Recovery of Antibody Production in Human Allogeneic Marrow Graft Recipients: Influence of Time Posttransplantation, the Presence or Absence of Chronic Graft-Versus-Host Disease, and Antithymocyte Globulin Treatment


One-hundred fifty-three recipients of HLA-identical sibling marrow transplants for aplastic anemia or hematologic malignancy were injected with bacteriophage ØX174 (phage), pneumococcal polysaccharide antigen (PPA), or keyhole limpet hemocyanin (KLH). Antibody levels were determined several times in the 6 wk after injection. Multiple regression techniques were used to determine what factors played significant roles in the antibody response. The most significant factors were the time elapsed from transplantation, chronic graft-versus-host disease (GVHD), and antithymocyte globulin (ATG) treatment. All patients had low antibody responses to all antigens in the first 180 days from transplant. Beyond 180 days patients without chronic GVHD showed antibody responses indistinguishable from those of normal donors. However, patients with chronic GVHD had the following impairments: (1) primary response to phage, (2) conversion from IgM to IgG in secondary response to phage, (3) secondary response to KLH, and (4) response to PPA. ATG treatment given to patients either prophylactically or therapeutically for acute GVHD was followed by lower primary responses to phage in the first 180 days and poor ability to switch from IgM to IgG antibody in the secondary response beyond 180 days postgrafting. Other factors did not yield additional significant information about ability to predict antibody responses including diagnosis, conditioning regimen, treatment in or out of laminar air flow rooms, transplantation in remission or relapse of hematologic malignancy, pretransplant refractoriness of the recipient to platelet transfusions from random donors, donor age or donor sex, and steroid administration for treatment or prevention of GVHD. The data indicate that, given enough time after transplantation, the ability to produce normal antibody function recovers except in those patients experiencing chronic GVHD.

W E HAVE DESCRIBED an evaluation of immunologic reactivity in 56 patients who survived for 1–6 yr after marrow transplantation for the treatment of aplastic anemia or hematologic malignancy. Other groups have reported similar studies. These studies showed a pronounced cellular and humoral immunologic deficiency during the first 4 mo after transplantation with gradual improvement of immune function thereafter. Patients with acute and chronic graft-versus-host disease (GVHD) appeared to have an extended period of immunodeficiency. The limited number of patients studied and the restriction of the observation to those who became long-term survivors did not permit us to delineate the influence of other factors on immunologic reconstitution. For example: (1) the age and sex of donors and recipients varied; (2) the patients had a spectrum of diseases for which they were transplanted, e.g., aplastic anemia, acute myelogenous leukemia, or acute lymphocytic leukemia; (3) the conditioning regimens used for transplantation varied, e.g., cyclophosphamide (CY), total body irradiation (TBI), or both; (4) some patients were treated in a laminar air flow room (LAF) and others were not; (5) some patients were given antithymocyte globulin (ATG) and/or steroids for treatment or prevention of acute GVHD; (6) some patients with leukemia were transplanted while being in remission and others were transplanted in relapse.

The present study extends previous work by analyzing entirely new data on antibody production to pneumococcal polysaccharide antigen (PPA) as well as presenting additional data for the T-dependent antigens bacteriophage ØX174 (phage) and keyhole limpet hemocyanin (KLH) in 153 patients tested at various times after transplantation. Multivariate regression techniques were used to evaluate the influence of various factors on the magnitude of the humoral antibody response.
**Antibody Response After Marrow Grafting**

**Materials and Methods**

**Marrow Transplantation**

One-hundred fifty-three patients receiving marrow transplants between July 1970 and October 1978 were studied. Seventy-two were transplanted for aplastic anemia and 81 for acute leukemia. Details on the selection of patients and donors for marrow transplantation, on the conditioning regimens for transplantation with immunosuppressive agents, on the transplant procedure, the patients' courses before and after transplantation, and the proof of allogeneic marrow engraftment have been described. Briefly, all patients and their donors were HLA-identical siblings. Patients with aplastic anemia were conditioned with CY, 50 mg/kg on each of 4 successive days. Patients with leukemia were given CY, 60 mg/kg on each of 2 days, followed 3 days later by 1000 rad TBI. All patients were given intermittent methotrexate for prevention of GVHD for no longer than 100 days postgrafting. Some patients were given steroids for acute GVHD. Forty-five of the patients received ATG for the prevention or treatment of acute GVHD, while others were given steroids for acute GVHD. Forty-five of the patients developed chronic GVHD of varying severity and 27 were treated with either prednisone alone or prednisone and CY, procarbazine, or azathioprine. Briefly, all of these 45 patients had at least two system involvement of skin (resembling scleroderma) and liver abnormalities, and many had multiple target organ involvement as described.

