Reprinted from ANNALS of SURGERY, Vol. 180, No. 4, October 1974. Copyright, © 1974, by J. B. Lippincott Company.
Printed in U.S.A.

334

A Decade Followup in Early Cases of Renal Homotransplantation

T. E. STARZL, M.D., K. A. PORTER, M.D., C. G. HALGRIMSON, M.D., B. S. HUSBERG, M.D., I. PENN, M.D., C. W. PUTNAM, M.D.

From the Department of Surgery, University of Colorado Medical Center and the Denver Veterans Administration Hospital, Denver, Colorado 80220; and the Department of Pathology, St. Mary's Hospital and Medical School, London, England

Sixty-four consecutive patients underwent renal homotransplantation 10 1/6 to 11½ years ago, 46 from related and 18 from nonrelated living donors. Thirty-six of these recipients were alive when this series was presented to the American Surgical Assocation in 1965. Now, nine years later, 26 (72%) of the 36 still survive, in 22 instances with function of their original grafts. The 10 who died in the interim tended to have subnormal renal function or graft failure. However, the actual causes of death included 2 or more examples each of myocardial infarction, hepatitis, or other systemic infections. The prognosis for achieving a one decade survival was not obviously related to HL-A tissue match. The best results were with related kidneys, within which subgroup 24 (52%) of the original recipients are still alive. However, there was no particular category of consanguineous donor that had a marked superiority. Only 2 of 18 nonrelated recipients are still alive. All 36 patients who were alive in 1965 had a biopsy of their renal homograft. Kidneys that were destined to function for a decade tended to have relatively minor histopathologic abnormalities. If serious glomerular lesions were found, the outlook for long graft survival was grave. Vascular lesions had a somewhat less serious import. Mononuclear cell infiltration, tubular atrophy, and interstitial fibrosis proved prognostically to be the least significant. Long-term followup of these early cases has shown the durability of chronic renal homografts, particularly if these are from related donors, and has demonstrated the very high degree of rehabilitation that could be achieved even in the early days of renal homotransplantation.

At the May 1965 meeting of the American Surgical Association a report[24] was given on 64 consecutive renal homograft recipients treated at the Colorado General and the Denver Veterans Administration Hospitals. Thirty-six of these patients were still alive 13½–30 months postoperatively.

The climate between November 1962 and March 1964, when the series was compiled, had overtones of anxiety as well as excitement. Because the degree of success being achieved had not been anticipated by basic immunologists and for that matter was not yet generally appreciated by clinicians, expressions of criticism and concern were common.[3] Even those aware of the encouraging statistics of 1962–1963 conceded that the ultimate prognosis of the renal recipients still living was not predictable, since only very isolated examples of long-term survival had been recorded before this time.[8,11,13–15,22]

With the passage of nine more years, followups exceeding a decade are now available for the 26 patients who still survive from the early Colorado series of 1962–1964. Using the data of the American College of Surgeons Transplant Registry for a reference, these residual 26 patients account for about half of those in the world who were treated before March 1964 with renal homotransplantation and who remain alive today. Thus a description of their fate may serve as a bellweather for recipients treated in subsequent years who have been followed for briefer periods.

Methods

The 64 cases have been described elsewhere in great detail, including surgical techniques and management.[23] Transplantation was from related donors in 46 instances, including 23 siblings, 20 parents, one aunt, one uncle, and one cousin. The other 18 donors were normal healthy volunteers. In six of the 64 cases, there was immediate or very early failure of an initial homograft which was promptly removed. A second kidney was provided 6–47 days after the original operation. In the foregoing description of organ source and

Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

Supported by research grants from the Veterans Administration; by grants AI-AM-08898 and AM-07772 from the National Institutes of Health; by grants RR-00051 and RR-00069 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

in subsequent remarks only the second or definitive donor for these six recipients is considered.

Typing procedures were not available when this series was compiled. After Case 23, the kind of red blood cell type incompatibility that can lead to hyperacute rejection[23] was avoided. Otherwise, the donor-recipient matching was not by any kind of immunologic guidelines. Parenthetically, one of our earliest recipients (LD 2) is still alive with perfect graft function eleven years and three months after transplantation from a B+ red cell type donor to an A+ type recipient, a combination which would no longer be used.

Between 1964 and 1970, retrospective HL-A typing was performed by Terasaki of Los Angeles on surviving recipients and their donors.[26] As a consequence, a statement about the quality of HL-A match can be made for the last 36 survivors. This was expressed as a letter histocompatibility grade. An A match indicated identity of the measured donor and recipient HL-A antigen groups. With a B match, no incompatibilities were present, but there were one or more examples of non-identity or else nonconformity of unclassified antigens. C and D-E matches were progressively less satisfactory with frank mismatches of one, two or more antigen groups. Because new HL-A groups were discovered and characterized throughout the period of analysis, the basis for grading was more complete and consequently more accurate at the end of the study than at the beginning.

Immunosuppression was with the double drug combination of azathioprine and prednisone. Two regimens were used.[23,25] In 45 cases azathioprine was started alone; prednisone was added in 43 of these 45 patients with the appearance of clinically obvious rejection. In the other 19 recipients both drugs were administered from the outset. Actinomycin C and local homograft irradiation were employed irregularly.

All 64 recipients had splenectomy. The first eight, of whom four are still alive (LD 1, 2, 3, 6) had pretransplantation thymectomy; patient LD 1 has undergone retransplantation. Nine additional patients had thymectomy 8½–17 months after transplantation in the hope of being able to reduce immunosuppression (LD 13, 15, 22, 30, 40, 41, 47, 50, 54). Five of the latter nine recipients are still alive but two are dependent upon retransplanted kidneys and a third one is presently anephric. Although thymectomy may have a subtle long-term immunosuppressive effect in adult humans,[26] it is no longer performed at our institution either before or after transplantation.

Between 21 and 26 months postoperative, 35 of the 36 patients living in 1965 had open homograft biopsy; the thirty-sixth graft (LD 44) was retrieved by homograft nephrectomy after 60 months. In seven cases, it was possible to compare two-year biopsies with the same kidney retrieved 2½–7 years later at autopsy or homograft nephrectomy. Invariably the same abnormalities were present both times but were more advanced on the later occasion.

All the tissues were examined by light microscopy. Sections were cut at both 5 μ and 0.5 μ. The former were stained with hematoxylin and eosin, periodic acid Schiff (PAS), Weigert's for elastic counterstained with hematoxylin and van Gieson, and methyl green pyronin. The 0.5 μ thick sections were stained with Azur 2.

Electron microscopy was carried out on all of the specimens. The tissue from biopsies was primarily fixed in Palade's buffered osmium tetroxide and embedded in Epon 812. Autopsy material was fixed in buffered formalin and then post-fixed in osmium tetroxide. Ultrathin sections were stained with lead citrate and examined in a Phillips 300 electron microscope.

From 27 of the homografts, samples of tissue were frozen in liquid nitrogen and stored at −70 C until examined. Sections 4 μ thick were cut in a cryostat and stained with fluorescein conjugated antisera. The fluorescent reagents used were antisera made in rabbits and goats to human IgG, IgM, fibrinogen, C'lq and β1C/β1A globulin. Specificity of the antisera was confirmed before application to the tissue by immunoelectrophoresis and double diffusion in agarose. Specificity of the fluorescence was established by blocking positive reactions with unconjugated antisera, by absorption of the labelled antisera with specific antigens, and by the use of an antihuman serum albumin control.

