Impact of Blood Transfusion on Renal Transplantation

THOMAS C. FULLER, PH.D., FRANCIS L. DELMONICO, M.D., A. BENEDICT COSIMI, M.D., CHARLES E. HUGGINS, M.D., MARY KING, B.S., PAUL S. RUSSELL, M.D.

From the Blood Transfusion Service and the Transplantation Unit of the Department of Surgery, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts

The relationship between transfusion of different preparations of blood, sensitization to HLA antigens and survival of subsequent kidney transplants was investigated in 90 consecutive recipients. HLA lymphocytotoxins in transplant candidates precluded or greatly delayed receipt of an allograft ($p < 0.0005$). Furthermore, only 17% of such sensitized recipients had functioning grafts one year after transplantation compared to 57% survival for nonsensitized recipients ($p < .02$). A small number of nonsensitized patients who were never transfused had surprisingly poor one year graft survival (25%). If frozen blood is used for transfusion rather than whole/packed RBC, the incidence of patient sensitization can be markedly reduced without subsequent compromise in transplant survival (51%). It is concluded that as a consequence of avoiding HLA sensitization by transfusion of frozen blood (processed by agglomeration), the period of hemodialysis required for potential graft recipients will be shortened and an increased proportion of potential recipients will be successfully treated by transplantation.

THAT LEUKOCYTES SHARE transplantation antigens with many other tissues has been well established. As originally described in the mouse by Medawar[18] and subsequently in man by Hattler and coworkers,[12] a single transfusion of whole blood can provoke a sufficient immune response to induce accelerated rejection of a skin graft from the blood donor. In the case of the renal transplant patient, however, there remains considerable controversy concerning the immunogenic potential of various red blood cell preparations to immunize a potential recipient, thereby influencing the survival of a subsequent allograft.

In an effort to reduce the incidence of sensitization to the major histocompatibility antigens of man (HLA), most centers have adopted the approach of avoiding the administration of blood to transplant candidates. Contrary to expectations, however, numerous studies[8, 24–26] now indicate that blood transfusions may actually be beneficial in prolonging the survival of renal allografts as compared to results in recipients with no prior history of transfusion. Unfortunately, most reports concerning this topic are difficult to evaluate because of a necessary reliance on the combined experiences of multiple institutions. Thus, complete transfusion histories, type(s) of blood preparations transfused and treatment protocols employed have been uncertain.

In 1973, we reported that transfusion of frozen deglycerolized red blood cells [RBC(H)DG] was followed much less commonly by serum hepatitis and sensitization to HLA antigens than transfusions of conventional blood.[14] In an effort to clarify further the relationship between the transfusion of various blood cell preparations, HLA sensitization and renal allograft survival, we have reviewed the data from our population of cadaver kidney transplant recipients and hemodialysis patients for the past five years. Based on our results, we present in this report a positive plan which should shorten the period of chronic hemodialysis required for patients awaiting transplantation and increase the proportion of waiting recipients who can be treated successfully by renal transplantation.

Materials and Methods

Patients

Between January 1969 and September 1975, 90 patients received primary renal allografts from nonliving donors at the Massachusetts General Hospital. All recipients included in the present study have been observed for at least six months following transplantation. No recipient was excluded from analysis because

Human blood for transfusion is recognized by the U.S. Bureau of Biologics (FDA) to exist in three district forms:[29] 1) *Whole Blood (human)*—WB(H). 2) *Red Blood Cells (human)*—RBC(H) commonly referred to as packed cells 3) *Red Blood Cells (human) deglycerolized* RBC(H)DG—glycerolized RBC(H) stored continuously colder than −65° and deglycerolized before transfusion by: a) agglomeration[13]—RBC(H)DG-A b) centrifugal washing[20]—RBC-(H)DG-C.

Reprint requests: Thomas C. Fuller, Ph.D., Histocompatibility Testing Laboratory, Blood Transfusion Service, Massachusetts General Hospital, Boston, Massachusetts 02114.

Supported in part by a grant (HL-18646-01) from the National Heart, Lung and Blood Institute (NIH), U.S. Public Health Service.

Submitted for publication: April 19, 1977.

0003-4932-78-0200-0211-0085

of technical or nonimmunologic failure of the graft. Immunosuppressive therapy consisted of azathioprine, prednisone and antithymocyte globulin (Upjohn Co.) as recently described.[4] Acute rejection was diagnosed by clinical and laboratory criteria as previously described.[4]

Allograft survival was calculated by the actuarial method[19] and statistical analysis performed by Student's t test. For purposes of the present report, an allograft was considered to be functioning satisfactorily if the recipient did not require hemodialysis; however, the majority of functioning allografts maintained serum creatinine levels of less than 2 mg/100 ml. Graft failure was declared at the time of nephrectomy, return of the patient to chronic hemodialysis, or death of the recipient.

Exposure to Allogeneic Immunogens

A complete *life* history of exposure to alloantigens (*re*: pregnancy and blood transfusion) was obtained for all recipients. Special care was taken to procure thorough blood transfusion histories including number and type of blood products transfused and the date and location of transfusion. This was accomplished by: a) detailed review of each patient's medical record, b) personal interviews with each patient or his immediate family, and most importantly, c) confirmation and, in many instances, expansion and correction of the initial data upon direct examination of the records held in the Blood Transfusion Services of other hospitals in which our patients had previously been treated.

