Reprinted from ANNALS OF SURGERY, Vol. 162, No. 4, October, 1965
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Chronic Survival After Human Renal Homotransplantation *

Lymphocyte-Antigen Matching, Pathology and Influence of Thymectomy

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FROM November 24, 1962 to March 30, 1964, 64 uremic patients were treated with renal homografts obtained from living volunteer donors other than identical twins. Thirty-seven of the original group lived for at least 1 year and 36 are still alive 13½ to 30 months after operation. Numerous post-transplant function studies have been obtained, and in the 8 patients with the longest follow up, homograft biopsies were performed from 21 to 24 months postoperatively. The recipients who are still alive were examined with a lymphocyte cytotoxicity test for the degree of antigenic matching with their respective donors to determine by retrospective analysis whether this method might be helpful in evaluating the results as well as in the selection of donors for future cases.

Methods

The surgical and postoperative technics employed have been documented elsewhere [57] and were based upon the pioneering methods developed in animals and man by Calne,[4-6] Dempster and Shackman,[12, 13, 52] Goodwin,[19-21] Hamburger,[23-25] Hume,[28-30] Küss,[33-36] Murray, Merrill and Harrison,[42-44] Simonsen [54] and Woodruff [69] and their associates. Azathioprine † was used for immunosuppression in every case, and prednisone in all but two. Actinomycin C and local homograft irradiation [31] were employed irregularly. One patient received 400 r total body iradiation. In 6 instances there was immediate or very early failure of the initial homograft. In these cases a second kidney was provided 6 to 47 days after the original operation (Table 1), and for statistical comparisons only the second or definitive donor is considered. All 64 patients had splenectomy before or at the time of homotransplantation. Bilateral nephrectomy was performed in all but three. Seventeen patients had thymectomy, 8 before and 9 from 250 to 520 days after transplantation.

The causes of mortality in this series during the first postoperative year,[57, 58, 60] as well as the pathologic changes in the homografts from these unsuccessfully treated pa-

* Presented before the American Surgical Association, May 12–14, 1965, Philadelphia, Pa.

** Markle Scholar.

Aided by Grants AM 06283, AM 06344, HE 07735, AM 07772, AI 04152, FR 00051, AM 02375, AI 04444, and AM 7513 from the United States Public Health Service; and by a grant from the Medical Research Council of Great Britain.

† Imuran® supplied by Burroughs Wellcome & Co., Tuckahoe, New York.

TABLE 1. *Sixty-four Consecutive Patients Treated with Renal Homografts from Living Donors (LD Series)*†

LD #	Age-Sex	Date of Operation	Living or Dead	Duration Survival (Days)	Donor-Recip. Blood Types	Donor Relation	CCr	BUN	BP	Prednisone
1*	12-M	11-24-62	Living	900	B+ to B+	Mother	100.2	20	100/62	—
2*	38-M	1-31-63	Living	832	B+ to A+	Sister	98	16	110/80	—
3*	21-M	2- 9-63	Living	823	A+ to A+	Frat. Twin	136.1	12	110/80	—
4*	35-M	2-25-63	Dead	113	A+ to AB+	Unrelated F	—	—	—	—
5*	50-M	3-26-63	Dead	11	A+ to A+	Unrelated M	—	—	—	—
6*	23-M	4-17-63	Living	756	O+ to O+	Brother	123.9	14	122/78	—
7	25-M	5- 3-63	Dead	79	O+ to A+	Unrelated F	—	—	—	—
8	29-M	5- 8-63	Dead	62	O+ to O+	Brother	—	—	—	—
9*	30-M	5-10-63	Dead	207	O+ to A+	Frat. Twin	—	—	—	—
10	47-M	5-15-63	Dead	295	O+ to O−	Unrelated M	—	—	—	—
11*	35-M	5-17-63	Dead	24	O+ to O+	Brother	—	—	—	—
12	48-M	6- 7-63	Living	705	A+ to A+	Brother	65	21	140/90***	15
13**	15-M	7- 3-63	Living	679	A+ to A+	Mother	105.3	18	104/68	7.5
14	42-M	7- 5-63	Living	677	A− to A−	Brother	102.8	13	130/80***	—
15**	23-M	7- 8-63	Living	674	O+ to A−	Brother	140.7	16	132/78	7.5
16	44-F	7-12-63	Dead	83	A− to A+	Brother	—	—	—	—
17	15-F	7-19-63	Living	663	O− to O+	Mother	58	10	140/96	2.5
18	39-M	7-24-63	Living	658	O+ to O+	Sister	100.3	31	126/90***	15
19	17-M	(1) 7-26-63	Removed 7-26-63	—	A+ to O+	Mother	—	—	—	—
		(2) 8- 9-63	Dead	95	O+ to O+	Unrelated M	—	—	—	—
20	6-M	7-29-63	Dead	202	A− to O+	Mother	—	—	—	—
21	41-M	7-31-63	Dead	76	O− to A+	Unrelated F	—	—	—	—
22**	15-F	8-12-63	Living	639	O+ to O+	Mother	80	19	120/58	7.5
23	47-M	(1) 8-16-63	Removed 8-16-63	—	B+ to O+	Brother	—	—	—	—
				—	B+ to O+	Brother	—	—	—	—
		(2) 8-26-63	Dead	405	O+ to O+	Unrelated M	—	—	—	—
24	42-M	8-19-63	Dead	37	A+ to A+	Unrelated M	—	—	—	—
25	33-M	8-21-63	Living	630	O+ to O+	Brother	91	19	114/80	2.5
26	16-F	8-29-63	Dead	1	A+ to A+	Father	—	—	—	—
27	20-F	9- 3-63	Living	617	A+ to A+	Unrelated M	51.1	20	108/78	15
28	49-M	9- 6-63	Dead	25	A+ to A−	Sister	—	—	—	—
29	40-M	(1) 9-23-63	Removed 9-25-63	—	AB+ to AB+	Sister	—	—	—	—
		(2) 10 -3-63	Dead	8	AB+ to AB+	Unrelated M	—	—	—	—
30**	40-M	9-30-63	Living	590	O+ to O+	Unrelated M	81.3	37	162/90 ***	25
31	55-M	10- 1-63	Dead	15	A+ to A+	Unrelated M	—	—	—	—
32	20-M	10- 4-63	Dead	41	A+ to A+	Brother	—	—	—	—
33	18-F	10- 7-63	Living	583	A+ to A+	Mother	93.8	15	120/70	—
34	8-F	10-11-63	Living	579	O+ to O+	Mother	63.3	17	98/60	—
35	38-M	(1) 10-12-63	Removed 11- 2-63	—	A+ to A+	Unrelated M	—	—	—	—

TABLE 1.—*Continued*

LD #	Age-Sex	Date of Operation	Living or Dead	Duration Survival (Days)	Donor-Recip. Blood Types	Donor Relation	CCr	BUN	BP	Prednisone
		(2) 11-20-63	Dead	9	A+ to A+	Sister	—	—	—	—
36	43-M	10-14-63	Living	576	O+ to B+	Unrelated F	61.2	35	126/74***	15
37	21-M	10-18-63	Living	572	O+ to O+	Mother	107.1	19	118/80***	7.5
38	21-M	11- 9-63	Dead	38	A+ to A+	Mother	—	—	—	—
39	17-M	11-13-63	Living	546	O− to O−	Mother	76.2	20	132/92***	10
40**	21-F	11-16-63	Living	543	O− to O+	Mother	64.9	24	130/70***	7.5
41**	3-M	11-23-63	Living	536	A+ to A+	Mother	30	24	108/78***	7.5
42	19-F	11-27-63	Living	532	O+ to O+	Father	84.5	26	112/76	7.5
43	25-M	12 -3-63	Dead	38	O+ to O+	Mother	—	—	—	—
44	48-M	12- 7-63	Living	522	O+ to A+	Sister	57	33	120/86***	12.5
45	35-M	12-10-63	Living	519	A+ to A+	Sister	54	18	122/70***	15
46	25-F	1- 3-64	Dead	43	O− to O+	Unrelated M	—	—	—	—
47**	37-M	1- 4-64	Living	494	A+ to A+	Brother	56.5	70	126/90***	60
48	34-M	1-10-64	Living	488	B+ to B+	Sister	73.8	35	170/100***	30
49	32-M	(1) 1-15-64	Removed 1-22-64	—	A+ to A+	Sister	—	—	—	—
		(2) 3- 3-64	Living	435	A+ to A+	Sister	59	18	118/80***	12.5
50**	16-F	1-25-64	Living	473	A+ to A+	Father	91.8	26	98/52***	15
51	18-M	2-10-64	Living	457	O+ to O+	Maternal Aunt	77.6	28	110/74***	10
52	15-F	2-17-64	Living	450	O+ to O+	Father	85.1	20	138/86***	7.5
53	15-M	2-22-64	Living	445	O+ to O+	Maternal Uncle	89.6	19	120/96***	10
54**	21-M	2-24-64	Living	443	O− to O−	Unrelated M	97.3	17	120/90***	12.5
55	21-M	2-26-64	Living	441	O+ to O+	Father	71.6	16	110/80***	10
56	26-F	2-28-64	Dead	155	A+ to A+	Mother	—	—	—	—
57	36-F	(1) 3-12-64	Not removed	—	O+ to O+	Mother	—	—	—	—
		(2) 3-18-64	Dead	71	O+ to O+	Unrelated M	—	—	—	—
58	27-M	3-13-64	Living	425	A+ to A+	Sister	83.3	16	132/82***	10
59	48-M	3-16-64	Dead	45	B+ to B−	Unrelated F	—	—	—	—
60	21-M	3-17-64	Living	421	O+ to O+	Cousin	86.8	28	124/80***	15
61	5-F	3-23-64	Dead	36	O+ to O+	Mother	—	—	—	—
62	38-M	3-24-64	Dead	110	O+ to A+	Sister	—	—	—	—
63	35-M	3-27-64	Living	411	A+ to A+	Unrelated M	112	21	140/80***	15
64	30-M	3-30-64	Dead	65	O− to O+	Brother	—	—	—	—

† Survival is to 12 May 1965. For patients still living, the creatinine clearance (CCr), BUN, blood pressure (BP) and prednisone dose are those recorded in April and early May of 1965. Additional details on all the cases have been published, using the same code numbers[57].

* Thymectomy before transplantation.

** Thymectomy from $8\frac{1}{2}$ to 17 months after transplantation.

*** Receiving antihypertensive drugs (Chlorothiazide, Hydralazine, Reserpine or methyl DOPA).

tients [47, 49, 58] have been described. In this report, attention will be confined to the subsequent mortality and to the histologic alterations in the homografts after residence in the host for 1 year or longer. In 8 cases, specimens for light and electron microscopy were obtained with a large open wedge biopsy from 21 to 24 months postoperatively, and in a ninth patient tissues became available from an autopsy at 13½ months. Material for examination by light microscopy was fixed in formalin and Carnoy's solution. The biopsy specimens were then completely serially sectioned. The stains used routinely were: hematoxylin and eosin, periodic acid Schiff reagent, Weigert's for elastic tissue (counterstained with hematoxylin and van Gieson), picro-Mallory 5, Martius scarlet blue, Mallory's phosphotungstic acid hematoxylin (PTAH) and methyl green pyronin. Other special stains were used when indicated. Fragments of kidney obtained at biopsy for examination by electron microscopy were fixed in Palade's buffered osmium tetroxide solution and embedded in an epoxy resin.†† Thin sections, stained with phosphotungstic acid or lead, were examined with a Siemen's Elmiskop I electron microscope.

The blood urea nitrogen (BUN) and creatinine clearance (CCr) were the most valuable routine measures of renal function. In 12 patients, inulin and para-aminohippurate (PAH) clearances were determined in triplicate in a fasting steady state by the methods of Schreiner [51] and Smith,[55] respectively. The ability of the homograft to concentrate and dilute urine was measured after a complete 14-hour overnight fast and a subsequent oral waterload (20 ml./Kg.); urine osmolality was measured by a standard cryoscopic technic.

The lymphocyte antigens of the surviving patients and their donors were analyzed from blood specimens shipped to Los Angeles, employing a modification of a previously described technic [64, 65] by which the lymphocytes are isolated by differential adherence of granulocytes on small glass beads and by lysis of erythrocytes with hypotonic balanced salt solutions. The lymphocytes of each individual were then reacted with a panel of 65 to 135 different antisera, using rabbit complement. The cytotoxic antisera * were obtained from blood donors who had been accidentally or deliberately sensitized to white blood cell antigens: women with multiple abortions or pregnancies, patients who had received multiple blood transfusions or volunteers who were deliberately immunized with either skin homografts or lymphocytes. The maximum potential reactivity (weight) of all the antisera had been defined on a unit basis by preliminary standardization. Using phase contrast microscopy the lymphocytotoxic properties of the antisera were determined at various dilutions, beginning with 0.003 ml. serum in the first droplet and proceeding with 1:3 dilutions thereafter. A serum which completely destroyed all test cells at the first dilution and none at the second was defined as having a one unit weight; destruction of all cells in the first dilution and 50 per cent in the second would imply a 1.5 unit weight. A 6 unit weight meant that the possibility of complete cytotoxicity was present through 6 dilutions. The weights of the antisera used ranged from 1 to 6 units.

Application of this technic to the study of the 36 surviving patients and their donors allowed both a qualitative and quantitative evaluation of their antigen differences (Table 2). When both members of a pair reacted the same to an antiserum, or if antigens not represented in the donor were demonstrable in the recipient, a mismatch

†† Araldite M® supplied by Ciba (A.R.L.) Ltd., Duxford, Cambridge, England.

* The following people donated sera to the antiserum panel: Drs. Ruggero Ceppellini, Jean Dausset, Rose Payne, Jon J. Van Rood and Roy Walford.

TABLE 2. *Mismatched Cytotoxicity Reactions of Donor-Recipient Pair LD 25**

Antiserum no.	20	21	24	46	50	58	64	68	81	94	101	106	122	128	154	155
Antiserum wt.	3	2	4	2	2	4	6	4	3	5	4	5	6	3	5	6
Cytotoxicity units—donor	2.3	0.9	1.6	0.3	1.5	2.9	4.0	3.0	0.6	1.4	2.0	2.6	6.0	1.6	4.3	5.3
Cytotoxicity units—LD 25	1.9	0	0	0	0	1.7	3.0	2.9	0	0	1.9	2.0	5.9	0.9	3.6	1.3
Units mismatch—complete		0.9	1.6	0.3	1.5				0.6	1.4						
Units mismatch—partial	0.4					1.2	1.0	0.1			0.1	0.6	0.1	0.7	0.7	4.0

* A total of 106 antisera were in the panel used. Only those antisera are shown which demonstrated incompatibility of the donor with the recipient. Note the distinction between complete and partial mismatches. See text for terminology.

was not considered to be present. Antigens present in the donor but not in the recipient were considered to be complete mismatches, the magnitude of antigen reactivity being defined by the units described above. If strong antigens were measurable in the donor lymphocytes and similar weak ones in the recipient cells, these were termed partial mismatches and also quantitated by their reactivity with the standard antisera. Thus, for every case it was possible, within the limits of the testing panel, to delineate the individual complete and partial antigen differences (Tables 2, 12), to estimate roughly the magnitude of these differences relative to the maximum possible disparity and to obtain a total picture of the measured dissimilarities which might be predicted to evoke a recipient antibody response. Several methods of expressing the degree of incompatibility were employed, utilizing the IBM 7094 computer.**

** Doctor M. R. Mickey, Jr. and Mr. Donald Goyette assisted in devising the programming for this analysis.

TABLE 3. *Time of Mortality after Homotransplantation to 64 Patients*

	Mean Survival		Range
	No.	(da.)	(da.)
Dead 1st 4 mo.	23	51.7	1–113
Dead 2nd 4 mo.	3	188	155–207
Dead 3rd 4 mo.	1	295	295
Dead after 1 yr.	1	405	405

Results

General Observations

Mortality During First Year. Twenty-three of 27 deaths in the first year were within 120 days after operation, three more were in the ensuing 4 months, and only one patient died in the final third of the first year (Table 3). The causes of failure and the pathologic findings in all these cases have been reported.[49, 57, 58]

Mortality and Survival After 1 Year. Only one of the remaining 37 homograft recipients died after 1 year (Table 3); the other 36 are alive from 411 to 900 days after homotransplantation (Table 4), with a mean survival of 19 months. For each patient still living, the number of days of survival after receipt of their definitive homograft is listed in Table 1. Since no patient has had a late second homograft, these data are identical with those of homotransplant function. Four patients are into their third year, 16 are 1.5 to 2 years, and 16 more have lived for 13.5 to 18 months.

TABLE 4. *Mortality and Survival in 64 Consecutive Patients Who Received Renal Homografts from Volunteer Living Donors 13½ Months or Longer Ago*

Total no. patients	64 (100%)
Died within 1st year	27 (42.2%)
Survived at least 1 year	37 (57.8%)
Died after 1 year	1 (1.56%)
Survived to date (12 May 1965)*	36 (56.25%)

* Mean survival of the 36 patients still alive is 576 days.

TABLE 5. *Effect of Genetic Relationship of Donor Upon 1-year Survival**

	No.	Survival 1 Year
Unrelated donor	18	6** (33.3%)
All related donors	46	31 (67.4%)
Parental	20	14 (70%)
Sibling	23	14 (60.9%)
Aunt, uncle or cousin	3	3 (100%)

* When two homografts were required, only the second or definitive donor is recorded. The difference in results between the related and unrelated groups is significant ($P < 0.01$).

** One of these patients died after 13½ months.

Cause of Death After 1 Year. A 48-year-old man, who originally had polycystic kidney disease (LD 23, Table 1), died 405 days after homotransplantation from a nonrelated donor. Despite a mild early rejection episode, there was excellent renal function until a more severe attempt at homograft repudiation after 223 days, which was apparently precipitated by discontinuance of prednisone.[58] The late rejection was reversed by resumption of steroid therapy, local homograft irradiation and administration of 400 μg. actinomycin C every 5 to 14 days. The depressed CCr and elevated BUN returned to 55 to 85 ml./min. and 25 to 40 mg./100 ml., respectively, despite which hypertension persisted. A renal arteriogram in June 1964 (by Dr. John Bergan of Chicago) showed patency of the major vessels but a generally reduced diameter of the peripheral branches (Fig. 1, left). The patient worked daily until September 1964 when he developed progressive jaundice. Although the azathioprine dose was halved and later discontinued (by Dr. C. Larkin Flanagan of Chicago), he became leukopenic, developed a gram-negative septicemia and died on October 4, 1964.