Using light microscopic and ultrastructural analysis, the presence or absence of the following features was determined in the homografts: 1) subendothelial glomerular capillary basement membrane thickening; 2) subepithelial glomerular capillary basement membrane thickening; 3) increased cellularity of the glomerular tufts; 4) increased amount of mesangial matrix; 5) tubular atrophy; 6) interstitial fibrosis; 7) mononuclear cell infiltration of the interstitium; 8) "hyaline" in the ateriolar walls; and 9) thickening of the intima of the interlobular arteries. In addition, the frozen tissues were used to determine deposits of IgG, IgM, complement or fibrinogen in the glomeruli. The lesions and deposits were graded in severity from 0 to 4.

Eventually, the Glomerular Categories 1–4 were combined and averaged to reach a summary score of the magnitude of abnormalities (glomerular index); the immunofluorescence examinations were always roughly confirmatory of the morphologic scores. The grades for all nine microscopic categories were averaged for an overall "pathologic index." The ultimate fate of these kidneys was correlated with the various pathologic lesions.

In 33 of the 36 cases, the patients' own diseased kidneys were examined and the findings were ultimately compared to those in the homografts. These specimens were all studied by light microscopy and in a few instances by immunofluorescence and/or electronmicroscopy.

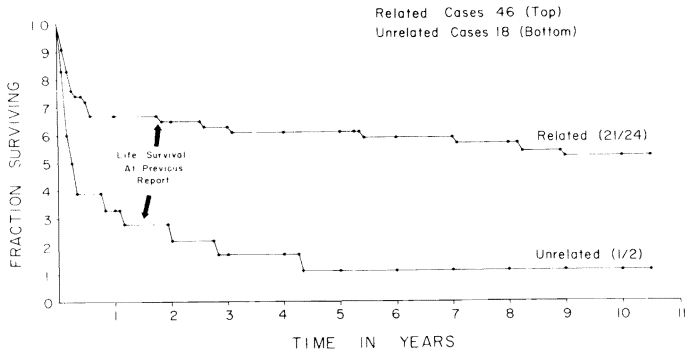

FIG. 1. The life survival curves of 64 patients treated by renal transplantation between the autumn of 1962 and March 1964. These cases were reported to the American Surgical Association in May 1965, at which time the life survival curves had evolved to the points indicated by the black arrow. Note that 72% of the survivors of 1965 are still alive 9 years later. The denominators in parentheses indicate the number of living recipients and the numerators indicate the original homografts that are still functioning.

Results

Survival

Related Cases. By May 1965, 15 of the 46 related recipients had died, leaving a residual group of 31 (Fig. 1). At the three-, five- and ten-year marks, the recipients remaining numbered 29, 28 and 24 respectively. There are 24 or 52% of the original 46 who are still alive after 10⅙–11½ years. No one of the survivors is now on dialysis. Twenty-one of the 24 have function of their original grafts. The other three underwent retransplantation (Table 1) when their original kidneys failed after 5½ years (LD 1), 6 years (LD 41) and 5 years (LD 50). Second grafts from the other parent have functioned satisfactorily for 6 years in Patient LD 1 and 4½ years in LD 50. The third patient (LD 41) has had four cadaveric retransplantations. The first three of these grafts underwent hyperacute, acute, or delayed rejection. The final kidney has been functioning satisfactorily for 16 months.

The survival in the consanguineous cases was not strikingly influenced by the nature of the relationship (Table 2). After parent-to-offspring transplantation, 14 of 20 recipients (70%) were alive at the end of six months. By 10⅙–11½ years there were still 13 (65%) alive, although three of these have undergone retransplantation. Also of interest was the fact that all of the three distantly related renal grafts (aunt, uncle, and cousin) were providing stable function more than a decade after their insertion (Table 2). The greatest attrition was of sibling recipients (Table 2), amongst whom a 61% one-year survival had eroded to 35% after a decade.

Nonrelated Cases. By May 1965, only five of the 18 nonrelated recipients were still alive (Fig. 1). In the intervening nine years, three more have died leaving only two. One of these two recipients who is now ten years, two months, probably has the longest continuously functioning unrelated homograft in the world. The second surviving patient lost his unrelated graft after a little more than two years (LD 54). He underwent successful retransplantation with his mother's kidney in September 1966 (Table 1). After six years of essentially normal function, he became mentally depressed and discontinued all immunosuppression. After five or six months the maternal kidney failed. He was returned to chronic hemodialysis and is awaiting a cadaver organ.

Causes of Late Death. The ten patients who died between 1965 and 1974 included seven recipients of related grafts and three recipients of unrelated organs; five of them (LD 15, 18, 36, 47 and 48) had life-sustaining although subnormal function of their original grafts from one-and-three-quarters to nine years postoperatively (Table 3). The deaths of two of these five patients were caused by acute myocardial infarction (LD 18 and LD 48). A third patient who died almost nine years after transplantation (LD 15) had moderately severe chronic aggressive hepatitis which was first diagnosed eight years earlier; in addition, the immediate cause of death was acute hemorrhagic pancreatitis. The two other patients who died with functioning original kidneys (LD 36 and 47) had multiple infections (Table 3).

One of the other five patients died after he was placed back on dialysis but before retransplantation could be considered (LD 45). He had a cardiac arrest just at the conclusion of a dialysis treatment.

The other four patients had attempts at retransplantation which were followed by a variety of lethal complications (Table 3), including suicide, perforated sigmoid diverticulitis and bronchopneumonia. The longest sur-

TABLE 1. *Four Patients Alive After One or More Late Retransplantations*

LD Number	Date First Transplantation	Original Donor	Date Retransplantation(s)	Retransplant Donor	Present BUN mg%	Present Ccr ml/min	Present BP mml/Hg	Prednisone mg/day	Total Survival Years
1	11/24/62	Mother	5/21/68	Father	18	60	100/70	15	11.4
41	11/23/63	Mother	1/22/70 6/29/70 2/27/71 12/29/72	Cadavers	29	40	124/90*	25	10.4
50	1/25/64	Father	11/7/69	Mother	29	48	120/85	14	10.3
54	2/24/64	Unrelated	9/26/66	Mother	Anephric for 1 1/2 yrs.			0	10.2

* Receiving reserpine and hydralazine.

TABLE 2. *Influence of Consanguinity Upon Present Survival in 46 Related Cases, 10 1/6–11 1/2 Years Later*

Donor	1 Year		3 Years		5 Years		Now	
	Patient	Graft	Patient	Graft	Patient	Graft	Patient	Graft
20 Parents	14	14	14	14	14 (70%)	14 (70%)	13 (65%)*	10 (50%)
23 Siblings	14	14	12	12	11 (48%)	11 (48%)	8 (35%)	8 (35%)
3 Aunt, Uncle, or Cousin	3	3	3	3	3 (100%)	3 (100%)	3 (100%)	3 (100%)

* Retransplantation was carried out after 5 1/2, 5 3/4, and 6 1/6 years.

viving patient (LD 40) died of hepatic failure secondary to chronic aggressive hepatitis, Australia antigen positive, 18 months after successful cadaveric retransplantation and eight years, two months after the original transplantation.

