100 HLA-identical Sibling Transplants

Prognostic Factors Other than Histocompatibility

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Analysis of 100 patients receiving HLA identical sibling transplants was performed. Excellent graft survival demonstrated in the group attests to the importance of matching serological determined antigens. There seems to be a modest beneficial effect on antilymphoblast globulin in low dosage, but not in high doses. Insulin dependent diabetes mellitus results in a significant negative influence on patient survival and graft function in the male recipient but not in the female. A particularly striking point that emerges is the potential hazard in incorrectly treating for rejection. Rejection occurs very rarely in these patients; in a patient with deteriorating renal function, etiologies other than rejection should be vigorously sought (including transcutaneous biopsy) prior to initiation of rejection therapy.

THE SURVIVAL OF TRANSPLANTED KIDNEYS from a sibling matched at the major histocompatibility locus (HLA) far surpass those from poorer matched relatives or even well matched cadavers. Nonetheless, the pooled results from transplant registries[11] and from individual centers[2,12,15,20] demonstrate a small but constant risk of graft failure in HLA identical grafts (as defined by serological techniques)[11] attesting to the importance of other factors in transplant success. The HLA identical sibling transplant population is a useful study group because histoincompatibility at least between the serologically determined HLA-A and B antigens has been eliminated. The purpose of the present paper was to analyze a relatively large population of HLA matched grafts at a single institution in order to a) define the risks of long-term immunosuppression, b) study the influences of weaker, nonserologically determined antigens, c) define specific infectious and cardiovascular complications and d) identify specific high risk groups.

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Materials and Methods

From January 1, 1968 through December 31, 1976 one hundred first transplants have been performed between HLA identical siblings at the University of Minnesota Hospitals. No second or subsequent transplants were included in this analysis. There was only one set of monozygotic twins in this group. Our tissue typing and crossmatching techniques have been previously described.[1] The following HLA antigen specificities are routinely identified in our laboratories: HLA-A1, A2, A28, A3, A9, AW23, A10, AW25, AW26, A11, A29, AW30, AW31, AW32, AW33, AW34, AW36, AW43; HLA-B5, BW35, B18, B7, BW22, B27, B8, B12, B13, BW40, B14, BW15, BW16, BW17, BW21, BW37, BW39, BW41, BW42. Although the following crossreacting antigens are identified, the designation of a donor–recipient pair as HLA identical did not include reclassification according to crossreacting antigens (HLA-A: A1 = A3 = A11, A2 = A28, A9 = A23-A24, A10 = A11-AW26 = AW24 = AW32, AW30 = AW32 = AW33, A10 = A17; HLA-B: B5 = B15 = B17 = B18 = BW21 = BW35, B7 = B27 = BW22, B7 = B13 = B40, B8 = B14, B12 = B21).[3] Sera to identify all antigenic specificities were not available for the first few years and sera to identify antigens determined by the C, D and Dw subloci have only recently become available. Genotyping was not routinely performed. Thus, "HLA identity" for the purposes of this paper is equivalent to phenotypic identity at the HLA-A and B subloci as determined by serotyping with reagents available prior to transplantation during these years. If less than four antigens were identified but all identified antigens were identical, the HLA match was none-

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theless considered identical. We recognize the potential errors in identification of incompatibilities utilizing these techniques but these are the methods which are clinically available at almost all centers and generally serve as the basis of donor selection.

Mixed leukocyte cultures were performed on 31 donor–recipient pairs using a micromethod.[16] Responding cells, 2×10^5, were used in each 0.2 ml culture with 1×10^5, 2×10^5 or 4×10^5 stimulating cells incubated with 50 μg of mitomycin C/ml of cell suspension. Mixed cultures were prepared using cells of the recipient as the responding cell population. To these cultures were added mitomycin treated cells of the donor or recipient as the stimulating cell population. After five days of incubation the cultures were labelled with 1 μCi of radioactive thymidine (specific activity 16–18 Ci/mmole). The cultures were harvested 18 hours later by precipitation onto glass fiber filters which were counted using a Unilux-2A liquid scintillation counter.® Means of triplicate culture counts per minute value were determined. A stimulation index was calculated by dividing the amount of proliferation seen after allogeneic stimulation (as determined by total thymidine incorporation) by the amount of proliferation induced by syngeneic stimulation. An index less than 2.5 was considered to represent no stimulation; between 2.5 and 5.0 the results were considered equivocal; and above 5.0 was considered positive stimulation.

