135

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Renal function was studied in twenty-nine of thirty-four surviving renal allograft recipients from an initial group of sixty-four patients two years after transplantation. Mean clearances of inulin and PAH were, respectively, greater than and equal to half the donors' initial predicted clearances. Minimum urine osmolality during water diuresis was greater, and maximum urine osmolality during hydropenia was less than normal, an effect attributable partly to enhanced solute load in a single transplanted kidney.

Patients with compatible donor-recipient lymphocyte antigens demonstrated statistically better function than those with one or more incompatibilities, although there was a definite degree of overlap between the two groups. In contrast, little correlation could be demonstrated between the cumulative histopathology and renal clearances.

Renal function in patients with compatible donors was statistically greater than half the donors' initial predicted function. Serial increase in renal clearances was documented in one patient with a compatible donor. Serial decreases were demonstrated in two patients with incompatible donors. These findings suggest that hypertrophy of the denervated, transplanted kidney occurs when immune reaction is minimal.

SURVIVAL for one to several years following human renal transplantation is achieved in a significant number of cases [*1*]. Chronic and late graft rejection, however, are problems of increasing concern in long-term survivors. Severe histologic abnormalities and presumptive evidence of continued immune attack have recently been reported in the overwhelming majority of successful long-term renal allografts [*2*].

The successful renal transplant controls body balance of electrolytes and water, and maintains a normal or nearly normal serum concentration of urea and creatinine. Since considerable renal damage may occur before overt disturbance of body homeostasis is evident under usual circumstances of stress, more exact study is necessary to assess the integrity and durability of chronic renal homograft function.

This study was undertaken to answer the following questions: (1) What degree of function can be achieved in a large group of renal transplant recipients? (2) Does progressive increase in function follow transplantation? (3) Does progressive deterioration of function occur in some or all renal allografts? (4) Does "normal" function imply histologic normality? (5) Does donor-recipient lymphocyte antigen compatibility correlate with transplant function? The answers to these questions are of importance to consideration of the clinical efficacy of renal transplantation.

METHODS

Twenty-nine patients who received renal allografts from living donors were studied eighteen to twenty-nine months following transplantation. These twenty-nine patients represent all but five of the thirty-

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TABLE I
RENAL FUNCTION TESTS AT TIME OF BIOPSY

Case No.	Months After Transplant	Prednisone Dose (mg./day)	GFR* (ml./min.)	ERPF† (ml./min.)	F.F. × 100‡	Urinary Osmolality (mOsm.)		Urinalysis		
						Minimum	Maximum	Protein	Red Blood Cells	Mononuclear Cells
LD 2	28	0	90.0	340	26.5	78	744	0	0	0
LD 3	26	0	104	524	19.8	147	818	...	...	...
LD 6	23	0	95.1	433	21.9	...	...	...	...	...
LD 12	29	15	71.9	228	31.5	243	684	0	Rare	0
LD 13	21	7.5	76.0	264	28.8	63	894	0	0	0
LD 14	21	0	116	394	29.3	68	771	...	...	...
LD 15	21	10	83.3	323	25.8	72	725	0	Rare	0
LD 18	26	20	53.8	110	49.0	144	417	0	Occ.	Rare
LD 25	25	0	53.4	187	28.5	79	709	1+	5	Rare
LD 27	19	12.5	53.6	198	27.0	125	495	0	0	0
LD 30	18.5	25	55.0	209	26.3	242	703	3+	0	0
LD 33	23	0	84.5	491	17.2	64	602	0	0	0
LD 36	18	0	58.3	323	18.1	210	426	2+	0	0
LD 37	23	7.5	66.0	365	18.1	...	...	0	Occ.	0
LD 39	23	7.5	73.0	314	23.2	58	412	0	10–12	Occ.
LD 40	23.5	7.5	113	456	24.8	207	498	0	0	0
LD 42	21.5	7.5	79.7	458	16.6	79	650	0	0	0
LD 45	25	15	39.0	273	14.3	120	487	2+	8–10	Occ.
LD 48	24	30	38.4	116	33.2	109	507	3+	3–5	0
LD 49	22	15	71.4	327	21.9	127	919	0	1–2	0
LD 50	23.5	7.5	74.2	345	21.5	162	819	0	0	0
LD 51	23	10	65.7	364	18.0	109	753	1+	6–8	Rare
LD 52	23	7.5	95.4	456	20.9	177	953	0	0	Occ.
LD 53	23	10	74.2	263	28.2	95	899	0	Occ.	Rare
LD 54	22	7.5	80.3	278	28.8	116	428	4+	Occ.	Occ.
LD 55	22.5	15	50.7	221	23.0	93	846	0	1–2	0
LD 58	22	10	93.9	370	25.3	159	984	0	0	0
LD 60	22	15	57.0	204	28.0	110	621	0	0	0
LD 63	21.5	15	70.0	342	20.5	141	819	0	0	0
Range	18–29	0–30	39.0–116	110–524	14.3–49.0	58–243	417–984			
Mean	22.9		73.7	316	24.7	126	688			
S.D.			20.1	108	6.7	54	179			
IDT 1	40	0	79.2	313	25.3	79	953	0	0	0
IDT 2	26.5	0	99.9	420	23.8	121	1,297	0	0	0