Only transfusion of formed blood elements prior to transplantation was considered for this study; transfusion of human plasma or plasma fractions was not included since only a few patients had received these components. The blood products were categorized as follows: a) whole blood (human) [WB(H)] or red blood cells (human) [RBC(H)],[29] stored between one and 6° and transfused within 21 days of collection and b) glycerolized, frozen RBC(H), stored continuously at −65° or colder and deglycerolized [RBC(H)DG] before transfusion by one of two techniques available in the Boston area. The first method is a noncentrifugal technique whereby erythrocytes suspended in nonelectrolyte solutions reversibly agglomerate and settle to the bottom of their container thus allowing decantation of the supernatant wash solutions containing glycerol [RBC(H)DG-A]. This method was developed by Dr. Charles E. Huggins at the Massachusetts General Hospital and has been used for more than 13 years at this institution.[13] The alternative method of preparing RBC(H)DG is currently used by the American National Red Cross[20] and involves continuous centrifugation and stepwise washing of glycerolized, previously frozen RBC(H) with 12%, 1.6% and 0.8% NaCl solutions [RBC(H)DG-C].

The only other blood cell product transfused to these patients was platelet concentrate (human),[29] multiple units of which were required by a single patient during a bleeding crisis.

Histocompatibility Testing

All donors of allografts and all recipients were serotyped for the HLA-A and B locus antigens[30,33] by the complement-dependent lymphocytotoxicity technique.[28] One hundred-forty to 174 alloantisera were used to identify between 12 (in 1969) and 32 (in 1975) HLA alleles. A similar distribution of various donor-recipient HLA match grades or apparent degrees of incompatibility was found in all patient categories described below.

Viable lymphocytes from the donor of the transplant and the most recent serum from the recipient (and in some cases, retrospective serum specimens) were crossmatched at the Interhospital Organ Bank (I.O.B.) regional typing facility using the standard two stage NIH cytotoxicity technique.[28] All crossmatches were reported to be negative.

Upon admission to the transplant program and monthly thereafter, patients were tested for the induction or persistence of HLA lymphocytotoxic antibody. Since 1972, serum alloantibody screens have been performed by Amos' modification of the NIH microdrop cytotoxicity method.[1] Each serum was tested against a relatively constant 25 member unrelated frozen[10] lymphocyte panel specifically selected from our total panel ($N > 100$) to represent the broadest spectrum of HLA-ABC locus alloantigens. Sera collected preoperatively from those patients who received transplants prior to 1972 were rescreened using the above technique and cell panel.

Transplant candidates were defined as alloimmunized ("presensitized") if during any month of serologic testing a serum contained a lymphocyte-reactive (>20% trypan blue stained cells) antibody which was cytotoxic against at least two members of the panel (*i.e.* each HLA antigen was represented a minimum of two times in the screening panel). Obviously, this definition does not establish that a patient is unequivocally nonsensitized to HLA or other alloantigens simply because lymphocytotoxic antibody is not demonstrable in the serum by currently available tests.

Results

Influence of Sensitization on Patient Acquisition and Transplantation

Sixty-four patients, all undergoing chronic hemodialysis, were accepted into our program as potential

recipients of kidney transplants from cadaver donors between January 1973 and July 1975 (complete information concerning prospective recipients acquired prior to 1973 was not available). More than one-third of the 64 patients were found to be sensitized (Table 1). Following a mean dialysis period of nearly eight months, only 44% of the sensitized patients underwent transplantation. In contrast, more than 90% of the nonsensitized group received an allograft within two months of their acceptance into the program ($p < 0.0005$). These findings could not be ascribed to differences in the procedures used for recipient selection or to underlying clinical factors. Therefore, the development of lymphocytotoxic antibodies in hemodialysis patients precluded or delayed receipt of a primary renal allograft from a crossmatch negative donor.

TABLE 1. *Patient Acquisition at the Massachusetts General Hospital, January 1973–July 1975*

Patients[a]	Nonsensitized[b] Waiting Pd. (mo) N	Mean	Median	Sensitized[b] Waiting Pd. (mo) N	Mean	Median	
Receiving an allograft	37	2.1	1.0	10	5.3	3.5	} c
Awaiting an allograft	4	3.0	2.5	13	9.9	10.0	} c
Waiting pd. (mo)	41	2.2	1.0	23	7.9	6.0	
Total patients receiving allografts	90.2%			43.5%			
Total patients with functioning allografts at 1 yr.	22/41 (54.4%)			1/23 (4.3%)			

[a] All patients accepted as candidates for a non-living donor primary renal allograft. [b] HLA allosensitization as assessed by complement-dependent lymphocytotoxicity panel screening (see *Methods* section) using at least two sera from each patient collected at intervals of one month. [c] χ^2 (Yates) = 14.20 ($p < 0.0005$).