At autopsy (performed by Dr. G. A. Lorenzo, Chicago Wesley Memorial Hospital), he was found to have bilateral bronchopneumonia and a retroperitoneal abscess in the old left nephrectomy bed from which the same organisms were cultured as were in the blood stream. The liver weighed 2,500 Gm. Microscopically there was acute liver necrosis involving primarily the centrilobular area and fat ac-

TABLE 6. *Influence of Donor and Recipient Blood Types Upon 1-Year Survival**

Blood Type	No.	No. 1 Yr. Surv.	Deaths in 1st Year
Type O recipient with:			
Related O donor	20	15 (75%)	5
Unrelated O donor	7	3* (43%)	4
Related A donor	1	0 (0%)	1
Type A recipient with:			
Related A donor	18	11 (61%)	7
Unrelated A donor	5	2 (40%)	3
Related O donor	4	2 (50%)	2
Unrelated O donor	2	0 (0%)	2
Related B donor	1	1 (100%)	0
Type B recipient with:			
Related B donor	2	2 (100%)	0
Unrelated B donor	1	0 (0%)	1
Unrelated O donor	1	1 (100%)	0
Type AB recipient with:			
Unrelated AB donor	1	0 (0%)	1
Unrelated A donor	1	0 (0%)	1
Total	64	37	27

* For the 6 patients who received a second homograft, because of immediate or early failure of the first transplant, only the second or definitive donor is tabulated.

** One of these patients subsequently died after 405 post-transplant days.

TABLE 7. *Relation of Original Renal Disease to 1-year Survival*

	No.	Related Donors	Alive 1 Year
Glomerulonephritis	49	37	32 (65.3%)
Pyelonephritis	10	6	3 (30%)
Polycystic kidney disease	3	1	2* (66.7%)
Congenital renal hypoplasia	1	1	0 (0%)
Surgical removal of sole kidney	1	1	0 (0%)

* One of these patients died after 13½ months. See text.

TABLE 8. *Effect of Age on 1-year Survival*

Age	No. Patients	No. 1-year Survivals	Non-related Donors
0–10	4	2	0
11–20	15	12	2
21–34	20	12	3
35–44	17	8	8
45–55	8	3	5
Total	64	37	18

TABLE 9. *Incidence and Effect of Late Rejection (after 3 Months) in 64 Patients of LD Series*

Patient (LD No.)	Days After Oper.	Days After Steroid Change*	Alive or Dead (May 1965)	Permanent Functional Damage
10	229	103	Died of rejection at 295 da.	Yes
12	300	154	Alive at 705 da.	Yes
13	240	20	Alive at 679 da.	No
22	244	60	Alive at 639 da.	No
23	223	16	Died of hepatitis & septicemia at 405 da.	Yes
30	112	30	Alive at 590 da.	Yes
41	290	30	Alive at 536 da.	Yes
47	270	50	Alive at 494 da.	Yes
48	390	150	Alive at 488 da.	Yes

* In 5 of the 8 cases prednisone had been stopped. For LD 30, the dose had been reduced from 45 to 30 mg/ day. For LD 41, 47 and 48, doses had been dropped from 5, 20 and 20 mg to 2.5, 15 and 15 mg/day, respectively.

cumulation in the remaining hepatocytes. In addition there was reticulin condensation and chronic fibrosis which was concentrated around and often interconnected the portal tracts. Lymphocytes, plasma cells, macrophages and occasional neutrophiles were in the portal areas.

Influence of Donor Genetic Relationship upon Mortality. More than two thirds of all patients treated with homografts from related donors are still alive (Table 5). With parent to offspring transfers, the survival after 13½ to 30 months is 70 per cent, slightly but not significantly greater than that with sibling donations (60%). Three patients who received a kidney from an aunt, uncle or cousin are also well.

The results after homotransplantation from unrelated donors are less favorable (Table 5). Six of 18 patients in this group lived for at least a year, but one subsequently died. The other five have stable homograft function 617, 590, 576, 443 and 411 days post-transplantation (mean 527 days).

TABLE 10. *Renal Function Tests—Adult Patients With Related Donors*

LD #	Survival @ Time of Study (Mo.)	GFR* (ml./min.)	ERPF** (ml./min.)	F.F.†	U_{osm} (mOsm./L.) Min.	U_{osm} (mOsm./L.) Max.	% of Water Load Excreted in 3 Hours
2	28	89.0	336	26.5	78	744	81.4
3	26	115	582	19.8	147	818	45.3
6	23	100	456	21.9			
12††	22.5	55.7	236	23.6	165	447	24.1
13††	21	76.0	264	28.8	63	894	97.0
14	21	115	392	29.3	68	771	97.4
15	21	95.3	370	25.8			
Mean	23.8	92.3	377	25.1	104	738	69.0

* Measured as inulin clearance.
** Measured as PAH clearance.
† Filtration fraction ($C_{in}/C_{PAH} \times 100$).
†† Had a previous late rejection. Note that these patients have the poorest function.

TABLE 11. *Renal Function Tests—Adult Patients With Unrelated Donors*

LD #	Survival @ Time of Study (Mo.)	GFR* (ml./min.)	ERPF** (ml./min.)	F.F.†	U_{osm} (mOsm./L.) Min.	U_{osm} (mOsm./L.) Max.	% of Water Load Excreted in 3 Hours
27	19	48.3	179	27.0	125	495	31.4
30††	18.5	56.0	213	26.3	242	703	28.7
36	18	62.0	343	18.1	210	426	46.7
54	12	70.7	266	26.6			
63	13	64	337	19.0	176	778	53.3
Mean	16.1	60.2	268	22.5	188	600	40.3

* Measured as inulin clearance.
** Measured as PAH clearance.
† Filtration fraction ($Cin/C_{PAH} \times 100$).
†† Had a previous late rejection.

Influence of Blood Types upon Results. The blood types of the donors and recipients in each case are given in Table 1 and summarized in Table 6. In an earlier report it was observed that recipients of A blood group who received kidneys from A-type donors had a high ultimate failure rate compared to patients with O, A and B

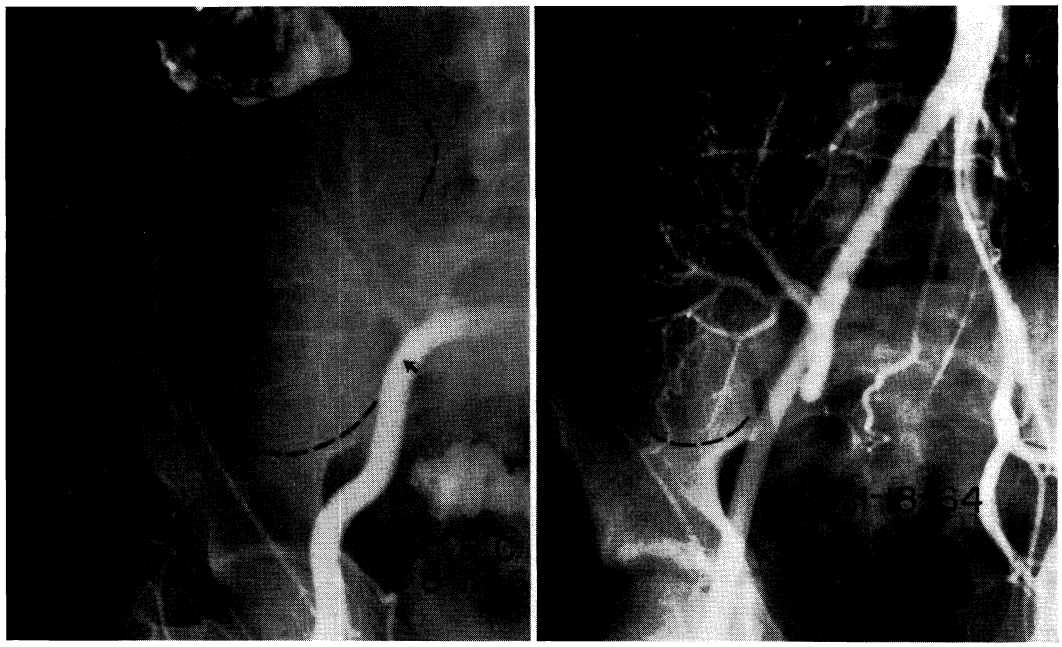

FIG. 1. Arteriograms of renal homografts. (Left) Patient LD 23, 10 months after homotransplantation. Arrow indicates end-to-side renal artery-iliac artery anastomosis. Note reduced caliber of the intrarenal vessels. Patient had suffered a late rejection several months earlier and had become hypertensive. He died from nonrenal causes 4 months after this x-ray and histologic studies of the homograft showed severe obliterative arterial lesions. (Right) Patient LD 1, 2 years after operation. Blood pressure was 100/70. Vascularity of the transplant seems normal. Despite this, biopsy on the same day revealed obliterative lesions of smaller vessels (Fig. 9, 12). Excellent function was present before and in the 6 months after examination. Note iatrogenic dissection of contralateral common and external iliac arteries by the catheter for which excision and prosthetic replacement of the entire iliac system was necessary.

TABLE 12. *Summary of Cytotoxicity Reactions in 36 Long-Term Donor-Recipient Pairs*†

Patient (LD No.)	Total No. Sera c̄ Complete Mismatches	Total No. Sera c̄ Complete Matches	% Sera c̄ Complete Mismatches	Complete Units Mismatch	Total Units Mismatch	Total Weight of Units Tested	% Total Units Mismatch
			Related				
44	1	79	1.2	1.0	2.0	276	0.7
1*	3	110	2.7	2.5	6.1	344	1.8
3*	5	101	4.7	4.6	10.5	311	3.4
12	6	110	5.2	6.1	11.9	352	3.4
25*	6	100	5.7	6.3	15.2	334	4.5
6*	5	84	6.0	7.3	12.3	242	5.0
52*	6	80	7.0	1.8	14.6	291	5.0
14*	8	113	6.6	5.4	19.1	366	5.2
48**	9	98	8.4	8.0	17.1	303	5.6
2*	11	104	9.6	4.3	23.8	346	6.9
34*	10	93	9.7	11.5	25.7	334	7.7
22	2	89	2.2	1.8	22.6	276	8.2
50	7	95	6.9	10.7	25.0	300	8.3
47**	9	96	8.6	16.6	28.7	347	8.3
42*	9	107	7.7	11.7	29.5	352	8.4
49	4	113	3.4	8.3	30.2	353	8.6
33*	3	62	4.6	5.0	21.2	231	9.2
17*	15	104	12.6	19.3	35.9	356	10.1
58	16	100	13.6	18.4	37.5	350	10.7
55	14	89	13.6	24.9	36.2	331	10.9
39	16	104	13.3	25.5	40.7	362	11.2
13	18	79	18.5	24.5	39.1	323	12.1
40	11	71	13.4	24.5	33.3	263	12.7
45	12	75	13.8	26.2	40.3	298	13.5
18	15	79	16.0	20.8	42.3	299	14.2
15	13	93	12.3	34.8	48.0	335	14.3
51	18	90	16.7	26.7	48.2	332	14.5
37	16	101	13.7	32.4	51.2	352	14.6
60	10	64	13.5	33.8	44.9	271	16.6
41**	26	110	19.2	50.2	67.1	398	16.7
53	23	66	25.8	32.3	51.7	250	20.7
			Unrelated				
63	8	69	10.4	9.4	14.5	252	5.8
36	8	112	6.7	11.9	23.4	365	6.4
30**	13	91	12.5	16.2	38.1	348	11.0
27	17	92	15.6	28.5	46.5	326	14.3
54	23	78	22.8	38.6	44.1	307	14.4

† Cases are listed in order of decreasing antigen compatibility.
* Indicates "superior" result.
Patients not designated with an asteric, have "satisfactory" result.
** Indicates "less than satisfactory" result.

type who were treated with homografts from type O donors.[60] With more cases and a longer follow up these findings persist, but the difference in results has considerably lessened (Table 6). At the moment it seems improbable that blood types influence the outcome providing the incompatibilities described below are avoided.

It is now recognized [29, 57] that tissue transfer bewteen donors and recipients of different blood types should conform to the general rules which apply for nonmatched

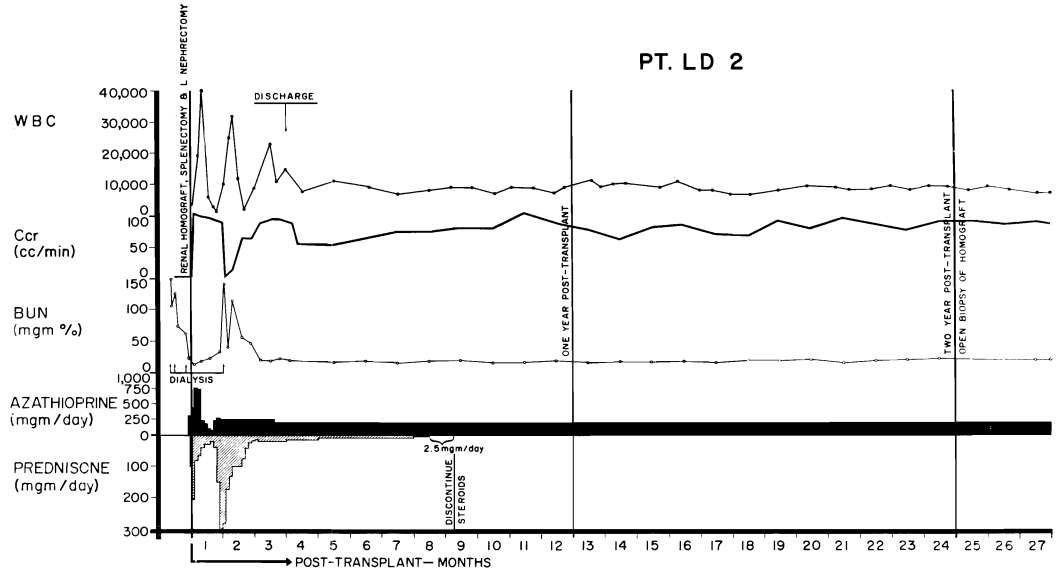

FIG. 2. Course of Patient LD 2 who received a homograft from his sister 27½ months ago. He was A+ blood type; hers was B+. Thymectomy was performed 2 weeks before transplantation. A severe rejection with anuria developed 25 days postoperatively, but this was totally reversible. Steroids were discontinued by the ninth month. A homograft biopsy at 2 years was completely normal both by light and electron microscopy.

blood transfusions. Early in our experience this scheme was violated in four cases. Two homografts of A and B type failed immediately in type O recipients, apparently due to binding of host isoagglutinins to the red cell antigens which are known to be present in renal tissue.[18, 27, 62] In a third case (A to O), the homograft functioned well for 202 days until the recipient's death from nonrenal causes (LD 20, Table 1). A fourth patient (LD 2) of A blood group who received a kidney from his B-type sister is in good health 832 days after operation with excellent renal function (Fig. 2). Thus the principal risk with the use of the unacceptable donor-recipient blood type incompatibilities seems to be an acute one which is based upon an immunologic reaction that may be quite distinct from that of rejection. Although such tissue combinations should not be used in the future because of the danger of immediate failure, it is pertinent in considering the role of red cell antigens in rejection that long-term function has been obtained in the above two cases.

Influence of Original Disease upon 1-Year Survival. Thirty-two of the 49 patients with chronic glomerulonephritis lived 1 year or more (Table 7). Three of ten patients with end-stage pyelonephritis survived for 1 year; these three all received homografts from related donors. Two of three patients with polycystic kidney disease lived for at least 12 months. The data are too small to do more than indicate that chronic survival is possible after homotransplantation for the treatment of various renal diseases.

Effect of Age upon 1-Year Survival. Twenty-six of 39 patients who were 34 years or younger (66.7%) lived for 12 or more months (Table 8). Only 11 of the 25 patients who were 35 or older (44%) had a comparable survival. The poor results in the older age groups were at least partially due to the higher number of nonrelated donors, but there was also an increased

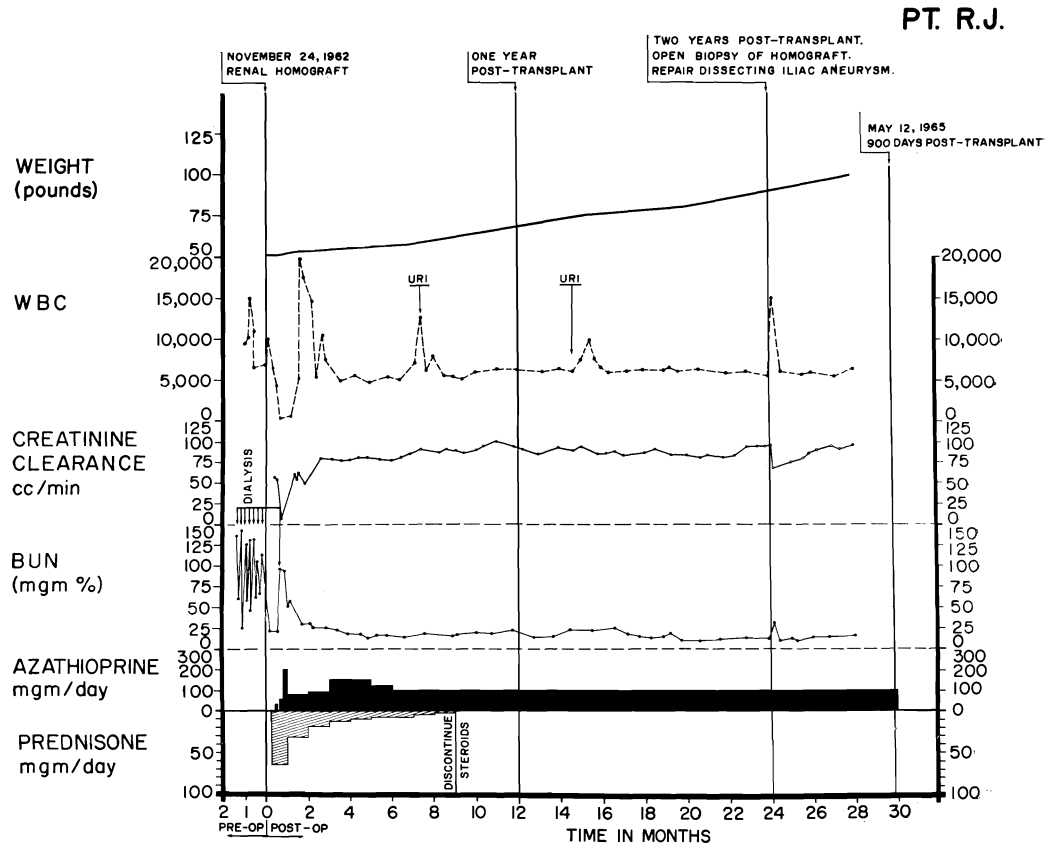

FIG. 3. Course of Patient LD 1 who received a homograft from his mother almost 30 months ago. Donor and recipient were both B+ blood type. Thymectomy was performed 30 days before transplantation. Total body irradiation was given before (300 r) and after (100 r) insertion of the homograft. An early, reversible rejection was followed by stable function except for a transient decline following repair of an iatrogenic dissecting iliac artery aneurysm (Fig. 1 right). Despite doubling of weight, the daily dose of azathioprine has remained constant. Steroids were discontinued 9 months postoperatively. Note the prompt leukocytic response to upper respiratory infections (URI) and surgical trauma. The second URI was accompanied by a herpes simplex which healed without incident. Sections of this patient's homograft after 2 years are illustrated in Fig. 9, 12–17.

incidence of complications from other organ systems.[57]

Chronic Immunosuppressive Therapy. All the chronic survivors are being treated with azathioprine, and the majority with prednisone as well. In most patients the dose of azathioprine per kilogram declined late after operation: first, because the actual daily amount was ultimately reduced to slightly less than that employed during the critical early period of recovery; and, second, because the dose was frequently held stable despite a substantial weight gain which usually followed successful transplantation. The influence of both factors is evident in Figure 3. Another example is in an adult patient (Fig. 4) who has had a slowly diminishing dose, despite a weight gain of 126 to 148 pounds. Late bone marrow depression has been observed only in the patient described earlier who died after 405 days.

