Serologic Factors in Human Transplantation

FELIX T. RAPAPORT,* JEAN DAUSSET, JEAN HAMBURGER, DAVID M. HUME, KYOICHI KANO, G. MELVILLE WILLIAMS, FELIX MILGROM

From the Departments of Surgery, New York University Medical Center, and The Medical College of Virginia; the Division of Immuno-Hematology, Institut de Recherches sur les Maladies du Sang; the Clinique Néphrologique, Hôpital Necker, and the Centre de Recherches de l'Institut National de la Sante et de la Recherche Médicale et de l'Association Claude Bernard; University of Paris, France; and the Department of Bacteriology and Immunology, State University of New York at Buffalo

THE DISCOVERY of leucocyte groups,[9] and the observation that blood leucocytes are active as transplantation antigens in man,[21, 39, 40, 42, 43, 46] have raised the possibility that leucocyte group determinants might be a factor in conditioning human histocompatibility responses. The role of leucocyte group antigens in skin transplantation was conclusively demonstrated in 1965,[14, 15] by the use of leucocyte group-incompatible skin allografts applied to recipients previously immunized against the same major leucocyte group antigen(s). By this technic, Antigens 1(Mac), 3(4a), and 7(4b) regularly induced accelerated or white graft rejection of skin allografts incompatible for such groups in pretreated subjects negative for those groups. Antigens 7c and 7d of van Rood [58] have also been shown to be active in this regard.

These observations, and the concept that most leucocyte group antigens defined by currently available typing sera may be components of a complex immunogenetic system termed the Hu-1 system,[13] considered a human equivalent of the mouse H-2 system, have raised the possibility that leucocyte group antigens may also condition the survival of human organ transplants. Dausset and Colombani in 1960, using a battery of leucoagglutinating antisera of as yet unknown specificity,[11] noted that initial transplant function was better in recipients found to be compatible by this technic. More recently, the retrospective studies of Terasaki, Porter, Starzl and associates [36, 54, 56, 57] have provided additional evidence of a relationship between leucocyte group antigens and the fate of human renal transplants. There was a particularly significant correlation between the number of leucocyte group incompatibilities found between donors and recipients and the histologic status of kidney transplants in long-term survivors.[35]

The first portion of this report is concerned with a retrospective correlation between leucocyte group antigens recognized by the Hu-1 battery of antisera and the fate of 59 renal transplants obtained from related individuals. Serologic ranks of compatibility will be correlated with the clinical outcome of such transplants, with particular reference to the long-term survival

Presented at the Annual Meeting of the American Surgical Association, May 11–13, 1967, Colorado Springs, Colorado.

Supported by a grant from The John A. Hartford Foundation, Inc.; supported in part by Grants GM 12748-01, AI 96754, CA-5573, AT 40-1 (2459), ACS-T 166B, HE 0823, and Contracts PH 43-65-638 and PH 43-65-986, National Institutes of Health, Bethesda, Maryland.

* Career Scientist of the Health Research Council of the City of New York, Contract I-349.

of renal transplants in these subjects. These results are discussed with reference to the possible applicability of serologic technics to the prospective selection of optimally compatible donor-recipient combinations for organ transplantation. The second portion of this report is concerned with the characterization of heterophile antibody responses associated with human allograft rejection.[49, 50] Antibody responses directed against sheep, guinea pig, and rat erythrocytes have been detected in 49 recipients of transplantation antigens (leucocytes, leucocyte extracts) and skin allografts, and in 22 recipients of kidney transplants. The results will be compared to similar antibody determinations in 86 normal individuals, and the specificity and immunoglobulin character of such antibodies will be described. The applicability of these antibody responses to the clinical monitoring of organ transplants in man will be described and discussed.