Sensitization and Allograft Survival

Follow-up of the above group of 64 potential graft recipients (Table 1) revealed that 54.4% of the 41 nonsensitized candidates and 4.3% of the 23 sensitized candidates had achieved a successful renal transplant at one year. A similar trend was evident in our total population of recipients of first transplants from nonliving donors since January 1969: 59% of the nonsensitized recipients continued to have functioning grafts at one year following transplantation whereas only 17% of the sensitized patients had similar function (Fig. 1). Moreover, sensitized patients appeared to be at equal risk for early allograft failure no matter whether they had a high or a low frequency of panel reactivity.

Influence of Blood Transfusions on the Development of Sensitization

Analysis of the transfusion histories of each hemodialysis patient awaiting transplantation as well as each recipient of a transplant revealed that all of the sensitized patients had received blood transfusions either prior to or during their period of hemodialysis.

The relationship of the type of blood preparation transfused to the incidence of sensitization to HLA antigens was analyzed. The 90 recipients of cadaver allografts were divided into three categories (Table 2) as defined by the types of red blood cell product they had received during their lifetime prior to transplantation: 1) no blood transfusions (11.1% of recipients), 2) only previously frozen RBC(H)DG transfusions (43.3%) and 3) WB(H) and/or RBC(H) transfusions (45.6%). Nearly two-thirds of this latter group had also received a variable number of units of RBC(H)DG while on dialysis.

No cytotoxic antibody was demonstrable at any time in the nontransfused recipients before transplantation. Nearly 27% of the patients who received WB(H)/RBC(H) were sensitized by the time of transplantation whereas patients who had been transfused solely with RBC(H)DG had an incidence of sensitization about half that of the WB(H)/RBC(H) group (Table 2). These findings could not be ascribed merely to quantitative differences in transfusion exposure (Table 2).

As two quite different physical methods are commonly used for deglycerolization of the frozen blood transfused in Massachusetts (Methods Section), the courses of the patients who received exclusively

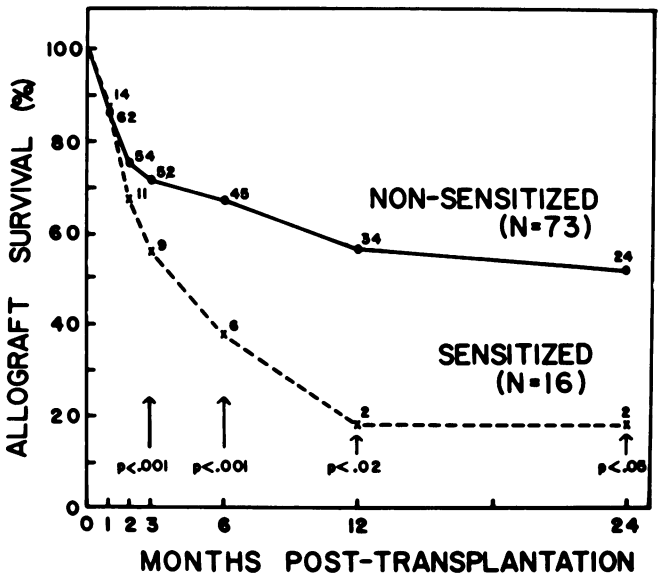

FIG. 1. Influence of HLA sensitization on subsequent survival of renal transplants. Patients were tested for the development or persistence of HLA antibody at monthly intervals prior to transplantation (*Methods Section*). One patient was excluded from the analysis because of an incomplete sensitization profile. All recipients were reported to be crossmatch compatible with the organ donor. Numbers at each point on curve refer to number of grafts at risk at the specified month posttransplantation.

TABLE 2. *Blood Transfusion History of Nonliving Donor Primary Renal Allograft Recipients, Jan. 1969–Sept. 1975*

Transfusion Category*	No. Patients	Mean (Median) Units of Blood Transfused	Incidence of Sensitization (%)†
No blood	10	0 (0)	0.0
RBC(H)DG Only (Combined)	39	11.9 (10.0)	13.2
a. Only RBC(H)DG-A	21	12.1 (12.0)	4.8‡
b. Only RBC(H)DG-C	12	8.8 (5.0)	16.6
c. Both RBC(H)DG-A&-C	6	17.7 (15.5)	40.0
WB(H)/RBC(H) ± RBC(H)DG (Combined)	41	18.7 (16.0)	26.8‡
a. WB(H)/RBC(H) Only	12	7.7 (3.5)	25.0
b. WB(H)/RBC(H) + RBC(H)DG	29	23.3 (21.0)	27.6
Total	90	13.9 (13.0)	18.0

* Transfusion history spans *entire* lifetime of each patient up to the day of transplantation; see *Materials* section for clarification of blood product abbreviations.

† Per cent of patients with demonstrable HLA alloantibody before transplantation as defined by lymphocytotoxicity panel screening at monthly intervals.

‡ Significant difference in sensitization incidence [χ^2 (Yates) = 3.032, $p < 0.10$] between these two transfusion categories.

