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THIRTY-TWO RECIPIENTS

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VII. SELECTION OF KIDNEY DONORS FOR THIRTY-TWO RECIPIENTS*

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Preliminary retrospective studies of tissue typing in man were based upon comparison of lymphocyte antigens of chronic survivors with their donors after renal homotransplantation.[1-3] In the last report[3] a statistically significant association was demonstrated between the excellence of the late clinical outcome and the donor-recipient compatibilities in the leukocyte groups tested. These initial efforts to establish the relationship between the antigens under analysis and human histocompatibility factors were not altogether satisfactory, however, since they involved solely retrospective observations on patients long after operation. These studies of surviving recipients and their donors excluded the early failures from consideration. Furthermore, although a correlation existed in the chronic survivors between the excellence of antigenic match and the benignancy of their course, several patients with mediocre matches had achieved good long-term results. Conversely, some patients with apparently good matches had developed late problems.[2]

Nevertheless, the results were sufficiently encouraging to warrant a trial of prospective matching. This has been carried out in 32 patients treated from October 12, 1964 to October 12, 1965. In each instance, the donors were selected in Los Angeles on the basis of the best available match, either from a related or nonrelated population. Transplantation was subsequently carried out either at the Colorado General Hospital or the Denver Veterans Administration Hospital. The collaboration provided certain advantages for evaluation of the results. First, the surgical and medical practices in the Denver institutions

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were relatively well standardized. In addition, the results obtained with 64 previous cases in which the donor and recipient were randomly selected[4] were available for comparison. Finally, all available pathologic material in the original unselected series had been examined by K. A. Porter, making possible a histopathologic correlation between the failures in the original nonselected group and those of the present studies.

METHODS

Subjects

Thirty-two consecutive cases are included. An additional patient who ultimately received a nonselected cadaveric kidney because of initial technical failures is excluded. The donor-recipient ABO groups were all compatible by previously defined criteria.[4]

Eighteen of the recipients received their homografts from blood relatives (TABLE 1); ten from parents, seven from siblings, and one from an uncle. In ten cases, only one donor was available. In the other eight, the choice was made between two or more donors.

The other 14 recipients had their homografts provided by unrelated volunteer donors (TABLE 2). These donors were members of a pool which was comprised of 108 members at its maximum.** The largest number of available volunteers in each ABO blood group was 51 type O, 46 type A, 7 type B, and 4 type AB. In practice, since the pool varied in composition, selection was generally made from about half of the above total.

Therapy

Whenever possible, azathioprine was administered starting several days in advance of homotransplantation and continued indefinitely after operation. Prednisone was initiated on the day of operation in doses of 30–200 mg; in the event of rejection, the dose was increased. Actinomycin C and local homograft irradiation were employed only at the time of diagnosed rejection. All patients had splenectomy and all but one had bilateral nephrectomy at the time of transplantation.

Thymectomy was carried out prior to transplantation on randomly selected patients in 17 of the 32 cases. In past experience, thymectomy has not had a demonstrable effect on the early course after human transplantation[2,4]; furthermore, in the time interval of the present series, thymectomy has not appeared to influence survival. Consequently, all results in the present series are pooled without further consideration of thymectomy.

**Penal volunteers.

TABLE 1
DATA ON PATIENTS WHO RECEIVED HOMOGRAFTS FROM BLOOD RELATIVES

LD #	Age–Sex	Date of Transplant	Blood Groups		# Sera Tested	Mismatch		Donor Relation
			R	D		% Sera	Groups	
65	35 – F	10-12-64	O+	O+	89	1.1	0	Sister
66	29 – M	10-26-64	O+	O+	91	1.1	0	Mother
68	24 – F	12- 2-64	O+	O+	113	1.8	0	Sister
73	27 – M	2- 1-65	A+	A+	120	10.0	2	Sister
75	18 – M	2-19-65	A+	A+	106	9.4	1	Father
76	27 – M	3-12-65	A-	A-	99	14.1	3-6†, 5 2	Brother
79	16 – M	3-23-65	A+	A+	128	10.9	1, x‡	Mother
81	19 – M	3-30-65	O+	O+	123	11.4	2, 1, x	Father
83	21 – F	4- 9-65	A+	A+	111	2.7	0	Brother
84	20 – F	4-12-65	A+	O+	109	15.6	2	Sister
85	18 – M	4-23-65	O+	O+	124	9.7	x	Sister
89	23 – M	6-15-65	O+	O+	129	0.8	0	Father
90	18 – F	7-23-65	A+	O+	113	11.5	3, 1 x	Mother
93	8 – F	8- 6-65	A_2B+	A_1B-	112	2.7	0	Mother
94	26 – F	8-24-65	A-	A+	94	13.8	2, x	Father
95	28 – M	8-30-65	O+	O+	107	21.5	1, 2, x	Mother
96	25 – M	9- 7-65	O+	O-	107	15.0	5, x	Father
97	17 – M	10-12-65	O+	O+	94	11.7	6, 5, x	Uncle