Methods and Technics

1. Source of Subjects and of Blood and Serum Specimens. Hu-1 leucocyte group compatibility was correlated with the clinical outcome of 59 renal transplantations performed at the Medical College of Virginia, Richmond (D. M. H.) and at the Hôpital Necker, University of Paris (J. H.). There were three dizygotic twin transplants, 25 maternal donor kidney transplants, 10 paternal donor kidney transplants, and 20 sibling donor grafts in this group. One individual received a kidney transplant obtained from a first cousin. All donors and recipients underwent complete leucocyte group determinations, and the results were recorded in blind fashion without knowledge of the clinical status of the transplant at the time of testing. Methods of collection of blood specimens have been described in detail previously.[12, 19]

The serum samples tested for heterophile antibodies were obtained from subjects sensitized with transplantation antigens and skin allografts, and from recipients of kidney allografts. The recipients of transplantation antigens and skin allografts were 49 normal volunteers who were part of a study of the *in vivo* effects of erythrocytes, blood leucocytes and their fractions as transplantation antigens in man.[48] Two weeks after intradermal sensitization with such antigens, the recipients were challenged with skin allografts obtained from the same donors. The technics of grafting and of graft observation, as well as criteria for the diagnosis of graft destruction have been described previously.[7, 36-38, 41, 44, 45, 47] Serum samples were obtained from each subject before the beginning of the study, at the time of pretreatment with antigens, and at weekly intervals thereafter, until 4 weeks after graft rejection. Baseline sera and an average of 10 postoperative serum samples were also obtained during a period of observation of approximately 1 to 48 months from 22 kidney transplant recipients at the Buffalo General Hospital (Drs. S. and R. Anthone), the Peter Bent Brigham Hospital, Boston (Drs. J. P. Merrill and R. J. Glassock), the Medical College of Virginia (Drs. D. Hume and G. M. Williams, and H. M. Lee), and the Denver Veterans' Administration Hospital (Dr. T. E. Starzl). Serum samples obtained from 86 normal volunteer blood donors served as controls. All sera were stored in sealed vials and kept at −22° C before use; they were inactivated at 52° C for 30 minutes before the standard hemagglutination tests described below.

2. Serologic Technics. Three different technics were used for the assessment of leucocyte group compatibility between donors and recipients of kidney allografts. These were: 1) Leucoagglutination, by the method of Dausset[11]; 2) Lymphocytotoxicity, by the method of Gorer and Gorman,[22] modified by Englefriet[19]; 3) Platelet complement fixation, by the method of Shulman.[52] The antisera used were obtained from multiparous women and poly-

transfused patients, and constituted the battery of reagents used to identify the major leucocyte group mosaics of the Hu-1 system [13]; an antiserum containing antibodies capable of recognizing the 5b leucocyte group described by van Rood's group [30] was also used.

For the detection of heterophile hemagglutinins, serum specimens were serially diluted in 0.1 ml. volumes; 0.1 ml. of a 1% erythrocyte suspension in phosphate buffered saline was added to each serum dilution. The mixtures were incubated at room temperature for 2 hours, and were centrifuged at 1,000 rpm for 2 minutes. Agglutination was assessed after gentle shaking of the tubes.

Erythrocyte suspensions were obtained from male Hartley guinea pigs and Wistar rats in this laboratory; sheep, ox and rhesus monkey erythrocytes were purchased from the Animal Blood Bank, Syracuse, New York. Human erythrocytes were obtained from normal volunteers of blood groups A and B. Red blood cells were washed at least three times in phosphate buffered saline before each test.

Serum samples showing high titers of heterophile hemagglutinins were used in absorption tests; for this purpose, the sera were diluted to 1:10, and 2 ml. aliquots of each serum were incubated with equal volumes of washed and packed sheep, guinea pig, rat, ox, and rhesus monkey erythrocytes, as well as A and/or B human erythrocytes. The mixtures were shaken for 30 minutes at 37°, and were incubated at room temperature for one hour. They were then centrifuged at 3,000 rpm for 10 minutes, and the supernatant was pipetted and reabsorbed again by the same technic. The final supernatant was then tested for its remnant heterophile hemagglutinating activity.