In two cases (LD 15 & 36) the azathioprine dose was attenuated even more drastically following the development of jaundice within the first year after operation. Because of the known hepatotoxicity of azathioprine[9, 59] the dose was reduced

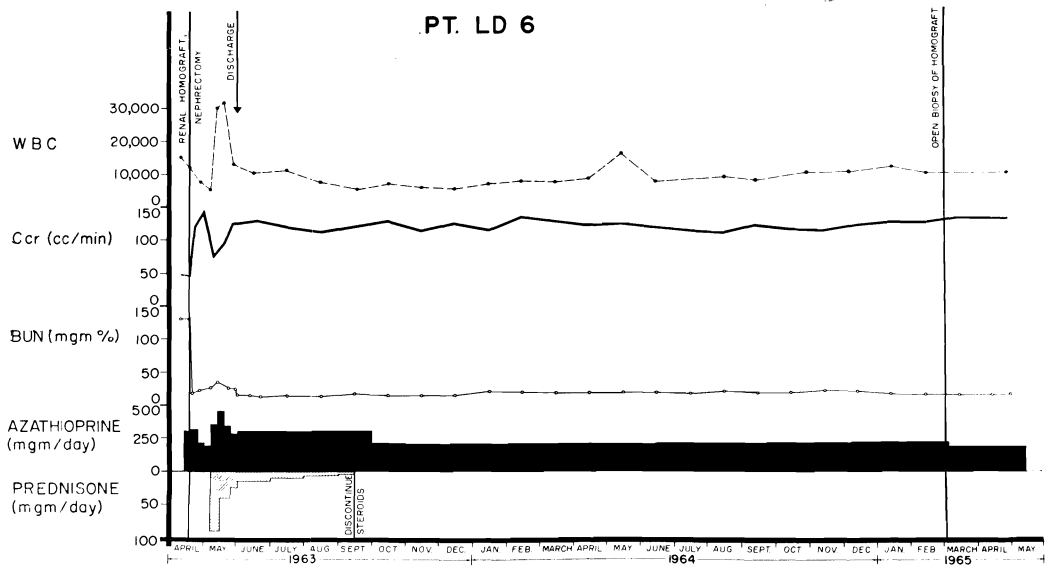

FIG. 4. Course of Patient LD 6 who received a homograft from his younger brother on April 17, 1963. Both were O+ blood type. Renal biopsy after 22½ months was essentially normal. The patient had a pretransplant thymectomy. Steroid therapy was stopped after 5 months. Note that the total azathioprine dose has been slowly reduced despite an increase in body weight from 126 to 148 pounds.

to 0.63 mg./Kg./day in one patient (Fig. 5) and 1.7 mg./Kg./day in the other. Results of liver-chemistry studies improved in both without deterioration of renal function in either.

Results with prednisone have been more variable. Two patients (LD 3 & 14) never had a rejection and have received only azathioprine. Prednisone was administered to the other 62, beginning either at the time of transplantation or within the first few weeks thereafter; in all an effort was made subsequently to reduce the dose.

In six patients it has been possible to discontinue prednisone with continuing stable renal function for the ensuing 3 to 21 months (Fig. 2–4). The maintenance doses for the others are 15 mg./day or less with a few exceptions. The present steroid therapy for each of the 36 surviving patients is individually recorded in Table 1. It is probable that others could have prednisone stopped without harmful effect. There has been a reluctance to test the possibility because of the evidence cited below that this practice led to late rejection episodes in 9 cases.

Late Rejection. The characteristics of delayed rejection (after 3 months) were described in an earlier report [58] based upon observations in 6 cases. It was pointed out that the complication seemed to have been related in each instance to reduction (Fig. 6) or discontinuance (Fig. 7) of the preexisting prednisone dose. Three additional examples have subsequently been encountered under similar circumstances, bringing the total to 9 (Table 9).

Late rejection occurred 112 to 390 days after transplantation, and in all but one patient it was controlled by resumption of or increased doses of prednisone with actinomycin C or local homograft irradiation or both. Six of eight patients in whom it was possible to reverse the process had measurable residual reduction of renal function, and in one the degree of long-term impairment has been relatively severe (Fig. 6). The present BUN, CCr and blood pressure for the surviving patients listed in

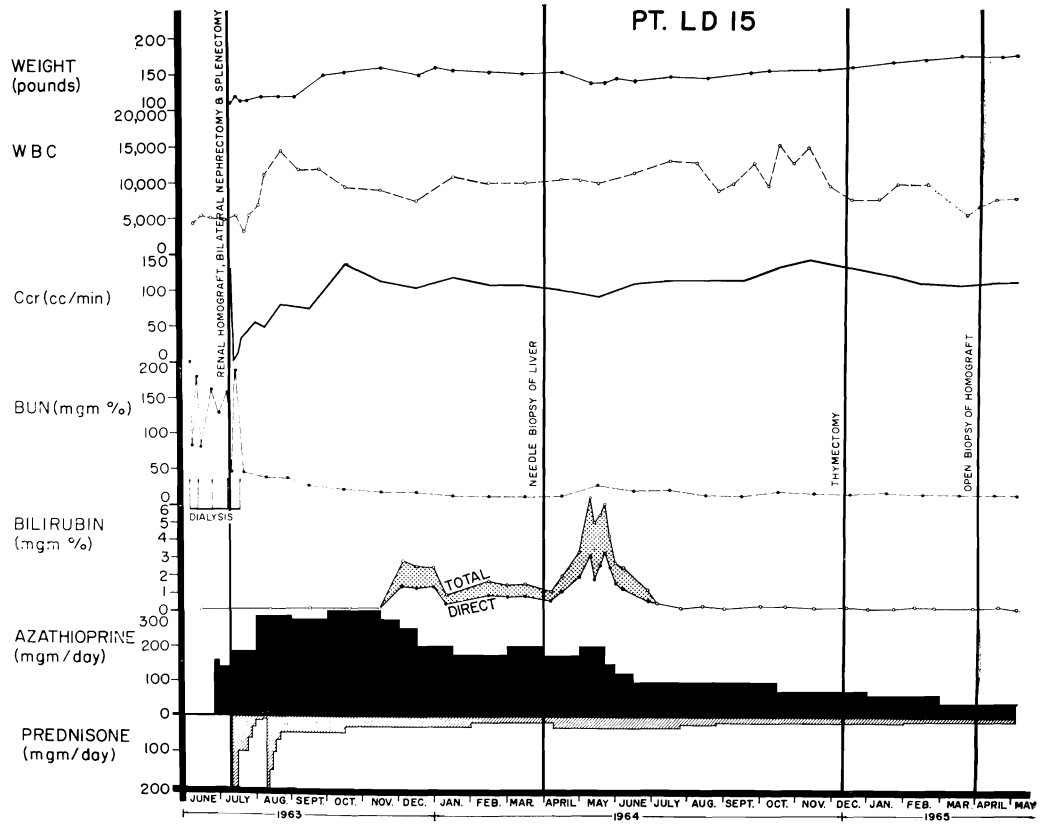

FIG. 5. Drastic reduction of immunosuppression in a patient who became jaundiced after transplantation. Note the development of hyperbilirubinemia while the patient was receiving large quantities of azathioprine, and its remission as the dose was reduced. His weight has steadily increased as both steroids and azathioprine have been withdrawn. Detailed function studies after 21 months were normal despite a few abnormalities in the renal biopsy performed at this time. The homograft was provided by the patient's brother. The recipient was A+ blood type; the donor was O+. Late thymectomy was performed because of the necessity for attenuation of immunosuppression; the value of this adjuvant procedure is unproved.

Table 9 are recorded under the same LD numbers in Table 1. It is probable that these patients will require steroid therapy for the rest of their lives.

Late Urologic Complications. Four patients required late reconstructive operations[58] for ureteric strictures either at the site of the ureterovesical anastomosis or proximal to this. All four (LD 27, 39, 44, 50) ultimately obtained a satisfactory mechanical result, in two cases after multiple operations, but one patient (LD 44) has been left with a mixed fungal and bacterial pyelonephritis, the only persistent urinary tract infection in the entire series of chronic survivors.

Degree of Rehabilitation. Whether or not the chronic survivors have returned to their previous social and vocational environment has been dependent largely upon the residual disability from pre-existing peripheral neuropathy or hypertensive retinal disease. Several of the patients with peripheral neuritis and marked paresis of their lower extremities still have incomplete motor control and one of these (LD 55) requires double cane support for ambulation after more than 1 year of normal renal function. Although many features of the retinopathy proved to be reversible, several of the patients have been left with serious visual disability.[16]

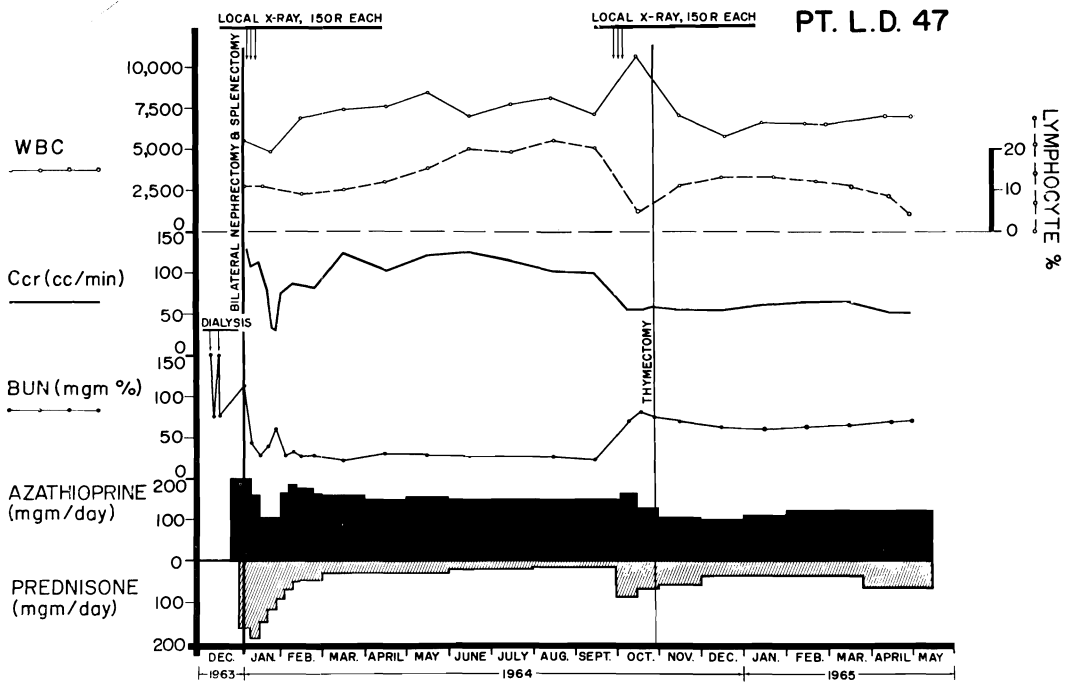

FIG. 6. Effect of late homograft rejection upon LD 47. The patient and his sibling donor were both A+ blood type. Deterioration of homograft function followed partial withdrawal of steroids and was not completely reversed after resumption of higher doses of prednisone and local homograft irradiation. Thymectomy was performed after the onset of the delayed rejection without demonstrable effect. Note the inverse relation of the lymphocyte fraction of the peripheral white cell count to the daily steroid dose.

Most of the late morbidity of immunosuppressive therapy has resulted from chronic steroid administration. Four patients (LD 22, 45, 50, 51) have had pathologic fractures of their femoral heads,[58] secondary to osteoporosis. Gastrointestinal bleeding, a frequent early complication,[57] has not been observed after 1 year. Two patients (LD 40, 54) have formed lens cataracts, requiring ocular surgery in one.

One patient died of septicemia with leukopenia; the only other late complication which may have been attributable to chronic use of azathioprine was liver injury. Whether the "hepatitis" alluded to earlier in three cases was a drug-induced injury or was of viral etiology cannot be stated with certainty. Other infectious problems have been minimal in those patients who lived beyond 1 year.

All but one of the living patients have returned either to school or to a former occupation or have been re-educated to some other form of gainful employment.

Chronic Homograft Function. All of the living patients have adequate renal function (Table 1). The highest BUN (LD 47) is 70 mg./100 ml.; none of the adults have a CCr below 50 ml./min. For the entire group, the mean BUN in April, 1965 was 22.5 mg./100 ml. and the mean creatinine clearance was 83.6 ml./min. Five of the living patients have proteinuria. The greatest loss is in a patient (LD 1) who has excreted 1.5 to 2 Gm. protein per day for more than 2 years.

During the early months after transplantation, varying degrees of hypertension are usually present,[57] frequently requiring aggressive treatment with antihypertensive agents. With the passage of time and the lowering of steroid doses, this problem has diminished in most cases. The average sitting blood pressures for April 1965 are

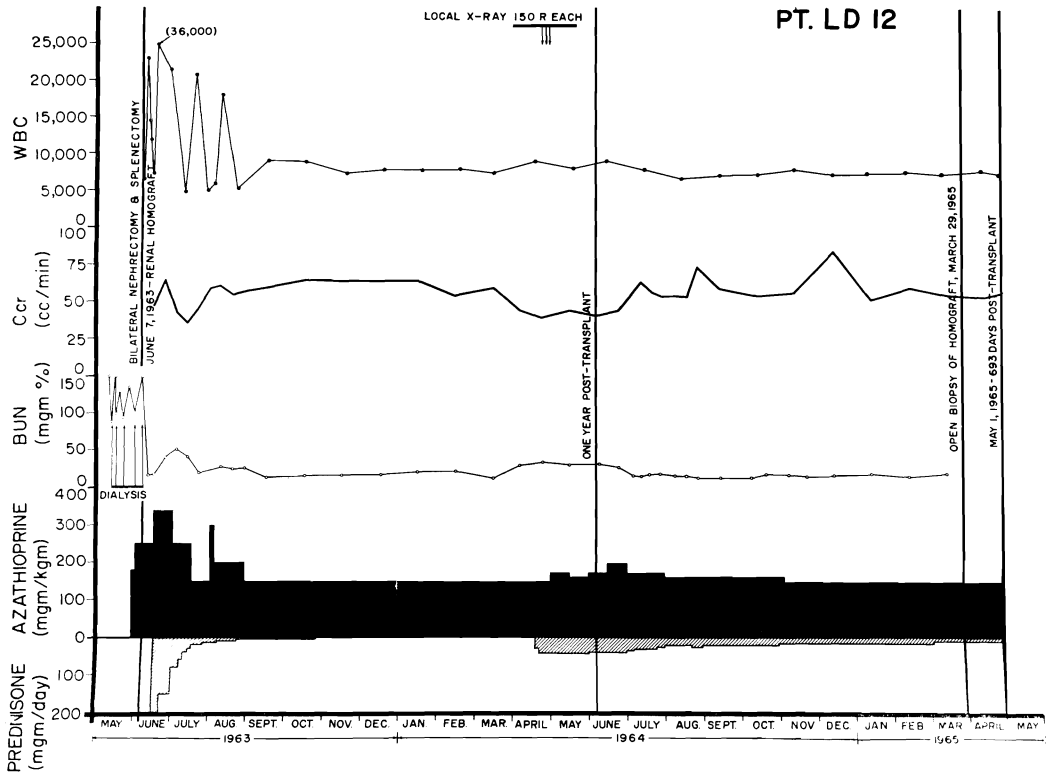

FIG. 7. Late rejection in LD 12 which followed discontinuance of steroids; this was reversed after resumption of steroids, local homograft irradiation and administration of intravenous actinomycin C. The prednisone dose has subsequently been dropped to 15 mg./day. Although the patient is in good health, his clearance of creatinine, inulin and PAH is somewhat reduced (Table 10) and the pathologic changes in his 21-month homograft biopsy are marked (Fig. 8). He is slightly hypertensive.

shown in Table 1 for each patient, and it is indicated whether or not any antihypertensive drugs (chlorothiazide, hydralazine, reserpine or methyl DOPA) are being used. Renal arteriograms were obtained in two cases. One patient (Fig. 1, left) who had hypertension had diffuse narrowing of intrarenal vessels contrasted to a normal vascular pattern (Fig. 1, right) in the other who was normotensive.

Additional Function Studies (DAO). Seven and five patients received homografts from related (Table 10) and unrelated (Table 11) donors, respectively. Although duration of survival in the related series (23.8 months) exceeded that of the unrelated group (16.1 months) at the time of study, both the glomerular filtration rate (inulin clearance) and effective renal plasma flow (para-aminohippurate clearance) were greater in the former ($p < 0.01$, $p < 0.1$). The ability to concentrate or dilute urine and to eliminate a water-load was also better preserved in the related homografts (Table 10, 11).

