Unrelated donor bone marrow transplantation was undertaken in eight infants with severe combined immunodeficiency (SCID) and two children each with Wiskott-Aldrich syndrome (WAS) and Chediak-Higashi syndrome (CHS) who did not have histocompatible siblings. Donors for three patients were phenotypically matched at all HLA-A, B, Dr, and Dw loci, whereas nine donors were mismatched from the recipients at one of the HLA-A or B loci but phenotypically identical at one of the Dw loci. All but one patient received conditioning chemotherapy and/or radiotherapy before infusion of donor marrow, which was not T-cell depleted. Prophylaxis for graft-versus-host disease (GVHD) consisted of methotrexate and prednisone combined with either cyclosporine A (six patients), antithymocyte globulin (five patients), or anti-CD5 antibody against a chain immunotoxin (one patient). All patients engrafted with donor cells, and only 4 of 12 experienced any GVHD (1 of 8 SCID, 1 of 2 WAS, 2 of 2 CHS). Two children who developed grade II and two who developed grade III GVHD were successfully treated and all are now alive, off immunosuppressive therapy, with no evidence of chronic GVHD greater than 18 months after transplant. Ten patients are alive with excellent immunoreconstitution ≥ 1 year to ≥ 3 years after transplant; actuarial survival is predicted to be 83% with a median follow-up of 2 years. Two children with SCID succumbed to pre-existing opportunistic infection early posttransplant. We conclude that closely matched unrelated donor bone marrow transplantation can correct congenital immunodeficiencies including variants of SCID, WAS, and CHS, with an acceptably low incidence of transplant-related complications, principally GVHD.

THE FIRST REPORTS of successful marrow transplantation for the correction of congenital immunodeficiencies appeared in 1968, involving patients with severe combined immunodeficiency (SCID) and Wiskott-Aldrich syndrome (WAS). During the following 15 years marrow transplantation from histocompatible siblings became accepted as curative treatment for children with SCID, WAS, Chediak-Higashi syndrome (CHS), as well as other congenital immunodeficiencies. Unfortunately, the percentage of infants with congenital immunodeficiencies (eg, SCID) who have healthy histocompatible sibling donors has been estimated at approximately 10%. For some children without matched siblings successful reconstitution of both T- and B-lymphocyte immune function has been achieved during the past decade through the use of T-cell-depleted transplantation from haploidentical, generally parental, family members. Immunoreconstitution has been achieved in a significant proportion of SCID patients and less frequently in WAS. T-cell–depleted haploidentical transplantation has several disadvantages: (1) it often requires intensive pretransplant conditioning therapy including the use of total body irradiation (TBI) in patients without malignancies; (2) it has been associated with severe graft-versus-host disease (GVHD); and (3) it has an alarming incidence of posttransplant Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorder (especially in WAS). The time course for immunoreconstitution following T-depleted haploidentical bone marrow transplantation (BMT) in many reported cases has been markedly prolonged and recovery of specific antibody synthesis has not been achieved in some cases.

For the rare cases of congenital immunodeficiency where the genetic defect is known, enzyme replacement therapy and/or gene therapy has been attempted, as in the case of SCID secondary to adenosine deaminase (ADA) deficiency. However, the long-term benefits of these approaches remain to be proven, and the genetic defects for the majority of prematurely lethal congenital immunodeficiencies are unknown. For these reasons we initiated a study of unrelated donor (URD) marrow transplantation to treat children who had the types of prematurely lethal immunodeficiencies that had been clearly demonstrated to benefit from marrow transplantation from HLA-matched siblings, but who lacked such histocompatible sibling donors. Twelve children who received URD transplants for lethal immunodeficiencies are the subject of this report.

MATERIALS AND METHODS

Patients. All consecutive patients with SCID, WAS, or CHS referred to our institution for BMT between January 1987 and March 1990 who lacked histocompatible siblings or closely matched related donors were referred to the National Marrow Donor Program (NMDP) for an unrelated donor search. This included 11 infants with SCID, two with WAS, and two with CHS.