The immunoglobulin character of the heterophile hemagglutinins was assessed by immunoelectrophoresis and by study of the effects of 2-Mercaptoethanol upon the activity of high-titered antisera. Rabbits were immunized with rat erythrocytes agglutinated by a pool of 4 human sera containing high titers of heterophile hemagglutinins. The resulting rabbit antisera were studied by immunoelectrophoresis against whole human serum and against Fraction II of pooled normal human serum in a concentration of 40 mg./ml.[28] Selected serum samples diluted 1:5 in phosphate buffered saline were also mixed with equal volumes of 0.2 M 2-Mercapto ethanol; the mixtures were incubated at 37° C for 1 hour, and the heterophile hemagglutinating activity of the resulting preparation was tested immediately thereafter.[23]

3. Criteria for the Correlation of Serological Compatibility and Clinical Outcome of Renal Transplantation. Recipients were placed in four major categories on the basis of leucocyte group compatibilities with the donors; these included: *Group A* —no detectable incompatibilities, even in isolated sera of unknown specificities; *Group B*—incompatibilities detectable only in occasional sera, without evidence of group incompatibility; *Groups C and D*—one of more defined leucocyte group incompatibilities, *D* being worse than *C*.

The clinical outcome of renal transplantation in this group of patients was classified in accordance with two different sets of criteria:

A) *Clinical Ranks,* based upon renal transplant function in individuals surviving a minimum of 6 months. A renal allograft was considered successful if the creatinine clearance continued to exceed 50 cc./min., the blood urea nitrogen was less than 30 mg/100 ml., and the serum creatinine was less than 2 mg/100 ml. If any of these criteria were not met, or if the patient died in spite of normal renal function, the transplant was considered a failure. By means of these criteria, the patients were separated into five major ranks, from "A" (excellent renal function) through "D" (unsatisfactory function or a failing kidney),

TABLE 1. *Correlation of Leucocyte Group Compatibility with the Clinical Status of Renal Transplants After 12 Months*

	Leucocyte Group Compatibility (Number of Subjects)							
	Incompatibles				Compatibles			
Clinical Rank	Richmond	Paris	Total	%	Richmond	Paris	Total	%
Rejected	4	3	7		1	2	3	
D	1	0	1	−55.6%	0	0	0	−15.7%
C	0	2	2		1	1	2	
B	4	1	5	−44.4%	6	1	7	−84.3%
A	3	0	3		9	11	20	
Total Subjects:			18				32	

and "R" for a completely rejected transplant.

B) *Types of rejection crises;* a rejection crisis was defined as any elevation of blood urea nitrogen and/or serum creatinine, or depression of creatinine clearance that could not be explained on the basis of acute tubular necrosis, urinary obstruction, infection, vascular occlusion, or increased nitrogen load. Four degrees of severity were recognized: A: patients with no loss of function or rejection episodes; B: subjects who had a single acute rejection episode lasting less than 30 days and not requiring hemodialysis; C: more than one acute rejection episode during the first 4 postoperative months; D: patients who suffered a rejection episode exceeding 30 days or severe enough to require hemodialysis, or one occurring during the first week, or after the first 4 months following transplantation.

Observations

Leucocyte Group Compatibility and Renal Transplantation. For the purposes of this study, donor-recipient combinations falling into histocompatibility classes A and B were termed "compatible," while those in classes C and D were considered "incompatible." Table 1 summarizes a correlation between clinical status and leucocyte group compatibiltiy in 50 recipients evaluated 1 year after operation. At this time, 32 compatible and 18 incompatible subjects were available for study. Unfavorable outcomes (Categories C, D, and R) occurred in 55.6% incompatible subjects, but in only 15.7% of compatible recipients.

Differences in transplant acceptance, as shown by rejection patterns became even greater as time went on, as shown in the group of 37 recipients considered 28 months after transplantation. It may be seen in Table 2 that 69.3% of subjects with

TABLE 2. *Correlation of Leucocyte Group Compatibility with the Long-Term Acceptance of Renal Transplants—Status at 28 Months*

	Leucocyte Group Compatibility (Number of Subjects)			
	Incompatibles		Compatibles	
Renal Status	Number	%	Number	%
Rejected or in late rejection process	9	69.3%	2	8.3%
Transplant Continuing to survive	4	30.7%	22	91.7%
Total Subjects	13		24	

TABLE 3. *Correlation of Leucocyte Group Compatibility with Types of Renal Transplant Rejection Crises—Richmond Series*

Types of Rejection Crises	Leucocyte Group Compatibility (Number of Subjects)			
	Incompatibles		Compatibles	
	Number	%	Number	%
C–D	9	75%	8	30%
A–B	3	25%	15	70%
Total Subjects:	12		23	

transplants obtained from incompatible donors had rejected their grafts or were in the process of rejecting them at this time; this was true for only 8.3% of the compatible subjects. It is also noted that 30.7% of kidneys obtained from incompatible donors retained satisfactory functions at 28 months, as compared to 91.7% of kidneys from compatible donors.