RBC(H)DG were analyzed further. The 21 patients who were transfused only with agglomeration washed RBC(H)DB [*i.e.*, RBC(H)DG-A] had a 4.8% incidence of cytotoxic antibody. In contrast, the incidence of sensitization in the 12 patients who received only cells washed by the centrifugation method [RBC(H)-DG-C] was 16.6%. These differences were not statistically significant, however.

The development of lymphocytotoxic antibody was also correlated with the quantity of each type of blood cell product administered. Patients were arbitrarily divided into two categories on the basis of having received a total of more or less than ten total units of blood prior to transplantation. Patients transfused with more than ten units of blood, no matter what type of red blood cell product was concerned, had a higher incidence of sensitization than those who received ten or fewer units of donor blood (Table 3).

Correlation of Type of Blood Transfusion and Allograft Survival

Renal transplant survival for the entire series of 90 consecutive graft recipients was 58.7%, 47.9% and 45.2% at six, 12 and 24 months, respectively. Allograft survival was similar in patients who received either WB(H)/RBC(H) ± RBC(H)DG or solely RBC-(H)DG (no sensitized patients excluded Fig. 2). However, the small group of nontransfused patients, none of whom showed evidence of sensitization, had exceedingly poor graft survival (75% of the grafts had failed within one year of transplantation).

There were no discernible differences in graft survival in those patients who had received solely WB(H)/RBC(H) or both WB(H)/RBC(H) and RBC(H)DG (data not shown). There was a suggestion, however, that recent exposure to WB(H)/RBC(H) prior to transplantation led to earlier allograft failure (Table 4).

Detailed comparison of graft survival in patients transfused exclusively with RBC(H)DG revealed a number of interesting differences. One year transplant

TABLE 3. *Presensitization and Renal Allograft Survival—Relation to the Number of Blood Transfusions Received Prior to Grafting*

Transfusion Category*	No. Units Blood Transfused	No. Patients	% Patients Sensitized	Allograft Survival (%) mos. 6	12	24
RBC(H)DG only (combined)	1 ≤ 10 (4.4)†	21	9.5	61.9	56.5	56.5
	> 10 (20.8)	18	16.7	61.2	44.5	34.1
			p =‡	N.S.	<0.02	<0.10
RBC(H)DG-A Only	1 ≤ 10 (4.6)	10	0.0	80.0	80.0	80.0
	> 10 (18.9)	11	9.1	54.5	45.4	45.4
			p =	<0.01	<0.01	<0.02
RBC(H)DG-C + RBC(H)DG-A	1 ≤ 10 (4.2)	11	18.2	45.4	34.1	34.1
	> 10 (23.7)	7	28.6	73.4	44.1	44.1
			p =	<0.10	N.S.	N.S.
WB(H)/RBC(H) + RBC(H)DG (combined)	1 ≤ 10 (5.1)	18	16.7	61.1	61.1	61.1
	>10 (29.4)	23	34.8	61.0	42.9	37.8
			p=	N.S.	<0.10	<0.02

* See *Materials* for definition of blood products.

† Mean units of blood transfused/patient category.

‡ Probability of a significant difference in allograft survival between patients receiving less than or greater than ten units of specified blood; N.S.—$p > 0.10$.

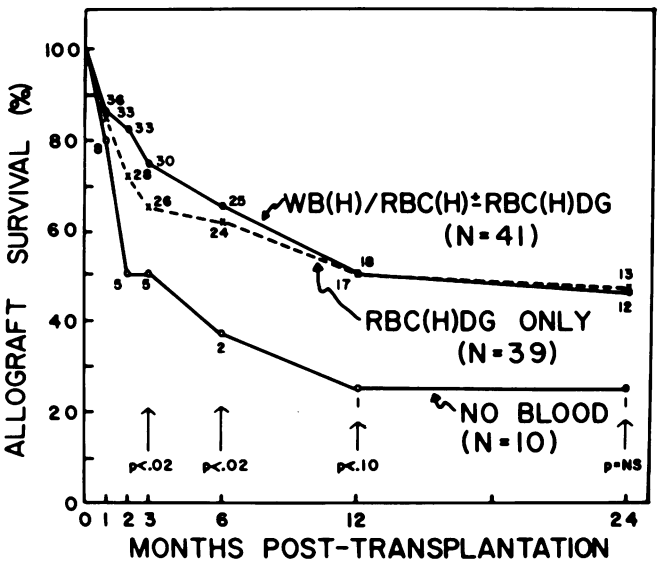

FIG. 2. Renal transplant survival in 90 consecutive recipients of primary allografts in relation to the patients' life history of blood exposure and type of blood cell preparation received prior to transplantation. No significant difference in graft survival was found in transfused patients who received either frozen blood deglycerolized [RBC(H)DG] or whole/packed red blood cells [WB(H)/RBC(H)] ± RBC(H)DG. A significantly lower proportion of grafts survived in patients never exposed to blood before transplantation when compared to either group of transfused graft recipients.

