IN THE LAST DECADE, marrow transplantation has been shown to provide a means for curative correction of a number of lethal congenital and acquired disorders of the hematopoietic and lymphoid systems. Marrow transplantation is the treatment of choice for aplastic anemia and has emerged as a highly promising approach to the treatment of high-risk forms of leukemia, particularly when applied to patients in remission early in the course of their disease. Graft-versus-host disease (GVHD), infection, graft rejection, and leukemic relapse remain major obstacles to the success of a marrow transplant. However, considerable recent progress has been made in circumventing these obstacles. Advanced radiotherapeutic techniques, new immunosuppressive agents, and new prophylactic and therapeutic antiviral agents promise marked improvement in results. Advances in the definition of human histocompatibility and techniques for selective removal of alloreactive T lymphocytes from the marrow graft have allowed extension of marrow transplantation to selected patients lacking an HLA-identical sibling. In this review, the current status of marrow transplantation in the treatment of lethal acquired and congenital disorders of the hematopoietic system will be discussed in the light of these advances.

FUNDAMENTAL ASPECTS OF MARROW TRANSPLANTATION

The development of marrow transplantation as a therapeutic modality has resulted from at least three major advances in transplantation biology. These include: (1) the definition of the allelic systems of the HLA gene complex, the major histocompatibility complex in man;1,4 (2) the development of chemotherapeutic and radiotherapeutic techniques immunosuppressive enough to allow engraftment of genetically foreign marrow and potent enough to achieve complete or near complete ablation of host leukemic cells prior to transplantation;5,6 and (3) development of systems for intensive support of patients during the period between pretransplant cytoreduction or immunosuppression and reconstitution of the donor's hematopoietic and lymphoid system within the transplanted host.7,8

At the present time, marrow transplants are almost exclusively reserved for the patient possessing an HLA-identical sibling donor. The HLA gene complex is usually inherited in its entirety as a component of autosome 6;10 the determinants coded by each of the parental haplotypes are codominantly expressed. HLA identity can thus be established by certifying inheritance of the same serologically typed HLA-A, B, C, and DR determinants and demonstration of HLA-D identity by mutual nonresponsiveness in mixed leukocyte culture (MLC).1,4
In the absence of a genetically determined selection at fertilization or during prenatal development, the likelihood that any one sibling will be matched is 1:4. In practice, the average patient has more than one sibling; thus HLA-identical sibling donors can be identified for 35%–40% of patients. For unclear reasons, not based on parental consanguinity, parents of patients with certain disorders, including Fanconi’s anemia, congenital agranulocytosis, severe combined immunodeficiency (SCID), and certain forms of leukemia, share HLA determinants or full haplotypes more commonly than do other married couples in the population, thus increasing the probability of identifying an HLA phenotypically identical sibling or parental donor for these patients. Indeed, in a series of 11 patients with Fanconi’s anemia, born of unrelated parents, we found 5 to be HLA-A,B,D phenotypically identical to their mothers.

Major ABO incompatibilities (e.g., A into O) do not constitute a significant barrier to marrow transplantation. To circumvent severe hemolytic reactions, two approaches have been used successfully: (1) multiple blood volume plasmaphereses of the host with either immediate replacement with specific isoagglutinin-free plasma from normal donors or autologous plasma replacement after removal of isoagglutinins on blood group antigen-bearing solid-state adsorbents, or (2) removal of ABO-bearing red cells from the marrow graft by differential centrifugation or by dextran or Hetastarch-potentiated red cell sedimentation. The latter approach is increasingly used because it avoids the fluid balance problems sometimes attending multiple volume plasmaphereses in children and cyclophosphamide-treated patients with cardiac toxicity. It also avoids other transfusion-related complications, such as hepatitis and cytomegalovirus (CMV) infection.

Engraftment of allogeneic marrow, that is, marrow from a donor other than an identical twin, in a relatively immunocompetent patient necessitates prior ablation of the host’s capacity to reject the graft or resist its development. Of the agents currently available, only cyclophosphamide and total body irradiation (TBI) administered in high doses are sufficiently immunosuppressive to permit engraftment of foreign hematopoietic cells. The standard immunosuppressive regimen that has been developed to prepare patients with aplastic anemia for transplantation is cyclophosphamide administered at a dose of 50 mg/kg on 4 consecutive days. The standard regimen used for disease ablation and immunosuppression in patients with leukemia is cyclophosphamide (60 mg/kg/day × 2 days) followed 3–4 days thereafter with total body irradiation (1,000 rad administered as a single dose at a dose rate of 5–7 rad/min. A number of modifications of these regimens have been recently introduced to improve the incidence of engraftment or to reduce the incidence of leukemic relapse or radiation-related complications. These will be discussed in reviewing results.

The actual transplant procedure has been well described. It involves harvesting of 500–800 cc of heparinized marrow from the anesthetized donor by multiple aspirations from the anterior and posterior iliac crests, heparinization, pooling and filtration of the aspirated marrow, and subsequent administration by intravenous infusion.

The major obstacles to the success of an HLA-identical sibling marrow graft are graft-versus-host disease, infections, graft rejection, and leukemic relapse. Graft-versus-host disease and associated infections are problems affecting all allogeneic marrow graft recipients. Patients with leukemia, in contrast to patients with aplastic anemia, rarely reject a matched marrow graft. However, these patients remain at risk for leukemic relapse in the posttransplant period.

Graft-versus-host disease (GVHD) is a pathologic process initiated by engrafted immunocompetent donor T lymphocytes responding to alloantigens expressed on host cells, particularly cells derived from the lymphohematopoietic system. These activated T lymphocytes are then thought to produce injury to tissues either directly, or indirectly, by educating other cell effector systems. GVHD is most commonly manifested by a generalized maculopapular rash, hepatitis, diarrhea, and a delayed reconstitution of hematopoietic and lymphoid function. Distinctive, but not pathognomonic, pathologic features include infiltration of lymphocytes and monocytes into perivascular spaces in the dermis and the dermoeidermal junction of the skin, into the epithelium of the oropharynx, tongue, and esophagus, into the base of the intestinal crypts of the small and large bowel, and into the periportal areas of the liver, with secondary necrosis of cells in infiltrated tissues.

Acute GVHD develops in 30%–70% of patients transplanted with HLA-identical marrow and may be an indirect cause of death in 20%–40% of affected individuals. Certain host characteristics have been associated with an increased risk of GVHD in multiple studies. These include: increased host age, recipients of marrow grafts from female donors, and recipients who, prior to transplant, are found to have normal to increased activity of natural killer cells, as assessed on herpes-infected fibroblast targets. The alloantigenic disparities stimulating GVHD following HLA-matched grafts are not known, but are presumed to be coded by genes unrelated to the major histocompatibility complex (MHC). Initial reports...
implicating disparities for minor red cell antigens (MNS) or sex-linked antigens in the pathogenesis of GVHD in man have not been substantiated in larger series. Lymphocytotoxins reactive against host non-HLA determinants frequently develop following transplantation. However, the allospecificities of these antibodies have not been characterized. Furthermore, their appearance has not been linked to GVHD. Cytoxic T cells specifically reactive against trinitrophenol (TNP)-modified host fibroblasts have recently been detected in a high proportion of patients with GVHD. The functions of “autoreactive” non-T-cell populations, presumptively of donor type, which are cytotoxic for donor-type fibroblasts and are capable of inhibiting the growth of donor-type myeloid progenitors (CFU-C) have also been found to be enhanced in patients with acute GVHD. Recent studies by Delmonte et al. suggest that these radioresistant non-T-cell suppressor cells can be generated in mixed leukocyte cultures (MLC) between certain HLA-identical sibling pairs. Generation of such suppressor cells in an MLC between a patient and his HLA-identical sibling has been highly predictive for subsequent development of acute GVHD. Minor allodisparities between donor and recipient likely stimulate the generation of both the “alloreactive” donor T cells and “autoreactive” non-T-cell populations observed during acute GVHD. Analysis of the reactivity of expanded populations of these cells against cells derived from related individuals within large family pedigrees should ultimately permit definition of these minor alloantigenic systems and their inheritance in relationship to other mapped determinants within the human genome. Accurate prediction of patients at risk for GVHD will permit more selective use of immunosuppressive agents for prevention of GVHD, agents which, of themselves, may delay hematopoietic and immunologic reconstitution in the posttransplant period.