Renal Function, Blood Pressure and Immunosuppression

The current renal functions of the four survivors who have undergone retransplantation is shown in Table 1. Table 4 contains the functions from 22 primary kidneys that have functioned for 10⅙ to 11½ years. On the average, the function of the organs is superb. Only one of the original grafts is distinctly subnormal.

The average daily doses of prednisone are small enough so that only one of the 26 patients (the most recent retransplant) has a Cushing's facies. There are no examples of steroid-induced diabetes. Most of the patients have had stable azathioprine doses for years.

Over the years, we have had a number of patients discontinue immunosuppressive treatment, usually because of indifference to the tedium of following a therapeutic schedule. One of the chronic survivors (LD 49) in this early series discontinued all medications about 14 months ago without any untoward effect to date. Another recipient (LD 3), who also was brain-damaged from a stroke prior to transplantation, has become an alcoholic in the 11¼ years of survival. This patient who has never required prednisone probably discontinued has azathioprine in 1970 or 1971.

Arterial hypertension is an almost universal finding in the immediate posttransplantation period and even for several years afterwards.[26] With longer followup, only one of the 25 survivors who has renal function (and this the retransplant recipient of 16 months ago) has severe hypertension. Four other patients receive small daily doses of antihypertensives. The other recipients require no antihypertensive therapy.

The Influence of HL-A Match

Among the 36 patients alive in May 1965, the quality of the HL-A match did not profoundly influence the durability of the homografts in the succeeding nine years (Tables 4, 5).

The Incidence of Malignancy

Neoplasia was not diagnosed in any of the 28 patients who died before May 1965, after survivals that had ranged from a few days to more than 13 months. Six (17%) of the 36 recipients who remained alive at that time developed malignant lesions at some time during the ensuing nine years. These tumors all originated in the skin and were all successfully treated with conventional means. The features of these carcinomas are summarized in Table 6.

Rehabilitation

The social and vocational rehabilitation amongst the 26 present survivors has been very nearly complete.

TABLE 3. *Cause of 10 Deaths Occurring Since May, 1965*

LD No.	Age at First Transplant	Patient Survival	Kidney Function Just Before Death			Cause of Death	Time Retransplantation Before Death
			BUN (mg%)	Cr (mg%)	Ccr (ml/min)		
15	23	8 yr., 11 mo.	70	2.5	30	Pancreatitis Chronic aggressive hepatitis	No
18	39	2 yr., 6 mo.	32	1.6	60	Myocardial infarction	No
27	20	2 yr., 9 mo.		Failed Kidney		Bronchopneumonia	1 Month
30	40	4 yr., 3 mo.	25	1.6	15	Perforated sigmoid diverticulitis	2 Months
36	43	1 yr., 11 mo.	50	1.5	30	Systemic CMV infection Chronic aggressive hepatitis Sacral cellulitis	No
40	21	8 yr., 2 mo.	60	1.4	40	GI bleeding Chronic aggressive hepatitis Hepatic failure	18 Months
44	48	5 yr., 4 mo.		Failed Kidney		Suicide by refusing dialysis	2 1/2 Months
45	35	3 yr., 1 mo.		Failed Kidney		Cardiac arrest while on dialysis	No
47	37	1 yr., 9 mo.	65	3.5	10	Aspergillus pneumonitis Pneumocystis carinii Fatty infiltration of liver Systemic CMV infection	No
48	34	7 yr., 3 mo.	60	3.0	15	Myocardial infarction	No

TABLE 4. *Data on Primary Homografts*

LD No.	Date Op	Donor	HL-A Match	BUN	Ccr (ml/min)	BP	Azathioprine mg/day	Prednisone mg/day
1	11/24/62	Mother	C	†	†	†	†	†
2	1/31/63	Sister	A	19	70	120/80	100	0
3	2/9/63	Brother	A	11	133	110/70	150	0
6	4/17/63	Brother	D	12	90	115/90	200	10
12	6/7/63	Brother	B	20	68	140/90	100	15
13	7/3/63	Mother	D	17	70	106/50	87.5	7.5
14	7/5/63	Brother	B	12	120	130/90	150	0
15	7/8/63	Brother	B	‡	‡	‡	‡	‡
17	7/19/63	Mother	B	10	64	130/95	100	2.5
18	7/24/63	Sister	D	‡	‡	‡	‡	‡
22	8/12/63	Mother	B	25	80	115/80	137.5	5
25	8/21/63	Brother	C	18	80	110/70	50	10
27	9/3/63	Unrelated	D	‡	‡	‡	‡	‡
30	9/30/63	Unrelated	D	‡	‡	‡	‡	‡
33	10/7/63	Mother	B	14	85	130/80	125	0
34	10/11/63	Mother	C	13	60	110/75	50	0
36	10/14/63	Unrelated	B	‡	‡	‡	‡	‡
37	10/18/63	Mother	C	24	80	120/80	75	15
39	11/13/63	Mother	C	23	65	115/80	125	10
40	11/16/63	Mother	A	‡	‡	‡	‡	‡
41	11/23/63	Mother	C	†	†	†	†	†
42	11/27/63	Father	D	24	70	110/70	125	7.5
44	12/7/63	Sister	A	‡	‡	‡	‡	‡
45	12/10/63	Sister	C	‡	‡	‡	‡	‡
47	1/4/64	Brother	B	‡	‡	‡	‡	‡
48	1/10/64	Sister	A	‡	‡	‡	‡	‡
49	3/3/64	Sister	B	15	70	110/70	0	0
50	1/25/64	Father	C	†	†	†	†	†
51	2/10/64	Aunt	E	17	68	90/75	125	10
52	2/17/64	Father	B	14	90	140/60	150	7.5
53	2/22/64	Uncle	C	26	57	90/60	100	5
54	2/24/64	Unrelated	C	†	†	†	†	†
55	2/26/64	Father	C	30	40	120/80	150	15
58	3/13/64	Sister	A	16	98	120/80	125	10
60	3/17/64	Cousin	D	59	35	150/110	62.5	25
63	3/27/64	Unrelated	B	26	90	130/90	125	12.5

1 = Subendothelial glomerular capillary basement membrane thickening.
2 = Subepithelial glomerular capillary basement membrane thickening.
3 = Increased cellularity of glomerular tufts.
4 = Increased amount of mesangial matrix.
5 = Tubular atrophy.
6 = Interstitial fibrosis.
7 = Mononuclear cell infiltration of the interstitium.
8 = "Hyaline" in arteriolar walls.
9 = Thickening of intima of interlobular arteries.
0 = No glomerular lesions compatible with glomerulonephritis
NO = Impossible to be transmission of glomerulonephritis because original disease in no way immunological.
NO = Very unlikely to be transmission because original disease chronic pyelonephritis.
(NO) = Unlikely to be transmission, but possible because original disease glomerulonephritis.

