antigen binding initiates the activation of two signal-transduction pathways through a conformational change in the TCR complex. The beta chain of the complex is phosphorylated by means of a CD4- or CD8-associated tyrosine-kinase-dependent pathway. The activated TCR complex is coupled via a G-binding protein to phospholipase C. The activation of phospholipase C results in the hydrolysis of phosphatidylinositol 4,5 biphosphate (PIP$_2$) to produce diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP$_3$). These are the second messengers that are responsible for the mobilization of intracellular and extracellular Ca$^{2+}$ that activate protein kinase C. The result of these changes is the transcription of early-activation genes (NFAT and c-fos) and the production of messenger RNA (mRNA) for IL-2 and its receptor (Fig. 26–5).[1]

Co-stimulatory Pathways

Two signals are required for T-cell activation: an antigen-specific signal and a co-stimulatory signal. The TCR/CD3 interaction (signal 1) required for cell activation has been well defined. The co-stimulatory pathways present on APC surface molecules provide the second signal for T-cell activation (signal 2). If these co-stimulatory pathways are interrupted or blocked, such as with monoclonal antibodies directed at the receptors, the result of signal 1 alone is clonal anergy. In the presence of TCR/CD3 complex providing the primary signal, without the secondary signal, the T cell is rendered anergic or functionally inactive. Co-stimulatory molecules on the T-cell surface specifically interact with molecules on the APC surface. The most well-characterized co-stimulatory important pathway involves the T-cell surface molecule CD28. This molecule binds to both CD80 (B7-1) and CD86 (B7-2) found on APCs (dendritic cells, monocytes, B cells), and signaling through CD28 enhances the T-cell response.
T-cell signaling through membrane inositol lipid metabolism. T-cell receptor (TCR)–associated protein tyrosine kinases activated by antigen presentation lead to the phosphorylation of phosphatidylinositol phospholipase C-\(
\gamma
\) (PI-PLC-\(
\gamma
\)) as well as docking sites for PI-PLC-\(
\gamma
\) on the plasma membrane. PI-PLC-\(
\gamma
\), activated tyrosine phosphorylation, catalyzes the breakdown of membrane phosphatidylinositol 4, 5-bisphosphate (PIP\(_2\)) into inositol 1,4,5-triphosphate (IP\(_3\)) and diacylglycerol (DAG). IP\(_3\) induces the release of Ca\(^{2+}\) stored in the endoplasmic reticulum (ER), and DAG plus Ca\(^{2+}\) activate protein kinase C (PKC). Cytosolic Ca\(^{2+}\) and PKC both serve to activate other enzymes and eventually transcription factors. The symbol (P) refers to phosphorylated tyrosine. (From Abbas AK, Lichtman AH, Pober JS: T lymphocyte antigen recognition and activation. In Cellular and Molecular Immunology, 3rd ed. Philadelphia, WB Saunders, 1997.)

Figure 26–5

The exact mechanism by which CD28 promotes T-cell activation has not been fully defined. Proposed mechanisms include CD28-mediated expression of T-cell IL-2. This expression is enhanced at the level of mRNA production, resulting in increased production. Another mechanism involving CD28 is the protection of T cells from programmed cell death, or apoptosis. CD28 is associated with an increased expression of Bel-\(\alpha\), a survival protein. The expression of this gene results in the resistance to T-cell death by apoptosis.\(^1\)\(^2\)

Closely related to this CD28/CD152/CD80/CD86 pathway is the CD40/CD154 (also known as CD40 ligand) pathway. CD40 is a surface molecule constitutively expressed on B cells. After antigen recognition by the B cells, there is upregulation of CD80 (B7-1) and CD86 (B7-2), which interacts with the T-cell CD28, causing an increased expression of CD154 by the activated T cell, which binds to CD40 receptor on the B cells. This interaction of CD40/CD154 provides the stimulus for B cells to continue activation and proliferation.\(^2\) Manipulation of both of these important pathways is under investigation in clinical protocols in transplantation. Co-stimulatory blockade using anti-CD154 monoclonal antibodies is very effective in inducing anergic and regulatory T cells. This further emphasizes the importance of the CD40/CD154 pathway in providing co-stimulation and upregulates the effects of CD28/B7 pathway.

T-Cell Effector Functions

In addition to acquiring the TCR complex during thymic maturation, T cells also acquire differentiation receptors called cluster of differentiation (CD) antigens. CD4 and CD8 are the best-known CD markers. Other frequently occurring CD markers can be found in Table 26–2. The subpopulations of T cells have several different functional activities. T cells bearing the CD8\(^+\) molecule interact with MHC class I peptide complexes and can directly lyse a foreign or tumor cell on activation. These activated CD8\(^+\) T cells are the cytotoxic T lymphocytes (CTLs). In contrast, CD4\(^+\) T cells recognize antigen in the context of MHC class II molecules. CD4\(^+\) T cells become T helper (Th) cells after activation and primarily function through the secretion of distinct cytokines to induce either a cell-mediated response (Th1) or a humoral response (Th2).\(^3\)\(^4\)

Even the recognition of foreign cells is a complex process. The initial responding and proliferating cells do not destroy foreign grafts; rather, they activate another group of T cells (cytotoxic), which in turn damage the graft. The first group of T cells are CD4\(^+\) Th cells. Th\(_{cyt}\)-cell proliferation is an important step in the amplification of the immune response, and these actively dividing cells are particularly vulnerable.
Co-stimulators on antigen-presenting cells (APCs) are required for effective T-cell activation. Resting macrophage APCs do not express co-stimulatory molecules such as B7-1 (CD80) or B7-2 (CD86), and they fail to activate T cells during antigen presentation. In the setting of an infection, microbial products such as endotoxin or cytokines elaborated by innate immune responses can upregulate B7-1 (CD80) and B7-2 (CD86) expression on the macrophage. Antigen presentation by the activated macrophage will then lead to T-cell activation characterized by cytokine production and proliferation. Cytokines secreted by the activated T cell, such as interferon-\(\gamma\), can induce co-stimulator expression on other macrophages, enabling them to serve as effective APCs and thereby amplifying the immune response. (From Abbas AK, Lichtman AH, Pober JS: T lymphocyte antigen recognition and activation. In Cellular and Molecular Immunology, 3rd ed. Philadelphia, WB Saunders, 1997.)

to antimetabolites. The activities of the CD4\(^+\) T\(_{in}\) cells are thus one of the major targets of clinical immunosuppression using drugs or monoclonal antibodies.

T\(_{in}\) cells have a central role in response to alloantigen. Once antigen has been processed and presented in the context of cell surface MHC class II molecules on an APC, the T\(_{in}\) cell proliferates. The two distinct T\(_{in}\) populations have been characterized (T\(_{in}\) 1 and T\(_{in}\) 2 subsets) based on their pattern of cytokine synthesis (Fig. 26-7). In T\(_{in}\) 1 responses, the main cytokines are IL-2 and interferon-gamma (IFN-\(\gamma\)). IL-2 is produced by activated T cells and is a potent T-cell growth factor. IL-2 enhances B-cell and natural killer (NK)-cell differentiation. IFN-\(\gamma\) activates macrophages and is involved in B-cell isotype switching. These responses are important for cell-mediated immunity. T\(_{in}\) 1 response is balanced by the T\(_{in}\) 2 response. The T\(_{in}\) 2 response results in the production of IL-4, IL-5, and IL-10. IL-4 is the T\(_{in}\) 2-polarizing cytokine and is required for the production of immunoglobulin E. In addition, IL-4 is an essential growth factor for T cells, and it stimulates the expression of MHC class II and adhesion molecules. An important feature of these CD4\(^+\) T\(_{in}\) cells is the ability of one subset to regulate the activities of the other. Thus, IFN-\(\gamma\) directly inhibits the proliferation of T\(_{in}\) 2 cells, whereas IL-10 (and IL-4) inhibits cytokine production by T\(_{in}\) 1 cells. This cross-regulation occurs at the level of the effector cells triggered by these subsets. Thus, IFN-\(\gamma\) inhibits IL-4–induced B-cell activation, whereas IL-4 suppresses IL-2–induced T- and B-cell proliferation. The current theory postulates that differentiation of naive CD4\(^+\) T cells, down either pathway, is directly related to the neighboring cells and the cytokines that these neighboring cells produce.

Regulatory T cells (T\(_{reg}\)) have received a great deal of recent attention and may hold significant promise for strategies to achieve antigen-specific tolerance in the clinic. T\(_{reg}\) are defined by their function: to suppress alloreactivity in vitro (a state reversed by exogenous IL-2) and downregulate the proliferation of other T-cell populations via IL-10. Initially, they are cell (antigen) contact dependent but on maturation become contact independent to amplify the response. The most important subset of T\(_{reg}\) is CD4\(^+\)/CD25\(^+\). In animal models T\(_{reg}\) have been shown to play a role in the maintenance of tolerance and prevention of graft-versus-host disease (GVHD) after marrow transplantation.
T-helper (CD4+) cells can be divided into functionally distinct subsets (TH 1 and TH 2) based on their cytokine secretion profiles. Cytokines secreted by TH 1 cells play a key role in cell-mediated immunity, whereas those produced by TH 2 cells are important in B-cell stimulation and antibody production. An important feature of the TH 1/TH 2 cell paradigm is that cross-regulation of function between TH 1 and TH 2 cells occurs. Thus, for example, IFN-γ stimulates TH 2 cells whereas IL-10 inhibits TH 1 cells. Cyclosporine and tacrolimus (FK-506) are potent inhibitors of IL-2 and IFN-γ production by TH 1 cells. There is evidence, however, that they may spare IL-10 (cytokine synthesis inhibitory factor) production by TH 2 cells. ADCC, antibody-dependent cell-mediated cytotoxicity.

B Lymphocytes

Similar to all other cells in the immune system, B cells are derived from the pluripotent bone marrow stem cell. IL-7, produced by bone marrow stromal cells, is a growth factor for pre-B cells, whereas IL-4, IL-5, and IL-6 are cytokines that stimulate the maturation and proliferation of mature primed B cells. B cells express immunoglobulin antibody on their cell surface. These membrane-bound immunoglobulins are the B-cell antigen receptors and allow for specific antigen recognition. Only one antigen-specific antibody is produced from each mature B cell. Each antibody is composed of two heavy chains and two light chains. Both heavy and light chains have a constant region (Fc), as well as a variable, antigen-binding region. The antibody-binding site is composed of both the heavy- and light-chain–variable regions. In the human there are nine different immunoglobulin subclasses: IgM, IgD, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, and IgE. Resting naive B cells express IgD and IgM on their cell surface. On antigen stimulation and T-cell cytokine, B cells undergo isotype switching. Distinct immune effector functions are assigned to each isotype. IgM and IgG antibodies provide a pivotal role in the endogenous or intravascular immune response. The first isotype produced in response to a foreign antigen is IgM, which is very efficient at binding complement to facilitate phagocytosis or cell lyses. B cells undergo isotype switching with the maturation of the immune response to a specific antigen. This results in a decrease in IgM titers with a concomitant rise in IgG titers (Fig. 26–8). A primed B cell may undergo further mutations within the variable regions that lead to increased affinity of antibody; this is termed somatic hypermutation.

Monocytes

Mononuclear phagocytes, which also have an integral role in the immune response, are derived from bone marrow. This cell type initially emerges as a monocyte while in peripheral blood. On settling in tissues, the mononuclear phagocytes are called macrophages or histiocytes. The main function of monocytes and macrophages is phagocytosis. After phagocytosis, they process antigen, present the antigen to lymphocytes, and produce various cytokines (see Table 26–3) that regulate the immune response.
Figure 26-8 Phases of helper T-cell–dependent antibody responses. Ig, immunoglobulin; FDCs, follicular dendritic cells. (From Abbas AK, Lichtman AH, Pober JS: T lymphocyte antigen recognition and activation. In Cellular and Molecular Immunology, 3rd ed. Philadelphia, WB Saunders, 1997.)

Dendritic Cells

The most potent APCs are CD11c+ bone marrow–derived dendritic cells, which are distributed ubiquitously throughout the lymphoid and nonlymphoid tissues of the body. Immature dendritic cells are located along the gut mucosa and other sites of antigen entry. Antigen presentation by immature dendritic cells leads to TCR signaling without co-stimulation and induces T-cell anergy. On contact with antigen, dendritic cells are activated to mature, increasing expression of both MHC and co-stimulatory molecules. As dendritic cells mature, they migrate to peripheral lymphoid tissue, where they can activate T cells. Dendritic cells provide signals that initiate clonal expansion of T cells as well as provide signals to promote naive T cells to either TH 1 or TH 2 response. Two lineages of dendritic cells have been described, the myeloid and lymphoid. It is speculated that myeloid dendritic cells (DC1) are more immunogenic whereas lymphoid dendritic cells (DC2) are more tolerogenic. Recent data in animals suggest that DC2, under specific conditions, can be potently tolerogenic in vivo and may therefore present the future for cell-based therapies.

Natural Killer Cells

Natural killer cells are bone marrow–derived cells capable of killing specific tumor cells and virally infected cells. NK
cells express different cell receptors that are distinct from the TCR complex. Functionally, these cells are defined by their ability to lyse target cells without prior sensitization. NK cells lyse cell targets that lack the expression of self MHC class I. These cells play an important role in immune defenses, especially after hematopoietic transplantation. They also contribute to the defenses against virus-infected cells, graft rejection, and neoplasia, and they participate in the regulation of hematopoiesis through cytokine production and cell-to-cell interaction. NK cells also mediate rejection in xenotransplantation.23

Figure 26-9 T-lymphocyte surface molecules and their ligands involved in antigen recognition and T-cell responses. Interactions between a CD4+ T cell and an antigen-presenting cell (APC) (A), or a CD8+ cytolytic T lymphocyte (CTL) and a target cell (B), involve multiple T-cell surface proteins that recognize different ligands on the APC or target cell. Some of these interactions promote adhesion (e.g., leukocyte function-associated antigen [LFA]-1–intercellular adhesion molecule [ICAM]-1 interactions), and some provide co-stimulatory signals (e.g., CD28-B7-1[CD80]/B7-2[CD86] interactions). MHC, major histocompatibility complex. (From Abbas AK, Lichtman AH, Pober JS: T lymphocyte antigen recognition and activation. In Cellular and Molecular Immunology, 3rd ed. Philadelphia, WB Saunders, 1997.)
MAJOR HISTOCOMPATIBILITY LOCUS: TRANSPLANTATION ANTIGENS

The MHC is a region of highly conserved polymorphic genes. The products of these genes are expressed on the cell surface of a wide array of cell types. MHC genes play a pivotal role in immune response. MHC is so important because antigen-specific T lymphocytes do not recognize antigens in the free form or in soluble form but only as small peptides, products of protein digestion, that are bound to MHC molecules. There are two types of cell surface MHC molecules: class I and class II. Any lymphocyte is restricted to one of these two classes. Antigens associated with class I are recognized by CD8+ T cells; antigens associated with class II are recognized by CD4+ T cells. (Fig. 26–9).

Human Histocompatibility Complex

The strongest antigens present in transplantation are the MHC molecules and the peptides they hold. The MHC in humans is located on chromosome 6. The gene products of the MHC molecules in humans are called human leukocyte antigens (HLA). Class I molecules important to transplantation in humans are expressions of HLA-A, HLA-B, and HLA-C genes. HLA-E, HLA-F, and HLA-G are more conserved but may later demonstrate importance in transplantation. The class II molecules are expressions of HLA-DR, HLA-DQ, HLA-DP, and HLA-DM genes. There are class III molecules, but they are not cell surface proteins involved in antigen recognition. Instead, class III molecules contain mainly soluble mediators of immune function and include tumor necrosis factor (TNF)-α and -β, complement components, heat shock protein, and nuclear transcription factor β.

Class I MHC

Class I molecules in humans are expressions of HLA-A, HLA-B, and HLA-C genes, which are recognized by cytotoxic CD8+ T cells. The class I molecules are composed of a 44-kD transmembrane glycoprotein in a noncovalent complex with a nonpolymorphic 12-kD polypeptide called β2-microglobulin. The peptide-binding region of class I, composed of the first and second domains of a protein, forms a binding cleft. The α3 immunoglobulin-like domain, which is the domain closest to the membrane and interacts with CD8, demonstrates limited polymorphism and contains the interaction region for CD8/class I and CD4/class II molecules. There is considerable homology between class I and class II molecules, suggesting a common evolutionary origin.

Class II MHC

Class II molecules in humans are expressions of HLA-DR, HLA-DQ, HLA-DP, and HLA-DM genes. The class II molecules contain two MHC-encoded polymorphic chains, one...
approximately 32 kD and the other approximately 30 kD. The peptide-binding region is composed of the α1 and β1 domains. The immunoglobulin-like domain is composed of the α2 and β2 segments. Similar to the class I immunoglobulin-like domain, there is limited polymorphism, and interactions are limited to CD4+ T cells. The class II molecules are constitutively expressed on professional APCs, including dendritic cells, B lymphocytes, and macrophages. Expression can be induced on endothelial cells with cytokine stimulation and on other cells in certain disease states such as bile duct epithelium in primary sclerosing cholangitis and beta islet cells in diabetes.

Expression of MHC Molecules

The presence of MHC molecules is essential for recognizing interactions between cells. This presence of MHC molecules is the primary determinant of whether T lymphocytes can interact with foreign antigens. For the most part, class I molecules contain peptides that originate inside the cell whereas class II molecules hold peptides that were outside the cell, have been internalized, and were degraded in lysosomes. Importantly in the regulation of cytokotoxic effector cell function, neither class I nor class II molecules can be expressed on the cell surface without a bound peptide. Therefore, the peptide-binding groove is always occupied with either self or foreign peptides. The class I and class II genes can generally be expressed in one of several states in a particular cell. First, the genes can be constitutively expressed and further upregulation can occur with the presence of cytokines. Second, the genes cannot be expressed but rather are induced by cytokines. Third, the genes are not expressed and not inducible. These states are of tremendous importance in clinical transplantation and in determining the antigenicity of the transplanted allograft. The expression of MHC molecules is important in T-cell–mediated rejection, owing to the recognition of nonself.

Antigen Presentation: Direct Versus Indirect Recognition

In conventional antigen recognition, the foreign antigen is ingested by the host APC, digested into small peptides, and presented to T cells that recognize the antigen as well as class I or class II of the APC. This is termed indirect antigen presentation or the indirect pathway. In addition, when a solid organ is transplanted, the professional (dendritic cells, macrophages) and nonprofessional (activated vascular endothelial cells) APCs of the donor can present themselves. This is termed direct recognition (Fig. 26–11). In a solid organ transplant, both pathways play an important role. Recent studies in knock-out mice show that tolerance induction through mechanisms of costimulatory blockade may be selective for the indirect pathway, since elimination of the direct antigen presentation alone does not induce tolerance when combined with co-stimulatory blockade. Tolerance is relatively easily achieved by blockade of the CD28/B7 or CD154/CD40 co-stimulatory pathways in mice.

HLA Typing: Prevention and Rejection

Organ transplantation in a recipient with a fully functional immune system may result in rejection. To minimize rejection,
Molecular techniques for performing HLA typing that use polymerase chain reaction (PCR) have been developed. PCR permits a more complete typing of class II loci (HLA-DR, HLA-DQ, and HLA-DP subsets) as well as precise typing of HLA-A and HLA-B. This DNA typing has become the predominant method because it better defines the crucial sequence of amino acids around the peptide-binding groove. Studies have been conducted that compare HLA-DR typing using traditional serologic methods and PCR methods. Serologic typing will likely be abandoned over time.

In clinical transplantation, crossmatching is performed using microcytotoxicity or flow cytometric techniques. Crossmatching differs from tissue typing. Crossmatching uses the serum from the recipient and is tested for preformed antibodies against donor cells to exclude the possibility of hyperacute rejection. Despite excellent histocompatibility matching, hyperacute rejection can still occur if preformed antibodies are present. Preservation time is more severely limited in heart, lung, and liver transplantation; therefore, in those organs, crossmatching is performed before organ recovery only for recipients with known antibody titers.

Rejection

Graft rejection requires the participation of various combinations of immunologically specific and nonspecific cells. Three types of graft rejection occur. Hyperacute rejection occurs within minutes to days after transplantation and is mediated primarily by preformed antibody. This type of rejection is prevented by screening the recipient for preformed antibodies, not by classic anti-rejection pharmaceuticals. Acute rejection is mediated primarily by T lymphocytes and first occurs between 1 and 3 weeks after solid organ transplantation without immunosuppression. Acute rejection episodes are most common in the first 3 to 6 months after transplantation but can occur at any time. Acute rejection can quickly destroy a graft if left untreated. The new immunosuppressive agents have made acute rejection increasingly less common. Chronic rejection occurs over months to years and is the most common cause of graft loss after 1 year. From an immunologic standpoint, chronic rejection is mediated by both T- and B-cell responses.

Hyperacute rejection is mediated by preformed antibodies that bind to endothelium and subsequently activate complement. This rejection is characterized by a rapid thrombotic occlusion of the vasculature of the transplanted allograft. The thrombotic response occurs within minutes to hours after host blood vessels are anastomosed to donor vessels. Hyperacute rejection is mediated predominantly by IgG antibodies directed toward foreign protein molecules, such as MHC molecules. These IgG antibodies are the result of prior exposure to alloantigens from blood transfusions, pregnancy, or previous transplantation.

There are two forms of acute rejection: acute vascular rejection and acute cellular rejection. Acute vascular rejection is the more severe form, with greater potential for long-term complications for the graft. In the setting of acute vascular rejection, the response is mediated by IgG molecules that develop in response to the graft against the endothelial antigens and involves the activation of complement. T cells contribute to the acute vascular rejection episode by responding to the foreign antigen. This response leads to direct lysis of the endothelial cells or the production of cytokines that further recruit and activate inflammatory cells. The end result is endothelial necrosis. This process occurs within the first week of allograft transplantation in the absence of immunosuppression.

In the setting of acute cellular rejection there is necrosis of parenchymal cells caused by the infiltration of T cells and macrophages. The exact mechanism that underlies this process has not been fully delineated. An effector mechanism in the macrophage-mediated lysis is similar to a delayed-type hypersensitivity response. The T-cell effector mechanism is mediated by a CTL-mediated lysis. Much of the evidence emerging has implicated the alloreactive CD8+ CTL. The CD8+ CTL recognizes and lyses foreign cells. To support this mechanism, the cellular infiltrate present in acute rejection is enriched for CD8+ CTL.

The mechanism for chronic rejection is less clearly defined and is an area of intense study. Chronic rejection appears as fibrosis and scarring in all organs currently transplanted, although the specific histopathologic lesions vary with the organ. It presents as accelerated atherosclerosis in heart recipients, as bronchiolitis obliterans in lung recipients, as “vanishing bile duct syndrome” in liver.
Hyperacute rejection results when preformed antibodies bind to vascular endothelium and activate complement. In acute rejection, CD8+ T cells attack alloantigens in parenchyma and vessels. Chronic rejection has a multifactorial etiology but leads to smooth muscle proliferation and fibrosis. (Adapted from Abbas AK, Lichtman AH, Pober JS: Immune mechanisms of graft rejection. In Cellular and Molecular Immunology, 4th ed. Philadelphia, WB Saunders, 2000.)

Recipients, and as fibrosis and glomerulopathy in kidney recipients. It is unlikely that chronic rejection is strictly an immunologic phenomenon: ischemia and inflammation, among other processes, also play a role. Risk factors for development of the lesions of chronic rejection include (1) previous acute rejection episodes, with increased severity and increased number of episodes further increasing risk of chronic rejection; (2) inadequate immunosuppression, including patient noncompliance; (3) initial delayed graft function; (4) donor issues such as age and hypertension; (5) organ recovery-related issues including preservation and reperfusion injury; and (6) recipient diabetes, hypertension, or post-transplant infections. In essence, almost any injury to the organ in the donor or post transplant can contribute to the development of chronic rejection. Therefore, given the multifactorial basis of chronic rejection, the transplant is not completely protected with currently available immunosuppression. Episodes of acute rejection are a very significant risk factor, however, for the subsequent development of chronic rejection. To the extent immunosuppressive agents prevent acute rejection episodes, the drugs do clearly decrease chronic rejection. New immunosuppressive drugs are evaluated not only by their ability to prevent acute rejection episodes and their safety profiles but also by their ability to prevent chronic rejection and improve the recipient's quality of life. Improved side-effect profiles may improve recipient compliance with immunosuppressive regimens.

The preceding, abbreviated description of the development of allograft immunity discloses many processes that may potentially be manipulated to suppress the immune response: (1) destroying the immunocompetent cells that would otherwise react to donor antigen before transplantation; (2) minimizing histoincompatibility or altering the antigen to make it unrecognizable or even toxic to the reactive lymphocyte clones; (3) interfering with antigen processing and presentation by the recipient cells; (4) inhibiting antigen recognition by lymphocytes; (5) inhibiting production or release by macrophages or lymphocytes of the signal substances or cytokines involved in differentiating lymphocytes into cytotoxic or antibody-synthesizing cells; (6) suppressing clonal expansion of lymphocytes; (7) activating sufficient numbers of suppressor lymphocytes; (8) interfering with the binding of immunoglobulins to graft target antigens; (9) preventing tissue damage by the nonspecific cells and molecules that are activated by sensitized cells or antigen-antibody complexes; and (10) inducing donor-specific transplantation tolerance. Potential sites for regulation are discussed in detail below.
CLINICAL IMMUNOSUPPRESSION

Immunosuppressive agents are, for the most part, essential to graft survival. It is rare for a transplant recipient to become drug free, even over a prolonged period of time. Shortly after cardiac transplantation, recipients must orchestrate taking approximately 60 pills per day. Over time, fewer numbers of medications are required, but the medication regimen still takes its toll. The relatively nonspecific mechanism of action with the currently available immunosuppressive agents is associated with increased rate of infections (particularly viral infections) and malignancy. In addition, the individual agents themselves have specific toxicities. The overall risks of immunosuppression, the individual agents used in modern-day immunosuppression, and possible immunosuppressive drug regimens are each discussed separately. As the effector mechanisms responsible for graft rejection have been increasingly well defined, strategies to develop immunosuppressive agents with increasingly specific actions have emerged. Although tolerance remains the unattained goal of research in transplantation, significant improvements in immunosuppressive medication regimens have occurred in the past few years as newer agents and newer protocols have been developed.

Overall Risks of Immunosuppression

Risks of Infection

Prevention of rejection in any recipient is possible, but prevention itself is achieved at a high cost in terms of increased risk of infections and malignancies due to increased immunosuppression. Immunosuppressive drugs do not specifically block alloreactivity, and a certain degree of increased susceptibility to opportunistic infection plagues all transplant recipients (Fig. 26–13). This increased risk is caused not only by environmental pathogens but also by reactivation of previously controlled internal pathogens. An important example of the latter is CMV infection. CMV infection can result in pneumonia, hepatitis, pancreatitis, and gastrointestinal side effects, among others, in the transplant recipient (Fig. 26–14). CMV has been implicated in the lesions of heart transplant recipients with chronic rejection. Risk of reactivation is highest 6 to 12 weeks after transplantation and again after periods of increased immunosuppression for rejection episodes.\[27\]

Prevention of CMV reactivation is one of the areas in which prophylaxis is used to prevent post-transplant infections. Transplant programs use various prophylactic regimens, depending on the specific organs transplanted. Many regimens include pneumococcal vaccine, hepatitis B vaccine, trimethoprim-sulfamethoxazole for Pneumocystis pneumonia and urinary tract infections (pentamidine nebulizers may be substituted in the sulfa-allergic patient), acyclovir, ganciclovir, or valganciclovir for CMV, and clotrimazole troche or nystatin for oral and esophageal fungal infections. Hyper-CMV immunoglobulins are also used to prevent Epstein-Barr virus (EBV)–derived lymphomas in some high-risk populations. Although outcomes have definitely improved, infections remain a major problem in transplantation despite prophylaxis.\[27\]

Increased attention has focused on the potential role of BK virus in the development of renal allograft dysfunction. Studies previously have reported the role of the virus in ureteral stenosis. BK virus–associated nephropathy is diagnosed by viral inclusion bodies on biopsy, along with urine and plasma PCR testing. Sixty to 80 percent of the adult population may be seropositive for the BK virus, so determining the true role of the virus as a pathogen may be difficult. The nephropathy has reportedly improved with decreases in immunosuppression. Studies also recount success in eradicating the virus with low doses of cidofovir.\[28\]

Risks of Malignancy

Malignancy is also a complication of chronic immunosuppressive therapy. Penn,\[29\] in reporting results from his transplant tumor registry over 30 years, found no increase in lung, breast, prostate, colon, or uterine cancer in transplant recipients. Most post-transplant malignancies are easily treatable in situ carcinomas of the cervix or low-grade skin tumors. Virus-mediated tumors occur in greater frequency in transplant recipients, similar to those found in patients with AIDS. Human papillomavirus is associated with cancers of the cervix, hepatitis B and C with hepatomas, and human herpesvirus 8 with Kaposi’s sarcoma. Lymphomas, particularly those associated with EBV, have an increased incidence in immunosuppressed transplant patients. Recipients treated repeatedly for
Figure 26-13 Usual sequence of infections after organ transplantation. Exceptions suggest the presence of unusual epidemiologic exposure or excessive immunosuppression. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PTLD, post-transplantation lymphoproliferative disease; RSV, respiratory syncytial virus; VZV, varicella-zoster virus. Zero indicates the time of transplantation; solid lines indicate the most common period for the onset of infection; dotted lines and arrows indicate periods of continued risk at reduced levels. (Reprinted from Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant patient. Am J Med 70:405–411, 1981. Copyright 1981, with permission from Excerpta Medica, Inc.)

acute rejection are at increased risk, as are young recipients of liver and small-bowel transplants. The EBV-associated lymphomas are often referred to as post-transplant lymphoproliferative disorders (PTLD) to better distinguish the differences in etiology and treatment from lymphomas in non-immunocompromised populations. PTLD varies from asymptomatic to life threatening, and treatment varies from no treatment, to reduction or withdrawal of immunosuppression in non-lifesaving transplants, to treatment with antiviral agents, to traditional chemotherapy. Rituximab, an anti-CD20 monoclonal antibody that results in depletion of B cells, has been successfully used in the treatment of EBV-PTLD in solid organ transplant recipients. Hyper-CMV immunoglobulin has also been used as prophylaxis in high-risk recipient groups.

Risks of Cardiovascular Disease

Cardiovascular disease remains a significant cause of morbidity and mortality in transplant recipients. After the first year, the most common causes of death in transplant recipients are (1) allograft loss from chronic rejection and (2) death of the patient with a functioning graft, secondary to cardiovascular death, disease, or infection. Atherosclerotic disease in heart transplant recipients is multifactorial. It can be related to chronic rejection, CMV infection, or classic hyperlipidemia. Pancreas allograft recipients suffer from the increased cardiovascular risk factors associated with diabetes, and renal allograft recipients are at increased risk for cardiovascular events as a result of underlying diseases, including diabetes or hypertension with concomitant left ventricular hypertrophy. These pre-transplant risk factors are amplified by post-transplant immunosuppression. Cyclosporine and corticosteroids, in particular, are associated with increased coronary artery disease. Adequate pre-transplant assessment of coronary artery disease, including liberal use of coronary angiography, helps identify those patients at risk. Post-transplant manipulation of immunosuppression in high-risk recipients should be undertaken. For instance,

switching from cyclosporine to tacrolimus should be considered, as well as avoiding or withdrawing corticosteroids in selected patients. HMG-CoA reductase inhibitors may lower lipid levels in transplant recipients, in addition to protecting the graft. Exercise and smoking cessation should also be emphasized.\[31\] \[32\]

### Induction Agents

Immunosuppressive drugs are divided naturally into two groups: those agents used for induction therapy immediately after transplant (often used also for treatment of rejection) and those drugs used for maintenance therapy. In contrast to the past decade, the first group includes primarily various antibody preparations.

There are currently five commercially available agents used primarily for induction. These include two polyclonal antilymphocyte agents, two monoclonal antibodies against the IL-2 receptor, and a monoclonal antibody against CD3 cells. Three other agents are also being tested experimentally in the perioperative period: an anti-CD20 monoclonal antibody, an anti-CD52 monoclonal antibody, and intravenous immunoglobulin (IVIG). These types are each discussed.

### Lymphocyte Depletion Measures

Many clinically important immunosuppressive agents are effective because they deplete the host of lymphocytes. As the mechanism of action of these agents becomes better understood, a more sophisticated classification system may evolve; but, for the present, antilymphocyte globulin therapy, irradiation, and traditional monoclonal antibody therapy appear to act by relatively nonselective lymphocyte depletion or inactivation.\[21\] The profound immunosuppression resulting from the use of antilymphocyte globulins (ALGs) or OKT3 increases the recipient’s risk for opportunistic infection or lymphoma. It is because of these risks that use of ALGs or OKT3 is usually limited to less than 3 weeks, if possible.

### Antilymphocyte Globulin

ALGs are a polyclonal sera produced when human lymphocytes are injected into animals of a different species. Rabbit, goat, and horse antisera are commonly used. The action of ALG appears to be directed mainly against the T cell; the use of thymocytes, therefore, creates the most potent sera. The suppression produced by ALG can be at least partially reversed by T cells but not by bone marrow cells. Thymectomy enhances the effect of ALG, and ALG decreases the number of circulating T cells. As would be expected, ALG administration interferes most with the cell-mediated reactions: allograft rejection, tuberculin sensitivity, and the graft-versus-host reaction. ALG can abolish preexisting delayed-type hypersensitivity reactions, and larger doses prolong the survival of some xenografts. ALG has a definite, but lesser, effect on T-cell–dependent antibody production. Lymphocytes coated with ALG are either lysed or cleared from the blood by reticuloendothelial cells in the liver and spleen.

ALG may be administered prophylactically during the early post-transplant period or used effectively to reverse ongoing rejection. Favorable results depend on potent ALG and prolonged administration rather than on a single dose. ALG is often used in kidney, pancreas, cardiac, and small bowel
transplantation, and beneficial results have also been reported in bone marrow transplantation. ALG pretreatment of the bone marrow recipient is of value in suppressing the response to the donor cells and for enlarging the marrow space. In addition, ALG may be useful in preventing the graft-versus-host reactions that arise in these patients.

The toxicity of any heterologous serum prepared against human tissue depends on two factors: (1) its cross-reactivity with other tissue antigens and (2) the ability of the patient to make antibodies against the foreign protein. Anemia and thrombocytopenia can occur and are presumably caused by a reaction between the ALG and host erythrocytes and platelets. Although prior absorption with human platelets and red cell stroma reduces its severity, some cross-reactivity with these cells persists in all ALG preparations.

Allergic reactions to the antiserum itself are the most common clinical problems associated with the use of ALG. Urticaria, anaphylactoid reactions, and serum sickness, including joint pain, fever, and malaise, all follow development of immunity to the heterologous globulin. These reactions are reduced, however, in the presence of the other immunosuppressive drugs used in transplantation.

Currently, there are two commercially available antithymocyte globulins. The first is a horse antithymocyte globulin, and the second is a rabbit antithymocyte globulin, which is much more commonly used. Clinical trials have demonstrated that the rabbit antithymocyte globulin has greater efficacy at preventing acute rejection episodes post transplant. The rabbit antithymocyte globulin has antibodies against CD2, CD3, CD4, CD8, CD11a, CD18, CD25, HLA-DR, and HLA class I. Both the horse and rabbit preparations have been effective in preventing acute rejection episodes and in reversing acute rejection episodes. Results of a multicenter trial demonstrated that the rabbit antithymocyte globulin had a higher rejection reversal rate than the horse preparation (88% vs. 76%) and that it had a lower incidence of recurrent rejection within 90 days after therapy (17% incidence in the rabbit antithymocyte globulin group vs. 36% with the horse preparation).

Much experience has been gained with the use of the rabbit preparation since it received U.S. Food and Drug Administration approval in the late 1990s, particularly as part of corticosteroid-avoidance protocols. Many centers have found excellent results using induction with rabbit antithymocyte globulin combined with two maintenance agents and corticosteroids for less than 7 days after transplant, if at all.

Monoclonal Antibody

OKT3

In 1975, Kohler and Milstein developed the technology for somatic cell hybridization (hybridoma formation), which could establish immortalized B-cell lines that each secrete a single, or monoclonal, antibody in limitless supply. They were rapidly awarded the Nobel Prize for this discovery. Subsequently, monoclonal antibodies generated against T cells in general (OKT3, anti-CD3) and various T-cell subsets (OKT4, anti-CD4; OKT8, anti-CD8) have made their way into the transplant surgeon’s armamentarium. OKT3, first used clinically in 1980, is used to treat established episodes of acute kidney, liver, heart, or heart-lung rejection. OKT3 binds to a site associated with the TCR (CD3) and functions to modulate the receptor and inactivate T-cell function.