The pathophysiology of acute GVHD in recipients of HLA-matched marrow grafts is still poorly understood. While it is generally accepted that engrafted alloreactive T lymphocytes initiate this process, the relative contributions of these cells and other cells of donor or host origin to the disease process are difficult to assess. Activated T lymphocytes with a suppressor/killer phenotype develop early in the posttransplant period in all patients, well before emergence of normal helper T-cell populations. In our sequential studies of allogeneic marrow graft recipients, we have observed persistent imbalances of T-cell subsets in patients with acute GVHD that have normalized with resolution of this process, suggesting that T cells of suppressor/killer phenotype might contribute to acute GVHD. As noted above, Tsoi et al. have detected T cells cytotoxic for hapten-modified host cells during acute GVHD. Delmonte et al. have also detected T cells capable of inhibiting CFU-C growth in the circulation of a large proportion of patients with acute GVHD. Recently, Tutschka et al. have also shown that cells of suppressor/killer phenotype predominate in the subepidermal lymphoid infiltrates of cutaneous GVHD, further suggesting that T cells of this class directly contribute to GVH pathology. As described above, non-T-cell populations, particularly certain natural killer (NK) cells, are also prominent during acute GVHD. Whether these cells directly contribute to GVH pathology or to the prolonged myelosuppression and immunodeficiency observed during GVHD is yet unclear.

The treatment of acute GVHD in HLA-matched marrow transplants currently involves administration of corticosteroids with or without antithymocyte globulin (ATG). This approach is still inadequate in many cases. Prophylactic administration of methotrexate at low dosage for the first 100 days posttransplantation was shown to significantly reduce the incidence and severity of GVHD when administered to dogs, and has become a standard, albeit only partially effective, GVH prophylaxis for human marrow graft recipients. Attempts to further abrogate GVHD through prophylactic administration of antithymocyte globulin have not been successful. Studies from the University of Minnesota suggest that prophylactic administration of a combination of methotrexate, steroids and antithymocyte globulin may reduce the severity of GVHD, but does not improve overall survival. Recently, highly selective immunosuppressive agents, particularly cyclosporine and antibodies specific for T lymphocytes, have shown promise in preventing severe acute GVHD both in animal models and in man.

Most patients with acute GVHD will experience a spontaneous resolution of this process. It has been hypothesized that the emergence of graft-host tolerance is an active phenomenon, dependent on the development of suppressor cells capable of controlling the GVH reaction. However, while the evidence for a suppressor-cell-mediated tolerance following allogeneic marrow grafts in rat models is impressive, it has not been well documented in other species, including man. Equally tenable is the hypothesis that GVHD resolves as critical blood-derived host targets in the tissues are replaced by donor cells. Early studies by Elkins et al. and Streihlein et al. had suggested that blood-derived cells in the tissues, such as Langerhans cells in the skin, were the principal targets of alloaggressive donor cells in the GVH reaction. Recent studies in transplant models, employing techniques...
such as local ultraviolet irradiation to deplete these cells from target tissues, such as the skin, have supported this hypothesis. Considerable research is thus needed to define the reasons for GVH resolution and the basis for the durable graft–host tolerance that ultimately develops.

Between 15% and 40% of transplanted patients will develop chronic GVHD, a process pathologically distinct from acute GVHD, which may result in localized or widespread scleroderma changes of the skin, skin and joint contractures, xerostomia, xerophthalmia, biliary cirrhosis, malabsorption, and failure to thrive. Immunologic abnormalities associated with chronic GVHD include increased populations of suppressor T lymphocytes and monocytes capable of nonspecific suppression of T-cell transformation and B-cell antibody production, in vitro IgG antibodies against host epithelial cells, immune complex deposition resulting in complement activation, complex deposition (particularly in skin), profound and prolonged deficiencies of humoral immunity, resulting in enhanced susceptibility to infection with encapsulated pathogenic bacteria. Recently, long-term treatment with a combination of azathioprine and prednisone has been shown to be effective in ameliorating the clinical manifestations of chronic GVHD.

The infectious complications of marrow transplantation distinguish the three major stages of development of the donor marrow in the posttransplant period. Prior to engraftment, patients are particularly sensitive to those infections observed in chemotherapyproduced pancytopenic states, such as septicemias due to fungi and enteric bacteria, and disseminated infections due to herpes simplex or herpes zoster. Latent papovavirus infections are also frequently activated during this period and may produce hepatitis or mild encephalitis. Decontamination with nonabsorbable antibiotics in laminar flow protective isolation and the use of prophylactic granulocyte infusions have been reported to be effective in reducing the incidence of serious bacterial and fungal infections in the immediate posttransplant period. However, prophylactic granulocyte infusions enhance the risk of acquiring certain virus infections, particularly infections due to CMV. Severe herpes simplex infections in transplant recipients can be prevented by prophylactic administration of acycloguanosine. This prophylaxis does not compromise engraftment. Studies in which acycloguanosine has been used for the treatment of disseminated herpes zoster and herpes simplex infections, such as occur in the early posttransplant period, have also been encouraging.

During early engraftment, particularly in patients with GVHD, infections eliciting and possibly requiring a significant mononuclear cell response for their pathology are observed, particularly cytomegalovirus (CMV), adenovirus, and Pneumocystis carinii-induced pneumonia. The allogeneic reaction between donor and host is important to the pathogenesis of severe CMV infections. Such infections are observed rarely, if at all, following twin transplants, and are most common in patients with severe GVHD. Whether such infections are activated by GVHD or promote the GVHD process by altering cell surface expression of alloantigens, as is seen in Epstein-Barr virus (EBV) transformed cells, or merely result from the selective immunodeficiencies associated with GVHD is unknown. In a series of 122 patients transplanted for leukemia at Memorial Sloan-Kettering Cancer Center (MSKCC), interstitial pneumonia was observed in 39 patients (32%). As in other series, the most common etiologies were CMV, followed by P. carinii. However, in 22/39 cases (56%), no etiology could be defined. A small proportion of these cases might be ascribed to radiation injury. However, the majority of these idiopathic cases probably reflect the continuing inadequacy of existing techniques for rapid and accurate detection and identification of viral pathogens. In the immediate future, the use of scanning electron microscopic techniques and pathogen-specific monoclonal antibodies for detection of antigens expressed by viruses or other pathogens in tissues, tissue homogenates, or body fluids may improve the accuracy and rapidity of diagnosis. Current treatment for interstitial pneumonia in the posttransplant period remains largely ineffective. Pneumocystis carinii infection can be treated and prevented by the administration of trimethoprim-sulfa. A number of antiviral agents, specifically interferon, adenine arabinoside, and acycloguanosine have failed either to arrest interstitial pneumonia due to cytomegalovirus or to prevent its development. Preliminary results from the MSKCC and UCLA transplant teams suggest that the prophylactic administration of hyperimmune globulin or plasma may be effective in preventing CMV infections. New antivirals, such as 2′-fluoro-5-ido-arabinosylcytosine (FIAC), are also under trial.