Sixty-three of these patients were nondiabetic; 37 were insulin-dependent diabetics. Sixty-seven patients were male. All patients have been followed a minimum of one year and several patients have been followed eight years. The immunosuppressive treatment of kidney recipients has been previously described in detail.[18] Briefly, the administration of azathioprine (5 mg/kg/day) is begun on the day of the transplant operation and the dose is tapered to a maintenance level of 2.0–2.5 mg/kg/day; the administration of prednisone between 1968–75 was begun at 2.0 mg/kg/day and tapered to maintenance levels of 0.25–0.2 mg/kg/day by the first year. Further, very gradual reductions were made thereafter but prednisone was not discontinued at any time. Since 1975, the initial prednisone dose has been 1.0 mg/kg/day but the maintenance doses have remained the same.

Almost all these patients received antilymphoblast globulin (ALG) daily for 14 days following transplantation.[8,9] The standard treatment for rejection was an increase in the patient's prednisone dose to 2 mg/kg/day with gradual tapering to maintenance levels without change in azathioprine dose. In some cases a steroid bolus of 1 g methyl prednisolone intravenously was given on each of three consecutive days. Results are noted in terms of patient survival and graft function; all causes of graft loss after transplantation including death with functioning kidney are included. All deaths including those occurring on dialysis long after transplant nephrectomy or following subsequent transplantation from any donor source are included. Life table analysis was utilized to compute the survival curves.[7]

Rejection was defined clinically as a rise in serum creatinine and/or blood urea nitrogen levels with associated clinical findings such as weight gain, increased blood pressure and decreased urine output suggestive of impaired renal function. In most cases an impression of rejection was confirmed by percutaneous needle biopsy of the transplanted organ.

Results

Patient Survival and Graft Function After Transplantation of HLA Identical Sibling Grafts (Fig. 1)

The entire population displays a two year patient survival of 92.6% and a graft function rate at two years of 88.5%. Analysis at eight years reveals a graft function rate of 79.7%. As is noted with other groups of transplant recipients, the majority of graft loss occurs within the first six months following transplantation; following this time period the graft function declines at a slower rate.

Effect of Diabetes on Patient Survival and Graft Function After Transplantation of HLA Identical Sibling Grafts (Fig. 2)

We have noted previously that diabetes is an important factor in patient survival and graft function; its importance is apparent among this population both in terms of patient survival (82% four year survival in diabetics vs 95% in nondiabetics) and graft function (80% four year in diabetics vs 92% in nondiabetic patients). In both groups the principal time for graft loss is within the first year after transplantation. These differences in patient survival and graft function are statistically significant ($p < 0.05$).

Effect of Recipient Sex and Diabetic Status on Graft Function in Recipients of HLA Identical Sibling Transplants (Table 1)

Female patients have better overall current patient survival and graft function than their male counterparts (100 vs 85% patient survival and 97 vs 82.1% graft function). Although diabetes continues to be a negative influence on graft function in male patients (75% in diabetics vs 87.5% in nondiabetics), its significance is not apparent in female patients (100% graft