As noted in Table 3, there was also a positive correlation between leucocyte group compatibility and the types of rejection crises observed. Nine of 12 incompatible recipients (75%) in the Richmond series had severe rejection crises, as compared to 8 of 23 compatible subjects (30%). When sibling transplants were considered separately, an even closer correlation was noted between compatibility and the severity of rejection crises. As illustrated in Table 4, *all* incompatible recipients of sibling transplants in this series fell into the more severe rejection types, while all but one of the compatible individuals were in the group of mild rejection crises.

TABLE 4. *Correlation of Leucocyte Group Compatibility with Types of Renal Transplant Rejection Crises—Sibling Transplants Only (Richmond Series)*

Types of Rejection Crises	Leucocyte Group Compatibility (Number of Subjects)	
	Incompatibles	Compatibles
C – D	5	1
A – B	0	8
Total Subjects:	5	9

The overall results in 59 kidney transplants performed in Richmond and Paris are summarized in Figure 1. At the end of 3 years, 7 of 21 incompatible grafts (33%), but only 3 compatible grafts (8%) had been rejected. Four other incompatible recipients had clinical ranks of C or D at this time, as compared to two clinical ranks of C in the entire series of 38 compatible grafts. Although a comparison of leucocyte group incompatibilities found in rejected and surviving kidney transplants did not indicate any significant differences in the incompatibilities encountered in these two groups, the results strongly suggest that the opportunities for long-term kidney transplant survival are generally greater in compatible recipients.

In three cases of kidney allograft rejection, no detectable evidence of leucocyte group incompatibility could be obtained. This problem will be discussed in greater detail below.

Heterophile Antibody Responses in Allograft Recipients. Average heterohemagglutinin titers of 1:5 against sheep and guinea pig erythrocytes and 1:40 against rat red blood cells were found in 49 recipients of human transplantation antigens and skin allografts before sensitization. These hemagglutinin titers rose in 33 individuals after application of skin allografts.

Further investigations were performed in subjects with at least an 8-fold increase in heterophile antibody titer during the