By engaging the TCR complex, OKT3 blocks not only the function of naive T cells but also the function of established cytotoxic T cells, thereby blocking cell-mediated cytotoxicity. OKT3 blocks the T-cell effector functions involved in allograft rejection. After intravenous administration, OKT3 binds to T cells. As a result, the TCR complex is internalized and no longer expressed on the cell surface. These key T cells are then removed by the reticuloendothelial cells that reside in liver and spleen. Circulating T cells decrease abruptly (30 to 60 min) after the first OKT3 injection. Once OKT3 is stopped, CD3+ cells rapidly return to their normal levels, probably owing to re-expression of the TCR complex on the cell surface.

The major limitation to use of OKT3 is that it is immunogenic and can elicit immune reactions. After prolonged use, OKT3 becomes less effective, owing to the production of human anti-mouse antibodies that bind to the circulating OKT3. An acute cytokine release syndrome can also be seen, usually with the first or second dose of the drug. Concomitant administration of corticosteroids or indomethacin can ameliorate this problem. Because of these problems the use of rabbit antithymocyte globulin has essentially replaced the use of OKT3 at many centers.

Interleukin-2 Receptor Inhibitors

The IL-2R is a complex of several transmembrane polypeptide chains. Three IL-2R binding chains, alpha (CD25, 55 kD), beta (75 kD), and gamma (64 kD) have been characterized. Noncovalent association of these chains forms the high-affinity binding site for IL-2. The alpha chain (IL-2Ra) is present only on activated T cells and a subset of activated B cells and APCs. Thus, anti-CD25 monoclonal antibody treatment targets the minor population of cells enriched for antigen-activated T cells. Two agents became available in 1998 that share as their mechanism of action binding of the alpha chain of the IL-2R. These monoclonal antibodies, basiliximab and daclizumab, are thought to decrease rejection by binding to IL-2R without activating it, leaving the cell with no free receptors for IL-2 to bind. The two agents differ in that daclizumab is a humanized anti-CD25 monoclonal antibody, whereas basiliximab is a chimeric anti-CD25 monoclonal antibody. The immunogenicity of these molecules, as measured by in vivo circulating half-life and by the appearance of antibodies against the agents, is significantly reduced when compared with strictly murine anti-CD25 monoclonal antibodies. Early studies demonstrated a decrease in acute rejection episodes without a concomitant increase in infections or malignancy. Both of these agents are well tolerated and can be administered through a peripheral intravenous line. Neither agent results in the type of cytokine-release syndrome occasionally found with OKT3 administration, nor the serum sickness seen with ALGs. Neither agent, however, provides adequate immunosuppression on its own to prevent rejection, because T-cell proliferation can occur through IL-2 βγ receptors or by other pathways. Therefore, both agents must be used in conjunction with other immunosuppressive drugs.

Anti-CD20 Monoclonal Antibody (Rituximab)

Rituximab, as mentioned earlier, has been used as an anti-PTLD agent owing to its depleting effect on B cells. CD20 is a surface molecule expressed on B cells. The antibody has also been used in some centers to decrease antibody production in recipients with high panel reactive antibody (PRA) or as part of positive crossmatch protocols. Additionally, rituximab has been used to treat humoral rejection in cardiac recipients.

Anti-CD52 Monoclonal Antibody (Alemtuzumab or Campath 1H)

Early results are available now in the use of alemtuzumab as a depleting induction agent in renal transplantation. Alemtuzumab is a humanized monoclonal antibody against CD52, which is expressed on B cells, T cells, monocytes, and macrophages. Administration of the agent results in a dramatic, prolonged depletion of lymphocytes lasting 2 to 6 months. Alemtuzumab has been used in the treatment of lymphoid malignancies, rheumatoid arthritis, and multiple sclerosis. Used with low-dose cyclosporine or sirolimus monotherapy, alemtuzumab has prevented rejection in renal allograft recipients. It has also been used to treat lung transplant rejection and as an induction agent in small bowel transplantation. Long-term results are not yet known, but the benefits of this type of protocol are exciting in terms of potential decrease in immunosuppressive risks and cost.
Intravenous Immunoglobulin

IVIG is made from the pooled plasma of thousands of screened donors and should contain all the antibodies found normally in humans. IVIG works through many mechanisms to modulate the immune system, including neutralization of circulating autoantibodies by anti-idiotypes and selective downregulation of antibody production. The preparation can also regulate production of T-cell cytokines, inhibit lymphocyte proliferation, and regulate apoptosis.

IVIG has been used primarily in positive crossmatch and ABO-incompatible protocols, often in combination with plasmapheresis. Additionally, IVIG has successfully treated humoral rejection in all types of organ transplants, including some rejection episodes resistant to corticosteroids and antithymocyte globulin.\[40\] \[41\]

Maintenance Agents

A general rule in the management of immunosuppression is that the greatest amount of drug is required early after transplantation. Usually, agents can be slowly tapered in dosages after the graft has been in place for a period of time. However, it is highly unusual for a transplant recipient to become drug free even after a prolonged time interval. The mainstay of human organ transplantation is daily immunosuppression with oral pharmaceuticals. Prednisone and azathioprine have been used for many years. In those early years of transplantation, though, severe complications with corticosteroid therapy were common when the high doses were used. Currently, many agents are available, all with different side-effect profiles. Multidrug therapy using immunosuppressive agents with a nonoverlapping mechanism of action is used in most organ recipients to decrease the side effects associated with any individual drug in doses large enough to adequately prevent rejection (Box 26-1).

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Adrenal Corticosteroids

Adrenal corticosteroids are the immunosuppressive agents most commonly used in clinical practice.\[52\] Glucocorticoids have many diverse anti-inflammatory actions, which make them potent immunosuppressants. A major effect of corticosteroids appears to be the inhibition of cytokine gene transcription in, and cytokine secretion (IL-1, IL-6, TNF) by, macrophages. Corticosteroids also suppress the production and the effect of T-cell cytokines, which amplify the responses of lymphocytes and macrophages. Thus, IL-2 production and binding of IL-2 to its receptor is inhibited by glucocorticoids. Moreover, the ability of macrophages to respond to lymphocyte-derived signals such as migration inhibition factor and macrophage activation factor is blocked by corticosteroids. This may underlie the marked inhibition of delayed-type hypersensitivity reactions observed with use of these agents. An additional effect is the suppression of prostaglandin synthesis. Corticosteroids have little net effect on antibody production.

Some of the molecular mechanisms by which glucocorticoids exert their effect have been elucidated. Much activity is initiated at the subcellular level by means of hormone receptors. Unlike polypeptide mediators with receptors on the cell surface, corticosteroids move freely through the cell membrane to bind receptors in the cytoplasm, producing a steroid-receptor complex. This complex then moves into the nucleus, where it attaches to the DNA. There it acts on gene promoters to either depress or activate part of the genome and cause transcription of specific mRNA. Thus, some protein synthesis is downregulated and other proteins are synthesized. These changes are the presumed effectors of glucocorticoid action.

Specific intracytoplasmic receptors for glucocorticoids have been identified in normal human lymphocytes, monocytes, neutrophils, and eosinophils. In addition, varying degrees of receptor density have been demonstrated in different lymphoid cell subpopulations. Presumably, the sensitivity of a particular subpopulation of lymphocytes relates to the relative density of the intracytoplasmic receptors for the corticosteroids. These messengers can inhibit DNA, RNA, and protein synthesis. Glucose and amino acid transport can also be affected.

The effectiveness of cortisone in suppressing allograft rejection was first recognized in the 1950s by its ability to prolong skin graft survival in rabbits. In organ allografts, corticosteroids are not effective by themselves, but they are valuable in combination with other agents. Corticosteroids, in high
doses, are especially effective at interrupting ongoing rejection reactions in clinical practice, but prolonged use leads to unacceptable side effects, such as hypertension, weight gain, peptic ulcers and gastrointestinal bleeding, euphoric personality changes, cataract formation, hyperglycemia that could progress to steroid diabetes, pancreatitis, muscle wasting, and osteoporosis with avascular necrosis of the femoral head and other bones. Susceptibility to pyogenic and opportunistic infections is a direct result of the suppression of phagocytic microbial killing by macrophages and neutrophils. Cushingoid features are the external signs of these dangerous processes. Clinical transplantation will be improved tremendously when more specific means of immunosuppression are developed and current corticosteroid dosages are reduced substantially or eliminated. These significant side effects have led many centers to develop steroid-avoidance protocols. Earlier attempts at steroid withdrawal have resulted in unacceptably high rejection rates. Current protocols, many using rabbit antithymocyte globulin for induction and less than 7 days of steroids, have had much better results. A possible explanation for the success of steroid avoidance over steroid withdrawal may be the prevention of upregulation of steroid receptors in the avoidance protocols; this just conjecture at this point.\textsuperscript{[22]}  

**Antiproliferative Agents**  

Antiproliferative agents inhibit the full expression of the immune response by preventing the differentiation and division of the immunocompetent lymphocytes after their encounter with antigen.\textsuperscript{[3]} They either structurally resemble essential metabolites or combine with certain cellular components, such as DNA, and thereby interfere with molecular function.  

The antimetabolites, the former group, either inhibit enzymes that regulate a particular metabolic pathway or are incorporated during synthesis to produce faulty molecules. They include purine, pyrimidine, and folic acid analogues that are most effective against proliferating and differentiating cells. These drugs are given at the time of transplantation when the immunocompetent cells are first stimulated, and for the life of the graft, to inhibit the continuing response of the immune system.  

**Azathioprine**  

Until the mid 1990s, the purine analogue azathioprine was the most widely used immunosuppressive drug in clinical organ transplantation. In fact, Hitchings and Elion were awarded the Nobel Prize for a simple modification that made the drug safe for use in transplantation. Azathioprine is 6-mercaptopurine (6-MP) plus a side chain to protect the labile sulfhydryl group. In the liver, the side chain is split off to form the active compound 6-MP. The mechanism of action of these two compounds is similar, although azathioprine appears to have the advantage of slightly lower toxicity.\textsuperscript{[30]}  

Full metabolic activity occurs in the cell with the addition of ribose-S6-phosphate from phosphoribosyl pyrophosphate to form 6-MP ribonucleotide. The structural resemblance of this molecule to inosine monophosphate is obvious, and 6-MP ribonucleotide inhibits the enzymes that begin to convert inosine nucleotide to adenosine and guanosine monophosphate. In addition, the presence of 6-MP ribonucleotides slows the entire purine biosynthetic pathway by fraudulent feedback inhibition of an early step. The steric similarity to either adenosine or guanine nucleotides is not sufficient to allow significant incorporation into DNA or RNA and synthesis of faulty molecules. The result of inhibiting these

several enzymes, however, is to block the synthesis of cellular DNA, RNA, certain cofactors, and other active nucleotides.  

The biologic activity of azathioprine and 6-MP is greatest when nucleic acid synthesis is most required.\textsuperscript{[22]} These agents thus strongly inhibit the development of both humoral and cellular immunity by interfering with the differentiation and proliferation of the responding lymphocytes. When the expansion of fully immunocompetent cells is complete, nucleic acid synthesis is less important, and the drug is less effective. An additional benefit of azathioprine is that it can also reduce neutrophil production and macrophage activation effects that suppress the nonspecific inflammatory components of the immune reaction.  

The toxicity of azathioprine derives from the same antimetabolite action.\textsuperscript{[3]} The primary effect is bone marrow suppression, leading to leukopenia. Liver toxicity may also occur, possibly because of the high rate of RNA synthesis by hepatocytes. Because hepatic dysfunction does not appear to be dose related, the mechanism is unclear.  

**Mycophenolate Mofetil**  

Mycophenolate mofetil (MMF) is another immunosuppressant that functions by the inhibition of purine metabolism. MMF inhibits inosine monophosphate dehydrogenase and serves to block the proliferation of lymphocytes late in the cell cycle. MMF has almost completely replaced azathioprine as part of traditional triple-therapy immunosuppression. The U.S. Renal Transplant Mycophenolate Mofetil Study demonstrated that in primary cadaver renal transplant recipients randomized either to azathioprine, MMF 2 g/day, or MMF 3 g/day, the incidence of rejection decreased from 38% in the first group to 19.8% in the 2-g/day group and to 17.5% in the 3-g/day group. The 3-g/day group, however, had significant gastrointestinal side effects. Most recipients currently receive 2 g/day. The major clinical side effects of this medication are leukopenia and gastrointestinal upset, particularly diarrhea.\textsuperscript{[22]}  

**Leflunomide**  

Approved for use in the United States in the treatment of rheumatoid arthritis, leflunomide has been used experimentally and clinically in solid organ transplantation. The drug reversibly blocks dihydroorotate dehydrogenase, an enzyme necessary for de novo pyrimidine synthesis in lymphocytes. Experimentally, the drug demonstrates synergy with calcineurin inhibitors and inhibits herpesviruses (including ganciclovir-resistant CMV). Major toxicities appear to vary by organ transplant type. Liver transplant recipients have had significant increases in transaminases; renal transplant recipients have suffered gastrointestinal upset and anemia. Because of sizable variations patient-to-patient in rates of metabolism, drug levels need to be monitored. Not enough experience with leflunomide has been gained to determine whether successes reported experimentally in preventing chronic rejection will translate into the clinical arena.\textsuperscript{[3]}  

**T-Cell–Directed Immunosuppressants**  

**Cyclosporine**  

Borel’s discovery in 1972 of the immunosuppressive properties of cyclosporine, a fungal metabolite extracted from *Tolypocladium inflatum* Gams, contributed enormously to the rapid and successful growth of the field of clinical organ transplantation, especially of livers and hearts.\textsuperscript{[22]} It represented a completely new class of clinically important immunosuppressive agents. Many of its selective, suppressive effects on T cells appear to be related to its selective inhibition of TCR-mediated activation events (Fig. 26-15). It inhibits cytokine production by T cells in vitro and impairs the development of mature CD4\textsuperscript+ and CD8\textsuperscript+ T cells in the thymus. Cyclosporine is a cyclic peptide (11 amino acids, molecular weight: 1202 daltons). Cyclosporine was discovered to be immunosuppressive by its ability to suppress antibody production in mice. Other in vivo properties include inhibition of antibody plaque-forming cell production, GVHD, skin graft rejection, delayed solid organ allograft rejection, and delayed-type
hypersensitivity reactions. Absence of myelosuppression was a major advance over other immunosuppressive agents and indicated that the mechanism of action was relatively specific for lymphocytes. Other inflammatory cells are much less sensitive to its inhibitory effects. Clinically, prophylactic administration of cyclosporine suppresses allograft rejection and GVHD.

Analyses of the effect of cyclosporine on T lymphocytes have shown (1) inhibition of both IL-2–producing T lymphocytes and cytotoxic T lymphocytes; (2) inhibition of IL-2 gene expression by activated T lymphocytes; (3) no inhibition of activated T lymphocytes in response to exogenous IL-2; (4) inhibition of resting T-lymphocyte activation in response to alloantigen and exogenous lymphokine; (5) inhibition of IL-1 production; and (6) inhibition of mitogen (concanavalin A) activation of IL-2–producing T lymphocytes. These T-cell responses involve both CD4+ (T helper) and/or CD8+ (T-cytotoxic/suppressor) cells, and the inhibition appears to occur at the level of activation, and perhaps even maturation, of the resting cell. In mice, maturation of T cells that occurs in the thymus is significantly suppressed by cyclosporine, thus enriching a population of immature and less responsive T cells.

Cyclosporine induces potent immunosuppression without myelosuppression. The addition of corticosteroids to cyclosporine permitted a lowering of the cyclosporine dosage and decreased nephrotoxicity (the principal clinical side effect of the drug). The introduction of cyclosporine into widespread clinical use in 1983 led to a substantial improvement in the outcome of cadaveric renal transplantation and permitted the widespread practice of heart and liver grafting.

Cyclosporine is metabolized in the liver by cytochrome p450 enzymes. Medications that increase or decrease cytochrome p450 function can dramatically increase or decrease cyclosporine or tacrolimus levels. The narrow therapeutic windows of these immunosuppressants require care in prescribing practices. Antibiotics, seizure medications, and some calcium-channel blockers are major culprits, but interactions should be verified before prescribing any new medication to a patient.
The potential adverse effects of cyclosporine include nephrotoxicity, hypertension, hyperkalemia, hirsutism, gingival hyperplasia, tremor and other neurotoxicities, diabetogenicity, and hepatotoxicity. As with other immunosuppressive agents, cyclosporine therapy increases the risk of infection and malignancy; but by reducing corticosteroid requirements, an overall general decrease in infection rates is seen compared with historical immunotherapy.

**Tacrolimus**

Tacrolimus (formerly known as FK-506) is a potent immunosuppressive agent isolated in 1984 in Japan from the soil fungus *Streptomyces tsukubaensis*. It is a macrocyclic lactone with a molecular weight of 822 daltons. Although structurally distinct from cyclosporine, it exhibits a very similar molecular action. Both drugs are regarded as pro-drugs. Their antilymphocytic effects result from the formation of active complexes between the drug and its respective intracellular binding protein or immunophilin (cyclophilin or FK-506 binding protein [FKBP]) (see Fig. 26–15). The activity of tacrolimus in vitro, however, is approximately 100 times greater than that of cyclosporine. Like cyclosporine, tacrolimus functions to inhibit (1) IL-2 gene expression and IL-2 production; (2) mixed lymphocyte culture cellular proliferation, which is mediated by Th cells; (3) the generation of cytotoxic T cells; and (4) the appearance of IL-2R on human lymphocytes. In vivo, tacrolimus prolongs the survival of MHC-disparate skin, as well as cardiac, renal, hepatic, and small bowel allografts. Tacrolimus has been approved for the treatment of liver allograft rejection. It also has efficacy in rescue therapy for recurrent acute allograft rejection in renal allograft recipients. The side effects of cyclosporine and tacrolimus are similar, but tacrolimus does not cause hirsutism or gum hypertrophy. It does, however, cause alopecia and has an increased incidence of post-transplant diabetes when compared with cyclosporine, particularly at higher doses. Drug levels must be monitored.

**Sirolimus**

Similar to tacrolimus, the immunosuppressant sirolimus (also known as rapamycin) is a macrolide antibiotic. It is a close structural analogue of tacrolimus and binds to the same cytoplasmic receptor (FKBP). Unlike tacrolimus or cyclosporine, however, sirolimus does not block T-cell cytokine gene expression but instead inhibits the transduction of signals from the IL-2R to the nucleus. Binding of sirolimus to FKBP inhibits p70S6 protein kinase activity, which is essential for ribosomal phosphorylation and cell cycle progression (see Fig. 26–15). Sirolimus potently inhibits allograft rejection. Two additional, important properties of this drug are that sirolimus is synergistically with cyclosporine and that it prevents rejection in rat transplant models. Sirolimus has been combined with cyclosporine, tacrolimus, or mycophenolate mofetil in attempts to decrease or avoid calcineurin inhibitors with their associated nephrotoxicity. Clinical trials are ongoing to assess its impact on chronic rejection in human renal allograft recipients. Sirolimus is also being used as a coating in cardiac stents to prevent restenosis. Clinical trials have demonstrated that sirolimus is not significantly nephrotoxic; however, it has been demonstrated to increase triglycerides and decrease platelets and hemoglobin in some recipients. Increased incidence of lymphocelees and delays in wound healing have also been reported with the use of sirolimus.

**Lymphocyte Sequestration**

FTY720

FTY720 uniquely works by sequestering lymphocytes in peripheral nodes and Peyer’s patches, preventing them from migrating to the graft. FTY720 administration results in a decreased lymphocyte count, which reverses when the drug is discontinued. Bradycardia, associated with the first or second dose, has been the major side effect. Activation of sphingosine-1-phosphate receptors on atrial myocytes, with which FTY720 shares structural homology, is likely the cause of the bradycardia. Clinical trials are ongoing. FTY720 is being used in combination with cyclosporine and other agents.

**Local Immunosuppression**

One approach toward reducing the drug-specific and general adverse consequences of systemic immunosuppression is the use of local drug administration systems to establish more selective presence of immunosuppressive agents in the transplanted organ. Experimental drugtargeting approaches include intra-arterial drug infusion, implantable infusion pumps, controlled-release matrices, drug-impregnated polymer rods, liposomes, topical application (skin or cornea), and aerosol inhalation (lung). Details on this topic are reviewed elsewhere. Currently, this approach is only used in composite tissue allotransplant recipients in whom topical immunosuppression is added to systemic immunosuppression to boost levels to the skin.

**Positive Crossmatch Protocols**

Previous transfusion, pregnancy, or transplant can prevent successful transplantation in sensitized individuals. Left ventricular assist devices also can result in high panel reactive antibody titers in potential heart recipients. These preformed antibodies can result in hyperacute rejection of transplanted organs. In the case of sensitized potential kidney recipients, such people may languish on the lists for years while waiting for their “perfect match.” New protocols have been developed utilizing various combinations of plasmapheresis, intravenous immunoglobulin administration, splenectomy, and anti-CD20 monoclonal antibodies, combined with conventional immunosuppression to allow for successful transplantation in these otherwise “untransplantable” individuals. These protocols have been successful, particularly for recipients with living donors, allowing for pretreatment before a scheduled transplant. Antibody levels can be measured and transplants undertaken when antibody levels decrease appropriately. A few potential recipients will not decrease their antibody levels, however, and will remain “untransplantable.”

**Possible Immunosuppressive Regimens**

In the past, immunosuppression has been of a “one-size-fits-all” mentality. Most allograft recipients received an induction agent of either ALG or OKT3, followed by cyclosporine, azathioprine, and prednisone as maintenance therapy. The new agents now available have allowed for many more options and finally for some tailoring of immunosuppression to the recipient’s situation. Although to provide a truly individualized regimen, or a drug-free state, remains the long-term goal in transplantation, the addition of new agents to the pharmacologic armamentarium has reduced the incidence of acute allograft rejection while decreasing the side effects for individual recipients. Decreasing side effects increases the likelihood that a recipient will actually continue the immunosuppressive medications. Noncompliance with medications remains a significant issue in long-term graft survival. A young woman with severe hirsutism may think twice about continuing her cyclosporine therapy; switching her to tacrolimus may be a more appropriate option. A recipient with inadequate financial resources may be more appropriately continued on prednisone and azathioprine than being switched to the more costly MMF. We are beginning to reach an era in transplantation in which we can “custom fit” immunosuppression to the recipient based on donor and recipient factors, as well as the organ transplanted. A greater emphasis is also being placed on withdrawal of corticosteroids in all organs. From experimental “tolerizing” protocols using alentuzumab or rabbit antithymocyte globulin followed by low-dose monotherapies with tacrolimus, cyclosporine, or sirolimus, to more traditional triple-therapy regimens with or without induction agents, to corticosteroid avoidance, no “standard” protocols exist today.
Treatment of Acute Rejection

Although there is great debate about the most appropriate agents and duration of therapy in the treatment of acute rejection, there is little debate over the importance of a prompt and accurate diagnosis, which usually requires biopsy. Most often, therapy is tailored to the degree of rejection. Mild rejections are usually treated with high-dose methylprednisolone with or without a subsequent oral prednisone taper. Mild liver allograft rejection is often treated with increased tacrolimus doses. Moderate to severe rejection is treated with either rabbit antithymocyte globulin or the monoclonal antibody OKT3; failing that, alemtuzumab, rituximab, and intravenous immunoglobulin have all been used with some success. CMV prophylaxis with ganciclovir or valganciclovir is usually administered concurrently with therapy for acute rejection. Repeated treatments for acute rejection increase the risk both of infection and malignant complications, particularly post-transplant lymphoproliferative disease.

Antirejection therapy is achieved at a high cost to the recipient, both financially and physically. Complete treatment of rejection is critically important, however, because inadequately treated acute rejection is a leading cause of chronic rejection and subsequent graft loss. Chronic rejection remains the primary cause of late graft loss. Even with perfect patient compliance, there is a fixed rate of graft loss for all transplanted organs. For example, whereas some graft loss is due to technical problems or patient death, at 5 years only 67% of transplanted hearts, 61% of transplanted cadaver kidneys, and 64% of transplanted livers function (OPTN/SRTR data). It has become clear that the immunosuppressive agents that are so effective at controlling acute rejection are not as effective at controlling chronic rejection.
XENOTRANSPLANTATION

There is a critical shortage of organs available for transplantation. Over 80,000 potential recipients are currently listed and awaiting organ transplantation. Many more patients could benefit from transplantation but, given the current shortage of organs, are not even considered for transplantation. Since 1990, over 20% of listed potential heart recipients have died while awaiting a heart transplant. Many experts in the field have concluded that the supply of human donors will never meet the demand. Currently, about 6,000 cadaver donors are recovered each year (UNOS data). This number has increased somewhat over the years as older donors have been included, but organ donation in the United States has reached a plateau. This shortage forces continued interest in xenotransplantation, which remains hotly debated. A possibility for expansion of the donor pool includes the use of nonhuman sources as donors. However, the mechanisms of xenoreactivity differ from alloreactivity, and the resulting rejection is vigorous. The principal barrier to the widespread use of xenotransplantation is the presence of natural antibodies. Similar to ABO blood groupings, natural IgM antibodies develop against nonself carbohydrate moieties. These naturally occurring antibodies are reduced in number as the species are more closely related, such as with humans and chimpanzees. These naturally occurring antibodies mediate the hyperacute rejection typically found with transplantation across species. The majority of the naturally occurring antibodies are against a carbohydrate moiety α-galactose.\(^{[10]}\) The preferred xenogeneic species for human clinical transplantation is the pig, because of size and availability. The pig also has the potential for less transmission of zoonoses than a primate species, but porcine endogenous retroviruses have been discovered in human cells used to reconstitute SCID mice after transplantation with pig tissue.\(^{[52]}\)

Xenogeneic hyperacute rejection has many similar features to the allogeneic hyperacute rejection seen immediately post transplant with ABO incompatibility. This reaction is dependent on complement with the generation of procoagulants and platelet aggregating substances. Unlike with allogeneic organ transplantation, in xenotransplantation the ability to limit or control the complement cascade is lost. In humans, a decay factor (CD55) is present that limits the complement-induced injury. In the pig cells, CD55 is not expressed. Strategies are emerging in which soluble factors such as human CD55 and complement receptors are administered that will limit the extent of the hyperacute rejection.\(^{[53]}\) Transgenic pigs that express human CD55 have been developed. Additionally, pigs have been cloned that do not produce the galactosyl transferase enzyme.\(^{[51]}\)

On inhibition of the soluble agents to eliminate the complement-mediated hyperacute rejection, the next problem is with delayed xenograft rejection. Research models that inhibit the complement system have made delayed xenograft rejection available for study. This form of rejection involves both NK cells and macrophages as mediators of the inflammatory process. NK-cell activities are initiated, and owing to the lack self-MHC molecules that normally provide the inhibitory signals for NK cells, the NK function remains unopposed. These activated NK cells secrete cytokines such as TNF and INF-\(\gamma\) that both recruit and activate macrophages.\(^{[1]}\)\(^{[10]}\)\(^{[23]}\)


TOLERANCE

Historical Background

The cherished goal of the transplant scientist and clinician is to induce donor-specific tolerance and eliminate the need for exogenous immunosuppressants. Although tolerance has been achieved in numerous species, including humans, the widespread clinical application is incumbent on improving the safety and reducing the risk of such an approach. Nevertheless, there are rare instances of the establishment of drug-free unresponsiveness to organ allografts in humans who have discontinued immunosuppressive therapy for various reasons. Moreover, some humans have been rendered drug free for acceptance of kidney allografts after a bone marrow transplant from the same donor for leukemia. Contemporary developments in our understanding of cellular and molecular immunology and of the basis of experimental tolerance induction hold promise for the development of clinically effective approaches. Authentic transplantation tolerance is antigen specific. It is induced as the result of prior exposure to antigen and does not depend on the continuous administration of exogenous antigen-non specific immunosuppressive agents.

In 1953, in a seminal study, Billingham and colleagues were among the first to demonstrate actively acquired donor-specific tolerance. They performed historic experiments in which they exchanged reciprocal skin grafts between Freemartin cattle twins. Freemartin cattle are genetically different cattle twins that share a common placenta. Billingham and colleagues predicted that the cattle would reject those grafts because they were genetically different. However, the grafts were accepted. This result was explained by Owen’s observation that the Freemartin cattle strain shared a common placenta; they are actually red blood cell chimeras. With this observation, the researchers returned to the laboratory to demonstrate that when they transplanted bone marrow-derived cells from a donor into a fetal mouse they could actively transfer acquired tolerance to the recipient. If a skin graft from the same bone marrow donor was transplanted, the graft was permanently accepted. The tolerance was donor specific, because when a third-party skin graft was transplanted the graft was rejected. An important lesson learned from this experiment was that the acquired tolerance was due to the immunologic incompetence of the graft recipient and not to any alteration in the grafted tissue itself. Similar mixed chimerism and tolerance was established in adult mice with the addition of conditioning.

Mechanisms

Reliable, nontoxic methods of inducing transplantation tolerance are needed to overcome the problems of chronic organ graft rejection and immunosuppression-related toxicity. Potential approaches for the induction of tolerance in adults include (1) cell depletion protocols using total body irradiation or total lymphoid irradiation or depleting monoclonal antibodies; (2) reconstitution protocols using allogeneic bone marrow; (3) a combination of (1) and (2); (4) cell surface molecule-targeted therapy (e.g., use of anti-CD4 or anti-intercellular adhesion molecule monoclonal antibodies); (5) immunosuppressive drugs (e.g., cyclosporine, sirolimus); (6) donor-specific blood transfusion combined with drug or monoclonal antibody therapy; and (7) manipulation of specific cell populations.

The principal hypotheses proposed for the cellular basis of transplantation tolerance are clonal deletion (cell death for donor-reactive T cells) and clonal anergy (functional inactivation without cell death). Clonal deletion of antigen-reactive lymphocytes occurs either in the thymus or peripherally. Clonal anergy of lymphocytes is caused by the delivery of the antigenic signal alone without co-stimulatory signals or suppressor mechanisms.Suppressor mechanisms involve anti-idiotypic regulatory cells directed against the TCR idiotype of the responsive T lymphocytes, veto cells, or suppressor cytokines, such as tumor growth factor-beta (TGF-β). It has yet to be definitely established whether clonal deletion and clonal anergy are stages along a continuum in the T-cell interactions or whether these are two independent pathways produced by exposure to different tolerogens under different conditions. An individual’s immune system may develop unresponsiveness to a particular antigen, despite the presence of normally responsive lymphocytes. The normally responsive cells may be inhibited by other mechanisms, such as suppressor cells. Thus, any combination of deletion or inactivation of T cells and B cells could result in the failure of the immune system to respond to an antigen.

Monoclonal Antibodies

One of the major goals in therapeutic immunosuppression has been to achieve a long-term benefit from a short-term therapy. A variety of monoclonal antibodies to cell surface molecules, in particular anti-CD4, used alone or in combination with other immunosuppressive modalities such as cyclosporine or total lymphoid irradiation, induce tolerance in rodents. Development of CD4 monoclonal antibodies that can induce immunologic tolerance without depleting CD4+ T cells has reawakened interest in the use of nondepleting monoclonal antibodies for reprogramming the immune system in autoimmunity and in transplantation. The mechanisms that are involved in tolerance induction and its maintenance are under debate. In a number of allogeneic transplant models (heart, skin, bone marrow), anti-CD4 (+CD8) antibodies block the rejection process by selectively promoting the development of CD4+/CD25+ regulatory T cells. As a result “infectious tolerance” occurs via these potent regulatory cells. This promotion of CD4+ provides a link between suppression and tolerance. In these models T cells that have never been exposed to CD4 antibodies become tolerant to grafted antigens when exposed to antigen in the microenvironment of regulatory T cells. In addition to anti-CD4 monoclonal antibodies, antibodies targeting adhesion molecules, other molecules on T cells, or other molecules on APCs have emerged as important approaches to promoting tolerance induction. Monoclonal antibody therapy has been used in attempts at tolerance induction in primates using combinations of anti-CD154, anti-CD80, and anti-CD86 monoclonal antibodies.

Donor Bone Marrow

Donor bone marrow has been shown to have a strong regulatory effect. The induction of unresponsiveness, with a combination of antilymphocyte serum and donor bone marrow, has been achieved in mice, dogs, and monkeys. It is thought that, under these circumstances, a naturally occurring regulatory cell (veto or suppressor cell) induces tolerance within the bone marrow inoculum. The development of these cells may be facilitated by appropriate growth factors, such as granulocyte-macrophage colony-stimulating factor and IL-3. In a limited human study conducted by Barber and colleagues, transfusion of donor-specific bone marrow was performed a week after a course of ALG in cadaveric renal allograft recipients. These patients received conventional immunosuppressive drugs—cyclosporine, prednisone, and azathioprine—and most subjects were also administered cyclophosphamide at the time of marrow cell infusion. Even though the number of rejection episodes and renal function were not affected, graft survival at 1 year was improved significantly.

Ciancio and colleagues have demonstrated a significant decrease in the incidence of chronic rejection in human cadaveric renal recipients receiving donor bone marrow at the time of renal transplant. Acute rejection episodes were similar in the group receiving bone marrow infusion when compared with controls. In 6 years of followup, only 2 of 63 recipients receiving bone marrow developed biopsy-proven chronic rejection compared with 41 of
Starzl and colleagues have reported long-lasting donor-cell chimerism in conventionally immunosuppressed human organ allograft recipients. Augmentation of this natural chimerism by infusion of donor bone marrow at the time of organ transplantation is being performed in patients who do not receive any form of cytoreductive therapy. The procedure has been shown to be safe and effective in augmenting chimerism, but the chimerism is not yet accompanied by donor-specific tolerance.

Suppressor Cells and Tolerance Induction

Suppressor cells have been implicated in a number of experimental models of tolerance induction. Thus, the existence of suppressor T cells generated in the presence of cyclosporine can be demonstrated by the adoptive transfer of tolerance from cyclosporine-treated allograft recipients. It has not been possible, however, to show that cyclosporine can induce authentic tolerance in human organ transplantation. In experimental animals, donor-specific blood transfusion before transplantation induces antigen-specific unresponsiveness associated with dysregulation of IL-2 production and the generation of suppressor cells. Donor-specific blood transfusion with cyclosporine has been shown clinically to reduce sensitization and improve renal allograft outcome.

Hematopoietic Stem Cell Chimerism and Tolerance

The most robust form of donor-specific tolerance is that associated with hematopoietic stem cell chimerism. As previously mentioned, the first association between chimerism and tolerance was observed in the 1940s when Dr. Owen reported that Freemartin cattle were red blood cell chimeras. The common placenta that they shared allowed exchange with hematopoietic stem cells. Although genetically disparate, these cattle accepted skin grafts from the other twin.Billingham and colleagues demonstrated that this active transfer of tolerance to donor antigens was due to bone marrow hematopoietic stem cells from the donor. Subsequently, chimerism has been demonstrated to be associated with tolerance in mice, rats, pigs, nonhuman primates, and humans. Until recently, the risk of conventional bone marrow transplantation was too great to tolerate in clinical attempts to induce tolerance. However, a number of advances have made the clinical application of hematopoietic stem cell chimerism to induce tolerance a clinical reality.

Sachs) produces mixed hematopoietic bone marrow chimerism and donor-specific tolerance to skin grafts. Most importantly, 1% donor chimerism is sufficient to provide robust deletional tolerance, opening the door to nonmyeloablative partial conditioning strategies to establish mixed chimerism. These nonmyeloablative approaches, using anti-T-cell monoclonal antibodies, cyclophosphamide, ALG, and tacrolimus, in addition to sublethal total body irradiation plus donor bone marrow, have been shown to induce tolerance in mice. Recent improvements in bone marrow processing and graft engineering to decrease the toxicity associated with GVHD may increase interest in this approach.

Mixed lymphopoietic chimerism has induced tolerance in humans treated by nonmyeloablative bone marrow transplantation for myeloma who also received a renal allograft. Both were free of myeloma and of rejection after receiving a nonmyeloablative conditioning regimen of cyclophosphamide, horse antithymocyte globulin, thymic irradiation with donor bone marrow infusion, kidney transplantation, and a 12-day course of cyclosporine. Chimerism was maintained for approximately 100 days before it became undetectable. Lack of durability of chimerism did not impact on the result; both recipients remain free of rejection without immunosuppressive drugs.

Manipulation of Dendritic Cells

In addition to traditional concepts regarding the role of the thymus in negative and positive selection in the development of tolerance, recent work has focused on other cell populations and mechanisms of tolerance induction. There is mounting evidence that other nonparenchymal cells may play a role in the development of donor-specific tolerance. In a recent review, Coates and coworkers emphasized the potential role of passenger dendritic cells as mediators of allorecognition and as a potential target to induce donor-specific tolerance. Dendritic cells are an excellent population to use for cell-based antirejection therapy in transplantation because they specifically target the T-cell–rich regions of draining lymph nodes. Immature dendritic cells can be driven to produce immunoregulatory properties by presentation of donor antigen in the absence of a second signal, inducing anergy in donornonspecific recipient T cells.