* GFR = inulin clearance corrected to 1.73 M². body surface area.
† ERPF = para-aminohippurate clearance corrected to 1.73 M². body surface area.
‡ F.F. = filtration fraction.

four two-year survivors from the initial group of sixty-four renal allograft recipients at this center. The five two-year survivors not included in this study were excluded because of technical difficulties in performing the clearance tests (one case), patient age of less than twelve years (two cases) or uncooperative attitude of the patient (two cases). Each of the patients is identified by the prefix LD (living donor) and a number. The same designation has been used in other reports from this center, from which additional details may be obtained [*3–5*]. Two additional patients who received renal transplants from their identical twins (IDT 1 and 2) were studied. All patients underwent bilateral nephrectomy before or at the time of transplantation except one (LD 2) who retained his right kidney. At the time of study all renal allograft recipients were receiving azathioprine daily, and twenty-two were receiving 7.5 to 30 mg. of prednisone daily. The two renal isograft patients were receiving no drugs.

Renal Function. Renal clearances of inulin and para-aminohippurate (PAH) were performed in the fasting state with the patient supine except when voiding. An oral water load was given one hour before the start of the infusion, and urine was replaced with an equal volume of water to maintain constant urine flow rate. Priming doses of inulin and PAH were calculated on the basis of body weight. Sustaining doses, based on estimated clearances, were administered in normal saline solution by constant infusion utilizing a Harvard Instrument Company pump Model No. 600-950. After allowing a minimum of forty-five minutes for equilibration, three thirty-minute urine collections were obtained by voiding in the standing or sitting position. Plasma samples were obtained before administration of the test substances and midpoint in the first and third collection periods. Plasmas and urines were analyzed for inulin by the method of Schreiner [*6*] and PAH by the method of Smith [*7*]. Glomerular filtration rate (inulin clearance) and effective renal plasma flow (PAH clearance) are expressed as the mean of values for the three collection periods, corrected to 1.73 M². body surface area [*8*].

Concentrating ability was assessed from a one hour voided specimen collected following a fourteen hour overnight total fast. An oral water load of 20 ml. per kg. of body weight was then administered, and voided urines were collected hourly for four hours to assess diluting ability. Osmolality was measured cryoscopically utilizing an advanced Instrument Osmometer Model No. 64-31.

Urinalyses were performed on freshly voided, first-morning specimens.

Renal Histology. Open renal biopsy was performed in each case. The tissue was fixed in 10 per cent neutral formalin or formol saline solution, embedded in paraffin, and serially sectioned in thin sections. Sections were stained in each case with hematoxylin and eosin, periodic acid-Schiff reagent, Weigert's for elastic counterstained with hematoxylin and van Gieson, picro-Mallory 5, Martius yellow-scarlet-blue, Mallory's phosphotungstic acid hematoxylin, and methyl green pyronin.