* The donors were selected on the basis of the best possible antigenic match within the family. The great variation in quality of match was necessitated by the limited number of donors in individual cases; frequently only one medically suitable donor was available.

† 3-6 classification: results from a mismatch in a group of antisera which are associated with both group 3 and group 6 sera.

‡ x = 3 or more mismatches in the group of unclassified antisera.

TABLE 1, Cont.

Thymectomy	Date of Death	Survival § (Days)	Current BUN	Ccr	Current Treatment: Imuran	Prednisone
9-24-64	-	492	17	79	137.5	7.5
10- 1-64	12-15-64	50	-	-	-	-
11-25-64	-	441	14	63	112.5	15-10
-	-	380	52	42	100	20-15
-	-	362	31	76	75	20-15
2-20-65	1-20-66	314	-	-	-	-
-	12- 4-65	254	-	-	-	-
-	5- 8-65	39	-	-	-	-
-	12- 8-65	242	-	-	-	-
4- 3-65	-	310	26	71	100	25
-	-	299	26	82	87.5	15
5- 5-65	-	246	22	45	100	25
-	-	208	27	66	87.5	20-15
7-30-65	-	194	20	42	37.5- 50	20-5
-	-	176	32	53	137.5	25
-	-	170	28	43	125	35
-	-	162	26	99	175	20
9-30-65	-	127	50	50	137.5	60

§ To death or to 16 February 1966.

TABLE 2
DATA ON PATIENTS WHO RECEIVED HOMOGRAFTS FROM NONRELATED
LIVING DONORS

LD #	Age–Sex	Date of Transplant	Blood Groups		# Sera Tested	Mismatch % Sera	Mismatch Groups	Thymec- tomy
			R	D				
67	36 - M	11-17-64	O+	O+	108	2.8	1	11- 7-64
69	27 - M	1- 4-65	A-	O+	117	4.3	1	-
70	27 - F	1- 8-65	A+	O+	103	6.8	0	12-31-64
71	37 - M	1-22-65	A+	A+	120	7.5	5	-
74	31 - M	2- 2-65	B+	O+	112	0.9	0	-
77	26 - M	1. 3-13-65	A+	A+	97	11.3	6, 1	-
		2. 4-27-65	A+	A+	109	4.6	0	2- 1-65
78	34 - M	3-19-65	A+	A+	124	·9.7	1	-
80	10 - M	3-30-65	O+	O+	109	17.4	3, 2	-
82	36 - M	4- 6-65	O+	O+	106	15.1	2, 5, 1	3-13-65
86	35 - M	5- 7-65	A+	O+	114	9.6	1, x	4-29-65
87	33 - F	5-18-65	O+	O+	134	9.0	3-6†, 2	4- 8-65
88	35 - M	6- 9-65	B	B	135	11.9	2	5- 8-65
91	22 - M	7-27-65	O+	O+	130	6.2	3, x	7-15-65
92	37 - M	8- 3-65	A+	O-	105	6.7	2	7-21-65

   * The donors employed were selected from a pool, on the basis of the best possible antigenic match.

   † 3-6 classification: results from a mismatch in a group of antisera which are associated with both group 3 and group 6 sera.

TABLE 2, Cont.

Date of Death	Survival ‡ (Days)	Current BUN	Ccr	Current Treatment: Imuran	Prednisone
-	456	28	65	137.5-125	25
1- 9-65	5	-	-	-	-
-	404	46	60	137.5	20
-	390	43	25	75	20
3-27-65	53	-	-	-	-
Removed 10 days					
-	295	25	114	100	20
-	334	28	115	125	25
1-18-66	295	-	-	-	-
7- 8-65	93	-	-	-	-
-	285	21	138	175	20
-	274	18	60	87.5	15
11-13-65	157	-	-	-	-
-	204	50	52	137.5	40
10-21-65	79	-	-	-	-

‡ To death or to 16 February 1966.