Additionally, another new and potentially important immune modulating strategy is the alternation of the antidonor response from a T effector 1 to a T effector 2 response. The vast majority of aggressive rejection immune responses are associated with a T effector 1 phenotype, whereas animals with demonstrated allograft acceptance generally have T cells with a predominant T effector 2 phenotype. It is thought that dendritic cells may promote this immune deviation from a T effector 1 rejection profile by selective activation of the T effector 2 cells. In the clinic, mobilization of hematopoietic stem cells with granulocyte colony-stimulating factor also mobilizes higher concentrations of precursor tolerogenic (plasmacytoid) dendritic cells. Studies to analyze the effect of these populations on tolerance induction in the clinic are in progress.
NEW AREAS OF TRANSPLANTATION

Composite Tissue Allotransplantation

Composite tissue transplantation could benefit millions worldwide with lost limbs and extensive tissue defects. Since the first hand transplant was performed in Lyon, France, in September 1998, much excitement has been generated in the area of composite tissue allotransplantation. Within 4 years, 12 recipients received single hand transplants and 4 recipients received double hand transplants. All have had good functional recovery; the first recipient, however, required amputation after he elected to stop immunosuppression. The longest surviving hand recipient received his transplant in Louisville, Kentucky, in January 1999. His current abilities include tying his shoes, dialing his cell phone, turning doorknobs, throwing a ball, and sensitivity to hot and cold.\[49\]

Hand transplantation combines two well-established procedures: hand reimplantation and immunosuppressive therapy (Figs. 26–16 (Figure Not Available) and 26–17 ). These transplant recipients have been maintained on standard immunosuppressive regimens of tacrolimus, mycophenolate mofetil, and prednisone. Tacrolimus speeds nerve regeneration in animal models, which also seems to be the case in the hand transplant recipients in whom nerve regeneration has proceeded more rapidly than would be expected from replant experience.\[49\] Despite the transplantation of vascularized bone marrow with the hand transplant, no evidence of donor chimerism or GVHD has been observed in the recipients.\[67\]

The success with hand transplantation has spurred research into other composite tissue allografts. Larynx transplantation successfully restored the voice of a 40-year-old man 20 years after a laryngeal crush injury.\[68\] If success is seen with tolerance protocols, further use of composite tissue allotransplants in areas of reconstructive surgery can be expected.

Islet Cell Transplantation

Nowhere in the field of transplantation are the advances in immunosuppression clearer than in the area of islet cell transplantation. Attempts at islet transplantation uniformly failed until the development of the so-called Edmonton protocol. A group in Edmonton, Alberta, reported their success in rendering recipients insulin free by using an immunosuppressive protocol of daclizumab, low-dose tacrolimus, and sirolimus. Corticosteroids and high doses of tacrolimus were avoided because both are known to be toxic to islets.\[69\]

Initially, islets from between two to four pancreata were needed to achieve insulin independence in these recipients. Subsequent progress in islet isolation technique at the University of Minnesota and other centers has achieved insulin independence using a single pancreas. Approximately 9,000 islet equivalents per kilogram of recipient body weight have been necessary to attain insulin independence.\[69\] The success with the Edmonton protocol has focused interest in corticosteroid avoidance regimens in other organ transplants.\[31\]

Tissue Engineering

The loss or failure of an organ or tissue is devastating. Current treatment methods include transplantation of organs, surgical reconstruction, use of mechanical devices, or supplementation of metabolic products. However, the ultimate goal of transplantation should reside in the ability to restore living cells to maintain or even enhance existing tissue function. This is emerging through the process of tissue engineering. Initial discoveries in engineered tissues were made in the mid-1980s with skin-based products. By developing replacement tissues that remain intact with bioactive properties after implantation, retaining physiologic functions as well as structure to the tissue or organ damaged by disease or trauma, tissue engineering could provide an alternative to transplantation and other forms of reconstruction. Skin replacement products are the most advanced, with several tissue-engineered wound care materials currently on the market worldwide. The potential impact of this field is endless, offering unique solutions to the medical field for tissue and organ replacement. Tissue engineering may eventually be applied to the regeneration of diverse tissues such as the liver, small intestine, cardiovascular structures, nerve, and cartilage. Work on bioartificial liver devices has been under way for several years.

The sources of cells required for tissue engineering are summarized by three categories: autologous cells (from the patient), allogeneic cells (from a donor, but not immunologically identical), and xenogeneic cells (donor from a different species). Each category may be further delineated in terms of stem cells (adult or embryonic) or “differentiated” cells obtained from tissue, where the cell population obtained from tissue dissociation comprises a
mixture of cells at different maturation stages and includes rare stem and progenitor cells. Recent discoveries have indicated that stem cells of one type can transdifferentiate to repair damaged tissue of another type (i.e., hematopoietic stem cells home to infarcted myocardium and repair the tissue). Tissue engineering will remain an area of intense research. Advances in the areas of growth factors, stromal matrices, gene encapsulation, and gene delivery will all play a role.
CONCLUSION

Progress continues in the areas of immunosuppressive therapy, xenotransplantation, transplant tolerance induction, tissue engineering, and our overall understanding of the immune system. Much remains to be learned, however, before patients with end-organ failure can live free of the risks and expenses now associated with solid organ transplantation. Still, it is an exciting time to be involved in transplantation: the “Holy Grail” of transplantation, namely, transplantation tolerance, does appear much closer.
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Selected References


This is a concise, well-illustrated textbook of immunology.


Auchincloss succeeds in simplifying a rather complex topic in this minireview.


Online review discusses the impact of dendritic cells on transplantation. It includes a helpful list of other online resources.


This review delineates the current barriers to xenotransplantation.


The group from the University of Maryland touches upon the many issues facing clinical transplantation today, including donor shortages, viral infections, long waiting times, and immunosuppression, as well as advances over 10 years.
References


Chapter 27 - Transplantation of Abdominal Organs

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The earliest attempts at organ transplantation in humans were made during the first decade of the 20th century. Since animal donors were used for these grafts, they functioned either briefly or not at all. However, the therapeutic promise of allografts became apparent from animal experiments also performed during the same decade by Alexis Carrel, who successfully transplanted kidneys and other organs into animals, utilizing this model to develop the technique of modern blood vessel surgery. This brilliant work resulted in a Nobel Prize in 1912 but was so far ahead of its time that it was not followed by further clinical trials for another 40 years. Not until the early 1950s did Medawar’s detailed description of rejection, and his discovery with Billingham and Brent that it could be prevented in mice by tolerance, stimulate surgeons to resume attempts at human renal transplantation. Medawar’s work was rewarded with a Nobel Prize in 1960. Some of the clinical trials that followed it were technically successful, but because immunosuppressive drugs were yet to be discovered the transplanted kidney allografts were all destroyed by rejection. However, transplants from identical twins begun in 1954 by Murray in Boston were successful. In the late 1950s, rejection was first circumvented in several patients by Murray, in Boston, and Hamburger, in Paris, by the use of whole-body irradiation. Murray was later (1990) awarded the Nobel Prize for his role in these pioneering studies. When immunosuppressive drugs became available in the early 1960s, prolonged allograft survival became more common, although not yet consistent. Progress in histocompatibility typing, immunosuppressive therapy, organ preservation, and the accumulation of clinical experience gradually resulted in improved results of transplantation, which now frequently allows successful replacement not only of failing kidneys but of the other vital organs as well.

This chapter describes transplantation of abdominal organs (kidney, liver, pancreas, small bowel). Because the kidney was the first organ to be transplanted extensively, experience acquired in renal transplantation programs has been the basis of much of the current management of other organ transplants as well. Therefore, renal transplantation is considered first; contained in this section are discussions of several topics, which are also relevant to all other organ transplants: histocompatibility, immunosuppression, management of cadaveric donors, and the possibilities of xenotransplantation.
RENA L TRANSPLANTATION

Indications

The three diseases most commonly leading to renal failure and treated by kidney transplantation are insulin-dependent diabetes mellitus, glomerulonephritis, and hypertensive nephrosclerosis, accounting for about 60% of the total. Other important causes include polycystic kidney disease, Alport’s disease, immunoglobulin (Ig) A nephropathy, systemic lupus erythematosus, nephrosclerosis, interstitial nephritis, pyelonephritis, and obstructive uropathy. In African Americans, hypertensive nephrosclerosis is the most common of all causes of renal failure.

The best recipients are young individuals whose renal failure is not due to a systemic disease that will damage the transplanted kidney or cause death from extrarenal causes. With the increasing appreciation that the results of transplantation are superior to those of chronic dialysis, the indications for transplantation have been broadened. The presence of infection or malignancy that cannot be eradicated remains an absolute contraindication to transplantation because immunosuppression encourages both microbial and tumor growth. Although history of a successfully treated cancer is not a contraindication to transplantation, it is a general rule to wait at least 2 years before transplantation is justified. Even then recurrent cancer may still occur, possibly encouraged by immunosuppression. In fact, 13% of recurrent cancers take place in recipients who were tumor free for over 5 years before their transplants. Predicted noncompliance is another contraindication because careful adherence to immunosuppression is necessary. Advanced age and severe cardiovascular disease, such as unreconstructable coronary artery or aortoiliac disease, are also deterrents. However, even in such patients, the long-term cumulative risks of dialysis are at least as great as those of transplantation. Therefore, because of improvements in perioperative care and immunosuppression, many patients who would previously have been denied transplantation are now considered acceptable. For example, diabetics, once considered poor candidates, clearly do better with transplantation than with dialysis. In fact, both graft and patient survival for 1 to 2 years are reported to be as good in diabetics as in other patients, whereas on chronic dialysis less than 20% of diabetics survive 5 years. Even patients with diseases in which the transplanted kidney may eventually be damaged by recurrent disease (e.g., lupus erythematosus, cystinosis, amyloidosis, diabetes, and some forms of glomerulonephritis) are often better palliated by transplantation than by dialysis. Indeed, the current results of transplantation mandate serious consideration of this therapy in virtually any patient with terminal renal disease. Not only is the quality of life far better with transplantation than with dialysis, but because the mortality of patients in the first year after transplantation is now less than 5%, survival is also superior. Unfortunately, however, the insufficient availability of donors keeps many appropriate transplant candidates on chronic dialysis. In fact, the number of patients awaiting transplantation is increasing more rapidly than the number of transplants done per year.

Recipient Evaluation and Preparation

The evaluation of all transplant candidates, in addition to a standard medical work-up, should include cytomegalovirus (CMV) antibody titer; creatinine clearance; serology for syphilis, human immunodeficiency virus (HIV), and hepatitis B (HBV) and C (HCV) viruses; evaluation of parathyroid status; coagulation profile; Papanicolaou smear; ABO and histocompatibility typing; urologic evaluation (including a voiding cystourethrogram in selected patients to assess outlet obstruction and reflux); gastrointestinal evaluation (as warranted by history of ulcer, diverticulitis, or other symptoms); and psychiatric evaluation.

The proper timing of transplantation is a delicate decision because the progression of renal dysfunction is variable and premature imposition of the risks of transplantation is not justified. However, dialysis or transplantation should not be withheld until advanced uremic symptoms, such as pericarditis, cardiac failure, severe anemia, osteodystrophy, and neuropathy, ensue because these complications may become irreversible. Even when a donor is readily available, pretransplant dialysis is often necessary, at least briefly, to optimize the patient’s general condition (nutrition, electrolyte balance, and coagulation status). Careful attention must be given to eradication of all infections, including those of the urinary tract, lungs, teeth, and skin (especially at the site of the planned incision). Because cardiovascular complications are as common as infection as a cause of post-transplantation mortality, the patient’s cardiovascular status should be carefully evaluated and optimized. In older patients and diabetics, this might require stress testing, cardiac catheterization, or even pretransplant coronary artery bypass.

Histocompatibility Typing and Crossmatching

Although opinions vary regarding the significance of histocompatibility testing for selection of unrelated donors, its importance is unquestionable for selection of the optimal donor within a family. Regardless of the donor source, compatibility for ABO blood groups and a negative leukocyte crossmatch are mandatory.

ABO BLOOD GROUPS

Because the major blood group antigens are not expressed by human leukocytes, it was initially assumed that they might be unimportant in transplant rejection. However, experimental and clinical evidence soon indicated that ABO antigens function as important histocompatibility antigens. In animals, prior exposure to erythrocytes from incompatible donors provoked accelerated rejection of skin grafts from donors of the same blood group. In the early days of renal transplantation, it was noted that ABO incompatibility often led to acute or hyperacute rejection, a finding that resulted in adherence to the rule of blood group compatibility. Because of the donor organ shortage and reports of some success with ABO-incompatible liver and heart allografts, attempts have been made at breaching the ABO barrier for kidney allografts. Successful transplantation is quite possible in blood group O or B recipients of kidneys from A2 donors (who have a lower number of A antigenic determinants on their cells than A1 donors). Successful ABO-incompatible transplants have also been reported in recipients whose ABO isoagglutinins have been removed by plasmapheresis or immunoadsorption. Because isoagglutinins eventually reappear and the long-term outcome of these transplants is likely to be inferior, most centers do not employ this strategy. However, it is an intriguing approach, especially for allowing utilization of ABO-incompatible family donors. One report of 67 ABO-incompatible kidney donor transplants indicates that 75% of such grafts can survive after 6 years.

LYMPHOCYTOTOXIC CROSSMATCHING

Sensitization to human leukocyte antigen (HLA), as indicated by the presence of lymphocytotoxic antibodies in the recipient’s serum, may occur as a result of pregnancy, blood transfusions, or prior transplantation. Presence of donor-reactive antibodies, detected by incubation of recipient serum with
donor cells in the presence of complement (a positive “crossmatch”), is a contraindication to renal transplantation because of its strong association with hyperacute renal allograft rejection. Serum from patients awaiting cadaveric renal transplantation is periodically screened against a panel of randomly selected HLA-typed lymphocyte donors. Nonreactivity of the patient’s serum to the panel cells indicates a high likelihood of obtaining a crossmatch-compatible donor, whereas uniform reactivity of the patient’s serum with panel cells greatly reduces this probability. The number of highly sensitized patients on most transplant waiting lists is increasing as lesssensitized patients receive transplants while sensitized individuals remain on the list and those with failed renal allografts (frequently sensitized) are returned to the list.

Successful transplantation can often be achieved despite positivity of certain types of crossmatch, a finding that allows transplantation of some apparently sensitized patients. For example, lymphocytotoxic autoantibodies do not cause rejection. In some patients, the titers of bona fide lymphocytotoxic antibodies decline or disappear with time. In the past, it was a common practice to store serum from the period of peak sensitization for later use in crossmatching, and if it was found positive, transplantation was denied, even if current serum was negative. Several reports now indicate that a positive crossmatch using peak serum may be disregarded with only a minimal risk of hyperacute rejection, provided that the current serum is negative. The conditions that allow transplantation in a patient with a “historical” positive but current negative crossmatch are not clearly defined. Most centers require a certain interval (1 to 12 months) between the last positive serum and transplantation. There is controversy whether the most sensitive crossmatching methods such as antiglobulin and flow cytometry techniques should be used because they may exclude donors that might have been used successfully. In addition, the clinical relevance of positive crossmatches to B lymphocytes (especially if performed in the cold) and those caused only by IgM antibodies is questionable. Attempts have also been made to define the role of antibodies against minor (non-HLA) specificities. For example, there is evidence that antibodies reactive to determinants on vascular endothelial cells can damage renal allografts.

To allow transplantation of sensitized patients, several methods have been tried to remove cytotoxic antibody (including thoracic duct drainage, total lymphoid irradiation, and plasmapheresis). Recently, several groups have explored the ability of intravenous immunoglobulin (IVIG) to inhibit anti-HLA antibodies by an anti-idiotypic mechanism. They have shown in a limited number of patients that IVIG can reduce the levels of antibody in highly sensitized transplant candidates, thus increasing the likelihood of finding a crossmatch-negative donor and allowing successful transplantation. Because none of these maneuvers has yet gained wide acceptance, the increasingly large sensitized patient pool remains a formidable problem.

Attempts to Induce Specific Unresponsiveness

Blood Transfusions

In the first two decades of renal transplantation, transfusions were avoided whenever possible to minimize the formation of lymphocytotoxic antibodies, which might exclude patients from transplantation or damage the allograft. However, in 1973, Opelz and colleagues made the surprising observation in a multi-institutional survey that renal allograft survival was actually 10% to 15% better in transfused than in nontransfused recipients. This resulted in a worldwide policy of deliberate pretransplant blood transfusions, which was subsequently credited with a substantial improvement in the outcome of renal transplants that occurred over the next decade.

Reasons for this beneficial “transfusion effect” were unclear. Some thought that transfusions simply prevented “high-responder” patients from being transplanted by sensitizing them so that they were crossmatch positive to most available donors, causing more kidneys to go instead to “low-responder” patients, who remained crossmatch negative despite transfusions and were likely to have a successful transplant, but for reasons unrelated to the transfusions. Another possible explanation was that transfusions had a true immunosuppressive effect, mediated through induction of suppressor T lymphocytes or enhancing alloantibodies.

With the improvement in graft survival that occurred when the new immunosuppressive agent cyclosporine became available in 1984, the need for blood transfusions was questioned. For a few years, there was disagreement as to whether cyclosporine-treated patients still benefited from transfusions, but within the ensuing 5 to 6 years it became apparent that whatever the mechanism of the transfusion effect, it was no longer discernible because of the improved outcome in all patients. Because of this finding and the risks of transmitting infection (HIV and hepatitis) or of sensitizing patients to prospective donors, pretransplant transfusions have largely been abandoned at most centers.

Bone Marrow Conditioning

Although pretransplant blood transfusions are now rarely practiced, there has been an interest in conditioning recipients with bone marrow from the organ donor. Although this procedure might act by the same (unexplained) mechanism as blood transfusions, an additional intriguing rationale is the self-replicating ability of bone marrow and the resultant potential for persistent microchimerism. For many years, animal experiments have shown that administration of donor bone marrow is an especially effective method of conditioning transplant recipients. Bone marrow was found by Billingham, Brent, and Medawar in the 1950s to be an ideal inoculum for induction of acquired donor-specific immunologic tolerance. Later, Monaco later found that donor bone marrow promotes skin allograft survival in adult rodents if combined with a brief course of antilymphocyte serum. In 1987, Barber and colleagues initiated a randomized study in which cryopreserved donor bone marrow was administered 10 to 14 days after kidney transplantation to recipients who were treated with antilymphocyte serum (ALS) and other standard immunosuppressive agents. Because the incidence of acute rejection was decreased, the early results were intriguing. However, improvement in long-term patient and graft survival was not impressive and, disappointingly, chronic rejection was not prevented.

Other investigators continue to study the administration of donor bone marrow as a possible method of inducing “tolerance” to human recipients of renal and pancreas transplants. Although they have reported that the incidence of rejection episodes is less and that there is greater likelihood that the patient can successfully be weaned from corticosteroid therapy, the long-term graft survival was not different than that of non–bone marrow–treated recipients. Microchimerism for donor cells can often be found in successful bone marrow–treated recipients (and also in tissues of non–bone marrow–treated recipients), but it remains controversial whether this is an epiphenomenon or the cause or effect of successful organ transplantation.

Pretransplant Operations

Any necessary urinary tract reconstructions must be carried out before transplantation (e.g., lysis of posterior urethral valves, transurethral resection for obstructing prostatic hypertrophy). The patient’s own bladder should be utilized for ureteroneocystostomy, even if this necessitates bladder reconstruction or augmentation of a small bladder by ileoceccocystoplasty. Careful intermittent catheterization of a neurogenic bladder three to four times daily after transplantation is preferable to the use of an intestinal conduit. In the absence of an alternative strategy, ileal conduits should be constructed at least 6 weeks before the transplant operation to avoid risk of infection.

Bilateral nephrectomy of recipients was once routine, the rationale being that even if current urine was sterile, pyelonephritic kidneys would remain a dangerous focus of infection and that glomerulonephritic kidneys, if retained, would be a stimulus for autoimmune destruction of the allograft. Because evidence to support these hypotheses was never forthcoming, bilateral nephrectomy is now performed only for special indications, such as recalcitrant
urinary tract infections (especially in the presence of stones, reflux, or obstruction), uncontrollable hypertension, massive proteinuria, bilateral renal tumors, or large polycystic kidneys, especially if they are bleeding or infected.

Splenectomy was at one time widely practiced on an empirical basis for its nonspecific immunosuppressive effect. A large randomized study eventually indicated that the procedure modestly improved early, but not late, graft survival.

**Selection and Management of Living Donors**

For the prospective recipient, there are major advantages to obtaining a living donor that obviates the discomfort, expense, and risks of prolonged dialysis while waiting for a cadaver kidney. Post-transplant morbidity is also minimized by decreasing the chances of acute tubular necrosis (ATN). Since the advent of cyclosporine therapy, short-term results of cadaveric transplantation now approach those with living related donors. Nevertheless, because of better histocompatibility, long-term results of related donor transplantation remain superior to those of cadaveric grafts. Thus, most authorities believe the use of living donors is still justified, and in the United States, they account for about 35% of kidney transplants.

**Histocompatibility Considerations in Living Donor Selection**

The HLA antigens are gene products of alleles at a number of closely linked loci on the short arm of chromosome 6 in humans. At least six HLAAs (A, B, C, DQ, DP, DR) have been defined, and the existence of several others has been deduced from family studies and immunohistochemical findings. The extreme polymorphism of the HLA system, which is the basis of infinite genetic variability of the human species, plays a pivotal role in regulation of the immune response. The gene products of the HLA-A, -B, and -C loci are referred to as class I major histocompatibility complex (MHC) antigens, and the products of the D region are class II MHC antigens. Class I MHC antigens are expressed on all nucleated cells and can be readily detected serologically using lymphocytotoxicity assays. Class II MHC antigens are important in antigen presentation and are expressed on B lymphocytes, dendritic cells, endothelium, and activated T cells.

HLA antigens are inherited as codominant alleles, and because of the relatively low recombinant frequency, the HLA genes are usually inherited en bloc from each parent. In immediate families, inheritance of the HLA, which is of overriding importance in transplant outcome, can be determined serologically and falls into four different combinations of haplotypes. Any two siblings have a 25% chance of being HLA identical, that is, of having inherited the same chromosome 6 (haplotype) from each parent, a 50% chance of sharing one haplotype, and a 25% chance of sharing neither haplotype. Parent-to-child donation always involves a one-haplotype identity.

The importance of matching HLA antigens in the selection of living related donors for renal transplantation is well established. Excellent graft survival (>95%) can be expected when a related donor and a recipient are HLA identical. There is a progressively lower graft survival associated with one or zero haplotype matches, although even totally mismatched related living donor grafts have a significantly better outcome than cadaveric grafts.

**Risks to the Living Donor**

Despite the major advantages of related donors, their use is justified only if the risks to the donor are minimal. Nevertheless, it is important to frankly present these risks to the donor. In addition to discomfort and morbidity associated with any operation, there is an operative mortality of about 0.05%. Concern for even a small mortality rate has led to a traditional policy of accepting as donors only individuals between 18 and 55 years of age and in virtually perfect health. Because donor age limits are now being extended at most centers, it is important to exercise even greater care to avoid unacceptable risks.

Obviously, the donor must have two normal kidneys, as confirmed by standard renal function tests, intravenous pyelography, and imaging of the renal arteries. Magnetic resonance angiography is now substituted for contrast arteriography at many centers. This minimizes the risk of the procedure to the donor, although it has the disadvantage that small accessory renal arteries may not be visualized by this technique. Despite the knowledge that unilateral nephrectomy is followed by compensatory hypertrophy of the remaining kidney, near-normal renal function, and normal life expectancy, concern has been expressed regarding the long-term status of living donors. This concern is based on the finding that ablation of renal tissue in an experimental rat model leads to hyperfiltration by the remaining kidney tissue and eventual functional deterioration owing to sclerosis. Ten years after nephrectomy, some human donors have also been noted to exhibit proteinuria and hypertension, and a small number have exhibited renal failure, although in the largest single-center study with more than 20 years’ follow up this number did not differ from the control population.

The identification of a donor from a family group is preferably based on histocompatibility factors, although selection of a less well-matched donor by a well-informed family must be respected. It is important that potential candidates be protected from pressure to donate against their will, especially if they are minors. However, most family members willingly donate, and the psychological benefits of doing so are often profound.

**Living Unrelated Donors**

Until recently, unrelated volunteers were excluded from donation because the results were assumed not sufficiently advantageous compared with those of cadaver grafts to warrant the risk. However, the improvement in unrelated kidney allograft survival with cyclosporine and the shortage of cadaver donors provoked re-examination of this issue. Whereas the use of paid donors is unlawful, genetically unrelated but emotionally related donors (especially spouses) are now considered acceptable by most centers and, by 2002, accounted for about 25% of living donor transplants. Surprisingly, these transplants have graft survival as good at 5 and 10 years as living related transplants, except for those from HLA-identical sibling donors, and were significantly better than the survival of cadaveric transplants.

**Techniques of Living Donor Nephrectomy**

The left kidney is chosen if possible because its longer renal vein facilitates the recipient operation. However, if the arteriogram shows multiple renal arteries on one side, the kidney with a single artery is usually selected to facilitate the anastomosis. A flank incision is used. After incising the Gerota fascia, the greater curvature of the kidney and upper pole are mobilized, and the hilar structures are exposed. On the left side, the adrenal and gonadal veins are ligated so that the full length of the renal vein can be utilized. Traction on the renal artery should be avoided because it causes spasm and decreased kidney perfusion, possibly compromising early function. The ureter should be mobilized along with its blood supply and a generous amount of periureteric tissue. It is divided close to the
In an effort to make the procedure more acceptable to prospective donors by reducing morbidity, minimally invasive kidney recovery is now commonly practiced at many centers. The laparoscopic approach was first employed in 1995 by Ratner and associates. The largest single-center experience with the technique has been accrued at the University of Maryland, where the results of more than 300 laparoscopic nephrectomies indicate that in experienced hands, the procedure is safe and effective at yielding high-quality organs. Donors undergoing the laparoscopic operation had a shorter hospital stay (2.2 vs. 4.5 days), a decrease in parenteral narcotic usage postoperatively, and earlier return to work (15.9 vs. 51.5 days). Serious operative complications are almost negligible. Nevertheless, waiting lists continue to rise for all organs out of proportion to cadaveric organs recovered, and the waiting time for a cadaveric renal transplant often exceeds 5 years (Fig. 27–2). The donor shortage is similarly severe in Europe. It is important that primary physicians, neurosurgeons, and intensive care nurses identify potential donors. Procurement personnel (usually part of a regional team) are then available to help obtain permission from the family and coordinate removal and distribution of viable organs.

Selection and Management of Cadaveric Donors

In the absence of a family donor, cadaveric renal transplantation is a satisfactory alternative. In most countries, acceptance of the concept of brain death allows removal of viable organs from heart-beating donors. The donor shortage is perhaps the most important impediment to transplantation. Although in the United States the Uniform Anatomical Gift Act has been adopted in all 50 states, few cadaver kidneys are actually recovered on the basis of donor right-sided kidneys is problematic and is infrequently employed. The shorter and thinner-walled right renal vein complicates the procedure, especially in kidneys removed laparoscopically, the long-term function of these grafts was equal or superior to those obtained by the conventional open approach.

Despite these encouraging results, several questions remain about the laparoscopic technique. First, an inadequate number of cases have been performed and too few centers have applied the technique for conclusive comparisons of open and laparoscopic procedures. Second, the laparoscopic removal of right-sided kidneys is problematic and is infrequently employed. The shorter and thinner-walled right renal vein complicates the procedure, especially because the stapling devices used to transect vessels shorten them by 1 to 1.5 cm. These impediments to right nephrectomy could lead to a decision to utilize the left kidney, which for other reasons, such as multiple renal arteries, might be suboptimal. However, the increasing employment of the laparoscopic approach appears justified and many are convinced that it has increased the number of living donors. Although the rate of serious complications is not statistically different than that from open donor nephrectomy, the two deaths reported in a U.S. survey of living donors between January 1, 1999, and July 1, 2000, both occurred in the 5186 laparoscopic donors while no death occurred in the 5660 open donors.

Figure 27-1 The shortage of cadaveric donors and the recognition that renal transplants from unrelated donors fare as well as those from genetic relatives (except HLA identical siblings) have encouraged the use of genetically unrelated but emotionally related donors, which now account for 25% of living donor kidneys.
surveys should be carried out to uncover factors that are contraindications to organ donation, such as the presence of generalized infections (including occult ones, such as human immunodeficiency virus, hepatitis B virus, and hepatitis C virus) or high risk of these (such as the use of intravenous drugs), malignancy other than nonmetastasizing brain tumors, and known renal disease, hypertension, or advanced arteriosclerosis. Donors older than 65 years of age may also sometimes be suitable, but the likelihood of vascular disease makes them less attractive. The use of bilateral adult renal transplants has been proposed as a means to salvage kidneys from older cadaver donors with suboptimal nephron mass that would otherwise be discarded. The use of kidneys from infants is also possible, but technical aspects are exacting, and both kidneys may need to be implanted into a single recipient, a procedure that is associated with an increased incidence of technical complications.

The use of cadaver donors raises the ethical and legal problems of defining brain death. Consideration of transplantation should never be allowed to influence the treatment of patients who have any chance to survive or the definition or declaration of death, which must always be the responsibility of the patient’s primary physician or of a neurologic consultant, with the full understanding and permission of the family. To avoid any conflict of interest, the transplant team must never be involved with care of the donor or with decisions regarding prognosis or therapy. Commonly accepted criteria for brain death include two in-hospital examinations at least 12 hours apart by a neurologist or neurosurgeon documenting loss of function of the entire brain. Loss of cerebral function is documented by lack of response to painful stimuli or movement except for spinal reflexes. The loss of brain stem function is documented by fixed pupils, absence of corneal, oculovestibular, and oculocephalic reflexes, loss of gag reflex, and absence of movement or spontaneous respiration off the respirator for 3 minutes, a test that is done only after other criteria indicate no brain function. The declaration of brain death may be accelerated by 6 hours if a confirmatory test is performed such as a flat electroencephalogram. Strict adherence to these criteria is not always possible. For example, electroencephalographic confirmation is not required to declare brain death in the presence of angiographic evidence for complete lack of blood flow to the brain, which may occur with severe brain swelling. The use of brain scans to document lack of blood flow is also an acceptable criterion for brain death, which may facilitate this decision. The diagnosis of brain death should not be made in the presence of severe hypothermia, marked hypovolemia, or toxic levels of depressant drugs such as barbiturates because these factors can produce an isoelectric electroencephalogram, a pattern that is reversible.

Donor Pretreatment

An interesting procedure that has been recommended, but never widely adopted, is donor pretreatment with immunosuppressive drugs, a strategy that could be employed only for cadaver donors. The rationale is that interstitial cells of hematopoietic origin normally present in the transplant organ ("passenger" cells) contribute importantly to graft immunogenicity and that their removal is beneficial. Conflicting results with pretreatment of donors with such agents as methylprednisolone, cyclophosphamide, or cyclosporine emphasize that circulating passenger cells are not the only source of transplantation antigens within kidney allografts. Interstitial dendritic cells and vascular endothelial cells, which cannot be removed, are probably also important in antigen presentation. It is conceivable that more complete eradication of passenger cells by vigorous prolonged treatment of donors or treatment of the ex vivo kidney might be more beneficial. However, current attention is focused on the possibly more likely benefits of employing an exactly opposite strategy, that is, augmenting passenger cell transfer. This is based on the recent observation by Starzl and Zinkernagel that in many successful organ transplant recipients of many years' standing, persistent donor lymphoid cells (especially dendritic cells) can be identified in various organs of the recipient (skin, thymus, brain). It remains to be seen whether these cells are the cause of successful organ transplantation or merely accompany it. Several trials are under way to condition transplant recipients with donor bone marrow.

HLA Considerations in Cadaver Donor Selection

Although the benefit of matching for HLA-A and -B antigens in selection of family donors is well established, its value for cadaveric grafts remains controversial. For many years, reports from European centers have indicated that matching has a beneficial effect. Not only was there a significant difference between grafts fully matched and totally mismatched for HLA-A and -B, but graded improvements in outcome could be related to the extent of the match. The value of HLA-A and -B typing has been confirmed by some reports from North America but not by others. The benefit of matching is more apparent in long-term rather than short-term results.[3] The difference between grafts fully matched and totally mismatched for HLA-A and -B, but graded improvements in outcome could be related to the extent of the match. The value of HLA-A and -B typing has been confirmed by some reports from North America but not by others. The benefit of matching is more apparent in long-term rather than short-term results.[3] Several possible explanations have been put forth for differences in American and European results, such as the greater genetic heterogeneity of the U.S. population and the uniformity of tissue typing, which in Europe is performed in only the select and highly experienced laboratories of Eurotransplant. Both in Europe and in the United States, class II (HLA-DR) matching appears to be of greater benefit than class I matching.[4] However, some, especially in the United States, believe the improved survival of kidney allografts in patients treated with cyclosporine and newer agents, such as tacrolimus and mycophenolate mofetil (MMF), largely overrides the effect of HLA matching.
appears that the DR matching is still important in selecting donors for patients who have rejected previous transplants.

Even in the United States, the benefits of six antigen-matched (or zero antigen-mismatched) kidney transplants are now uncontested, causing UNOS to mandate their sharing on a national basis. Whether lesser degrees of matching are important is controversial (especially since the introduction of cyclosporine and other potent new immunosuppressive agents) and is the central issue of an ongoing debate whether to change UNOS’s point system for cadaveric kidney allocation, which currently emphasizes HLA matching. Two analyses on the outcomes of over 30,000 renal transplants led to opposite conclusions. Takemoto and coworkers \[28\] noted that HLA matching and transplant success were correlated, whereas Held and colleagues \[29\] who stratified other risk factors, found little benefit and argued that the ischemic damage inherent in transportation necessary for national sharing would outweigh the advantage of matching. An additional consideration in sharing nationally is the potential negative impact on a second kidney that will subsequently need to be shipped to “pay back” the first shipped kidney. \[30\]

Operative Technique for Cadaveric Donors

After declaration of brain death, the donor is brought to the operating room and optimal respiration and circulation are maintained during the procedure. Before and during the operation, it is often necessary to administer large volumes of intravenous fluids because of diabetes insipidus or to restore blood volume that may have been depleted during the premortem attempts to decrease brain swelling and achieve neurologic recovery. For non–heart-beating donors, the recovery team must be poised in the operating room ready to start the procedure as soon as death is pronounced on the basis of cessation of cardiac function.

Before the widespread application of extrarenal transplantation, the technique of cadaver nephrectomy was similar to that described for related donors. Because multiorgan recovery has now become almost routine, the following technique of in situ perfusion and en bloc dissection has evolved as the standard (Fig. 27–3). The peritoneal cavity is entered through a midline incision, usually extended to the suprarenal notch to facilitate heart, lung, and liver donation. After exploration for unsuspected neoplasia or infection, the small bowel is retracted and the posterior peritoneum is incised in the midline up through the ligament of Treitz to expose the aorta and inferior vena cava. The peritoneal reflection around the cecum is incised and continued cephalad, allowing visualization of the retroperitoneum. By retraction of the duodenum and pancreas superiorly, the proximal aorta and vena cava are exposed. After dissection of the vascular structures of the extrarenal organs to be concomitantly recovered (liver, pancreas, heart, lung), the aorta and vena cava are divided just above their bifurcations after proximal insertion of large-bore cannulas for retrograde in situ perfusion. Anticoagulation is achieved by intravenous heparin, and the aorta is clamped proximally (at the aortic arch for cardiac recovery, above the celiac axis for liver and pancreas, and just above the renal arteries if only the kidneys are to be removed), and infusion of cold (4°C) preservation solution via the aortic cannula is initiated along with simultaneous decompression via the caval cannula. The kidneys, which rapidly become pale and cold, are then mobilized while avoiding damage to the hilar structures or ureters. The divided distal aorta and vena cava are mobilized cephalad by securing the lumbar vessels between clips, and the aorta is divided above the renal arteries. The entire bloc of kidneys, ureters, aorta, and vena cava are transferred to a basin of cold solution where careful dissection of the renal vessels is performed. The kidneys are then separated by division of the vena cava and aorta and packaged for cold storage to allow time for recipient selection, tissue typing, and transportation. Additional “bench surgery” for accurate dissection of the renal vessels and ureter is usually carried out later under continued hypothermic conditions just before transplantation.

Preservation of Cadaveric Kidneys

Two methods of kidney preservation (simple cooling and continuous pulsatile perfusion) have been widely utilized. Both allow sufficient time for transportation of kidneys to distant transplant centers. Simple cooling is achieved by flushing the allograft with a cold iso-osmolar or hyperosmolar buffered solution followed by storage at 4°C to 10°C. Additives to the solutions include various ratios of K⁺, Na⁺, Cl−, citrate, PO₄³⁻, SO₄²⁻, glucose, sucrose, mannitol, bicarbonate, and magnesium. These solutions are used for short-term (<48 hours) preservation. Although some disagreement exists, it is generally held that if longer preservation of organs is necessary (48 to 72 hours), it would require the use of a pulsatile perfusion apparatus, which circulates through the kidney either cryoprecipitated homologous plasma or a preservation solution.