**ABO Incompatibility**

Thirty-six patients had major incompatibility with their donors for ABO blood groups, e.g., donor was A and recipient was O. The recipients of ABO-incompatible marrow underwent plasma exchange prior to transplant as previously described. After transplant isohemagglutinin titers were determined at regular intervals.

**Antigen Injections**

Primary and secondary antigen injections were performed at varying times posttransplant. The injections clustered at 3-mo and yearly intervals. Primary and secondary injections in any individual were separated by periods varying from 8 wk to slightly more than 1 yr. Sera were collected several times in the 6 wk after injection, most commonly at 1, 2, and 4 wk.

**Bacteriophage ΦX174 (Phage)**

One-hundred-four patients and 25 healthy individuals were tested for antibody formation against phage. Fifty-six of the patients were transplanted for hematologic malignancy and 48 for aplastic anemia.

Phage was grown, harvested, and purified as previously described. Phage was given intravenously in a dose of 2 × 10⁸ plaque-forming units (PFU)/kg body weight to give an initial concentration of 3–5 × 10⁹ PFU/ml of serum. The phage neutralizing antibody titer was expressed as K value (Kv).

**Pneumococcal Polysaccharide (PPA)**

One-hundred twenty-nine patients and 26 marrow donors were tested for antibody formation to PPA. Sixty-nine of the patients were grafted for hematologic malignancy and 60 for aplastic anemia.

PPA containing types 1, 2, 3, 4, 6, 8, 9, 12, 14, 19, 23, and 25 was obtained from Lederle Laboratories, Pearl River, N.Y. Subcutaneous injection of 0.5 ml containing 50 μg of polysaccharide was carried out, and serum was collected 2 and 4 wk after first or second injections. The method of determining the antibody titer used chromic-chloride-treated human red blood cells. In order to screen this large number of patients, antibody to PPA type 3 was investigated. Individuals found to be negative to type 3 were additionally tested for types 6 and 8.

**Keyhole Limpet Hemocyanin (KLH)**

One-hundred thirty-six patients and 36 marrow donors were tested for antibody formation to KLH. Sixty-seven of the patients were grafted for hematologic malignancy and 69 for aplastic anemia.

The preparation of KLH, technique of immunization, and antibody determination from serum samples have been described.

**ABO Isohemagglutinins**

Serum isohemagglutinins in the recipients of marrow from ABO-incompatible donors were determined by standard methods at the Puget Sound Blood Center. The time from transplantation to complete disappearance of antibody in serum and/or antibody on cells (IgG or nongamma indirect Coombs' tests) was determined.

**Consent**

All patients gave consent for these studies in accordance with the principles established by the University of Washington and/or the Fred Hutchinson Cancer Research Center.

**Statistical Analysis**

Multiple regression techniques were used to analyze the relationships of antibody titers to factors that might influence immune function. The factors studied are listed in Table 1. Interactions among the factors were also allowed. For each antigen a final model was selected that included only those factors that jointly had significant influences on the antibody titer.

For each antigen the maximum titer for each patient within 8 wk of antigenic exposure was selected as the measure of the magnitude of response. The factors were first screened for statistical significance at a time using univariate analysis of variance. The final multiple regression models were then built from the selected factors using a stepwise approach, i.e., by adding at each step the most significant of the variables not yet in the model. The Statistical Package for the Social Sciences was utilized except in the specific cases for KLH and PPA analyses cited below.

**Table 1. Factors of Possible Significance in Immunologic Recovery Following Allogeneic Marrow Transplantation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Days from transplant to antigen injection</td>
<td></td>
</tr>
<tr>
<td>Acute GVHD</td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (aplastic anemia or hematologic malignancy)</td>
<td></td>
</tr>
<tr>
<td>Conditioning regimen (cyclophosphamide or TBI + cyclophosphamide)</td>
<td></td>
</tr>
<tr>
<td>Patient age</td>
<td></td>
</tr>
<tr>
<td>Patient sex</td>
<td></td>
</tr>
<tr>
<td>Donor sex</td>
<td></td>
</tr>
<tr>
<td>Donor age</td>
<td></td>
</tr>
<tr>
<td>Sex match of donor-recipient pairs</td>
<td></td>
</tr>
<tr>
<td>Treatment in or out of laminar air flow rooms</td>
<td></td>
</tr>
<tr>
<td>Disease status of bone marrow at time of transplantation (remission or relapse)</td>
<td></td>
</tr>
<tr>
<td>Steroid administration</td>
<td></td>
</tr>
<tr>
<td>ATG treatment +</td>
<td></td>
</tr>
</tbody>
</table>