Histocompatibility testing. Lymphocytes from all patients were tested by HLA-A, B, C, and Dr typing using standard serologic techniques. Dr typing was performed with homozygous typing cells. Mixed lymphocyte cultures between recipients and potential donors were performed as previously reported. In some cases DNA analyses using restriction fragment length polymorphisms were used to confirm Dr identity between patients and potential marrow donors.
UNRELATED DONOR TRANSPLANTS FOR IMMUNODEFICIENCIES

BMT. All patients were hospitalized in private HEPA-filtered rooms on the acute marrow transplant unit from the time that pretransplant conditioning was initiated until an acceptable absolute neutrophil count was achieved posttransplant. Careful hand washing precautions were used for all patients. Infants with SCID were maintained in gown, glove, and mask isolation and provided with sterile formula (when fed enterally) until relevant laboratory assays showed evidence of donor type engraftment and functional immuno-reconstitution (typically 2 to 3 months post grafting). All patients received trimethoprin/sulfamethaxozole 2 days/week as *Pneumocystis carinii* prophylaxis and weekly intravenous (IV) IgG until day +180 (because all donors were EBV- and/or cytomegalovirus [CMV] seronegative). Acyclovir until day +180 (one SCID patient); (2) busulfan 2 mg/kg p.o. bid until day +1 and +2 (nine patients: seven SCID, two WAS); (3) cyclophosphamide 60 mg/d IV × 2 days followed by fractionated TBI (165 cGy bid × 4 days, total 1,350 cGy [one CHS patient]); or (4) cyclophosphamide 60 mg/d IV × 2 days on days −7, −6, etoposide (VP-16) 500 mg/(m²/L)² IV × 3 days on days −7 to −5, fractionated TBI (165 cGy × 4 days) and antithymocyte globulin (ATG) 15 mg/kg bid IV on days −2 and −1 and 15 mg/kg/d IV on days +1 and +2 (one CHS patient). All patients were infused with $3 \times 10^8$ donor bone marrow mononuclear cells/kg recipient weight.

GVHD prophylaxis was administered according to the pilot protocols in effect for all unrelated donor transplants conducted at our institution during that particular time period. MCP: methotrexate 15 mg/kg IV on day +1, 10 mg/kg IV on day +3, +6, +11, cyclosporine A 1.5 mg/kg bid IV day −1 to day +30 then 5 to 6 mg/kg bid p.o. until day 180, prednisone 5 mg/d until day 30 and then tapered; MAP as previously published,²¹ or MXP−“short course” methotrexate: 15 mg/kg/d IV on day +1, 10 mg/kg/d on d. +3, +6, +11, anti-CD5 monochlonal antibody-ricin A chain conjugate 0.1 mg/kg IV qd. on days +1 to +10 then q.o.d. on days +12 to +20 and prednisone 40 mg/(m²/L)² qd. on day +1 to day +20 then tapered over 1 week.

Conditioning therapy was assigned according to the underlying diagnosis as outlined (see the footnote to Table 3). For the patients in this report it consisted of either: (1) no pretransplant therapy (one SCID patient); (2) busulfan 2 mg/kg p.o. bid × 4 days followed by cyclophosphamide 50 mg/kg/d IV × 4 days and antithymocyte globulin 15 mg/kg bid IV on days −2 and −1 and 15 mg/kg/d IV on day +1 and +2 (nine patients: seven SCID, two WAS); (3) cyclophosphamide 60 mg/d IV × 2 days followed by fractionated TBI (165 cGy bid × 4 days, total 1,350 cGy [one CHS patient]); or (4) cyclophosphamide 60 mg/d IV × 2 days on days −7, −6, etoposide (VP-16) 500 mg/(m²/L)² IV × 3 days on days −7 to −5, fractionated TBI (165 cGy × 4 days) and antithymocyte globulin (ATG) 15 mg/kg bid IV on days −2 and −1 and 15 mg/kg/d IV on days +1 and +2 (one CHS patient). All patients were infused with $3 \times 10^8$ donor bone marrow mononuclear cells/kg recipient weight.