The presence or absence of the following seven major histopathologic features was determined: (1) fibrous thickening of the intima of the interlobular arteries; (2) hyalinization of the walls of the arterioles; (3) thickening of glomerular capillary basement membranes; (4) generalized interstitial fibrosis; (5) superficial subcapsular interstitial fibrosis; (6) cellular infiltration; and (7) tubular atrophy. The lesions present were arbitrarily graded in severity from 1 to 3, and the graded lesions summed to give a final score for each biopsy. A transplant showing all seven lesions in maximal degree would be scored as 21, whereas a graft displaying no abnormalities would be scored as 0. Grading was determined by one of us (K.A.P.) geographically separated from the patients and the other investigators, and without prior knowledge of the results of the function tests.

Lymphocyte-Antigen Matching. Blood lymphocytes obtained from each patient and donor were tested against a panel of 65-121 different cytotoxic antiserums in the presence of rabbit complement by a previously described technic [*9*]. Computer factor analysis based on act alike behavior permitted separation of antiserums into seven major groups. Each patient was then "typed" with respect to the presence or absence of each group by regression analysis [*10*]. An incompatibility was considered to be present whenever one or more group antigens were present in the donor but not in the recipient.

RESULTS

Renal Function. Table 1 details the time of study after transplantation, prednisone dosage, and the results of renal function studies and urinalysis in each case.

The twenty-nine renal allograft recipients averaged 22.9 months after transplantation at the time of study. Glomerular filtration rate (GFR) ranged from 39 to 116 ml. per minute with a mean of 73.7 ml. per minute per 1.73 M^2. Effective renal plasma flow (ERPF) averaged 316 ml. per minute per 1.73 M^2. with a range of 110 to 524. Mean filtration fraction (F.F.) $\times$ 100 was 24.7 with a range of 14.3 to 49.0. Figure 1 shows the relationship between GFR and ERPF in these twenty-nine patients. A positive correlation with a correlation coefficient of 0.78 ($p < 0.001$) is demonstrated.

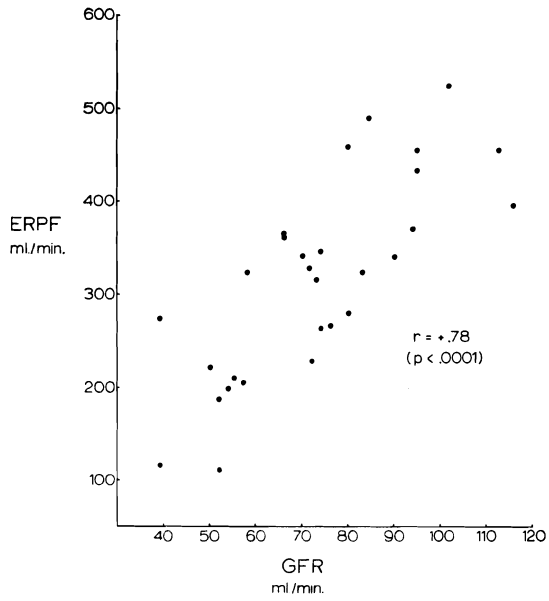

FIG. 1. Relationship between effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in twenty-nine renal allograft recipients.

The maximum urinary osmolality achieved with dehydration averaged 688 mOsm. with a range of 417 to 984. A positive correlation ($r = +0.41$, $p < 0.03$) between maximum osmolality and GFR is illustrated in Figure 2. Min-

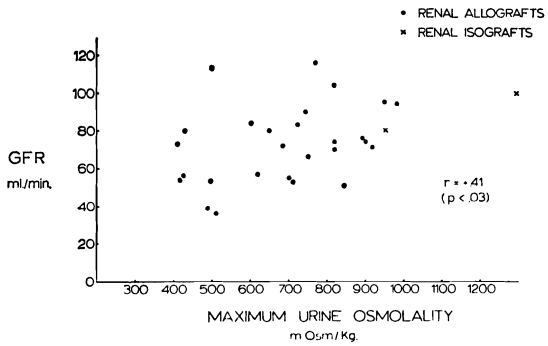

FIG. 2. Relationship between glomerular filtration rate and maximum urine osmolality following fourteen hours total fast in twenty-seven renal allograft recipients and two renal isograft recipients.

imum osmolality demonstrated after oral water loading ranged from 58 to 243, with a mean of 126 mOsm.