Serologic Testing

Blood samples were drawn from the prospective donor and recipient into heparinized tubes containing small glass beads and sent by air mail, special delivery to Los Angeles where the lymphocytes were isolated. Antigen testing was performed by reacting the lymphocytes with a panel of 89 to 135 antisera. The technique was slightly modified from that previously described[1] in that the results were expressed as positive or negative scores on the basis of reactivity with 2 dilutions of each antiserum (0.003 ml and 0.001 ml).

Mismatches were recorded whenever the donor was positive and the recipient negative with any given antiserum. A match was considered to be present in all instances in which the donor's cells failed to react with any given antiserum, even if the corresponding recipient cells were not tested against the same antiserum, and in all instances in which the recipient cells reacted with a given serum, even if the corresponding donor cells were not tested with that particular antiserum.

The relative compatibility of any donor-recipient combination was stated in two ways. The first test of compatibility expressed the number of mismatches as a percentage of the total mismatched antisera which were either measured or deduced (as described above). The second expressed the mismatches as incompatibilities in one or more of six major antigenic groups into which the antisera had been placed on the basis of chi-square associations.[5] For purposes of this study, a group incompatibility was assumed to exist when three or more antisera within that group were mismatched. Three or more mismatches with nongroupable antisera were also arbitrarily classified as a single group mismatch (group X).

It should be noted that the above groups have recently been found to be associated with the following leukocyte groups described by others[5]: group 1: LA1, 7d, Dausset group 8; group 2: Dausset Mac or group 1, Shulman B1, LA2, 8a, Amos 1; group 3: 4a, Dausset group 3; group 5: 6b, Dausset group 9, 4d; group 6: 4c, 9a; and group 7: Dausset group 7, 4b.

Histopathologic Analysis

Eleven patients in the present series died 5, 39, 50, 53, 79, 93, 157, 242, 254, 295 and 314 days after operation. During this interval in the original series of 64 nonmatched homotransplants, 26 autopsy specimens became available for similar analysis.

RESULTS

Antigenic Matching with Related Donors

A detailed listing of the specific incompatibilities encountered in matchings with the unused donors and the actually selected donors for each recipient is given in the right-hand half of FIGURE 1. Mismatches, indicated by the dots,

FIGURE 1. Incompatibilities of individual sera in the selected series of kidney transplant recipients. The antisera are listed vertically in groups. The dots represent mismatches that occurred between the donors and the recipients whose numbers are given across the top line. The mismatches that occurred with the actual donor used are given for each recipient. In instances in which related donors were also considered, the actual donor is denoted by "A" and the other nonselected donors, by "B", "C", etc.

can be noted to occur frequently in clusters within the subdivided groups of antisera. Selection of the donor was based on two criteria, the lowest percentage of total antisera which were mismatched and the fewest groups mismatched. Mismatches in group six were avoided whenever possible on the basis of earlier indications that this group may be stronger than the others.[3]

The pool of suitable prospective donors for any given case was, of course, limited, often making it necessary to proceed, despite the presence of a significant number of incompatibilities. With respect to the percentage of antisera mismatched, the mean among the 18 related pairs was 9.56 ± 1.43 (s.e.) as compared to a mean of 11.32 ± 0.71 (s.e.) in 203 matchings among 66 random related family groups. These means are not significantly different (P = 0.3).