Individual patients in both groups had inulin and PAH clearances which were more than half the adult normal, suggesting that homograft function can increase—similar to the normal remaining kidney after ordinary nephrectomy. It is interesting that the filtration fraction was somewhat high in most cases even in those patients (LD 2, 6) with completely or nearly normal 2-year biopsies (Table 10).

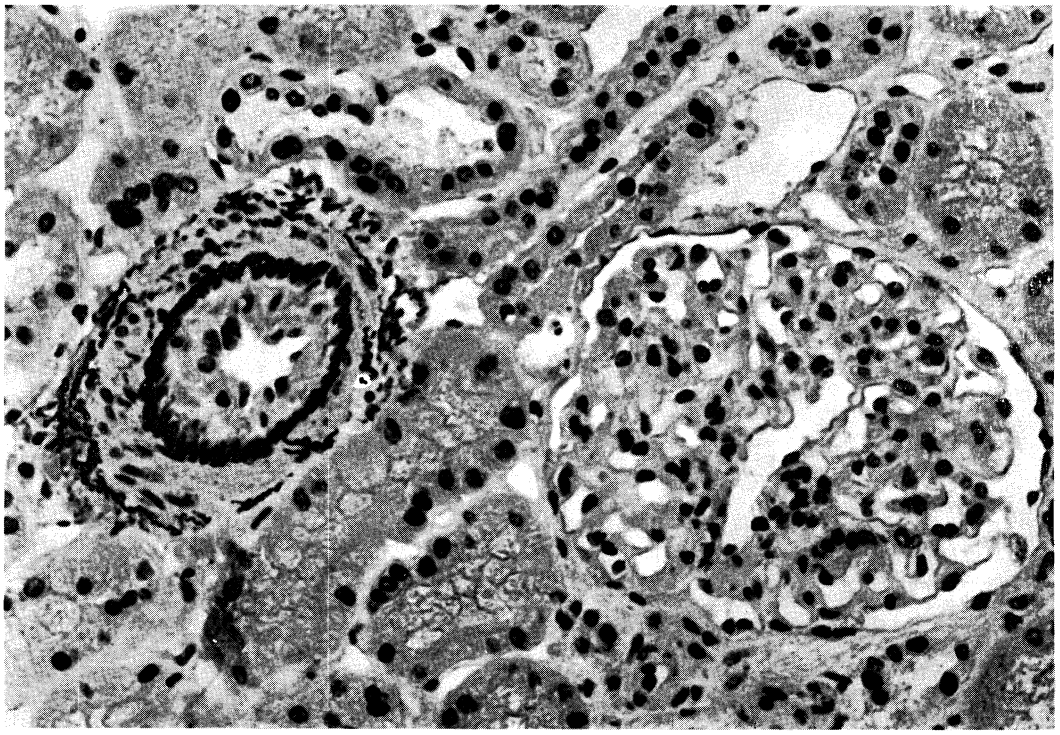

FIG. 8. Biopsy of renal homograft 1 year, 10 months after transplantation (LD 12). The lumen of a small interlobular artery is narrowed by fibrous thickening of the intima. There is some focal thickening of the capillary basement membranes in the glomerulus and a few adhesions between tuft and capsule. This patient's clinical course is depicted in Fig. 7. Carnoy fixation. Elastic counterstained with hematoxylin and van Gieson. (× 300.)

Pathology of Renal Homografts After 1 Year (KAP)

One renal homograft (LD 2) was absolutely normal; another (LD 6) showed only a little scarring in the superficial cortex just beneath the capsule but was elsewhere normal. The remaining seven transplants all showed appreciable pathologic changes.

Vascular Changes. *Interlobular Arteries.* In 4 of the biopsies from living patients (LD 1, 12, 13, 15) and in the homograft removed at autopsy (LD 23) intimal thickening was present in the interlobular arteries, often accompanied by rupture of the internal elastic lamina (Fig. 8). This change did not affect all the vessels and was often focal within an individual artery. The thickening was caused by a layer of fine collagen fibrils lying between the internal elastic lamina and the endothelium (Fig. 9). The elastic layer was wider than normal and the individual elastic fibers were fragmented, separated and arranged in an irregular fashion. Hyaline material, with a fine granular structure, formed irregular patches both in this layer and in the intimal collagen. The endothelial lining was intact, but its cells were swollen and contained many vacuoles and a few dense bodies. In some small interlobular arteries the lumen was almost occluded. The medial muscle cells were compressed and granular hyaline material was present between them. In the biopsies small interlobular arteries were the largest vessels sampled, but in the one autopsy specimen similar intimal thickening and elastic damage extended into the arcuate and interlobar arteries.

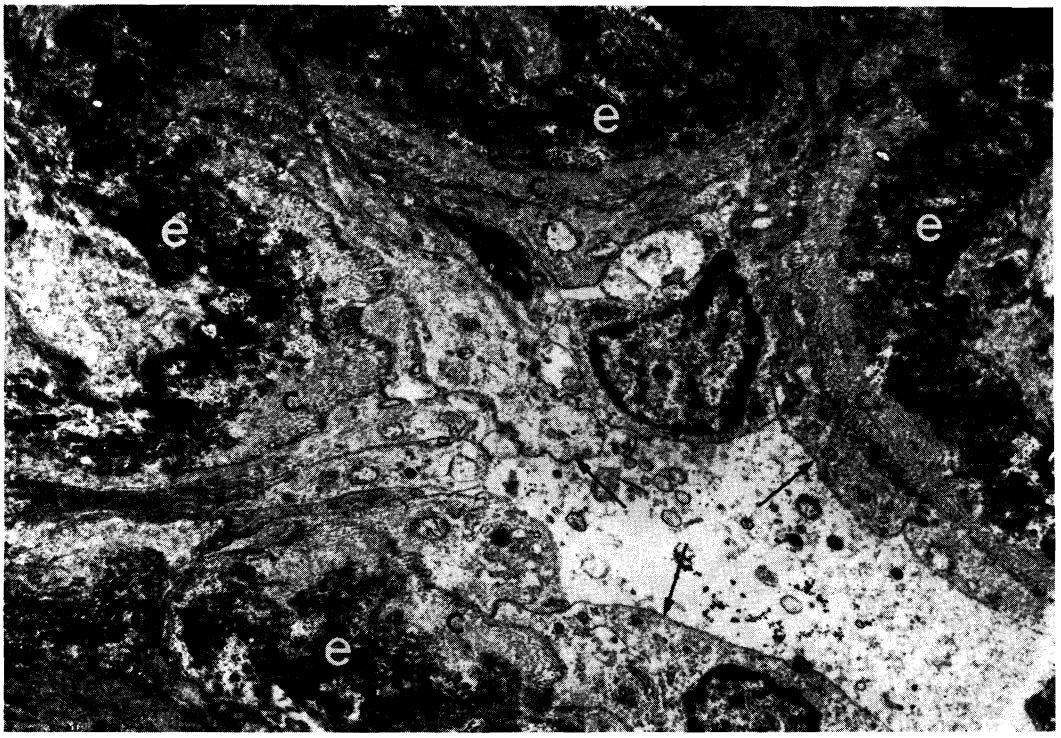

FIG. 9. Biopsy of renal homograft 2 years after transplantation (LD 1). Internal elastic lamina (e) of a small interlobular artery branch is fragmented and infiltrated with hyaline material. Intima is thickened by fine collagen fibrils (c). Endothelium (arrows) is intact but cells are swollen and contain vacuoles and electron dense bodies. Renal angiogram in this patient after 2 years was essentially normal (Fig. 1 right). Electronmicrograph. Phosphotungstic acid. (× 5,000.)

Afferent Arterioles. Homogeneous "hyaline" material, staining pale pink with eosin, was present in the arteriolar walls of six of nine homografts examined (Fig. 10). Five of these were the cases with interlobular artery changes; the sixth was LD 14. The "hyaline," composed of compactly arranged granules measuring about 200 angstroms in diameter, lay beneath the endothelium between the basement membranes of the endothelial and the smooth muscle layers (Fig. 11). In severely affected arterioles the whole wall was replaced by this material (Fig. 12).

Peritubular Capillaries. In one transplant (LD 23) there was appreciable loss of peritubular capillaries in the fibrotic interstitium, but in the other cases they appeared normal, even when surrounded by collagen. Where there was cellular infiltration of the interstitium, pyroninophilic cells were usually found marginating in the local peritubular capillaries.

Cellular Infiltration. Three transplants showed no cellular infiltration (LD 2, 3, 6) and one other contained only a very few cells (LD 15). In the remaining five cases there were focal, dense collections of infiltrating mononuclears (Fig. 13) which were most frequent in LD 13 and 23. Between 10 to 50 per cent of these cells had cytoplasm which stained deep red with pyronin and in three of the homografts a few were in mitosis. Ultrastructurally some of the infiltrates were large lymphoid cells with abundant cytoplasm lacking rough endoplasmic reticulum but full of RNA in the form of ribosome rosettes (Fig. 14, 15). Mitochondria were not abundant in these cells, the Golgi apparatus was well de-

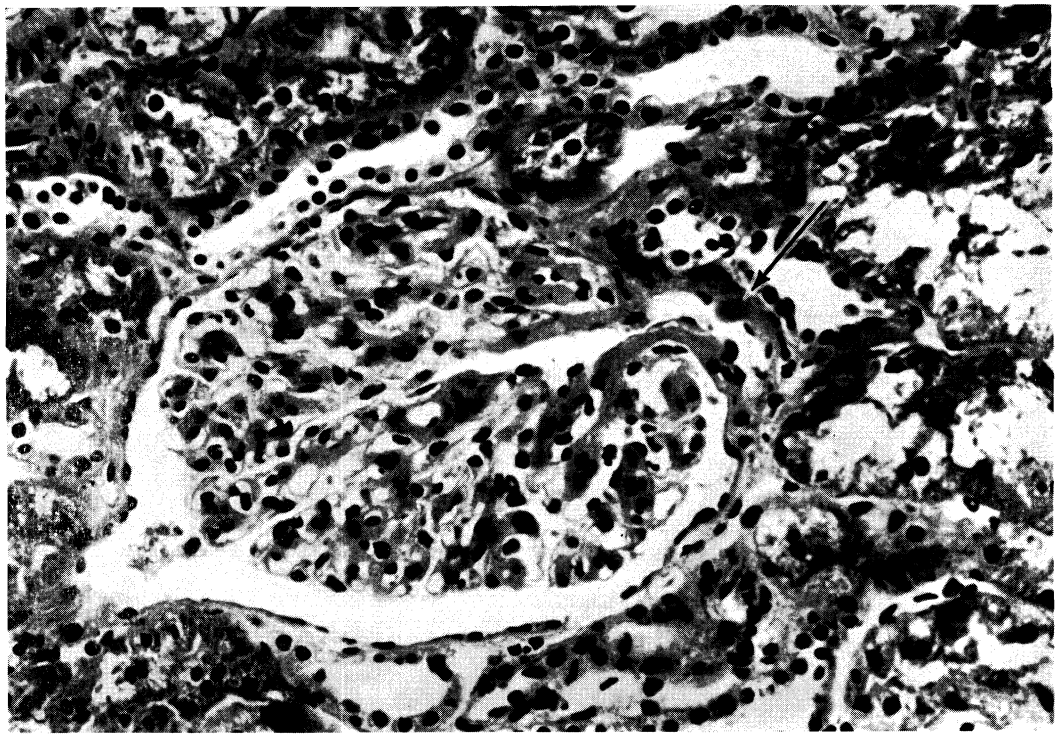

FIG. 10. Biopsy of renal homograft 1 year, 9 months after transplantation (LD 15). There is hyaline material (arrow) in the wall of an afferent arteriole. Focal deposits of similar material are present in the glomerular tuft. Clinical course of this patient is shown in Figure 5. H & E (× 300).

veloped, multivesicular bodies were frequent and the nucleus was often indented. The number of large lymphoid cells varied from case to case but seemed to be roughly proportional to the number of pyronin-positive cells in the conventional sections. Other cells in the interstitium were fibroblasts (Fig. 16) and macrophages. The latter were characterized by an abundance of cytoplasmic vacuoles and the presence of mostly smooth endoplasmic reticulum (Fig. 17). Small lymphocytes, plasma cells and neutrophils never composed more than 10 per cent of the infiltrate and in most of the biopsies were far less frequent. In only one homograft were eosinophils present, a case (LD 14) in which protracted eosinophilia had characterized a strange febrile episode which commenced about 20 days after transplantation.

Interstitial Fibrosis. Only one case showed a completely normal interstitium (LD 2). There was slight fibrosis in the superficial subcapsular cortex of three cases. More generally distributed fibrosis was present in the other five homografts (Fig. 16). It was most marked in LD 13 and 23.

Glomerular Changes. Periglomerular fibrosis, partial tuft fibrosis and occasional complete fibrotic obliteration of the whole glomerulus occurred in those kidneys with vascular narrowing. In four of the transplants (LD 1, 3, 12, 15) there were focal deposits of finely granular hyaline material on the glomerular capillary basement membranes and between the tuft endo-

FIG. 12. Biopsy of renal homograft 2 years after transplantation (LD 1). Wall of a small arteriole has been replaced largely by granular hyaline material (hy). The endothelial cells (end) have swollen, vacuolated cytoplasm. Electronmicrograph. Phosphotungstic acid (× 3,510).

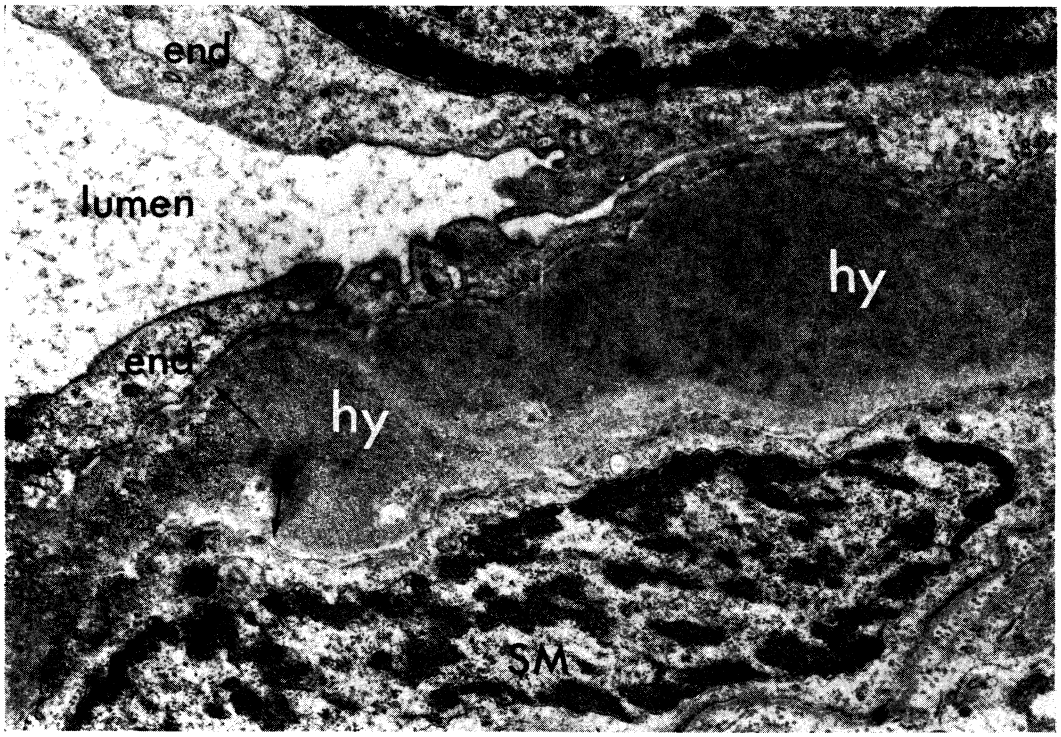

FIG. 11. Biopsy of renal homograft 1 year, 9 months after transplantation (LD 15). Granular hyaline material (hy) is deposited between the endothelium and the smooth muscle (SM) in the wall of an arteriole. The patient does not have hypertension. Electronmicrograph. Phosphotungstic acid (× 16,800).

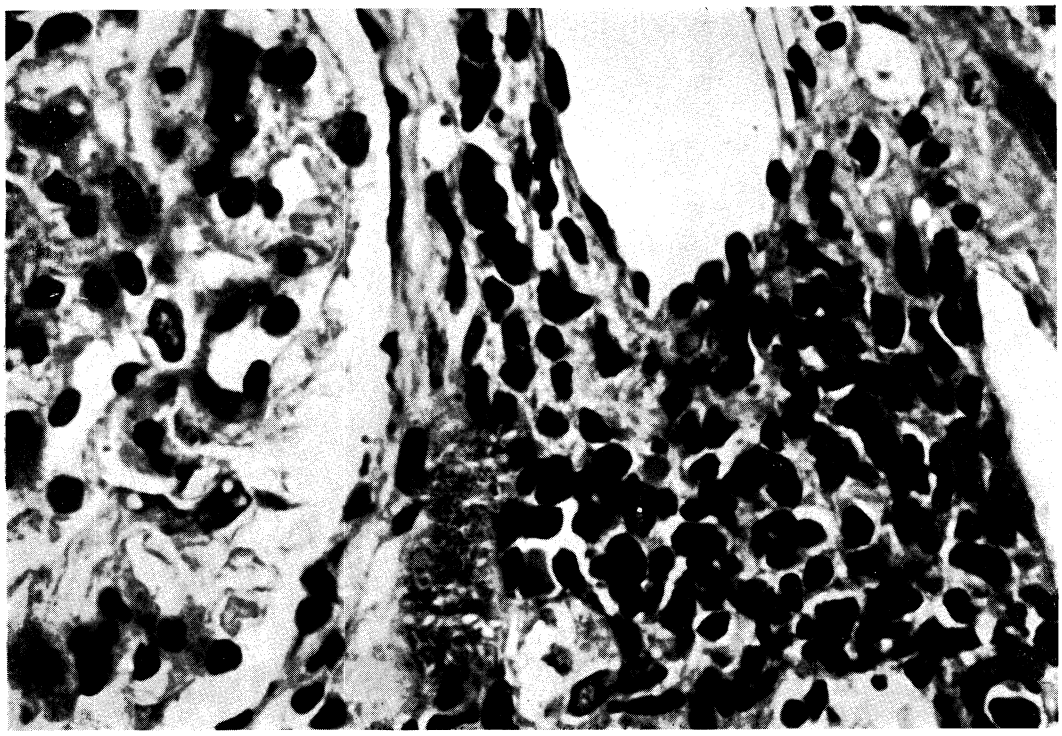

FIG. 13. Focus of dense cellular infiltration adjacent to a glomerulus. Two-year biopsy on LD 1. Clinical course is shown in Fig. 3. H & E (× 680).