Seven of twenty-six patients demonstrated significant proteinuria. Four of the twenty-six showed more than 2 red blood cells per high power field in the centrifuged sediment, and eight of the twenty-six demonstrated rare or occasional mononuclear leukocytes in the sediment.

Identical studies of the two renal isograft recipients revealed a mean GFR of 89.6 and ERPF of 367 ml. per minute per 1.73 M^2. Mean F.F. × 100 was 24.6. Mean maximum and minimum urinary osmolality was 1,125 and 100 mOsm., respectively. Urinalysis was normal in both patients.

Three or more serial clearance studies were performed in four cases in the first two years after transplantation. The results of these studies are detailed in Table II. A change in GFR or ERPF of greater than 15 per cent of the initial value is considered to exceed methodological error and to represent a true change in function.

Two patients (LD 48 and LD 60) demonstrated a serial decrease in both GFR and ERPF in the second year after transplantation. Biopsy in these two cases coincident with the last clearance studies revealed cumulative scores of morphologic abnormality of 7 and 11, respectively. One patient (LD 45) revealed subnormal initial graft function, but demonstrated no significant change in function in the ensuing twenty-five months. Biopsy at twenty-five months demonstrated a score of 11. One patient (LD 2) showed a progressive increase in function at thirteen months and at twenty-eight months after transplantation. The histologic appearance of this kidney was normal at twenty-four months. Of these four patients, only one (LD 2) had a compatible donor by lymphocyte-antigen testing.

Renal Histology. Table III details graded histologic lesions and the presence or absence of donor-recipient lymphocyte compatibility.

Normal or nearly normal morphology was found in only four of the twenty-nine patients (LD 2, LD 6, LD 33 and LD 55). The remaining twenty-five demonstrated a spectrum of morphologic abnormality producing cumulative scores of 2 to 16 on the previously defined arbitrary scale of 0 to 21. A detailed report of the morphologic abnormalities in these cases has been published [2]. Figures 3 through 6 depict each of the major histologic abnormalities encountered.

Figure 7 indicates the relationship between graded cumulative morphologic abnormality and renal clearances. An inverse correlation of a low degree is demonstrated between GFR and cumulative morphologic abnormality ($r = -0.38$, $p < 0.05$) and between ERPF and abnormal morphology ($r = -0.34$, $p < 0.10$).

TABLE II
SERIAL RENAL CLEARANCES FOLLOWING TRANSPLANTATION*

Case No.	Months After Transplant	GFR† (ml./min.)	Net Change in GFR		ERPF‡ (ml./min.)	Net Change in ERPF	
			ml./min.	Per Cent		ml./min.	Per Cent
LD 2	8	62.2			233		
	13	67.5			273		
	28	89.0	+26.8	+43.1	336	+103	+44.2
LD 45	1/30	45.8			259		
	16	42.0			258		
	25	39.0	−6.8	−14.8	273	+14	+5.4
LD 48	12	61.9			192		
	13	68.0			162		
	16	52.0			139		
	24	41.5	−20.4	−33.0	125	−67	−34.9
LD 60	11	106			412		
	14	73.2			251		
	22	59.3	−46.7	−44.1	212	−200	−48.5

* Clearance values are uncorrected for body surface area since comparison is within the same patient, and since body weight increased markedly after transplantation.
† GFR = inulin clearance.
‡ ERPF = para-aminohippurate clearance.