All 14 of those who were adults (18 or older) at the time of transplantation are employed, frequently in jobs for which they were specifically trained postoperatively. Twelve of the survivors were "pediatric" patients (ages 3–17). The three-year-old who is now almost 14 is a healthy, but physically stunted school boy. The other 11 have reached adulthood and are college students or job holders. Our patient who was a 21-year-old unskilled brain-damaged student is now a 32-year-old alcoholic day field worker.

Three of the patients who were adolescents at the time of transplantation developed necrosis of one or both of the femoral heads during the early postoperative period. Two of the three learned to walk adequately despite this handicap. The third had bilateral total hip replacement performed successfully nine years post-transplantation.

Eleven of the 64 patients of the original series have had children after transplantation. Two of these parents who were female have had three children and the nine male parents have fathered 13 children. One of the offspring of a male patient (LD 63) had a meningomyelocele which was surgically repaired. None of the patients who became parents during the post-transplantation period has died.

*of 36 Renal Recipients.**

Time Biopsy (Months)	1	2	3	4	Glomerular Index	5	6	7	8	9	Overall Pathologic Index	Original Diagnosis	Glomerular Nephritis in Transplant	Time Primary Graft Function (Months)	Time Patient Survival (Years)
24	2	0	2	1	1.25	2	1	2	1	2	1.44	CPGN	(T)	65	11.4†
24	0	0	0	0	0	0	0	0	0	0	0	CPGN	0	135	11.3
24	2	0	0	0	.5	0	1	0	0	0	.33	CLGN	(NO)	134	11.2
23	0	0	0	0	0	0	1	0	0	0	.11	CPGN	0	132	11
22	0	0	0	0	0	2	2	1	1	3	1.0	RPGN	0	131	10.9
21	0	0	0	0	0	1	1	3	1	1	.78	CPGN	0	130	10.8
21	0	0	0	0	0	1	1	1	2	0	.55	Unknown	0	130	10.8
21	1	0	0	0	.25	1	1	1	1	1	.67	CPGN	(NO)	107	8.9‡
26	0	0	0	0	0	1	1	1	0	1	.44	CPYN	0	129	10.7
26	2	0	0	2	1.0	2	2	2	2	2	1.56	CMGN	(NO)	30	2.5‡
25	1	0	0	0	.25	1	2	1	0	2	.78	POLY	NO	129	10.7
24	0	0	0	0	0	0	1	1	0	0	.22	Unknown	0	128	10.7
24	3	0	2	2	1.75	1	1	1	1	3	1.56	CPGN	(T)	31	2.8‡
24	3	0	1	2	1.5	3	3	3	3	3	2.33	CMGN	T	48	4.3‡
23	0	0	0	0	0	0	0	0	0	0	0	CPGN	0	127	10.6
23	0	0	0	0	0	0	1	1	0	1	.33	CPGN	0	127	10.6
22	2	0	0	0	.5	3	3	1	2	3	1.56	CPYN	*NO*	23	1.9‡
22	0	0	0	0	0	1	1	1	0	1	.44	CPGN	0	126	10.5
22	0	0	0	0	0	1	1	1	0	0	.33	CPGN	0	126	10.5
22	2	0	3	3	2.0	1	1	2	3	3	2.0	CLGN	(T)	77	8.2‡
22	3	0	2	1	1.5	1	1	1	1	2	1.33	CPGN	(T)	73	10.4†
22	0	0	0	0	0	1	1	1	0	1	.44	Unknown	0	125	10.4
60	4	4	2	4	3.5	4	4	2	4	2	3.11	CPGN	T	60	5.3‡
25	3	0	1	1	1.25	1	1	1	2	2	1.33	CPGN	(T)	34	3.1‡
22	2	0	0	1	.75	2	3	2	0	4	1.56	CPGN	(NO)	20	1.8‡
24	2	0	0	2	1.0	1	1	0	0	1	.78	CPGN	(NO)	87	7.3‡
22	1	0	0	1	.5	1	1	0	0	0	.44	CLGN	(NO)	122	10.2
24	1	0	0	0	.25	1	1	1	0	2	.67	CPGN	(NO)	69	10.3†
23	2	0	0	1	.75	1	1	1	3	1	1.11	CPGN	(NO)	123	10.2
23	1	0	0	0	.25	0	1	0	0	1	0.33	CPGN	(NO)	122	10.2
23	1	0	0	0	.25	0	1	1	1	1	.55	CPGN	(NO)	122	10.2
22	4	2	3	3	2.75	3	3	3	2	3	2.89	CPGN	T	27	10.2†
23	1	0	0	1	.5	1	1	1	2	3	1.11	CPGN	(NO)	122	10.2
21	0	0	0	0	0	0	0	0	0	0	0	CPGN	0	122	10.2
22	2	0	0	3	1.25	2	2	2	0	0	1.22	CPGN	(NO)	121	10.1
22	4	0	2	4	2.5	1	2	2	1	1	1.89	CPGN	(T)	121	10.1

(T) = Probably transmission of glomerulonephritis.
T = Almost certainly transmission of glomerulonephritis.
CLGN = Mesangiocapillary chronic lobular glomerulonephritis
CMGN = Chronic membranous glomerulonephritis
CPGN = Chronic proliferative glomerulonephritis
CPYN = Chronic pyelonephritis
POLY = Polycystic disease
RPGN = Proliferative glomerulonephritis with crescents

* Patients were alive when reported in 1965[24] and 26 of them survive 9 years later in 1974. Additional data on the patients who required retransplantation are in Table 1.
† Alive following retransplantations.
‡ Dead.

Histopathologic Correlations

The two-year biopsies were included as part of a report made to the American Surgical Association in 1970.[26] These analyses were accepted as the histopathologic basis for the following correlations.

Overall Pathologic Index. When the nine light microscopic categories at two years were averaged (Table 4) it was found that kidneys having a mean index less than 1.33 had a 87.5% chance of functioning for the ensuing eight to nine-and-one-half years (21 of 24). Two of the three patients whose kidneys no longer function despite a score less than 1.33 died of pancreatitis after 107 months (LD 15) and myocardial infarction after 87 months (LD 48). These kidneys had not failed although they were subnormal in their performance (Table 3). The third patient (LD 50) had a score of 0.50 at two years with homograft failure after five-and-one-half years. She underwent retransplantation. A pattern of sporadic discontinuance of immunosuppression for long intervals was later uncovered.

Ten of the 11 two-year biopsies with an overall pathologic index of 1.33 or greater were eventually lost (91%), after a total functional interval of 23 to 77 (mean 43) months (Table 4). In one case (LD 18), in which the index score was 1.56, the patient had a

TABLE 5. *HL-A Matches of 36 Kidneys Which Were Functioning in May, 1965*

Match*	Primary Kidney Still Functioning	Primary Kidney Failed	Death Without Failure of Primary Kidney
A†	3 (50%)	2	1
B	8 (73%)	2	1
C	6 (55%)	5	0
D-E	5 (63%)	2	1

* Five of the 36 kidneys functioning in May, 1965, were unrelated. The only one still functioning had a B match. One of the 4 unrelated kidneys which failed also had a B match, one was a C and 2 were D-E.