GVHD prophylaxis was administered according to the pilot protocols in effect for all unrelated donor transplants conducted at our institution during that particular time period. MCP: methotrexate 15 mg/kg IV on day +1, 10 mg/kg IV on day +3, +6, +11, cyclosporine A 1.5 mg/kg bid IV day −1 to day +30 then 5 to 6 mg/kg bid p.o. until day 180, prednisone 5 mg/d until day 30 and then tapered; MAP as previously published,²¹ or MXP−“short course” methotrexate: 15 mg/kg/d IV on day +1, 10 mg/kg/d on d. +3, +6, +11, anti-CD5 monochlonal antibody-ricin A chain conjugate 0.1 mg/kg IV qd. on days +1 to +10 then q.o.d. on days +12 to +20 and prednisone 40 mg/(m²/L)² qd. on day +1 to day +20 then tapered over 1 week.

GVHD prophylaxis was administered according to the pilot protocols in effect for all unrelated donor transplants conducted at our institution during that particular time period. MCP: methotrexate 15 mg/kg IV on day +1, 10 mg/kg IV on day +3, +6, +11, cyclosporine A 1.5 mg/kg bid IV day −1 to day +30 then 5 to 6 mg/kg bid p.o. until day 180, prednisone 5 mg/d until day 30 and then tapered; MAP as previously published,²¹ or MXP−“short course” methotrexate: 15 mg/kg/d IV on day +1, 10 mg/kg/d on d. +3, +6, +11, anti-CD5 monochlonal antibody-ricin A chain conjugate 0.1 mg/kg IV qd. on days +1 to +10 then q.o.d. on days +12 to +20 and prednisone 40 mg/(m²/L)² qd. on day +1 to day +20 then tapered over 1 week. Documentation and quantitation of donor cell engraftment was performed using restriction fragment length polymorphisms (RFLP) for discriminating DNA markers on bone marrow aspirates or blood at approximately day +28, day 100, and later time points in the majority of patients. Immune function studies. Evaluations of serum Ig levels, specific antibody titers, T-cell phenotypes, T-cell mitogen, and antigen proliferation were sequentially performed by standard methods.

Statistical analysis. Clinical data were retrieved from the University of Minnesota Bone Marrow Transplant Database which contains systematically and prospectively collected data on all bone marrow transplant patients. The end points of survival, mean day of engraftment, and acute GVHD were determined using the Kaplan-Meier product limit methods.²³

### RESULTS

Patient characteristics. Characteristics of the 12 children with SCID, WAS, or CHS who received URD BMT are described in Table 1. Median age at BMT for SCID patients was 8.5 months (range 3 months to 23 months). Two infants were identified as very high risk secondary to (1) pretransplant transfusion-acquired GVHD and aplastic anemia with opportunistic infection in one case (unique patient number [UPN] 1024), and (2) a prolonged pretransplant ventilator course secondary to pneumonitis with *Pneumocystis carinii* pneumonia resulting in chronic oxygen compromise in another case (UPN 1265). One patient with WAS (UPN 966) developed pure red blood cell aplasia 2 months before BMT and both children with CHS were in the accelerated phase at the time of BMT.

Donor selection. Results of histocompatibility antigen testing for donors and recipients are shown in Table 2. Acceptable donors were found for 8 of 11 infants with SCID, 2 of 2 patients with WAS, and 2 of 2 patients with CHS. (The three infants with SCID for whom closely matched unrelated donors could not be identified received T-depleted BMT from parental donors.) Three patients had phenotypically identical donors (all with SCID) while the rest of the patients had donors mismatched at one A (six patients) or B (three patients) locus.

BMT. Regimens of pretransplant conditioning and GVHD prophylaxis are shown in Table 3, as are outcomes with respect to engraftment, GVHD, and current status. Three patients with SCID (in the group 1 diagnostic category (footnote, Table 3) UPN 807, 937, and 1049) were initially infused with donor marrow without any preconditioning. No evidence for engraftment of donor cells was found after 6 weeks of observation in two of three patients:

### Table 1. Patients With Lethal Congenital Immunodeficiencies Treated With Unrelated Donor BMT

<table>
<thead>
<tr>
<th>UPN</th>
<th>Immunodeficiency</th>
<th>Age/Sex</th>
<th>Significant Pretransplant Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>807</td>
<td>SCID ↓ B.↓ T cells, ↑ NK cells</td>
<td>7 mo F</td>
<td>PCP, Parainfluenza pneumonia</td>
</tr>
<tr>
<td>937</td>
<td>SCID ↓ T, hypogammaglobulinæmia</td>
<td>10 mo M</td>
<td>PCP</td>
</tr>
<tr>
<td>1024</td>
<td>SCID Omenn's syndrome</td>
<td>6 mo F</td>
<td>Transfusion acquired GVHD and aplasia</td>
</tr>
<tr>
<td>1049</td>
<td>SCID ADA deficiency</td>
<td>21 mo F</td>
<td>PCP</td>
</tr>
<tr>
<td>1091</td>
<td>SCID ↓ B, ↓ T cells, ↑ NK cells</td>
<td>23 mo M</td>
<td>Adenoviral hepatitis</td>
</tr>
<tr>
<td>1107</td>
<td>SCID Absent CD8+ T cells, nonfunctional CD4+ cells</td>
<td>27 mo M</td>
<td>Severe pulmonary compromise (2 to prolonged ventilator course for PCP and CMV pneumonia)</td>
</tr>
<tr>
<td>1289*</td>
<td>SCID Absent CD8+ T cells, nonfunctional CD4+ cells</td>
<td>3 mo M</td>
<td></td>
</tr>
<tr>
<td>966</td>
<td>WAS</td>
<td>30 mo M</td>
<td>Pure red blood cell aplasia</td>
</tr>
<tr>
<td>1204</td>
<td>WAS</td>
<td>8 mo M</td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>818*</td>
<td>CHS</td>
<td>4 yr F</td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>1118*</td>
<td>CHS</td>
<td>8 yr M</td>
<td>Accelerated phase</td>
</tr>
</tbody>
</table>

*Siblings.

For personal use only.on October 22, 2017. by guest

From www.bloodjournal.org by guest on October 22, 2017. For personal use only.
Table 2. Histocompatibility Typing of Unrelated Donors for BMT of Lethal Congenital Immunodeficiencies

<table>
<thead>
<tr>
<th>UPN</th>
<th>Immunodeficiency</th>
<th>Donor Typing</th>
<th>Donor Mismatch</th>
<th>MLC (relative response) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RDx</td>
</tr>
<tr>
<td>807</td>
<td>SCID</td>
<td>A2,32</td>
<td>B7,62</td>
<td>31yM</td>
</tr>
<tr>
<td>937</td>
<td>SCID</td>
<td>A2,2</td>
<td>B60,62</td>
<td>Dr2,4</td>
</tr>
<tr>
<td>1024</td>
<td>SCID</td>
<td>A1,28</td>
<td>B8,44</td>
<td>Dr2,4</td>
</tr>
<tr>
<td>1049</td>
<td>SCID</td>
<td>A1,3</td>
<td>B8,7</td>
<td>Dr3,3</td>
</tr>
<tr>
<td>1051</td>
<td>SCID</td>
<td>A2,2</td>
<td>B44,35</td>
<td>Dr1,6</td>
</tr>
<tr>
<td>1107</td>
<td>SCID</td>
<td>A2,32</td>
<td>B44,62</td>
<td>Dr2,4</td>
</tr>
<tr>
<td>1265</td>
<td>SCID</td>
<td>A1,11</td>
<td>B8</td>
<td>Dr3</td>
</tr>
<tr>
<td>1289</td>
<td>SCID</td>
<td>A1,11</td>
<td>B8,57</td>
<td>Dr3,7</td>
</tr>
<tr>
<td>966</td>
<td>WAS</td>
<td>A1,3</td>
<td>B7,57</td>
<td>Dr5,7</td>
</tr>
<tr>
<td>1204</td>
<td>WAS</td>
<td>A26,33</td>
<td>B17,38</td>
<td>Dr6</td>
</tr>
<tr>
<td>818</td>
<td>CHS</td>
<td>A2,3</td>
<td>B7,44</td>
<td>Dr8</td>
</tr>
<tr>
<td>1118</td>
<td>CHS</td>
<td>A1,3</td>
<td>B8,7</td>
<td>Dr3,3</td>
</tr>
</tbody>
</table>

Abbreviations: MLC, mixed lymphocyte culture; RDx, relative response of recipient cells responding against irradiated donor cells; DRx, relative response of donor cells responding against irradiated recipient cells; SI, stimulation index of RDx/RDx.