* TBI, total body irradiation.
+ ATG, antithymocyte globulin administration for treatment or prevention of acute GVHD.
The bacteriophage maximum titers were assumed to follow a log-normal distribution. Because the logarithms of the maximum titers did not appear linearly related to the entire time period after transplantation, analyses were performed separately for injections occurring before and after 180 days posttransplantation. To illustrate the results of these analyses, Figs. 1 and 2 were drawn from the estimated mean titers for patients, assuming the maximum titers followed distinct logistic distributions for patients with and without chronic GVHD over the entire observation time.

The analysis of PPA and KLH titer data distinguished between individuals whose titers were negative in undiluted serum and those with positive titers. The former have titers indistinguishable from minus infinity and cannot be included directly in the kind of analysis described above. In order to avoid this problem and include patients with negative and positive titers, statistical analysis of the proportions of patients with positive titers in the study population was completed and yielded results in accord with those to be described below and will not be reported.

The PPA and KLH titers of individuals with positive titers were treated as grouped and censored data, since they were obtained from serial dilution assays, which can only determine a range of dilutions within which reactivity ceases. PPA and KLH maximum titers were assumed to follow logistic probability distributions. Titers obtained from normal marrow donors were assumed to not vary with time.

The computer program for PPA and KLH data analysis was designed locally to deal with the logistic regression for grouped and censored data. The final models for the mean titer were selected as mentioned above.

To assess how well the final multiple regression models fitted the data, the coefficients of correlation between the observed data and the predicted values derived from the model were calculated. The squares of these coefficients, denoted $R^2$, are given in the tables. A value close to unity indicates that a model fits the data well. $R^2$ shown in Table 2 also expresses the cumulative proportion of the variation in the data, which is explained by differences in the mean titer due to the factors in the model.

The results of the analyses are displayed in the figures as regression lines of the mean titer as a function of time from transplantation or from primary injection. Individual lines are shown for groups of patients sharing a particular characteristic.

**RESULTS**

**Phage**

The factors that in univariate analyses seemed to influence antibody activity most significantly were
Table 2. Significance of Interacting Factors for Antibody Responses to Phage

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Factors</th>
<th>Time Period</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Posttransplant Period</td>
<td></td>
<td>&lt; 180 Days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 180 Days</td>
<td></td>
</tr>
<tr>
<td>Primary Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99 Patients</td>
<td>&lt; 0.0005</td>
<td>66 Patients</td>
<td>0.021</td>
</tr>
<tr>
<td>Days post-transplant</td>
<td></td>
<td>33 Patients</td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td>ATG therapy†</td>
<td>0.005</td>
<td>ATG therapy</td>
<td>0.028</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>0.011</td>
<td>Days post-transplant</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Secondary Response — Total Antibody Activity</td>
<td>Days post-transplant</td>
<td>13 Patients</td>
<td>0.051</td>
</tr>
<tr>
<td>39 Patients</td>
<td></td>
<td>Diagnosis‡</td>
<td>0.013</td>
</tr>
<tr>
<td>ATG</td>
<td>0.04</td>
<td>ATG</td>
<td>0.060</td>
</tr>
<tr>
<td>Patient Sex</td>
<td>0.57</td>
<td>Patient sex</td>
<td>0.022</td>
</tr>
<tr>
<td>IgG Portion of Secondary Response</td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>26 Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days post-transplant</td>
<td>&lt; 0.0005</td>
<td>20 Patients</td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td>ATG</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>0.021</td>
<td></td>
<td>ATG</td>
</tr>
<tr>
<td>ATG</td>
<td>0.024</td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Days from transplant to antigen injection.
†ATG given prophylactically or therapeutically for acute GVHD posttransplant.
‡Diagnosis either aplastic anemia or hematologic malignancy.