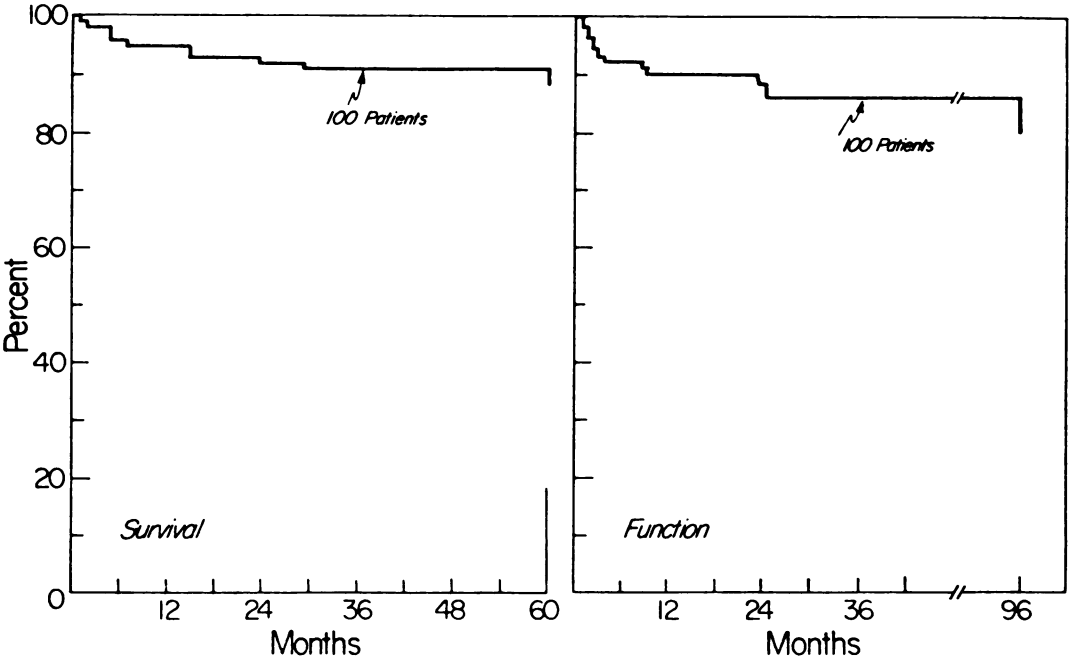

FIG. 1. Cumulative patient survival and graft function in 100 patients at the University of Minnesota receiving renal allografts from HLA-identical siblings from January, 1968 through December, 1976. Note early graft loss (within six months of transplantation) and more gradual loss after that time.

function in diabetics vs 95.7% in nondiabetics). Cardiovascular and infectious complications which are frequently seen in diabetic patients appear to affect only the males in this study population. Because of the poorer diabetic results (at least in males) the remainder of this analysis separates patients according to their diabetic status.

Effect of Recipient Age and Diabetic Status on Graft Function in Recipients of HLA Identical Sibling Transplants

If the diabetic population was skewed toward younger (<10 years) or older (>40 years) patients who might be at higher risk,[10,17] the worst results in the diabetics might be explained on this basis. The nondiabetic and diabetic recipient populations were analyzed according to age distribution. There are no diabetic recipients in the pediatric high risk group and no disproportion of diabetics in the older groups. The diabetic patients are clustered in the 20–49 year age range and diabetic patients in each decade have similar graft function rates. However, matched for age, diabetic patients have poorer patient survival and graft function than nondiabetics (data not shown).

Effect of Age and Recipient Sex on Graft Function in Nondiabetic and Diabetic Recipients of HLA Identical Sibling Grafts (Table 2)

When the three variables of patient age, sex and diabetic status are examined in combination, several points emerge. Diabetic females have comparable overall patient survival and graft function with their nondiabetic counterparts. Diabetic and nondiabetic females of both age ranges have equivalent patient survival and graft function. Similarly, in nondiabetic males, there is no difference seen when the patient's age is considered. Diabetic males, however, have poorer results and in particular, males under 40 years of age are the highest risk group with only 67% current overall patient survival and graft function. Seven of 27