With respect to groups of mismatch, the proportion of selected transplants with few groups of mismatch was almost like that found[3] in earlier studies of kidney transplant recipients who had survived more than one year (FIGURE 2), differing, however, in that a fairly high proportion of transplants with
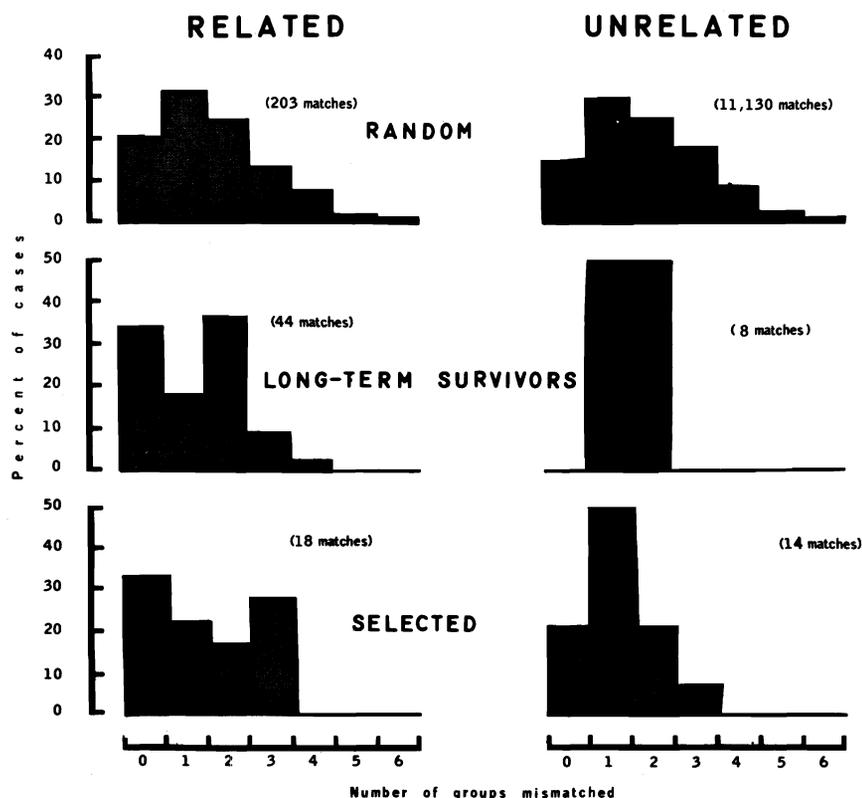

FIGURE 2. Distributions of the total number of groups that mismatch. The number of groups that mismatch (counting the antisera which were unclassifiable as a miscellaneous x group), for any given pair of individuals were first totalled. The proportion of pairs which were mismatched in a total of 0, 1, 2, 3, etc. groups were plotted for each category.

three groups of mismatch had to be accepted. From a limited family donor pool, the "selection" often consisted of ruling out extremely badly matched donors and donors mismatched in group six (except in LD97 and partially, in LD76).

Antigenic Matching with Nonrelated Donors

Certain observations were much clearer in the nonrelated than in the related donor matching program. A minority of the donor pool, for example, did not have a good representation of the antigens being tested. Such people would be suitable for many recipients and might be considered to be "universal donors." At the other end of the spectrum there were a few volunteers whose lymphocytes possessed many antigens, thus making them unsuitable as donors for almost all the recipients.

Conversely, patients with many antigens were "universal recipients" and presented no difficulty in matching. Those with few antigens created a serious problem. An example is shown in FIGURE 3 of the incompatibilities that occurred when 40 type O volunteers were considered as prospective donors for a type O patient (LD70). This patient's own mother, aunt and cousins were also badly mismatched (FIGURE 1, 70E, D and B,C respectively). It was only by selecting the rare donor (the first donor of FIGURE 3) that a matching was achieved in which low numbers of incompatibilities and no groups of mismatch were present. This patient is alive with good renal function 13 months after operation.

In spite of the presence of the relatively large donor pool, a significant number of mismatches had to be accepted in many of the 14 transplanted recipients (FIGURES 1 & 2). The mean percentage of antisera mismatched attained for the 14 pairs of recipients of nonrelated kidneys was 8.04 ± 1.22 (s.e.). This was significantly less than the mean, 13.58 ± 0.52 of 11,130 matches in a random population of 106 subjects, (P = 0.001). The distribution of incompatibilities considered by groups was towards the favorable side among the selected pairs (FIGURE 2), and highly mismatched pairs appear to have been avoided. It was not possible, in every case, to select a donor with only one or no groups of incompatibility.

Survival of Related Patients

The dates of operation, current function, and immunosuppressive therapy are documented in TABLE 1. Two of the 18 patients died during the first 120 days and three more died 242, 254 and 314 days after transplantation. Of the surviving 13 patients, six have survived 4 to 8 months; four, 8 to 12 months; and three, more than one year.

In TABLE 3 these results are compared with those obtained previously,[2,4] using unmatched donors. It will be noted that although no trend in improvement of survival had been noted with increasing experience in the three earlier

FIGURE 3. Incompatibilities of individual sera found in matchings of a random pool of 40 volunteers to one recipient (LD70). Comparison with FIGURE 1 shows that numerous mismatches had occurred with most of the donors to this one recipient. The first donor shown was chosen.