In the late 1970s, there was a trend away from machine pulsatile preservation (which previously was used by about two thirds of centers) toward simple cooling, which is now employed at almost all centers. Responsible for the change were the greater costs and inconvenience of machine perfusion, including the need for a trained attendant during transportation to distant centers. In addition, it was shown that for short preservation times (<24 hours), simple cooling, which is now employed at almost all centers, is generally held that if longer preservation of organs is necessary (48 to 72 hours), it would require the use of a pulsatile perfusion apparatus, which would probably have little advantage. In 1987, Belzer and Southard introduced a solution (University of Wisconsin [UW] solution) containing several new components (lactobionate, raffinose, hydroxyethyl starch) that substantially extended the period of storage possible for liver and pancreas to 24 hours. Although the solution is in wide usage by others for simple cold storage of kidneys, it has also been used by Belzer and Southard with excellent results as a perfusate for machine preservation. Because, even with improved preservation solutions, simple cooling has a finite time limit, it seems likely that major progress in preservation can come only from advances in perfusion techniques. Several groups that resisted the trend...
toward simple cooling and that continue to use machine perfusion have reported an extremely low incidence of ATN. The additive adverse effects of ischemia, nephrotoxic immunosuppressive drugs, and the use of older and suboptimal donors has induced some centers to resume pulsatile preservation. In fact, from 1996 to 2000 this method was utilized for 12% of kidneys transplanted in the United States.\textsuperscript{2} These kidneys had a significantly lower rate of delayed graft function than those preserved by cold storage, but so far no graft survival advantage is apparent.

**Xenogeneic (Interspecies) Grafts**

The growing shortage of human organs for transplantation has rejuvenated interest in using donors of alien species. Although the success of cross-species organ grafts could revolutionize the field of transplant surgery, uncertainty exists as to when this will be feasible.\textsuperscript{\textsuperscript{\textsuperscript{3}}} The xenograft barrier consists of several components: humoral, cellular, and physiologic. In the first two components, experimental advances were considerable during the 1990s. Most striking was the prevention of humorally based hyperacute rejection of organ from distantly related donor species by genetic engineering of donors.\textsuperscript{2} Progress has also been made in defining and overcoming the cellular aspects of xenorejection. In fact, no specific evidence exists that in the absence of humoral response, the cellular response to xenografts would be substantially more formidable than to allografts or any less susceptible to conventional immunosuppression.

Despite these experimental advances, experience with clinical xenografts is less encouraging. About 40 whole-organ xenografts were performed in humans during the 20th century. However, the longest functional survival (9 months) was a chimpanzee-to-human kidney xenograft performed by Reemtsma in 1964.\textsuperscript{3} Other primato-human kidney transplants failed earlier in patients immunosuppressed with azathioprine and corticosteroids.\textsuperscript{4} Careful studies done by Starzl and coworkers in 1992\textsuperscript{5} in which baboon livers were transplanted to two human patients were quite informative. These xenografts were transplanted with the optimal immunologic advantages of the day: (1) a concordant donor species, (2) the known relative resistance of the liver to antibody-mediated damage, and (3) potent immunosuppression. Despite the well-conceived nature of this trial, graft and patient survival were short lived (25 days and 70 days, respectively). Moreover, the development of graft dysfunction in the absence of significant histologic evidence of rejection raises concerns that some as-yet-undefined physiologic incompatibility existed between graft and recipient.

Considering that the outcomes that could now be obtained with clinical xenografts might well be comparable with those of allografts of the 1950s and 1960s and that recent progress in experimental xenobiology has been considerable, one might predict that eventual clinical success is likely. In fact, limited success might be within reach now if primate donors could be used. However, the shortage of these animals in most parts of the world, the difficulty of breeding them in captivity, and the ethical question of their use are major deterrents. Another important cautionary note deserves mention: the possible dangers of zoonoses.\textsuperscript{3} The consequences of transferring microorganisms from other species into immunosuppressed humans via organ xenografts is unknown. However, it seems likely that the origin of the HIV epidemic in humans was a transfer of a virus originating in nonhuman primates.

In view of the problems noted, further attempts at clinical xenotransplantation with primate donors seems unlikely. However, progress in controlling hyperacute rejection in nonhuman primates of organs transplanted from more distantly related species (i.e., pigs) suggests that these discordant donors could be used successfully. Specific carbohydrate epitopes have been defined that serve as the dominant targets of the natural antibody response in the primate antiporcine response. Progress has been made in preventing preformed and induced antibody-mediated graft damage with immunosuppressive regimens that blunt the induced response and with the novel strategy of inducing transgene-encoded regulators of complement activation to avoid the attack of natural antibodies.\textsuperscript{3} The survival for several months in nonhuman primates of heart and kidney xenograft from pigs (genetically engineered to express human proteins on endothelial cells) is quite encouraging because preformed antibody and complement activation otherwise destroys xenografts from normal pigs in 60 to 90 minutes.\textsuperscript{6} Possibly even more promising is another genetic engineering approach. In pigs, both alleles of the gene responsible for synthesizing α1,3-galactosyltransferase epitopes on the cell surface were knocked out.\textsuperscript{7} Because these epitopes are the major xenantigens responsible for hyperacute rejection in pig-to-human transplants, their complete removal from pig organs is predicted to preclude this phase of the xenograft response. In addition, because the same epitopes may also be involved in the next formidable barrier (acute vascular rejection), the results of xenotransplants from these porcine donors could be far superior to those with donors modified to express human complement regulators. The value of this potentially important work remains to be tested by transplanting nonhuman primates with organs from these modified porcine donors.

Porcine donors would have several important advantages over primate donors, including greater supply and less ethical concern. However, the possibility of zoonoses has made some centers wary of using organs from pigs in patients who are likely to die of other causes. Although it is reassuring that in a survey of 160 patients treated with living porcine tissue (skin, cells, heart valves), there has been no evidence of virus transmission.\textsuperscript{8}

**The Recipient Operation**

General anesthesia is usually employed, although spinal anesthesia is also satisfactory. Good success is frequent during the vascular and ureteral anastomosis, but excessive use of muscle relaxants (especially succinylcholine) must be avoided because low cholinesterase levels in dialysis patients may otherwise lead to prolonged apnea. The muscle relaxant atracurium can be used safely because this agent has a short half-life and its degradation is independent of renal and hepatic metabolism.

The iliac vessels are exposed retroperitoneally through an oblique incision just above the inguinal ligament (Fig. 27). The dissection is slightly easier on the right, but a more important consideration in selecting the appropriate side is avoiding sites of previous transplants, other operations (e.g., appendectomy, hysterectomy, or bladder or ureteral operations), or peritoneal dialysis catheters. Lymphatics that must be divided to expose the iliac fossa are ligated to prevent prolonged lymph drainage or lymphocele formation. Exposure of the bladder is facilitated by dividing the inferior epigastric vessels and, in females, the round ligament. Division of the spermatic cord should be avoided because this may cause epididymitis, testicular ischemia, and atrophy.

Historically, vascular anastomoses were performed between the end of the donor renal artery and the proximal end of the recipient’s divided internal iliac artery and between the end of the donor renal vein and the side of the external iliac vein. More commonly, an end-to-side anastomosis of renal artery to external iliac artery is now used, especially if there is significant atheromatous disease.
in the internal iliac artery, as there often is in older or diabetic recipients, or if the contralateral internal iliac artery has been ligated during a previous transplant operation. Most transplant surgeons routinely favor the end-to-side procedure because exposure of the external iliac artery requires less dissection and because stenosis at the anastomosis may be less likely, especially if a Carrel patch of donor aorta is used (as is usually the case for cadaveric but not living donors).

If there are multiple donor renal arteries that are not on an aortic cuff, we favor anastomosis of the end of the smaller renal arteries to the side of the largest renal artery. These anastomoses can be performed deliberately under magnification while the ex vivo kidney is protected by immersion in a basin of cold saline solution. Revascularization in the recipient can then be accomplished rapidly by a single anastomosis. The sacrifice of even small accessory donor renal arteries should be avoided because occlusion of these end arteries will cause renal infaracts. Preservation of accessory arteries to the lower portion of the kidney is especially important because they may constitute the blood supply of a segment of collecting system or ureter and their ligation may lead to necrosis and urinary fistula. In 470 living related donors studied at the University of Pennsylvania, multiple renal arteries were found to be present in one kidney in 30% and bilaterally in 9%.[22] In 42 patients in whom the type of ex vivo anastomosis described previously was performed for multiple arteries, only one kidney was lost, owing to a technical complication, and the 1-year survival of 76% was no different from that of single-artery kidneys in the precyclosporine period. Venous collateral circulation is almost always adequate, so that in instances of multiple renal veins (which are even more common than multiple arteries), only one large vein need be saved for anastomosis. If a large adult kidney is to be transplanted into a small child, a transperitoneal approach is used to provide adequate room for the kidney, which is revascularized via the aorta and vena cava.

Urinary tract continuity is usually established by ureteroneocystostomy. The ureter should pass beneath the spermatic cord to avoid obstruction. Ureteropyelostomy (anastomosis of the recipient’s ureter to the pelvis of the donor kidney) is an alternative procedure, which should be used in instances of donor ureteral devascularization or injury. A few surgeons prefer this procedure to ureteroneocystostomy, but it is associated with a higher incidence of urinary fistula.

Meticulous technique and hemostasis are particularly important because of the coagulopathy and susceptibility to infection of uremic immunosuppressed patients. We prefer to close the wound without drains, but if hemostasis is suboptimal, closed suction catheters may be used.

Post-transplant Management

If the transplanted kidney has not suffered ischemic damage, a brisk diuresis is likely to begin within minutes of revascularization. Responsible for the diuresis (which may reach 3000 mL/hr) are (1) osmotic factors secondary to uremia or high glucose concentrations in intravenous fluids, (2) total body fluid and electrolyte overload secondary to chronic uremia, and (3) mild proximal tubular damage resulting from allograft ischemia. Early in the postoperative period, mild diuresis is reassuring and should be encouraged by replacement of urine volumes and, if necessary, by diuretics. Initial under-replacement of fluid may lead to oliguria or impaired transplant function interfering with diagnosis of vascular occlusion, urinary obstruction, or early rejection. Severe dehydration can be the outcome of inadequate replacement of losses during a massive diuresis, especially in children. During the first few days, there may also be a need for colloid or blood replacement because of losses into the wound.

Serious problems may also result from overreplacement of volume, especially if the transplant is not producing urine. Hyperkalemia is particularly dangerous in this setting and may necessitate administration of an ion exchange resin (sodium polystyrene sulfonate [Kayexalate], 25 to 50 g orally or by enema). In more emergent circumstances, administration of intravenous glucose and insulin or prompt dialysis may be necessary to control hyperkalemia. Suggested replacement fluids include 0.45% saline solution, with or without isotonic glucose, and sodium bicarbonate (30 mEq/L) and potassium (10 to 15 mEq/L), depending on the status of the serum electrolytes and blood glucose. If diuresis continues, fluid replacement should lag behind the urine output, allowing gradual return to normal urine volumes over the next 12 to 24 hours.

Because of the retroperitoneal approach, the transplant operation is relatively nondisruptive to intestinal function, and medications and fluids can usually be given by mouth within 12 to 24 hours. Ambulation on the first postoperative day is beneficial. The Foley catheter can be removed within the first few days. Hypertension, which is common, should be managed conventionally with drugs such as hydralazine, β blockers, calcium channel blockers, or angiotensinconverting enzyme inhibitors. Antacids are given to prevent ulcers, and nystatin (Mycostatin) is used for prophylaxis against candidal infections. Perioperative antibiotics (which should be given for no more than 48 hours) decrease the incidence of wound infection. Trimethoprim and sulfamethoxazole are used routinely by most centers for prophylaxis against urinary tract infections and Pneumocystis carinii. If
rejection and other postoperative complications do not occur, the subsequent care is relatively simple because the restoration of renal function is associated with a rapid return to normal health in patients previously suffering from single-organ system failure.

**Immunosuppression**

Thus far, the success of solid organ transplantation has been dependent on lifelong administration of nonspecific pharmacologic immunosuppressants. Since the early 1980s, advances in understanding mechanisms of T-cell activation have facilitated the development of more powerful and somewhat more selective immunosuppressive drugs that target the distinctive cell surface molecules of T cells, which initiate rejection.

**Azathioprine**

Prevention of rejection of human renal allograft rejection was first attempted by whole-body irradiation in the 1950s. Although one irradiated patient retained his allograft for 25 years without ever receiving immunosuppressive drugs, 11 others died of infections owing to the profound immunodepression caused by this treatment. In 1959, Schwartz and Dameshek discovered that the antimetabolite 6-mercaptopurine inhibited humoral immunity in rabbits. Shortly thereafter, Calne and associates and Zukowsky and colleagues found that the drug could prevent kidney allograft rejection in dogs. This drug and its derivative azathioprine had more predictable, reversible, and safer action than radiation and were soon used with considerable success in human renal allograft recipients. In 1988, the Nobel Prize was awarded to Gertrude Elion and George Hitchings for the development of these drugs.

**Adrenal Corticosteroids**

The previously known immunosuppressive effects of adrenal corticosteroids, although not sufficient in themselves to prevent rejection, were noted in the early 1960s to be synergistic with those of azathioprine. The combination of azathioprine and corticosteroids then became standard therapy for the next two decades. The complex impact of corticosteroids on the immune system involves blockade of postreceptor events occurring after engagement of the T-cell receptor with antigen and the inhibition of certain cytokine gene activation such as interleukin (IL-)1 and IL-6. Corticosteroids also possess potent anti-inflammatory properties, which reduce the migration of monocytes to sites of inflammation. This probably explains why brief intensification of corticosteroid therapy often aborts the "rejection crises" that precede desensitization with immunosuppression. Because of the adverse impact of chronic corticosteroid therapy, attempts are being made at many centers to withdraw these agents or to avoid their use altogether. Although this may be possible in some patients, others appear to suffer either acute or chronic rejection when corticosteroids are withdrawn from immunosuppressive protocols.

**Antithymocyte Antibodies**

In the 1960s, Woodruff, Medawar, Monaco, and others studied antilymphocyte serum (ALS), which in animals proved to be a more potent and more specific immunosuppressant than azathioprine. ALS contained xenon antibody raised by immunization of heterologous animals (e.g., rabbits, horses) with lymphoid cells of the prospective allograft recipient species. In rodents, small doses of ALS strikingly reduced the number of circulating lymphocytes and often prevented rejection of allografts. Although ALS also proved to be a potent immunosuppressant in humans, several problems limited its usefulness. Even the purified globulin fraction of antilymphocyte globulin (ALG) of the foreign serum sometimes provoked allergic reactions. The therapeutic window of ALG was quite small, and large doses or prolonged therapy often led to leukopenia, thrombocytopenia, and serious infections, especially of viral origin (e.g., herpesvirus, cytomegalovirus, varicella-zoster). In addition, patients formed antibodies to the heterologous protein, diminishing the feasibility of prolonged or repeated courses. Thus, ALS or antilymphocyte globulin (ALG) could be given only for a limited time, at marginal doses, and only as an adjunct to "conventional" immunosuppressive agents. ALS was also found to be very effective in reversing rejection crises, even those resistant to high-dose corticosteroid therapy, and this has become a common indication. Thymoglobulin (a rabbit antihuman thymocyte globulin [Sangstat]), available in Europe since 1985, has also been effective in preventing or reversing acute rejection and has become the most commonly used polyclonal agent.

The effectiveness of ALS was the basis for the introduction by Cosimi and coworkers of monoclonal mouse antihuman T-cell antibodies. Monoclonal anti-T-cell antibodies induce rapid depletion of T lymphocytes from peripheral blood while having little detrimental effect on other populations, such as red blood cells, platelets, or granulocytes, all of which are affected by cross-reacting antibodies present in the polyclonal ALG preparations. Because of lower cost and greater availability, specificity, and standardization of the preparation, monoclonal antibodies such as OKT3 have largely replaced ALS and ALG in many centers. The structure recognized by OKT3, the CD3 antigen, is linked to the T-cell antigen receptor, which is critical for the activation of human T cells. In vivo depletion of T cells after exposure to OKT3 is believed to be mediated by mechanisms such as complement-mediated lysis or opsonization of cells. In the presence of bound OKT3, the CD3 T-cell receptor complex is internalized by the cell, further rendering the T-cell population inactive. Multi-institutional, randomized prospective trials revealed the efficacy of OKT3 in reversal of acute rejection in 94% of cadaveric renal allograft rejections, a figure significantly better than that obtained with corticosteroid treatment.

Side effects associated with OKT3 therapy (particularly the initial doses) include fever, shaking chills, headache, nausea, vomiting, diarrhea, wheezing, and pulmonary edema. These phenomena are probably due to release of cytokines, especially tumor necrosis factor, and have been termed the cytokine release syndrome. Fortunately, such side effects can often be ameliorated by pretreatment with methylprednisolone, acetaminophen, and antihistamines or, more recently, antibodies against tumor necrosis factor or its receptor. As with polyclonal ALG, the use of monoclonal antibody OKT3 may induce rapid sensitization to mouse antibody, which results in the neutralization of OKT3 and reappearance in the peripheral blood of CD3+ cells. Concomitant administration of a cancel and corticosteroids may delay the production of anti-OKT3 antibody and prolong its immunosuppressive effect. Beyond return of graft function, in vivo efficacy of OKT3 may be monitored by sequential analyses of the CD3+ T-cell populations in the peripheral blood and the circulating level of OKT3 could be given only for a limited time, at marginal doses, and only as an adjunct to "conventional" immunosuppressive agents. ALS was also found to be very effective in reversing rejection crises, even those resistant to high-dose corticosteroid therapy, and this has become a common indication.

**Cyclosporine**

The introduction of cyclosporine in the early 1980s revolutionized transplantation by facilitating successful extrarenal transplants and improving cadaveric kidney graft survival. Cyclosporine is a fungal derivative that appears to block T-lymphocyte production of the lymphokine IL-2 through inhibition of the production of its messenger RNA. Like azathioprine, cyclosporine is most useful for prophylaxis rather than reversal of rejection. Calne, using it for single-drug immunosuppression in 1979, found it to be potent but also quite toxic at higher doses and its administration to be associated with infections, tumors, and renal failure. By reducing the dose of cyclosporine and combining it with small doses of prednisone, Starzl
subsequently reported spectacular improvement in the outcome of liver and kidney allografts. Similarly improved results were confirmed by multicenter randomized studies in Europe and Canada. After its release for general use in 1983, cyclosporine was adopted by virtually all centers.

Cyclosporine has the major advantage over azathioprine of lacking bone marrow toxicity but the disadvantage of nephrotoxicity, which is its major side effect. Nephrotoxicity may be manifest as a delay in function of a newly transplanted kidney or impairment of function of a well-established renal allograft. Although therapeutic drug monitoring and maintenance of blood levels in the therapeutic range are helpful, these do not eliminate the possibility of nephrotoxicity, which may occur even at “subtherapeutic” levels or after prolonged, stable dosages. Elevated blood levels of the agent and toxicity may appear, especially during concurrent use of certain drugs (such as ethromycin, cimetidine, diltiazem, and ketoconazole) that increase bioavailability through inhibition of hepatic metabolism. Conversely, decreased blood levels may result from patient noncompliance or interactions with drugs such as phenobarbital, phenytoin, and trimethoprim-sulfamethoxazole, which activate the hepatic P-450 cytochrome system and increase conversion of the parent compound to immunologically less active metabolites. In addition to nephrotoxicity, other side effects attributable to cyclosporine include hypertension, hepatotoxicity, seizures, tremor, hypertrichosis, nausea, vomiting, and diarrhea. Delayed renal allograft function from ischemic damage of cadaveric kidneys may be accentuated by nephrotoxic drugs. Therefore, many centers avoid the use of cyclosporine until delayed function has resolved. A prophylactic course of polyclonal or monoclonal anti-T-cell antibodies is advocated by some, along with corticosteroids to delay rejection until graft function allows institution of cyclosporine therapy. Even without initial ischemic renal damage, patients on cyclosporine tend to have persistently higher serum creatinine levels than azathioprine-treated patients and histologic changes of interstitial fibrosis in the kidney over the long term. Because of uncertainty regarding the risk of permanent renal damage from long-term cyclosporine therapy, most centers use lower doses of cyclosporine in combination with prednisone and azathioprine or MMF. The risks of chronic renal damage appear to be outweighed by the substantial advantages of cyclosporine, including the possibility that in selected cyclosporine-treated patients, corticosteroid therapy could eventually be minimized or completely withdrawn. Doses are determined by trough levels in whole blood, which are maintained at 100 to 200 µg/L (as determined by high-performance liquid chromatography). Absorption and bioavailability of cyclosporine were found to be quite variable after oral administration, complicating regulation of blood levels. A microemulsion formulation of cyclosporine (Neoral) allows faster and more consistent absorption and facilitates management.

Tacrolimus (FK-506)

Tacrolimus has properties similar but perhaps superior to those of cyclosporine. The antilymphocytic effect of tacrolimus results from the formation of active complexes between the drug and the respective intracellular binding protein or immunophilin. The FK-506 immunophilin complex inhibits the phosphatase activity of calcineurin, which is important in the regeneration of IL-1 gene transcription. Tacrolimus was first described by Kino and colleagues in 1987 and introduced clinically in the United States at the University of Pittsburgh in 1989. It is about 100 times more potent as an anti-T-cell agent than is cyclosporine (on a per-milligram basis). Initially, tacrolimus was used to “rescue” liver transplants observed to be failing on cyclosporine-based immunosuppression. Subsequent trials have assessed the efficacy of tacrolimus as primary immunosuppression. Prospective randomized trials in the United States and Europe initially showed that patient and graft survival were comparable with tacrolimus and cyclosporine but that the incidence of rejection, both acute and corticosteroid-refractory, was significantly lower with tacrolimus. A subsequent randomized study in the United States comparing the efficacy and safety of tacrolimus with cyclosporine immunosuppression in patients receiving cadaveric kidney transplants revealed 1-year graft survival rates of 91.2% for tacrolimus and 87.9% for cyclosporine. Acute rejection episodes were significantly reduced for tacrolimus patients, as was the requirement for antilymphocyte therapy for rejection. Tremor and paresthesias were more frequent in patients on tacrolimus, and the incidence of post-transplant diabetes was 19.9% for tacrolimus versus 4% for cyclosporine. Several studies have addressed the use of tacrolimus induction and rescue therapy after kidney or kidney-pancreas transplantation. These observations have encouraged the adoption of tacrolimus-based primary immunosuppressive regimens for kidney-pancreas transplant recipients. The adverse effects of tacrolimus are similar to those of cyclosporine: nephrotoxicity, neurologic problems (tremor, headache), and diabetes.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), the morpholino-ethyl ester of mycophenolic acid (MPA), which in vivo is hydrolyzed to free MPA (the active immunosuppressive moiety), is a potent and specific inhibitor of de novo purine synthesis. MPA blocks the proliferation of both T and B lymphocytes because these cells lack a significant purine biosynthetic salvage pathway activity. The use of MMF in combination with cyclosporine dramatically reduced both the incidence and the severity of acute rejection. Subsequent trials combining MMF with cyclosporine indicated that the risk of biopsy-proven acute rejection declined to less than 20% and the frequency of resistant rejection was markedly decreased. As a result, MMF has virtually replaced azathioprine at many transplant centers. The trials indicated a slight increase in the risk of viral infection in MMF-treated patients, although this can usually be controlled by prophylactic drugs. Unfortunately, MMF has not altered the rate of chronic graft rejection, despite the lower incidence of acute rejection episodes after use of this combination. Its most common side effects involve the gastrointestinal tract. MMF has also been extremely effective in pancreas transplantation. In a single-center study, simultaneous pancreas and kidney transplant (SPK) recipients demonstrated a markedly improved survival of allografts, with 2-year renal and pancreas graft survival rates increasing from 86% to 95% and 83% to 95%, respectively, with the use of MMF rather than azathioprine.

Sirolimus (Rapamycin)

Sirolimus, which is structurally similar to tacrolimus, was discovered in a search for novel antifungal agents. It is a macrocyclic triatibiotic produced by Streptomyces hygroscopicus, an Actinomycete that was isolated from a soil sample collected from Rapa Nui (Easter Island). Although sirolimus also binds to FKBP25, its effect is distinct from the calcineurin-based activity of tacrolimus or cyclosporine. Sirolimus and cyclosporine were found to be strikingly synergistic in experimental animal studies of heart and kidney transplantation. Phase II studies in human kidney transplantation show that the incidence of acute rejection may be reduced to approximately 10% by using both drugs. Phase III studies are now under way to determine the risks and benefits of this combination. Sirolimus is not nephrotoxic but may cause thrombocytopenia and hypercholesterolemia. It also appears to be associated with delayed wound healing.

Other Immunosuppressive Agents

Development of new, less toxic immunosuppressive therapies is very important. A new class of biological agents that target co-stimulatory molecules necessary for T-cell activation holds great promise for this purpose. Unlike conventional agents such as tacrolimus and cyclosporine that inhibit T-cell activation by blocking the effects of T-cell receptor triggering by antigen (termed signal I), these agents target the interaction of T cell CD28 with antigen-presenting cell (APC) B7 molecules, or T cell CD154 with APC CD40 (signal II). The theoretical attractiveness of this approach is based on
greater probability of inducing a state of tolerance to the graft. In large animal studies, Kirk and coworkers reported long-term survival of kidney allografts utilizing simultaneous blockade of CD154 and B7. In subsequent work, even monotherapy with anti-CD154 alone administered for a 5-month course resulted in prolonged function of all grafts without graft loss owing to rejection. Interesting in these studies was the finding that combination therapy with conventional agents and anti-CD154 produced inferior results to monotherapy with anti-CD154, perhaps indicating that conventional therapy inhibits anergy induced by co-stimulatory blockade.

**Rejection**

Considerable effort has been made to correlate allograft morphology with the clinical course of rejection. However, histologic study of a kidney biopsy can never provide more than a narrowly focused “snapshot” of the target of a complex systemic process that is in continuous evolution while also being modified by immunosuppression. Rejection is conveniently categorized as hyperacute, acute, or chronic, but there are overlapping features and transitions among these categories. The introduction of newer potent immunosuppressive agents has also changed the classic histologic changes of rejection. The outcome of an interventional conference in Banff was the proposal of new criteria for the semiquantitative analysis of rejection and the development of standardized nomenclature.

**Hyperacute Rejection**

In the 1960s, several instances were noted in which transplanted kidneys that initially seemed viable were rejected within minutes of revascularization, as evidenced by bluish discoloration of the kidney, deterioration of perfusion, and cessation of function. Histologically, extensive intravascular deposits of fibrin and platelets and intraglomerular accumulation of polymorphonuclear leukocytes, fibrin, platelets, and red blood cells along with accumulation of leukocytes in the peritubular and glomerular capillaries were seen. This process proved refractory to immunosuppressive or anticoagulant therapy and inevitably led to rapid destruction of the kidney. It soon became evident that the occurrence of hyperacute rejection was usually correlated with the presence of preformed circulating antibodies against donor antigens and that these could be identified by a pretransplant crossmatch. The classic form of hyperacute rejection has become rare because transplants are no longer performed when the crossmatch is positive.

**Acute Cellular Rejection**

Acute cellular rejection most commonly becomes evident during the early days or weeks after transplantation, although it may occasionally occur months or years later. The diagnosis of acute rejection is based on a constellation of findings that include clinical signs and symptoms, laboratory assays of blood and urine, radioisotope studies, and allograft biopsies. Classic signs and symptoms are malaise, fever, oliguria, hypertension, and tenderness from swelling of the allograft. However, most of these symptoms are rarely seen in patients receiving newer immunosuppressive agents, such as cyclosporine and tacrolimus. Under the influence of these agents, rejection takes on a more subtle clinical picture in which fever and allograft swelling may be absent and impaired renal function may be the only signal. Under these circumstances, we usually obtain a radioisotope renal perfusion scan, a test that cannot provide specific evidence of rejection, but that helps to exclude several other conditions that can cause impaired renal function, such as vascular occlusion, ureteric obstruction, or urinary fistula.

Because the diagnosis of rejection on clinical grounds alone may be difficult, a biopsy is often performed when rejection is suspected. This procedure may be performed transcutaneously with little risk. Early microscopic signs of acute rejection include the adherence of lymphocytes to the endothelium of peritubular capillaries and venules, which then progresses to disruption of these vessels, tubular necrosis, and interstitial infiltrates. Cellular infiltration, which is the hallmark of rejection, is composed at first of small lymphocytes and later consists of a variety of cells such as large lymphocytes and macrophages. As rejection proceeds toward irreversibility, there is greater involvement of the vascular elements of the graft. Swelling of the intima and focal fibrinoid necrosis of the media take place, followed by endothelial cell proliferation and obliteration of the lumina of small arteries by fibrin, platelets, and lymphoid cells.

In the Banff schema, glomerular, interstitial, tubular, and vascular lesions are graded 0 to 3+, depending on whether they are absent (0), mild (1), moderate (2), or severe (3). Total reliance cannot be placed on a biopsy as the “gold standard” for diagnosing acute rejection. Not only are biopsies subject to sampling error, but lymphocytic infiltration in itself cannot be taken as conclusive evidence of rejection because, for obscure reasons, even perfectly functioning renal allografts may exhibit some degree of mononuclear infiltration.

Distinguishing impairment of renal function owing to rejection from nephrotoxicity induced by cyclosporine or tacrolimus is a challenging problem. In cyclosporine nephrotoxic states, variable degrees of lymphocytic infiltration in the interstitium of the kidney have been observed. Careful attention to trends and fluctuations of cyclosporine blood levels may aid in decision making. Cyclosporine nephrotoxicity characteristically causes smaller increments in serum creatinine than rejection does, and these are usually reversible within a few days after dose reduction. Arteriolar hyalinosis is another factor considered in the Banff criteria because this is thought to be a feature of cyclosporine toxicity.

A particularly challenging clinical problem is the diagnosis of rejection in the setting of ATN. Under this circumstance, a biopsy may be the only aid to diagnosis. Unfortunately, however, even a skilled pathologist cannot always distinguish the histologic picture of rejection from that of ATN (or cyclosporine toxicity). Therefore, enthusiasm for repeated biopsies varies, some transplant surgeons being content in most instances to rely on their clinical judgment. At times, empirical antirejection therapy is employed as a diagnostic test for suspected rejection. In the presence of acute rejection (and the absence of ATN), this usually promptly lowers the creatinine value.

When the diagnosis of acute rejection is made, prompt institution of antirejection therapy (corticosteroids, anti–T cell antibodies) is necessary to prevent permanent damage to the allograft. This treatment is usually capable of reversing the process, although it may recur. Intravenous high-dose corticosteroids (0.5 to 1.0 g methylprednisolone) are used as first-line therapy for rejection at most centers. We find that about 65% of acute rejections will respond to three to five doses. Corticosteroid-resistant rejection may respond to anti–T-cell antibodies in an additional 30% of cases. Rejection refractory to both corticosteroid and antilymphocyte antibody therapy may still respond to treatment with newer agents such as tacrolimus or MMF.

It is important that antirejection therapy not be employed needlessly or for a prolonged period, because this is the cause of most morbidity and mortality. During the 1970s (before the introduction of cyclosporine), a progressive improvement in patient survival took place in most centers. This was probably the result of the realization that overly intense immunosuppression and repeated courses of antirejection therapy were unwise and dangerous and that better long-term results could be accomplished by more conservative therapy. Many groups adopted the policy of refusing to aggressively treat more than two episodes of acute rejection. Experience taught the important lesson that eventual loss of some grafts could not be avoided. Early recognition
and acceptance of this eventuality, transplant nephrectomy, reinstitution of dialysis, and the chance of a later successful transplant were obviously preferable to pushing heavy immunosuppression to the point of serious infection and death.

**Chronic Rejection**

The border between acute and chronic rejection is not always sharply defined, but the typical course of chronic rejection is gradual, progressive loss of renal function. It may begin after years of stable function but is more often seen in patients who have had multiple early and incompletely reversible episodes of acute rejection. Humoral injury (thought to be a more important factor in this condition than in acute cellular rejection) is manifested histologically by intimal fibroproliferative arterial lesions that probably stem from repetitive cycles of immune injury to the endothelium with focal thrombosis and incorporation of thrombus into the arterial wall. Also seen in chronic rejection are glomerular changes. Histologically, increased mesangial matrix and mesangial proliferation are seen. The glomerular basement membrane is thickened, and focal deposition of IgM, IgG, and complement may be identified along capillary walls and within the mesangium. Clinically, these are manifested by proteinuria, microscopic hematuria, and slowly deteriorating function. As with acute rejection, a semiquantitative analysis of assessing renal progress for chronic rejection has been proposed under the Banff schema.

In the presence of these morphologic vascular and glomerular changes, antirejection therapy is ineffective. Employment of high-dose corticosteroid or ALS or OKT3 therapy in hopes of reversing the process should not be risked because this will be of no benefit and may lead to opportunistic infection or other serious sequelae. An abrupt cessation of immunosuppression is also unwarranted early in the course of chronic rejection because its progression may be slow and significant periods of useful, although diminishing, transplant function may be possible. However, immunosuppression should generally be reduced as renal failure progresses because the additive immunodepressive effects of uremia and immunosuppressive drugs are particularly dangerous.

It is important to remember that acute cellular rejection is also occasionally encountered after years of stable transplant function, sometimes as the result of discontinuation of immunosuppression by the careless or noncompliant patient. This must be distinguished from chronic rejection if possible, although a timely diagnosis of late acute rejection is usually fortuitous because symptoms are uncommon. A prompt biopsy is warranted in cases of unexpected or precipitous deterioration in stable function because late cellular rejection (unlike chronic rejection) can often be reversed if treated before severe damage occurs.

**Recurrent Disease in Transplanted Kidneys**

Because transplantation does not modify the underlying etiology of the renal disease, it is not surprising that the transplanted kidney is sometimes regarded by the host as an appropriate new target for destruction by the original disease process, especially in autoimmune or metabolic diseases.

**Glomerulonephritis**

In identical twin donor transplants performed in the 1950s, Murray recognized recurrent glomerulonephritic damage, which sometimes became apparent within only a few months. Late follow-up of 30 twin grafts indicated that 8 had failed from recurrent glomerulonephritis, making a strong case for the use of mild immunosuppression even in recipients of twin grafts. Fortunately, recurrent disease is less common in allografts, but in this setting it is more difficult to diagnose because its clinical manifestations and even histologic changes may be confused with those of chronic rejection. A recent report from Australia indicates that recurrent glomerulonephritis may be a more important cause of allograft loss than previously recognized. All 1505 renal transplants performed in that country between 1988 and 1997 were analyzed. Graft loss from biopsy-proven recurrent glomerulonephritis occurred in 52 patients (8.4%). It was more common than acute rejection and in fact was the third most common cause of allograft loss after chronic rejection and death with a functioning transplant. Independent risk factors included peak levels of panel reactive antibodies and the type of glomerulonephritis, especially mesangiocapillary type I, focal segmental membranous nephropathy, IgA nephropathy, and immune crescentic glomerulonephritis. Recurrent disease is most likely in patients whose original disease process has run a rapid course. It appears to be most likely in twins and next most likely in recipients of closely matched related donor allografts. However, the other advantages of related living donors seem to override the risks of recurrent glomerulonephritis and their graft survival remained superior to that of mismatched cadaveric grafts in a large U.S. study of transplants in patients with glomerulonephritis. The graft loss from recurrent glomerulonephritis appears to be quite low (2% to 4%), at least for the first several years, and in an Australian series even at 10 years it was no higher than in patients who had other causes of renal failure. Thus, the risk of recurrent glomerulonephritis should not be considered a contraindication to transplantation, although its very long-term impact is not fully known.

**Collagen Diseases**

Collagen diseases such as lupus erythematosus are possible but unlikely causes of recurrent damage and are often well palliated by transplantation.

**Metabolic Diseases**

**Cystinosis** causes intracellular deposition of cysteine crystals in various organs, usually leading to end-stage renal disease by age 10 years. Although recurrent renal disposition may occur after transplantation, its effects appear to be mild.

**Oxalosis** is likely to reappear and destroy transplanted kidneys very rapidly (although these changes may be delayed by prolonged pretransplant dialysis and posttransplant diuresis). However, hepatic transplantation, which will reverse the metabolic defect, and concomitant renal transplantation are the ideal treatments, especially in patients with renal and other systemic oxalate damage.

**Diabetes**, when it causes end-stage nephropathy, has become one of the most common indications for renal transplantation. Diabetic nephropathy is thought to be caused by protracted abnormal glucose homeostasis that, of course, is not corrected by successful renal transplantation. Thus, in diabetic patients, it is not surprising that Kimmelstiel-Wilson lesions may be found on biopsies of the transplanted kidney within 2 years. However, because 10 to 20 years are probably required for these changes to cause functional deterioration, the threat of recurrence is certainly not a contraindication to renal transplantation, which gives diabetics a better chance of survival than chronic dialysis. Successful pancreatic transplantation, if performed concomitantly with renal transplantation, may prevent the early morphologic changes of diabetes in the transplanted kidney.