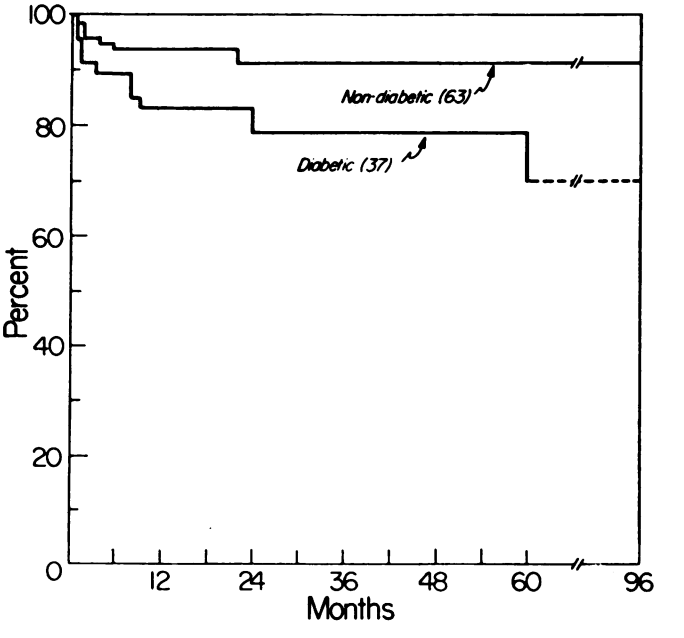

FIG. 2. Cumulative graft function in 100 recipients of HLA-identical sibling transplants according to the diabetic status of the recipient. Note superior graft function results in the nondiabetic patients.

TABLE 1. *Effect of Recipient Sex and Diabetic Status on Current Patient Survival and Graft Function in Recipients of HLA-identical Sibling Grafts*

	Nondiabetic		Diabetic		Total	
	Survival (%)	Function (%)	Survival (%)	Function (%)	Survival (%)	Function (%)
Male	37/40 (93)	35/40 (88)	20/27 (74)	20/27 (74)	57/67 (85)	55/67 (82)
Female	23/23 (100)	22/23 (96)	10/10 (100)	10/10 (100)	33/33 (100)	32/33 (97)
Total	60/63 (95)	57/63 (91)	30/37 (81)	30/37 (81)	90/100 (90)	87/100 (87)

diabetics have died; all males, and six of seven were younger than 40.

Effect of Donor and Recipient Sex on Graft Function in Nondiabetic and Diabetic Recipients of HLA Identical Sibling Grafts (Table 3)

There has been some evidence that weak, sex linked antigens may play some role in allograft rejection in animals. If this were the case, we would expect poorer graft function results among female recipients of grafts from male donors. Instead, both nondiabetic and diabetic females who received "mismatched" grafts in terms of donor–recipient sex matching had 100% graft function. The number of patients is small, but certainly weights the existing evidence against the significance of sex linked antigen disparity.

Correlation of Stimulation Index on Graft Outcome in Recipients of HLA Identical Sibling Transplants

In five of 31 patients in whom mixed lymphocyte cultures were performed, the stimulation index was greater than 5.0 and considered positive. One of these patients suffered early rejection with massive proteinuria eventuating in graft loss; a septic death followed a second (cadaver) transplant. A second patient suffered two early rejections but has kept her graft. The remaining three patients had no rejection episodes and enjoy normal renal function. Among the remaining 26 patients with negative stimulation indices (all <2.5) there were three episodes of rejection, all of which were reversed; one of the three patients currently has compromised renal function (serum creatinine 2.1 mg%). Unfortunately too few of our patients were tested by mixed lymphocyte culture test to draw conclusions about its usefulness.

Effect of Antilymphoblast Globulin (ALG) Dose on Graft Function in Nondiabetic and Diabetic Recipients of HLA Identical Sibling Transplants (Table 4)

In 86 patients precise data was available specifying the exact dose of ALG administered following transplantation. In contrast to the results seen in well-matched cadaver recipients in whom high dose (>25 mg/kg/day) ALG is beneficial;[9] increments in ALG dose have proven to be of no value in determining the rate of graft function; in fact, doses over 15 mg/kg in these patients are associated with poorer graft function. Five patients received no ALG and three of the five had early reversible rejection episodes but currently have good graft function.