Late in the posttransplant period, herpes zoster infections and infections due to encapsulated pyogenic bacteria are most common and are particularly seen in patients with chronic GVHD. Indeed, the spectrum of bacterial infections observed in such patients is similar to that seen in patients with Bruton’s agammaglobulinemia and may well reflect the prolonged state of humoral immunodeficiency affecting patients with chronic GVHD.

Susceptibility to severe forms of GVHD and to
transplant-associated infections increases with age, resulting in an increased mortality, particularly for patients transplanted in the third and fourth decades of life. This is illustrated in Fig. 1, which displays a comparison of disease-free survival observed in “good-risk” patients transplanted at MSKCC for acute leukemia in first or second remission who are younger or older than 20 years of age. Relapse incidence was equal in both groups; differences in disease-free survival were principally due to differences in early infection-related deaths, which affected 15% and 40% of the younger and older patient groups, respectively. Similar age-related disparities in disease-free survival have also been reported by other groups in patients transplanted both for aplastic anemia and for leukemia.

Multiple factors may contribute to the high incidence of lethal infections observed in older transplant recipients. Severe forms of GVHD, which are more common in patients after the first decade, may delay immune and hematopoietic reconstitution. Immunosuppressive treatment of GVHD likely accentuates this problem. Immune reconstitution may also be limited in older patients, particularly patients over 25, due to age-related deficiencies of the thymus and factors such as thymic hormones and interleukins, which are necessary for expansion and differentiation of engrafted donor lymphoid elements. Insults sustained by lung, liver, or gastrointestinal tissue may also have a cumulative effect, reducing tissue resistance in older patients. Furthermore, seroepidemiologic evidence clearly establishes that patients in the second and later decades are more likely to be seropositive and presumptively latently infected with CMV, herpes simplex virus (HSV), and herpes zoster, thereby enhancing their risk of an infection due to reactivation of these viruses. Indeed, Neiman et al. have shown that seropositive patients have a higher incidence of CMV infections.

Improved prophylactic measures against GVHD and viral infections may reduce early mortality in older transplant recipients. A number of groups are also exploring therapies designed to facilitate immunologic recovery. For example, Atkinson et al. initially examined whether administration of cultured thymus to transplant recipients would enhance immune reconstitution and thereby reduce infectious deaths in the early posttransplant period. In these early trials, no benefit was realized in the treated group. However, these therapeutic trials were initiated in patients without prior determination of their thymic secretory function. In future trials, improved selection of patients who might be benefited by thymus replacement may yield a different result. Additional trials are in progress to determine the therapeutic effects of other potential immunomodulators, such as the interleukins or isolated thymic peptides, on the course and quality of immunologic recovery in older patients and, concurrently, to assess the effects of such therapeutic manipulations on the susceptibility of older patients to transplantation-related infectious complications.

Fig. 1. The Memorial Sloan-Kettering Cancer Center experience with allogeneic marrow transplantation for patients with AML in first or second remission and ALL in second remission. (○) Age less than 20 yr (37 patients), (△) age greater than or equal to 20 yr (26 patients). Tick mark (') indicates last follow-up.
py. As reported by Thomas et al.,38 of 100 such patients prepared with a lethal dose (1,000 rad) of total body irradiation and cyclophosphamide (60 mg/kg/day x 2) and transplanted with marrow from a normal HLA-identical sibling, 13 survived over 5 yr in continuous remission without further chemotherapy. Similarly treated patients transplanted with marrow from identical twins enjoyed a 30% incidence of long-term disease-free survival.134,135 Differences in results between twin and HLA-matched marrow grafts reflected principally an increased mortality in allogeneic marrow graft recipients caused by graft-versus-host disease and associated infections. Recurrence of leukemia was common in both transplant groups, but was particularly prominent (60%) in recipients of twin marrow grafts.134,135

In 1979, Thomas et al.136 reported a 63% long-term disease-free survival in a series of patients transplanted for acute myelogenous leukemia (AML) in first remission. Subsequent reports from other major centers (summarized in Table 1)137-144 have confirmed these results. At present, the cumulative results from reporting centers indicate a 60% probability of disease-free survival. The cumulative incidence of relapse in the posttransplant period has been low (12%).137-144

Transplantation for acute lymphocytic leukemia in second remission has also emerged as a particularly promising approach, with long-term disease-free survival in 40% of cases or more.139, 145-149 Reported experience of transplants for acute lymphoblastic leukemia (ALL) in second remission is summarized in Table 2. As can be seen, the incidence of posttransplant relapse is higher than that observed in patients with AML in first remission. Whether this relapse rate is due to the biology of acute lymphoblastic leukemia itself or to a resistance to chemotherapy and radiotherapy developed during induction and maintenance of the patient’s primary remission remains to be determined.

To date, only two centers have analyzed their experience with transplants for AML in second remission. The patient groups are small and the results divergent. Buckner et al.150 have described 24 such patients, 8 of whom survive, 7 in continuous remission 4-42 mo postransplant. In this group, 5 patients relapsed, 4 within 6 mo of transplant. The disease-free survival at 2 yr was 24% and did not differ from that of patients with AML transplanted in relapse. In our own series, of 11 patients prepared for transplants by a different cytoreductive regimen, 7 survive in continuous remission 16-37 mo postgrafting. To date, no relapse has been recorded in this group.157 The 3-yr disease-free survival for this group (64%) does not differ from that obtained for patients transplanted in first remission. More extensive comparative studies of transplants applied to patients with AML in first or second remission are needed to assess to what degree transplants performed in primary remission are more advantageous to a patient’s long-term disease-free survival, and to further clarify how and when transplants can be most effectively applied towards the curative treatment of AML both in children and adults.

While few now contest the advantages of marrow transplants over chemotherapy in the treatment of leukemic patients who have relapsed during maintenance of their initial remission, the comparative merits of chemotherapy and transplantation in the initial treatment of acute nonlymphoblastic leukemia (ANL)

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**Table 1. Marrow Transplantation: AML in First Remission**