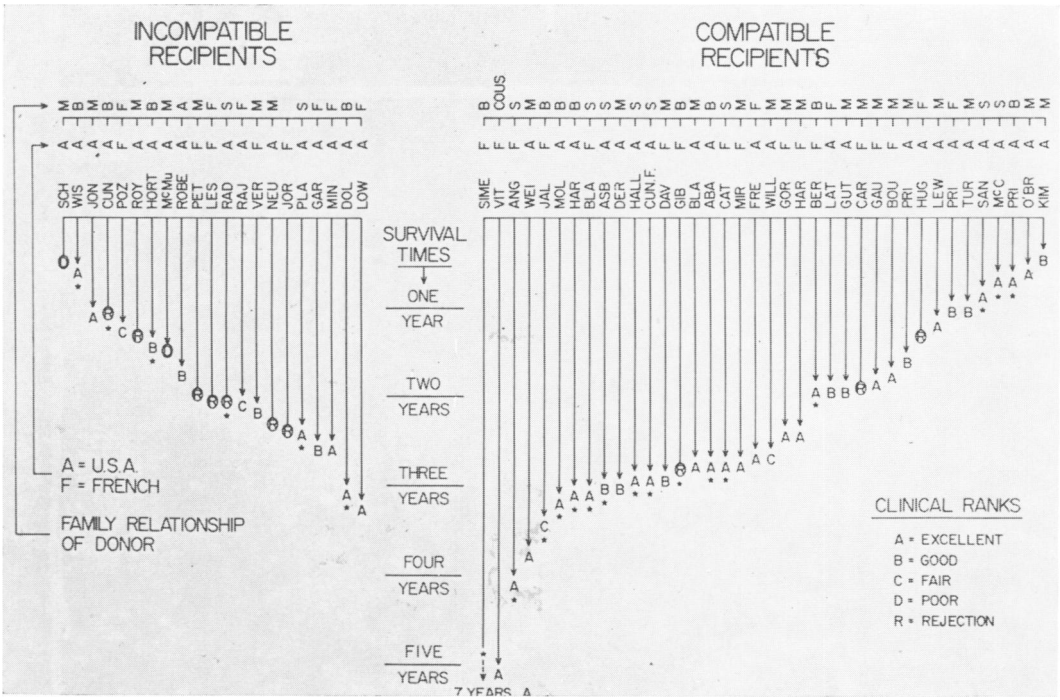

FIG. 1. Follow-up status of 59 cases of renal allotransplants. Correlation with leukocyte group compatibility.

course of this study. In 24 such individuals, hemagglutinin occasionally reached titers of 1:640 against sheep erythrocytes, 1:1280 against guinea pig red blood cells, and 1:5120 against rat erythrocytes. Peak heterophile hemagglutinin titers usually appeared one week after skin grafting, generally in association with allograft rejection. The intensity of the antibody response appeared to be proportional to the intensity of the antigenic stimulus applied to each individual. As noted in Table 5, there was no relationship between the presence or absence of ABO incompatibility between donor and recipient and the development of such heterophile antibody responses. The appearance of such hemagglutinins was also not associated with any rise in anti-A or anti-B isoantibody titers in ABO incompatible recipients.

There were increases in heterophile hemagglutinin titers in 20 of 22 kidney transplant recipients. All individuals in this group were under immunosuppressive therapy with azathioprine [24, 51] and prednisone,[53] and the majority suffered at least one rejection crisis during the period of study. The most impressive rises in titer in this group were observed against rat erythrocytes. In 11 instances, there were 8-fold or greater rises in anti-rat hemagglutinin titers, in two instances as high as 1:1280. It is of particular interest that such rises in antibody titer appeared to bear a relation to the clinical status of the patients, in that peak titers were frequently associated with impending rejection crises, or were seen after kidney rejection and nephrectomy.

Figure 2 compares the titers of naturally occurring and experimentally induced heterophile hemagglutinins in the subjects studied. It is noted that the majority of normal individuals had hemagglutinating titers of 1:20 or below for sheep and guinea pig erythrocytes, and titers of 1:40

TABLE 5. *Peak Heterophile Antibody Titers and ABO Erythrocyte Groups in Recipients of Skin Allografts*

Subject	ABO Group of:		Peak Heterophile Antibody Titers Noted		
	Recipient	Donor	Sheep	Guinea Pig	Rat
CHE	0+	0+	40	160	640
WEIN	0+	0+	10	10	640
WEIO	0+	0+	40	40	320
WEIS	0+	0+	640	1280	2560
LAM	0+	0+	80	1280	5120
DeS	0+	0+	20	40	320
KOL	0+	0+	320	160	160
FRA	0+	0+	80	160	1280
HOP	0−	0+	40	80	320
MAI	A+	0+	80	320	80
GUN	A+	0+	40	80	320
BOR	A+	0+	160	320	160
MAR	A−	0+	40	160	640
BLO	B−	0+	40	1280	2560
IBR	AB+	0+	40	160	640
LEF	A+	A−	80	40	640
BER	A+	A−	40	1280	5120
BERG	A+	A−	40	160	320
COH	0+	A+	40	80	160
BLA	0+	A−	40	160	640
COHE	0+	A−	40	320	640
GER	0+	A−	40	640	640
BRO	0+	A−	40	640	320
PFE	B+	A+	40	160	40

or less against rat cells. In contrast, 20 of 24 recipients of transplantation antigens and skin grafts had anti-sheep hemagglutinin titers exceeding 1:20, with three individuals exhibiting peak titers of 1:640 in association with skin allograft rejection. In the kidney allograft recipient group, only 4 individuals had anti-sheep hemagglutinins exceeding a titer of 1:20.