During the entire posttransplant period, the significant factors for primary response were the time elapsed between transplantation and antigen injection, ATG treatment, and chronic GVHD. The proportion of the variation in titers ($R^2$) that could be attributed to the differences in log mean response associated with these three factors was 0.46. Antibody production improved with increasing time elapsed between transplantation and antigen injection, except in patients who had chronic GVHD or received ATG. ATG was associated with poor antibody production and exerted its major influence in the first 180 days posttransplant, whereas after 180 days its influence was lost, and chronic GVHD played the most significant role. Only 0.13 of the variation in titers ($R^2$) determined within the first 180 days posttransplant was attributable to ATG and time posttransplantation. Titters produced in all patients during the early time period were low, making it difficult to detect differences between groups. In the period after 180 days, 0.41 of the variation was attributed to chronic GVHD and time elapsed posttransplantation. The final statistical models were not significantly improved when recipient sex, patient age, conditioning regimen (TBI and CY or CY alone) and diagnosis (leukemia or aplastic anemia) were taken into account. Figure 1 illustrates the poor primary antibody responses early after transplantation and the subsequent increase in antibody responses as time elapses after transplantation. It further illustrates that patients with chronic GVHD have consistently poorer primary antibody titers throughout most of the postgrafting period when compared to patients without chronic GVHD.

With regard to the secondary response, time elapsed between transplantation and antigen injection, ATG treatment (treated patients had lower titers) and patient sex (males had lower titers) had a significant influence on antibody titers when data of the entire posttransplant period were analyzed. However, when data obtained during the first 180-day period were analyzed, only marginal significance of any factor was attained presumably because of the uniformly low antibody titers observed in that period. In the time period beyond 180 days, time elapsed posttransplantation and patient sex were the only factors emerging as statistically significant.

The titer of IgG produced in the secondary response was influenced most significantly by time between transplant and secondary phage injection, chronic GVHD, and ATG treatment. Only six patients were tested in the first 180 days. In the period greater than 180 days chronic GVHD and ATG treatment were
responsible for the lowest titers. Figure 2 shows best fit curves for the mean levels of IgG antibody and illustrates the impaired production in patients with chronic GVHD.

Eleven patients with chronic GVHD received immunosuppressive treatment to ameliorate their condition and 11 were untreated. We determined whether treatment of chronic GVHD was responsible for the low activity in primary, secondary or secondary IgG response. Treated and nontreated patients with chronic GVHD at comparable times posttransplant had similar antibody levels.

**PPA**

Pneumococcal antibody titers were significantly influenced by time between transplantation and initial injection of PPA and chronic GVHD (Table 3). Patients without chronic GVHD ultimately had titers within the normal range, but those with chronic GVHD had prolonged impairment (Fig. 3). Other factors failed to show a significant influence on antibody titers. Thirteen patients were treated for chronic GVHD and 23 were untreated when the antigen was injected. Treated and nontreated patients with chronic GVHD at comparable times posttransplant had similar antibody levels.

**KLH**

Antibody titers rose as the time elapsed from transplantation to primary KLH antigen injection increased. Patients who had experienced acute GVHD recovered more slowly (Fig. 4). The negative influence of acute GVHD on KLH antibody titers was significant when patients who subsequently developed chronic GVHD were excluded from the analysis. Other factors did not have significant influence on the primary response (Table 4).

In the secondary response, the titer increased with longer intervals between primary and secondary injection, and the magnitude of increase depended on age, chronic GVHD, and ATG treatment. These relationships are depicted in Fig. 5. Younger patients, patients receiving ATG, and having chronic GVHD had lower titers. In contrast, older patients without chronic GVHD or ATG treatment developed normal titers. Additionally, patients with low total or IgG primary titers had lower secondary responses than patients with higher primary responses. These factors were statistically significant (Table 4). The other factors examined did not influence the secondary response. The IgG portion of the secondary response to KLH increased.

![Fig. 3. Antibody responses to pneumococcal polysaccharide type 3 in 129 patients at varying times postgrafting. The curves represent the estimated mean titers for 36 patients with and 93 without chronic GVHD. The hatched area represents the 5–95 percentile response of 26 normal marrow donors tested with PPA.](image1)

![Fig. 4. Primary responses to keyhole limpet hemocyanin in 136 patients at varying times postgrafting. The curves represent the estimated mean titers for 66 patients with and 70 without acute GVHD. The hatched area represents the 5–95 percentile response of 36 normal marrow donors tested with KLH.](image2)

![Fig. 5. Secondary responses to keyhole limpet hemocyanin in 73 patients at varying intervals between primary and secondary injection. The curves in the left panel depict the estimated mean titers for 10-yr-old patients and the right panel for 30-yr-old patients. The hatched area represents 5–95 percentile response of 36 normal marrow donors tested with KLH. Lines 1 – patients without chronic GVHD or ATG treatment. Lines 2 – patients without chronic GVHD who received ATG treatment. Lines 3 – patients with chronic GVHD who did not receive ATG. Lines 4 – patients having both chronic GVHD and ATG treatment.](image3)
Table 4. Significance of Interacting Factors for Responses to KLH in 136 Patients and 36 Marrow Donors