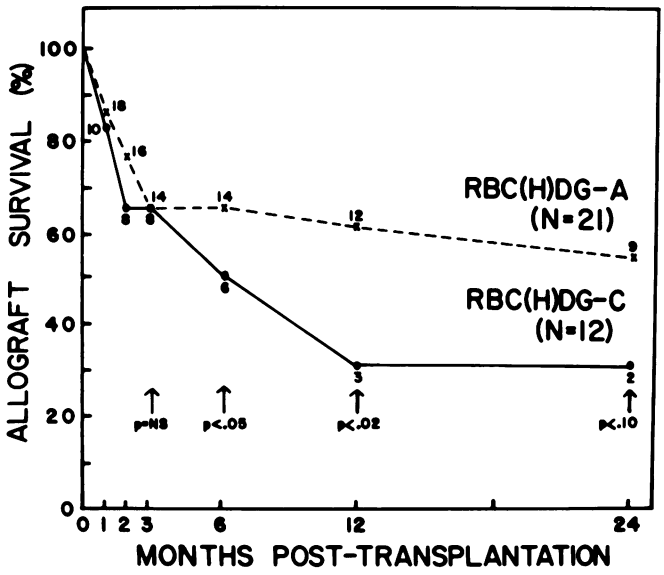

FIG. 3. Comparison of transplant survival in 33 patients who had previously received only frozen blood which had been deglycerolized before transfusion either by the agglomeration [RBC(H)DG-A] (13) or by the centrifugal washing [RBC(H)DG-C] (20) method. A significant difference in graft survival can be noted at six and 12 months following transplantation.

survival in patients who received only RBC(H)DG-A was nearly twice that observed in patients who received only RBC(H)DG-C (Fig. 3) ($p < 0.02$). Although there was a higher incidence of HLA antibody development in those patients who received RBC(H)DG-C, only a slight improvement in one year graft survival was noted if one excludes from the analysis the two sensitized recipients or includes the six patients who received a combination of both RBC(H)DG products. These findings may suggest a difference in the immunogenic capacity of the final RBC(H)DG products.

An inverse relationship was observed between the number of blood transfusions administered before transplantation and long-term graft survival. With the exception of the RBC(H)DG-C group, allograft survival was noted to be improved in those patients who had received ten or fewer units of any form of blood during their lifetime (Table 3). These differences were most evident at 12 and 24 months after transplantation and tended to correlate with the development of HLA sensitization before transplantation.

Discussion

With few exceptions, patients with demonstrable humoral HLA sensitization against graft antigens will experience irreversible immunologic destruction of the organ soon after its circulation is restored. Considerable disagreement (for example, ref. 7 vs. 22) remains, however, concerning the influence of existing HLA presensitization (against a random lymphocyte panel) on transplant survival where antibody specific for donor alloantigens has not been detected prospectively by the lymphocytotoxicity crossmatch. Some of the confusion surrounding this difference in results has undoubtedly arisen from variations both in the selection procedures used for initial acceptance of presensitized transplant candidates and in the degree of HLA compatibility of the transplant pair.[8] However, we contend that the extraordinarily poor success rate in sensitized recipients (Fig. 1)[22] is a reflection of second-

TABLE 4. *Allograft Survival in Relation to Time Interval Between Last WB(H) or RBC(H) Transfusion and Transplantation*

Last WB(H) or RBC(H) Transfusion	No. Patients	% Patients Sensitized	Allograft Survival (%) mos.				
			1	3	6	12	24
≤6 mo.	17	24.4	88.2	58.8	47.0	47.0	47.0
>6 mo.	24	25.0	87.5	83.3	70.8	53.1	48.1
		p =	N.S.	<0.001	<0.001	<0.20	N.S.

set rejection in many cases and is due to inadequate and insensitive donor crossmatch procedures. Indeed, recent revision of our crossmatch protocol to include the use of multiple, sensitive crossmatch methods in conjunction with the testing of all sera previously collected from each sensitized transplant candidate,[7] has greatly improved graft survival: 11 of 11 grafts continue to function six months following transplantation.[11]

Nevertheless, a point of greater significance, which unfortunately has received insufficient consideration in any previous report, is that induction of the sensitized state in a potential graft recipient will often delay or even preclude a successful search for a crossmatch negative organ donor (Table 1). Therefore, if one reflects back to the time of the original diagnosis of chronic renal failure and the identification of a potential transplant recipient, avoidance of HLA allosensitization greatly facilitates transplantation both by increasing the proportion of patients in the *entire* recipient waiting pool who receive transplants and by shortening the period of waiting on hemodialysis.

Notwithstanding previous transplantation or fetal–maternal sources of exposure to alloantigens, the leading mode of HLA immunization in hemodialysis patients is from the transfusion of blood. Between 52%[21] and 76%[2] of transplant candidates who have been transfused with multiple units of WB(H) and/or RBC(H) will become immunized. Thus transfusion-induced sensitization to HLA alloantigens is more the rule than the exception.

In recent years, a policy of avoiding HLA sensitization by avoiding the transfusion of blood has gained widespread support in dialysis facilities.[24] However, a perplexing finding,[23] which has rapidly gained international corroboration, is that patients who have never received transfusions are *not* the optimal recipient population. Indeed patients who have received blood transfusions prior to transplantation appear to accept a significantly higher proportion of kidney transplants successfully.[8,24–26] A similar trend in recipients of heart allografts has also been noted by the Stanford group.[3]

It was originally thought that these effects were not actually a result of the transfusions themselves, but rather due to a separation of patients into different categories because of predisposing factors associated with the type of kidney disease or due to other underlying influences. However, an extensive search by ourselves and by many of the investigators cited above has yet to reveal any common factor other than blood transfusion which can account for the marked improvement in graft survival.