<table>
<thead>
<tr>
<th>Center</th>
<th>Preparative Regimen*</th>
<th>GVT Prophylaxis</th>
<th>No. of Patients</th>
<th>Disease-Free Survival (%)</th>
<th>Relapse Rate (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fred Hutchinson</td>
<td>CTX + 1,000 rad TBI</td>
<td>MTX</td>
<td>75</td>
<td>55 (2 yr)</td>
<td>10</td>
<td>136, 138</td>
</tr>
<tr>
<td>Seattle</td>
<td>CTX + FrTBI - 1,200 rad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>CTX + 1,000 rad TBI</td>
<td>Cyclosporine-A</td>
<td>22</td>
<td>64 (1 yr)</td>
<td>18</td>
<td>140</td>
</tr>
<tr>
<td>London</td>
<td>CTX + Hyperfractions TBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Memorial</td>
<td>CTX + 1,320 rad with lung shielding</td>
<td>MTX</td>
<td>34</td>
<td>60 (2 yr)</td>
<td>8</td>
<td>137</td>
</tr>
<tr>
<td>Sloan-Kettering</td>
<td></td>
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<tr>
<td>New York</td>
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<td></td>
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<tr>
<td>UCLA</td>
<td>CTX + 1,000 rad TBI</td>
<td>MTX</td>
<td>22</td>
<td>52</td>
<td>20</td>
<td>142</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>CTX + 1,000 rad TBI</td>
<td>MTX</td>
<td>11</td>
<td>45</td>
<td>18</td>
<td>139</td>
</tr>
<tr>
<td>City of Hope</td>
<td>CTX + 1,000 rad TBI</td>
<td>MTX</td>
<td>17</td>
<td>64 (2 yr)</td>
<td>12</td>
<td>143</td>
</tr>
<tr>
<td>Dominican</td>
<td>CTX + 750 rad TBI</td>
<td>MTX</td>
<td></td>
<td></td>
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<tr>
<td>Minneapolis</td>
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<td></td>
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<tr>
<td>Johns Hopkins</td>
<td>CTX + Bu</td>
<td>CYA</td>
<td>11</td>
<td>64 (1 yr)</td>
<td>0</td>
<td>141</td>
</tr>
<tr>
<td>Baltimore</td>
<td>CTX + 800 rad TBI with lung shielding</td>
<td>MTX</td>
<td>11</td>
<td>70 (2 yr)</td>
<td>0</td>
<td>144</td>
</tr>
</tbody>
</table>

*CTX, cyclophosphamide; TBI, total body irradiation; FrTBI, fractionated dose total body irradiation; MTX, methotrexate.*
and some forms of ALL are subjects of intense debate. Until recently, chemotherapeutic approaches to the treatment of AML have been marked by remission inductions in only 40%-60% of patients, with only 30%-50% of these patients sustaining their remissions through the first year. In the last 3 yr, however, the application of more intensive induction, consolidation, and maintenance regimens to the treatment of AML has resulted in remission inductions in 70%-90% of patients, with up to 69% of the remissions sustained for more than 1 yr. The results of the VAPA protocol developed by Weinstein et al. have been particularly heartening. In a recent update of this experience, Mayer et al. have reported a remission induction rate of 70%. Of 67 patients initially induced into remission, 33 (49%) have survived in continuous remission for a median of 19 months postinduction, a disease-free survival comparable to that reported by several centers in patients transplanted for ANL in first remission. However, these results principally reflect the success (55% disease-free survival at 2 yr) achieved in younger patients (<17 yr), a group for which a transplant now offers a >70% probability of long-term (>3 yr) disease-free survival in a number of centers. Of concern, also, is the high incidence of relapse both during and after completion of maintenance therapy, a complication affecting 50% of the patients who achieve initial remission. Thus, a comparison of the efficacies of transplantation or chemotherapy in the treatment of AML in first remission would appear to hinge on the relative advantages of the higher early survival observed in patients receiving chemotherapy, and the increased curative potential of a transplant that may significantly differentiate the transplant group only later in the treatment course. Such a comparison must also consider the morbidity associated with 15 or more months of intensive maintenance chemotherapy, a feature of chemotherapy regimens that is rarely discussed, and the often cited problem of graft-versus-host disease. To place the problem of GVHD in perspective, it should be remembered that while GVHD affects 30%-70% of transplant recipients and is a major, albeit indirect, contributor to early mortality, it usually resolves early in the posttransplant course and imposes a clinically significant, long-term impairment to normal health and activity in only a small fraction (10%-15%) of the transplanted population.

Recently, a series of single institutional and multiinstitutional cooperative trials have been established to compare chemotherapy and marrow transplantation in the treatment of AML in first remission. A preliminary report of one such trial being conducted at MSKCC indicates some, as yet insignificant, advantage in disease-free survival for the transplant group. This advantage principally reflects the excellent results of transplants in patients under 20 yr of age. In older groups, there is, as yet, no discernible difference in disease-free survival between the chemotherapy arm and the transplant arm of the study. Further patient accrual and follow-up will be necessary before a definitive result can be established.

The low incidence of leukemic relapse and high rate of disease-free survival observed following transplants for ANL in first remission has stimulated a number of investigators to ask whether a transplant should be considered for transplantation in first remission. Children developing lymphoblastic leukemia in the first year of life, adolescents presenting with the leukemia-lymphoma syndrome, and patients with acute B-cell leukemias have a high risk of relapse and have been considered for transplantation in first remission. However, experience with such transplants is still restricted. Furthermore, the acute mortality in reported cases has been high enough to obfuscate any short-term advantage of transplants. Recent improvements in chemotherapy have also significantly improved chances for extended remission, even in patients with high-risk forms of ALL, thereby further limiting accurate identification of appropriate candidates for transplants. Thus, considerably more...
experience is needed to determine whether transplants offer a higher probability of extended relapse-free survival to the patient who, by the phenotypic characteristics of his/her leukemia or its slow response to initial induction therapy, is currently considered at high risk for early relapse.

Leukemic relapse is now the major obstacle to the success of transplants for acute leukemia, particularly acute lymphocytic leukemia. In the past, attempts to intensify pretransplant cytoreduction regimens have failed to increase long-term disease-free survival. Long-term antileukemic benefits have been outweighed by a high mortality in the early posttransplant period resulting from drug toxicity. As transplants are applied to patients earlier in their disease course, such regimens may prove more tolerable and effective. Many groups are exploring the use of higher fractionated doses of radiation for leukemic ablation. For example, at MSKCC, we have been evaluating the use of hyperfractionated total body irradiation with partial lung shielding in an attempt to reduce tissue injury that predisposes to complications such as interstitial pneumonia, while increasing the antileukemic effect of pretransplant cytoreduction. Initial results, summarized in Table 2, are encouraging. The incidence of leukemic relapse in patients with ALL and AML in secondary remission transplanted with this regimen has been extraordinarily low. The use of interferon and leukemia-reactive monoclonal antibodies to potentiate host resistance to leukemia in the posttransplant period is also under study.

The advantage of an allogeneic marrow graft in reducing the incidence of posttransplant relapse is increasingly apparent. For example, in a compilation of the reported experience of major centers with transplants for AML in first remission (Table 3), the incidence of relapse in the posttransplant period has been found to be 12% in recipients of HLA-matched marrow grafts, whereas the incidence in recipients of identical twin marrow grafts is over 50%. Weiden et al. have presented evidence that patients with GVHD experience a lower incidence of leukemic relapse and are now exploring methods to potentiate this graft-versus-leukemic response. However, mounting evidence from studies in rodent transplant models (Table 4) suggests that the “graft-versus-leukemia” effect can often be distinguished from GVHD and may be achieved by transfer of hematopoietic cells derived from genetically resistant donors. Further research into the biology of the allogeneic transplant advantage in leukemic patients may identify analogous, genetically controlled resistance systems in man.

Allogeneic marrow transplantation is also being explored as an approach to the treatment of other refractory hematologic malignancies. Applebaum et al. reported a favorable experience with transplants of marrow from identical twins in the treatment of non-Hodgkin’s lymphoma. Reports of patients with non-Hodgkin’s lymphoma, Burkitt’s lymphoma, and multiple myeloma successfully treated with allogeneic marrow grafts have spawned formal clinical trials in a number of transplant centers. Allogeneic marrow grafts for chronic myelogenous leukemia (CML) were initially evaluated by the Seattle group in patients after onset of blast crisis, with disappointing results. Recently, however, the Seattle group and others have recorded sustained disease-free survival in over 60% of patients with CML who have been transplanted either in chronic phase or early in the accelerated phase of their disease. Follow-up observations over the next 5 yr will document whether these transplant recipients, who are now Ph-chromosome negative, remain free of disease, and whether a potentially curative approach has been realized.