**Complications of Renal Transplantation**

**Technical Complications**

Complications occurring in the first few hours or days after transplantation are commonly related to technical problems in establishing vascular and urinary continuity or to damage that occurs during donor nephrectomy or preservation. Because rejection may also be an early event, its differentiation...
from various other causes of poor function may be difficult.

VASCULAR COMPLICATIONS

Arterial obstruction, although less common than ATN or urinary tract complications as a cause of early postoperative oliguria or anuria, should be considered promptly if an established diuresis suddenly ceases. A diseased hypogastric artery is likely to thrombose and should never be used to vascularize the transplant. Instead, the usually more normal common or external iliac artery that is also accessible with less dissection should be utilized. Partial occlusion of the transplant vessels may be caused by kinking from unfortunate positioning of the kidney. Although radioisotopic scanning and arteriography will confirm suspected vascular occlusion, immediate reoperation without delay for diagnostic studies is usually the only chance for salvaging such a graft because only a few minutes of total ischemia can be tolerated before damage becomes irreversible.

Oclusion of the transplant renal vein, although rare, can result from technical anatomic errors or from kinking or compression. Iliofemoral thrombosis occasionally follows renal transplantation, presumably because of clamping of the vein or compression by the transplant. The thrombus rarely extends into the renal vein, and standard anticoagulant treatment is generally effective. In a few cases, therapy with urokinase has been successfully employed to lyse clots occluding the renal vein. If pulmonary embolus occurs despite adequate anticoagulation, caval interruption should be performed by standard techniques such as a Greenfield filter and rarely compromises transplant function.

HEMORRHAGE

Imperfect operative hemostasis in the setting of uremic coagulopathy or anticoagulation during hemodialysis is the usual cause of early postoperative bleeding. Fracture and frank rupture of the transplanted kidney are unusual causes of bleeding, but these may occur from rapid swelling of the transplant during acute rejection. Rupture is more common in kidneys from infant or child donors, in which the small organ is sometimes unable to tolerate adult levels of blood pressure and flow.

Bleeding from the arterial suture line, except in the early hours postoperatively, should bring to mind the strong possibility of infection. Resuturing of an infected suture line is futile because recurrent disruption is virtually ensured. The kidney should be removed and the hypogastric artery securely ligated. If the anastomosis is in the common or external iliac artery, the problem is more serious. Even removal of the kidney necessitates a suture line to close the iliac arteriotomy. This then becomes a potential site of arterial disruption. Ligature of the iliac artery and extra-anatomic bypass (femorofemoral or axillofemoral) may be necessary.

HYPERTENSION AND RENAL TRANSPLANT ARTERY STENOSIS

More than half of renal transplant recipients are hypertensive. Impaired allograft function and administration of cyclosporine and corticosteroids are the major causes. In about 10%, the native kidneys may be the source, and alleviation can be accomplished by nephrectomy. A source of hypertension, which is important to diagnose, is renal transplant artery stenosis (RTAS). This condition may be confused with rejection because both may result in hypertension and diminished renal function. Although RTAS is a relatively unusual cause of decreased renal function, which is more commonly the result of rejection or cyclosporine toxicity, a high index of suspicion should be maintained because it is correctable. The usual time of presenting symptoms is between 3 months and 2 years after transplant (peak, 6 months). The true incidence of RTAS is not known, but in patients suspected on clinical grounds of having renal artery stenosis, confirmation of the diagnosis by biplanar arteriography occurs in 4% to 12%. However, when 100 consecutive transplant patients were subjected to routine postoperative arteriography by Lacome, a surprising prevalence of stenosis was found (23%).

The etiology of RTAS is frequently technical: improper anastomosis, injury of the intima of the renal artery during washout, or perfusion or kinking at the anastomotic site from redundancy or twisting of the arteries. Arteriosclerotic lesions of the donor or recipient vessels may be a contributing factor, especially in recent years as the donor shortage has mandated the use of older donors. An immunologic pathogenesis also seems likely because intimal proliferation and subintimal fibrotic changes seen in RTAS are similar to small vessel changes caused by rejection. About 70% of the lesions are at the anastomotic site, but 20% are beyond the anastomosis in the transplant renal artery proper. Thus, even the use of a Carrel patch does not preclude this complication. Fortunately, not all instances of RTAS are clinically relevant. Because the incidence of at least mild hypertension is as high as 50% in transplant patients, RTAS is by no means always its cause. Thus, its correction cannot always be expected to be followed by normotension.

We presently advocate percutaneous transluminal angioplasty in most instances of RTAS. Of 547 consecutive renal allograft recipients, 39 suspected of RTAS because of refractory hypertension had the diagnosis confirmed by arteriography and underwent balloon dilatation. Seventy-six percent of percutaneous transluminal angioplasties were successful, whereas only one graft was lost as a result. Three patients initially treated successfully developed recurrent stenosis, which was corrected operatively by patch angioplasty. Although some authors favor operation over percutaneous transluminal angioplasty, the surgical treatment is difficult and not always successful. The long-term results of percutaneous transluminal angioplasty and surgery are probably roughly comparable, but because of simplicity and patient acceptability, most surgeons advocate percutaneous transluminal angioplasty as the initial approach, with surgery reserved for persistent or recurrent stenosis. If surgery is necessary, preserved cadaveric iliac artery may be useful in the repair.

Urinary Tract Complications

The most common cause of sudden cessation of urinary output in the immediate postoperative period is the presence of a blood clot in the bladder or urethral catheter, which can be relieved by irrigation. Other more serious causes of urinary obstruction are unusual and should be investigated simultaneously with consideration of vascular occlusion, ATN, or rejection. A ureteroneocystostomy may become occluded by a hematoma at the site of the submucosal tunnel in the bladder or by a technically unsatisfactory anastomosis. An adynamic ureter or edema at the orifice in the bladder can also cause temporary partial obstruction.

Devascularization of the ureter during donor nephrectomy is a more serious problem that may lead to ureteral necrosis and fistula within the first few days or weeks. Mild ureteral ischemia is the probable cause of an occasional late distal ureteral stenosis, which may lead to partial or total occlusion. Fluid obtained from wound drains or needle aspiration can be identified as urine by its urea content, which is severalfold higher than that of serum or lymph. Ultrasound studies (for fluid collections), radioactive scans, and cystograms (which via reflux may visualize the ureter) are other helpful studies. However, urography is usually necessary to define the status of the ureter and is best accomplished by percutaneous fine-needle puncture of the kidney and antegrade catheterization of the pelvis and ureter. Treatment must be individualized and may consist either of reconstruction of the ureteroneocystostomy (if it is not ischemic) or of ureteropyelostomy using the patient’s own ureter.

Acute Tubular Necrosis

Ischemia occasionally precipitates ATN in a related donor transplant, but in cadaver transplants the incidence is much higher. Even in transplants from
“heart-beating cadavers,” some degree of ATN occurs in 5% to 30%. Therefore, in the absence of vascular or ureteral problems, initially nonfunctional cadaver kidneys may be assumed to suffer from ATN, especially if technetium and iodhippurate scans demonstrate good blood flow and poor tubular function. At times, however, a kidney has adequate urine output briefly and then lapses into ATN. Estimating the true output of the transplanted kidney may be difficult if the patient’s own kidneys are producing substantial amounts of urine.

Oliguria in the early transplant period should be treated with aliquots of fluid and colloid to exclude hypovolemia, while care is taken not to fluid-overload the patient. Mannitol, 12.5 to 25 g, and furosemide, 100 to 200 mg, intravenously in divided doses may be used to increase the output but are unlikely to alter the course of true ATN. The impact of ATN is definitely an adverse one. Delayed graft function reduces the 5-year graft survival by 10%. Some kidneys that never produce urine (termed primary nonfunction) are no doubt lost because potentially reversible damage from ATN is compounded by undiagnosed rejection before function returns, with the result that antirejection therapy is delayed until immunologic damage progresses to an irreversible stage. In an attempt to avoid this sequence, many authors employ ALG or monoclonal anti-T-cell antibodies prophylactically in all instances of ATN. Because there is no specific treatment for ATN, the return of function (usually within 1 to 4 weeks) must be patiently awaited while adequate but safe immunosuppression and good general condition are maintained, if necessary, by dialysis. If there is reasonable clinical confidence in the diagnosis of ATN, it is best to minimize the use of invasive studies such as cystoscopy, arteriography, or biopsy, none of which will provide positive evidence of ATN. Serial renal scans to identify decreases in blood flow may be helpful in making the difficult diagnosis of rejection during ATN, but biopsy is often necessary for confirmation. Even in the absence of rejection, management of immunosuppression is difficult during ATN. The nephrotoxic potential of cyclosporine is particularly disturbing when renal function cannot be assessed. Blood levels of this agent should be carefully monitored during ATN. Many centers avoid cyclosporine entirely during ATN because of the additive damage of ischemia and cyclosporine toxicity.

LYMPHOCELES

Extensive mobilization of the iliac vessels during the transplant operation or failure to ligate lymphatics crossing them may predispose to lymphoceles, which have a variable reported incidence (0.6% to 18%). Possible manifestations that can occur weeks or months postoperatively are swelling of the wound; edema of the scrotum, labia, and lower extremity; and urinary obstruction from pressure on the collecting system or ureter. Ultrasound to identify a fluid-filled mass is the most useful diagnostic study. Aspiration of the cyst will be of only temporary benefit because lymph rapidly reaccumulates. External drainage should be avoided because this will place the kidney and vascular suture line at risk from infection. The treatment of choice is fenestration of the cyst into the peritoneal cavity. This can often be accomplished by laparoscopic technique. We have also successfully employed a nonoperative treatment of percutaneous drainage followed by repeated instillation of tetracycline or povidone-iodine to sclerose and obliterate the cyst.

Nontechnical Complications

INFECTIONS

Factors predisposing to infection of transplant recipients include a major surgical operation involving the urinary tract, infection carried over from the donor, and indwelling catheters in the bladder, bloodstream, and peritoneal cavity. Because of these and the immunodepression associated with uremia and antirejection therapy, 10% to 60% of patients suffer some type of infection during the first transplant year; and in half of the deaths that occur during the first year, infection is an important contributing feature. More cautious use of immunosuppression in the 1980s and the introduction of cyclosporine have reduced the magnitude of this problem, but infection remains the most common and most lethal complication of renal transplantation.

Bacterial Infections.

During the first month after transplantation, conventional bacterial infections are the most common, and the urinary tract, respiratory system, and wound are the most prevalent sites. These infections usually respond to prompt vigorous conventional antibiotic therapy. Acute bacterial infections may have a clinical presentation that can be confused with rejection: fever, malaise, swelling, and tenderness of the wound, or even rising creatinine level in the case of a urinary tract infection. It is especially important to exclude the possibility of infection before instituting antirejection therapy because, during infection, immunosuppression should be decreased rather than intensified, even though this action may lead to acute rejection. The incidence of wound infections (reported to be anywhere from 1% to 10%) can probably be reduced by preoperative or intraoperative prophylaxis with a cephalosporin, none of which will provide positive evidence of ATN. Extension of the infection should be identified in blood flow may be helpful in making the difficult diagnosis of rejection during ATN, but biopsy is often necessary for confirmation. Even in the absence of rejection, management of immunosuppression is difficult during ATN. The nephrotoxic potential of cyclosporine is particularly disturbing when renal function cannot be assessed. Blood levels of this agent should be carefully monitored during ATN. Many centers avoid cyclosporine entirely during ATN because of the additive damage of ischemia and cyclosporine toxicity.

Opportunistic Infections.

The period between 30 and 180 days after transplantation, usually the time of most intense immunosuppression, is the most common time for infection with opportunistic organisms, which in normal individuals rarely cause significant illness. In recent years, it has become evident that viral infections are even more important than bacterial ones in this regard, in terms of prevalence, diagnostic and therapeutic difficulty, and immunologic and neoplastic ramifications. This epidemiologic change is probably due to cyclosporine therapy, which allows lower doses of azathioprine and corticosteroids and has decreased the incidence of bacterial infections. At the same time, the use of antibodies against T lymphocytes, which cause seriously impaired antiviral defenses, has increased.

Cytomegalovirus (CMV).

CMV, a member of the herpesvirus family, is the most important viral pathogen. This ubiquitous agent infects most normal people at some point in their lives. Although in healthy individuals CMV infections are either clinically silent or mild, the presence of the latent virus and seropositivity persists for life. After renal transplantation, previously seropositive patients usually excrete CMV and exhibit elevations of antibody titer, on the basis of either reactivation of latent virus during immunosuppression or transmission of virus latent in the donor tissues. Under these circumstances, symptomatic illness sometimes occurs (20%) and is usually mild, supporting the hypothesis that previous exposure and immunity to the virus confer protection. However, seronegative recipients who receive a kidney from a seropositive donor are subject to a three times greater incidence of symptomatic illness, and of affected patients 25% have severe disease. CMV “disease” (as distinguished from asymptomatic seroconversion) varies in severity from mild fever and malaise to a debilitating syndrome marked by leukopenia, hepatitis, interstitial pneumonia, arthritis, central nervous system changes including coma, gastrointestinal ulceration and bleeding, renal insufficiency, bacterial
or fungal infection, and even death.

Distinguishing CMV disease, which has its usual onset 4 to 6 weeks after transplant, from rejection can be especially difficult because the viral infection can cause renal insufficiency. Seroconversion may not occur for an additional 3 to 6 weeks, and viral cultures consume several weeks. A rapid diagnosis can be made by utilizing tests for antigenemia or polymerase chain reaction assays using blood samples or the demonstration of virus on biopsy of infected tissues. 

The causes of renal malfunction during CMV infections include direct damage from the virus (“glomerulopathy”) and triggering of rejection. This is a dilemma because delay in institution of antirejection therapy may lead to irreversible renal damage, but intensification of immunosuppression may lead to lethal superinfection. In cases of decreasing renal function, a decision for or against antirejection therapy must often be based on clinical grounds; however, biopsy should probably be done first if CMV is suspected because it may distinguish rejection from CMV.

Because CMV disease has an adverse impact on morbidity, mortality, and graft loss, it is important to find ways of avoiding it. One obvious partial solution would be to avoid transplantation of all kidneys from seropositive donors to seronegative recipients. Although this might substantially improve graft survival as well as avoid morbidity in seronegative recipients, it would have the disadvantage of greatly reducing the donor pool for seronegative recipients because most adult donors are CMV seropositive. Another possibility would be active immunization for CMV because the most severe disease occurs in seronegative recipients. A live attenuated CMV vaccine was developed that, although not totally preventing infection after transplantation, strikingly reduced the incidence of symptomatic and severe illness. However, it is not available commercially. Passive immunization with immune globulin has also been used effectively by some centers.

Fortunately, both the incidence and the severity of CMV disease appear to be diminished in cyclosporine- or tacrolimus-treated patients. There is impressive evidence that preemptive ganciclovir therapy decreases the incidence of CMV disease. In established clinical CMV disease, intravenous ganciclovir is required for 2 to 4 weeks; viremia should be cleared before discontinuance of therapy.

**Polyomavirus Nephropathy.**

Primary infections with the polyomavirus (type BK) are known to occur in up to 90% of the population, typically without specific signs or symptoms. This virus persists in the kidney where reactivation and shedding into the urine may be detected in 0.5% to 20% of healthy individuals depending on the sensitivity of the assay (polymerase chain reaction vs. detection of viral inclusion bearing “decoy cells” on urinary cytology). Before 1996, BK virus nephropathy was either unrecognized or virtually nonexistent in many transplant centers. Whether the increasing recognition of its prevalence since then is a function of new risk factors such as new immunosuppressive agents, emergence of more virulent viral gene types, or simply greater awareness is uncertain. In any event, it now appears that up to 5% of renal allograft recipients can be affected. The diagnosis can be suspected on the basis of screening urinary cytology, but definitive diagnosis requires allograft biopsy to demonstrate nuclear inclusions in tubular epithelial cells and to rule out rejection or drug toxicity. Progression from an inflammatory stage to a fibrotic stage and finally to sclerosis and irreversible allograft failure has been observed in as many as 45% of affected cases. Current management is based on judicious decreases in immunosuppression to allow clearance of viral replication. In a few instances, the antiviral agent cidofovir has been used with success.

Other opportunistic infections such as aspergillosis, blastomycosis, nocardiosis, toxoplasmosis, and cryptococcosis are particularly likely to occur in transplant patients. The protozoan *P. carinii*, which has infected most individuals by age 10 years, is a pulmonary pathogen only in immunodepressed patients. It is the organism most commonly causing fatal pneumonia in this group. A prompt diagnosis by aggressive measures such as bronchoscopy or alveolar lavage and brushing or percutaneous transbronchoscopic or open-lung biopsy is important in cases of *P. carinii* infection because effective treatment exists (trimethoprim and sulfamethoxazole). Prophylaxis with the same agents is warranted in the early postoperative period and also reduces the incidence of bacterial urinary tract infections. Mycobacterial infections are unusual, but their potential lethality mandates constant vigilance.

**HYPERGLYCEMIA**

For reasons not entirely clear, but generally attributed to intensive or persistent corticosteroid administration, previously normoglycemic patients may become diabetic in the post-transplant period. Uncontrolled hyperglycemia may cause “pseudo-rejection” on the basis of interference with the laboratory determination for creatinine and increased serum osmolality with resultant intracellular and extracellular dehydration and impaired renal function. In this condition, control of the blood glucose level promptly results in correction of the elevated creatinine value.

**GASTROINTESTINAL COMPLICATIONS**

Ulceration and perforation of the stomach, duodenum, and small and large intestine are relatively common after transplantation. The colon is especially vulnerable to perforation, and in immunosuppressed patients, abdominal pain or signs of peritoneal irritation merit very close attention if not immediate laparotomy. Diverticulitis is the most common cause of perforation (36%) followed by ischemic colitis (24%). Pancreatitis is another recognized complication of both azathioprine and corticosteroid therapy in transplant patients, in which its course is frequently fulminating and fatal. Infectious gastrointestinal complications such as *Candida* stomatitis and esophagitis, pseudomembranous colitis, and CMV ulceration are also common. Symptoms and signs of these conditions may be masked by corticosteroid therapy.

**HYPERPARATHYROIDISM**

Secondary hyperparathyroidism from chronic renal failure usually subsides after a successful transplant. However, its persistence (“tertiary hyperparathyroidism”) has been reported in 2.6% to 70% of patients, with the smaller number being closer to the true incidence. In cases in which significant hypercalcemia and elevated parathyroid hormone levels persist for more than 12 months after transplant despite normal renal function, we advocate total parathyroidectomy and autotransplantation of fragments from a portion of one gland into the muscle of the forearm, where they are easily accessible for further resection without neck exploration should hyperparathyroidism persist and recur. Hyperparathyroidism is a sequelae of hyperparathyroidism, such as renal calculi, bone pain, and muscle weakness, are usually benefited by this procedure. In some unfortunate patients, a devastating complication of persistent hyperparathyroidism has been seen in which diffuse cutaneous vascular calcification leads to extensive ulceration and gangrene. Despite total parathyroidectomy, most such patients never heal their ischemic ulcers, which eventually lead to sepsis and death.

Common to these patients is persistent post-transplant elevation of serum calcium and radiographic evidence on xerography of extensive small- and medium-vessel calcification. Fortunately, this complication is uncommon, but in the face of nonhealing ulceration that occurs in unusual areas such as the upper extremities, elevation of serum calcium level, and increased parathyroid hormone levels, this diagnosis should be entertained.

**TUMORS**

In the early days of transplantation, it was found that utilization of apparently uninvolved kidneys from donors with known cancer sometimes resulted in transmission of the malignancy. Since then, in occasional instances, tumors have inadvertently been transplanted from donors with unrecognized cancer. If this complication is recognized early, cessation of immunosuppression is sometimes followed by rejection not only of the transplanted kidney but also...
of the allogeneic tumor. However, once the transplanted tumor becomes well established, it may continue to flourish and cause death even in the absence of immunosuppression.

It has been known for many years that both naturally occurring and iatrogenic states of immunodeficiency are accompanied by an increased risk of neoplasia. For example, chronic dialysis patients have an increased risk of malignancy that causes death in 1% to 4%. One hypothesis invoked to explain the more striking prevalence of malignancies in immunosuppressed patients is a breakdown of normal immunologic surveillance mechanisms that allows persistence of mutant malignant cells that would be recognized and destroyed by an intact immune system. It is theorized that such “forbidden clones” are particularly likely to go unrecognized in the brain, an immunologically privileged site. Other etiologic possibilities for the increased neoplasia are chronic immunologic stimulation of the lymphoreticular system by the transplant, direct carcinogenic action of immunosuppressive drugs, and oncogenesis by the viral pathogens whose growth is encouraged by immunosuppression. The latter possibility is supported by the finding that tumors in which a viral pathogenesis seems likely (lymphoma, skin, lip, uterine cervix, and perineal cancers) are especially prevalent in transplant patients. Since 1968, Israel Penn’s Cincinnati Transplant Tumor Registry has collected data from around the world on tumors in transplant patients. This registry has received reports on 11,663 post-transplant malignancies, 8,868 of them in renal transplant patients. In renal transplant recipients, the reported incidence of 6% de novo malignant neoplasms represents a risk approximately 100 times greater than that in normal age-matched populations. The increased incidence of tumors appears to be related to the degree and duration of immunosuppression rather than to any particular agent. These tumors often occur in young patients, and their behavior is unusually aggressive. Cancers common in the general population (lung, breast, prostate, and colon) are not increased, but certain uncommon neoplasms are extremely prevalent (lymphomas, lip cancers, renal cancers, various other sarcomas, hepatobiliary carcinomas, Kaposi’s sarcoma, and carcinomas of the vulva and perineum). Carcinomas of the uterine cervix are also very common, although most of these are in situ lesions. Most common of all are squamous cell carcinomas of skin and lip, which are especially prevalent in sunny areas such as Australia and New Zealand, where their incidence is increased 21-fold and patients who survive 15 years after transplantation have a striking 44% incidence of skin cancer. These cancers kill 5.1% of their victims.

Transplant recipients in all parts of the world have a disproportionately high incidence of lymphomas (350 times normal) that constitute 20% of all tumors in this population. Of the 1953 post-transplant lymphomas and lymphoproliferations reported to the Cincinnati registry, well-defined entities such as Hodgkin’s disease and plasma cell myeloma were less common than in the general population, accounting for 2.8% and 3.9% of lymphomas, respectively, compared with 10% and 19% in nonimmunosuppressed populations. There has been considerable disagreement regarding the classification of the more usual lymphomatous lesions of transplant patients. As a result, the nonspecific term post-transplant lymphoproliferative disease (PTLD) is now widely used, covering a spectrum of lesions ranging from benign hyperplasia to frankly malignant lymphomas. According to the UNOS database of 205,114 recipients transplanted between 1988 and 1999, 2,365 (1.15%) developed PTLD. The highest incidence was in intestinal transplants (6.0%). The hyperplasias include infectious mononucleosis and plasma cell hyperplasia, whereas the neoplasias include polymorphic PTLD, monomorphic PTLD, myeloma, plasma cell myeloma, and lymphomas with Hodgkin’s disease–like features. Hyperplastic PTLDs are polyclonal in origin, whereas neoplastic PTLDs contain a monoclonal component that can be detected by sensitive assays. Of 765 PTLDs in the Penn registry that were studied immunologically, 85% were of B-cell origin, 15% were of T-cell origin, and rare cases were of null-cell origin or were combined B- and T-cell lymphomas. In patients with these tumors, extranodal involvement is unusually common (69%) and the transplanted kidney is often involved (23%). Twenty-two percent of these tumors are in the central nervous system, an unusual site for lymphomas.

De novo lymphomas may begin as lymphoproliferative lesions induced by viruses. Although other viruses may also be involved, growing evidence implicates infection with the Epstein-Barr virus as the most important factor in PTLD. Compelling evidence of this is the finding of Epstein-Barr virus incorporated into the genome of lymphoma cells. These patients often have a syndrome resembling mononucleosis with fever, pharyngitis, and diffuse lymphadenopathy. Indicating monoclonal B-cell proliferation rather than true malignancy is the finding in these early lesions of a diversity of cellular immunoglobulins. During the stage of polyclonality, cessation of immunosuppression may allow regression of the lesions. The use of the antiviral agent acyclovir, which blocks Epstein-Barr virus–inhibited oropharyngeal shedding of the virus, has also been reported to contribute to remissions. Tumors that are initially polyclonal may eventually undergo a cytogenetic alteration, leading to malignant transformation and the monoclonal characteristic of true B-cell lymphomas. Monoclonal tumors do not regress after cessation of immunosuppression or acyclovir therapy. They are aggressive malignancies that can be treated only by surgery and irradiation, neither of which is very effective. The outcomes were studied in 1366 patients with PTLD reported to the Cincinnati registry. Of these, 224 patients had no treatment; the tumor was discovered at autopsy in 104 of them. No treatment data were available in 62 patients. Treatment was given to 1080 patients (79%), and, of these, 411 (38%) had complete remissions. In 69 of these recipients (17%), the only treatment was reduction or cessation of immunosuppressive therapy, and in 50 (12%) the only treatment was chemotherapy.

Results of Renal Transplantation

The outcome of each renal transplant depends on a number of complex and interrelated variables. The cumulative influence of these variables is analyzed annually by the UNOS Scientific Registry, which by federal law receives data on all transplants performed in the United States. The most recent registry report details the outcome of the 53,055 primary transplants done from 1996 to 2000, including 19,692 living and 33,363 cadaveric transplants. The results in this era of the current immunosuppression were also compared with those of earlier eras and especially to the 84,982 transplants performed from 1988 to 1995. Because rejection is the chief deterrent to success, it is not surprising that histocompatibility remains an influential factor. During the early days of transplantation, the success of HLA-identical sibling donor grafts was twice that of cadaveric transplants. Since then, the short-term results of cadaveric grafts have improved greatly and now, at least for a year, approach the success of HLA identical sibling grafts (89% vs. 96%) (Fig. 27–5). However, when long-term survival is examined, the importance of histocompatibility remains obvious. At 5 years, 90% of HLA-identical sibling grafts survive and at 10 years, 65%, but despite striking advances in immunosuppressive therapy, the survival of cadaveric grafts at 5 years is only 65% and
Although the short-term success of kidneys transplanted from cadaveric donors approaches that of related donors, the long-term survival increasingly favors related donor grafts. The half-life of HLA-identical living donor grafts is three times longer than that of HLA-mismatched cadaveric donor grafts.

Many other factors also influence the results of transplantation. Those compromising outcomes include unusually young or old recipients or donors (<5 or >50 years); interracial grafts; broadly sensitized recipients as identified by preformed antibodies against a panel of donor lymphocytes; previous failed transplants, especially if lost from early rejection; delayed transplant function, requiring dialysis; poor early function (serum creatinine > 3 at time of hospital discharge); and certain disease states (e.g., hypertensive nephrosclerosis, oxalosis). There is considerable evidence that donor brain death itself is accompanied by physiologic and immunologic changes that may cause or predispose to further renal damage. This may account in part for the fact that about one fourth of cadaveric grafts have delayed function.

Despite improvements in crossmatching and immunosuppression, sensitized recipients of first cadaveric kidneys had a 14% greater incidence of delayed graft function and an 8% lower graft survival at 5 years. Loss of a previous transplant was also a negative predictor. For recipients of cadaveric grafts, 5-year graft survivals were 66% for a primary graft but only 62% and 56% for second and third grafts, respectively.

Recipient race was another important factor in graft survival. Late graft loss was twice as frequent in blacks as in nonblack recipients whether the donor was living or cadaveric. Because of racially associated histocompatibility differences, blacks have also been at a disadvantage for allocation of cadaveric kidneys (the majority of which come from white donors) since the distribution algorithm has been heavily influenced by matching. To address this inequity, the UNOS Board of Directors recently voted to discontinue matching at the B locus as a consideration in allocation of cadaveric donor organs.

Factors associated with favorable outcome include relatively young donors (especially those 6 to 50 years old); good histocompatibility (especially complete HLA identity); and living donors (even if not related to the recipient by blood). The addition of tacrolimus and MMF to the immunosuppressive armamentarium as well as availability of a variety of antilymphocytic antibodies utilized for induction therapy appears to have greatly diminished the incidence of early rejection crises and improved graft survival at least for the first few years. The impact of these agents on chronic rejection and very long-term graft survival is more difficult to assess.

Since about 1980, the 1-year survival of first cadaveric grafts has gradually improved from 50% to almost 89%. The 20% improvement, which occurred between 1973 and 1984, was attributed to the policy of deliberate pretransplant blood transfusions (a strategy that was abandoned with the availability of cyclosporine). The additional 19% improvement since then was due to the introduction of cyclosporine in 1983 and the subsequent introduction of tacrolimus, MMF, and newer antilymphocytic antibodies. Cumulative experience and improvements in the art and science of transplantation undoubtedly also played a role in these impressive and progressively better short-term results. The 1-year survival of patients who receive cadaveric grafts has improved even more dramatically than graft survival and now for 1 year closely approaches that seen for recipients of related donor grafts at greater than 90%. But at 10 years, it is only 63% versus 80% for recipients of living donor grafts.

A disappointing aspect of the results of renal transplantation is evident from examining long-term cadaveric graft survival. Despite the dramatic short-term improvements in both patient and graft survival since about 1980, substantive attrition of cadaveric grafts continues after 1 year. Until 1988, this attrition remained almost constant at about 7% per year despite the introduction of cyclosporine. Since then, the half-life of cadaveric grafts has improved to 14.5 years if they were HLA-matched with the recipient but to only 10.2 years for other cadaveric grafts. Patients who received cadaveric grafts in 1967 had...
Renal transplants from living donors have the best survival, even if the donor is not genetically related to the recipient.\[3\] Continuing damage of grafts appears to be the result of chronic rejection, and in some patients recurrence of glomerulonephritis, entities for which we still lack effective therapy.

The excellent results of transplantation relative to dialysis and the donor shortage have resulted in a growing list of patients awaiting transplantation. By 2001 more than 50,000 candidates awaited cadaveric kidneys, in the United States whereas only about 9,000 renal transplants were done. For older patients, a 3- to 5-year waiting time represented a significant portion of their remaining life.

Impatience with long waiting times for cadaveric donor kidneys (during which many dialysis patients die) has led to a considerable increase in the use of living donors, which now exceed the number of cadaveric donors in the United States compared with less than 20% a decade ago. Unfortunately, donation of cadaveric kidneys has increased little, and most of this minimal increase has been from suboptimal donors; either younger than 5 or older than 50 years. The surprisingly good success of unrelated living donor transplants and the introduction of laparoscopic donor nephrectomy are responsible for much of this increase (Fig. 27–7). Overall results of transplantation have benefited from this shift to living donors because, at 10 years, there is an 18% better survival of living donor versus cadaveric grafts. For HLA-identical sibling donors, better than 90% 1-year graft survival has been reported since the mid 1970s and is now over 96%. The 1-year graft survival of parental or one-haplotype sibling transplants has also steadily improved since about 1980 from about 70% to the current 90% to 93%.\[3\]

Another impact of the donor shortage has had an adverse effect on overall results: the utilization of kidneys from suboptimal donors. The percentage of cadaveric kidneys from donors older than 50 years of age increased from 26% in 1988 to 46% in 2000. Unfortunately, age has a profound effect on 5-year graft survival, which was 72% for donors 6 to 18 years old but only 50% for donors older than 60 years (see Fig. 27–6). The use of kidneys from non-heart-beating donors might also have been expected to result in inferior outcomes, and indeed the incidence of delayed graft function was nearly double that of transplantation from heart-beating brain-dead donors (43% vs. 22%). Surprisingly, the 1- and 5-year survivals of 509 of these grafts transplanted between 1996 and 2000 were the same as for the heart-beating donors, perhaps because there donors were selected more carefully for other criteria, such as age.
LIVER TRANSPLANTATION

Indication for Liver Transplantation

Liver transplantation is the procedure of choice for a wide range of diseases that result in acute or chronic end-stage liver disease (ESLD), as well as for several diseases in which a major genetic error affects production of an essential liver protein. It may also be considered as a treatment for a limited number of carefully selected patients who have nonresectable liver tumors that have not metastasized outside the liver.

Indications for liver transplantation in adults and children are summarized in Table 27–1. Despite the differences in the etiology of these diseases, their shared pathophysiology leads to a common set of symptoms and signs typical of end-stage liver failure. The Child-Turcote-Pugh (CTP) score was established in an attempt to standardize the severity of chronic liver failure by using a reliable set of criteria that reflect the residual function of the liver (Table 27–2). A combination of clinical

* Most alcoholic patients are co-infected with the hepatitis C virus.

Figure 27-7 Only a minor increase has occurred in the number of cadaveric donors over the past 15 years (and this only in suboptimal ages younger than 6 and older than 50 years). Living donors have increased on the basis of acceptance of genetically unrelated donors and the perceived lesser morbidity of laparoscopic donor operations.

<table>
<thead>
<tr>
<th>TABLE 27-1 -- Indications for Liver Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Noncholestatic cirrhosis</td>
</tr>
<tr>
<td>Viral hepatitis B and C</td>
</tr>
<tr>
<td>Alcoholic</td>
</tr>
<tr>
<td>Cholestatic</td>
</tr>
<tr>
<td>Cholestatic</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>

* Most alcoholic patients are co-infected with the hepatitis C virus.

<table>
<thead>
<tr>
<th>TABLE 27-2 -- Child-Turcote-Pugh Score of Severity of Liver Disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
</tr>
<tr>
<td>For PBC/PSC</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
</tr>
<tr>
<td>PT (INR)</td>
</tr>
</tbody>
</table>
symptoms and laboratory data are used to provide insight into the severity of the disease and the residual function of the liver. In the absence of more reliable methods, the CTP scoring system was adopted as the standard method for the placement of patients suffering from ESLD on the transplant waiting list. Because categorization based on CPT was not a continuous scale, waiting time on the list was used to stratify patients within a CPT score group.

In 2002 the United Network for Organ Sharing put into place a new system for allocation that did not suffer from emphasis on waiting time and subjective clinical parameters (such as degree of ascites or encephalopathy) integral to the CPT base system. The overall goal of this major revision to liver allocation was to give priority to the sickest patients using a system based on objective variables. To accomplish this, a statistical model for end-stage liver disease (MELD) was employed for adult patients that had been shown to have a high predictive capacity in identifying those patients with ESLD at greatest risk of mortality within 3 months. The MELD score was based on three laboratory values: total bilirubin, International Normalized Ratio, and creatinine value and demonstrated a better correlation with 3-month survival than the CPT score (Table 27-3). A similar approach was developed for pediatric patients, although the relevant variables suffer slightly (PELD score).

This approach is not applied to urgent patients with fulminant liver failure (status 1 patients) but appears to work well for those with chronic liver disease. It is modified for certain conditions that express unique variables, such as small and potentially curable but nonresectable hepatocellular carcinomas and inborn errors of metabolism. The system is also adjusted to meet the special needs of children whose liver disease may be characterized by failure to thrive or recurrent cholangitis. It is recognized that no scoring system is perfect at identifying those at greatest risk; however, multiple laboratory tests such as serum levels of hyaluronate, amino-terminal propeptide collagen type III, indocyanine green clearance, or galactose elimination proved no better in quantitating hepatocyte function or in correlation with the progression of liver disease.

Specific exclusion criteria for liver transplantation are not formally established, although it is generally agreed that the presence of active sepsis or the findings of extrahepatic malignancy should be considered absolute.

<table>
<thead>
<tr>
<th>Score</th>
<th>Concordance</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model for End-Stage Liver Disease (MELD)</td>
<td>0.88</td>
<td>0.85, 0.90</td>
</tr>
<tr>
<td>Child-Turcote-Pugh (CTP)</td>
<td>0.79</td>
<td>0.75, 0.83</td>
</tr>
</tbody>
</table>

### Contraindications

Still controversial are conditions such as human immunodeficiency virus infection in the absence of the acquired immunodeficiency syndrome, large-size hepatocellular cancer (>6 cm), or cholangiocarcinoma. Several other entities such as portal vein thrombosis once considered contraindications for transplantation are no longer so categorized.

It is essential for the general surgeon to recognize the dynamics of chronic liver disease and to be able to assess the residual liver function in the presence of chronic liver disease. It is not uncommon for minor surgical procedures to exhaust the residual reserve and precipitate the development of acute on chronic failure. Management of these complications is extremely difficult. If liver transplantation must be performed during such circumstances it is associated with higher morbidity and mortality.

#### Diseases Treated by Liver Transplantation

The conditions that result in end-stage acute or chronic liver failure are different in the pediatric and adult populations. Whereas the incidence of most liver diseases has remained relatively constant over recent times, the prevalence of liver failure from viral hepatitis is increasing, reflecting the increased rate of infection in the past two decades. It is expected that the relatively recent availability of the hepatitis B vaccine and the ability to detect persistent infection is associated with the continuous host immune attack against HBV and the ability to detect the hepatitis C virus in donated blood will lower the rate of new infections and the number of individuals who subsequently develop chronic disease.