When post-transplant heterophile antisera were tested with guinea pig erythrocytes, 23 of 24 recipients of transplant antigens and skin grafts had hemagglutinin titers exceeding 1:20, and 4 individuals had titers as high as 1:1280. In contrast, only one kidney transplant recipient had an anti-guinea pig hemagglutinin titer exceeding 1:20.

When rat erythrocytes were used in the hemagglutination test, 23 of 24 transplant antigen and skin graft recipients exhibited anti-rat hemagglutinin titers exceeding 1:40; in 13 individuals, titers of 1:640 or more were observed. The rat hemagglutination system also appeared to be a more sensitive monitor of kidney allograft, in that 16 of 22 subjects in this group had peak anti-rat hemagglutinins exceeding 1:40, with some titers rising as high as 1:1280.

In order to assess the specificity of the heterophile responses observed after transplantation, high-titer antisera were absorbed with human A and B erythrocytes and with erythrocytes obtained from sheep, guinea pig, rat, ox, and rhesus monkeys. Extensive absorption leading to the disappearance of anti-A and/or anti-B isoantibodies in such sera did not affect their titer of sheep, guinea pig, or rat hemagglutinins. The species-specific erythrocytes regularly removed hemagglutinating activity against cells of that species. A certain degree of cross-reactivity was noted, however, between sheep, guinea pig, rat, ox, and rhesus monkey red blood cells, in that cells from each species were capable of absorbing some of the hemagglutinins directed against

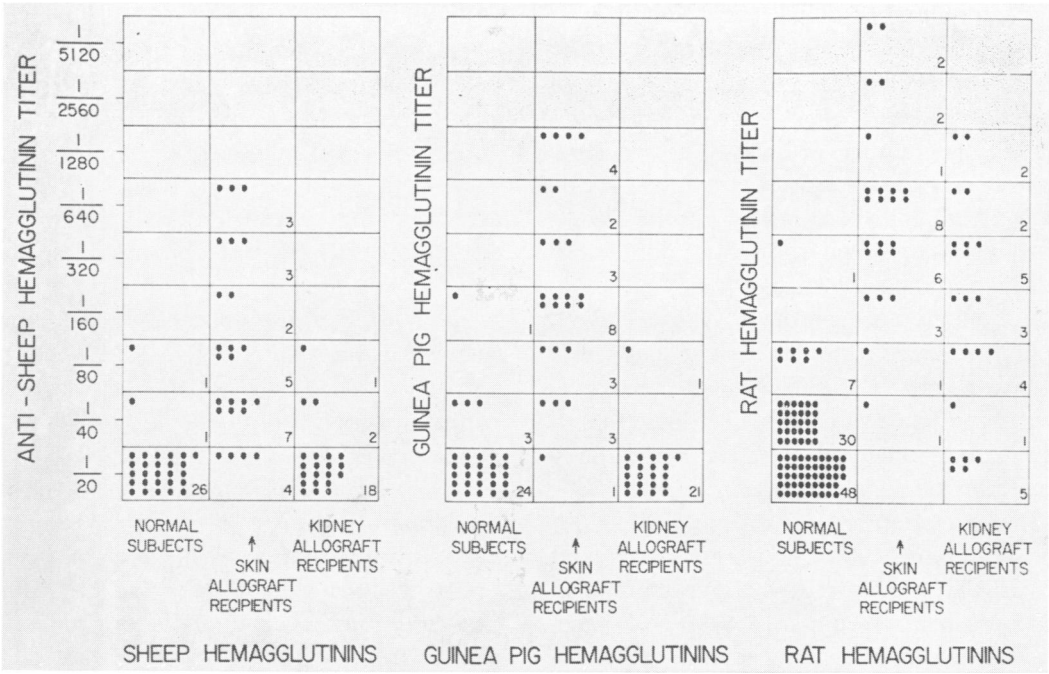

FIG. 2. Comparison of heterophile hemagglutinins in normal and in transplant subjects.

other species. Rat and ox erythrocytes were the most effective antigens in this regard.

Immunization of rabbits with rat erythrocytes agglutinated by a pool of 4 human post-transplant sera containing high titers of heterophile hemagglutinins resulted in rabbit antisera which, on immunoelectrophoresis, formed two lines of precipitation with whole human serum and Fraction II of pooled normal human serum. The position of these lines of precipitation was consistent with the IgG and IgM nature of the human serum components recognized by rabbits immunized with agglutinated rat erythrocytes.