† Five of the 6 A matches were siblings and were thought to represent double haplotype HL-A identity of the donor and recipient.

functioning graft but died of a myocardial infarction 30 months post-transplantation. Nine other grafts either failed and were removed or were functionless in place at the time of the recipients' death. Homograft loss was avoided only in Patient LD 63 who had a two year overall pathologic index of 1.89. Now after ten years and two months, the BUN is 26 mg% and the creatinine clearance is 90 ml/min. During all this time he has not had significant proteinuria. Reassessment of the two-year biopsy did not show any features which explained the atypical subsequent behavior of this damaged graft. It is of interest that this patient was studied in 1966 by Dr. Fritz Bach of Madison, Wisconsin who performed a mixed lymphocyte culture examination with the peripheral blood of the recipient and his donor. Although a clear donor-recipient histoincompatibility was detectable by serologic typing, the recipient lymphocytes no longer underwent blast transformation when exposed to killed donor white cells, although they reacted vigorously to third party lymphocytes. The findings were interpreted as indicating specific acquired immunologic tolerance.[1]

Homograft Glomerulonephritis. When the two-year biopsies were reviewed in 1970,[26] a diagnosis of definite glomerulonephritis in the homograft was made if, by light microscopy, over 50% of the glomeruli showed one or more of the following features: 1) focal or diffuse hypercellularity of the tufts and 2) focal or generalized thickening of the capillary basement membranes. These two basic pathologic changes might, or might not, be accompanied by epithelial cell crescents, by a focal or generalized increase in the amount of mesangial matrix, and by the presence of deposits of immunoglobulins and complement on the glomerular capillary wall.

Glomerulonephritis was considered a possibility if the glomeruli appeared normal on light microscopy but: 1) electronmicroscopy revealed an excess of predominantly non-cellular material on either aspect of the glomerular capillary basement membranes; the material could be of any degree of electron density; and/or 2) immunofluorescence demonstrated deposits of immunoglobulins and complement on the glomerular capillary walls. The deposits could be in a granular, linear or mixed pattern.

Using these criteria, 22 of the 35 renal homografts biopsied at two years were diagnosed as having glomerulonephritis, for an incidence of 63%. All 13 kidneys without glomerular lesions at two years are functioning today, whereas only nine of the 22 kidneys with such lesions continue to support life.

The homograft attrition was even greater when the glomerular lesion in the two year biopsies were thought to either certainly or probably represent transmission of the patient's original disease, as judged by comparison with the histopathology of the destroyed native kidneys. Seven (LD 1, 27, 30, 40, 41, 45 and 54) of the eight homografts carrying the firm two year diagnosis of "transmission glomerulonephritis" failed 27–77 months post-transplantation (average 51 months). An eighth

TABLE 6. *Features of Cancers in Original Colorado Transplant Recipients*

LD No.	Age at Time of Transplant (Years)	Time of Onset After Transplant (Month)	Type of Tumor	Treatment	Outcome	Followup After Initial Diagnosis of Tumor (Month)
6	23	75	Basal cell carcinoma of face	Excision	No recurrence	58
30	40	32	Squamous cell carcinoma of skin of ear	Wide excision	No recurrence; died of perforated diverticulitis	20
48	34	74	Squamous cell carcinomas of forearms, right arm, and scalp	Multiple excisions	Died of myocardial infarction	14
55	21	87	Squamous cell carcinoma of face; pre-auricular lymph node	Excision and skin graft	Eight months later had resection of pre-auricular lymph node metastasis and parotid gland	35
60	21	78	Multiple squamous cell carcinomas both upper extremities, face, right knee, lower lip	Multiple excisions	Recurrences; currently being treated with topical 5FU	43
63	35	66	Squamous cell carcinoma of lower lip	Excision	No recurrence	55

kidney which was not biopsied at two years failed at five years and was found also to have transmission glomerulonephritis (LD 44). The only kidney with the stigmata of transmission glomerulonephritis at two years which still functions after ten years is in Patient LD 63.

The devastating prognostic impact of two-year glomerular lesions upon late graft survival could be seen from the glomerular index which was the average of histopathologic Categories 1–4. If the index was less than 1.00 at two years, renal function at one decade was achieved in 83% (20 of 24). With a glomerular index of $\geq$1.00, the decade success rate was only 18% (two of eleven).

Next to the glomerular abnormalities, the presence or absence of arteriolar and arterial lesions provided the best prognostic insight (Table 4). Cellular invasion, tubular atrophy and interstitial fibrosis were progressively less reliable. However, all categories of lesions scored higher in the kidneys which eventually failed.

Discussion

In 1962 and 1963, three American[9,16,25] and one European[29] centers were acquiring experience with the drug combination of azathioprine and prednisone for the prevention or reversal of renal graft rejection. The progress and the avalanche of observations that followed had amplified significance because of parallel advances in renal dialysis technology by which preoperative recipients could be resuscitated and held in preparation for transplantation or else maintained postoperatively in the event of homograft failure.

The results from the early days of azathioprine-prednisone therapy were unsatisfactory by present day standards, mainly because of the very heavy death rate during the first postoperative year which was particularly devastating in the nonrelated cases. The marked reduction in the early mortality and the means by which this has been achieved have been recently reviewed.[27] The important collateral issue of the long-term outlook of the patient who has passed through a successful early course is a question which the present communication partly answers.

In 1965, when these cases were brought to the attention of the American Surgical Association, the summary statement was made that ". . . for the present it would seem most reasonable to regard homotransplantation as an effective, but incompletely characterized, form of palliative therapy."[24] Now, nine years later, with 26 (72%) of the 1965 survivors still alive and 22 bearing their original homografts, more optimism than ever seems justified about the lasting qualities of homografts if the donors are related.

Using unrelated donors, late losses occur more frequently. In our experience, improvement in patient survival with the use of unrelated organs under presently employed immunosuppressive regimens, including those using ALG, will require acceptance of a much heavier rate of retransplantation than with consanguineous donors.[27]

The hypothetical Achilles' heel of successful organ transplantation under chronic immunosuppression was once projected to be death from complications of immunologic invalidism. The fallacy of this fear has been demonstrated by the followups in the present report. The survivors have had remarkable long-term rehabilitation, both social and vocational, and most have had a very nearly unrestricted return to society. Except for hepatitis, infection has played no role in the deaths after three years. The increased incidence of *de novo* malignancies in the transplant population is acknowledged to be a penalty for chronic immunosuppression and the consequent partial loss of immunologic competence,[26] but the resulting neoplasms have usually been treatable by conventional means with the notable exception of mesenchymal malignancies.[17]

The greatest risk to life that the transplant recipient faces is late slow deterioration of the homograft and cardiovascular and other complications of the recurrent uremia. The correlations in the present report have shown how the quality of the two year biopsy can predict the functional future of the homografts. In passing, it may be noted that with the possible exception of perfectly matched siblings, neither the biopsies nor the chronic clinical course correlate well with the HL-A match.

In the past, the most prognostically serious stigmata to be found in chronic renal homografts have been thought to be arterial occlusive lesions.[21,23] However, in the cases herein reported, glomerular abnormalities were even more discriminating than the vascular ones. A kidney with serious glomerular pathology at two years, had less than a 10% chance of being functional at a decade.