UPN 937 and 1049. These two patients subsequently underwent chemotherapy as outlined for group 2 diagnoses (footnote, Table 3), and second grafts of cryopreserved marrow from the same donor. The five remaining SCID patients who had unusual variants (not described in the World Health Organization classification) received chemotheraphy conditioning for the first BMT. Three of the patients (UPN 1107, 1205, and 1289) had a variant form of SCID characterized by lack of CD8+ T cells,24 a unique activation defect, and a reduced capacity to respond to allogeneic stimuli. UPN 1024 with Omenn's syndrome had acquired GVHD from an unirradiated erythrocyte transfusion pretransplant.25 UPN 1091 had low numbers of T cells but demonstrated a slight degree of responsiveness to allogeneic cells, although mitogen responses were markedly decreased.

The two boys with WAS were treated with a conditioning protocol patterned after Kapoor et al5 and identical to the one that has been used successfully for transplantation of WAS patients from histocompatible siblings at our institu...
tion. Patients with CHS in accelerated phase received doses of cyclophosphamide and fractionated TBI standardly administered for BMT of leukemias at our center.26 UNP 1118 also received VP16 because this agent has been reported to be effective in the transplantation of hemophagocytic syndromes27 and had been added along with ATG to the protocol for transplantation of patients with CHS (with matched related or unrelated donors) at our institution during the intervening period (footnote, Table 3).

GVHD prophylaxis was assigned sequentially according to the protocol that was being used at our institution for all unrelated donor BMT during a given period of time. Thus, the first six patients were treated with the combination of MCP: methotrexate, cyclosporine A, prednisone; the next four with MAP: methotrexate, ATG, prednisone; the subsequent patient (UNP 1265) with MXP: methotrexate, anti-CD5 ricin A chain immunotoxin (Xoma-zyme), and prednisone. The most recent patient (UNP 1289) again received MAP secondary to parental refusal of the MXP protocol.

Ten patients demonstrated donor engraftment within the first month after their initial transplant. As previously mentioned, two SCID patients did not show evidence of donor cells for 6 weeks after marrow infusion without prior conditioning, but engrafted rapidly after a second transplant following chemotherapy (Table 4). GVHD was clinically apparent in four patients: one 7-month-old infant with SCID (UNP 807, the only child who did not receive pretransplant conditioning) and the three oldest patients (ages 2.5 to 8 years) with either WAS (UNP 966) or CHS (UNP 818, 1118). Three of six patients who developed GVHD had received prophylaxis with MCP while one of six patients who had MAP prophylaxis developed GVHD. These differences were not statistically significant. Grade II, III GVHD were easily controlled in three of four patients who developed this complication. Moderate dose systemic steroids were used in two cases and anti-CD5 ricin A chain immunotoxin (Xoma-zyme) infusion in UNP 807 (who was eligible for a multi-institutional pilot protocol28 of this agent as primary therapy of GVHD at the time she developed this complication). UNP 1118 with CHS, the oldest child in this series, developed an acute/chronic GVHD overlap syndrome along with severe pancreatitis while on prednisone therapy. He subsequently received a course of ATG and was maintained on cyclosporine A for 9 months. He is currently off all immunosuppressive therapy greater than 20 months post-BMT with no evidence of chronic GVHD, normal Ig levels, and normal T-cell responses to mitogens (Table 4). Kaplan-Meier estimate of survival for this patient series is 83% with a median follow-up of 2 years (Fig 1).

Reconstitution of hematologic and immune function. The 11 patients who received conditioning therapy achieved 3 consecutive days of white blood count of greater than 1,000/mm³ by a median of 24 days. All patients have recovered normal blood counts post BMT including persistently normal platelet counts in two of two patients with WAS and absence of Chediak-Higashi granules in peripheral blood lymphocytes and bone marrow in two of two...
CHS patients. Both patients with WAS and both patients with CHS continue to demonstrate 100% donor cell engraftment.

A summary of immune function studies performed at most recent time points post-BMT are shown in Table 4. Total absolute lymphocyte counts, IgM, A, E, and phytohemagglutinin (PHA) blastogenesis are normal in all patients. Although mixed chimerism has been apparent in five of six SCID patients who received BMT more than 1 year ago (Table 3) all children show persistent and improving immunocompetence. UPN 1049 has had normal white blood cell ADA levels since first measured at day 27 post BMT. The three children with SCID with the absence of CD8+ T cells and a T-cell activation defect have demonstrated CD8+ CD3+ T cells postgrafting and normal proliferation to PHA in two of two surviving patients (Table 4).