The nature of the mechanism(s) of graft "protection" as conferred by the transfusion of blood therefore poses an intriguing scientific question. Interestingly, these observations are reminiscent of some of the earliest studies of "immunological enhancement" in which prior exposure of a recipient to a small amount of donor antigen (in nonviable form) promoted the later acceptance of incompatible tumor transplants.[16] Further investigation in animals has made it clear that multiple factors determine whether pretreatment of a potential recipient (with antigen preparations of donor origin) will result in either prolongation or curtailment of graft survival.[34]

One particular aspect of the clinical situation is difficult to reconcile with the results in animal studies.[15] This is the immunologic specificity of kidney graft protection in view of the extensive polymorphism of the HLA alloantigen system.[30] Moreover, even a few transfusions of blood, from volunteers unrelated to the eventual donor of the graft, appear to be sufficient to improve the chances of graft survival.[25] Recent studies in the mouse, however, suggest that a particular group of antigens, the immune-region associated (Ia) antigens which are determined within the H-2 histocompatibility complex, are of cardinal importance in enhancement.[5] A system which may be homologous to the murine Ia system, with similar serologic characteristics and tissue distribution, has been identified in man, but its diversity also appears to be extensive.[31,32] Nevertheless, it is of special importance that immunological enhancement, in combination with irradiation or other nonspecific immunosuppressive treatment, can act synergistically to greatly prolong the survival of skin,[15] heart[17] and renal[9] allografts. The immunologic specificity and other factors necessary for procuring successful enhancement have not yet been studied under the above conditions. However, we speculate that with the additional influence of immunosuppression, a modified, less stringent requirement for the humoral development of immunity to all relevant alloantigens that will be subsequently presented by the graft could apply.

A particularly urgent question which is now raised frequently is whether or not to practice intentional transfusion of potential transplant recipients who have no prior history of blood exposure.[6] The evidence of a beneficial effect of blood transfusions on the subsequent survival of renal grafts is approaching international unanimity and cannot be ignored. Similarly, the risks inherent in the administration of blood to transplant candidates, namely possible transmission of the hepatitis B agent and HLA alloimmunization, must also be considered.

In discussing this question, it is important to recall that in our series no significant difference in allograft survival was found between those patients who received WB(H)/RBC(H) ± RBC(H)DG or exclusively

TABLE 5. *Consequences of Blood Transfusion on Successful Renal Transplant to Patients on Chronic Hemodialysis*

Blood Preparation Transfused	Patients on Chronic Hemodialysis Waiting for Grafts from Nonliving Donors	Patients Sensitized (S) vs. Nonsensitized (N) as a Result of Blood Transfusion		Patients Receiving an Allograft within 8 Mos. of Admission to Program		No. of Recipients with Functioning Grafts One Year Following Transplantation		Total No. of Potential Graft Recipients Successfully Removed from Chronic Dialysis through Transplantation
		S	N	S	N	S	N	
WB(H)/RBC(H)	100	50	50	22	45	4	30	34
RBC(H)DG-A	100	5	95	2	86	1	56	57

The incidence of HLA sensitization from WB(H)/RBC(H) transfusion is a conservative estimate (see text) drawn from the report of Miller and coworkers.[21] The proportion of patients transplanted and the one year graft survival rates are derived from Table 1 and Figures 1–3. Most important to note is the increased number of waiting recipients who can be successfully rehabilitated by avoidance of HLA sensitization through the use of frozen blood deglycerolized by agglomeration [RBC(H)DG-A].[13]

RBC(H)DG prior to transplantation (Fig. 2). Although Opelz and Terasaki[23] did originally report a lower graft survival (20% at one year) in patients who had been transfused only with "frozen blood," this has not been confirmed in their subsequent studies (G. Opelz, personal communication) nor by others.[26]

The impact of various transfusion policies must be viewed in respect of their consequences on the *entire* subsequent course of patients from the point at which they are *first* identified as suffering from terminal renal failure. The perspective which emerges is illustrated in Table 5. The relative incidence of sensitization to histocompatibility antigens as a consequence of transfusing either WB(H)/RBC(H) or RBC(H)DG–A preparations and the further effect of these two alternatives on both the proportion of patients receiving transplants and their rates of success have been taken into account. At least 50% of patients receiving WB(H)/RBC(H) become sensitized,[21] whereas only five per cent of those receiving RBC(H)DG–A are immunized (Table 2).[14] This has the important result of greatly reducing the fraction of patients from among those who have received whole blood transfusions who will receive kidney transplants in a given period of time. Thus over an eight month period 90% of unsensitized versus only 44% of sensitized patients received transplants in our study (Table 1). The success rate of transplantation in nonsensitized patients was the same, however, after either type of transfusion treatment so that a considerably larger *proportion* of the entire candidate group received transplants successfully after frozen blood (57%) than after whole blood (34%) transfusion. Even if the survival of grafts in sensitized patients approached that in nonsensitized recipients (65%), only 43% of the total group of candidates transfused with whole blood would be successfully treated. It is interesting that if a similar diagram is constructed for patients who have not received blood transfusions, only some 27 of 100 recipients would be expected to accept transplants successfully in the same period of time when based on the combined experiences reported by Opelz and Terasaki.[24]

Therefore, a dependency on whole blood for transfusion can have the economic impact of increasing both the number of waiting patients on chronic dialysis and the duration of their dialysis treatment. In contrast, withholding blood transfusions can increase the percentage of unsuccessful operations in terms of functional grafts which result.