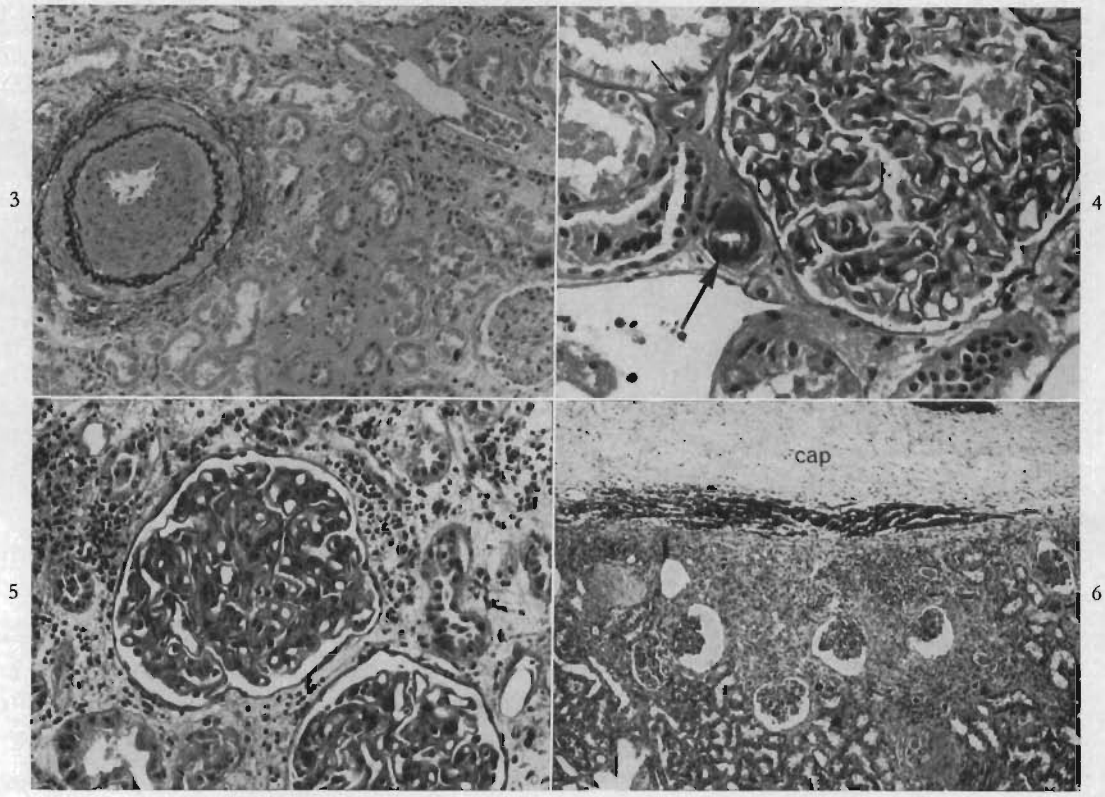

FIG. 3. LD 36. Fibrous thickening of the intima of an interlobular artery. The lumen of the vessel is greatly narrowed. There is also generalized interstitial fibrosis, and tubular atrophy. Elastic stain, original magnification × 150.

FIG. 4. LD 51. Hyalinization of the walls of arterioles. Deposits of homogenous, periodic acid-Schiff–positive material are present in the walls of the afferent (*broad arrow*) and efferent (*slender arrow*) arterioles. There is also some mesangial and capillary basement membrane thickening in the adjacent glomerulus. Periodic acid-Schiff reagent original magnification × 500.

FIG. 5. LD 45. Thickening of glomerular capillary basement membranes. Two glomeruli show periodic acid-Schiff–positive thickening of their tuft capillary basement membranes. There is also tubular atropy, interstitial fibrosis and cellular infiltration of the interstitium. Periodic acid-Schiff stain, original magnification × 300.

FIG. 6. LD 48. Superficial subcapsular interstitial fibrosis. The renal tissue immediately beneath the capsule (*cap*) is scarred; the deeper part of the kidney is relatively normal. In the scarred zone there is also cellular infiltration, tubular atrophy and glomerular damage. Hematoxylin and eosin stain, original magnification × 70.