Nine patients have been immunized at 1 year with a single dose of the pediatric diphtheria Tetanus vaccine. The six patients tested post-immunization all showed evidence of immune response to one or both antigens: 2 of 6 made antibody to diphtheria, 5 of 6 made antibody to tetanus, 5 of 5 developed a proliferative response to tetanus in vitro, and 3 of 3 showed positive delayed type hypersensitivity reactions (3 of 3 tetanus, 2 of 3 diphtheria). UPN 807, the first patient to undergo unrelated donor BMT in this series, showed an increase in antibody titers to parainfluenza type 3 within 5 weeks post BMT. This virus had been the cause of recurrent pneumonitis before transplantation. UPN 807 experienced an uneventful primary infection with varicella zoster at 24 months post BMT. Over the past 3 years, she has been immunized with a pediatric diphtheria Tetanus booster × 2, injectable polio × 2 and the measles, mumps, rubella (MMR) vaccines. She now demonstrates protective antibodies to all these agents as well as positive delayed-type hypersensitivity skin tests to diphtheria, tetanus, mumps, candida, and streptococcus.

All surviving patients are well at home and do not receive IVIgG infusions. There is no evidence for acquisition of CMV infection associated with BMT in any of the children, although two patients were CMV seropositive pre-BMT. To date no patient has developed symptoms suggestive of EBV-associated B-cell lymphoproliferative disease.

**DISCUSSION**

Opportunistic infections and malignancies, respectively, are the major causes of death in children with premature, lethal congenital immunodeficiencies including SCID, WAS, and CHS. Successful immuno-reconstitution with marrow transplantation effectively reduces the long-term risks of both of these complications. In the present era transplantation of SCID and WAS with whole marrow from histocompatible sibling donors is associated with disease-free survival rates of greater than 90% and 85%, respectively.

Unfortunately, the majority of children with premature lethal immunodeficiencies lack histocompatible sibling donors. O'Reilly et al. undertook the first unrelated bone marrow transplant for SCID in 1977. Partial engraftment was finally achieved after six attempts with the subsequent development of extensive chronic GVHD contributing to death from squamous cell carcinoma 5 years later. In the early 1980s, with the development of a physical method of marrow T-cell depletion involving soybean lectin agglutination and sheep erythrocyte rosetting, children with leukemia and SCID began to receive marrow transplants from haploidentical parental donors. Initial reports indicated that nearly half of SCID patients experienced improvement in T-cell immunity because of partial engraftment of parental cells, such that they could be removed from strict protective isolation, but continued to require Ig replacement indefinitely. More recently, with the use of pretransplant combinations of busulfan, cyclophosphamide, and/or cyclosporine and ATG the rate of successful engraftment of T-depleted marrow in classical forms of SCID has increased to 86%. However, recovery of T- and B-cell function remain variably delayed and the reconstitution of SCID variants such as Omenn's syndrome is still problematic. It has been even more difficult to achieve hematolymphopoetic engraftment in WAS with T-depleted haploidentical donors with some exceptions, and the rate of posttransplant EBV-associated B-cell lymphoproliferative disorder (BLPD) is prohibitively high (nearly 50%).

In early attempts at our institution to use T-depleted haploidentical transplantation, we encountered several discouraging consequences including EBV-associated BLPD, transfusion-acquired CMV infection, and engraftment failure in non-SCID immunodeficiencies despite the use of TBI. For those reasons, we initiated a pilot study of URD BMT for patients with lethal immunodeficiencies who lacked histocompatible siblings or closely matched related donors.