### Table 3. Marrow Transplantation for AML—First Remission

<table>
<thead>
<tr>
<th></th>
<th>Total Patients</th>
<th>Relapses—Posttransplant</th>
<th>Overall Proportion Relapsing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic (HLA-matched)</td>
<td>181</td>
<td>22</td>
<td>12%</td>
</tr>
<tr>
<td>Identical twins</td>
<td>15</td>
<td>8</td>
<td>53%</td>
</tr>
</tbody>
</table>

*Data compiled from reported experience at Memorial Sloan-Kettering Cancer Center, the Fred Hutchinson Cancer Research Center, UCLA, the Royal Marsden Hospital, City of Hope Medical Center, and the University of Minnesota.
long-term survival with hematopoietic recovery, a result not significantly different from that observed in age-matched controls. The success of marrow transplants for aplastic anemia has been limited by problems of graft-versus-host disease and infection, which affect all marrow transplant recipients, and by graft rejection. Rejection of a marrow graft is heralded by the persistence or recurrence of aplasia in the posttransplant period and is documented by the relatively abrupt replacement of donor-derived hematopoietic and lymphoid elements with lymphoid cells of host origin. As demonstrated by Storb et al., most instances of graft rejection can be ascribed to relatively cyclophosphamide-resistant host lymphocytes previously sensitized to minor donor alloantigenic determinants through prior blood transfusions. Thus, the incidence of graft rejection among untransfused aplastic marrow transplant recipients prepared with cyclophosphamide alone is 10%, but is as high as 30%–59% in similarly prepared patients who have received extensive transfusion support. Sensitization may, indeed, preclude engraftment if the patient has been previously transfused with cells from related donors. Rare instances of graft failure may also be ascribed to abnormalities of the marrow microenvironment of the host. Two aplastic anemia patients transplanted in our series, for example, developed full donor-type lymphoid chimerism, yet failed to recover hematopoietic function.

Attempts to reduce the incidence of graft rejection by intensifying the preparative immunosuppressive regimen have yielded equivocal results (Table 5). Aplastic patients prepared with cyclophosphamide (60 mg/kg/day × 2) and 1,000 rad TBI rarely reject marrow grafts, but have poor (30%) long-term survival. The use of chemotherapeutic combinations, such as procarbazine and antithymocyte globulin or cytosine arabinoside and 6-thioguanine, or limited dose or field irradiation (e.g., total body irradiation in conjunction with cyclophosphamide, have reduced the incidence of rejection to less than 10% in multiply transfused patients, yet long-term survival with hematopoietic reconstitution is still only 50%–60%. Recently, however, Ramsay et al. have reported a reduced incidence of rejection and improved long-term survival in sensitized patients prepared for transplantation with total lymphoid irradiation and cyclophosphamide.

The Seattle group has continued to use cyclophosphamide alone to condition patients with severe aplastic anemia for marrow transplantation. Reviewing the features of transplants resulting in rejection, they noted that this complication was rarely observed in patients receiving high marrow cell doses. Accordingly, their preparative regimen has been modified to include daily infusion of donor peripheral blood buffy coat during the first week posttransplant. Of 16 heavily sensitized patients receiving marrow alone, 13 rejected the graft, while only 3 rejections have been observed in 23 sensitized patients receiving both marrow and buffy coat.

### Table 4. Evidence for Dissociation of GVH From Graft-Versus-Leukemia

<table>
<thead>
<tr>
<th>Tumor Model</th>
<th>Resistant Marrow Donor</th>
<th>Susceptible Host</th>
<th>GVH Abrogation Technique</th>
<th>Development of Tumor in Chimeras</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKR leukemia</td>
<td>DBA/2</td>
<td>AKR</td>
<td>Germ-free</td>
<td>Prevented</td>
<td>171, 172</td>
</tr>
<tr>
<td>AKR leukemia</td>
<td>C57BL/6J</td>
<td>AKR</td>
<td>Graft pretreatment with anti-θ</td>
<td>Prevented</td>
<td>176</td>
</tr>
<tr>
<td>AKR leukemia</td>
<td>DBA/2</td>
<td>AKR</td>
<td>Graft pretreatment with anti-θ</td>
<td>Decreased incid. of recurrence</td>
<td>175</td>
</tr>
<tr>
<td>Reticulum cell sarcoma</td>
<td>SJL</td>
<td>C3H/He</td>
<td>Germ-free</td>
<td>Prevented</td>
<td>173</td>
</tr>
<tr>
<td>Rauscher’s leukemia</td>
<td>F₁ (SJL/J x C57BL/10J)</td>
<td>SJL/J</td>
<td>F₁ donor</td>
<td>New disease prevented, delayed recurrence</td>
<td>174</td>
</tr>
<tr>
<td>BN myelogenous leukemia</td>
<td>Lewis</td>
<td>F₁ (Lewis x BN)</td>
<td>None</td>
<td>Decreased incid. of recurrence</td>
<td>177</td>
</tr>
<tr>
<td>B-cell leukemia</td>
<td>C57BL/6</td>
<td>F₁ (BALB/c x C57BL/6)</td>
<td>TLI</td>
<td>Decreased incid. of recurrence</td>
<td>178</td>
</tr>
</tbody>
</table>
Table 5. Allogeneic Marrow Transplantation for Aplastic Anemia: Single Center Experiences

<table>
<thead>
<tr>
<th>Center</th>
<th>Type of Patient</th>
<th>Preparative Regimen</th>
<th>Total Patients Evaluable</th>
<th>Incidence of Rejection</th>
<th>Survival With Hematopoietic Engraftment and Recovery</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. Hutchinson Cancer Ctr.—Seattle</td>
<td>Untransfused</td>
<td>CTX</td>
<td>30</td>
<td>10%</td>
<td>75%</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>Transfused</td>
<td>CTX vs. CTX + buffy coat Pcb, ATG, CsA</td>
<td>22</td>
<td>32%</td>
<td>50%</td>
<td>212</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>43</td>
<td>9%</td>
<td>70%</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>38%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Brigham—CHMC—Boston</td>
<td>Transfused</td>
<td>Pcb, ATG, TBI</td>
<td>14</td>
<td>9%</td>
<td>64%</td>
<td>205</td>
</tr>
<tr>
<td>UCLA—Los Angeles</td>
<td>Transfused</td>
<td>CTX + 300 rad TBI</td>
<td>23</td>
<td>6%</td>
<td>50%</td>
<td>209</td>
</tr>
<tr>
<td>Switzerland (Basel)</td>
<td>Transfused</td>
<td>CTX</td>
<td>19</td>
<td>17%</td>
<td>47%</td>
<td>239</td>
</tr>
<tr>
<td></td>
<td>Transfused</td>
<td>CTX + 800 rad TBI</td>
<td>18</td>
<td>0%</td>
<td>55%</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23</td>
<td>15%</td>
<td>39%</td>
<td>210</td>
</tr>
<tr>
<td>Johns Hopkins—Baltimore</td>
<td>Transfused</td>
<td>CTX or Pcb, ATG + 800 rad TBI (with partial lung shielding)</td>
<td>23</td>
<td>9%</td>
<td>52%</td>
<td>207</td>
</tr>
<tr>
<td>MSKCC—New York</td>
<td>Transfused</td>
<td>CTX, Ara-C, 6-TG</td>
<td>23</td>
<td>9%</td>
<td>52%</td>
<td>207</td>
</tr>
<tr>
<td>Minnesota</td>
<td>Transfused</td>
<td>CTX, TLI</td>
<td>37</td>
<td>3%</td>
<td>69%</td>
<td>211</td>
</tr>
<tr>
<td>Royal Postgrad. Med. Sch.—London</td>
<td>Transfused</td>
<td>CTX, CsA</td>
<td>23</td>
<td>4.5%</td>
<td>73%</td>
<td>213</td>
</tr>
</tbody>
</table>

Long-term survival in this group was 70%, but an increased incidence of morbidity due to chronic GVHD has been observed.