TABLE 3

DEATHS IN ALL PATIENTS TREATED IN DENVER WITH HOMOGRAFTS
FROM LIVING VOLUNTEER DONORS*

	Dates of Transplant	No.	120 days	120-365 days
RANDOM DONORS:				
	11-24-62 to 8-12-63			
	Related	16	3 (19%)	2 (12.5%)
	Nonrelated	6	5 (83%)	1 (17%)
	8-16-63 to 12-7-63			
	Related	15	6 (40%)	0
	Nonrelated	7	3 (43%)	0
	12-8-63 to 3-30-64			
	Related	15	3 (20%)	1 (7%)
	Nonrelated	5	3 (60%)	0
SELECTED DONORS:				
	10-12-64 to 10-12-65			
	Related	18	2 (11.1%)	3 (16.6%)
	Nonrelated	14	4 (29%)	2 (14.3%)

* For analysis of a possible trend in improvement with time, the original series of 64 recipients who received kidneys from random donors was divided into thirds.

groups, there is a slight increase in early survival in the present series. This early improvement is also evident, if the life-survival curves of the present series are plotted against those of the pooled earlier series of 64 patients (FIGURE 4).

The survival data of the earlier series of 64 patients and the selected series of 18 related patients can be described in terms of early deaths and longer-term survivors. In the unselected series, the early deaths follow a negative exponential distribution of survival time, with average survival of 73.5 days, or a half-life of 51 days. The distribution of survival time of early-death patients was essentially the same for the nonrelated and the related groups (average 73 and 74 respectively). In the present selected series of 18 patients, the average survival time of the five patients who died within the first year (TABLE 1) is 180 days. The increase in average survival is of statistical significance ($P = 0.02$).

In the early series of 64 patients, the main difference between the related and nonrelated groups was the percentage of longer-term (> 12 months) survivors (related 67 per cent, nonrelated 33 per cent). This difference is statistically significant at $P = 0.03$ as obtained by chi-square. The fraction of longer-
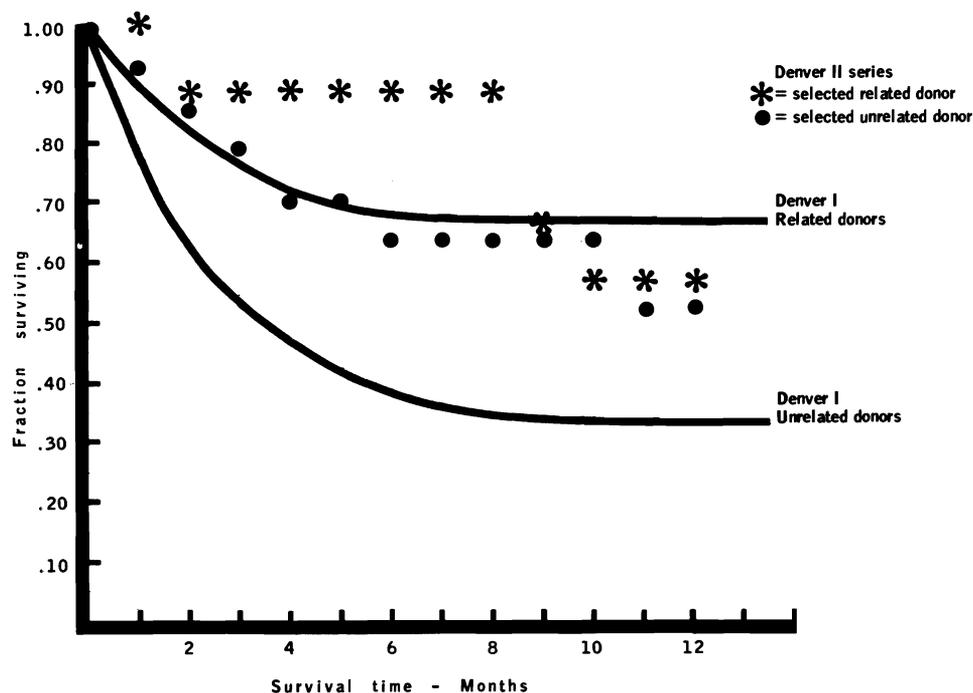
FIGURE 4. Survival curve of the first Denver series (random donors) versus the Denver II series. The cumulative proportion of survivors was calculated by a computer program.[6] Because of the limited number of patients in the second selected series and the statistical variability of the curve, only the computed points are indicated for the second series.

term survivors among the 18 selected related patients, 58 percent (as estimated from life table calculations[6]), does not differ materially from that of the earlier series.

Severe difficulty with control of rejection was encountered in only one patient (LD79). This patient had a progressive decline in renal function during the first several months after operation and ultimately had a creatinine clearance of 10–20 ml per minute, with a BUN of 40–100 mg per cent. No instances of renal shutdown occurred during rejection crises.