With the exception of two children with SCID (one with no laboratory evidence of allogeneic reaction who accepted a third-party skin graft [UPN 937] and the other with ADA deficiency [UPN 1049]) who did not engraft after marrow infusion alone, all other conditioning protocols used for this series of patients resulted in acceptable engraftment and reconstitution of all previously deficient immunologic and hematologic functions. These results were achieved with doses and regimens of chemotherapy and radiation therapy that are commonly used in children undergoing histocompatible sibling transplantation, and were not associated with any unacceptable toxicities. Graft rejection has been documented in phenotypically identical and HLA-mismatched unrelated donor transplants in conjunction with T-cell depletion. While our series of patients is
relatively small, our experience suggests that stable engraftment can be achieved despite mismatching at class I antigens if T-replete grafts are used.

In contrast to the eight of eight patients with SCID who engrafted after unrelated donor bone marrow transplant, two of three children with SCID variants who underwent T-depleted haploidentical BMT during the same time period with the same conditioning protocol used for URD BMT did not engraft with donor cells and ultimately died (A.H.F., unpublished data). One of these children went on to develop EBV-associated B-cell lymphoproliferative disease.

The rate of GVHD in this series was lowest for infants with SCID (one of eight patients), comparable to that expected with histocompatible transplantation and T-depleted parental grafts. While three older children developed grade II to III GVHD, all symptoms of GVHD were successfully reversed with conventional doses of prednisone used for treatment of GVHD. This rate of ≥ grade II GVHD (actuarial rate = 55%, 95% confidence limits ± 28%) is significantly lower than that reported from series of adults treated with URD BMT with and without T-cell depletion and the experience at our institution (actuarial GVHD rate for patients >18 years old = 73%, 95% confidence limits ± 15%). Because the methods of GVHD prophylaxis for URD BMT were the same for children and adults at our institution, we can speculate that young recipient age, and possibly the SCID background, contributed to lowering the risk of GVHD in URD BMT as it does in histocompatible BMT. Because GVHD prophylaxis was administered in several sequential protocols to small numbers of patients, no clear conclusion can be reached regarding the most effective regimen. However, nephrotoxicity and hypertension requiring medical intervention was observed in two of six children who received cyclosporine A as part of their prophylaxis, and the rate of GVHD was not lower than that observed with the combination of methotrexate, ATG, and prednisone.

The recovery of nonspecific and specific immune function has been monitored sequentially in all patients. Because of donor seropositivity for CMV and EBV all patients received IVIgG infusions weekly until at least 6 months post BMT, and those who were still receiving immunosuppression for GVHD, for longer periods of time. All but one patient have now discontinued IVIgG therapy and demonstrate efficient endogeneous synthesis of Igs as well as specific antibody formation (partial data shown in Table 4 and described in the Results section).

In summary, marrow transplantation using phenotypically identical or one HLA A or B antigen mismatched unrelated donors was undertaken without the use of T-cell depletion or unusually intensive pretransplant conditioning protocols in a group of 12 children with lethal immunodeficiencies. Ten children are well at home, and have documented T- and B-cell immunoreconstitution with a median follow-up of 2 years posttransplant. More detailed analysis of the tempo of immune recovery and comparison with results achieved with T-depleted haploidentical BMT will be necessary to identify the potential advantages of the transfer of unmanipulated marrow with immunocompetent T cells from unrelated donors as treatment of lethal immunodeficiencies.

NOTE ADDED IN PROOF

A third patient with WAS was treated with URD BMT after completion of this report. UPN 1463 was an 8-year-old boy who had suffered from refractory thrombocytopenia after splenectomy. He had been treated with daily steroids for most of 7½ years and developed liver dysfunction 8 months before BMT. Pretransplant evaluation showed oligoclonal EBV-associated BLPD apparently confined to the liver. This was treated with surgical resection and α-interferon for 3 weeks. The early posttransplant course was unremarkable and complete donor engraftment was documented before day 28. Unfortunately, UPN 1463 developed severe venoocclusive disease of the liver and died of infected aspergillosis 55 days post BMT. At autopsy there was no evidence of GVHD or BLPD. This case illustrates the need for ongoing careful evaluation of the role of marrow transplantation with nonsibling donors in WAS and better definition of pretransplant criteria warranting referral for nonsibling BMT.

REFERENCES

11. Fischer A, Landais B, Friedrich W, Morgen G, Gerritsen B,


Unrelated donor bone marrow transplantation for correction of lethal congenital immunodeficiencies

AH Filipovich, RS Shapiro, NK Ramsay, T Kim, B Blazar, J Kersey and P McGlave