We believe that a policy of indiscriminate transfusion of whole blood or packed cells is not advisable nor warranted. The intrinsic dangers from blood transfusion need not be assumed, however. As illustrated by our extensive experiences,[14] and confirmed in this latest series, preparations of frozen blood deglycerolized by agglomeration are beneficial in furthering the goals of transplantation and are relatively free of the hazards inherent in conventional blood support. While saline-washed, "leukocyte-poor" blood cells may be an alternative to frozen blood for reducing the rate of patient sensitization,[21] prolonged use of this product apparently leads to a much higher sensitization incidence.[27] Moreover, evidence as to its value in graft "protection" is presently not available.

Lastly, the deglycerolization procedures used for preparing "frozen blood" for transfusion are varied.[13,20] The estimates of residual leukocytes and platelets in deglycerolized RBC(H)DG–A and RBC(H)DG–C are similar (10–20% and 1–2% of normal with each cellular component, respectively). These preparations should not at present be classified together as a single entity, nor should they be confused with "leukocyte-poor" washed RBC(H). Comparative studies of RBC(H)DG–A and RBC(H)DG–C indicate that the HLA–ABC locus antigens are still present on the leukocyte and membrane fragments of both types of products, but the leukocytes remaining in the latter product are viable and may explain the higher rate of patient sensitization with RBC(H)DG–C. However, contrary to our very small series, RBC(H)DG–C has apparently been of comparable benefit to allograft survival.[26]

In conclusion, while our data would not support a policy of extreme parsimony in dispensing blood to patients with terminal renal failure, a cautious policy of

intentional transfusion of at least a few units of RBC(H)DG–A can be supported by the information presently at hand. Our experiences using an intentional, but prudent, transfusion policy will be reported in the near future.

Acknowledgments

We would like to acknowledge the expert technical assistance of Christine Greenaway and Christine Drakopoulos, the perseverence of Helen Malone in typing the manuscript, Jack Darnell for illustrations and Henry J. Winn, Ph.D., for review and suggested revisions of the manuscript. We are indebted to the numerous Transfusion Services in other hospitals for their interest and cooperation in allowing us to confirm the transfusion histories of several patients.