Current Status of HLA Identical Transplant Recipients Who Had No Rejection Episodes (Table 5)

Seventy-five per cent (47/63) of nondiabetics and 76% (28/37) of diabetics had no rejection episodes and currently enjoy good health. The average serum creatinine for the two groups are 1.2 mg% and 1.1 mg% respectively and their average daily prednisone dosages are 12.5 mg and 11 mg respectively.

TABLE 2. *Effect of Recipient Sex, Age and Diabetic Status on Current Patient Survival and Graft Function in Recipients of HLA-identical Sibling Grafts*

	Nondiabetic		Diabetic	
	Survival (%)	Function (%)	Survival (%)	Function (%)
Male	37/40 (93)	35/40 (88)	20/27 (74)	20/27 (74)
<40 years	26/28 (93)	24/28 (86)	12/18 (67)	12/18 (67)
≥40 years	11/12 (92)	11/12 (92)	8/9 (89)	8/9 (89)
Female	23/23 (100)	22/23 (96)	10/10 (100)	10/10 (100)
<40 years	16/16 (100)	15/16 (94)	10/10 (100)	10/10 (100)
≥40 years	7/7 (100)	7/7 (100)	—	—

TABLE 3. *Effects of Matching or Mismatching Donor and Recipient Sex on Current Graft Function in Nondiabetic and Diabetic Recipients of HLA-identical Sibling Grafts*

	Donor	
Recipient	Male (%)	Female (%)
Male	27/32 (84)	28/35 (80)
Nondiabetic	18/18 (100)	18/23 (78)
Diabetic	9/14 (64)	10/12 (83)
Female	20/20 (100)	12/13 (92)
Nondiabetic	16/16 (100)	6/7 (86)
Diabetic	4/4 (100)	6/6 (100)

TABLE 4. *Effect of Average Antilymphocyte Globulin (ALG) Dose on Current Patient Survival (PS) and Graft Function (GF) in Recipients of HLA-identical Sibling Grafts*

	Nondiabetic		Diabetic		Total	
ALG Dose	PS (%)	GF (%)	PS (%)	GF (%)	PS (%)	GF (%)
0–15 mg/kg	25/25 (100)	24/25 (94)	12/13 (92)	12/13 (92)	37/38 (97)	36/38 (95)
16–25 mg/kg	23/25 (92)	21/25 (84)	14/16 (88)	14/16 (88)	37/41 (90)	35/41 (85)
>25 mg/kg	2/2 (100)	2/2 (100)	3/5 (60)	3/5 (60)	5/7 (71)	5/7 (71)

Note: Since 7/75 ALG dose = 10 mg/kg/day.

Current Status of HLA Identical Transplant Recipients Who Have Been Treated for Rejection Episodes (Table 6)

Twenty-five per cent (16/63) of nondiabetic patients were treated for rejection, defined as rise in serum creatinine, clinical evidence of abnormal renal function and abnormal renogram. Of these 16 patients, five were in fact misdiagnosed as rejection. Three patients had technical complications (two ureteral complications and one renal artery stenosis), the diagnoses of which were made while the patients were being treated for rejection; these three patients have recovered following correction of their technical problems and have good renal function. Two patients with cytomegalovirus infection were incorrectly diagnosed as having rejection and begun on rejection therapy; both of these patients died of overwhelming viral sepsis. Thus, of the 16 (25%) nondiabetic patients treated for rejection, only 11/63 (17%) in fact had actual rejection episodes. Seven patients had a single reversible rejection episode with recovery of slightly compromised renal function (current average serum creatinine of 1.37 mg%). One patient treated for two rejections has also recovered; though with compromised renal function (serum creatinine of 2.3 mg%). Three nondiabetic patients had more than two rejections and ultimately lost their grafts. Two of these patients are currently well (one is being treated with hemodialysis and the other has received a second allograft) and the third patient died following a second transplant.

Nine of the 37 diabetic patients (25%) were treated for rejection. Two with sepsis were misdiagnosed initially (treatment for rejection was begun) and ultimately died. Seven patients (19%) had "real rejections." Four patients with only one rejection are currently well with slightly compromised renal function (average serum creatinine of 1.6 mg%). Two patients had two rejections and have recovered (average serum creatinine of 1.5 mg%). One patient with greater than two rejections lost his graft and died following a second transplant.