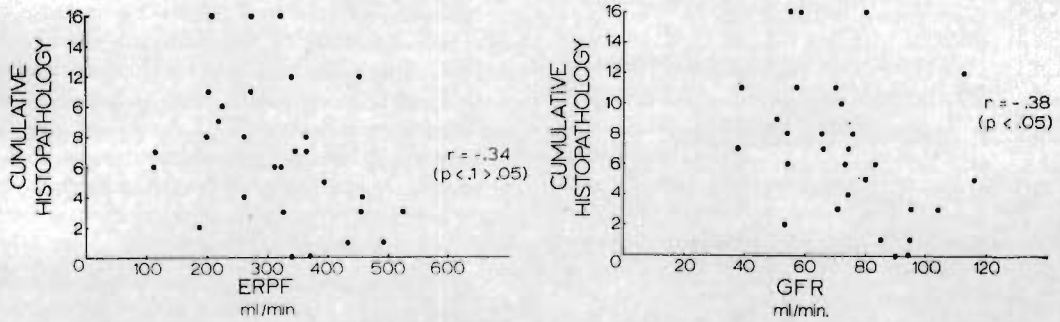

FIG. 7. Relationship between cumulative histopathology and effective renal plasma flow (*left*), and cumulative histopathology and glomerular filtration rate (*right*) in twenty-nine renal allograft recipients.

TABLE III
GRADED MORPHOLOGIC ABNORMALITY* AND DONOR-RECIPIENT LYMPHOCYTE COMPATIBILITY

Case No.	Type of Histopathologic Abnormality†							Cumulative Histopathologic Score	Lymphocyte Compatibility‡
	1	2	3	4	5	6	7		
LD 2	0	0	0	0	0	0	0	0	C
LD 3	0	0	2	0	1	0	0	3	C
LD 6	0	0	0	0	1	0	0	1	C
LD 12	2	1	1	1	2	1	2	10	C
LD 13	1	1	0	1	1	3	1	8	I
LD 14	0	2	0	1	0	1	1	5	C
LD 15	1	1	1	0	1	1	1	6	C
LD 18	2	1	0	1	0	1	1	6	I
LD 25	0	0	0	0	1	1	0	2	I
LD 27	2	1	1	1	1	1	1	8	I
LD 30	2	2	3	2	2	2	3	16	I
LD 33	0	0	0	0	1	0	0	1	C
LD 36	3	2	2	2	3	1	3	16	I
LD 37	1	0	1	1	2	1	1	7	I
LD 39	1	0	0	1	2	1	1	6	I
LD 40	2	2	2	1	2	2	1	12	I
LD 42	1	0	0	1	1	1	1	5	C
LD 45	2	2	3	1	1	1	1	11	I
LD 48	1	0	1	1	3	0	1	7	I
LD 49	0	0	0	1	1	0	1	3	C
LD 50	1	0	0	1	2	2	1	7	I
LD 51	1	2	1	1	1	1	1	8	I
LD 52	1	0	0	1	1	0	0	3	C
LD 53	0	1	0	1	1	1	0	4	C
LD 54	2	1	3	2	2	3	3	16	I
LD 55	2	1	1	1	1	2	1	9	I
LD 58	0	0	0	0	0	0	0	0	C
LD 60	0	0	1	2	3	3	2	11	I
LD 63	1	1	3	2	2	2	1	12	C

* See text for details of grading system.

† Type 1 = fibrous thickening of intima of interlobular arteries; type 2 = hyalinization of walls of arterioles; type 3 = glomerular capillary basement membrane thickening; type 4 = interstitia fibrosis—generalized; type 5 = interstitia fibrosis—superficial subcapsular; type 6 = cellular infiltration; and type 7 = tubular atrophy.

‡ C = compatible; I = incompatible.

The latter is of borderline statistical significance.

Lymphocyte-Antigen Compatibility. In thirteen of the twenty-nine donor-recipient pairs, the donor demonstrated no antigen group not shared by the recipient, and compatibility was said to exist. In eleven instances recipients demonstrated one, and in five instances two antigen groups not present in the donor, and incompatibility was said to exist (Table III).