Causes of Death in Related Group

Sepsis was the direct cause of death in each of the five unsuccessfully treated patients: pancreatic abscesses secondary to gastric ulcer penetration (LD66); *Pneumocystis carinii* pneumonitis and *Pseudomonas aeruginosa* septicemia (LD76); *Aspergillus fumigatus* brain abscess (LD79); monilial enterocolitis (LD81); and *Pseudomonas aeruginosa* wound infection and *Pneumocystis carinii* pneumonitis (LD83). Patient LD83 developed a ureteric fistula after

transplantation which could not be closed despite several reoperations; the ultimately fatal sequence of events thus followed a technical complication.

Pathology of Related Homografts

One (LD81) of the four kidneys was normal. Two (LD66 and LD83) showed acute tubular necrosis due to hypotension in the last few days of life. Changes related to rejection were encountered in the other two homografts (LD76 and LD79). Both showed fibrous intimal thickening of many interlobular, arcuate and interlobar arteries and several of the vessels were completely occluded by this obliterative process. In some arteries, these changes were accompanied by reduplication of the internal elastic lamina, whereas, in others, the elastic layer was ruptured. Tubular atrophy and interstitial fibrosis were prominent in these two homografts as a result of the ischemia.

In TABLE 4, these pathological changes are compared with those found ir the 14 related renal homografts from the original nonselected series. It will be noticed that fibrinoid necrosis of arteriolar and arterial walls, a change not seen in the matched series, affected 43 percent of the grafts in the original series. This type of vascular lesion is almost invariably associated with active acute rejection[7] and its high incidence in the series of unselected transplants reflects the greater number of these patients who died with unreversed rejection. Arterial fibrous intimal thickening, a common legacy of past rejection episodes, also tended to be more frequent in the original series. Deposits of PAS-positive material on the glomerular capillary basement membranes, generally a late manifestation of incompatibility, only occured in one transplant from the original unmatched series. Cellular infiltration was equally common in both groups of transplants; this can be a feature of acute tubular necrosis as well as rejection.

Survival of Nonrelated Homografts

Four of the 14 patients died during the first 120 days and two subsequently died after 157 and 295 days. The shortest follow-up on the eight surviving patients is 6 and $\frac{1}{2}$ months. Four have survived 9 to 12 months and three, more than one year.

The comparison of these results with those obtained previously, using nonselected nonrelated donors is provided in TABLE 3. In these three nonmatched groups done at different time intervals, the four-month mortality rate was 83, 43 and 60 percent. The four-month mortality rate in the present, antigenically matched series was 29 percent. The increased survival rate with the selected unrelated donor group can be seen in the life-survival curves of FIGURE 4. The decrease from the pooled results of the earlier series, however, falls short of statistical significance ($X^2 = 2.17$, $P = 0.14$). The increase in survival of the six early deaths, from 73 days to 114 days, also falls short of statistical significance ($P = 0.14$). In view of the limited number of patients, the lack of statisti-

TABLE 4

HISTOLOGICAL CHANGES IN RENAL HOMOGRAFTS FROM PATIENTS WHO DIED IN THE FIRST YEAR AFTER RECEIVING A TRANSPLANT FROM A RELATIVE

Type of Lesion	Recipient Number (LD)																		
	Group 1*														Group 2†				
	26	35	11	28	61	43	32	38	8	64	16	62	56	9	81	66	83	79	76
Intimal thickening of interlobular arteries			++	++														+++	++
Fibrinoid necrosis in arterial and arteriolar walls			+		+	+	+	+	+	+	+	+							
Glomerular capillary basement membrane thickening										+									
Cellular infiltration				+		+++	+	+	+	+	+			+	+	+	+	+	
Interstitial fibrosis					+	+	+	+		+	+		++			+	+++	+++	
Tubular atrophy				+	+	+	+		+	+			++	++				+++	++
Onset of rejection (day after transplantation)	1	13	3, 14, 25	1	11	3	4	44	5, 29, 35	17	7	5, 34, 71			1			8	4
Survival (days)	1/2	9	25	25	36	38	42	48	62	65	83	116	155	207	39	50	242	254	314

* In group 1 there was no attempt to match donor and recipient.

† In group 2, where possible, the donors were selected by lymphocyte serotyping.

cal significance of the improved survival suggested by the life survival curves of FIGURE 4 should be interpreted as indicating that the increase in survival has not been firmly demonstrated.