**Hepatitis B**

HBV belongs to a family of closely related DNA viruses called the hepadnaviruses. Chronic HBV infection affects 1.25 million people in the United States and is characterized serologically by the persistent presence of HBV DNA and usually HBV antigen in serum. Treatment with recombinant interferon alfa-2b leads to remission in 40% of the patients. Persistent infection is associated with the continuous host immune attack against HBV proteins expressed on the surface of the hepatocyte and results in the development of cirrhosis. HBV infection is also a risk factor for hepatocellular carcinoma, which arises almost exclusively in patients with cirrhosis. As with other forms of liver cancer, tumors associated with hepatitis B result from chronic inflammation and repeated cellular regeneration, typically occurring only after 25 to 30 years of infection. Most patients with chronic hepatitis B undergoing liver transplantation will reinflict the hepatic graft, and some undergo rapidly progressive liver failure. Fortunately, prophylaxis consisting of high-titer hepatitis B immune globulin and/or lamivudine is highly effective in the control of viral replication and recurrent disease post transplant.

**Hepatitis C**

The hepatitis C virus is an RNA virus of the flavivirus family that leads to chronic inflammation of the liver in about 85% of infected individuals. It is detected by the persistence of anti-HCV antibodies, serum viral proteins, and HCV RNA. Virtually all patients with chronic HCV infection develop histologic features of chronic hepatitis, and as many as 20% of patients develop cirrhosis within 10 to 20 years of HCV infection. They develop the typical complications of chronic liver disease including portal hypertension, hepatocellular failure, and hepatic encephalopathy. Hepatocellular carcinoma may ensue in 1% to 4% per year of chronic active hepatitis C patients with established cirrhosis. Serial liver biopsies every few years may be an important tool for following the course of chronic hepatitis C because they determine the degree of inflammation and the amount of fibrosis present. For patients with advanced liver disease, liver transplantation is often the only therapeutic option. The initial results of transplantation are good, with patient and graft survivals of 85% and 90%, respectively, at 1 year. However, virtually all patients become reinfected with HCV after transplantation and about half of them develop histologic evidence of chronic hepatitis within a few months. There is growing concern regarding the eventual recurrence of liver failure in these patients 5 to 10 years after transplantation, and recent evidence indicates that the long-term survival for patients transplanted for HCV may be significantly inferior in comparison to transplantation for other causes of liver disease.
Alcoholic liver injury results from toxic effects of ethanol to hepatocytes, the accumulation of fatty acids within the cells, and subsequent degeneration and necrosis. The intensity of the inflammatory process is directly related to the amount of alcohol consumed and is associated with fibrosis and subsequent cirrhosis. The coexistence of hepatitis C infection accelerates liver injury in most cases. Discontinuation of alcohol consumption may arrest hepatocyte destruction and allow regeneration and relatively compensated cirrhosis. Continued deterioration of liver function in the absence of alcohol and an appropriate CTP score is an indication for transplantation, just as in other liver diseases. Transplant candidates with alcoholic cirrhosis should undergo careful psychosocial evaluation in an attempt to document their sobriety for at least 6 months and the likelihood of post-transplant recidivism. Careful selection results in a low rate of recidivism in most centers. Outcomes of the transplant procedure are similar to those in other disease processes.

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) share many clinical, biochemical, and pathologic features. Clinically, both give rise to characteristic symptoms and signs of chronic biliary tract disease (e.g., pruritus and jaundice). In both conditions, the most characteristic biochemical abnormality is an increased serum alkaline phosphatase level. Central to the pathologic changes in both PBC and PSC is damage to bile ducts; in the case of PBC, this involves mainly the smaller intrahepatic ducts, whereas in PSC it also affects large ducts outside the liver as well as the gallbladder and even pancreatic ducts. Unique to PSC is its association with inflammatory bowel disease, which occurs in 70% of the patients. There is an increased incidence of cholangiocarcinoma in PSC patients. Liver failure in both diseases is manifested by hyperbilirubinemia. Transplantation is highly successful in both groups leading to long-term survival of more than 90% and an insignificant incidence of recurrence.

Hepatocellular Carcinoma

The rationale for liver transplantation in patients with nonresectable hepatocellular carcinoma is based on the logical potential of complete removal of disease that is confined to the liver. Unfortunately, it has become evident that in most cases the tumor recurs. However, the procedure can provide significant benefit in a specific subgroup of patients identified by the following characteristics: histologic grading of G1–2 and tumor size less than 5 cm, limited multifocally. The initial work-up in all transplant candidates must exclude extrahepatic metastases and macrovascular invasion of the liver on imaging. The results of transplantation for this selected group are variable but have been reported to have a disease-free survival of 60% to 85% at 3 years. It is yet to be determined whether the addition of adjuvant chemotherapy after transplantation could be an important factor in the control of recurrence.

Biliary Atresia

Extrahepatic biliary atresia is an obliterator cholangiopathy affecting all or part of the extrahepatic biliary tree. The condition occurs in 1 of 10,000 newborns. The diagnosis is suggested in neonates who remain jaundiced for 6 weeks or more after birth and have pale stools and dark urine. By then, the liver is enlarged and firm or hard, a reflection of the presence of underlying portal fibrosis. The Kasai procedure (hepatic portoenterostomy with resection of the obliterated bile ducts and reestablishment of biliary drainage to the intestine) can increase survival rates at the early stage. However, progressive intrahepatic bile duct destruction by chronic inflammation, fibrosis, and cirrhosis commonly occurs. Failure of the Kasai procedure is manifested by failure to thrive, recurrent cholangitis, and typical signs of ESLD. These are indications for transplantation.

Failure of Previous Liver Graft

An important and growing indication for transplantation is the failure of a previous graft. This occurs in the acute setting immediately post transplant arising from technical failures discussed later or chronically because of chimeric rejection or disease recurrence. Retransplantation can be particularly complex in the chronic setting owing to the usual factors associated with reoperative surgery. Overall, the results of retransplantation are inferior to those achieved with primary grafts and each subsequent transplant is associated with an additional decrement in survival.

Patient Selection and Preoperative Consideration

Patients who experience progressive deterioration or acute decomposition of preexisting chronic liver disease, or previously normal patients who suddenly develop fulminant liver failure, are candidates for transplantation and should be promptly referred for evaluation to a transplant center. An extensive work-up is done to assess the degree of liver disease and the potential for recovery, as well as to determine the existence of other extr hepatic conditions that might preclude the outcome of a transplant. Comprehensive medical assessment is mandatory to establish the candidate’s ability to withstand complex major surgery and to determine the potential for long-term survival. Only a few specific contraindications totally preclude transplantation in high-risk candidates (i.e., extrap epatic malignancy, irreversible brain damage, severe cardiopulmonary failure, or uncontrollable sepsis). In patients with liver failure, deterioration of the kidneys (hepatorenal) or the lungs (hepatopulmonary) are well-defined syndromes that may be reversible in the presence of a functioning liver and should not exclude candidates from liver transplantation. Irreversible kidney damage can be well managed by combined liver-kidney transplantation.

Assessment of Acute Liver Failure

The hallmarks of fulminant liver failure include the development of encephalopathy, coagulopathy, and hypoglycemia. Careful neurologic evaluation must determine the stage of hepatic coma. Progression from a state of confusion to one of unresponsiveness is associated with an increased likelihood that brain damage is irreversible. At this stage, assessment must include brain imaging with CT or MRI, and monitoring of intracranial pressure (ICP) should be considered. An attempt should be made to help promote cerebral perfusion (above 60 mm Hg) by reducing ICP and maintaining high mean arterial pressure. Irreversible injury is associated with persistent elevation of ICP, which leads to the development of severe brain edema and herniation. Other variables that define the extent of liver injury and predict chances of recovery relate to changes in prothrombin time, levels of factor V, phosphorus levels, and persistence of hypoglycemia. Coagulopathy may be resistant to correction but is best treated with transfusion of fresh frozen plasma. Plasmapheresis may be beneficial in small children in whom administration of large fluid volumes is problematic. Severe hypoglycemia is usually controlled by a dextrose infusion. Interestingly, changes in liver transaminases are not reliable indicators of the potential for recovery. Superimposed acute liver failure in patients with chronic liver disease may have a clinical presentation similar to that of fulminant liver failure in previously normal patients. In most cases the precipitating factor is related to acute bleeding or infection. Management should be directed toward resuscitation and control of the bleeding or infection. Ideally, successful stabilization and clinical improvement should be followed
by urgent transplantation. However, these candidates are at higher risk of morbidity and mortality, mostly owing to the development of bacterial and fungal infections. The surgeon must use clinical judgment to determine the presence of irreversible multiorgan system failure and avoid an unnecessary or futile transplant.

In the absence of a definitive therapy for most types of liver diseases, it must be expected that the natural course of decompensated liver disease will lead to worsening of the patient’s general condition and development of life-threatening complications, including variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Unfortunately, there are few effective means to prevent such complications. Thus, patients who are judged to be at risk for decompensating should be given priority for urgent transplantation.

**Donor Assessment**

A major limitation to clinical transplantation is the availability of organ donors. Appropriate management of brain dead donors and the avoidance of potential injuries during the procurement procedure are essential to good function of the transplanted graft. It is important to establish aggressive donor management protocols to minimize the adverse physiological consequences of brain death. These protocols should include respiratory and hemodynamic support, adequate fluid resuscitation, and the initiation of hormone replacement. Brain death is associated with significant instability, and minute-to-minute management by experienced personnel in the intensive care unit (ICU) is necessary to ensure adequate perfusion of all organs. Simultaneously, the donor’s liver function must be determined. A rapid screening and a serial follow-up of liver enzymes and synthetic functions are indicative of the degree of liver injury and predict the potential for recovery. Routine assessment for diseases, which might be transmitted by the liver graft, must include hepatitis screening as well as the history of use of toxic substances such as long-standing alcohol consumption.

The donor shortage has led to the more frequent use of livers that would have been discarded in the past. The terms *marginal donor* and *expanded criteria donor* have evolved as transplant programs have been forced to utilize suboptimal donors. These include older donors, hepatitis C and hepatitis B core Ab-positive donors, and livers with a moderate amount of steatosis. Although donor age has been shown to have an adverse impact on outcome, most programs now consider the use of donors up to 75 years of age. This approach has been necessary because of the desperate need for lifesaving organs and is supported by scientific evidence of a relatively slow aging process occurring within the liver parenchyma. It appears that grafts from donors with serologies positive for a pathogen present in the recipient (i.e., hepatitis B or C) can be utilized with results equal to those of transplantation with uninfected grafts as long as the liver does not have established severe hepatitis or fibrosis. Severe steatosis in liver grafts is associated with a high degree of primary nonfunction, but acceptable results can be obtained if steatosis is mild to moderate (10% to 30%). Whenever a marginal graft is used, controllable variables, such as cold ischemic time, should be kept to a minimum.

Donor and recipient matching are based on ABO blood group compatibility and size. However, these barriers may be crossed when transplantation is urgent. Most surgeons try to match donor-recipient age for pediatric recipients, because variation may have an impact on long-term graft survival.

**Donor Operation**

Liver procurement is almost always part of a multi-team approach aiming to maximize the number of transplantable organs that can be recovered from a single donor. A midline incision extending from the suprasternal notch to the symphysis pubis allows access to thoracic and abdominal organs. The round ligament is ligated and divided, the falciform ligament is incised, and the left lateral segment is freed from the diaphragm. Inspection of the gastrohepatic ligament will reveal a replaced left hepatic artery. Medial reflection of the right colon and small bowel allows the exposure of the infr-hepatic vena cava and renal veins, control of the distal aorta, and identification of the inferior mesenteric vein. The attention is turned to the hepatoduodenal ligament, where a variable order of dissection is performed with the aim to identify one or more of the structures, including the common hepatic artery, common bile duct, and portal vein. Attention must be directed toward preservation of abnormal and/or accessory arteries to the liver. Technique varies between procurement surgeons, with some preferring to perform the majority of the dissection while the heart is still beating, whereas others first identify basic anatomy and then complete the dissection after cold perfusion. After all teams complete dissection of all organs, the donor is heparinized, followed by perfusion with cold preservation solution via cannulas inserted in the distal aorta and a branch of the portal vein and placement of topical ice. The liver is then removed with the entire length of the celiac artery and/or any other accessory or replaced arteries, a significant length of the portal vein, the common bile duct, and the entire retrohepatic vena cava (Fig. 27-8). Further preparation of the graft before transplantation is done on the bench while the liver is kept immersed in ice. This will usually include removal of the diaphragm and the excess tissue around the blood vessels and, if necessary, reconstruction of replaced hepatic arteries to one common trunk.

The tolerance of liver grafts to extended periods of cold ischemia is directly dependent on the composition of the preservation solution, donor age, the presence of steatosis, and hemodynamic stability before procurement. In theory, preservation in University of Wisconsin solution may extend cold ischemia time up to 24 hours before revascularization. However, most experienced surgeons prefer to minimize the length of cold ischemia to less than 10 hours.
Recipient Operation

The unpredictable nature of organ availability dictates that most liver transplants must be done without extensive preoperative preparation of the recipient. Most patients do not need complete bowel preparation, but they should receive preoperative prophylaxis with antibiotics to cover gram-positive and -negative bacteria. The administration of pretransplant immunosuppression is dictated by the specific immunosuppressive protocol being employed.

Anesthesia management in most cases should begin by preparation for continuous monitoring of arterial blood pressure, pulmonary artery pressure, and cardiac output. Large-bore intravenous cannulas and a rapid infuser may be inserted in anticipation of possible major blood loss. Correction of coagulopathy and replacement of blood loss should be initiated early in the operation before any possible extensive bleeding or the development of significant circulatory compromise.

Orthotopic liver transplantation is a three-step surgical procedure, each step of which presents different unique challenges for the surgeons and anesthesiologists.

Recipient Hepatectomy

The abdominal cavity is entered via a bilateral subcostal incision with a midline extension toward the xiphoid. The round ligament is clamped, divided, and ligated. Exploration of the abdominal cavity is performed, and ascites is removed. The falciform ligament is divided down to the suprahepatic vena cava. Placement of an appropriate mechanical retractor should allow adequate exposure of the liver and its attachments. At this stage, the left lateral segment is separated from the diaphragm and the hepatogastric ligament is divided. The rest of the dissection is done on the hepatoduodenal ligament. The right and left branches of the hepatic artery are then ligated and divided. Similarly, the common bile and cystic ducts are ligated and divided. At this stage, the portal vein is skeletonized. The rest of the dissection includes detachment of the liver from the retroperitoneum (bare area) and exposure of the infrahepatic and suprahepatic vena cava. At this stage, clamps are placed on the portal vein and suprahepatic vena cava and the liver is removed. To keep the blood loss to a minimum, the majority of the dissection is carried out using the electrocautery and hemostasis achieved with the use of the argon beam coagulator.

This standard technique is slightly modified in some centers, specifically with regard to the surgeon’s preference for the use of venovenous bypass. The reduction of venous blood return from the portal system and the infrahepatic inferior vena cava may result in hemodynamic instability and portal venous congestion. This can be avoided by inflow cannulation of the portal and femoral/iliac veins (either by percutaneous or cut-down techniques) and outflow via a cannula in the internal jugular vein, allowing return of more than 2.5 L/min. Additional important advantages of this technique include control of body temperature with the use of a warming circuit and the potential for ultrafiltration using attached filters. Many surgeons do not advocate the routine use of the venovenous bypass, contending that most patients can tolerate clamping the portal vein and that the entire vena cava may be preserved without interrupting blood flow.

Anhepatic Phase

After hemostasis, the retroperitoneum may be reapprroximated to cover the bare area. The suprahepatic vena caval cuff is prepared by opening the orifice of the right, middle, and left hepatic veins and oversewing of the phrenic branches. Transplantation is done by end-to-end anastomosis of the donor’s to the recipient’s suprahepatic vena cava, followed by similar end-to-end anastomosis of the infrahepatic vena cavae. Alternatively, an end-to-side anastomosis of the vena cavae may be utilized in a “piggyback” fashion in which the recipient’s entire vena cava is left intact. The preservation solution is next flushed out with lactated Ringer’s solution, the portal bypass cannula is removed, and portal vein anastomosis is carried out using a continuous suture, utilizing a “growth factor” to prevent stenosis at this anastomosis. The clamps are then released, and the liver is reperfused with portal blood. This part of the procedure is critical and is characterized by varying degrees of “reperfusion syndrome,” which is manifested by hypotension, bradycardia, arrhythmias, and, rarely, cardiac arrest, owing to a sudden influx of cold, hyperkalemic, acidic blood into the heart.

Arterial Revascularization and Biliary Reconstruction

After hemostasis reperfusion, the recipient hepatic artery is freed from surrounding tissue. The preferred method
for reconstruction is an end-to-end anastomosis using an aortic Carrel patch of the donor celiac artery and a branch-patch of the recipient artery at the level of the gastroduodenal bifurcation. This method allows for the creation of a relatively wide anastomosis and minimizes the potential for hepatic artery thrombosis. In most cases, biliary drainage can be achieved using a duct-to-duct anastomosis with or without placement of a T tube. Alternatively, pathology of the bile duct such as in the presence of PSC or biliary atresia requires biliary drainage via a choledochojejunostomy. The completion of this phase is demonstrated in Figure 27–9. After adequate hemostasis, three drains are placed around the liver and the abdominal cavity is closed.

Segmental and Lobar Liver Transplantation

The necessity to maximize the number of liver grafts has led to several surgical innovations, including the transplantation of “split livers” from cadaveric and living donors.[107] These procedures are possible owing to the unique segmental anatomy of the liver and its regenerative capacity. For pediatric recipients, transplantation of left-lateral segments split from cadaveric donors or a living donor has become a standard practice. Especially for very young children for whom cadaveric grafts of the appropriate size are rare, the availability of these options in addition to whole cadaveric grafts has led to significant reduction in waiting time for pediatric patients and a reduction in waiting-list mortality.

Translating this experience to benefit adults awaiting transplantation required development of new approaches. The limitation of segmental liver graft transplantation for larger adult recipients is related to a minimum liver mass necessary for the adequate support of the recipient in the immediate post-transplant period. It is generally accepted that the graft to body weight ratio of more than 1% would allow adequate synthetic function. For this reason, right lobe grafts have recently been favored for live-donor transplantation to adults.[108] The removal of up to 60% of the donor’s liver mass is naturally associated with greater potential for morbidity and mortality than with a left-lateral segmentectomy used for small children. This had led to cautious application of the procedure at experienced centers to target patients who are at risk of waiting-list mortality before a cadaveric donor liver becomes available. Frequent recipients in this group have been patients with hepatocellular carcinoma. Motivated by the ever-increasing number of patients waiting, the increase in living donor liver transplantation has been steady and over 400 such procedures were performed in 2001 (Fig. 27–10).

Recent analysis of recipients of live-donor right lobe grafts documents that a massive amount of regeneration occurs in the first 1 to 2 weeks. Recipients of partial grafts have rapid proliferation of liver mass, with the majority reaching a calculated standard liver volume by 1 month. The donors, however, do not reach their complete starting volume, even by 1 year. This is contrary to what was believed and different from rodent models and remains to be studied in detail in the human setting. It also became apparent that graft size to recipient ratio was critical, in that grafts that were too small had decreased survival. These findings correlated with clinical experience in that small-for-size grafts regenerate to an appropriate size for the recipient; however, there was significant functional impairment of grafts that were less than 50% of expected weight, demonstrated by prolonged cholestasis and histologic changes consistent with ischemic injury. Liver grafts with a graft weight/standard liver volume of less than 40% have poor graft survival and prolonged hyperbilirubinemia.
Removal of a segment from a living donor, or the attempt to split a cadaveric liver for use in two recipients, is a complex procedure that requires precise knowledge of hepatic anatomy of the donor. In the case of the living donor, the surgeon’s primary responsibility is to remove the donated segment without harming the donor. Similarly, splitting a cadaveric liver should be done without compromising either segment. Preoperative assessment of the live or cadaveric donor is similar to that previously described. In addition, it is helpful to use imaging studies in the living donor before surgery, aiming to determine the volume of the donated segment and its vascular supply.

The living donor operation is begun before the recipient hepatectomy and includes isolation of the individual branches of the hepatic artery, portal vein, and bile duct leading to the donated segment. The liver is separated from the vena cava that is left intact, and all small hepatic vein branches are ligated. Further preparation includes isolation of the main hepatic vein that provides the outflow tract. Completion of hepatic division is done via careful parenchymal dissection along the anatomic planes, using finger fracture technique, the harmonic scalpel, or the Cavitron ultrasonic aspirator (CUSA) (Fig. 27-11). It is important to preserve an intact blood flow to the segment until after transection of the hepatic parenchyma, when the vessels are clamped and transected and the segment is flushed with cold preservation solution. To minimize cold ischemia, the recipient operation is started once the donor anatomy is clearly identified to be favorable and the parenchyma is dissected. The diseased liver is then completely removed from the recipient when the donated segment is available for transplantation.

Transplantation of the donated lobe is performed by techniques similar to those developed for whole liver grafts, with a few modifications: The entire length of the recipient vena cava is preserved, and the lobe is transplanted in a “piggyback” fashion. The graft is placed in the usual anatomic position. This allows anastomoses of the portal vein and the hepatic artery without the need for interposition grafts. In most cases, bile duct reconstruction is done using hepaticejejunostomy.

Safety issues are of the highest priority for the living donor. Careful selection of the candidate, combined with fastidious surgical technique should minimize the potential complications. Early data regarding donor morbidity or mortality in the adult-to-adult cases suggest that the procedure can be performed with a high degree of safety. Despite this, donor mortality from the procedure has been reported. In addition, the recipient of these grafts may have an increased risk of postoperative complications such as bleeding or bile leak from the cut surface and potential short- and long-term problems with the biliary-enteric anastomosis. This reinforces the notion that living donor transplantation for adult recipients should be reserved for those who are unlikely to undergo transplant in time with conventional cadaveric transplantation.

Operative Complexities and Complications

Operative Bleeding

Excessive bleeding from portal hypertension may occur during hepatectomy and is likely to be accentuated by coagulopathy or adhesions from previous surgery. The removal of the cirrhotic organ, transplantation of a graft with normal function, and correction of coagulopathy by the appropriate use of platelets and fresh frozen plasma best control bleeding during hepatectomy and after reperfusion.

Thrombosis of the Portal Vein

The dissection may be more complex in the presence of a partially or totally thrombosed portal vein. In most cases, the thrombosed portion extends to the bifurcation of the splenic/superior mesenteric vein confluence, and the thrombus can be removed using endarterectomy techniques while preserving an intact main portal vein. Rarely, a vein graft may need to be placed to the superior mesenteric vein. Complete occlusion of the portal venous system is not an absolute contraindication for transplantation, because the infrahepatic vena cava can be split and anastomosed to the donor portal vein, providing adequate venous flow. At times, a large collateral vein, such as the coronary, may be used for inflow.

Hepatic Arterial Reconstruction

The surgeon is faced with arterial complexities more often than venous abnormalities. Intimal dissection or other pathology of the hepatic artery may necessitate the placement of an allogeneic vascular graft to the recipient’s supraceliac or infrarenal aorta. The potential need for venous or arterial grafts for revascularization mandates that the procuring team always obtains adequate donor blood vessels for potential extension grafts. In addition, any unused blood vessel grafts must be kept refrigerated under sterile conditions for a few days after transplantation in case of emergent need for subsequent vascular reconstruction.

Post-transplant Management

Liver transplant recipients may require a short stay in the ICU after surgery. This period should be used to observe the recovery of the graft and ensure hemodynamic and respiratory stability as well as adequate kidney function. The principles of care are similar to those for other critically ill patients in the ICU setting but are rendered more complex by the necessity for immunosuppressive therapy. Common complications encountered in the early postoperative period are related to the initial graft function, technical misadventures, infections, and rejection. Treatment with anti-rejection drugs may be associated with the expression of several serious side effects such as metabolic encephalopathy, hypertension, and diabetes.

Common Complications

PRIMARY NONFUNCTION

The mechanisms of immediate graft failure after successful revascularization of the transplanted liver are not completely understood but may relate to donor variables, inadequate preservation, prolonged cold ischemia, or the humoral immune response. This problem is encountered in 2% to 5% of liver grafts. It is characterized by clinical and laboratory findings indicating poor synthetic function and severe hepatocytes injury. The recipient may present...
postoperatively with progressive hemodynamic instability, multiorgan system failure, and encephalopathy. Laboratory findings demonstrate worsening acidosis, coagulopathy, and extremely elevated liver enzymes (lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase). The development of primary nonfunction is a surgical emergency and can be successfully treated by early retransplantation. The failure to find a suitable graft within 7 days is associated with high morbidity and mortality. Delayed nonfunction of the graft is characterized by failure of all liver functions, leading to persistent coagulopathy and progressive hyperbilirubinemia. Under these circumstances vital organs fail and/or infection ensues, in most cases rapidly leading to death from bacterial or fungal sepsis.

**INTRA-ABDOMINAL BLEEDING**

The persistence of immediate post-transplant coagulopathy, fibrinolysis, and the presence of multiple vascular anastomoses places these patients at high risk for postoperative bleeding. However, coagulopathy spontaneously corrects itself in the presence of recovering liver graft function and with infusion of platelets. A persistent drop in hemoglobin and the need for transfusion of more than 6 units of packed red blood cells are usually indications for re-exploration and evacuation of the hematoma. In most cases, removal of the clot will be sufficient to arrest further fibrinolysis and will stop bleeding. Occasionally, it will be necessary to repair bleeding sites.

**VASCULAR THROMBOSIS**

Vascular complications after liver transplantation are more common in the pediatric population and are directly related to the small size of the vessels that are used for reconstruction. The most frequent complication is the occurrence of hepatic artery thrombosis. The pathology can present as rapid or indolent worsening of graft function or as necrosis of the bile duct and dehiscence of the biliary enteric anastomosis. Early recognition and successful thrombectomy may salvage the graft. However, deteriorating liver function and bile duct necrosis indicate the need for immediate retransplantation.

**BILIARY LEAK**

Reconstruction of the biliary system with either duct-to-duct anastomosis or choledochojjunostomy may be complicated with a bile leak, usually secondary to technical error or ischemia of the donor duct. Early leaks can be diagnosed by the appearance of bile in the drains and are confirmed by a T-tube cholangiogram or HIDA scan. Surgical exploration and revision of the anastomosis are mandatory and will solve the problem in most cases. Ischemic bile duct injury secondary to early hepatic artery thrombosis is an indication for retransplantation.

**INFECTIONS**

Infections remain the most significant complications in liver transplantation and are responsible for most of mortalities in the early postoperative period. There seems to be a direct correlation between the preoperative status of the recipient, the pattern of recovery after transplantation, and the incidence of bacterial and fungal infections. The probability for the development of such complications is the highest among patients who await a transplant in an ICU. These are chronically ill and malnourished patients who are usually susceptible to resistant hospital flora before surgery and then are placed at further risk of infection by high-dose immunosuppression after the procedure. The development of organ system failure or graft malfunction further contributes to the morbid outcome. The spectrum of infection is evolving to more common occurrences of infections by resistant gram-positive bacteria (enterococci and staphylococci) rather than those caused by gram-negative bacteria. The deliberate use of broad-spectrum antibiotics in the immunosuppressed patient contributes in part to the development of systemic fungal infection (Candida, Aspergillus). It is wise to begin antibiotic therapy for common bacteria as soon as a patient’s clinical status suggests the presence of infection. The treatment can then be modified when and if results of culture and sensitivity studies dictate a change.

**Immunologic Aspects of Liver Transplantation**

The relatively low immunogenicity of liver allografts and the unique ability of the liver to regenerate are probably the main reasons for the excellent long-term outcome. Good results are achieved when graft and recipient are ABO blood group compatible. Preoperative human leukocyte antigen (HLA) matching does not appear to be necessary. Most recipients are treated with combination therapy, which includes a calcineurin inhibitor (cyclosporine or tacrolimus), along with prednisone, with or without azathioprine or mycophenolate mofetil. The protocols are adjusted for a rapid taper of the calcineurin inhibitors, as well as the withdrawal of corticosteroids beginning 3 to 6 months after surgery as a result of immunosuppression. Donors that are mismatched at an HLA antigen are associated with the development of chronic rejection.

**Acute Rejection**

T-cell–mediated acute rejection is seen at a rate of 30% to 50% within the first 6 months after transplantation, most often within the first 10 days. Its clinical presentation is variable and may include the development of fever, abdominal pain, elevated liver enzymes, and bilirubin. Patients with a T tube may manifest a decrease in quantity and change in character of the bile. The diagnosis is confirmed by a liver biopsy that will demonstrate the presence of periportal lymphocytic infiltrate that extends into the liver parenchyma, as well as the invasion of inflammatory cells into the vascular endothelium. Most rejection episodes are responsive to the administration of high-dose corticosteroids. More potent monoclonal or polyclonal anti–T-cell antibodies are effective against corticosteroid-resistant rejection, leading to the reversal of the acute episode in more than 90% of the recipients. Rejection seems to be less responsive if an acute episode occurs long after transplant and/or in the case of chronic rejection.

**Chronic Rejection**

This type of rejection is seen months to years after transplantation. It is manifested by poor synthetic liver function and hyperbilirubinemia. It is usually characterized histologically by paucity of the bile ducts, thus often described as “vanishing bile duct syndrome.” The etiology for this phenomenon is not well understood and may be related to a humoral reaction involving antibodies and fibrogenic cytokines. The treatment of chronic rejection is limited, and some of these patients may be considered as candidates for retransplantation.

**Recurrent Disease**

Replacement of the liver may not permanently cure recipients of their original disease. Recurrence of viral hepatitis is likely within a short time after transplantation in infected recipients. Control of active hepatitis B infection is possible in most patients using lamivudine, which inhibits the virus DNA polymerase, as well as hepatitis B immunoglobulin. In contrast, interferon alfa and/or ribavirin are less effective in hepatitis C infection. Reinfection of the liver graft may be mild and in many cases will not result in liver failure. Re-transplantation for recurrent hepatitis B or C remains controversial. The obvious recurrence of viral hepatitis contrasts to reports describing the pattern of early pathologic findings seen in patients transplanted for PBC and PSC. The significance of these findings is not clear, because it rarely results in liver failure necessitating retransplantation.

Most liver transplant recipients who survive the immediate post-transplant period enjoy full functional recovery. However, restoration of a fully
functional status depends on the patient’s preoperative condition, an appropriate support system, and his or her attitude to rehabilitation.

**Long-Term Results**

UNOS registry data on nearly 30,000 liver transplants demonstrate impressive long-term survival. At 10 years, patient and graft survival for adults is 59% and 51%, respectively. The results in children are even better, with 78% of patients and 63% of grafts surviving at 10 years (Fig. 27–12).

**Figure 27-12** Survival curves: patient percentage survival (PS) and graft survival (GS) of primary liver transplants in over 4000 pediatric and 8000 adult patients.

Morbidity and mortality after orthotopic liver transplantation is directly correlated with the recipient preoperative status and the immediate function of the liver allograft. A higher mortality has been reported for recipients whose UNOS status was categorized as urgent and those who had multiorgan system failure (see Fig. 27–10). Other variables associated with decreased survival include older age group, ventilator dependency, the need for dialysis, and retransplantation. Controversy exists whether scarce livers should be utilized under these circumstances, because there would be greater chance of their long-term function in patients less seriously ill. However, the rationale for continuing to offer the procedure to these high-risk patients is based on their inability to survive if a transplant is not performed.

Overall, long-term survival after liver transplantation is excellent; however, recipients may suffer from significant side effects of the immunosuppressive drugs. Physical and psychosocial growth may be inhibited in the pediatric group. In contrast, most adults will experience an average gain in weight of 15 to 20 lb. Recognized outcomes of corticosteroid and calcineurin inhibitors include osteoporosis, hypertension, hyperglycemia, and hyperlipidemia. Recipients have an increased incidence of malignancies, particularly in the form of post-transplant lymphoproliferative disease, an entity resembling lymphoma. This condition can often be resolved by reduction or complete withdrawal of corticosteroids and significant reduction in the cyclosporine or tacrolimus. However, attempts to stop all immunosuppression usually results in the development of acute and/or chronic rejection.
The purpose of pancreas transplantation is normalization of the diabetic recipient’s blood glucose, thus preventing eventual microvascular complications, a goal unlikely to be possible with exogenous insulin therapy. The outcome of pancreas transplantation in the 1960s and 1970s was far inferior to that with other organs (frequent fatalities and less than 20% graft survival). However, owing to improvements in surgical technique and immunosuppression, the results of the procedure have progressively improved to the level of other transplants. The usual candidates for pancreas transplants are patients with diabetic nephropathy who are obligated to chronic immunosuppression to prevent rejection of a kidney allograft. Ironically, those diabetics who have no renal or other complications of their disease would be the ones most likely to benefit from the procedure because if it were carried out at that stage it would be likely to prevent microvascular complications. However, most diabetologists have been reluctant to recommend pancreatic transplantation in nonuremic diabetics because it would obligate them to chronic immunosuppression.

Indications for Pancreas Transplantation and Patient Selection

Because insulin is effective therapy for most diabetics (except for its failure to prevent eventual microvascular complications), pancreas transplantation is not considered a lifesaving procedure unless the patient is experiencing episodes of severe hypoglycemic unawareness. Thus, in considering pancreas transplantation, the requisite dangers of a major operation and lifelong immunosuppression must be balanced against the possible benefits. The evidence is now convincing that optimizing exogenous insulin therapy favorably influences microvascular complications. That successful pancreas transplantation would also do so is based on softer evidence, although the assumption seems quite safe that the even better control of hyperglycemia associated with this method would provide optimal protection from complications. Microvascular sequelae, such as ocular, neurologic, and renal disabilities, will eventually occur in over 50% of diabetics on insulin therapy. Thus, the possibility of achieving glucose homeostasis by pancreas transplantation and avoiding microvascular complications is very attractive to patients, including many with advanced complications in whom objective analysis of the risks and benefits does not support its use. It is important for patients to understand that advanced complications (e.g., blindness, pregangrenous extremities, end-stage nephropathy) will not be reversed. Transplant surgeons are in the best position to understand the risks and benefits and, along with their diabetologist colleagues, should serve as the patients’ advisors and advocates in considering transplantation. Because of the poor results of transplantation in the precyclosporine era, most clinicians then considered the risk unacceptable. Even now that success is more common, only a relatively small proportion of the world’s many diabetics are appropriate candidates for pancreatic transplantation. In most centers, the procedure is usually employed only in patients who require immunosuppression for a kidney transplant necessitated by diabetic nephropathy.

Because of the prevalence in diabetics of microvascular disease, especially in the coronary arteries, evaluating the risks of major surgery is especially important. Indeed, one of the most common causes of pancreas transplant failure is death from myocardial infarction. Therefore, if substantial coronary artery disease is identified, it may need to be corrected before transplantation is undertaken.

Uremic Type I diabetics who are candidates for cadaver donor kidney transplants are the most usual patients to be considered for pancreas transplantation, which is most often carried out simultaneously with the kidney transplant. Also appropriate for pancreas transplantation are diabetics who harbor a previously transplanted functioning kidney allograft because they are already committed to immunosuppression. In nonuremic diabetics who either do not need a kidney transplant or have not previously had one, the indications for pancreas transplantation are controversial. However, extremely labile diabetics who are at substantial risk from repeated episodes of dangerous hypoglycemia should be considered for transplantation even if they are not uremic.

In patients with seemingly early diabetic nephropathy, macroalbuminemia or microalbuminuria indicates that significant renal disease exists and that it will eventually progress to end stage, if they remain diabetic. In these cases, it seems likely that progression of nephropathy could be halted, or at least slowed, by a successful pancreas transplant, although actual evidence for this is scarce because the procedure has been uncommon in this early stage. Between 1988 and 2000, 10,562 pancreas transplants were performed: 83% of these were simultaneous pancreas-kidney transplants, 12% pancreas after kidney, and only 5% pancreas alone transplants. In other parts of the world, 93% of pancreas transplants were performed simultaneously with a kidney transplant.

Donor Selection and Management

Selection of acceptable cadaveric donors of pancreas allografts is based on the standard criteria, avoiding donors who are aged, infected, hemodynamically unstable, or afflicted with malignancies. Hyperglycemia occurring after brain death is not necessarily a deterrent because this finding may be the result of an insulin-resistant state that often develops after head trauma. Serum amylase levels are not particularly helpful in evaluating prospective donors. Inspection of the pancreas by an experienced observer at the time of organ recovery is probably the best indicator of whether the pancreas is suitable for transplantation. The outcome of the transplant also appears to be strongly influenced by the care and expertise with which the donor operation is conducted.