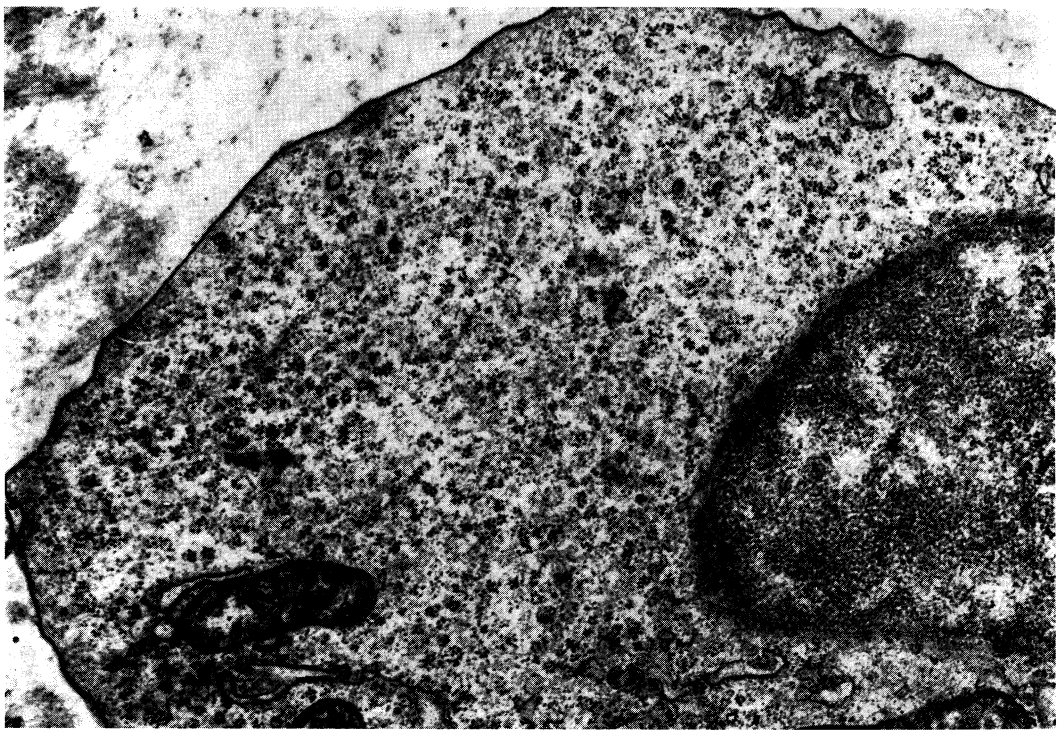

FIG. 15. Detail of a lymphoid cell infiltrating the renal homograft from Patient LD 1 two years after transplantation. The cytoplasm is densely packed with tiny rosettes, each composed of 4–6 ribosomes. Electronmicrograph. Lead (× 21,000).

thelial cells (Fig. 8, 18). These deposits were only severe in two of the cases (LD 1, 3). A few of the glomerular epithelial foot processes were fused in these cases and in LD 1 there was also hyperplasia of the endothelial cells.

Hyperplasia of the Juxtaglomerular Apparatus. Some enlargement of the juxtaglomerular body was present in six of nine homografts (Fig. 19). This was very striking in LD 3 and 15—the macula densa was prominent, vacuolated cells were present in the afferent arteriolar wall and the lacis cells were greatly increased in number. Excess granularity was not a feature of this hyperplasia.

Tubular Atrophy. Focal tubular atrophy was present in all those cases with vascular lesions. It was most severe in LD 23. In the latter case recent tubular damage, bile pigment casts and calcification of a few of the distal tubular cells were also present as a result of this patient's terminal illness.

Histopathologic Correlations. *With function.* The two kidneys which were histologically unaltered at about 2 years had completely normal function. Conversely, the two homografts which had the most severe disruption of general architecture in the late biopsy (LD 12, 13) had the lowest clearances of creatinine, inulin or PAH; the patient who died after 13½ months (LD 23), who was found at autopsy to have pronounced renal damage, also had moderate depression of the CCr. More precise correlations between specific

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FIG. 14. Ultrastructure of two lymphoid cells infiltrating a renal homograft (Patient LD 1) 2 years after transplantation. Each has a prominent nucleolus (N) and Golgi body (g). Cytoplasm is full of polyribosomes but lacks rough endoplasmic reticulum (see Fig. 17). Electronmicrograph. Lead (× 9,550).

FIG. 16. Greatly increased number of collagen fibrils in the interstitium of a renal homograft 2 years after transplantation (LD 1). A fibroblast (F) and a lymphoid cell (L) lie embedded in the fibrous tissue. Electronmicrograph. Phosphotungstic acid (× 8,000).

pathologic changes and function were often not found in individual cases.

For example, only two of four patients with glomerular basement membrane abnormalities had proteinuria, and in one of these (LD 3) the quantities were of doubtful significance (15 to 400 mg./day). Similarly, vascular damage at the interlobular artery level was not incompatible with good function; the four patients with such lesions had a mean CCr of 103 ml./min. compared to 115 ml./min. in the four with normal vessels. Likewise, cellular infiltration was pronounced in some of the kidneys which had the best function (LD 1, 14).

With Late Rejection. Homograft tissue was available from three patients who suffered a late rejection 223 to 300 days after transplantation; all three had interlobular artery lesions and prominent cellular infiltration. In six other cases without late rejection, two homografts had vascular lesions and four did not; four of these six homografts were almost or completely free of invading cells.

With Blood Pressure. Three of the six renal homografts which showed lesions in the arteries or arterioles at biopsy or autopsy came from patients who late in their clinical course developed an elevated diastolic blood pressure; the three patients without such histologic changes were all normotensive. The presence of juxtaglomerular hyperplasia in the graft did not correlate either with vascular lesions in the graft or hypertension in the patient. The fact that these enlarged juxtaglomerular bodies did not show excess granularity is probably significant.

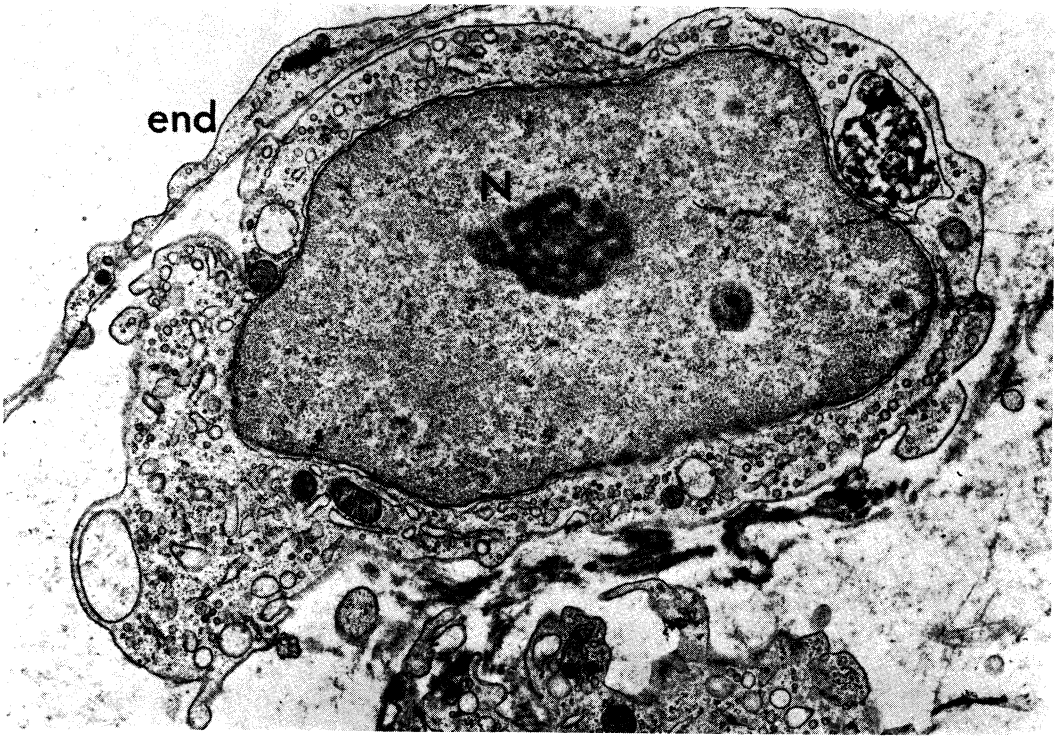

FIG. 17. Macrophage lying in interstitium adjacent to the endothelial lining (end) of a peritubular capillary in a renal homograft 2 years after transplantation (LD 1). The macrophage has a prominent nucleolus (N); cytoplasm is full of vacuoles and contains endoplasmic reticulum. Electronmicrograph. Lead (× 10,970).

Antigen Analysis (PT and DLV)

A summary of the cytotoxicity reactions between each of the long surviving patients and their donors is given in Table 12. Unfortunately, not all lymphocyte specimens could be examined with a full antibody panel due to the periodic unavailability of several of the antisera, thereby somewhat reducing the accuracy of cross-comparison from case to case. This necessary variation in testing was partially corrected in each instance by dividing [total units mismatch/total weight of units tested], a calculation which indicates for each pair the ratio of actual mismatch units to the maximal number of mismatch units which could have been detected with that particular panel in the event of total incompatibility. These results, which are expressed as percentages in the right column, were used for two lines of retrospective inquiry.

Distribution Curve of Mismatches. The attainment of long-term homograft function in such cases implies that a reasonably satisfactory degree of histocompatibility had been achieved fortuitously, with the assumption that the less fortunate patients with a poor tissue match would not be represented in this residual group. If the method of antigen analysis employed were capable of detecting histocompatibility, the test should be able to demonstrate that the surviving patients and their donors were in fact more satisfactorily matched than would have been expected by chance. To test this hypothesis, the antigenic mismatches of the donor-recipient pairs were compared to those which were obtained from control studies of a random population sample.[66] The most important data are those from the five living patients in whom homografts from nonrelated donors were

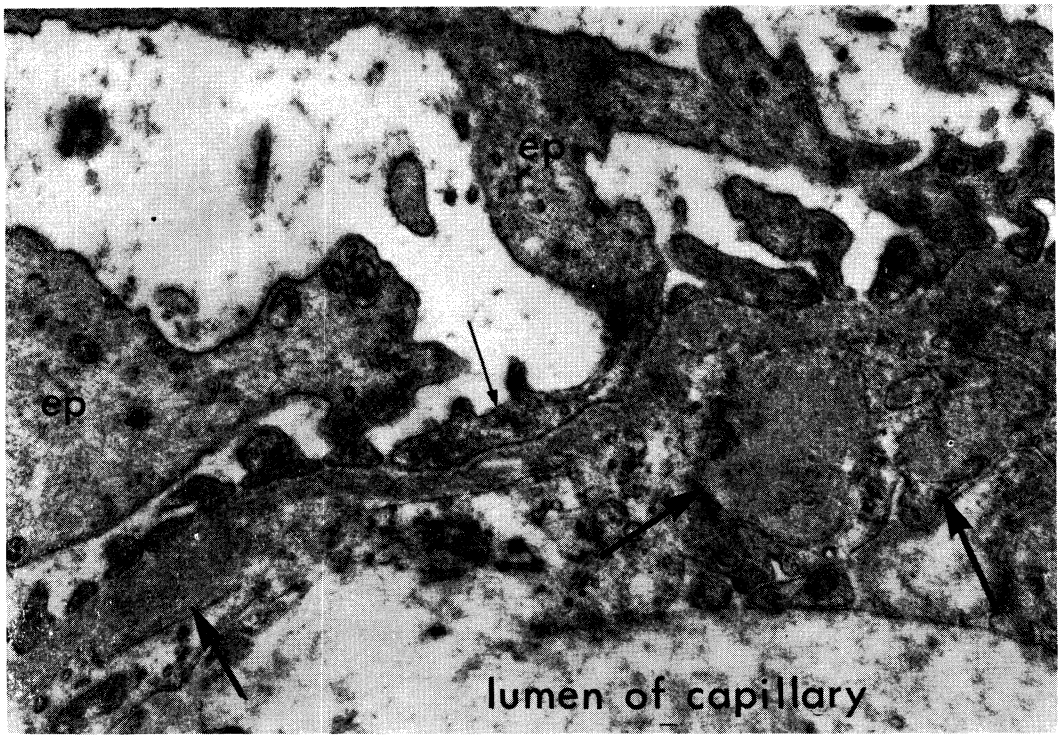

FIG. 18. Biopsy of renal homograft 2 years after transplantation (LD 3). Part of glomerulus showing granular hyaline material (coarse arrows) deposited on the glomerular capillary basement membrane and between the damaged endothelial cells. There is fusion (fine arrow) of some epithelial (ep) foot processes. Electronmicrograph. Phosphotungstic acid (× 21,700).

employed; the results from these cases in comparison to those expected from random population matching between nonrelatives are summarized in Figure 20. In all five instances, the incidence of mismatches of those possible was 14.4 per cent or less. Thus the surviving recipients were clustered in the favorable half of a random distribution curve of antigenic compatibility (Fig. 20). None fell into the unfavorable portion.

A similar statistical study of the patients who had homografts from related donors suggests that fortuitous antigen matching may have been a determinant of success or failure in this group as well, although the variability of findings was much greater.[66]

Correlation of Antigenic Compatibility with Clinical Course. If the discriminatory ability of the test were highly sensitive, it should also be possible with antigen analysis to predict which of the surviving patients had the most satisfactory clinical course to date. Such an attempt at correlation proved to be difficult for a number of reasons. First, it is known from studies by Kirkpatrick, Wilson and Talmage[32] that the attenuation of immunologic reactivity which accompanies uremia[11] is extremely variable and that the degree of consequent preoperative immunologic impairment is an important factor in determining the magnitude and timing of early rejection; such variations, which could profoundly influence the clinical course, are not detected with antigen studies. Second, clinical ranking of the survivors on the basis of current renal function was not generally useful since most of these patients have normal BUN's and good or excellent creatinine clearances. Third, the immunosuppression in different cases was often not

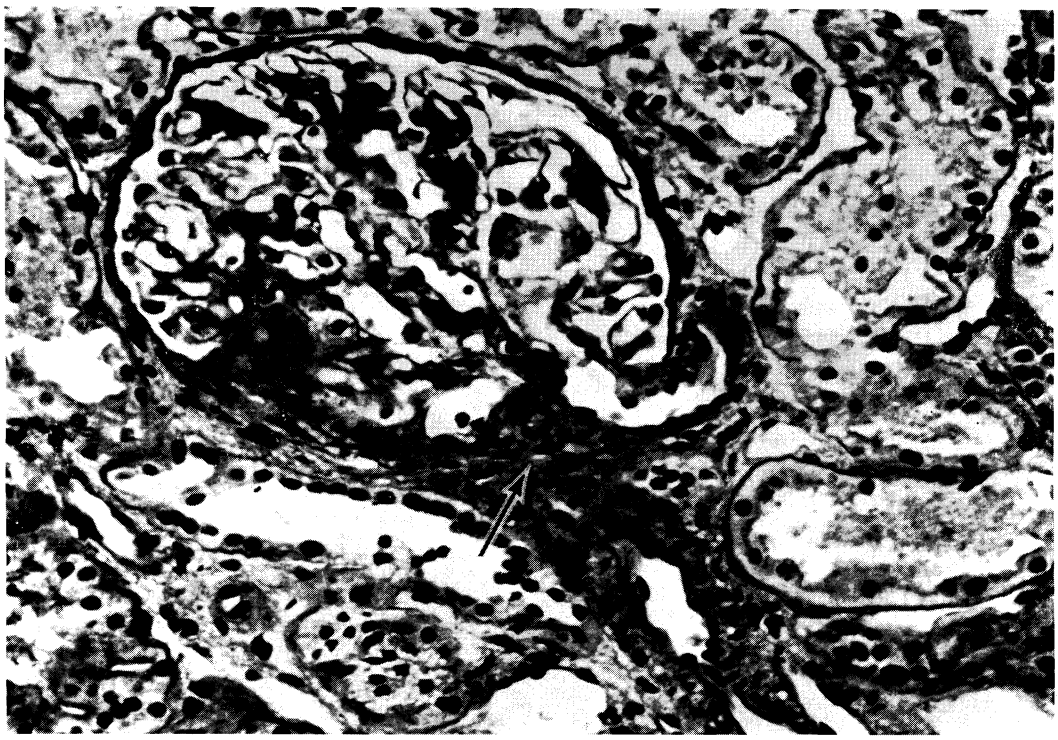

FIG. 19. Hyperplastic juxtaglomerular body (arrow) in a renal homograft 1 year, 9 months after transplantation (LD 15). There are also focal deposits of hyaline material in the glomerular tuft. Periodic acid Schiff (× 300).

comparable, the variations being principally in the amount, timing and duration of steroid therapy. Finally, it frequently proved impossible to say that one patient had a better course than any one of a half dozen or more others.

It was finally decided to rate each case clinically as "superior," "satisfactory," or "less than satisfactory." The "superior" 11 patients, all of whom received kidneys from related donors, presented few management problems after the early postoperative convalescence. None had a late rejection. Two (LD 3, 14) never required steroid therapy at any time; in the other 11, prednisone was either ultimately discontinued or reduced to 7.5 mg./day or less. Four patients (LD 30, 41, 47, 48) were judged "less than satisfactory," primarily because large prednisone doses per weight basis were necessary long after operation to pre-

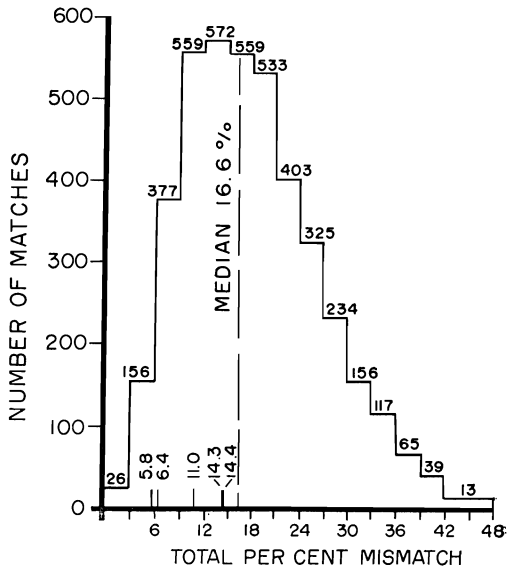

FIG. 20. Frequency distribution of human antigenic mismatches in a random population of 65 individuals, each of whom was matched against all the others; approximately 4,200 donor-recipient combinations were possible. See text for details.

vent late deterioration of renal function; all four have residual functional damage to the homograft from late rejection. The rest of the patients, 21 in all, who were termed "satisfactory" are receiving 7.5 to 15 mg. prednisone/day.