TABLE 5. *Current Clinical Status of HLA-identical Sibling Graft Recipients Who Have Had No Rejection Episodes*

	# Patients (%)	Average Serum Creatinine	Average Prednisone Dose/Day
Nondiabetics	47/63 (75)	1.2 mg%	12.5 mg
Diabetics	28/37 (76)	1.1 mg%	11.0 mg

Complications Following HLA Identical Nondiabetic and Diabetic Sibling Transplantation

As shown in Table 7, a significant number of nondiabetic patients have complications following transplantation, though the majority of complications were not life threatening. Thirty-two per cent (20/63) patients had minor infections defined as those infectious processes not necessitating parenteral antibiotics or patient hospitalization. Ten per cent (6/63) had major infections which proved to be of viral origin in five; in two patients as noted previously, rejection therapy was incorrectly administered and these patients ultimately died. One patient had a myocardial infarction with recovery, four patients displayed chemical evidence of liver dysfunction (without clinical evidence of progression) and one patient developed squamous cell carcinoma of the skin treated with local excision. Seven patients (12%) suffered from technical complications after transplantation; two had bowel adhesions re-

TABLE 6. *Ultimate Diagnosis and Outcome in Nondiabetic and Diabetic Recipients of HLA-identical Sibling Grafts Who Were Treated for Rejection*

	Number of Patients	(%)	Ultimate Diagnosis	Outcome
Nondiabetics	16/63	(25)	3 (Tech)	Recovery
			2 (CMV)	Death
	11/63	(17)	"real rejections"	
			7 (1 rejection)	Recovery (1.37)
			1 (2 rejections)	Recovery (2.3)
			3 (>2 rejections)	1 well on dialysis
				1 well post 2nd Tx
				1 died post 2nd Tx
Diabetics	9/37	(25)	2 (Sepsis)	Death
	7/37	(19)	"real rejections"	
			4 (1 rejection)	Recovery (1.6)
			2 (2 rejections)	Recovery (1.5)
			1 (>2 rejections)	Death post 2nd Tx

TABLE 7. *Complications in Nondiabetic and Diabetic Recipients of HLA-identical Sibling Grafts*

	Minor Infection	Major Infection	Vascular	Technical	Liver Dysfunction	Cancer
Nondiabetics	20/63 (32%)	6/63* (10%)	1/63 (2%)	7/63** (12%)	4/63 (6%)	1/63*** (2%)
Diabetics	13/37 (35%)	5/37† (14%)	5/37‡ (14%)	3/37§ (11%)	1/37 (3%)	—

* CMV in 5 (2 fatal). **Two bowel adhesions (intraperitoneal grafts). Four ureteral complications (1 → graft loss, 2 → "rejection"). One renal artery stenosis → "rejection". ***Squamous cell carcinoma of the skin. †Two treated for "rejection" → fatal. ‡Four myocardial infarctions (2 fatal). §Two ureteral complications (1 → graft loss). One renal artery stenosis thrombosis → graft loss.

quiring lysis following placement of intraperitoneal grafts, four patients had ureteral complications (one led to graft loss and two were misdiagnosed initially as rejections) and one patient had renal artery stenosis. There were no primary wound infections. Postoperative complications among the diabetic patients in this group generally followed the pattern of the nondiabetic. The one notable exception shown is the seven-fold increased incidence of vascular complications in this group including four myocardial infarctions leading to death in two. These infarcts all occurred in males. No females had vascular complications and the higher incidence of atherosclerotic complications in diabetic males may play an important role in their overall poorer patient survival and graft function.

Etiology of Graft Loss and Recipient Death in HLA Identical Sibling Transplants

Table 8 summarizes the various causes of graft failure and ultimate outcome of each patient. One half of the nondiabetic patients are well following graft loss; death in this group of patients was always due to some type of sepsis. In contrast, graft loss in diabetic patients was invariably followed by death either immediately in four patients or after a second graft in three. More than half of the diabetic patients died with functioning first allografts; two following myocardial infarcts and two with sepsis. There were no deaths (and only one graft loss due to rejection) among nondiabetic and diabetic female patients.