The Donor Operation

Whenever possible, multiorgan en bloc excision is performed so that several transplantable organs can be obtained from the same donor. Through a midline abdominal incision (extending from the midline thoracic incision usually present for removal of the heart or lungs), the abdominal viscera are inspected. The blood supply to the liver is evaluated because anomalies in its arterial circulation sometimes prevent utilization of both the pancreas and the liver. If both organs cannot be safely used, priority must be granted to the liver because it is a lifesaving organ.

Once the decision is made that both pancreas and liver can be recovered, the gastrectocolic ligament is divided, exposing the anterior surface of the pancreas. The transverse colon is mobilized, allowing the pancreas to be freed from the surrounding retroperitoneal tissues. The short gastric vessels are ligated and divided. The left gastric vessels are ligated and divided near the stomach, to preserve the blood supply to the liver via the celiac axis. After a povidine-iodine/amphotericin/antibiotic solution is instilled into the duodenal segment through a nasogastric tube, the duodenum is divided just distal to the pylorus.

Division of the lienophrenic ligament allows the mobilization of the pancreaticoduodenal allograft. The pancreas is freed from its posterior attachments to the left kidney and the left adrenal gland. The spleen is left in continuity with the pancreas to serve as a handle to minimize manipulation of the pancreas. The celiac axis, superior mesenteric, and splenic arteries are dissected from the surrounding lymphatic tissue and celiac ganglion. The infrahepatic inferior vena cava is exposed above the renal veins to facilitate dividing the inferior vena cava after the in situ irrigation of the donor organs.
with a cooled preservation solution. If both liver and pancreas are to be used, the gastroduodenal artery is ligated and divided. If only the pancreas is to be transplanted, this artery is left intact. The common bile duct is ligated and divided close to the pancreas. Through an opening in the gallbladder, the biliary ducts are irrigated with normal saline solution until clear of bile. A Kocher maneuver is performed to mobilize the head of the pancreas. The hepatic artery is freed from the surrounding lymphatics, and the proximal 1 to 2 cm of the splenic artery is dissected to complete exposure of the portal triad structures.

The donor is then systemically heparinized. The jejunum at the level of the ligament of Treitz is divided with a GIA stapler. The abdominal aorta is ligated at its bifurcation and cannulated for perfusion. The supraceliac aorta is then clamped and the portal vein divided about 1 cm cephalad to the superior margin of the pancreas. An in situ arterial flush with cooled UW solution at 4°C is begun, and the suprahepatic vena cava is divided. The liver can also be flushed through the open end of the portal vein (Fig. 27–13). Topical cooling of the liver and pancreas is also employed. If the liver and pancreas are procured en bloc, the portal vein is not divided in situ and the portal circulation can be flushed through the inferior mesenteric vein.

The pancreas and the liver can be separated in situ or ex vivo. If the liver is to be used, the celiac axis is usually left in continuity with the hepatic artery. The splenic artery is divided about 0.5 cm beyond its origin from the celiac trunk. The mesentery of the small intestine, which courses through the parenchyma of the pancreas, is divided inferior to the pancreas either by individual ligature of the mesenteric vessels or en mass occlusion by a TA90 stapler. This completes the pancreas dissection. Long segments of the common, internal, and external iliac arteries and veins are also removed to use as vascular extension grafts if necessary.

**Ex Vivo Preparation of the Donor Pancreas for Transplantation**

The pancreaticoduodenal graft is submerged in a basin of cold UW solution for further preparation. The splenic hilar vessels are ligated and the spleen removed, avoiding injury to the tail of the pancreas. About 5 cm of duodenum beyond the ampulla of Vater should be retained with the graft. It is important to be sure that the proximal duodenum was divided distal to the pylorus and that no gastric mucosa is transplanted with the graft. If the mesenteric axis was divided with staples, the staple line is reinforced with a running suture. Commonly, an arterial extension Y graft is used to facilitate the transplant operation so that only one arterial anastomosis will be required in the recipient. The external iliac artery of the extension graft is anastomosed to the superior mesenteric artery of the pancreas graft, and the internal iliac artery of the extension graft is anastomosed to the stump of the splenic artery of the pancreas graft (Fig. 27–14). If there is sufficient length on both arteries, the splenic artery of the pancreas graft can be anastomosed end-to-side to the superior mesenteric artery. If the donor liver was not procured or if the liver team allowed the celiac axis to remain with the pancreas graft, a patch of aorta, including the origins of the celiac axis and the superior mesenteric artery, is available for anastomosis directly to the recipient’s vessels. An extension of the portal vein can be fashioned utilizing the external iliac vein of the donor, but this is rarely necessary and may be associated with increased risk of thrombosis of the portal vein.

**The Recipient Operation**

Although segmental grafts (consisting of only the pancreatic body and tail) were once common, the entire pancreas and its associated duodenal segment are now almost always transplanted (unless a living donor is used). Ligation or obliteration of the pancreatic duct was also once commonly practiced, but these techniques have also been abandoned. Instead, the pancreatic exocrine secretions are drained internally into either the small intestine or the bladder. Until recently, most centers employed only the bladder drainage technique, but since the late 1990s, enteric drainage has become the

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**Figure 27-13** The pancreas and liver have been removed en bloc from a cadaveric donor. The portal vein, inferior vena cava, and aorta have been divided and cannulated for infusion of cold preservation solution.

**Figure 27-14** The pancreas has been separated from the liver and is ready for further ex vivo dissection on the back table while immersed in cold solution. The spleen will be removed and the distal duodenum shortened. The superior mesenteric and splenic arteries will be anastomosed to a Y-shaped extension graft of the donor’s common, internal, and iliac arteries so that only a single arterial anastomosis will be needed in the recipient. The portal vein can be extended utilizing the external iliac vein of the donor, but this is rarely necessary and may be associated with increased risk of thrombosis of the portal vein.
most common method in simultaneous kidney-pancreas grafts. The kidney and the pancreas grafts can both be placed within the peritoneal cavity through a midline incision. However, we have sometimes utilized two lateral incisions because they provide easier access to the iliac vessels and allow the kidney to be transplanted to its usual extraperitoneal location more easily. To avoid the consequences of fluid collection around the pancreas, the pancreas graft is placed intraperitoneally.

If a combined kidney-pancreas transplant is done, the pancreas is usually transplanted first to minimize ischemia time for the pancreas. However, if two teams are operating, the kidney can be transplanted while the pancreas is prepared for transplantation on a separate back table.

The external iliac arteries and veins are mobilized, preferably on the right side. The anatomic relationship of the vessels, as well as the presence of the colon, makes placement of a pancreas graft on the left more difficult, possibly resulting in a higher incidence of vascular thrombosis. Some surgeons advocate systemic heparinization, although others believe that this is not necessary in uraemic recipients, whose clotting mechanisms are impaired. The arterial anastomosis is performed end to side to the external iliac artery, using either the aortic patch (containing the ostia of the celiac axis and superior mesenteric artery) or the common iliac artery portion of the Y-graft extension or the superior mesenteric if the splenic artery was anastomosed to it. The portal vein of the graft is anastomosed to the side of the external iliac vein of the recipient. A venous interposition graft is rarely needed and may increase the chance of thrombosis. The venous anastomosis is facilitated by complete mobilization of the common and external iliac veins with ligation of all venous branches; alternatively, the graft can be implanted to the aorta and vena cava and oriented with the head facing cephalad. The later orientation may facilitate enteric drainage. Alternatively, portal venous drainage is accomplished by anastomosing the portal vein of the pancreas allograft to branches of the superior mesenteric vein.

For bladder drainage of pancreaticoduodenal secretions, a horizontal cystotomy is made on the posterolateral aspect of the bladder and a two-layer anastomosis is constructed between the bladder and the duodenum (Fig. 27-15 A). Absorbable sutures are used for the inner layer to avoid leaving a nidus for stone formation. If enteric drainage is chosen, this can be performed as a simple side-to-side anastomosis of the donor duodenal segment to a convenient loop of small bowel or to a roux-en-Y loop (see Fig. 27-15 B). Because the procedure involves opening the intestine, the wound is irrigated with antibacterial and antifungal agents. Drains are generally unnecessary. A Foley catheter is left in the bladder for 5 to 7 days.

An additional technical factor of possible importance is whether venous drainage should be systemic (via the iliac vein) or by the portal system. Portal venous drainage prevents the hyperinsulinemia resulting from systemic venous drainage but whether normal serum insulin and the somewhat more physiologic lipoprotein profile seen in patients with portal vein drained grafts have meaningful benefits is uncertain. In view of the well-documented but subtle immunologic advantage of portal vein drainage of allografts in rodent models, it is intriguing that in a larger retrospective study at the University of Maryland portal vein–drained pancreas grafts had fewer acute rejection episodes and better survival than those systemically drained. Interest in these findings resulted in 22% of all U.S. pancreas transplants between 1997 and 2000 being performed with portal drainage. However, the 1-year survival of these grafts was the same as for those with systemic venous drainage.

**Biologic Factors Influencing the Outcome of Pancreas Transplantation**

**Histocompatibility Matching**

That donor-recipient histocompatibility is advantageous for pancreas transplants has been shown by the somewhat superior outcome of the 142 living related donor pancreas transplants that had been reported as of October 2001 compared with cadaveric pancreas grafts. Despite this immunologic advantage of related donors, they have been used in only 0.8% of pancreas transplants because of the potential risks to the donor. These risks include not only morbidity of the operation itself but also the possibility of impairing the donor’s glucose metabolism. In addition, there is a theoretical concern that a pancreas transplant from an HLA-matched related donor may be subject to increased susceptibility for the development of recurrent autoimmune diabetes in the graft, a risk analogous to that for development of recurrent autoimmune glomerulonephritis in kidney transplants from identical twin or HLA-identical sibling donors.

Most of the information regarding living donor transplants comes from the University of Minnesota, where 120 such transplants have been done, constituting 8.5% of that institution’s pancreas transplants. The graft survival of living donor transplants was 6% to 11% better at 1 year than that of cadaveric transplants done at the same institution.

For cadaveric transplants, the advantage of matching is subtle. Analysis of the results from 1997 to 2001 indicated no benefit of HLA matching for simultaneous pancreas kidney grafts, although with the pancreas after kidney and the pancreas alone transplants there was slightly better survival for HLA-A and HLA-B matching but surprisingly not for the HLA-DR matching.

**Immunosuppression**

The immunosuppressive therapy used for pancreas transplant recipients is very similar to that employed for other solid organ transplants. Between 1983 and 1994, cyclosporine, in combination with azathioprine and prednisone, was employed in most centers. Between 1997 and 2000, 80% of recipients were treated with tacrolimus and MMF, instead of azathioprine and cyclosporine. More recently, sirolimus has been used in some patients. Most centers also continue to employ corticosteroids, although because of their known diabetogenic effect some groups

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**Figure 27-15** A, The extension Y graft has been anastomosed to the recipient’s iliac artery and the portal vein of the graft to the iliac vein. The donor duodenum is anastomosed to the

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have tried to withdraw them. Anti–T-cell antibodies are also commonly used for induction immunosuppression because of the prevalence of early rejection and the difficulty of diagnosing it.

An interesting new immunosuppressive strategy being employed in pancreas transplantation at several centers is the administration of donor bone marrow cells. Stimulated by Starzl’s emphasis on the role of microchimerism in the long-term success of some allografts, several groups inoculate donor bone marrow cells to recipients of pancreas transplants to augment the chimerism normally caused by migration of passenger leukocytes from the transplant. Although the Pittsburgh group did not find that bone marrow augmentation improved the 1-year graft survival they obtained without it (83%), they succeeded in maintaining graft survival after discontinuing corticosteroid therapy in two thirds of their bone marrow–treated patients, suggesting to them that a tolerant state may have been promoted by this treatment.[125

**Rejection**

**Prevalence and Severity**

Whether human vascularized pancreatic allografts are more or less vulnerable to rejection than vascularized allografts of other organs is a difficult question, especially because the pancreas is a composite organ with distinct exocrine and endocrine components, which may not be equally subject to rejection. Rejection of a kidney and pancreas transplanted simultaneously from the same donor is often manifested at the same time. However, either organ may undergo earlier or more severe rejection. In patients who receive pancreas and kidney transplants, rejection episodes tend to be more frequent than in those receiving only a kidney. Yet pancreatic graft loss from rejection is more frequent if the pancreas alone is transplanted than if both kidney and pancreas are transplanted.[126

**Diagnosis of Rejection**

The early diagnosis of pancreatic allograft rejection is particularly important because physiologic evidence of islet damage (hyperglycemia) is a late indicator of rejection. Once islet damage is advanced, it is often difficult or impossible to reverse it by intensifying immunosuppression. The importance of identifying early rejection has led to exploration of a number of methods, such as imaging techniques and blood and urine tests. None of these has proved to be very reliable. Thus, in the effort to recognize early rejection, a combination of nonspecific indicators is utilized. These include increases in serum amylase, lipase, and anodal trypsinogen; decreases in urinary amylase (in the case of bladder-drained allografts); impaired function of a concomitantly transplanted kidney allograft; biopsy of the kidney or pancreas allograft; and, finally, hyperglycemia.

Particularly useful in patients receiving a simultaneous kidney–pancreas transplant is careful monitoring of kidney function. Because increased serum creatinine level is a sensitive indicator of kidney rejection, an increase in this value often takes place before manifestations of pancreas damage occur. Patients with pancreas-alone transplants lack the diagnostic advantage of monitoring function of a concomitantly kidney transplant. In these patients, if bladder drainage of the pancreatic secretions was employed, decreased urinary amylase values are the best index of rejection. In patients with enteric drainage, and without a concomitant kidney transplant, the diagnosis of rejection must rely on serum amylase value, biopsy, and hyperglycemia (a late sign).

Histologic evidence of rejection is, of course, the most definitive indicator of rejection. Biopsy of the concomitantly transplanted kidney or the duodenum associated with the pancreas may be helpful, but most specific of all is a biopsy of the pancreatic allograft itself[127 which can be obtained by ultrasound-guided transcannulate or transcystoscopic techniques. If necessary, open biopsies can also be performed safely.

**Treatment of Rejection Episodes**

Although early initiation of antirejection therapy is more important in pancreas than in kidney transplantation, the treatment of rejection episodes is similar to that utilized for kidney allograft rejection, high-dose corticosteroids and anti–T-cell antibodies. Early rejection episodes can usually be reversed, but if extensive islet damage is allowed to occur there is much less chance of rescue than in the case of kidney or liver transplants. Because corticosteroids, cyclosporine, tacrolimus, and OKT3 all have a propensity for islet damage, increasing antirejection or heavy-maintenance immunosuppression should be avoided if possible. In this regard, Laftavi and coworkers found that utilization of biopsy in cases of questionable rejection avoided needless antirejection treatment in 44% of patients.[128

**Autoimmune Recurrence**

In addition to rejection, an immunologic threat to pancreas transplants is the autoimmune response to islets, which was responsible for elimination of the native pancreatic beta cells. In the case of kidney transplants, an analogous vulnerability of transplanted kidneys was noted in the early 1960s when patients with glomerulonephritis were found to be subject to autoimmune damage of the transplanted kidney even if rejection was avoided by using an identical twin donor.

In 1979, we first examined whether autoimmunity alone would destroy transplanted pancreatic islets. To study this question, we used an experimental model, in which the autoimmune response to transplanted islets could be examined independently of allograft rejection. BB rats (a strain that spontaneously develops autoimmune diabetes in adulthood) were rendered tolerant to allografts from the prospective normal islet donors by neonatal inoculation with donor strain bone marrow. Because specific tolerance was confirmed by permanent acceptance of donor strain skin allografts, donor strain islets were exempt from rejection. Although in these tolerant recipients islet transplantation reversed diabetes, hyperglycemia recurred rapidly, indicating that transplanted islets are susceptible to destruction by autoimmunity.

Several years after this demonstration that in animals recurrent autoimmunity could rapidly destroy transplanted islets in the absence of allogeneic rejection, it was found in humans that an analogous process could damage the islets of whole-organ pancreatic grafts transplanted from identical twin donors. However, in these patients islet destruction occurred only after many weeks. This suggested that a vascularized pancreas graft might differ in its immunologic vulnerability from that of isolated islets, a question we also studied in immunologically tolerant BB rat recipients. Whereas isolated islet grafts were routinely destroyed by autoimmunity within a few days, only a minority of whole-organ recipients became diabetic within 100 days, indicating that recurrent autoimmunity, although a substantial threat to isolated islet transplants, might be easy to overcome with immunosuppression in the case of vascularized pancreas.
A unique experience at the University of Minnesota with identical twin donor pancreas transplants provides definitive information on this issue. Seven technically successful identical twin segmental pancreas transplants have been done there. The first three recipients were transplanted before the risks of recurrent disease were recognized. They received no immunosuppression. Biopsy-proven recurrent disease took place in 1 to 4 months. The fourth patient received only azathioprine and suffered recurrence at 5 years post transplant. The last three twins transplanted between 1987 and 1990 received induction and cyclosporine-based maintenance immunosuppression. Two remained normoglycemic for more than 10 years. One who received only low-dose immunosuppression experienced recurrence at 4 years and graft failure at 8 years. This experience confirms the autoimmune etiology of diabetes and indicates that low dose immunosuppression cannot prevent recurrence in twin transplants.

Recurrence of autoimmune diabetes with selective beta cell destruction has also been observed in pancreas transplants from living related HLA-identical donors. Until recently, it was thought that it would be unlikely to occur in HLA-mismatched cadaveric transplants, either because the disease was major histocompatibility complex restricted or because the more intensive immunosuppression routinely utilized to prevent rejection of mismatched allografts would easily prevent autoimmune islet damage. Recently, however, in several recipients of cadaveric pancreas transplants, failures have been reported in which histologic evidence indicates that autoimmunity, rather than rejection, was the cause. The transplanted pancreas in these patients exhibited selective destruction of beta cells with preservation of alpha and delta cells, a pattern characteristic of patients with insulin-dependent diabetes.

Complications of Pancreas Transplantation

Pancreas transplant patients are susceptible to the complications common to all immunosuppressed patients (e.g., infection, malignancy, corticosteroid-induced osteonecrosis). In addition, they are subject to several nonimmunologic complications specific to this type of transplant.

**Vascular Thrombosis**

The most common nonimmunologic cause of pancreas allograft failure is vascular thrombosis. This complication is most frequent during the first 7 days. It almost always results in loss of the graft and is responsible for about 70% of technical failures. The reported incidence of this complication varies from 10% to 30%. Its etiology appears to be the relatively sluggish blood flow to the pancreas, estimated as only 1% of cardiac output, compared with the rapid blood flow through kidney, heart, or liver transplants. Risk factors were analyzed in a large experience (438 patients) at the University of Minnesota. They were at various times most of the technical variations have been evaluated with regard to duct management, vascular reconstruction, and segmental versus whole-organ transplants. Their overall thrombosis rate was 12% (5% arterial, 7% venous). There were no instances of obvious technical problems such as faulty vascular anastomoses. Thromboses did not appear to be caused by mechanical obstruction of the major vessels of the allograft but instead by abnormalities or changes in the microcirculation of the pancreas. Therefore, it is not surprising that strategies devised to increase blood flow in the major vessels (e.g., arteriovenous fistulas) have failed to decrease the incidence of thrombosis. Other findings of the Minnesota study were that the risk of thrombosis was highest in pancreas after kidney transplant patients (20%). Segmental grafts also had a propensity for thrombosis. Other risk factors identified were advanced donor age, cardiocerebral cause of donor death, prolonged preservation time (greater than 30 hours), the use of donor artery reconstructions other than Y-extension grafts, portal vein extension grafts, allograft pancreatitis, and transplantation of the pancreas graft to the left rather than the right iliac vessels. Although some centers advocate the use of anticoagulants, this remains of unproven benefit and, at least for the former, is associated with bleeding complications in the perioperative period.

**Allograft Pancreatitis**

Allograft pancreatitis in the early post-transplant period occurs in 10% to 20% of recipients. Predisposing factors are donor abnormalities (hemodynamic instability, vasopressor administration), procurement injury, perfusion injury (excessive pressure or volume), ischemic damage during preservation, and reperfusion injury. In severe pancreatitis, compromised pancreatic microcirculation causes necrosis and then arterial thrombosis. Mild edematous pancreatitis may be obvious at the time of allograft revascularization, but the diagnosis of significant pancreatitis and determination of its severity and progression are difficult. Serum amylase levels may not accurately reflect the degree of pancreatitis. Allograft pancreatitis may be difficult to differentiate from rejection or other complications.

such as extravasation of pancreatic juice, urine, or enteric contents. All of these can present as abdominal pain and tenderness, leukocytosis, hyperamylasemia, and computed tomographic abnormalities demonstrating graft edema. Unlike major leaks, however, graft pancreatitis should be treated nonsurgically, with Foley catheter drainage for bladder-drained grafts and, perhaps, with octreotide.

**Fistula and Abscess**

Extravasation of pancreatic juice from the pancreatic anastomosis is a more serious complication in enteric-drained than in bladder-drained allografts. During an era of more dangerous immunosuppression, this accounted for a substantial difference in survival from the two methods between 1987 and 1992 (for bladder-drained pancreas transplants, survival was 75% compared with only 54% for those enterically drained). However, as immunosuppression and patient management have improved, this difference has become minimal and from 1997 to 2001 in enteric-drained grafts the 1-year survival was 82% versus 85% in bladder-drained grafts. At least in the short term, bladder drainage may still be the safer procedure for several reasons. First, extravasation of succus entericus is much more serious than leakage of urine, not only because of microbial contamination but also because it activates pancreatic proenzymes. Second, minor leaks from bladder-drained pancreata can usually be controlled with Foley catheter drainage until they heal. However, there is unlikely to be an alternative to operative therapy for a leaking duodenenterostomy. In addition, enteric leakage is often difficult to diagnose and differentiate from pancreatitis, whereas in bladder drainage the problem can usually be visualized on cystogram. In leaks occurring within the first month, leakage is usually from one of the anastomoses. Later leaks may also occur at suture lines, but perforated ulcers in the duodenal pouch are another source of leakage because of ischemia, rejection, or CMV infection.

Leakage in bladder-drained patients causes abdominal pain and tenderness, ileus, leukocytosis, elevated amylase and lipase levels, and computed tomographic abnormalities. A normal serum amylase value essentially rules out a leak in bladder-drained patients unless a Foley catheter is in place. In leaks occurring within the first month, leakage is usually from one of the anastomoses. Later leaks may also occur at suture lines, but perforated ulcers in the duodenal pouch are another source of leakage because of ischemia, rejection, or CMV infection.

**Urologic Complications**

Urologic complications, such as urethritis, urethral disruption, hematuria, and recurrent urinary tract infections, are quite common in bladder-drained recipients. These problems, and bicarbonate losses, are the major disadvantages of this technique. Urethritis often resolves after a period of Foley catheter drainage, but, if not, enteric conversion is required to prevent scarring or disruption of the urethra. Hematuria may sometimes respond to simple bladder irrigation. If it persists, fulguration of the bleeding site may be effective; if not, enteric conversion is necessary.

**Results of Pancreas Transplantation**

During an era of more dangerous immunosuppression, this accounted for a substantial difference in survival from the two methods between 1987 and 1990.
Impact on Metabolic Defects of Diabetes

Successful pancreatic transplantation restores normoglycemia and normal levels of hemoglobin A1c. The response to glucose challenge and to intravenous arginine and secretin is also normalized. The counter-regulation of glucose, which occurs in instances of insulin-induced hypoglycemia, is also improved by pancreatic transplantation. Although recipients of successful pancreatic transplants may occasionally experience hypoglycemia, this is not nearly as severe or dangerous as it is in insulin-treated diabetics.

Successful recipients exhibit hyperinsulinemia owing to the systemic venous drainage of the allograft and insulin resistance caused by corticosteroid therapy. These abnormalities cause no symptoms. Their long-term significance is unknown, although hyperinsulinemia can elevate triglyceride levels, which could accelerate atherosclerosis. However, pancreas transplantation generally has a beneficial impact on the abnormal lipid profiles of diabetics. Although systemic venous drainage of the graft via the donor’s iliac vein has been the standard method, several groups have evaluated the alternative of directing the venous effluent into the recipient’s portal vein. Because this is the physiologic route there has been speculation that it would have a metabolic advantage. It does, in fact, prevent hyperinsulinemia. However, the procedure is more complex and there is little evidence that it has a meaningful advantage.

Graft Survival

After disappointing outcomes during the early years of pancreas transplantation, patient and graft survival rates for the procedure now approach those of other solid organ transplants. From December 1966 to August 2002, more than 17,800 pancreas transplants were reported to the International Pancreas Transplant Registry. For the more than 12,900 transplants in the United States, reporting was complete because since 1988 it has been mandatory for all centers in this country to submit regular reports on their activity and outcomes. In the most recent registry report of August 31, 2002, the 1997–2001 cases were analyzed. Patient survival at 1 year was over 95%. For graft survival several important variables were studied, including recipient selection, donor factors, graft ischemia time, immunosuppressive regimen, recipient category (i.e., simultaneous pancreas and kidney [SPK] vs. pancreas after kidney [PAK] or pancreas alone [PTA]), and duct management.

Recipient Category

SPK recipients were the largest category, accounting for 83% of U.S. transplants. For all U.S. SPK transplants

![Figure 27-16 Improvement in results of pancreas transplantation during the later part of the 1980s and in the 1990s led to increasing application of the procedure. Although simultaneous pancreas and kidney (SPK) transplants are still the most common, improved outcomes of pancreas-after-kidney (PAK) transplants have also encouraged an increase in this category. PTA, pancreas-alone transplants.](image-url)
Figure 27-17 Graft survival continues to remain somewhat better for simultaneous pancreas and kidney (SPK) grafts than for pancreas-alone (PTA) transplants, probably because the diagnosis of rejection is facilitated by monitoring the function of the kidney transplant. PAK, pancreas-after-kidney transplants; Cad, cadaver.

performed between 1997 and 2001, 1-year patient and pancreas graft survival rates were 95% and 83%, respectively. Fortunately, kidney graft survival (92%) was not compromised by combining this procedure with a pancreas transplant. For PAK cases, 1-year patient and pancreas graft survival rates were 95% and 79%, respectively. For all PTA cases, 1-year patient and pancreas graft survival rates were 95% and 78%, respectively. Thus, although patient survival was essentially the same for the three groups, pancreas graft survival remained somewhat higher in SPK recipients than for PTA transplants (Fig. 27–17). That pancreas rejection can be diagnosed by monitoring kidney function in SPK recipients (when both organs are from the same donor) is the likely explanation for the higher functional survival rates in this category. However, the difference was less than in earlier eras. In the 1994–1998 analysis, the PAK graft survival was 71% and the PTA survival was only 64%.

The improvement in results by era was particularly evident in the outcome of PAK transplants (Fig. 27–18). The factor that seemed most likely to be responsible for the improvement was the introduction of tacrolimus immunosuppression. That pancreas rejection can be diagnosed by monitoring kidney function in SPK recipients (when both organs are from the same donor) is the likely explanation for the higher functional survival rates in this category.

Impact of Duct Management Technique

In the United States, bladder drainage was until recently by far the most common technique for duct management because of its relative safety and because it facilitates early diagnosis of rejection by serial measurement of urinary amylase, which decreases if the graft suffers immunologic damage. From 1989 to 1996, over 90% of transplants were done by this method. Unfortunately, the bladder-drainage technique carries its own urologic and metabolic morbidities, including cystitis, urethritis, and chronic acidosis from bicarbonate loss. In fact, in 15% of bladder-drained transplants, these problems are serious enough to warrant enteric conversion within 3 years. Formerly the second most common duct management technique in the United States, the use of enteric drainage has now become the most common method. Whereas in 1988 only 2% of U.S. transplants were performed by enteric
method, in 1997 48% of SPK transplants were drained enterically and between 1999 and 2001 71% were performed by this method. Although in earlier years bladder-drainage grafts fared substantially better, from 1997 to 2001 the 1-year graft survival of SPK transplants was nearly the same for bladder drained (85%) versus enteric drained (82%) (Fig. 27–19). Complications remained somewhat more common in enteric-drained grafts (11% vs. 8%). In PAK transplants (in which the simultaneous kidney could not be used to monitor rejection), bladder-drained grafts continued to have a significantly better survival at 1 year (85%) than did enteric-drained grafts (74%). In this category, complications were twice as frequent in enteric-drained grafts (22% vs. 12%). For PTA transplants, pancreas graft survival rates were significantly higher at 1 year with bladder-drainage (81%) versus enteric-drainage grafts (74%). Interestingly, when early graft losses due to technical problems were avoided, the subsequent loss of pancreas transplants was surprisingly small. In 2978 technically successful SPK cases, the pancreas graft failure rate from immunologic causes was only 2% at 1 year. In SPK grafts, the immunologic risk of failure did not differ according to duct management technique. However, for technically successful PAK cases, the immunologic graft loss was higher (5% at 1 year). For technically successful PTA cases, the risk for immunologic graft loss was highest (7% at 1 year). Transplantation of SPK grafts into uremic recipients may in part explain the lower immunologic graft loss in this category. Some failures categorized as technical (thrombosis) may actually be immunologic from thrombosis secondary to rejection, especially in enterically drained solitary transplants where changes in urinary amylase level cannot be used to diagnose rejection.

Influence of Immunosuppression

New immunosuppressive regimens, especially tacrolimus, appear to be responsible for the improvement noted in pancreas graft survival rates in the 1997–2001 era.

Impact of Pancreas Transplantation on the Microvascular Complications

Evaluating the impact of successful pancreas transplantation on the secondary complications of diabetes is difficult because randomized control studies are for the most part lacking. Defining appropriate control groups is also complicated because, in SPK recipients, uremia and diabetes are corrected at the same time. Some complications of diabetes such as neuropathy are likely to be improved by kidney transplantation alone. Thus, uremic diabetics who receive only a kidney transplant are a necessary control group for assessing the benefits of pancreas transplantation on microvascular complications.

NEUROPATHY

In nonuremic diabetic PTA recipients at the University of Minnesota Hospital, improvement in nerve conduction velocities was documented after 1 year. Evoked muscle and nerve action potentials and amplitudes remained stable or improved in patients with long-standing pancreas grafts whereas amplitudes continued to decrease in diabetic recipients whose pancreas transplants failed early. Thus, in the Minnesota patients, restoration of normoglycemia by successful pancreas transplantation appeared to halt the progression of diabetic neuropathy fairly promptly. However, other investigators believe that improvement in neuropathy including autonomic neuropathies is delayed by as much as 2 years.

RETINOPATHY

Several investigators have reported improvement in retinopathy in uremic diabetic patients after a successful pancreas transplant, but most of these studies have been poorly controlled. In nonuremic patients at the University of Minnesota Hospital, the retinas of successful pancreas recipients were compared over a 5-year period with those of patients with early graft failure. In the first 3 post-transplant years, the probability of progression of retinopathy was the same (30%) in both groups. However, after 3 years, retinopathy appeared to stabilize in patients with successful pancreas transplants while it continued to worsen in those with failed grafts. After 5 years, 55% of patients with failed grafts had progressed to a more severe state of retinopathy, whereas in successful recipients, similar progression in retinopathy had occurred in only 30%. In contrast to these patients with mild retinopathy, it seems unlikely that a pancreas transplant will benefit those with advanced retinal change.

NEPHROPATHY
Microscopic lesions of diabetic nephropathy commonly appear within 1 to 2 years in kidneys from normal donors transplanted to diabetic patients who are treated only with insulin. However, in recipients of successful SPK transplants in the Minnesota study, development of diabetic nephropathy in the transplanted kidney was generally prevented, presumably because the blood glucose level was normalized. The ability of a pancreas transplant to prevent nephropathy was also suggested in serial biopsies by the Stockholm group.

The Minnesota group has also contended that a PAK transplant may halt the progression of lesions that evolved in the renal graft before pancreas transplantation was done. In patients whose kidneys were sampled an average of 8 years after transplantation, the mean glomerular mesangial volume was significantly less in those patients who had a successful pancreas transplant than in those who did not.

Whether restoration of normoglycemia with a pancreas transplant can influence the course of early lesions of diabetic nephropathy in the native kidneys of nonuremic, diabetic patients remains controversial. In a preliminary report from the University of Minnesota, native kidneys were sampled in seven nonuremic pancreas recipients who had early to moderately advanced diabetic nephropathy (albuminuria was present in all; mean creatinine clearance was 90 ± 20 mL/min) 2 years after a successful pancreas transplant. Mean glomerular mesangial volume was significantly reduced post transplant, compared with pretransplant biopsies. However, despite this histologic improvement the creatinine clearance had deteriorated in these pancreas transplant patients from 90 ± 15 mL/min to 60 ± 14 mL/min over the same 2-year period. The nephrotoxic effect of cyclosporine may explain this apparent paradox. The lesions of diabetic nephropathy in the patient’s native kidneys were not ameliorated by pancreas transplantation, even after 5 years of normoglycemia. However, neither of these studies proves that restoring normoglycemia after a pancreas transplant cannot prevent or retard progression of diabetic nephropathy.

Several other PTA recipients have been observed to progress to a uremic state in spite of a successful pancreas graft but in most nonuremic diabetic PTA recipients, serum creatinine and creatinine clearance values at 1 to 5 years post transplant did not deteriorate from those obtained 6 months post transplant. In summary, in all three categories of diabetic pancreas graft recipients (those with SPK, those with PAK, and those with PTA), there is encouraging histologic evidence that restoring euglycemia can prevent or halt progression of diabetic nephropathy. Whether this benefit is sufficient to offset the nephrotoxic effect of immunosuppressive agents such as cyclosporine or tacrolimus is a critical question.

Whereas these studies strongly suggest that pancreas transplantation may improve diabetic retinopathy, nephropathy, and neuropathy, no controlled or randomized studies have yet confirmed these. Whether transplantation can also prevent diabetic complications in otherwise unaffected patients, as tight insulin control has been shown to do, has not been investigated because pancreas transplantation, before the onset of any complications, is rarely performed. Therefore, the potential benefits of pancreas transplantation over other forms of intensive diabetic treatment cannot be fully assessed at this time, although it seems likely that the optimal control of blood glucose possible from a pancreas transplant would be the optimal prophylaxis for microvascular complications.

**Conclusion**

The results of pancreas transplantation have improved remarkably since the mid 1980s, and the likelihood of success now approaches that of other solid organ transplants. Because pancreas transplants are not immediately lifesaving, except in patients with profound hyperglycemic unawareness, the serious side effects of lifelong immunosuppression must be weighed against the somewhat unpredictable sequelae of insulin-managed diabetes. Currently, transplantation is limited at most centers to diabetics who require a kidney transplant or have already had one. Prevention of microvascular complications of diabetes by pancreas transplantation seems likely but has not been proved by randomized studies. Advanced complications are much less likely to be stabilized or reversed.

Recent reports indicate that a successful kidney-pancreas transplant is associated with improved long-term patient survival relative to successful renal transplantation alone. A 10-year follow-up of 13,467 diabetics on the UNOS waiting list indicated that despite more early complications and deaths in pancreas recipients the calculated life expectancy was 23.4 years for kidney-pancreas recipients versus 20.9 years for related kidney alone recipients and 12.6 years for cadaveric kidney alone recipients.

The morbidity and monetary expense of conventional insulin therapy, along with its complicating factors, must also be compared with those of successful transplantation and immunosuppression to determine the eventual place of pancreatic and islet transplantation. Possibly as important a consideration as the impact of a pancreas transplant on microvascular complications is its potential for improving quality of life. Recipients of successful pancreatic allografts usually report increased vitality, greater capability for self-care, and general improvement in quality of life.
TRANSPLANTATION OF ISOLATED PANCREATIC ISLETS

The advantage of transplanting isolated pancreatic islets rather than the pancreas is the avoidance of the complex vascular reconstruction required with whole-pancreas transplantation and elimination of the unnecessary transplantation of the associated exocrine component of the gland. In the early 1970s, the initial descriptions of partial and complete reversal of experimental diabetes in animals by transplantation of isolated islets of Langerhans excited considerable interest because the risks of this procedure seemed minimal, whereas pancreatic transplants of that era were dangerous and rarely successful. It was also theorized that because some endocrine tissues were known to have minimal immunogenicity, islet allografts might succeed without immunosuppression. However, initial human islet transplants during the 1970s all failed, probably from technical difficulty in producing preparations with adequate islet yield or purity or because of immune destruction. Although considerable knowledge has been accumulated since then, both in the techniques of islet isolation and in preventing damage to the transplant by rejection or autoimmunity, much of the progress has been in experimental models. Until very recently, successful human islet transplantation has been exceedingly rare.

With the report in the year 2000 of 7 consecutive successful human islet transplants by an investigator in Edmonton, Alberta, a new era appears to have begun for this field. Within 3 years of this report almost 300 islet transplants have been performed worldwide. The results of these transplants are much better than before. One-year islet graft survival rates in many of the approximately 30 centers performing them are comparable to those of pancreas transplantation. If this persists, islet transplantation will gradually assume a greater role in treatment of patients’ type I diabetes. Briefly summarized below are the history of islet transplantation, the barriers that remain, and the recent clinical results.