In summary, each of the above modifications of the standard cyclophosphamide regimen for pretransplant immunosuppression has resulted in a reduction in the incidence of graft rejection, but has been associated with a higher incidence of morbidity due either to increased immunosuppression or to GVHD. Thus, the overall survival for sensitized aplastic recipients of marrow grafts has been only slightly improved. Recently, Hows et al. have reported a study of cyclosporine prophylaxis against GVHD in 23 multiply transfused aplastic marrow transplant recipients prepared for transplant with cyclophosphamide alone. Of these patients, 16 (70%) are surviving with reconstitution. While the incidence of GVHD was not significantly altered, GVH-associated mortality appeared to be reduced. More importantly, only 3 instances of graft failure or rejection were observed in the cyclosporine-treated group. This initial study and the experience with total lymphoid irradiation reported by Ramsey et al. suggest that more selective methods for modulation of the host environment in which the donor’s immune system develops may not only modify GVHD, but may also influence engraftment in the sensitized patient, thereby leading to improved results.

The application of bone marrow transplantation to the treatment of patients with aplastic anemia was initially based on the assumption that the primary disorder in most cases is a defect in hematopoietic stem cells. This concept was strongly supported by the successful outcome of initial syngeneic marrow infusions in monozygotic twins with severe aplastic anemia who received no prior immunosuppression. In the past 7 yr, this concept of the pathogenesis of aplasia has required extensive revision.

In 1970, Mathe et al. reported 7 patients with aplastic anemia, 3 of whom experienced partial recovery of autologous hematopoietic function following immunosuppression with an antilymphocyte globulin (ALG) and an infusion of HLA-mismatched marrow. Subsequently, Speck et al. demonstrated that similar treatment of rabbits with 32P-induced or benzene-induced aplasia was often followed by spontaneous recovery of autologous hematopoietic function. Thereafter, a number of studies attributing reduced in vitro growth of erythroid and myeloid progenitors in patients with aplastic anemia to an active I-cell-mediated suppression were reported. However, the significance of these in vitro observations to the pathogenesis of aplastic anemia has been questioned. First, cell depletion experiments are frequently difficult to interpret when severely aplastic marrow is used as the source of hematopoietic indicator cells and cell concentrations are so reduced as to magnify test variability. Second, results of other experiments utilizing allogeneic cells in coculture may reflect transfusion-induced sensitization rather than a true autoimmune response. Third, correlations between results of in vitro tests and subsequent in vivo responses to immunosuppressive therapy have been, until recently, very inconsistent.
have reinforced the hypothesis that “autoimmune” phenomena contribute to the pathogenesis of aplastic anemia in a significant proportion of cases. For example, Lu et al. \(^232\) recently reviewed the published reports of 23 patients with severe aplastic anemia who received syngeneic marrow grafts. In 10 of these patients, aplasia recurred, suggesting that the disease was ultimately based on causes other than a defective stem cell. \(^232\) In 7 of these 10 cases, the bone marrow infusion was repeated following conditioning with cyclophosphamide; these secondary grafts produced prompt marrow recovery. Autologous bone marrow repopulation has also been seen in a number of patients following treatment with high-dose cyclophosphamide alone or cyclophosphamide and allogeneic marrow transplantation. \(^233\)-\(^237\) These results again suggest that certain forms of aplastic anemia may be due to an active cell-mediated suppression of hematopoiesis that can be overcome by pretreatment with immunosuppressive agents such as cyclophosphamide.

In 1977, Speck reported on 29 patients with severe aplastic anemia who were treated with anti-thoracic duct lymphocyte globulin (ATDLG) alone or ATDLG followed by infusion of hemiallogeneic marrow. \(^238\) The overall response to both forms of treatment (expressed as survival at 1 yr) was 55%, with 12/29 showing a sustained hematologic improvement during a period of observation of up to 4.5 yr. More recently, Speck et al. have reported results of a trial comparing marrow transplantation with a treatment protocol involving administration of androgens and ATDLG, with or without an infusion of HLA-haploidentical marrow. Survival in the transplant group was 44%, whereas that in the ATDLG group was 70%. \(^239\) Although patients treated with ATDLG did not often achieve the full hematopoietic recovery seen postransplantation, 62% were rendered transfusion independent.

Initially, certain centers, using different equine antibody preparations, failed to confirm the findings of Speck et al. \(^240\) Favorable results were therefore ascribed to the higher proportion of patients in Speck’s series with chronic or less severe forms of aplasia who would likely enjoy an improved chance of survival. \(^241\),\(^242\) However, recently, the groups at UCLA and Seattle, using an identical lot of horse antithymocyte globulin (Upjohn, Kalamazoo, MI), have reported survival rates of 69% and 50% in two series of patients with severe aplasia. \(^243\),\(^244\) Furthermore, a multicenter trial to investigate the regimen proposed by Speck et al., \(^239\) which included the preparation of ATDLG used in their study, is now completed. Results of this prospective, randomized trial confirm Speck’s observations. \(^245\) Of the patients treated with ATDLG, androgens, and an infusion of hemiallogeneic marrow, 76% survived at 2 yr, as compared to a 31% 2-yr survival in the control group treated with androgens and supportive care alone (\(p < 0.002\)). An important finding of this study was that each of 8 patients > 20 yr of age treated with ATDLG achieved transfusion independence and survival.

Given these increasingly encouraging results, a question must be raised as to the appropriate primary therapeutic approach to a patient with severe aplasia who has a matched sibling donor. A transplant would still seem appropriate for the young or minimally transfused aplastic patient. However, for multiply transfused or older patients, primary immunosuppressive therapy may be the most salutary approach. Further research is needed to define the specificities of antibodies in therapeutically useful anti-thoracic duct or antithymic lymphocyte globulin preparations and to determine how this brief course of “immunosuppressive” therapy so alters the immune or hematopoietic system as to stimulate or permit recovery of autologous marrow function.

**OTHER INDICATIONS FOR MARROW TRANSPLANTATION**

Marrow transplantation has long been the treatment of choice for all forms of severe combined immunodeficiency (SCID). \(^246\),\(^247\) In a recent review of the international experience with transplants for SCID, \(^247\) we found a 55% disease-free survival following marrow transplantation. Failures were principally ascribed to interstitial pneumonia developing early in the course of immune reconstitution. Both the lymphoid and platelet abnormalities of the lethal sex-linked disorder, Wiskott-Aldrich’s syndrome, can be corrected by a marrow transplant, provided a myeloablative agent, such as total body irradiation or busulfan, is administered in conjunction with standard high-dose cyclophosphamide. \(^248\),\(^249\) The combination of busulfan and cyclophosphamide has been particularly tolerable, with successful grafts and long-term survival documented in each of 9 cases in which it has been used.

Marrow transplantation has also been applied to the treatment of a number of congenital aregenerative anemias. Successful grafts have been reported in patients with reticular dysgenesis, \(^250\) congenital agranulocytosis, \(^251\) agranulocytosis with cartilage-hair hypoplasia syndrome, \(^252\) and congenital red cell aplasia \(^253\) (Table 6).