The compatibility rating in the 36 surviving cases is shown in Table 12 for both the related and unrelated pairs, in the order of completeness of the antigen match. In the related group the correlation of these precise numeric rankings with the less detailed clinical ones described above was not good in a number of individual instances. For example, the patient with the poorest antigen match (LD 53) has never had an overt rejection, is not being treated with heavy immunosuppression and has a "satisfactory" result after almost 16 months. The same situation pertains to five of the next six poorest matches. Conversely, two of the "less than satisfactory" results were in patients who had relatively well-matched donors (LD 47, 48). With nonrelated pairs, there was no evident correlation between the clinical result and the results of the immunologic study.

Nevertheless, there was a heavy concentration of the patients with clinically "superior" results near the top of the compatibility scale in the related series. All 11 of these patients were from the top 18 matches; none had an antigenic mismatch greater than 10.1 per cent (Table 12). These results indicate that chronic homograft function can be obtained despite considerable donor-recipient incompatibility of the antigenic systems being studied, but they also suggest that the chance of achieving an outstanding clinical result is increased by the presence of a close match of these lymphocyte antigens.

Correlation of Antigen Compatibility with Pathologic Findings (KAP). A clear correlation did not exist between the degree of donor and recipient antigen incompatibility and the extent of late histologic damage.

Thymectomy

In eight of the first cases, thymectomy was performed 14 to 85 days before transplantation [57, 58, 61] at the suggestion of Dr. David W. Talmage. Four patients died early after operation from causes other than rejection.[58] The other four (LD 1, 2, 3, 6) are still living more than 2 years later. Their uniformly smooth late convalescence has prompted speculation that the adjuvant procedure may have been of long-term benefit.[58]

The value, if any, of thymic excision in human homotransplantation cannot yet be proved. Nevertheless, it seems appropriate to consider the present evidence on this important point. The following is a further analysis of the original four cases with pretransplant thymectomy and an account of nine additional patients in whom thymectomy was carried out long after homotransplantation.

Histologic Features of the Thymus Glands Removed before Transplation (KAP). Three of the thymuses were from patients aged 12 to 23 who had not previously received corticosteroids (LD 1, 3, 6); all three had glomerulonephritis. The weight of the gland, 17 Gm., was recorded only for the oldest patient. In each case the thymus contained abundant cellular tissue. The cortex was well preserved and packed with small lymphocytes. In two of the glands the medulla contained a few germinal centers (Fig. 21), each consisting of a central collection of large cells with pale nuclei surrounded by a rim of small lymphocytes; these two thymuses also contained many small groups of plasma cells. The abnormal presence of the germinal centers is of great interest inasmuch as several workers, particularly Burnet and Mackay, recently have stressed the significance of such structures which have been described in the thymus of patients with rheumatoid arthritis,[3] systemic lupus erythematosus,[2, 37] myasthenia gravis,[7] thyro-

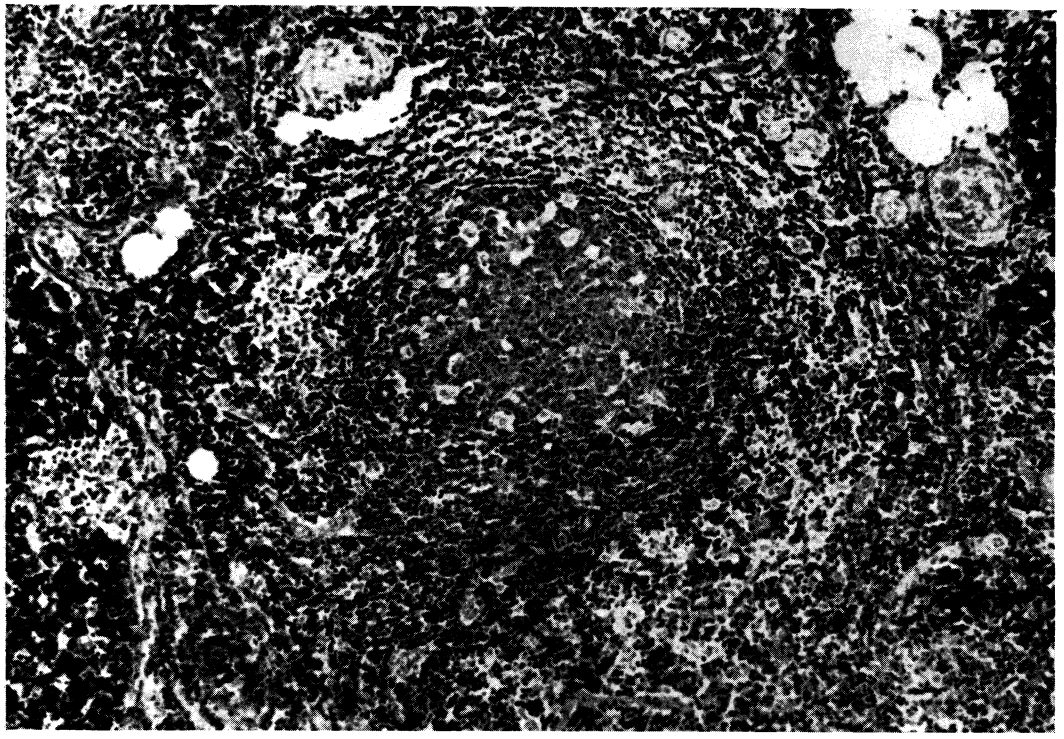

FIG. 21. Thymus removed before homotransplantation from Patient LD 3; the renal disease was chronic glomerulonephritis. There is a lymphoid follicle with germinal center in the medulla. H & E (× 130).

toxicosis and Hashimoto's disease.[22] Our patients were suffering from chronic glomerulonephritis and, as far as we are aware, this is the first time that such an association of thymic and renal changes had been recorded.

The fourth thymus, from a patient (LD 2) aged 28 years who for the 2 months prior to thymectomy had received corticosteroids, was atrophic microscopically and lacked recognizable cortex. No germinal centers were present in this specimen. All four thymuses contained more Hassal's corpuscles than normal in the medullary tissue. In two of the glands some of these corpuscles were cystic.

Clinical Correlations with Pretransplant Thymectomy. One of the surviving four patients (LD 3) with pretransplant thymectomy has never had homograft deterioration and has not received prednisone. The other three had moderate or severe early rejection (Fig. 2–4) which was reversed after prednisone and actinomycin C were administered. All four patients have had essentially unvarying renal function during their entire late course. None has received any steroid therapy from the sixth to the tenth postoperative month onward. Each was classified as a "superior" result.

The other 33 chronic survivors in whom pretransplant thymectomy was not performed also included seven patients who were considered to have a "superior" result. All have either normal or excellent renal function; one has never received steroids, two others have had steroids discontinued without harmful effect and four are receiving 2.5 to 7.5 mg. prednisone per day. Such cases prove that stable chronic homograft function is not necessarily dependent upon steroid therapy even when

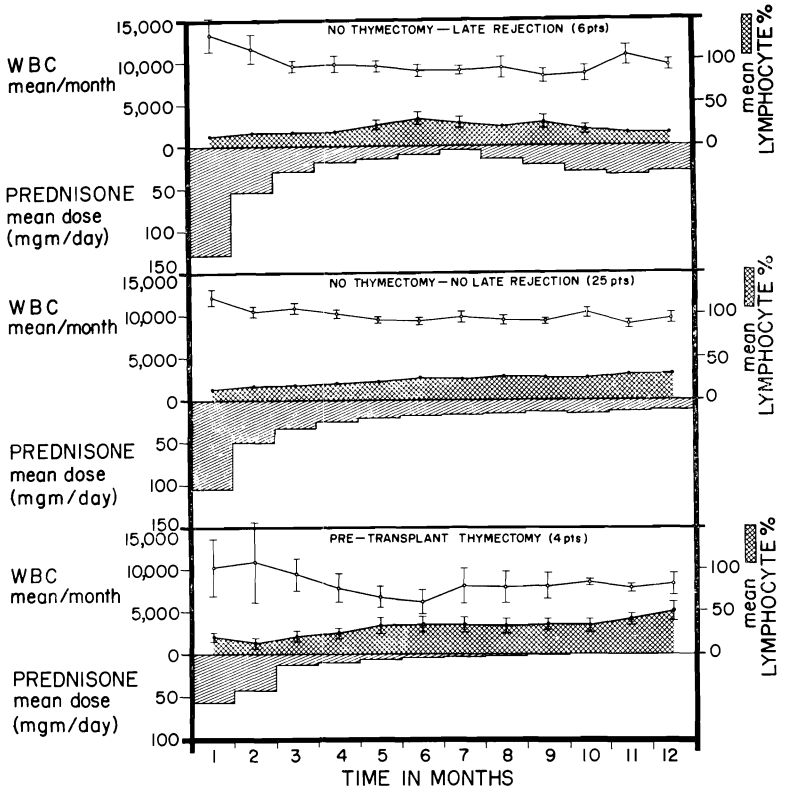

FIG. 22. Relationship of thymectomy and steroid dose to peripheral lymphocyte fraction in 3 distinct groups of patients. (Lower) Mean values in 4 patients who had thymectomy prior to homotransplantation. Vertical bars represent standard error (SE). Note progressive lymphocytosis in postoperative period as average steroid dose was decreased. None of the patients developed late rejection. (Middle) Twenty-five patients who did not have pretransplant thymectomy and who did not have a late rejection during the first year. SE values in the lymphocyte fraction were too small to depict. Note rise in lymphocyte component as steroid doses were decreased. (Upper) Six patients who did not have pretransplant thymectomy and who developed delayed rejection between the 7th and 10th postoperative months. Note the inverse relationship of the lymphocyte fraction to the steroid dose, both early and late after transplantation.

thymectomy has not been performed. Nevertheless, a substantial fraction of the 33 patients who did not have pretransplant thymectomy have been demonstrated to require chronic administration of prednisone, since its complete or partial withdrawal has preceded late rejection in nine of these patients. As will be pointed out below, this late steroid dependence may be due to factors other than the presence of the thymus.

Pretransplant Thymectomy and the White Blood Cell Count. The average monthly white cell count and percentage of lymphocytes in the four patients with pretransplant thymectomy are shown for the first postoperative year in Figure 22. The total count remained relatively stable. The contribution of lymphocytes to the total count progressively increased after the first several months, at a time when the average steroid dose was being reduced or discontinued.

Two sets of control data are available against which to compare the above findings. The first was obtained from 25 patients who did not have thymectomy but who had either a "satisfactory" or "superior" course during the first year. These patients were generally managed in the same way as those of the thymectomy group although attenuation of the steroid dose was somewhat more gradual. The white cell counts and lymphocyte fractions (Fig. 22) followed the same pattern as that observed in the thymectomy group with a rising lymphocyte component late in the course.

A second group of six nonthymectomized patients were grouped for study since they had delayed homograft rejection between the seventh and tenth postoperative months.

The early management of these cases had been similar to that of the above two groups, during which the white blood cell counts and differentials had been comparable. With the increased doses of prednisone used to treat the late complication, there was an abrupt change with a secondary fall in the lymphocyte percentage (Fig. 22).

These findings suggest: 1) thymectomy does not strikingly influence the number of circulating lymphocytes in the human under the conditions of these experiments; 2) steroid therapy, in contrast, has a marked lymphopenic effect when large doses are employed both early and late after operation; and 3) the level of peripheral lymphocytes cannot be related to the presence or absence of rejection.

Histopathologic Correlation (KAP). The homograft biopsies in the eight most chronic cases provide some basis for histopathologic correlation since four of these patients had pretransplant thymectomy and the other four did not. The donors in each category were a mother and three siblings. There was a difference between the two groups. Whereas only one of the four patients thymectomized before transplantation had evidence of vascular lesions in his homograft (LD 1), all four patients in the nonthymectomized or post-transplant thymectomy group developed lesions in either the arterioles or the interlobular arteries of their graft. Similarly, cellular infiltration was only present in one of the transplants from the pretransplant thymectomy group but involved every transplant in the other group. Glomerular basement membrane changes occurred with equal frequency in the two groups.

Correlation with Antigen Analysis. Earlier, evidence was presented that close antigen matching increased the chances of obtaining an outstanding clinical result. If the patients with pretransplant thymectomy were demonstrated to have antigen compatibility comparable to the average pair in which this adjuvant operation was not carried out, the evidence for the value of preliminary thymic excision would be increased. In actuality, all four of the patients who received thymectomy prior to transplantation had a total unit mismatch of 6.9 per cent or less, placing them within the first ten most compatible donor-recipient pairs. This finding makes it impossible to exclude the possibility that these favored patients had such an excellent long-term result primarily as the consequence of a high degree of donor-recipient histocompatibility rather than because pretransplant thymectomy had been carried out.

Thymectomy after Transplantation. Nine patients with a complicated late course received thymectomy from 8½ to 17 months after homotransplantation in the hope that reduction of immunosuppression would thereby be facilitated. Five of the patients had developed late rejection, two had steroid-induced cataracts, one had a ureterovesical stricture requiring extensive reparative operation and one had become jaundiced. There is as yet no reason to believe that the subsequent course was influenced by the operation. All but one of the patients had been on a slowly diminishing dose of prednisone for several months, a drug withdrawal which was continued afterwards. Late rejection or further deterioration of renal function has not occurred in this group but it is possible that the same result would have been obtained without superimposition of the surgical procedure. The lymphocyte fraction of the white count was not decreased by thymectomy. Instead, the per cent of peripheral lymphocytes actually increased after removal of the thymus, a finding probably due to the further reduction of prednisone after the late operation.

The findings in these thymuses were of interest in view of the facts that all of the patients had chronically functioning homografs and had been on steroid therapy for many months. The gross morphology of all

of the glands was easily distinguishable at operation; their weights ranged from 4 to 46 Gm. Microscopically, all nine glands lacked recognizable cortex. Germinal centers and mast cells were not found. Four of the thymuses, from patients aged 22 to 41 years (LD 54, 15, 47, 30), were enlarged (mean weight 29.1 Gm.), but microscopically they contained only tiny strands of thymic medullary tissue embedded in a large quantity of relatively acellular fibro-fatty tissue. The true thymic tissue was composed of loose collections of spindle-shaped cells, larger "epithelial" cells and a few small lymphocytes. Occasional plasma cells were scattered amongst the other elements. Similar atrophic microscopic changes were present in two unenlarged thymuses (mean weight 6.3 Gm.) removed from patients aged 17 and 21 years (LD 50, 40).

Three small thymuses (mean weight 7 Gm.) from patients aged 4 to 16 (LD 13, 22, 41) contained plenty of cellular, thymic tissue composed of densely packed lymphocytes and some epithelial cells. Hassal's corpuscles, cystic in one case, were abundant but within the normal range for this age group. Plasma cells, scattered throughout the thymic tissue, were slightly more frequent than in the other six thymuses.

Discussion

Although greatly improved early results after human renal homotransplantation have been reported from several centers,[15, 23, 29, 45, 46] the procedure is still of limited utility for two fundamental reasons. First, the explanation for success or failure in individual cases is often not evident, a fact which has made it difficult to either evaluate the effect of variations in immunosuppressive therapy or extrapolate accurately from past experience for improvement of donor selection in future trials. Second, the ultimate prognosis of those patients who have already reached a chronic phase of recovery is not known. In the present study an attempt has been made to acquire data which bears on both of these general questions.

From the experience to date it seems certain that the most important single determinant of the outcome is the degree of histocompatibility which exists between the donor and recipient, a concept previously well established with animal experiments employing genetically controlled strains.[50, 56] The favorable outlook with homografts from blood relatives is explicable on this basis since the statistical probability of accidentally obtaining a satisfactory histocompatibility is good; with nonrelated donors this possibility is greatly reduced.[53] In both groups a spectrum of donor acceptability apparently exists, making it imperative that the several technics for assessing donor-recipient compatibility in advance of operation [26] be perfected and given a clinical trial.

The data on antigen analysis in the present study provide hope that the lymphocyte cytotoxicity determination may be of some value for this purpose. The patients still living had a better antigen match with their donors than would have been expected by chance; the corollary deduction is that most of those in this series with highly unfavorable matches are already dead. Moreover, the really superior clinical results tended to be in those patients whose lymphocytes lacked the fewest antigens possessed by the donor.

Despite these encouraging notations, the detailed correlation between the retrospective matching and the clinical results in the chronic survivors was irregular and incomplete. Thus, the method in its present form has several distinct disadvantages which seem due principally to the fact that antigens of unknown histocompatibility significance are being tested with polyvalent antisera and to the likelihood that antigenic screening is incomplete. An analysis of the deficiencies and advantages of the technic and the means by which the

information already obtained can be used to improve its performance are considered in detail in a separate publication.[66, 67] In addition, prospective typing studies have been undertaken in fresh cases of renal homotransplantation in order to determine if an increased rate of success can actually be attained by attention to matching.

Imperfect though antigen typing is at the present stage of development, the results from these studies are important in considering the possible influence of thymectomy upon the long-term results. The four patients with pretransplant thymic excision who have had excellent sustained homograft function also had exceptionally complete antigen matches with their donors. Until matching technics are perfected to the degree that histocompatibility can be defined with greater precision, it will be difficult in humans to prove decisively that thymectomy is of value. Should that time come, it will be possible to study series with comparable histocompatibility, half treated with and half without removal of the thymus gland.