Lessons Learned from Experimental Islet Transplantation

Techniques of Islet Preparation

Separating the islets from the pancreas is begun by distending the pancreas by infusing a collagenase enzyme solution into the pancreatic duct. After mechanical disruption, islets are separated from acinar, ductal, lymph nodal, and vascular elements by handpicking under magnification or by density gradient centrifugation. Although most non-islet tissue is thus eliminated, many islets are destroyed or discarded in the process.

Sites of Islet Transplantation

A potentially important advantage of a free graft, such as isolated islets graft, is the flexibility that exists in selecting a site for transplantation. Surprisingly, unlike the situation with other free grafts of endocrine tissue, only a few transplant sites will support engraftment and adequate function of transplanted islets. The peritoneal cavity is advantageous because remaining exocrine tissue that has not been separated from the islets can be tolerated there, but this transplant site is also relatively inefficient, requiring large numbers of islets for reversal of diabetes. For reasons not completely understood, the most easily accessible sites (subcutaneous or intramuscular) have not proved successful unless extremely large numbers of islets from multiple donors were transplanted. The spleen has been used successfully as a transplant site; however, the risk of splenic injury and bleeding is a deterrent. Thus, somewhat surprisingly, the liver via portal vein embolization has become the most commonly employed transplant site. The liver’s dual vascular supply allows embolized islets to completely occlude portal venules without infarcting the transplant site, which remains nourished by hepatic arterial blood (Fig. 27–20). The renal subcapsular space is another excellent islet transplant site in rodents, but it has rarely been used in humans.

A number of immunologically privileged transplantation sites have been evaluated, including the anterior chamber of the eye, the brain, the pregnant uterus, the placenta, the testis, and the thymus. Several of these sites have been shown to provide at least partial sanctuary for allogeneic islets while allowing normal physiologic function. However, the technical considerations and potential morbidity of engraftment into these sites discourage their clinical use.

In animal models, genetic alteration of islets to delete important alloantigens has allowed successful transplantation without immunosuppression. Genetic modifications of islet allografts have also been attempted to create a protective environment that would be similar to a privileged site. An example of this strategy would be to induce the transplanted islets to produce immunosuppressive cytokines such as IL-10 and transforming growth factor. To test this method, Min transfected isolated murine islets with the genes encoding these factors. When the transfected islets were transplanted to allogeneic hosts, their survival was significantly prolonged.
Contrary to the early hope that islet tissue would be immunologically privileged like certain other endocrine tissues (e.g., parathyroid), the earliest reversal of experimental diabetes by islet transplantation indicated that unless the donor was genetically identical to the recipient, rejection was prompt. Subsequent experiments indicated that rejection could be overcome by immunosuppression and also identified several other unusual strategies by which rejection can be avoided. For example, pretransplant storage of islets in tissue culture was found to reduce their immunogenicity, sometimes allowing successful transplantation without immunosuppression. This outcome was found to depend on depleting the islets of passenger leukocytes, especially class II major histocompatibility complex antigen-presenting cells (APCs) such as macrophages and dendritic cells. Prolonged tissue culture of islets (1 to 2 weeks) allowed selective survival of the endocrine cells but not the antigen-presenting lymphoid cells. Other methods that deplete or render nonfunctional APCs from islets include ultraviolet irradiation, gamma irradiation, and treatment with antibodies directed against APCs along with complement. So far, these methods have been shown effective only in rodent models.

**Immunosuppression**

Conventional pharmacologic immunosuppressive agents, such as cyclosporine or tacrolimus, are relatively ineffective in prolonging islet allograft survival, requiring dangerously higher doses to prolong islet allograft survival beyond what is necessary for surgically vascularized solid organ allografts. In addition, cyclosporine, tacrolimus, and corticosteroids have been found to have toxic effects on islets. Antilymphocytic antibodies and specific anti–T-cell agents such as anti-CD4 have proved far more successful in preventing islet allograft rejection.

Stimulatory blockade (see Immunosuppression under Renal Transplantation) has also been applied to islet transplants with encouraging results. Kenyon and colleagues reported the results of anti-CD154 treatment on the survival of isolated islet allografts in rhesus monkeys. Each of six monkeys treated with anti-CD154 antibody monotherapy demonstrated prolonged restoration of normoglycemia.

**Tolerance**

Classic immunologic tolerance induced by neonatal intravenous administration of allogeneic lymphoid cells from a prospective donor strain was shown many years ago to prevent skin allograft rejection. Only donor lymphoid cells, but not other cell types such as kidney cells, which cannot migrate to host lymphoid organs, proved effective as tolerogens. Knowledge that the thymus serves as the primary site for self-tolerance initiation led Posselt and associates to investigate whether nonlymphoid donor cells such as islets might also possess tolerogenic properties if introduced directly into the thymus. They injected allogeneic islets into the thymus of adult rats that were briefly immunosuppressed with a single dose of ALS to delete their mature T cells. Not only did these islets survive in the thymus, but they also allowed a second islet allograft from the same donor strain to be successfully transplanted under the kidney capsule 100 to 200 days later without any additional immunosuppression. Attempts to induce tolerance by this method in larger animal models are not as encouraging.

**Autoimmune Recipients**

Successful islet transplantation in human type I diabetics requires avoidance not only of rejection but also of damage by the autoimmune process, which causes failure of the native islets in this disease. Insight into this possible importance of autoimmune recurrence in transplant islet failure has been provided by studies in two rodent models of spontaneous autoimmune diabetes: the BioBreeding (BB) rat and the nonobese diabetic (NOD) mouse. These animals are similar to human type I diabetics in many ways, including abrupt disease onset in early adulthood and the presence of both cellular and humoral immune responses directed specifically against the beta cells of the islets. Without insulin therapy, ketoacidosis and death are inevitable. Thus, NOD mice and BB rats are suitable models for determining the vulnerability of transplanted islets in autoimmune recipients and possible methods for avoiding it. Studies in BB rats demonstrated that islets are more vulnerable to autoimmune recurrence after transplantation when they are isolated than they are if transplanted as part of a whole pancreas.

**Xenografts**

Even if the technical and immunologic difficulties of islet transplantation were overcome, the donor shortage would leave millions of diabetics waiting for a transplant because of the donor shortage. An often discussed solution to a demand of this magnitude would be the use of xenogeneic tissues. Porcine insulin is effective in the treatment of human diabetics, suggesting that the pig may be a promising source of islet tissue for xenotransplantation. Preformed antibodies are present in humans against porcine histocompatibility antigens, and these antibodies have been shown to bind islets and activate complement. However, unlike the situation for vascularized xenografts, there is apparently no hyperacute rejection of islets. Instead, the problems of cellular immunity seem to play a more prominent role in islet xenograft rejection.

**Clinical Islet Transplantation**

In theory, islet transplantation is the ideal treatment for patients with insulin-dependent diabetes because it has the potential to completely normalize blood glucose without the substantial risks associated with the operation of whole-pancreas transplantation. In rodent models, the technical and immunologic problems of islet transplantation have been overcome, routinely allowing consistent success. Recent improvement in the success of clinical islet transplantation suggests that islet transplantation could eventually replace both insulin therapy and whole-pancreas transplantation as the optimal treatment for type I diabetes.

**Isolation Methods**

Digestion of the compact fibrous pancreas and isolation of viable islets is more difficult in humans than it is in rodents. In addition, hemodynamic instability and hyperglycemia of cadaveric human donors and prolonged pancreatic ischemia before initiation of the separation process have compromised efforts to obtain islet preparations of high quality. The fact that pancreata from the best donors are likely to be utilized for whole-organ grafts further reduces the likelihood of optimal islet recovery. Most centers now use an automated method of islet isolation described by Ricordi and coworkers. The pancreas is digested enzymatically by collagenase in a chamber. During a period of agitation, islets and small fragments of the contaminating exocrine tissue fall through a screen and are collected, remaining in the bottom of the chamber. After the collagenase solution is washed from the islets, they are separated from acinar fragments and ductal elements by centrifugation through density gradients. Islets account for about 2% of the mass of an intact pancreas. Current islet separation methods are sometimes capable of yielding preparations composed of 90% pure islets, while at other times the same procedure may yield a preparation of less than 50% purity. The more manipulation carried out in an effort to reduce acinar tissue contamination, the more islets are lost. Even with the best techniques, many islets are lost or damaged. An important variable that contributes to inconsistency in the isolation process is the collagenase enzyme that is used to digest the pancreas. Recent refinement of the enzyme preparation
has led to a marked improvement in isolation yield, purity, and number.

Another important technical achievement is islet preservation. Short-term preservation (days to several weeks) can be achieved by in vitro tissue culture. Islet culture has been shown to diminish the immunogenicity of islets in animal experiments, but this has not been evaluated in humans. Although even short-term culture (12 to 24 hours) also helps to decrease the acinar tissue contaminating islet preparations, this is at the expense of substantial loss of viable islets. Frozen islets can probably be stored permanently, and, after thawing by appropriate techniques, appear to have virtually normal function. These complications are probably related to rapid infusion of insufficient pur islet preparations containing large amounts of enzymatically rich acinar tissue. With islet preparations of high purity, these sequelae have been rare. However, the procedure is not without other risks. Even in the recent experience, a mortality has been reported as a result of a hepatic arterial injury during transhepatic portal vein cannulation.

Surgical Technique and Complications

In human transplants, the islets have usually been transplanted by embolization to the liver via the portal vein. Other transplant sites, proven effective in animals, such as the peritoneal cavity and the renal subcapsular space, have rarely been employed in humans. Islets can be inoculated into the portal venous system by cannulating the umbilical vein via a minilaparotomy, or by transcatheter, transhepatic cannulation of the portal vein itself. Islets are suspended in a heparinized solution for portal vein infusion. Portal venous pressure is monitored during islet infusion because the development of portal hypertension may be an indication of intravascular clotting. Although most patients tolerate the inoculation of intraportal islets, severe complications have been reported in a few, including portal vein thrombosis and disseminated intravascular coagulation. These complications are probably related to rapid infusion of insufficiently pure islet preparations containing large amounts of enzymatically rich acinar tissue. With islet preparations of high purity, these sequelae have been rare. However, the procedure is not without other risks. Even in the recent experience, a mortality has been reported as a result of a hepatic arterial injury during transhepatic portal vein cannulation.

Metabolic Factors Influencing Success

During islet engraftment in the immediate post-transplant period, it is believed that maintenance of normal blood glucose levels is important to avoid islet damage. During the early post-transplant period, to avoid even brief episodes of hyperglycemia, patients are treated with continuous intravenous infusions of insulin. In most cases, after several more weeks, even if the transplanted islets appear to be capable of maintaining normoglycemia. This intensive early insulin therapy is thought to be critical because islets traumatized by recent isolation may be particularly sensitive to increases in metabolic demand. Hyperglycemia might damage the beta cells by stimulating them to produce insulin until they became “exhausted.” However, no randomized studies have been done to support this theory, and it should also be noted that successful islet engraftment in rodents does not require concomitant insulin therapy.

Islet Autotransplantation

Transplantation of pancreatic fragments to diabetics was attempted (unsuccessfully) as early as 1893. Modern human islet transplantation began in 1977 when Sutherland and colleagues at the University of Minnesota performed an intraportal autotransplant of islets in a patient who was undergoing a near-total pancreatectomy for the persistent pain of chronic pancreatitis. This patient remained insulin independent for 6 years after the transplant, proving that transplanted islets could function in humans. Since then, more than 20 institutions have reported a combined series of 170 human islet autotransplants to the International Registry. The largest experience is at the University of Minnesota, where between 1977 and 1995, 59 patients with chronic pancreatitis were subjected to total or near-total pancreatectomy for relief of pain. Islets, isolated from the excised organ, were transplanted into the pancreaticectomized patient’s liver via the portal vein to prevent the otherwise inevitable diabetes. Because the exocrine pancreas in such patients is almost always atrophic, no purification of the digested pancreas is necessary. Because the islets were autologous, rejection was not a possibility; and because these patients were not type 1 diabetics, there was no concern over recurrent autoimmune damage. In these patients, the incidence of insulin independence after 2 years was 34%. Since they adopted the automated islet isolation method of Ricordi to increase their islet yield, these patients, freshly isolated islets were added to cryopreserved islets from other donors to increase the total number of islets transplanted. One patient in whom the indication for islet transplantation was dangerous hypoglycemic unawareness. Three months after transplantation, 64% of the kidney- and liver-allograft recipients had discernible function of the transplanted islets. Later on, those patients who exhibited initial function had a significant reduction in their daily insulin requirement and maintained normal hemoglobin A1c levels. One patient eventually died of recurrence of their malignancy, one remained insulin independent for 58 months and had normal insulin C-peptide levels at 18, 30, and 57 months post transplantation and, at autopsy, had histologically normal intrahepatic islets. In these cases, the transplanted islets were from the same cadaveric donor as the liver (although several of them received islets from third-party donors in addition). The substantially better result of islet transplantation in these patients than other islet transplants of that era has two possible explanations that are not mutually exclusive: (1) The recipients were not type 1 diabetics and thus autoimmune damage of the transplanted islets was not a threat, and (2) successful liver allografts are known to have a protective influence that prevents rejection of allografts of other tissues transplanted from the same donor.

Islet Allografts After Total Pancreatectomy for Patients With Malignant Disease

Prior to the Edmonton report in 2000, the most consistent success with pancreatic islet allografts may have been in patients at the University of Pittsburgh who had their pancreas and liver removed as part of an upper abdominal exenteration for malignant disease. Eleven such patients were treated with combined liver and islet allotransplantation. Six of them exhibited sustained insulin independence after the procedure. Although they all eventually died of recurrence of their malignancy, one remained insulin independent for 58 months and had normal insulin C-peptide levels at 18, 30, and 57 months post transplantation and, at autopsy, had histologically normal intrahepatic islets. In these cases, the transplanted islets were from the same cadaveric donor as the liver (although several of them received islets from third-party donors in addition). The substantially better result of islet transplantation in these patients than other islet transplants of that era has two possible explanations that are not mutually exclusive: (1) The recipients were not type 1 diabetics and thus autoimmune damage of the transplanted islets was not a threat, and (2) successful liver allografts are known to have a protective influence that prevents rejection of allografts of other tissues transplanted from the same donor.

Islet Allografts for Insulin-Dependent Diabetes

By far the largest number of candidates for allogeneic transplantation are type 1 diabetics. Ironically, it is in such patients that a successful outcome has until recently been so difficult to achieve. Between 1990 and 2000 over 300 type 1 diabetics were transplanted worldwide at 35 institutions, but insulin independence at 1 year was less than 10%. During the 1990s, results improved somewhat, especially at the University of Giessen where 27 islet transplants were done between 1992 and 1996. These patients had a previous or concurrent kidney transplant except for five nonuremic type 1 diabetics. In whom the indication for islet transplantation was dangerous hypoglycemic unawareness. Three months after transplantation, 64% of the kidney- and islet-transplanted patients had discernible function of the transplanted islets. Later on, those patients who exhibited initial function had a significant reduction in their daily insulin requirement and maintained normal hemoglobin A1c levels. One patient eventually became insulin independent 400 days after transplantation and has remained so for over 2 years, whereas two others became insulin independent at 312 and 363 days post transplant, and both have remained so for more than 100 days. In the nonuremic recipients of islet transplants without kidney transplants, all five initially exhibited islet function. However, because chronic immunosuppression was considered an unacceptable risk in these patients who had no kidney allograft to be protected, the immunosuppression was eventually stopped in all. When immunosuppression was withdrawn, all five soon lost all evidence of islet function.

Others also reported occasional success during this period, including a series of a simultaneous islet-kidney transplants performed in Edmonton. In these patients, freshly isolated islets were added to cryopreserved islets from other donors to increase the total number of islets transplanted. One patient became insulin independent after 69 days and remained so for more than 2 years before eventual return of diabetes. A second patient was briefly insulin
independent between 155 and 166 days post transplant and again between 837 and 990 days post transplant. Eventually, insulin dependence recurred in this patient, although for only 1 to 5 units daily.\textsuperscript{121} Of note, both of the Edmonton patients had biopsy-proven evidence of chronic rejection of their renal allografts, which were from the same cadaveric donor as the non-cryopreserved transplanted islets. Although the mechanisms causing the eventual failure of initially successful islet allografts are unclear, chronic rejection and autoimmune islet damage seem the best possibilities.

A multivariative analysis of all islet transplants reported to the International Transplant Registry identified four characteristics that were associated with success (defined as achievement of insulin independence or at least some evidence of islet engraftment).\textsuperscript{122} These were (1) preservation of the donor pancreas for less than 8 hours before islet isolation, (2) transplantation of at least 6000 islets per kilogram of body weight, (3) choice of the liver via the portal vein as the transplant site, and (4) the use of ALG or ATG for induction immunosuppression. In cases in which all four of these positive predictive parameters were present, 70\% of patients had some evidence of transplant islet function, 83\% had normal hemoglobin A1c levels, and 20\% were insulin independent 1 year after transplantation.\textsuperscript{123} Although this analysis is based on a small number of successful cases, it provided a framework for design of further trials of islet transplantation including the landmark 2000 report by the Edmonton workers.\textsuperscript{124}

A problem in devising optimal immunosuppressive protocols for islet transplantation is the known diabetogenic nature of the commonly employed immunosuppressive drugs. Prednisone may cause insulin resistance and hyperglycemia, whereas both cyclosporine and tacrolimus suppress insulin secretion. The diabetogenic effect of these drugs may in part explain the requirement for a larger than anticipated number of islets needed for successful allografts and the longer than expected time to engraftment. That induction immunosuppression with anti–T-cell antibodies has a positive correlation with islet allograft success may be explained by the lack of islet toxicity of these agents. However, the use of OKT3 for induction therapy may cause islet cell damage from the cytokine release associated with this agent. Induction therapy with a new agent, antihuman thymocyte immunoglobulin, with islet allograft success may be explained by the lack of islet toxicity of these agents. However, the use of OKT3 for induction therapy may cause islet cell damage from the cytokine release associated with this agent. Induction therapy with a new agent, antihuman thymocyte immunoglobulin, rabbit (Thymoglobulin), has been found to provide superior protection from rejection compared with ALG in renal allografts without the severe cytokine release syndrome common with OKT3. This agent may be ideal for use with isolated islet allografts.

In the setting of the usual failure of islet transplantation even in the 1990s, the report by the Edmonton group of seven consecutive successes gained much attention.\textsuperscript{125} The approach employed by these investigators relied on several innovations. First, corticosteroids, the mainstay of traditional immunosuppressive regimens, were completely avoided because of their known diabetogenic properties. Also novel was the immunosuppressive regimen selected that included induction therapy with anti–IL-2 receptor antibody and maintenance therapy with a combination of low-dose tacrolimus and sirolimus. Although the reasons for success still remain to be fully explained, it seems likely that this unique combination of agents is unusually effective against both the autoimmune and alloimmune threats to transplanted islets. Perhaps the most important factor in the success achieved by what is now routinely termed the Edmonton protocol is that multiple infusions of islets were administered. Whereas many prior investigators had achieved evidence of islet transplant function by detectable C-peptide levels following an infusion of islets from a single donor, unless their patients became insulin independent they usually considered the transplant a failure and discontinued immunosuppression. These earlier patients were not maintained on immunosuppression and regrafted with more islets. Shapiro and colleagues, on the other hand, maintained the immunosuppression and administered second and even third doses of islets from additional donors until insulin independence was achieved. As in the rodent experiments detailed earlier, the inefficiencies of the isolation process and engraftment in the recipient may make the islet yield obtained from a single donor insufficient to completely reverse hyperglycemia.

Based on the encouraging results in Edmonton, numerous centers in the United States and abroad have initiated islet transplant programs, usually copying the Edmonton approach to immunosuppressive protocol and retransplantation. Early results from several other centers are promising. In our own experience, each of nine consecutive patients completing the protocol have gained insulin independence. A result of improvements in isolation technique in four of these, success was achieved with single infusion, whereas in the others a repeat islet transplant was required.

Despite the encouraging nature of recent successes in the field, the frequent need for multiple infusions from multiple cadaveric donors poses practical problems. At present only about 5500 cadaveric donors are available each year in the United States, of which approximately 1500 pancreata are utilized for whole-organ transplantation. Even if the remainder were suitable for islet isolation, this would allow only 2000 diabetics to be successfully treated if two organs are needed for each recipient. Because there are nearly 1.5 million type I diabetics in the United States, other sources of transplantable beta cells would be necessary for transplantation to have its full impact in the treatment of type I diabetes.

Several possible alternative sources of beta cells have been suggested, including xenogeneic donors, genetically altered tissues, stem cells, and living donors. None of these sources is immediately at hand except living donors who volunteer to donate part of their pancreas. Living donors have been used successfully for segmental pancreatic grafts. That islets from two entire cadaveric pancreata are generally required for success using today’s isolation techniques makes the utility of a half an organ doubtful unless the function and/or engraftment of the recovered islets could be markedly improved.

**Autoimmune Damage of Islet Allografts**

Recurrence of autoimmune disease, that is, the destruction of the transplanted islets by the original diabetogenic immune process, has been postulated as an important contributing factor to the poor results previously seen in type I diabetes. This hypothesis is based on extensive animal studies in the BB rat\textsuperscript{126} and the NOD mouse\textsuperscript{127} and a few humans who have received pancreas transplants from identical twin donors.\textsuperscript{128} Definitive proof of recurrence of autoimmune disease has been difficult to find in humans because biopsies of islet grafts are not practical. The important success of islet allografts in patients who lost their pancreatic function not from autoimmune diabetes but from pancreatectomy during upper abdominal exenteration suggest that if autoimmune recurrence is not an issue, islet allografts might be more successful.\textsuperscript{129} The experience with whole-pancreas transplantation indicates that autoimmune damage of the allograft is usually controlled by intensive immunosuppression with conventional agents. However, pancreatic grafts from identical twin donors have failed from recurrence of autoimmunity even if immunosuppression was given.\textsuperscript{130} In addition, recurrence of autoimmunity has been described in two recipients of whole-pancreas islet allografts from cadaveric donors.\textsuperscript{131} In these patients, autoimmune recurrence was assigned as the cause of graft failure because histologic examination of the pancreatic grafts revealed clear patterns of selective beta cell destruction with sparing of alpha and delta cells of the islets.

Islet grafts are fully susceptible not only to T lymphocyte–mediated rejection and to damage by the autoimmune process of diabetes but also to the phenomenon of primary nonfunction. The causes of this problem are obscure. Although inadequate numbers of transplanted islets and ischemic damage of islets before transplantation play a role in some cases, there may be other reasons. Islets are vulnerable not only to a variety of cytokines but also to inflammatory mediators and oxygen free radicals. Antibody- or macrophage-mediated islet damage could also occur before or during the engraftment phase.\textsuperscript{132}

**Fetal Islet Allografts and Xenografts**

It is believed that over 5000 transplants of fetal islets have been performed, mostly in Russia and China. Apparently, most of these patients either received no immunosuppression or were treated with agents of unknown immunosuppressive activity (e.g., Chinese “traditional medicines”).\textsuperscript{133}
Information of any sort is available on fewer than 200 of these procedures. Thus far, it is doubtful that insulin independence has been achieved in any of the recipients who were type I diabetics, although increases in C-peptide levels have been reported. Lafferty and associates performed 16 human fetal pancreas allografts in type I diabetic patients who were receiving simultaneous renal transplants. They cultured fetal pancreatic fragments (1 mm³) for 5 to 10 days before transplantation under the renal subcapsule of the kidney transplant. They obtained histologic evidence that the grafted fetal pancreas became revascularized within 14 days and by 3 months after implantation had differentiated into islets. Eight patients received tissue from a single fetal donor, and eight others received tissue from two to four donors. The latter group exhibited some reduction in their insulin requirements compared with a control group of diabetics who received a kidney transplant alone. One patient had a 65% reduction in insulin requirement, measurable serum C-peptide levels, and a normal hemoglobin A1c level 2 years after transplantation. Evidence of meaningful islet function was never evident sooner than 3 to 6 months after transplantation. Even if insulin independence could be achieved with fetal pancreas allografts, the political and ethical issues surrounding the use of human fetal tissues remain a substantial barrier to widespread use of this method.

The use of animal donors for fetal islet transplants might circumvent ethical issues, an interesting possibility that has been explored by Groth and coworkers. They transplanted fetal porcine islets into 10 type I diabetic patients. In 8 patients with functional renal transplants, the grafts were placed in the liver, and 2 patients had the fetal islets placed in the renal subcapsular space of a concomitantly transplanted kidney. The presence of preformed antibodies to this discordant xenogeneic tissue, as well as strong cellular rejection, would be expected to cause rapid destruction of these transplants. Surprisingly, porcine C-peptide was detectable in the urine of 4 patients from 200 to 400 days after transplantation; however, no change was observed in the insulin requirement of these patients.

Postoperative Monitoring for Rejection

A management problem nearly unique to islet transplantation is lack of a reliable marker for early graft rejection. Hyperglycemia is likely to be a late indication of rejection that becomes apparent when the graft is not salvageable by anti-rejection therapy. More sensitive measures of insulin reserve, such as Sustacal stimulation tests or arginine-induced insulin-release assays, are cumbersome and not practical for serial monitoring of graft function.

Immune markers of graft dysfunction have been sought. Olack and colleagues reported a rise in panel-reactive antibody in patients with islet graft dysfunction. Islet grafts in this series were from multiple donors, which may have been responsible for the marked increases in panel-reactive antibody that were observed. Elevations in islet autoantibodies have also been reported after transplant, and their presence before transplant may correlate with poorer graft survival. Whether either alloreactive or autoreactive humoral responses have an important role in islet graft destruction is unknown but would not be surprising given the liver’s potential for antibody-dependent cytotoxicity with its large population of resident phagocytes. However, it is unlikely that serologic markers are of promise for routine graft monitoring.
INTESTINAL TRANSPLANTATION

The introduction of intravenous hyperalimentation by Dudrick and associates in 1968 allowed long-term survival of patients with complete intestinal failure who would previously have died rapidly. However, total parenteral nutrition (TPN) severely affects quality of life and may be associated with a number of highly morbid and sometimes fatal complications. In addition, it is estimated that the annual cost of total intravenous nutrition exceeds $200,000.

An alternative to lifelong intravenous nutrition is restoration of enteral absorptive function by intestinal replacement. The earliest experimental transplants of the intestine performed by Lillehei in the 1960s indicated that success of intestinal grafts would be more difficult to achieve than that reported for other solid organ grafts. In fact, it was not until the availability of cyclosporine that even occasional success was achieved. However, since then the results have greatly improved. Three varieties of intestinal transplantation have been reported: (1) small bowel with or without a portion of the colon (SI), (2) combined liver-small bowel grafts (LI), and (3) multivisceral grafts in which up to five organs are transplanted simultaneously (MV). Nearly equal numbers of SI and LI grafts have been reported, whereas only a few MV grafts have been done (about 10% of the total). It is speculated that a concomitantly transplanted liver graft from the same donor would provide immunologic protection to the more immunogenic intestinal graft, as shown in some animal models. Although the issue is far from resolved, recent clinical results indicate that in humans, this protective effect is minor. This and the fact that failure of a small bowel graft alone may be successfully treated by removal of the graft and retransplantation of TPN, whereas a failed liver graft is fatal without urgent liver retransplantation, cause most groups to perform combined transplants only if both organs are failing.

Selection of an isolated small intestinal graft would allow the possibility of utilizing a living related donor, a procedure with considerable technical and immunologic advantages.

The most frequent etiology of intestinal failure is the “short gut” syndrome, which follows extensive resection for intestinal ischemia or disease. At present, the most common indication for intestinal replacement is inability to sustain successful TPN owing to lack of intravenous access sites or because of severe complications from chronic TPN, such as liver failure. That successful intestinal transplantation allows resumption of normal oral intake would make intestinal transplantation the preferred method of therapy for intestinal failure, if the risks of this relatively new procedure can be further decreased.

The principal barrier to widespread application of intestinal replacement at present is the unusually vigorous rejection response elicited by intestinal grafts. Unlike other solid organ grafts such as kidney or liver, which may incite a rejection crisis in 10% to 40% of recipients, 90% to 100% of small bowel grafts undergo rejection crisis within the first 6 months. The reasons for this difference are not entirely clear, but it is assumed that the large amount of gut-associated lymphoid tissue is responsible. Which of the transferred lymphoid cells may be most important in this regard or the antigenic characteristic of these cells has not been elucidated.

A uniquely dangerous consequence of intestinal transplantation rejection is the loss of the protective mucosal barrier of the gut, consequent bacterial translocation, and systemic sepsis in an immunocompromised host. Thus, it is not surprising that the most common cause of death after small bowel transplantation is sepsis and multiorgan failure. Early diagnosis of rejection is therefore crucial. Ironically, intestinal rejection is associated only with nonspecific clinical signs and symptoms, such as fever, anorexia, abdominal pain, and changes in the output and character of intestinal content (often observable as output from an ostium). Even endoscopic biopsies are not entirely reliable in diagnosing rejection because the histologic manifestations of rejection can be patchy, with some areas of the graft appearing entirely normal.

Because the intestine is the largest lymphoid organ in the human body, an intestinal graft can mount a formidable immune response against the graft-versus-host (GVH) disease. In the simplest manifestation of GVH disease, the immune cells and antibody produced by blood group-compatible but nonidentical grafts mediate a severe hemolytic reaction by targeting foreign blood group antigens on the host’s red blood cells. A more severe form of GVH disease occurs when T cells of the graft respond to foreign histocompatibility antigens of diverse host tissues, leading to a spectrum of pathology, the most fulminating form including destruction of host hematopoiesis. Interestingly, despite the outcome predicted by animal experiments, GVH disease has not been a severe problem in most clinical cases. Perhaps the potent immunosuppressive regimens administered to human patients are especially effective in preventing GVH disease. If so, development of tolerogenic protocols to obviate heavy immunosuppression would ironically be counterproductive for intestinal grafting because in experimental bowel transplant models induction of tolerance leads to dramatically more severe GVH disease.

Results

Data from the most recent International Intestinal Transplant Registry accumulated from 33 programs indicate that by February 1997 there were 273 transplants performed in 260 patients. Forty-one percent of grafts were isolated bowel, and 48% included a simultaneous liver graft. Only 11% of grafts were multivisceral. For grafts transplanted since 1995, 1-year graft survival was nearly equivalent in all three groups (SI, 55%; LI, 63%; MV, 63%), as was patient survival. Better survival was observed in patients transplanted after 1991 and in those transplanted at centers with the greatest experience (>10 transplants). The importance of experience was emphasized by the superior results at the University of Pittsburgh. This center has performed more than 165 intestinal transplants. It reported an actuarial patient survival rate of 75% at 1 year, 54% at 5 years, and 42% at 10 years. For the 93 patients transplanted since 1994, results were substantially improved. One-year survival was 78%, and 5-year survival was 63%. The improvement was attributed to several changes in the immunosuppressive regimen, including cyclosporamide anti-IL-2 receptor antibody therapy, and, in some recent recipients, to administration of donor bone marrow cells to and/or pretransplant irradiation of the graft. If this early success is sustained and is attainable by other groups as well, transplantation would become the preferred therapy for patients with intestinal failure.
Transplantation is an expensive treatment, although in many cases not as expensive as medical treatment of end-stage organ failure. For example, the median charge for renal transplantation is $38,487 in 1988 U.S. dollars, including hospital charges, professional fees, and charges for the acquisition of donor organs. Second or subsequent kidney transplantations cost even more ($41,980). Although dialysis costs remain constant over the years, those for transplantation decrease to about $4,000 after the first year, which is about one third the cost of dialysis. Thus, after 3 years, patients with functioning grafts represent a net savings to the Medicare program, which funds the treatment of end-stage renal disease in most patients. In addition to its cost effectiveness and better survival, renal transplantation is superior to dialysis because it returns 75% of patients to work (compared with 25% to 60% of dialysis patients), with substantial consequent saving in expenses of dialysis and welfare payments, not to mention benefit to patients’ families. During the 1990s, improved survival and other advantages of transplantation over dialysis have been widely recognized by the public and nephrologists, greatly increasing the demand for transplants. Only elderly or very poor risk patients are now treated preferentially by dialysis rather than transplantation. Despite this, because of the donor shortage, the number of patients awaiting a cadaveric kidney continues to increase (to nearly 40,000 by 1998), while the number of cadaveric renal transplants performed remains relatively constant at about 9000 per year. The total number of renal transplants has increased since the mid 1990s mainly on the basis of utilizing living unrelated donors and suboptimal cadaveric donors.

With regard to intestinal transplantation versus chronic TPN, it appears there would also be a substantial cost advantage of successful transplantation. Pancreas transplantation is more expensive than the annual cost of insulin therapy, but over several decades, it could be cost effective if it prevents blindness and renal failure. This is perhaps the rationale in the Health Care Financing Administration’s recent decision for Medicare to provide coverage of pancreas transplants, which were previously considered by them to be experimental.

For other organs, costs of transplantation versus medical therapy are more difficult to analyze. Successful liver or heart transplantation may be more expensive than repeated prolonged hospitalizations for liver failure and bleeding esophageal varices or multiple bouts of heart failure. However, other transplant-associated costs, such as a long period of support with ventricular-support devices before heart transplant, would greatly increase the total expense. Failure of a vital organ and rapid death are no doubt less expensive than transplantation, but few patients would prefer this option, if a reasonable chance of survival is possible with transplantation.

Public interest in transplantation during the 1980s led to appointment of a national task force to address issues such as the donor shortage, establishment of standards, and provision of transplant services to all citizens. As a result, the National Organ Transplant Act was passed by Congress, which mandated a National Organ Procurement and Transplantation Network. In 1986, a government contract to provide these services was awarded to UNOS, a private nonprofit organization that had been formed by representatives of the majority of transplant centers in anticipation of these governmental actions.

UNOS’s board of directors includes representatives of 11 regions that have been established in the United States and is composed of transplant surgeons and physicians, nurses, representatives of voluntary health organizations, transplant recipient families, lawyers, ethicists, theologians, and health care financing representatives. UNOS has established criteria for accreditation of transplantation centers, histocompatibility laboratories, and local organ procurement organizations. All patients awaiting transplants must now be registered with UNOS. A central computer and a point system based on medical criteria determine the assignment of kidneys, which local organ procurement organizations distribute first locally, then regionally, and then nationally. Because hospitals performing transplantation must be members of UNOS to be eligible for Medicare funding, the organization has assumed a powerful role. Each center must now submit outcome data on every transplant performed, and these data are published regularly.

The severe donor shortage, which limits application of transplantation as a lifesaving treatment, causes an ethical dilemma. Criteria for distribution of cadaveric kidneys are the subject of continuing debate. By law, age, race, and socioeconomic status can play no role. Should scarce organs go to high-risk patients, for example, older, highly sensitized individuals whose need might be more pressing but who are unlikely to experience long-term benefit because of rejection or death? Or should younger, better-risk patients whose need is less acute be transplanted because they will have a more lasting benefit? An additional related issue is whether organ allocation should be based on national or regional listing of patients.

The sale of human organs has been condemned by the (International) Transplantation Society and is forbidden by law in most Western countries. It remains an issue because needy individuals in many parts of the world are sometimes willing to sell one of their kidneys for the high price it will bring. Of additional concern are reports of use of organs from executed criminals in China. These tarnish the image of transplantation.

The number of patients dying while awaiting an organ transplant grows every year. This increase in mortality is the result of an expanding number of candidates listed for organ transplants, coupled with a continuing shortage of donor organs. In the United States, obtaining organs from a cadaver donor relies on voluntary consent of a family to donate the organs of a deceased relative or, less commonly, the documented intent of the deceased. In the past 10 years the number of cadaveric organs recovered has increased by only 10%, clearly inadequate to meet the demand. The inadequacy of the current system is based on a decrease in the number of dying individuals suitable for organ donation and on the low rate of family consent for donation from suitable donors (40% to 60%).

A panel of ethicists, organ procurement organization executives, physicians, and surgeons was recently convened by the American Society of Transplant Surgeons to consider whether to recommend a pilot trial to provide a financial incentive for a family to consent to organ donation from a deceased relative. Currently, financial compensation for donation of organs is against the law in the United States. Another concern is that an offer of payment for donated organs might be offensive to some families and decrease their inclination to make an altruistic donation. The panel was unanimously opposed to the exchange of money for donor organs because it would violate the standard of altruism and commercialize the value of human life. However, a majority of the panel supported reimbursement for funeral expenses or a charitable contribution as an ethically permissible approach. The concept of a pilot project of this sort has been supported by the UNOS Board of Directors and the AMA, but this remains controversial, as shown by the opposition of others, including the American College of Surgeons.

The evolution of transplantation from an experimental curiosity to a highly successful therapy represents one of the remarkable achievements of 20th century medicine. Terminal diseases of the kidney, liver, and other organs were uniformly fatal until the 1960s but can now be treated with greater success than most cancers. Because many victims of these diseases are relatively young and productive, the achievement of a successful transplant is one of the most gratifying of all surgical therapies.
References


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