Control of rejection was not difficult in any of these cases. Brief renal shutdown during a rejection crisis was observed on two occasions, for one and two days, respectively.

Causes of Death in Unrelated Series

Four patients died of sepsis: *Pneumoncystis carinii* pneumonitis and cytomegalic inclusion disease (LD82); viral hepatitis resulting in acute yellow atrophy (LD88); pneumonitis and cytomegalic inclusion disease (LD92) and systemic histoplasmosis (LD80). The two other patients died as the result of technical complications. In one (LD69), the smaller of two renal arteries to the homograft was accidentally ligated, resulting in a large renal infarct with hematuria and obstruction of the collecting system by clot. Urinary drainage was re-established at a second operation but function was poor throughout, also partly as the result of an excessive ischemic interval of 51 minutes. He died of acute heart failure five days postoperatively. In the other patient (LD74), the tail of the pancreas was fractured during removal of a large polycystic kidney, resulting in a pancreatic fistula. This was ultimately treated with resection of the tail of the pancreas but he eventually died 53 days after operation of *Pseudomonas aeruginosa* pneumonitis.

Pathology of Unrelated Homografts

Two of these kidneys (LD82 and LD92) showed acute tubular necrosis due to hypotension associated with the terminal infection. Margination of lymphoid cells with pyroninophilic cytoplasm in the peritubular capillaries, the presence of small groups of similar cells in the edematous interstitium, and early focal proximal tubular damage was presumed to indicate commencing rejection in three of the transplants (LD69, LD74 and LD88). This was accompanied by fibrinoid necrosis of the arteriolar walls in LD74, but in none of these cases was renal damage which was due to the homograft reaction a factor in the patient's death. Fibrous intimal thickening of the interlobular arteries was only found in one homograft (LD80). It was not severe and had produced little ischemic damage.

Comparison with the 12 unselected, unmatched kidneys treated in the past (TABLE 5) shows that before selection was practiced, obliterative and fibrinoid necrotic vascular lesions were more commonly encountered. Fifty-eight per cent of the unmatched kidneys showed fibrous intimal thickening of many of their interlobular arteries and 42 percent contained fibrinoid necrotic arteriolar lesions. In the matched series only 17 percent of the transplants were affected by each of these complications. This difference is an indication of the frequency with which patients in the first series died while experiencing

TABLE 5

HISTOLOGICAL CHANGES IN RENAL HOMOGRAPHS FROM PATIENTS WHO DIED IN
THE FIRST YEAR AFTER RECEIVING A TRANSPLANT FROM AN UNRELATED DONOR

Type of Lesion	Recipient Number (LD)																	
	Group 1*												Group 2†					
	29	5	31	24	46	59	57	21	7	19	4	10	69	74	92	82	88	80
Intimal thickening of interlobular arteries	++			+	+++	+	++				+	++						+
Fibrinoid necrosis in arterial and arteriolar walls			+	+	+	++					++	++		+				
Glomerular capillary basement membrane thickening											+							
Cellular infiltration	+	+	+	++	+	+			+	+	+	++	++	++	++		+	++
Interstitial fibrosis				+	+		+				++	++				+		+
Tubular atrophy	+	+	+	+	+	+	+	+	+		+	++						
Onset of rejection (day after transplantation)	2	5	2	2	31	37	2 32 53	4	19	9	7 42	3 229	?		1 56			
Survival (days)	8	10	14	37	43	45	71	76	79	95	113	296	5	53	79	93	157	295

* In group 1 there was no attempt to match donor and recipient.
† In group 2 the donors were selected by lymphocyte serotyping.

rejection, and of the infrequency with which this happened in the second series.

Significance of Individual Leukocyte Antigens

The relative significance of individual antigens in histocompatibility is, as yet, not apparent from this study. Because many of the deaths were not directly attributable to problems in antigenic matching, no pattern of antigenic mismatch could be correlated with nonsurvival. The two patients in whom rejection was a contributory factor in death were mismatched in group 1 plus the unclassified serum group (LD79) and in groups 3–6, 2 and 5 (LD76). Other patients mismatched in group 1 or groups 3–6 are currently surviving with good function.

Discussion

The results in the presently reported series of cases in which donors were selected on the basis of leukocyte antigen matching are improved compared to those previously obtained in the Denver institutions. The four-month survival was considerably better in the patients receiving related homografts, although three subsequent deaths reduced the ultimate one year life expectancy to that of the original unselected series. However, the average survival time of the patients who died during the first year in the selected related group is significantly better than that in the previous series (P = 0.02). In the unrelated group, survival appears to have been very considerably influenced, now approaching that obtained in related cases, a result which would have been predicted, if the antigen matching had measured histocompatibility factors either directly or indirectly.