The meaning of glomerular abnormalities in renal homografts has been the subject of much discussion but two principal mechanisms could contribute. In one instance, the autoimmune disease which destroyed the host kidneys could be recapitulated in the new kidneys, as has been particularly well documented in identical twins.[4] On the other hand, the immunologic events of rejection can probably manifest as glomerulonephritis since glomerulonephritis has been seen after animal transplantation[20,30] or transplantation to humans whose original disease was not autoimmune in nature.[7,19] The probable contribution of both kinds of damage to the loss of transplants has been emphasized by a number of authorities.[2,5,6,10,12,18,28] The prognostic reliability of glomerular pathology is probably as high as it is because it picks up both of the aforementioned main pathways of graft injury. With either recapitulation of the original disease or glomerulonephritis secondary to rejection, the immunologic injury could be produced by fixation of anti-GBM antibodies in the graft or more commonly,

lodgement of antigen-antibody complexes in the graft. More precise conclusions about these mechanisms will require identification of the specificity of both antigens and antibodies within grafts by elution and other immunologic techniques.

References

1. Amos, D. B. and Bach, F. H.: Phenotypic Expressions of the Major Histocompatibility Locus in Man (HL-A): Leukocyte Antigens and Mixed Leukocyte Culture Reactivity. J. Exp. Med., **128**:623, 1968.
2. Busch, G. J., Galvanek, E. G. and Reynolds, E. S.: Human Renal Allografts. Analysis of Lesions in Long-term Survivors. Hum. Pathol., **2**:253, 1971.
3. Elkinton, J. R.: Moral Problems in the Use of Borrowed Organs, Artificial and Transplanted. Ann. Intern. Med., **60**:309, 1964.
4. Glassock, R. J., Feldman, D., Reynolds, E. S., Dammin, G. J. and Merrill, J. P.: Human Renal Isografts: A Clinical and Pathologic Analysis. Medicine, **47**:411, 1968.
5. Halgrimson, C. G., Wilson, C. B., Dixon, F. J., Penn, I., Anderson, J. R., Ogden, D. A. and Starzl, T. E.: Goodpasture's Syndrome. Treatment with Nephrectomy and Renal Transplantation. Arch. Surg., **103**:283, 1971.
6. Hamburger, J., Berger, J., Hinglais, N. and Descamps, B.: New Insights into the Pathogenesis of Glomerulonephritis Afforded by the Study of Renal Allografts. Clin. Nephrol., **1**:3, 1973.
7. Hamburger, J., Corsnier, J. and Dormont, J.: Observations in Patients with a Well-tolerated Homotransplanted Kidney: Possibility of a New Secondary Disease. Ann. N.Y. Acad. Sci., **120**:558, 1964.
8. Hamburger, J., Vaysse, J., Corsnier, J., Auvert, J., Lalanne, C. M. and Hopper, J.: Renal Homotransplantation in Man After Radiation of the Recipient; Experience with Six Patients since 1959. Am. J. Med., **32**:854, 1962.
9. Hume, D. M., Magee, J. H., Kauffman, H. M., Jr., Rittenbury, M. S. and Prout, G. R.: Renal Transplantation in Man in Modified Recipients. Ann. Surg., **158**:608, 1963.
10. Hume, D. M., Sterling, W. A., Weymouth, R. J., Siebel, H. R., Madge, G. E. and Lee, H. M.: Glomerulonephritis in Human Renal Homotransplants. Transplantation Proc., **2**:361, 1970.
11. Küss, R., Legrain, M., Mathe', G., Nedey, R. and Camey, M.: Homologous Human Kidney Transplantation: Experience with Six Patients. Postgrad. Med. J., **38**:528, 1962.
12. McPhaul, J. J., Dixon, F. J., Brettschneider, L. and Starzl, T. E.: Immunofluorescent Examination of Biopsies from Long-term Renal Allografts. N. Engl. J. Med., **282**:412, 1970.
13. Merrill, J. P., Murray, J. E., Harrison, J. H., Friedman, E. A., Dealy, J. B., Jr. and Dammin, G. J.: Successful Homotransplantation of the Kidney Between Non-identical Twins. N. Engl. J. Med., **262**:1251, 1960.
14. Murray, J. E., Merrill, J. P., Dammin, G. J., Dealy, J. B., Jr., Alexandre, G. W. and Harrison, J. H.: Kidney Transplantation in Modified Recipients. Ann. Surg., **156**:337, 1962.
15. Murray, J. E., Merrill, J. P., Dammin, G. J., Dealy, J. B., Jr., Walter, C. W., Brooke, M. S. and Wilson, R. E.: Study on Transplantation Immunity After Total Body Irradiation; Clinical and Experimental Investigation. Surgery, **48**:272, 1960.
16. Murray, J. E., Merrill, J. P., Harrison, J. H., Wilson, R. E. and Dammin, G. J.: Prolonged Survival of Human Kidney Homografts by Immunosuppressive Drug Therapy. N. Engl. J. Med., **268**:1315, 1963.
17. Penn, I. and Starzl, T. E.: Immunosuppression and Cancer. Transplantation Proc., **5**:943, 1973.
18. Porter, K. A.: Clinical Renal Transplantation. Int. Rev. Exp. Pathol., **11**:73, 1972.
19. Porter, K. A., Andres, G. A., Calder, M. W., Dossetor, J. B., Hsu, K. C., Rendall, J. M., Seegal, B. C. and Starzl, T. E.: Human Renal Transplants. II. Immunofluorescent and Immunoferritin Studies. Lab. Invest., **18**:159, 1968.
20. Porter, K. A., Calne, R. Y. and Zukoski, C. F.: Vascular and Other Changes in 200 Canine Renal Homotransplants Treated with Immunosuppressive Drugs. Lab. Invest., **13**: 809, 1964.
21. Porter, K. A., Thomson, W. B., Owen, K., Kenyon, J. R., Mowbray, J. F. and Peart, W. S.: Obliterative Vascular Changes in 4 Human Kidney Homotransplants. Br. Med. J., **2**:639, 1963.
22. Schackman, R., Dempster, W. J. and Wrong, O. M.: Kidney Homotransplantation in the Human. Br. J. Urol., **35**:222, 1963.
23. Starzl, T. E.: Experience in Renal Transplantation. Philadelphia, W. B. Saunders, 1964.
24. Starzl, T. E., Marchioro, T. L., Terasaki, P. I., Porter, K. A., Faris, T. D., Hermann, T. J., Vredevoe, D. L., Hutt, M. P., Ogden, D. A. and Waddell, W. R.: Chronic Survival After Human Renal Homotransplantation. Ann. Surg., **162**:749, 1965.
25. Starzl, T. E., Marchioro, T. L. and Waddell, W. R.: The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance. Surg. Gynecol. Obstet., **117**:385, 1963.
26. Starzl, T. E., Porter, K. A., Andres, G., Halgrimson, C. G., Hurwitz, R., Giles, G., Terasaki, P. I., Penn, I., Schroter, G. T., Lilly, J., Starkie, S. J. and Putnam, C. W.: Long-term Survival After Renal Transplantation in Humans: (With Special Reference to Histocompatibility Matching, Thymectomy, Homograft Glomerulonephritis, Heterologous ALG, and Recipient Malignancy). Ann. Surg., **172**:437, 1970.
27. Starzl, T. E., Porter, K. A., Husberg, B. S., Ishikawa, M. and Putnam, C. W.: Renal Homotransplantation. (*2 parts*) Curr. Probl. Surg., Chicago, Year Book Medical Publishers, Inc., 1974 (April, May).
28. Wilson, C. B. and Dixon, F. J.: Anti-glomerular Basement Membrane Anti-body Induced Glomerulonephritis. Kidney Int., **3**:74, 1973.
29. Woodruff, M. F. A., Robson, J. A., Nolan, B., Lambie, A. T., Wilson, T. I. and Clark J. G.: Homotransplantation of Kidney in Patients Treated by Preoperative Local Radiation and Postoperative Administration of an Antimetabolite (Imuran). Lancet, **2**:675, 1963.
30. Zukoski, C. F. and Ende, N.: Membranous Glomerulonephritis Complicating Prolonged Survival of a Homografted Kidney. Transplantation, **3**:118, 1965.