Discussion

Since the HLA complex represents the major histocompatibility locus in man, renal transplantation between HLA identical siblings would be expected to result in superior patient survival and graft function when compared to recipients of all other related or cadaver allografts. These results are borne out both in studies pooling the results of many small centers in which 82% two year graft function is seen[11] and in single center studies where two year function ranges from 85 to 100%.[2,14,15,20] Although immune responsiveness has been documented between serologically determined HLA identical sibling pairs using mixed lymphocyte culture techniques,[4] inhibition of macrophage migration[21] and skin grafting experiments, in general these patients are felt to represent a minimal risk population for receiving grafts.[2,11,12,14,15,20] Almost 25% of

TABLE 8. *Etiology of Death and Graft Loss in Recipients of Phenotypically HLA-identical Grafts*

	Age/Sex	Graft Failure	Outcome
Nondiabetics			
1	25/M	Rejection (8 months)	Well post 3rd tx
2	39/M	Tech TUN (1 month)	Well post 2nd tx
3	19/F	Rejection (4 months)	Well on dialysis
4	29/M	Rejection (22 months)	Death—sepsis post 2nd tx
5	52/M	Death* (5 months)	Death—CMV
6	24/M	Death* (2 months)	Death—CMV
Diabetics			
1	30/M	Thrombosis renal artery (10 days)	Death—sepsis post 2nd tx
2	33/M	Rejection (8 months)	Death—sepsis post 2nd tx
3	30/M	Tech TUN (3 months)	Death—uremia post loss of 2nd tx
4	35/M	Death* (24 months)	Death—myocardial infarction
5	28/M	Death* (9 months)	Death—myocardial infarction
6	24/M	Death* (1 month)	Death—sepsis
7	47/M	Death* (1 month)	Death—viral sepsis

* Death = died with functioning kidney.

Seigler's patients are maintained on azathioprine without daily steroid.[15]

In all these series as well as our own, a small percentage of patients lose their grafts and lives. We feel this is an important group to study for two major reasons. First, it would be desirable to achieve optimal transplant results in the group immunologically best suited for transplantation; and we hope a critical assessment of our failures in this group might improve our results. In addition, because major serological histoincompatibility is not an obstacle to graft function, these patients afford us an opportunity to study the effects of diabetes mellitus, recipient age, recipient sex, recipient–donor sex matching, ALG dose, long-term steroid use and minor degrees of histoincompatibility for which *in vitro* testing has not yet been developed.

Diabetes once more[10] proves to be an important risk factor even in the face of serological histocompatibility both for patient survival and graft function. We have previously found that diabetic transplant recipients have a higher incidence of technical problems,[10] vascular disease[10] and septic complications.[10,17] The effect of the underlying disease process is further magnified in this subgroup of well matched patients. Nineteen per cent of our diabetic patients have died compared to 6% of the nondiabetic patients. Whereas sepsis was the major etiologic factor resulting in death in both groups of patients; an additional two diabetic patients died of cardiovascular disease. It is striking that the poorer results are limited to male diabetics. It is likely that steroid induced atheromatous changes are particularly marked in the male diabetic but their increased susceptibility to infectious complications when compared to female diabetics was unexpected.

The three diabetic patients who lost their kidneys all died following retransplantation from cadaver donors. This contrasts to three of the four nondiabetic patients who lost their grafts and are currently well (two following retransplantation). This strongly supports our previous findings that diabetic patients do not tolerate graft loss and retransplantation.[10]

There were four graft losses from within the entire group due to rejection, presumably on the basis of minor histoincompatibilities, although the early inability to identify entire sets of serological determinants make it possible that rejection was on the basis of HLA differences. One of the five patients with positive mixed lymphocyte reaction against the donor suffered progressive unrelenting rejection with massive proteinuria (within one month); likely reflecting major incompatibility at the HLA-D or Dw locus. MLC reactivity was not determined in the other three so that it is impossible to determine whether such incompatibilities only correlate with rejection. Reversible rejection reactions appear to be slightly more common in the five patients who had known MLC incompatibility, but 80% of them still maintain graft function suggesting that MLC reactivity is certainly not a complete contraindication to transplantation form an otherwise compatible sibling. Other investigations have clearly shown the value of MLC testing in predicting rejection: it is possible that altering the immunosuppressive protocol may be indicated in these patients.