<table>
<thead>
<tr>
<th>Primary Response</th>
<th>Secondary Response</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Significant Factors</td>
</tr>
<tr>
<td></td>
<td>Patients versus normals</td>
</tr>
<tr>
<td></td>
<td>Days posttransplant*</td>
</tr>
<tr>
<td></td>
<td>Acute GVHD</td>
</tr>
<tr>
<td></td>
<td>Chronic GVHD</td>
</tr>
<tr>
<td></td>
<td>ATG†</td>
</tr>
<tr>
<td></td>
<td>Primary KLH titer</td>
</tr>
<tr>
<td></td>
<td>Primary KLH IgG</td>
</tr>
</tbody>
</table>

*Days from transplant to antigen injection.
†ATG, antithymocyte globulin given prophylactically or therapeutically for acute GVHD posttransplant.

Disappearance of Host Isohemagglutinin in ABO-Incompatible Transplant Recipients

The time to disappearance of original host isohe-magglutinin titers is plotted in Fig. 6. Six patients were censored because of demise (1 patient), relapse (1 patient), or weak titers in undiluted serum that were not repeatedly determined (4 patients). The titers became undetectable from 0 to 116 (median 38.5) days.

DISCUSSION

The humoral immune system in murine\(^7\) and human\(^10\) recipients of marrow grafts is derived from cells of donor origin. The magnitude of the antibody responses, in particular to the neoantigens phage and KLH, is a reflection of the immunologic activity of cells derived from the stem cells infused with the marrow inoculum. The major determinant of the pace of recovery of the immune reactivity in marrow graft recipients appears to be the time required for the host lymphoid tissues to be repopulated by functional donor cells. This second round of ontogeny is expressed in two characteristic periods of immunologic reactivity: the early posttransplantation period (3–4 mo) when all patients have poor antibody responses; the later period when patients without chronic GVHD have recovered their ability to produce antibody while those with chronic GVHD remain immunologically impaired.

The uniformly impaired serum antibody levels in the first half year postgrafting are consistent with in vitro findings of poor antibody secretion by peripheral blood lymphocytes after stimulation with killed Staphylococcus aureus bacteria, a polyclonal B-cell activator.\(^19\) Separation of lymphocytes into T and non-T subpopulations and culture with polyclonal\(^{20,21}\) and antigen-specific activators are likely to aid our understanding of T- and B-cell dysfunction underlying the poor in vivo antibody secretion early after grafting.

In spite of poor antibody production during the first 180 days, most patients manage to survive this period of greatest risk for infections. Defense against infection during the early postgrafting period is probably made up of a number of factors other than ability to produce antibody to neoantigens: (A) most patients are treated with antibiotics; (B) a number are given granulocyte transfusions; (C) some are treated in the "germfree" environment of LAF rooms; (D) passive transfer of mature donor lymphoid cells already sensitized to certain pathogens but as yet unable to be sensitized to new antigens may have occurred with the marrow infusion; and (E) host immunity to certain...
pathogens may persist for some time after grafting. Evidence supporting this latter hypothesis comes from the demonstration of persistence of host-produced isohemagglutinins for up to 3–4 mo in patients given marrow from ABO-incompatible donors.

As patients survive beyond 180 days from grafting, most do well and experience either no or very few infections. However, patients with chronic GVHD have a high incidence of serious and sometimes fatal pneumococcal or other gram-positive infections. This morbidity and mortality in patients with chronic GVHD is most likely related to their poor antibody responses to PPA, secondary KLH, and primary phage immunization as well as their inability to switch from IgM to IgG antibody in the secondary response to phage. An additional factor contributing to infections in patients with chronic GVHD may be their significantly impaired neutrophil chemotaxis.

The mechanisms underlying decreased antibody secretion in patients with chronic GVHD have been examined in vitro by evaluating B- and T-cell function with hemolysis in gel plaque assays or cytoplasmic immunoglobulin staining after culturing patients' lymphocyte subpopulations with the polyclonal B-cell activator pokeweed mitogen. Antibody secretion following stimulation with pokeweed mitogen is known to be T-dependent. A number of deficiencies were detected: (1) patient B cells did not make antibody in the presence of normal donor T helper cells; (2) patient T cells did not help normal donor B cells make antibody; (3) patient T cells suppressed antibody production when cultured with normal T plus B cells. In previous work published from this center, suppressor T cells from chronic GVHD patients have been found to diminish blastogenesis of lymphocytes from normal marrow donors stimulated by allogeneic lymphocytes from a third party. Other workers have described increased numbers of suppressor cells bearing the TH-2+ serologic marker in the peripheral blood lymphocytes of patients with chronic GVHD. These data suggest a spectrum of immunologic abnormalities involving both cellular and humoral immunity in chronic GVHD patients.