In the meanwhile, there is a growing body of evidence from well-controlled experiments with inbred lower animals that thymectomy in adult life can prevent or slow restoration of immunologic competence after a period of depression. Miller and associates[10, 38, 39] have demonstrated in adult mice that total body irradiation plus thymectomy results in much longer potentiation of skin homograft survival than irradiation alone. The protocol in some of these studies[38] was almost identical to that employed for the early treatment of Patient LD 1 in the present report. In other experiments[10, 39] it was noted that reinfusion of isologous splenic cells prevented the protracted immunologic depression after thymectomy and irradiation, a point deserving special mention since splenectomy has been carried out routinely in our human series. Similar observations concerning the role of the adult mouse thymus in recovery of depressed immunologic capacity were recently reported by Monaco, Wood, and Russell,[40] using a heterologous antilymphocyte serum as the immunosuppressive agent and skin homotransplantation as a test system. Finally, the studies of Claman and Talmage[8] and Taylor[63] suggest that prior sensitization to an antigen does not necessarily preclude the same general effect of thymic excision in adult life, a finding which might apply in those human cases in which thymectomy was performed long after homotransplantation. In their investigations, mice were rendered tolerant to bovine gamma globulin or bovine serum albumin by intermittent injection from birth. Thymectomy in adult life materially slowed recovery from the tolerant state.

The above remarks indicate the direction of basic research being followed in a number of laboratories, involving the development of methods for detection of histocompatibility. The consequences of these efforts should be a reduction in future mortality and the establishment of criteria for the clinical evaluation of drugs, biologic methods of preventing rejection and adjuvant procedures such as thymectomy or splenectomy. An immediate practical question remains; what is the long-term prognosis of that growing body of chronic survivors treated at a less sophisticated earlier time?

Barnes[1] recently has attempted a statistical answer to this question with survival data obtained from the world Registry in Human Kidney Transplantation of September 15, 1964.[46] His study was based principally upon the death rate in the overall group during the first 1 to 2 years. The fact that almost all the mortality was early rather than late after operation led him to predict that few additional deaths would occur during the first 5 years and that sibling homografts might prove to be as durable as, or even superior to, those from identical twins. As he pointed out, the

greatest weakness of the highly optimistic predictions is the very small number of patients who actually had lived more than 2 years at the time of these calculations.

Examinations of this problem with broader criteria than death or current survival may be useful, especially since all 64 patients in the present study had been submitted to the Registry and were included in Barnes's statistics. The 37 recipients who were still alive at that time were already 5½ to 22 months postoperative and therefore contributed a sizable fraction to the total of the chronic group which occupied his attention. The fact that only one of these 37 patients has died in the subsequent 8 months tends to support Barnes's general conclusion that the late attrition after renal homotransplantation will be extremely gradual for some time to come.

Nevertheless, several considerations warn against full acceptance of these conclusions. The acute late rejection in nine patients is clear evidence of continuing host reaction against the homograft. In many of the others the same process may be occurring at a subclinical level; the reduced, although still adequate, function of the nonrelated homografts after 12 to 19 months is probably a manifestation of such a process. In many others, stable homograft performance has been possible only by continuation of potentially toxic doses of steroids.

Study of the histology of the homografts after 1 to 2 years also engenders concern that even kidneys with completely normal function may be the site of active transplant disease. Five of these nine homografts showed obliterative lesions in the interlobular arteries. Such changes have often been seen previously in the vessels of transplanted kidneys and their possible etiology has been discussed at length elsewhere.[47] The ultrastructural studies performed on the present cases now show that in these vessels not only is the intima thickened by fine collagen fibrils, which seemed probable from the earlier investigations, but that there is also a deposition of finely granular material among the fragmented elastic lamina and between the medial muscle fibers. Similar "hyaline" is also found beneath the endothelium in the afferent arterioles and glomerular capillaries of several of these homografts. The fine structure of this substance is not particularly distinctive and it resembles that found on the glomerular capillary basement membranes in both human[41] and experimental nephritis.[14] Subendothelial and intercellular deposits in renal transplants, together with proliferation of the glomerular capillary endothelial cells, have been illustrated beautifully by Hamburger *et al.*[23] They describe a patient, still alive, in whom these lesions developed in the renal homograft about 6 months after transplantation. A slow spontaneous reversal of the clinical manifestations followed and 2 years after operation proteinuria ceased. In a second case the same authors were able to show fixation on the glomerular tuft of fluorescent antibody to human globulin. Two further cases showed smaller glomerular deposits. These changes may represent chronic deposition of antibody directed against the homograft, but in our cases we have no evidence whether this material is 7s gamma globulin, let alone specific antibody.

A further indication that some at least of these homografts are still under active attack is the presence in the cellular infiltrate of a variable proportion (the highest was 40%) of characteristic lymphoid cells with abundant cytoplasm full of ribosomes. These cells were first described by Galle and Montera[17, 35] in two human renal homografts 70 and 63 days after transplantation. They found that approximately 40 per cent of the infiltrating cells were of this lymphoid type. These cells are typically found in the acute stage of renal homograft rejection in untreated animals,[48]

but similar cells infiltrate rejecting skin homografts.[68]

Despite its recent more liberal application, workers in the field have repeatedly warned of the experimental nature of human renal homotransplantation. The time has not come for changing this position, although it has become possible to predict with greater insight the ultimate role of this form of treatment in the overall medical armamentarium. It has become increasingly clear that many patients with terminal uremia can be benefited materially, with relatively complete social and vocational rehabilitation over considerable periods of time. Furthermore, the regularity with which this can be achieved, even without refinements of histocompatibility matching, is quite predictable in statistical terms. Already a prospective candidate and his or her family can be given in advance an idea of the 1- to 2-year prognosis based upon the source of the homograft. In the collection of the world results the sibling has seemed to be the most suitable donor[1, 46] although in the present study recipients of parental kidneys fared better. The outlook with homografts from nonrelated sources is poor with random donor selection such as that practiced in the past. Whether the results in all groups can be improved by histocompatibility matching, by better immunosuppressive management and by adjuvant biologic measures such as thymectomy remains to be seen. Conclusions beyond these appear unwarranted for reasons cited earlier, and for the present it would seem most reasonable to regard homotransplantation as an effective, but incompletely characterized, form of palliative therapy.

Summary

Sixty-four patients were treated from 13½ to 30 months ago with homografts from volunteer donors. Thirty-seven of these recipients lived 1 year or more; 36 are still alive with a mean survival of 19 months. Thirty-one of the 46 who received kidneys from blood relatives are still alive (67%), contrasted to only 5 of 18 who had unrelated donors (28%). In most cases, the necessary dose of immunosuppressive agents declined with the passage of time. Nevertheless, nine patients in whom steroids were partially or completely withdrawn developed a late rejection.

The function of the homografts after 13½ to 30 months ranged from adequate to completely normal. A measurable reduction in excretory capacity was present in all homografts obtained from nonrelatives and in most of the transplants which had passed through a clinically reversible late rejection. Mild and easily controlled hypertension was common. All but one of the patients is in school or gainfully employed. The principal late morbidity from the chronic administration of immunosuppressive agents has been from steroids rather than from azathioprine.

Eight renal homografts were biopsied after 1¾ to 2 years; a ninth transplant was examined at autopsy 13½ months after transplantation. Two of the biopsies were within normal limits. Six of the other seven specimens showed vascular lesions and cellular infiltration which were often not reflected in depressed function.

There were two forms of vascular change: fibrous intimal thickening of the interlobular arteries and deposits of finely granular "hyaline" material in the afferent arteriolar walls. In the glomeruli deposits of similar granular material were present on the capillary basement membranes and between the endothelial cells. The transplant examined at autopsy had severe obliterative vascular lesions affecting the arcuate and interlobar as well as the interlobular arteries. Hyperplasia of the juxtaglomerular apparatus was present in five of the eight biopsied transplants, including one which was otherwise normal. Tubular atrophy and interstitial fibrosis were present in those cases with vascular narrowing.

Up to 40 per cent of the cells infiltrating the interstitium were large, of the lymphoid series and characterized by a prominent Golgi apparatus and cytoplasm packed full of polyribosomes. Macrophages and fibroblasts were less common. Small lymphocytes and plasma cells were rare.

White blood cell antigens of the 36 surviving patients and their donors were studied with a lymphocyte cytotoxicity test to determine by retrospective analysis if this method might be helpful in evaluating the results as well as in the selection of donors for future cases. The correlation of the immunologic rating with the clinical result was imperfect in individual cases; many patients with poor matches have done well and two with good matches have had late difficulty. Nevertheless, the patients with the best course tended to be those with the least degree of antigenic incompatibility with their donors. Furthermore, the extent of donor-recipient incompatibility in the entire group was less than that which would have been predicted by indiscriminate pairing. These results suggest that the antigens being measured may have some relation, if only indirect, with histocompatibility.

Evidence is reviewed concerning the influence of thymectomy upon the course after homotransplantation in the adult human. Four patients who had their thymus glands excised before transplantation are alive after 2 to 2½ years; the adjuvant procedure did not influence the per cent of peripheral lymphocytes. All four patients have excellent and stable renal function. None are receiving steroids, and none have had any evidence of delayed rejection. The ease of late management of these patients and the degree of histologic preservation of their homografts exceed that of most of the nonthymectomized group. These findings are difficult to interpret since the degree of antigenic matching with their donors was exceptionally favorable in all four instances.

Nine additional patients have had thymectomy long after homotransplantation without demonstrable benefit to date. The lymphoid components of these glands were atrophic but the "epithelial" elements were preserved.

Addendum

During the more than 3 months since submission of the manuscript, there has been no additional mortality or loss of homografts. Twenty-four of the 36 surviving patients are currently 17 to 24 months postoperative; the other 12 are now 2 years or longer.

References

1. Barnes, B. A.: Survival Data of Renal Transplantation in Man. New Engl. J. Med., **272**: 776, 1965.
2. Burnet, F. M. and I. R. Mackay: Histology of a Thymus Removed Surgically from a Patient with Severe Untreated Systemic Lupus Erythematosus. J. Path. Bact., **89**:263, 1965.
3. Burnet, F. M. and I. R. Mackay: Lymphoepithelial Structures and Auto-immune Disease. Lancet, **2**:1030, 1962.
4. Calne, R. Y.: Inhibition of the Rejection of Renal Homografts in Dogs by Purine Analogues. Transplant. Bull., **28**:65, 1961.
5. Calne, R. Y., G. P. J. Alexandre and J. E. Murray: A Study of the Effects of Drugs in Prolonging Survival of Homologous Renal Transplants in Dogs. Ann. New York Acad. Sci., **99**:743, 1962.
6. Calne, R. Y. and J. E. Murray: Inhibition of the Rejection of Renal Homografts in Dogs by Burroughs Wellcome 57-322. Surg. Forum, **12**:118, 1961.
7. Castleman, B.: In Thymectomy for Myasthenia Gravis, (edited by M. R. Viets and R. S. Swab). Springfield, Ill., Charles C Thomas, 1960.
8. Claman, H. N. and D. W. Talmage: Thymectomy: Prolongation of Immunological Tolerance in the Adult Mouse. Science, **144**: 1193, 1963.
9. Clarke, D. A., F. S. Philips, S. S. Sternberg, C. C. Stock, G. B. Elion and G. H. Hitchings: 6-Mercaptopurine: Effects in Mouse Sarcoma 180 and in Normal Animals. Cancer Res., **13**:593, 1953.
10. Cross, A. M., E. Leuchars and J. F. A. P. Miller: Studies on the Recovery of the Immune Response in Irradiated Mice Thymectomized in Adult Life. Proc. Soc. Exp. Biol. Med., **119**:837, 1964.
11. Dammin, G. J., N. P. Couch and J. E. Murray: Prolonged Survival of Skin Homografts in Uremic Patients. Ann. New York Acad. Sci., **64**:967, 1957.
12. Dempster, W. J.: Kidney Homotransplantation. Brit. J. Surg., **40**:447, 1953.
13. Dempster, W. J.: The Effects of Cortisone on the Homotransplanted Kidney. Arch. Int. Pharmacodyn., **95**:253, 1953.

14. Dixon, F. J., J. D. Feldman and J. T. Vazquez: Experimental Glomerulonephritis. The Pathogenesis of a Laboratory Model Resembling the Spectrum of Human Glomerulonephritis. J. Exp. Med., **113**:899, 1961.
15. Dunea, G., S. Nakamoto, R. A. Straffon, J. E. Figueroa, A. Versaci, M. Shibagaki and W. J. Kolff: Renal Homotransplantation in 24 Patients. Brit. Med. J., **1**:7, 1965.
16. Fonken, H. A. and P. P. Ellis: Retinopathies of Chronic Renal Disease: Reversals after Renal Transplantation. Ann. Intern. Med., **62**:499, 1965.
17. Galle, P. and H. de Montera: Examen au Microscope Electronique des Cellules Infiltrant le Tissu Interstitiel d'un Homotransplant Renal Humain. Rev. Franc. Etud. Clin. Biol., **7**:40, 1962.
18. Glynn, L. E. and E. J. Holbrown: Distribution of Blood Group Substances in Human Tissue. Brit. Med. Bull., **15**:151, 1959.
19. Goodwin, W. E., J. J. Kaufman, M. M. Mims, R. D. Turner, R. Glassock, R. Goldman and M. M. Maxwell: Human Renal Transplantation: Clinical Experiences with 6 Cases of Renal Homotransplantation. J. Urol., **89**:13, 1963.
20. Goodwin, W. E. and D. C. Martin: Transplantation of the Kidney, Spring 1963. Urol. Survey, **13**:229, 1964.
21. Goodwin, W. E., M. M. Mims and J. J. Kaufman: Human Renal Transplantation. III. Technical Problems Encountered in 6 Cases of Renal Transplantation. J. Urol., **89**:349, 1963.
22. Gunn, A., W. Michie and W. J. Irvine: The Thymus in Thyroid Disease. Lancet, **2**:776, 1964.
23. Hamburger, J., J. Crosnier, and J. Dormont: Observations in Patients with a Well-tolerated Homotransplanted Kidney: Possibility of a New Secondary Disease. Ann. New York Acad. Sci., **120**:558, 1964.
24. Hamburger, J., J. Vaysse, J. Crosnier, J. Auvert, C. M. Lalanne and J. Hopper, Jr.: Renal Homotransplantation in Man after Radiation of the Recipient: Experience with 6 Cases since 1959. Amer. J. Med., **32**:854, 1962.
25. Hamburger, J., J. Vaysee, J. Crosnier, M. Tubiana, C. M. Lalanne, B. Antoine, J. Auvert, J. P. Soulier, J. Dormont, C. Salmon, M. Maisonnet and J. L. Amiel: Transplantation d'un Rein Entre Jumeaux non Homozygotes apres Irradiation du Receveur. Presse Med., **67**:1771, 1959.
26. Histocompatibility Testing. National Academy of Sciences—National Research Council. Washington, D. C., 1965.
27. Hogman, C. F.: Blood Group Antigens A and B Determined by Means of Mixed Agglutination on Cultured Cells of Human Fetal Kidney, Liver, Spleen, Lung, Heart and Skin. Vox Sang., **4**:12, 1959.
28. Hume, D. M., J. H. Magee, H. M. Kauffman, Jr., M. S. Rittenbury and G. R. Prout, Jr.: Renal Homotransplantation in Man in Modified Recipients. Ann. Surg., **158**:608, 1963.
29. Hume, D. M., J. H. Magee, G. R. Prout, Jr., H. M. Kauffman, Jr., R. H. Cleveland, J. D. Bower and H. M. Lee: Studies of Renal Homotransplantation in Man. Ann. New York Acad. Sci., **120**:578, 1964.
30. Hume, D. M., J. P. Merrill, B. F. Miller and G. W. Thorn: Experiences with Renal Homotransplantation in the Human: Report of Nine Cases. J. Clin. Invest., **34**:327, 1955.
31. Kauffman, H. M., Jr., R. J. Cleveland, J. J. Dwyer, H. M. Lee and D. M. Hume: Prolongation of Renal Homograft Function by Local Graft Radiation. Surg. Gynec. & Obstet., **120**:49, 1965.
32. Kirkpatrick, C. H., W. E. C. Wilson and D. W. Talmage: Immunologic Studies in Human Organ Transplantation. I. Observation and Characterization of Suppressed Cutaneous Reactivity in Uremia. J. Exp. Med., **119**: 727, 1964.
33. Küss, R., J. Teinturier and P. Millienz: Quelques Essais de Greffes du Rein Chez l'Homme. Mem. Acad. Chir., **77**:755, 1951.
34. Küss, R., M. Legrain, G. Mathé, R. Nedey and M. Camey: Homologous Human Kidney Transplantation: Experience with Six Patients. Postgrad. Med. J., **38**:528, 1962.
35. Küss, R., M. Legrain, G. Mathé, R. Nedey and M. Camey: Homotransplantation Renale chez l'Homme hors de Tout Lien de Parente. Survie Jusqu'au Dix-septieme Mois. Rev. Franc. Etud. Clin. Biol., **7**:1048, 1962.
36. Küss, R., M. Legrain, M. Camey, J. Désarmenine, G. Mathé, R. Nedey and C. Vourc'h: Homotransplantation Renale chez l'Homme. Mem. Acad. Chir. (Paris), **87**:183, 1961.
37. Mackay, I. R., G. Goldstein and I. M. McConchie: Thymectomy in Systemic Lupus Erythematosus. Brit. Med. J., **2**:792, 1963.
38. Miller, J. F. A. P.: Immunological Significance of the Thymus of the Adult Mouse. Nature (Lond.), **195**:1318, 1962.
39. Miller, J. F. A. P., E. Leuchars, A. M. Cross and P. Dukor: Immunologic Role of the Thymus in Radiation Chimeras. Ann. New York Acad. Sci., **120**:205, 1964.
40. Monaco, A. P., M. L. Wood and P. S. Russell: Effect of Adult Thymectomy on the Recovery from Immunologic Depression Induced by Heterologous Antilymphocyte Serum. Science, **149**:432, 1965.
41. Movat, H. Z., J. W. Steiner and D. Huhn: The Fine Structure of the Glomerulus in Acute Glomerulonephritis. Lab. Invest., **11**:117, 1962.
42. Murray, J. E. and J. H. Harrison: Management of 50 Patients with Kidney Transplants Including 18 Pairs of Twins. Amer. J. Surg., **105**:205, 1963.
43. Murray, J. E., J. P. Merrill, G. J. Dammin, J. B. Dealy, G. W. Alexandre and J. H. Harrison: Kidney Transplantation in Modified Recipients. Ann. Surg., **156**:337, 1962.
44. Murray, J. E., J. P. Merrill, G. J. Dammin, J. B. Dealy, C. W. Walter, M. S. Brooke and R. E. Wilson: Study on Transplantation Immunity after Total Body Irradiation: Clinical and Surgical Investigation. Surgery, **44**: 272, 1960.
45. Murray, J. E., J. P. Merrill, G. J. Dammin, J. H. Harrison, E. B. Hager and R. E. Wilson: Current Evaluation of Human Kidney Transplantation. Ann. New York Acad. Sci., **120**: 545, 1964.
46. Murray, J. E., R. Gleason and A. Bartholomay: Third Report of the Human Kidney Transplant Registry. Transplantation, **3**:294, 1965.