Marrow transplantation was initially expected to provide a definitive treatment for Fanconi’s anemia (FA). \(^199\) Recently, however, Gluckman et al. have reported an increased incidence of lethal complications in this transplant group. \(^254\) Of five patients transplanted for Fanconi’s anemia, only one became a
Table 6. Allogeneic Marrow Transplants for Other Lethal Blood Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Abnormality</th>
<th>Patients</th>
<th>Preparative Regimen*</th>
<th>Engraftment</th>
<th>Surviving (with Reconstitution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticular dysgenesis</td>
<td>Hematopoietic Stem Cell</td>
<td>1</td>
<td>Busulfan, CTX</td>
<td>Complete</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fanconi’s anemia</td>
<td>Hematopoietic</td>
<td>23</td>
<td>Cytoxan</td>
<td>Complete</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Congenital red cell aplasia</td>
<td>Red Cell</td>
<td>1</td>
<td>ATG, Pcb, TBI</td>
<td>Complete</td>
<td>0</td>
</tr>
<tr>
<td>Congenital agranulocytosis</td>
<td>Neutrophil Precursors</td>
<td>2</td>
<td>Cytoxan (1)</td>
<td>Lymphocytes (transient)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Cartilage-hair hypoplasia</td>
<td>Neutrophils, Lymphocytes</td>
<td>2</td>
<td>Cytoxan, (Ara-C)</td>
<td>Complete with mixed chimerism</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Neutrophils</td>
<td>3</td>
<td>Cytoxan</td>
<td>Not evaluable</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil actin deficiency</td>
<td>Neutrophils</td>
<td>1</td>
<td>ATG, TBI</td>
<td>Complete†</td>
<td>0</td>
</tr>
<tr>
<td>Wiskott-Aldrich’s syndrome</td>
<td>Lymphocytes, Platelets</td>
<td>4</td>
<td>PCB, CTX + ATG Ara-C</td>
<td>Lymphocytes</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>ATG, TBI</td>
<td>Complete (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>Busulfan, CTX</td>
<td>Complete</td>
<td>9 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>DMM, CTX</td>
<td>Complete</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*CTX, cyclophosphamide; DMM, dimethylmyleran; ATG, antithymocyte globulin; Ara-C, cytosine arabinoside; Pcb, procarbazine.
†Post complete reconstitution, died of interstitial pneumonia.

long-term survivor. All five patients engrafted; however, four died early from severe acute GVHD, cyclophosphamide toxicity, or interstitial pneumonia. A review of reported transplants for Fanconi’s anemia (Table 6) confirms this impression. Gluckman et al. hypothesized that the increased incidence of severe complications resulted from the unusual sensitivity of somatic cells of patients with Fanconi’s anemia to cyclophosphamide and TBI, reflected in a markedly increased fragmentation of chromosomes observed after in vitro exposure to these agents. Procarbazine, another potent immunosuppressive agent, has been shown by Auerbach et al. at our center to exert little effect on the chromosomal stability of Fanconi’s cells. Accordingly, we are currently exploring whether pretransplant immunosuppressive regimens incorporating this and other agents with limited potential for inducing chromosomal breakage will improve transplantation results for this disorder.

Transplants of allogeneic histocompatible marrow may reverse the encroachment on the marrow spaces produced by myelofibrosis, myelosclerosis, or congenital osteopetrosis and thereby correct associated aplasias. In osteopetrosis, as seen in man and rodents, engraftment of normal donor osteoclasts also results in extensive restructuring of the bones, with clearing of the osteosclerotic changes characteristic of this disorder.

Thomas et al. have reported sustained and complete engraftment of donor hematopoietic cells, with consequent correction of thalassemia major in a young, minimally transfused child transplanted after immunosuppression and myeloablation with cyclophosphamide and dimethyl myleran. A transplant of normal histocompatible marrow, if durably engrafted, should replace host erythroid cells affected by thalassemia major or severe sickle cell anemia, thus insuring normal hemoglobin synthesis. However, except for patients transplanted early in the course of their disease, the risks of a transplant are likely to be formidable, possibly exceeding those associated with transplants for aplastic anemia. To assure complete and durable replacement of host erythroid elements with cells from the normal donor, preparative therapy must include both cyclophosphamide and a myeloablative agent, such as myleran, dimethyl myleran, or total body irradiation. Of these agents, only total body irradiation in combination with cyclophosphamide is likely to provide both myeloablation and sufficient immunosuppression to insure complete engraftment in multiply transfused patients. The effects of such therapy on the heart, liver, and other tissues affected by prior microinfarctions or iron deposition is likely to be significant. Nevertheless, given the limited benefit of chelation therapy, the reductions in the morbidity and mortality associated with marrow transplantation that have been achieved through improved preparative regimens and supportive care, and particularly the
favorable results of marrow transplants in pediatric patients, trials to test the potential of transplantation to correct lethal hemoglobinopathies are warranted.

Recently, Hobbs et al. and Krivit et al. have reported significant resolution of the visceral manifestations of types I, II, and VI mucopolysaccharidoses in severely affected patients following engraftment of hematopoietic cells transplanted from a histocompatible normal donor. Following these grafts, serum and leukocyte levels of defective enzymes have also increased to those maintained by their heterozygotic donors.265-267 Hobbs has rightly voiced concern that the central nervous system complications of some of these diseases may not be altered by engraftment of hematopoietic cells.267 Indeed, in investigations of mannosidotic cattle, Jolly et al. have found in an affected free-marten (a calf chimeric with hematopoietic cells from its normal fraternal twin by virtue of crossplacental circulation in utero) a significant reduction in the pathologic changes of mannosidosis in the liver and other extraneural tissues. A reduction in the brain concentrations of mannosides was also observed. Nevertheless, the animal’s lethal neurologic degeneration continued unabated.270 Prolonged observation and further experience with marrow grafts applied to the treatment of these storage disorders is necessary to determine whether transplants are efficacious only for disorders not affecting the central nervous system or are also useful in limiting the neurologic degeneration associated with certain storage diseases in as yet minimally damaged individuals.