References

1. Amos, D. B.: Cytotoxicity testing. *In* Manual of Tissue Typing Techniques. Ray, J. G. Jr., Hare, D. B., Pederson, P. D., Kayhoe, D. E. (eds.) DHEW Publication No. (NIH) 76-545. Washington, D. C., Government Printing Office, p. 25, 1976.
2. Caseley, J., Moses, V. K., Lichter, E. A., et al.: Isoimmunization of Hemodialysis Patients: Leukocyte-poor Versus Whole Blood Transfusion. Transplant. Proc., III:365, 1971.
3. Caves, P. K., Stinson, E. B., Griepp, R. B. et al.: Results of 54 Cardiac Transplants. Surgery, 74:307, 1973.
4. Cosimi, A. B., Wortis, H. H., Delmonico, F. L. et al.: Randomized Clinical Trial of Antithymocyte Globulin in Cadaver Renal Allograft Recipients: Importance of T Cell Monitoring. Surgery, 80:155, 1976.
5. Davies, D. A. L. and Staines, N. A.: A Cardinal Role for I-region Antigens (Ia) in Immunological Enhancement and the Clinical Implications. Biochemistry and Biology of Ia Antigens. Transplant. Rev., 30:18, 1976.
6. Editorial: Pretransplant Blood-Transfusion—Bad or good? Lancet, 2:959, 1975.
7. Ferguson, R. M., Yunis, E. J., Simmons, R. L. et al.: Does Host Presensitization Influence Renal Allograft Success? Transplant. Proc., IX:69, 1977.
8. Festenstein, H., Sachs, J. A., Paris, A. M. I. et al.: Influence of HLA Matching and Blood-Transfusion on Outcome of 502 London Transplant Group Renal-graft Recipients. Lancet, 1: 157, 1976.
9. French, M. E. and Batchelor, J. R.: Enhancement of Renal Allografts in Rats and Man. Interaction Between Humoral Antibodies and Cell-Mediated Immunity. Transplant. Rev., 13:115, 1972.
10. Fuller, T. C.: A simple inexpensive procedure for freezing, storage and recovery of viable human lymphocytes. *In* Manual of Tissue Typing Techniques. Ray, J. G. Jr., Hare, D. B., Pedersen, P. D., Kayhoe, D. E. (eds.) DHEW Publication No. (NIH) 76–545. Washington, D.C., Government Printing Office, 1976, pp 190–196.
11. Fuller, T. C., Cosimi, A. B. and Russell, P. S.: Use of an Antiglobulin-ATG Reagent for Detection of Low Levels of Alloantibody-improvement of Allograft Survival in Presensitized Recipients. Transplant. Proc., in press.
12. Hattler, B. G., Young, W. G., Amos, D. B. et al.: White Blood Cell Antibodies. Arch. Surg., 93:741, 1966.
13. Huggins, C. E.: Practical preservation of blood by freezing. Red Cell Freezing: A Technical Workshop Presented by Committee on Workshops of the American Association of Blood Banks. Washington D.C., American Association of Blood Banks, pp 31–54, 1973.
14. Huggins, C. E., Russell, P. S., Winn, H. J. et al.: Frozen Blood in Transplant Patients: Hepatitis and HL-A Isosensitization. Transplant. Proc., V:809, 1973.
15. Jeekel, J. J., McKenzie, I. F. C. and Winn, H. J.: Immunological Enhancement of Skin Grafts in the Mouse, J. Immunol., 108:1017, 1972.
16. Kaliss, N.: Regression or Survival of Tumor Homiografts in Mice Pretreated with Injection of Lyophilized Tissues. Cancer Res., 12:379, 1952.
17. Marquet, R. and Heystek, G.: The Induction and Abolition of Specific Immunosuppression of Heart Allografts in Rats by Use of Donor Blood and Cyclophosphamide. J. Immunol., 115:405, 1975.
18. Medawar, P. B.: Immunity to Homologous Grafted Skin. II. Relationship Between Antigens of Blood and Skin, Br. J. Exp. Pathol., 27:15, 1946.
19. Merrell, M. and Shulman, L. E.: Determination of Prognosis in Chronic Disease, illustrated by Systemic Lupus Erythematosis. J. Chronic. Dis., 1:12, 1958.
20. Meryman, H. T.: A high glycerol red cell freezing method. Red Cell Freezing: A Technical Workshop Presented by Committee on Workshops of the American Association of Blood Banks. Washington, D.C., American Association of Blood Banks, pp 73–86, 1973.
21. Miller, W. V., Schmidt, R., Luke, R. G. et al.: Effect of Cytotoxicity Antibodies in Potential Transplant Recipients of Leukocyte-poor Blood Transfusions, Lancet, 1:893, 1975.
22. Opelz, G., Mickey, M. R. and Terasaki, P. I.: HLA and Kidney Transplants: Reexamination. Transplantation, 17:371, 1974.
23. Opelz, G. and Terasaki, P. I.: Poor Kidney-transplant Survival in Recipients with Frozen-blood Transfusions or no Transfusions. Lancet, 2:696, 1974.
24. Opelz, G., and Terasaki, P. I.: Prolongation Effect of Blood Transfusions on Kidney Graft Survival. Transplantation, 22: 380, 1976.
25. Persijn, G. G., van Hooff, J. P., Kalff, M. W. et al.: The Effect of Blood Transfusions and HLA Matching on Renal Transplantation in the Netherlands. Transplant. Proc., IX: 503, 1977.
26. Polesky, H. F., McCullough, J. J., Yunis, E. J. et al.: Reevaluation of the Effects of Blood Transfusions on Renal Allograft Survival. Transfusion, 16:536, 1976.
27. Suarez-Ch, R. and Jonasson, O.: Isoimmunization of Potential Transplant Recipients: General Frequency and Some Associated Factors. Transplant. Proc., IV:577, 1972.
28. Staff, Transplantation and Immunology Branch, NIAID: NIH lymphocytotoxicity technique. *In* Manual of Tissue Typing Techniques. Ray, J. G. Jr., Hare, D. B., Pedersen, P. D., Kayhoe, D. E., (eds.) DHEW Publication No. (NIH) 76–545. Washington, D. C., Government Printing Office, 1976.
29. Standards for Human Blood and Blood Products, Code of Federal Regulations Chapter 1F, Part 640.
30. Thorsby, E.: The Human Major Histocompatibility Complex. Components of Immune Recognition: Detection and Analysis. Transplant. Rev., 18:51, 1974.
31. Ting, A., Mickey, M. R. and Terasaki, P. I.: B-lymphocyte Alloantigens in Caucasians, J. Exp. Med., 143:981, 1976.
32. van Rood, J. J., van Leeuwen, A., Termijtelen, A. et al.: B-cell Antibodies, Ia-like Determinants, and Their Relation to MLC Determinants in Man. Biochemistry and Biology of Ia Antigens. Transplant. Rev., 30:122, 1976.
33. WHO-IUIS Terminology Committee: Nomenclature for factors of the HLA system. Transplantation, 21:353, 1976.
34. Winn, H.: The mechanisms of immunological enhancement. *In* Progress in Immunology II, Volume 3. Brent, L., Holborow, J., (eds.) Amsterdam, North-Holland Publishing Company, 1974, pp 207–216.