47. Porter, K. A.: Pathological Changes in Transplanted Kidneys *In* Experience in Renal Transplantation, ed by T. E. Starzl. Philadelphia, W. B. Saunders Co., 1964. pp. 299–358.
48. Porter, K. A., N. H. Joseph, J. M. Rendall, C. Stolinski, R. J. Hoehn and R. Y. Calne: The Role of Lymphocytes in the Rejection of Canine Renal Homotransplants. Lab. Invest., **13**:1080, 1964.
49. Porter, K. A., T. L. Marchioro and T. E. Starzl: Pathological Changes in 37 Human Renal Homotransplants Treated with Immunosuppressive Drugs. Brit. J. Urol., **37**: 250, 1965.
50. Rogers, B. O.: Genetics of Transplantation in Humans. Dis. Nerv. System, **24** (monograph suppl):3, 1963.
51. Schreiner, G. E.: Determination of Inulin by Means of Resorcinol. Proc. Soc. Exp. Biol. Med., **74**:117, 1950.
52. Shackman, R., W. J. Dempster and O. M. Wrong: Kidney Transplantation in the Human. Brit. J. Urol., **35**:222, 1963.
53. Simonsen, M.: Strong Transplantation Antigens in Man. Lancet, **1**:415, 1965.
54. Simonsen, M., J. Buemann, A. Gammeltoft, F. Jensen and K. Jorgensen: Biologic Incompatibility in Kidney Transplantation in Dogs. I. Experimental and Morphologic Investigations. Acta Path. Microbiol. Scand., **32**:1, 1953.
55. Smith, H. W., N. Finkelstein, L. Aliminosa, B. Crawford and M. Graber: Renal Clearances of Substitutes Hippuric Acid Derivatives and Other Aromatic Acids in Dog and Man. J. Clin. Invest., **24**:388, 1945.
56. Snell, G. D.: The Genetics of Transplantation. J. Nat. Cancer Inst., **14**:691, 1953.
57. Starzl, T. E.: Experience in Renal Transplantation. Philadelphia, W. B. Saunders Co., 1964.
58. Starzl, T. E., T. L. Marchioro, K. A. Porter, C. A. Moore, D. Rifkind and W. R. Waddell: Renal Homotransplantation: Late Function and Complications. Ann. Intern. Med., **61**:470, 1964.
59. Starzl, T. E., T. L. Marchioro, K. A. Porter, P. D. Taylor, T. D. Faris, T. J. Herrmann, C. J. Hlad and W. R. Waddell: Factors Determining Acute and Chronic Survival after Orthotopic Liver Homotransplantation in the Dog. Surgery, **58**:131, 1965.
60. Starzl, T. E., T. L. Marchioro, D. Rifkind, J. H. Holmes, D. T. Rowlands, Jr. and W. R. Waddell: Factors in Successful Renal Transplantation. Surgery, **56**:296, 1964.
61. Starzl, T. E., T. L. Marchioro, D. W. Talmage and W. R. Waddell: Splenectomy and Thymectomy in Human Renal Homotransplantation. Proc. Soc. Exp. Biol. Med., **113**:929, 1963.
62. Szulman, A. E.: The Histological Distribution of the Blood Group Substances A and B in Man. J. Exp. Med., **111**:785, 1960.
63. Taylor, R. B.: An Effect of Thymectomy on Recovery from Immunological Paralysis. Immunology, **7**:595, 1964.
64. Terasaki, P. I., T. L. Marchioro and T. E. Starzl: Serotyping of Human Lymphocyte Antigens. II. Preliminary Trials on Long Term Kidney Homograft Survivors, *in* Nat. Acad. Sci. Monograph, Histocompatibility Testing, 1965. pp. 83–96.
65. Terasaki, P. I. and J. D. McClelland: Microdroplet Assay of Human Serum Cytotoxins. Nature (Lond.), **204**:998, 1964.
66. Terasaki, P. I., D. L. Vredevoe, T. E. Starzl, T. L. Marchioro, T. D. Faris and T. J. Herrmann: Serotyping for Homotransplantation. V. Evaluation of a Matching Scheme. Submitted for publication.
67. Vredevoe, D. L., P. I. Terasaki, M. R. Mickey, R. Glassock, J. P. Merrill and J. E. Murray: Serotyping of Human Lymphocyte Antigens III. Long Term Kidney Homograft Survivors. Submitted for publication.
68. Wiener, J., D. Spiro and P. S. Russell: An Electron Microscopic Study of the Homograft Reaction. Amer. J. Path., **44**:319, 1964.
69. Woodruff, M. F. A., J. S. Robson, B. Nolan, A. Lambie, T. I. Wilson and J. G. Clark: Homotransplantation of Kidney. Lancet, **2**: 675, 1963.

Discussion

Dr. Wilhelm Brosig (Berlin-Charlottenburg, Germany): Dr. Starzl's work and results in the field of kidney transplantation are outstanding, and the best which have been reported. I wish to extend my congratulations to him and the other American surgeons who have done pioneer work in the field of organ transplantation.

In Germany have been made only reluctant attempts in kidney transplantations; stimulated by a talk by Dr. Goodwin at the Free University of West Berlin in 1959 we started first in experimental work.

Since October, 1963, we have performed five homotransplantations in man. One patient is living over 12 months with good kidney function. All others have died, one 8 months after transplantation from sepsis; another 4 weeks after transplantation, also from sepsis; another 6 days from a disruption of the transplanted kidney, and the fifth one from acute rejection within 5 days.

Our results are rather poor compared with the achievements made in the American clinics. But we have made a start, and this was only possible by the support and advice of our American colleagues.

Dr. David M. Hume (Richmond): I had the pleasure of reading Dr. Starzl's manuscript, and should like to say that our own results and conclusions are very similar to his.

We have carried out renal homotransplants in 40 patients more than a year ago. Of this group, 21 patients are alive at the present time. Thirty-

one of 40 patients had living donors, of which 27 came from relatives. Nine of the group had cadaver kidneys; 53 per cent of the entire group are alive after more than one year. There are eight patients, all told, who were transplanted over two years ago. Five of the eight patients (63%) are living at the present time. Six had living donors; two had cadaver donors; two had second transplants.

In our own group, no matching was attempted, and all the cases, including the cadavers, are counted. Twenty of the 21 patients surviving over a year have essentially normal kidney function. No patient in the entire series has died after one year, although two have chronologically rejected their transplants at 15 and 16 months and are doing well with retransplants.

Of these patients receiving transplants in the last year over 90% are living at the present time, and half of this group had cadaver donors. Splenectomy was performed in 30 of 60 patients. We no longer do splenectomies because of the increased complication rate in splenectomized patients of infection and thrombo-embolic phenomena, and because we could not demonstrate any immunologic benefit from this procedure. We have had no late ureter problems of the sort Dr. Starzl has seen and ascribed to rejection of the ureter. There has been only one significant ureter complication in 60 transplants. We have seen some late microscopic changes which are identical to the ones he described here, and we certainly agree with him that the kidney has to fight to keep its place in the sun.

We think that perhaps there may be good donors and bad donors, rather than donors which precisely match their recipients. Some of our studies have suggested the possibility that there may be a sort of universal donor, whose kidney is good for any recipient, while other donors are not very good no matter who gets the kidney.

Dr. Paul S. Russell (Boston): I should like to comment upon three points: First, the very real importance of donor selection. The basic rules of immunogenetics are well substantiated in the results of the world experience of more than 500 kidney transplants. It is quite clear that the more closely related the donor is to the recipient, the less will be the antigenic barrier between them. The method of matching now being developed by Dr. Terasaki of UCLA, with whom Dr. Starzl has collaborated, is an ingenious improvement over Dausset's original work, and appears to be quite promising from the retrospective studies so far done.

It is only one of several different matching approaches currently under study, and does not, of course, result in knowledge of characterized and defined antigens as is now possible with the erythrocyte groups. It is my guess that full definition or typing of the operative antigens provoking transplantation immunity will eventually be possible. If so, this will be preferable to any of the matching methods alone.

The second point I would like to raise is that even after these transplants have been doing well for periods of weeks and months, their immunologic relationship to the host is highly variable. In general, there tends to be a low-grade process of immunologic destruction in many of the transplants over a long period of time. This is not always the case, however, and here is an example of what appears to be just the opposite.

(Slide) This is a biopsy, taken at 60 days, of a kidney transplant to a 35-year-old man with terminal glomerulonephritis, who received this kidney from an older brother. There is a heavy infiltrate, predominantly of mononuclear cells, which we thought was a very ominous sign, indeed. Nevertheless, his kidney function continued to be nearly normal, and the second biopsy (Slide) at 10½ months showed considerable clearing of the cellular infiltrate, even though no change in his basic program of immunosuppressive treatment had been made in the meanwhile.

(Slide) At a year and a half, the infiltrate had reached almost completely. The patient now has entirely normal renal function and has been back to his full program of work over 2 years after operation.

I will not labor you as to our guesses as to the mechanism of this striking improvement, but it probably represents a phenomenon of fundamental importance.

Finally, I should just like to mention that in a current series of experiments Dr. Anthony Monaco and I have found clear evidence that thymectomy in the adult mouse, quite distinguished from the newborn mouse, greatly delays the animal's ability to restore its lymphoid tissues following injections of the specific antilymphocyte serum. Splenectomy does not have this effect. These observations, therefore, suggest that thymectomy may prove to have a certain place in clinical transplantation in the future.

Dr. Willard E. Goodwin (Los Angeles): I have had the privilege of reading the manuscript and can assure you that for anyone interested in the field of kidney transplantation, this represents the best synthesis of information and summary of results from one group to date. It is truly impressive.

Future hopes for transplantation, as Dr. Starzl pointed out, are in better matching, better drugs, and perhaps some manipulations to change the immunologic mechanism. We wish we could get Dr. Terasaki to do more of these matching tests for us at U.C.L.A.; but often he has been so busy working for Dr. Starzl that we could only get him to do it once in a while.

May I show you an example of unexpected transplantation of a cancer from donor to recipient, along with a renal homograft. The donor died of bronchogenic carcinoma with brain metastases.

This slide shows the clinical course of the recipient who received the transplanted kidney in August 1964. At the time of the transplantation there was nothing to suggest local involvement of the transplanted kidney with cancer. You see that the patient received immuran and prednisone. In December, he began to be sick and had a swelling in the transplanted kidney. Nonetheless renal function remained nearly normal up to the time of death. A biopsy of the transplanted kidney showed normal cortex, but in this next slide we see cancer growing in the medulla.

We thought that when immunosuppressive drugs were stopped the cancer would die. However, it did not work out that way. Things moved too rapidly. The transplanted tumor metastasized and killed the recipient. This case will be reported in detail by my associate, Dr. Donald Martin. (J.A.M.A., 192:752, 1965.)

We are still continuing to use some kidneys for transplantation from cadavers. Nonetheless, we are very concerned about what they die of.

In my view, we should not give up totally the idea of patients with cancer as prospective renal donors. We have one very striking success about which I told you a year ago. An entirely unrelated man received a *free kidney* from a man who had cancer of the ureter, which was treated by nephroureterectomy in June 1963. The receipient is still alive and well.

One may even speculate that: *the very fact that the donor* HAD *a cancer may in some unexplained way account for this uncommonly good result* of unrelated renal homotransplantation.

DR. RALPH STRAFFON (Cleveland): I had an opportunity to review the manuscript. As you might imagine, securing live donors in a large series of patients is always difficult. Dr. Starzl's series concerns the use of kidneys from live donors. We have a fairly large series in which cadaver donors have been the primary source of kidney homografts.

(Slide) This deals with our experience from January 1963 until April 15, 1965. During this period of time, 40 patients received 47 renal transplants from cadaver donors. At the present time 23 patients have survived. Twenty-one have functioning kidneys, which gives an over-all survival of about 52%.

If you look at it from the years, during the first year, 1963, our results were not very good, perhaps because of the poor selection of donors. Since then, results have steadily improved.

(Slide) It is difficult to obtain kidneys for transplantation whether using living or cadaver donors. In all cases we have used both kidneys of the cadavers for transplantation, doing two simultaneous transplantations, which is an added advantage. We found from experience that patients who died suddenly are the best source of donor kidneys in the cadaver group.

Other hospitals in Cleveland have co-operated in supplying cadaver donors. Three kidneys for transplantation were brought from other hospitals to our hospital. Two of them are successful and one is so recent it is too soon to evaluate.

(Slide) When one is employing cadaver kidneys, one must usually expect a period of acute renal failure in the recipient. In our 47 patients, only 5 have not required dialysis postoperatively. The period of oliguria has ranged from a few days to 24 days.

The logistic problem in cadaver transplants prolongs the period of renal ischemia. The ischemic period has ranged from 1⅔ hours to 5½ hours in cadaver transplants in contrast to 20 or 30 minutes when live donors are used.

(Slide) This shows the duration of survival after transplantation with cadaver homografts. The survival periods are not so long as Dr. Starzl's group with live donors—we have one now that is approaching two years. We have three surviving more than a year, and eight patients in the 9 to 12-month category, with functioning kidneys.

The patients that are alive beyond the 3-month period are doing well and their renal function is as good as that in our live donors in the same category. There are enough encouraging results with cadaver transplants to encourage investigation in this field.

DR. RICHARD WILSON (Boston): I can only second what Dr. Goodwin had to say about this paper. It is a magnificent exposition of his work with these patients.

I would like to make a couple of comments. First of all, the problem at the moment with the early postoperative lack of survival is, in part, due to acute rejection phenomena—an inability to predict which patients are going to be able to go on and fall into long-term periods.

One of the things that we have been trying to do to improve the initial results is to add thoracic duct fistula and antigen competition to the initial treatment of these patients, in an attempt to carry some people through this early period. It is still too early to say what the results are, but they are suggestive that we have not had to place patients on therapy for acute rejection within the first 3 weeks since we have begun this program.

Secondly, we have done a series of splenectomized and nonsplenectomized patients and have also given up splenectomy, as Dr. Hume has, because we were not able to show any evidence that splenectomy provided a better result.

With regard to the thymectomy in the long-term patients, it is interesting that we have two patients over 2 years not on steroids. One of them received steroids for 4 days only, at about 6 weeks after transplant, and then they were stopped. Another one was placed on steroids at about a year and a half in an attempt to reverse what we thought was beginning difficulty with a late rejection. The steroids were stopped because he developed GI bleeding, and he has never had them since. Both patients have creatinine clearance which are normal, and it is, as Dr. Starzl intimated

in both his talk and his manuscript, very difficult to know what the role of thymectomy in the long-term results are, with the lack of definite antigen matching.

Finally, I would like to ask Dr. Starzl a question because we believe that with the therapy at the moment still being rather empiric, or quite empiric, the most important thing that we can do is to diagnose rejection as early as possible in these patients, and then institute the most efficient treatment—whatever you think it is—for this acute rejection phenomenon, in order to improve the result and prevent progressive damage to the kidney.

We have been trying to do arteriograms on these patients to pick up early rejection. We have done a large study with renograms and are continuing to do many serial renograms. We are doing frequent biopsies, and I would like to hear more about his thoughts about the early diagnosis of acute rejection.

MR. ROY CALNE (London, England): Anybody who has had the privilege to visit Denver recently must have been impressed by the phenomenal energy that is being devoted by this group toward studying the problems of organ transplants.

I think that there are two major contributions that this paper provides. First it shows what can be achieved with technical excellence and attention to the minuitiae of details in clinical care. Secondly, the collection and very careful documentation of comprehensive data on these cases will be of lasting importance.

Everybody working in this field is worried by the ethical problems that transplantation from live donors raises, and I think that Dr. Starzl's extremely careful approach to the patients has provided data which will always be of value to future workers in live and cadaver organ transplantation.

I would like to comment on the Terasaki test, and most other methods that have been used for donor typing. They may be relevant to the donor and recipient in question, but they do not provide definitive tissue groups that can be related from one case to another throughout the world in the same way as A.B.O. blood groups. I fear that even if we do get a perfect method of tissue-typing we will be faced with new problems of finding a good donor who happens not to want to give his kidney.

With regard to the question of thymectomy. We have thymectomized adult dogs and found this procedure to be of no value in prolonging survival of transplants when combined with the standard immunosuppressive therapy. However, there are obviously great species differences, and as you heard, the adult mouse seems to respond well to a thymectomy.

DR. T. E. STARZL (closing): Since the hour is late I will confine my remarks to those specific questions which have been raised. First, Dr. Hume has already told you that his over-all results include not only those patients with living donors but those with cadaver homografts as well. Our cadaver group, consisting of three unsuccessfully treated patients, has not been included in this analysis. By confining our attention to those cases with living donors the experimental situation was largely equivalent throughout the series, allowing somewhat clearer conclusions to be drawn. Dr. Hume's results and those from the Cleveland Clinic have really been magnificent in the cadaver field, and their efforts, I am sure, will promote research in this area.

I meant to make clear the fact that we have reached no conclusions about the effects of thymectomy in the human; the results are uninterpretable. The point that I did wish to make was that those patients, who received this additional procedure and who lived for a long time after subsequent transplantation, seemed not to have very much late immunologic activity directed against their graft. Whether or not thymectomy contributed to the benignancy of the late course is not known.

Concerning the early diagnosis of rejection, we have been very interested in the work done by Kountz and Cohn and their associates at Stanford, concerning the diminution of blood flow which seems to precede overt rejection.

Although it is too early to be certain, it may be that importance of early diagnosis of rejection may be somewhat lessened with refinements of antigen matching technics. Since last fall, Dr. Paul Terasaki has been performing prospective typing on our new patients, and the vigor of rejection in these later cases has seemed to be generally less than that observed in the original series. In fact, there have been no acute secondary anurias since Dr. Terasaki has selected our donors for us.

I think Dr. Terasaki, if he were here, would probably make the same remarks about his technic, in a self-critical vein, as Dr. Calne already has. The weakness of the method is, of course, the fact that one is measuring something unknown with a polyvalent antiserum, and as Dr. Calne has pointed out, it is a little bit like shooting buckshot in the air, hoping to strike an unspecified target.

Dr. Terasaki's objective is to use the data from these and other human cases to try to distinguish which of the antigenic units now being measured are related to histocompatibility, so that in the long run a practical and simple method of histocompatibility measurement can be evolved.