Treatment with 2-Mercaptoethanol abolished the heterophile hemagglutinating activity of 17 of 24 high-titered sera tested; the seven remaining sera were not affected by treatment with 2-Mercaptoethanol.

Discussion

Correlation of the Fate of Renal Allotransplants with Leucocyte Group Compatibility. Under the conditions of this study, a clear relationship existed between leucocyte group compatibility and the response of human recipients to kidney allografts. Despite experimental shortcomings and clinical variables inherent in the pooling of patients from different sources, the results obtained in the Richmond and Paris series were closely similar, and are in close agreement with those reported in the Denver series.[54] The results of this study indicate a particular correlation between leucocyte group compatibility and the long-term survival and function of renal transplants. This finding confirms the suggestion of Porter and associates,[35] that the degree of leucocyte group compatibility existing between donor and recipient may be a factor in determining the rate of progression of chronic rejection changes responsible for the failure of long-term renal transplants.

Although these results are highly suggestive, a definitive evaluation of the role of leucocyte group compatibility in organ transplantation awaits the accumulation of

a greater number of patients studied on a prospective basis, and the availability of leucocyte typing sera of a more monospecific nature. It must be recalled that a significant number of long-term survivors showed satisfactory renal function in the face of definite leucocyte group incompatibilities with the transplant donors. In addition, some subjects rejected renal transplants in the absence of any serologic evidence of leucocyte group incompatibility, indicating that the battery of antisera currently in use was incapable of detecting all of the antigenic specificities which may condition transplant rejection in man.

Interpretation of results obtained with this battery of testing sera is also weakened by the fact that such sera were obtained in response to antigenic stimuli (blood transfusions, multiparity, leucocytes, skin allografts) which may have differed qualitatively and quantitatively from the situation encountered in renal allografting. In this regard, the addition of sera obtained from transplant recipients after kidney rejection and nephrectomy[1, 32] may constitute a new and particularly useful source of reagents for typing purposes.

The multispecific nature of many of the typing sera employed constitutes another variable which may have caused some errors in the interpretation of leucocyte group phenotypes of transplant donors and recipients. The survival of kidney transplants in spite of detectable leucocyte group incompatibilities between donor and recipient may also be a function of differences in the ability of each individual to respond to this type of antigenic stimulation. Indeed, broad variations have been noted in the response of Rh negative recipients to immunization with antigen D,[33] and in the incidence of leucocyte antibodies in multiparous women and polytransfused subjects.[25] The regimen of immunosuppressive therapy employed in renal allograft recipients may also have had an influence upon such variables in host responsiveness.[53]

In spite of these shortcomings, however, a statistically significant correlation has been shown to exist between leucocyte group compatibility and the duration and quality of renal allograft survival in man. The results justify the inclusion of leucocyte grouping technics in the preoperative evaluation of transplant donors and recipients. This policy may permit further improvements in the current results of clinical organ transplantation.[4] Avoidance of antigenic differences between donor and recipient which are amenable to detection by currently available serologic methods may also lower the requirements for effective immunosuppressive drug therapy in organ transplantation. Extension of histocompatibility testing methods to the selection of optimally compatible organ transplants from cadaver sources may also improve the results of this type of transplantation, and raise them to levels comparable to those currently reported in related donor transplants.[4]

Heterophile Antibody Responses in Allograft Recipients. Sensitization of recipients with transplantation antigens (leucocytes, skin or kidney allografts), has resulted in the development of rising titers of serum antibodies detectable with sheep, guinea pig, and/or rat erythrocytes. Such antibodies have been identified as IgG and IgM by immunoelectrophoresis; treatment with 2-Mercaptoethanol has confirmed this observation, although, only 19S antibodies were detectable by this technic in 17 of 24 subjects tested.