As far as can be determined, this improvement did not represent the continuation of a trend observed during the treatment of the original 64 non-matched cases. The position that improved histocompatibility was a significant factor could further be supported by the fact that acute and healed vascular lesions in the matched homografts were less frequent than in comparable kidneys from the earlier series.

Nevertheless, the present study highlights the difficulties that exist in attempting to evaluate any human antigen matching technique in the experimental environment of whole organ transplantation. First, a certain number of treatment failures were due either to technical mishaps or to septic complications which terminated the patient's life in spite of good homograft function. By and large, such cases can not reasonably be said to have presented a fair biologic test of the method. Secondly, differences in recipient immunologic reactivity vary in the individual uremic patients.[8] Thus, an equal mismatch in two patients might be manifested as rejections of quite different intensity. Third, it is impossible to treat each patient in exactly the same way. The toler-

ance to azathioprine therapy, and the quantities of steroid doses can not be easily standardized, and adjustments in the regimen are often dictated by subjective clinical judgment.

Finally, it was impossible to obtain highly desirable matches in every case. Even with the best histocompatibility pairs there was a significant number of antigenic differences between the donors and recipients, and in some cases these were quite high.

Because of these important reservations, it is essential to refrain from overinterpretation of the presently reported data. It is conceivable that some unrecognized improvement in general management could have occurred, although the breakdown of past cases into successive thirds did not indicate that this was occurring. In other centers, however, a trend of improvement has been noted with transplantation of nonmatched cadaveric kidneys.[9] Whether these results can be presumed to indicate that antigenic matching plays a relatively minor role in renal transplantation with current means of immunosuppression is not yet determined.

The antigenic matching method described here can not be considered to be a definitive method. The use of over 100 antisera to type each patient is cumbersome and the exact criteria by which mismatches in groups can be shown are as yet uncertain. Although an ever-increasing agreement as to leukocyte groups is being obtained by different laboratories,[5,10] much remains to be done in the recognition of definitive leukocyte types. Until these types are established with monospecific sera and by thorough genetic studies, the matching results must be considered only provisional. The present study, however, suggests that even with the current, rather limited knowledge of leukocyte groups and the sera available, some measure of assistance may be rendered above that of random selection of donors.

SUMMARY

An attempt was made to select donors for human kidney transplantation on the basis of lymphocyte antigen matching. Compatibility was assayed by reactions of individual antisera on donor and recipient lymphocytes, as well as by matching on the basis of the six recognized leukocyte groups. The donor judged to be the best match was chosen from pools of related and unrelated donors. Although the choice was often limited, a group of donors was selected which, as a whole, was slightly more compatible than that achieved by random matching. Mismatches which were extremely high or from group 6 were avoided whenever possible.

Eighteen transplants were done from related donors: sixteen of these recipients lived for at least 4 months postoperatively; three more died after $10\frac{1}{2}$, $8\frac{1}{2}$ and 8 months. Thirteen of the original 18 patients are still alive, 6, after 4 to 8 months, four, after 8 to 21 months and three, after more than one

year. This represents a slight improvement over the first unmatched Denver series treated 2 to $3\frac{1}{2}$ years ago.

Of the 14 recipients in the present series who received kidneys from matched unrelated donors, ten lived for more than 4 months; two more died after 5 and 10 months respectively. Eight of the original patients are still alive with a minimum follow-up of $6\frac{1}{2}$ months; four of these patients are surviving 9 to 12 months after operation, and the other three, more than one year. These results are improved over that of an original nonselected series of unrelated homotransplants performed in Denver. Furthermore, the survival curve in these nonrelated donors and recipients now approximates that which was obtained in the past Denver experience with randomly selected related donors. Because of the relatively small numbers involved, however, this improvement is not statistically significant.

Pathological studies of the kidneys from the recipients who died were compared to the kidneys of the dead recipients of the first Denver series in which donors were randomly selected. Acute vascular lesions which result from severe rejection were less frequent in this series as compared to the earlier unmatched series.

It was concluded that coincidental to matching for provisional leukocyte types, an improved early clinical outcome of transplantation was obtained with respect to survival and minimization of pathologic changes associated with rejection. Whether the improvements are attributable to the matching procedure or to other unrecognized factors in the clinical management of the patients could not be determined.

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