Discussion

Dr. Folkert O. Belzer (San Francisco): We are fortunate enough to have followed one of Dr. Starzl's original patients in San Francisco. This man is now 11 years post operative, has not missed a day of work, and has never been in the hospital since his transplant.

I would like to discuss something that Dr. Starzl has also been interested in and, in fact, he published a paper on this in 1968; namely, how much can we decrease our immunosuppressive therapy in these long-term patients, and can we ever discontinue these drugs completely.

After reading Dr. Starzl's paper, I never had the courage to drop immunosuppression completely, but seven of our patients did this by themselves and the results were disastrous.

Some of these patients, fortunately, came to the followup clinic

in time; they had elevated creatinines and were restarted on immunosuppressive therapy. Their renal function improved, although rarely to the pre-existing level; some of these patients lost their kidney.

One of these patients, transplanted by Sam Kuntz at Stanford, was a young woman, seven years postoperative, with a creatinine of 0.9 and taking 10 mg of Prednisone and 100 mg of Imuran. She became pregnant and her obstetrician suggested that she drop her immunosuppressive therapy, which she did without telling us. She delivered a normal child, did well for six months, and then arrived at our hospital with a creatinine of 11. We were never able to reverse the rejection.

I think there are three points to be made from this. First, I do not believe we should drop immunosuppression, even for long standing patients, below a certain level; and in adult patients, we should not drop the Prednisone dose below 10 mg.

Second, we must remember that even long-term patients should be followed for the rest of their lives.

Lastly, we should emphasize to long-term survivors that the three or four little pills they take in the morning are still the difference between life and death.

DR. RICHARD E. WILSON: (Boston) I thought it would be of interest to the Association for me to provide a comparable series of patients for discussion of Dr. Starzl's valuable presentation. Dr. Tilney and I recently reviewed the results of renal transplants, exclusive of identical twins, performed at the Peter Bent Brigham Hospital in exactly the same time period, September 1, 1962 to March 31 1964.

Forty such allografts were performed, 19 from living related donors, five from cadaver donors, and six from obligatory unrelated living donors of Matson type of kidney. None of the cadaver or obligatory unrelated donor kidney recipients transplanted during that time period lived the one year maximum, although one patient, transplanted in April of 1962 from a cadaver donor lived for two years on his transplant.

Of the living related donor recipients, therefore, 16 of 19 lived more than one year, or 84%; 8 of 19 lived more than five years, 42%; and 7 of 19 lived more than ten years, 37%.

One patient who lived four years received three kidneys before he died, two of those cadaveric. One patient now living over ten years received a second kidney from a cadaver after five years on his first kidney. He, by the way, was a patient in whom we had tried to stop his prednisone; when we tried to restart it, we could never retrieve the rejecting kidney.

No malignancies developed in any of these recipients. Another patient that I transplanted in Oslo in 1963 from his mother is still alive and well, never having had a rejection in these eleven years.

I think it is interesting that, while a greater proportion of our patients lived more than one year than those that Dr. Starzl reported, there has been a greater patient attrition at the 5- and 10-year period. With these small numbers, these variations from Dr. Starzl's series may not be significantly different, but I wonder whether there was any selective process, on the basis of tissue typing, in choosing his donor-recipient pairs.

We have never excluded any patients, and still don't, for tissue type, just for positive crossmatch.

DR. JOHN SARKIS NAJARIAN (Minneapolis): Dr. Starzl stressed the durability of the transplant, and I think this is important. In our own experience, using our pediatric group as an example, of over 100 children during a ten-year period, we have found the same, or perhaps slightly better, degree of durability.

For instance, an actuarial table of our related kidneys in children reveals that we have 70% kidney survival at ten years, and practically no attrition between five and ten years. In our series of cadaveric kidney recipients 50% of the children are alive at ten years with functioning kidneys.

The remarkable thing is that 80% of the 100 children are still alive with first, second and third kidneys. None of the children are presently on dialysis. These data emphasize not only the durability of children, but also their ability to accept retransplantation so well.

Why are our results in children slightly better than those of an adult population? You will note from Dr. Starzl's slides that the parent group was his best group. The kidneys in our pediatric group were predominately from parent donors.

Another factor contributing to the poorer results in our adult recipient population is that deaths that occur in chronic patients are usually from causes other than immunologic causes. These non-immunologic causes of death, such as myocardial infarction, are becoming more and more of a factor as time progresses. In small children, however, this is not a problem.

I'm a bit perplexed by a couple of things, so I would like to ask two questions. First, in his typing data on the related donors his worst results were with the A-matched patients, those in which we would expect the best results. I wonder, when you look back on those patients, whether or not those patients were actually "overly immunosuppressed." In those early days we didn't really attempt to type them as we should have, and today if we transplant an A-matched patient, we reduce our immunosuppression, as I'm sure you do. If we had done so in the past perhaps we would have salvaged more patients.

If the same degree of immunosuppression is given to an A-matched patient as is given to a D- or E-matched patient, the patient is "over immunosuppressed", and can succumb to steroid problems and infections. I wonder if this is the way Dr. Starzl would look at that particular data.

The second question has to do with the glomerular lesion. It's intriguing to think about possible antigen-antibody viral glomerulonephritis, as Tom has mentioned. The lesion he showed was of membranoprolific disease. We have shown that in children and adults this disease has about a 50–60% recurrence, and is quite characteristic in pathology. I'm wondering if those that Dr. Starzl saw had membranoprolific nephritis as their original disease?

DR. THOMAS C. MOORE (Torrance, California): When Dr. David Hume and I reviewed the Richmond transplant experience six years ago, we had the impression that a 2–3-year followup was needed to assess the results of the transplant effort. This appeared particularly true for the recipients of cadaveric donor kidneys. Approximately one-third of these recipients of cadaver donor kidneys in the Richmond experience at risk a minimum of three months had contracted hepatitis in the early posttransplant months, of which the majority died in liver failure between one and two years posttransplant.

In recent years my thoughts have changed somewhat concerning the period of major, if not exclusive, hazard to renal transplant function from the immune response to the transplant. I now feel that the great bulk, if not all, of the transplant damage from the host immune response in recipients who take their immunosuppressive medication as directed comes in the first year posttransplant.