Figure 8 depicts a comparison of renal clearances in the compatible and incompatible groups. Mean GFR was 86.9 ml. per minute per 1.73 M^2. in the compatible and 63.0 ml. per minute per 1.73 M^2. in the incompatible group. This difference is statistically significant ($p < 0.001$). Mean ERPF was 381 ml. per minute per 1.73 M^2. in the compatible and 264 ml. per minute per per 1.73 M^2. in the incompatible group, a difference which is also statistically significant ($p < 0.01$). The numbers of patients with incompatibilities in each antigen group were too few to permit comparison of function between particular antigen group mismatches.

In the thirteen patients with compatible donors, GFR and ERPF were significantly greater than half the donors' initial predicted function* ($p < 0.001$ and < 0.05, respectively). In contrast, in the sixteen patients with incompatible donors, no difference was found between measured functions and half of the donors' initial predicted function.

COMMENTS

There has been little assessment of the integrity or durability of renal function in renal transplant recipients. Normal GFR and ERPF, normal ability to concentrate and dilute and to acidify and alkalinize the urine, normal response to salt-retaining steroids and to diuretics, and the ability to maintain a normal extracellular fluid volume have been demonstrated in single, identical twin transplants, within the first several months after transplantation [*12,13*]. Serial measurements of GFR and ERPF for nine [*12*] and twelve [*13*] months in the same two isografts showed neither progressive improvement nor deterioration of these parameters of function.

In five of six renal allograft recipients, normal GFR and ERPF have been documented within twenty-four hours of transplantation [*14*]. In the same patients tubular reabsorption of glucose, sodium and solute-free water, and tubular excretion of potassium were demonstrated. The effect of graft rejection and rejection reversal on GFR and solute excretion has also been reported [*15*].

This study documents renal function in all available renal allograft recipients two years after transplantation, and compares function with concomitant histopathology and with

* Predicted donor function was based on normal values for each sex [*11*]. Comparison of present recipient function with one half of the predicted donor function was accomplished by the paired-difference technic.

donor-recipient lymphocyte-antigen compatibility. It is to be noted that in all but one of the patients studied, bilateral nephrectomy had been accomplished before or at the time of transplantation, assuring a single source of urine production. It is reasonable to assume that patients with the poorest function succumbed in the early months after transplantation, and that those surviving at the time of this study represent a natural selection of the best functional results.

In the entire group of twenty-nine patients studied an average of 22.9 months following transplantation, the mean GFR of 73.7 ml. per minute per 1.73 M^2. was greater than half of the donors' predicted original function ($p < 0.001$). However, the mean ERPF of 316 ml. per minute per 1.73 M^2. was not significantly different than half of the predicted initial donor function. This finding is reflected in the greater than normal mean filtration fraction of 24.7 found in the transplant recipients. No correlation was found between the presence of significant arterial and arteriolar changes and high filtration fraction. Vascular lesions, however, did not occur alone but were invariably accompanied by significant other histopathology.

The mean maximum urine concentration of 688 mOsm. following fourteen hours of dehydration is below the mean value reported for both healthy [*16*] and hospitalized subjects [*17*]. The mean minimum urine concentration of 126 mOsm. evidenced after a 20 ml. per kg. body weight water load is above the reported normal minimum [*18*]. In a patient with a single kidney and less than normal GFR, the solute load per nephron would be increased, and both concentrating [*19*] and diluting ability [*20*] would be expected to be compromised. Indeed, a positive correlation between GFR and concentrating ability was demonstrated. Although information concerning only two renal isografts is reported, maximum concentration achieved by these patients was greater than that achieved by twenty-seven of the twenty-nine allograft recipients. Since the GFR of many of the renal allografts was greater than that of the isografts, some factor compromising renal concentrating ability other than solute load is suggested. Twenty-two of the twenty-nine allograft recipients were still receiving steroids at the time of study. It is probable that these patients had an expanded extracellular fluid