Patients with chronic GVHD have normal or elevated serum immunoglobulin levels and yet, they are not able to produce normal antibody titers to phage, KLH, and PPA, and in vitro antibody secretion after polyclonal stimulation of their lymphocytes with pokeweed mitogen is poor. The reasons for these seemingly paradoxical findings are not entirely clear. Perhaps the normal or elevated serum immunoglobulin levels are the result of polyclonal lymphocyte activation in vivo due to histocompatibility differences between donor and host. Once polyclonally activated, lymphocytes no longer respond to new antigens in vivo and in vitro. Circumstantial evidence for this hypothesis comes from the recent observation in patients with chronic GVHD of unidirectional lymphocyte reactivity in vitro to host antigen, most likely due to in vivo sensitization to non-HLA antigens.

Some additional independent factors, while not as striking as chronic GVHD or time between transplantation and antigen injection, exert some influence on antibody production after grafting. One is the suppression by preceding ATG treatment of the primary phage, the secondary KLH antibody responses, and the switch from IgM to IgG antibody in the secondary phage response. ATG was given prophylactically within the first 3 wk postgrafting to some patients who never experienced subsequent GVHD. It appears that ATG can affect lymphocyte function beyond 6 mo from the time it was administered. Three other factors seemed also to be of minor importance. For unknown reasons, the transient presence of acute GVHD, independent of chronic GVHD, was able to impair the primary antibody response to KLH throughout the entire posttransplant period. It was also not clear why male patients had lower primary antibody responses to phage than females and why younger patients had lower secondary antibody responses to KLH than older patients.

Finally, other factors previously thought to play a role in the speed with which the immune system is reconstituted after transplantation, namely conditioning regimen with CY or TBI, underlying diagnosis of aplastic anemia or acute leukemia, sex match, transplantation in remission or relapse of hematologic malignancy, treatment in or out of laminar air flow rooms, or treatment with steroids, had no significant influence on humoral antibody production.

This study provides a basis for practical considerations regarding protection from infection. Infection in marrow transplant recipients has been discussed previously, and in particular, the frequency of pneumococcal infection in patients with chronic GVHD has been emphasized in patients who survived 7 mo postgrafting. Although some workers have proposed immunization with pneumococcal vaccine as a useful protective measure, it is clear from the present data that efforts at immunization will be ineffective until the lymphocytes are capable of responding to the antigen. The data suggest that by 1 yr posttransplant immunization to many of the common antigens, such as tetanus, diphtheria, pertussis, and PPA, is likely to be effective in patients without chronic GVHD. Earlier immunization is likely to be ineffective. In contrast, patients with chronic GVHD have a more prolonged period when immunization will probably...
not result in normal antibody responses, and some may never respond. Whether it would ever be safe to utilize live virus vaccines such as oral polio, mumps, and measles in either group is unknown.

The earlier period after grafting when immunologic responsiveness is poorest is an appropriate time to consider attempts to accelerate immune recovery with additional donor lymphocytes, thymic hormones, thymus transplants, or to protect with other means such as trimethoprim-sulfamethoxazole or injections of cytomegalovirus-immune globulin. Later, when patients have become long-term survivors, the patients with chronic GVHD may benefit from protection by prophylactic antibiotics, treatment to ameliorate the chronic GVHD, or attempts to correct the underlying immunodeficiency.

ACKNOWLEDGMENT

We would like to thank Daniella Livnat, Jean Syrotuck, Sam Heller, and the Puget Sound Blood Center for excellent technical assistance; Deborah Gayle and Joni Coble for organizing and collecting serum samples; Gary Schoch for computer programming; and Janis Korbol for typing the manuscript.

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Recovery of antibody production in human allogeneic marrow graft recipients: influence of time posttransplantation, the presence or absence of chronic graft-versus-host disease, and antithymocyte globulin treatment

RP Witherspoon, R Storb, HD Ochs, N Fluornoy, KJ Kopecky, KM Sullivan, JH Deeg, R Sosa, DR Noel, K Atkinson and ED Thomas