MARROW TRANSPLANTATION FOR PATIENTS LACKING AN HLA-IDENTICAL SIBLING DONOR

To date, marrow transplants have been almost exclusively reserved for the patient possessing an HLA-identical sibling donor. The consistent observation of lethal graft-versus-host disease in SCID patients engrafted following infusions of marrow or blood from HLA haplotype-mismatched parental donors indicated the relatively rigid requirement for HLA identity for marrow grafts. From 1968 on, 18 transplants from related donors HLA genotypically haploidentical to the recipient and phenotypically identical for at least the HLA-D determinant on the unshared haplotype, have been attempted to correct SCID.247 Of these patients, 9 have achieved immunologic reconstitution and 7 are long-term survivors. Moderate to severe GVHD (grades 2–4) was observed in over half of these cases and contributed to death in 3 cases. More recently, this approach to donor selection has also been applied with increasing success to transplants for leukemia and aplastic anemia.272,273 Reported results of transplants for these 3 diseases suggest at least 5 early findings: (1) By virtue of genetic selection or other unknown mechanisms, certain allelic determinants are linked to other alleles within the HLA complex (e.g., the haplotypes HLA-A3, B7, Dw2 or HLA-A1, B8, Dw3), forming intact haplotypes that are detected at significant frequency within populations of common ethnic ancestry.274 Recognition of these manifestations of genetic dysequilibrium permits identification of relatively histocompatible related nonsibling donors for an estimated 5% of individuals lacking an HLA-identical sibling. (2) Engraftment of HLA-disparate marrow requires more intensive immunosuppression. Indeed, graft rejection or failure has been observed in at least 50% of aplastic anemia patients prepared for transplantation with cyclophosphamide273 and in up to 15% of leukemic patients transplanted after cytotherapy with cyclophosphamide and total body irradiation. (3) The severity of graft-versus-host disease is increased and contributes to an increased acute morbidity and mortality.247,272,273 (4) Disparities for HLA-A, C and/or B on one haplotype have been tolerated without lethal GVHD when the donor has been HLA-D compatible with the recipient. Furthermore, transplants of marrow from donors selectively mismatched with the recipient at HLA-D have also been tolerated without lethal GVHD in some instances. Thus, contrary to expectations, no single disparity (e.g., HLA-D) has been shown to incur a specific risk for lethal GVHD.273,276 (5) Despite these limitations, transplants of such genotypically nonidentical grafts for leukemia and congenital immune deficiencies are only slightly less effective than transplants from HLA-identical siblings.247,271,276 Recognition of common HLA-A, B, D haplotypes also permits identification of HLA phenotypically identical unrelated donors, but only for those individuals who inherit two such haplotypes.277 To date, only nine individuals have been reported to have been transplanted with marrow from an unrelated, histocompatible donor.278 Of these patients, four (one transplanted for SCID between 1973 and 1975, three transplanted for aplasia in 1981284,285 are alive, chimeric, with full hematopoietic and lymphoid function but with significant chronic GVHD. One patient transplanted for leukemia experienced no GVHD, but ultimately died with leukemic relapse. A sixth patient, transplanted for chronic granulomatous disease, survives with clinical improvement, but was never convincingly engrafted.281 The other patients either
failed to engraft or died very early in the posttransplant course. This limited experience indicates the feasibility of such transplants, but underscores the possibility that graft rejection and severe GVHD may be more common, enhancing morbidity and mortality. Results of experimental marrow transplants between unrelated, DLA-compatible dogs are in accord with such predictions.386

Recently, significant progress has been made in developing techniques to allow transplants of histoincompatible marrow without risk of lethal GVHD. Early studies in murine models established that GVHD is initiated by thymus-derived T lymphocytes.287 Subsequent work in rodent systems has demonstrated that depletion of T lymphocytes from the hematopoietic grafts, or manipulation of the host environment in which alloreactive T lymphocytes develop, can permit engraftment and hematopoietic reconstitution in lethally irradiated histoincompatible marrow graft recipients without GVHD. Techniques for T-cell depletion that have been found to be effective in preventing GVHD in inbred rodent models include transplants of fetal liver,288,289 treatment of allogeneic marrow or spleen cell grafts with cytotoxic antibodies specific for T lymphocytes,290-292 differential separation of hematopoietic precursors by agglutination with lectins293 or by extended cell culture,294 and selective elimination or “suicide” of host-specific alloreactive donor T cells by pulse-labeling sensitized cultures of donor marrow with 3H-thymidine, BUDR, viruses lytic for activated T cells (such as vesicular stomatitis virus), or idioype-specific antibodies.273,295-298 In certain genetic combinations, GVHD may also be abrogated by pretreatment of the recipient with total lymphoid irradiation299 or treatment with cyclosporine during the posttransplant period.300

Experience with fully allogeneic or HLA-haploype-mismatched hematopoietic grafts in man is extremely limited and largely derived from attempts to reconstitute lymphoid function in patients with severe combined immunodeficiency. Early transplants incorporating in vitro “suicide” techniques either did not engraft or failed to prevent GVHD.277,278,301-303 A limited number of successful transplants of allogeneic fetal liver have been reported.304-306 These transplants have led to durable engraftment and partial immunologic reconstitution without GVHD. However, recent reviews of the world’s experience with such transplants for SCID indicate that the incidence of engraftment following such transplants is low (25%), and persistent deficits of certain immune functions, particularly antibody production, are common.308 Analysis of our own experience with fetal liver transplants in children with SCID suggests that nonspecific resistance mechanisms available to such patients may limit engraftment of fully allogeneic hematopoietic cells, and further, that the absence of genetic homologies between the allogeneic fetal donor and the host may limit the ultimate reconstitution of immune function achieved.308 To date, durable engraftment of fetal liver cells with reconstitution of hematopoietic function has not been convincingly documented in any patient transplanted for aplasia or leukemia.309-311

Many of the difficulties attending the use of fully allogeneic hematopoietic tissues, such as fetal liver, might be obviated through the use of HLA-haploidentical donors (e.g., parents), since sharing of HLA specificities might not only reduce the genetic disparities potentiating rejection, but also promote effective cooperation of developing donor lymphoid elements with host tissues in the generation of an immune response.312 Recently, Reisner et al. have modified a lectin-based technique for marrow progenitor isolation developed in murine models293 to permit effective depletion of alloreactive T lymphocytes from both human and primate marrow populations.313,314 The technique, which involves differential sedimentation of T lymphocytes agglutinated with soybean agglutinin followed by E-rosette depletion, was initially tested in a primate model, and subsequently, was used successfully to fractionate HLA-A,B-mismatched, D-compatible paternal marrow for transplantation in a child with leukemia.314 More recently, we have used this technique to deplete T cells from parental marrow transplanted into children with severe combined immunodeficiency. Each of the first six patients was durably engrafted with HLA-A,B,D haplotype-mismatched parental marrow. Donor lymphoid precursors have matured normally; immunologic function in all but one of the patients is fully reconstituted.315-317 GVHD, limited to a transient grade 1 skin rash, was observed in only one case. Graft rejection was observed in one of the six patients, necessitating a secondary graft after immunosuppression. This case underscored again the potential limitations to engraftment that may attend transplantation of HLA-disparate cells.

Histoincompatible marrow grafts treated with the T-cell-specific monoclonal antibody, OKT3, and complement have been used for transplantation of a small number of patients with SCID or leukemia. These patients have not survived because of either early infections or severe GVHD.318,319 Recently, Reinherz et al. have reported a patient with SCID successfully transplanted with HLA haploype-mismatched parental marrow treated with a different T-cell-specific monoclonal antibody, T12, and complement. The patient required three transplants with intensive immunosuppression prior to the last two grafts before
engraftment and function was achieved. A severe acute GVHD reaction was reversed by T12 infusions. This experience reiterates the problem of engraftment. Further improvements in the methods whereby T-cell-specific monoclonal antibodies are applied to large scale cell separations are forthcoming, which may obviate the current limitations of complement-dependent antibody systems for selective cell lysis.

Taken together, the above clinical experiences with mismatched transplants of hematopoietic cells suggest that depletion of T cells from human marrow will prevent or markedly ameliorate GVH reactions and permit transplants of HLA-histoincompatible marrow for patients lacking a donor. Improved immunosuppressive regimens will be needed to insure engraftment. Whether or not the antileukemic effect of an allogeneic graft will be maintained in the absence of GVHD remains to be determined.

In conclusion, transplants of histocompatible marrow are being applied with increasing success to the treatment of leukemia and other lethal acquired and congenital disorders of the hematopoietic system. The obstacles of infection, graft-versus-host disease, rejection, and leukemic relapse remain, but real progress toward their control is evident. New applications of marrow transplantation and extensions of marrow grafts to patients lacking histocompatible donors are currently being explored. Initial promising results suggest a continued and expanded role for marrow transplantation as a therapeutic approach in the future.

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Allogenic bone marrow transplantation: current status and future directions

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