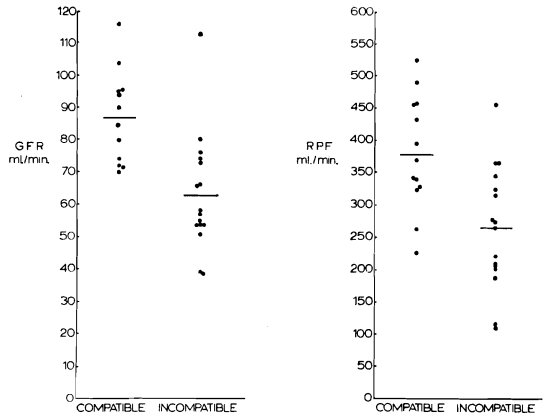

FIG. 8. Comparison of glomerular filtration rate (*left*), and effective renal plasma flow (*right*), in thirteen patients with compatible and sixteen patients with incompatible donor-recipient lymphocyte-antigen matches. The solid line in each group of values represents the mean.

volume and that fourteen hours of dehydration would not, therefore, be expected to produce the same degree of dehydration and urine concentration as in normal subjects with comparable solute loads. Mineralocorticoid administration also increases free water clearance [*21*] and might explain part of the compromised concentrating ability demonstrated by these patients. It is apparent from these studies that a significant impairment in renal handling of water exists under the conditions of treatment two years following transplantation. Although this impairment is not sufficient to produce symptomatic dehydration or water retention under normal circumstances, it must be considered in treating these patients during illness leading to dehydration and during conditions of water loading.

A rapid increase in function of the remaining kidney follows uninephrectomy in healthy adults [*22*]. Although the mechanism or mechanisms effecting renal hypertrophy and increase in function are poorly understood, cross circulation experiments [*23*] and the ability of serum from rats with uninephrectomy to increase tritiated thymidine uptake of renal cells of intact animals [*24*] suggest the primacy of circulating rather than neurogenic factors. It is logical to assume, therefore, that hypertrophy and increase in function of the transplanted kidney might also occur if damage from rejection is controlled.

Glomerular hypertrophy and hypertrophy of the juxtaglomerular body have been found to

be usual features of allografts in living recipients [2]. The present study demonstrates that renal clearances in patients with compatible donors, but not in patients with incompatible donors, were clearly greater two years after transplantation than the 50 per cent of the donor's initial predicted function which should result from transplantation of a single kidney. Serial clearance studies revealed increasing function over twenty-eight months in a single patient with a compatible donor (LD 2). Biopsy in this case revealed normal histology. These findings support the concept that renal hypertrophy and increase in function follow transplantation when immune reaction is minimal. In contrast, stable or serially decreasing function was documented in three patients with an incompatible donor, and significant histopathology was found on biopsy of these kidneys. Durability of renal function as much as two years following transplantation appears to relate to initial donor-recipient compatibility.

Measured clearance values were adjusted to 1.73 M^2. body surface area from the recipient's estimated surface area. This correction produced little change in mean data and no change in the interpretation of results. The recipients', not the donors', body surface area was used since it was thought that factors influencing renal function were more likely to reside in the host than in the kidney itself.

Although an inverse correlation was found between scored cumulative histopathology and renal clearances, it is apparent from Figure 7 that histopathology cannot be predicted accurately from measured function, nor function from histologic abnormality. The presence of normal function, therefore, does not imply the absence of histologic abnormality or even of continued immune reaction in the renal parenchyma or vasculature. Serial biopsy of renal transplants is impractical and attended by significant risk. A simple test of blood or urine which reflected immune activity would be of great value in the long-term control of immunosuppressive therapy.

Although recipients with an incompatibility by lymphocyte antigen testing of donor and recipient had a lower mean GFR and ERPF than those without an incompatibility, it is apparent from Figure 8 that there is considerable overlap between the two groups. The presence of a donor-recipient mismatch by this test does not preclude excellent function of the graft. It is suggested that improved typing technics should permit more precise anticipation of the functional result, and that such technics will play an increasing role in selecting donor-recipient pairs suitable for successful transplantation.

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