The development of this heterophile antibody response was not related to ABO-incompatibility between donor and recipient[17, 18] and absorption of active sera with human A or B erythrocytes failed to remove their activity. Cross-absorption experiments indicate that such heterophile antibody responses are primarily directed against antigen(s) present on rat erythrocytes, and shared to varying degrees by the other species tested. The ability of the

heterophile antibodies to agglutinate erythrocytes of Forssman-negative species,[5] and the capacity of such erythrocytes to absorb post-transplantation anti-sheep hemagglutinins exclude the possibility that such antibodies are in the Forssman category. Their strong activity against red blood cells other than those obtained from sheep and ox also suggest that they differ from Paul-Bunnell-like antibodies.[3, 20, 34, 55] These observations are in agreement with Iwasaki, Talmage, and Starzl,[25] who have reported the presence of IgG antibodies distinct from Forssman antibodies in renal allograft recipients by the indirect antiglobulin consumption test, utilizing sheep erythrocyte stromata as the antigen.

Skin allograft recipients generally developed higher heterophile antibody responses than the renal transplant patients. It is possible that such differences may have been a function of the different routes of transplantation antigen release and rates of host stimulation encountered in these two categories of subjects. Both factors are known to condition the host responses to tissue transplants.[29] Such differences may also be related to the uremic status of kidney transplant recipients [8] and to the use of immunosuppressive agents in these individuals.[24, 53]

The mechanisms responsible for the appearance of heterophile immunoglobulins in the course of tissue transplantation are not clear at present. The frequent association of peak antibody titers with skin of kidney allograft rejection responses suggests, however, that such antibodies might constitute a response to antigens which are released, altered, or exposed because of the resulting tissue damage. This type of antigen may resemble antigens normally present on the surface of heterologous cells, and has been implicated in the triggering of the autoimmune type of disease.[31] Reports of similar heterophile antibodies in response to thermal injury in the guinea pig, rabbit and man provide additional support for this hypothesis.[26]

The appearance of a heterophile antibody response against sheep, guinea pig, and rat erythrocytes in the course of allografting bears further witness to the ubiquitous nature of antigenic determinants conditioning mammalian host responses to tissue transplantation. It may also be of practical pertinence to problems reported in regularly demonstrating serum antibody responses in transplant recipients.[1, 27, 32] Indeed, the association of peak antibody responses with allograft rejection suggests that serial serum heterophile antibody determinations (particularly anti-rat hemagglutinins) may provide a simple early warning system for the prompt recognition and management of transplant rejection crises.

Preliminary observations that such heterophile antibodies may reflect a response to tissue and/or organ specific [2, 6] isoantigens which may be distributed in group fashion in man also suggest that this type of immune response may provide a useful approach to the development of additional methods for human histocompatibility testing.

Summary

Retrospective study of 59 recipients of renal transplants obtained from related donors has shown a significant correlation between major leucocyte group incompatibilies and the duration and quality of kidney transplant survival in man.

Sensitization of human recipients with transplantation antigens (leucocytes, skin or kidney allografts) has resulted in the development of a heterophile antibody response detectable with sheep, guinea pig and rat erythrocytes. Such antibodies have been identified as IgG and IgM antibodies, and are not of the Forssman or Paul-Bunnell-type. Their appearance is closely associated with the events of allograft destruction in man.

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Discussion

Dr. Joseph E. Murray (Boston): Dr. Creech, Members and Guests: This excellent, timely and incisive presentation covers one of the three major avenues of the current study of transplantation biology, namely, tissue typing and matching. The other two major areas of study, improved methods of immune suppression and better organ procurement and preservation, are overlapping and complementary, so that the results presented by Dr. Rapaport and his workers are better evaluated not only in their own context but in relationship to the other two.

Dr. Rapaport's results using a lymphoagglutination technique are similar to those of others using lymphocytotoxic assay, and they clearly indicate that if the donor and the recipient are a good match, the chances of a successful transplant are very high—about 90%. If the donor and the recipient are mismatched, the chances of a successful transplant are only about 50%. Therefore, if these tests were universally used prospectively, we would eliminate about a third or a half of our good results.

This is in no way negating the value of lymphocyte typing, and if a choice of donors exists, obviously the better matched one would be selected.

Unfortunately, usually only one donor is appropriate, even from large families, because the rest are eliminated for medical, social, economic, or psychological reasons. The decision often be-