It is more alarming that in this serologically well matched population an equal number of patients (four) lost their lives when an incorrect diagnosis of rejection was made and treatment initiated in the face of a mild initially unrecognized infectious process. In these patients, in whom real rejection episodes (utilizing our current immunosuppressive regime) are relatively uncommon (<20%) all effort should be made to clearly establish a diagnosis of rejection (utilizing renogram, echogram and percutaneous biopsy) *before* additional immunosuppressive therapy is instituted.

Technical complications (12%) and losses were relatively common among these patients and probably reflect a more realistic incidence of such complications which in other patient populations are masked by the concurrent presence of rejection. We have previously emphasized that technical complications are often mistaken for rejections and that "pseudorejection" responds, at least transiently, to increased steroid administration.[5,19] Overtreatment of "rejection" can be avoided by a skeptical attitude toward rejection in these patients and a more thorough clinical evaluation (including biopsy).

The extrarenal complications seen in these patients usually did not affect longterm graft function. We have not yet found steroid induced ulcers, steroid cataracts or steroid induced diabetes mellitus in this well matched group of patients. We have seen all of these complications in less well matched patients[18] and they have been seen in HLA identical graft recipients at other centers.[2,15] Histological evidence of diabetic renal disease has been found in our diabetic HLA matched patients:[6] though the clinical significance of these changes is not yet apparent even in grafts surviving more then eight years. Clinical and histological evidence of other recurrent disease has not been recognized in these patients in contrast to that reported in other series.[2,15]

In our search for possible effects of minor histocompatible loci we cannot attach any significance to the influence of the antigens linked to the sex chromosome; females receiving grafts from male donors had perfect graft function. The number of patients involved is admittedly small but nonetheless agrees with pooled center Registry data.[13]

Unlike our results in cadaver transplantation, the beneficial effect of antilymphoblast globulin in HLA identical sibling transplantation is not clear. The best results appear at low ALG doses (0–15 mg/kg); poorer graft function results are seen at higher dosages. This raises the question of whether ALG is of any benefit whatsoever in these optimally serologically matched patients. Among the 45 HLA identical recipients in the Duke series who received no ALG, only 17 (38%) had no rejection episodes.[15] In contrast, in our own series where ALG was almost uniformly administered, 76% of the 100 patients had no rejection episodes. Additionally, three of the five patients who received no ALG did have rejection episodes. Because of our results in these patients who were only phenotypically matched (as opposed to Seigler's group who were also genotyped and as such should theoretically enjoy less rejections), we feel ALG may still play an important beneficial role in the management of these patients. However, the lower doses would appear to be sufficient since overimmunosuppression appears to be the major problem in the well matched patient.

In summary our data confirm the superior results possible in HLA identical transplantation, support the modest beneficial effects of ALG, and underline the significant negative influence of insulin dependent diabetes mellitus on patient survival and graft function in the male recipient. In this high risk group, the additional atherosclerosis inducing potential of steroids may be particularly detrimental and perhaps these patients should be maintained on a lower steroid dosage or converted to alternate day steroid therapy. A particularly striking point that emerges from these data is the hazard involved in incorrectly treating for rejection. An equal number of patients died as a result of rejection therapy as those who lost grafts as a result of rejection. In these patients, in whom rejection is comparatively rare, a careful search for other etiologies of impaired renal function should be made prior to institution of rejection therapy. Mixed lymphocyte reactivity may well provide a helpful additional test in predicting those patients who might be expected to have more severe or more frequent rejection episodes.

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