When I visited Richmond four years ago to review the continuing function of transplants I had reported with Dave Hume, I was dismayed to find that three of the ten functioning related living donor transplants, at risk at minimum of six years—a group which corresponds to Dr. Starzl's current decade plus followup—that three of these ten, 30%, had been lost in the prior 12-month period, all to nontransplant failure causes. Two transplants were lost to rapidly fatal recipient malignant lymphomas, and one to recipient suicide. All three transplants had excellent function, with serum creatinines in the 0.8–1.1 range at the time of recipient death.

(Slide) We have recently studied the role of early transplant function classes F, F^{AR}, SF and NF, as shown on this slide, of Belzer machine preserved cadaveric kidneys on a long-term function, one to three years, of 146 kidneys transplanted at the USC County, UCLA Harbor, and UC Irvine transplant centers in our area.

One-year transplant survival was 51% for the F class, presumably nonpresensitized recipients; 29% for the F^{AR}, the accelerated rejection class; 65% for the SF, or the slow-functioning class; and 40% for the NF, or nonfunctioning class.

In the F functioning class, none of the five kidneys which survived for one year was lost after one year due to transplant rejection failure. There was one loss from death, a malignant perirectal lymphoma, at UC Irvine.

It is of particular interest to look at the non-F classes that may be presumed to be sensitized in varying degrees to donor antigens in terms of humoral antibody. In this particular group we find that the long-term function of cadaveric kidneys, which have experienced some degree of presumed immunological assault, is remarkably good for those transplants which recover from this early assault. For example, one year plus transplant survival of 88% for the F^{AR} group of kidneys; it is 79% for the SF group of kidneys; and it is 89% for the NF group of kidneys. The kidney in the presumably presensitized recipient which is not, in a sense, killed by early immunologic injury from humoral antibody and "primed" lymphocytes appears to acquire the privilege of long-term functional survival, possibly due to the development of enhancement.

The F-class transplants also offer a unique opportunity to study the effect of other factors in long-term function in presumably non-presensitized recipients. HL-A matching appears to play no significant role in long-term function.

Also for F recipients the use of splenectomy, carried out by Dr. Berne at USC County, appears to have a beneficial effect; 88% one-year survival of splenectomized recipients, as compared with only 44% for nonsplenectomized recipients, splenectomy having been carried out for either excessive transfusion requirements or for leukopenia.

I wish to ask Dr. Starzl three questions: 1) What per cent of the transplants lost after one year were due to rejection? 2) What was the role of early transplant function, if this data is available, in long-term survival of patients in his long-term series? And 3) what is your current feeling concerning the value of splenectomy clinically in the renal transplant patient?

PROFESSOR MAURICE ROSSIE EWING (Melbourne, Australia): At the Royal Melbourne Hospital we have a modest experience in renal transplantation, only recently having passed the 200 mark. Of these patients, all of them save two or three have been cadaver grafts. Only a handful of them, thus far, has passed the ten-year mark, so my remarks are not really relevant to the title of this paper; but we are, in fact, deeply disturbed already by the premature development, in the young, of the kind of degenerative changes in the skin with which we are very familiar in the elderly, after exposure over a lifetime to the sun. The incidence of skin cancer in the survivors after four years is 18%, and, of course, many of these patients have multiple skin cancers.

Thus far—I think, with only one exception—these skin cancers have been contained by simple surgical excision.

It's also a matter of interest that we have encountered a few patients, who have been put on long-term azothioprine for other causes, with skin cancer, but how these numbers relate to the total number at risk, and against a backdrop of a really high incidence of skin cancer in our community, it's not very easy to determine the relevance of this experience.

PROFESSOR LARS-ERIK GELIN (Goteborg, Sweden): I rise to report the long-term results in our own series, (slide) which, however, only counts for the first eight years. And as seen, in the living donor series it's a 40% graft survival after eight years but only 18% cadaver grafts.

(Slide) This shows the patient survival for the same period of time, 65% in the living donor series and 40% in the cadaveric donor series.

(Slide) Our series is based on the principle that transplantation is the method of choice. We have no mortality in dialysis in our department. Everything goes on transplantation, and as soon as a graft is failing, we perform retransplantation and during a retransplant series we observed that in case we could do the retransplant while the prior, primary graft still had marginal function, the graft survival was very much superior to the situation when there is an interval between transplantectomy and regrafting, and this is the series showing this.

What is the mechanism behind this privileged time for retransplantation?

DR. THOMAS E. STARZL (Closing discussion): It seems to me that Professor Gelin's remarks illustrate the imperfections of treatment as it has been carried out in the last ten or 12 years, and, I would think, should be a real admonition not to consider this field fully developed.

It's my own conviction that some time in the next year or two there will be a very significant advance in immunosuppression, and possibly related to the kind of research work that is being carried out by Monaco and his associates in Boston, in which much more emphasis is being placed on the possibility of tolerance induction.

Professor Ewing's remarks could be used to make the same point as Professor Gelin's, because, obviously, the risk from the skin cancers—and we too have observed this—is clearly related to chronic immunosuppression. This matter may come up again in connection with Dr. Simmons' paper on the role of viruses in the oncogenetic mechanisms.

Naturally, I want to thank my old friend, John Najarian, and to try to answer his questions. Ours is a small series of A-matched sibling cases. We do believe there is an advantage of receiving an A-matched sibling kidney which did not, however, show up in our small early series but only later in our larger experience.

I don't think that over-immunosuppression led to the loss of those grafts that were still functioning in 1965, because we had already pulled off the heavy immunosuppression that we were using. By then, the patients were a year to two years posttransplantation, and by and large were in a pattern of light immunosuppression.

The question about the type of glomerulonephritis is an important and perceptive one. I tried to answer it in the manuscript, but it would take too long, and I'm not expert enough in pathology to warrant going into it at this time.

Dr. Wilson, you asked two questions. One concerned the type of selection. Like you, our selection was fortuitous in those years, 1962 to 1964, since there were no good or even acceptable donor-recipient typing techniques at that time. In fact, we did not even bother to follow the rules of red blood type matching, which have become recognized to be of such paramount importance since then. Thus, good matching was not a factor.

Dr. Wilson, with his customary modesty, focused only on this period of time that I did, and failed to mention that the longest homotransplant survival in the world is a Boston recipient of a fraternal twin kidney treated in 1958. As I understand it, that patient is still alive.

Dr. Belzer raised the question about whether kidneys can be permanently accepted in the human being, as they can in animals. In our manuscript we relate an experience with two patients who stopped their immunosuppression—probably, in one case, in 1971. The second patient definitely stopped his immunosuppression about 15 months ago. Neither recipient has suffered any ill effects. But we certainly have our fingers crossed, because the story that Dr. Belzer has told has been repeated now on many occasions, and usually with dire consequences.

Dr. Moore asked three specific questions. One concerned our opinions about the stability of grafts after one year, and we agree with him, in general, that as the life survival curves would indicate, there is relative stability. Second, we believe the greatest risk the transplant recipient must face is not cancer or infection, but slow failure of his homograft with physical deterioration before retransplantation or return to dialysis.

The question about early function versus late results is one I cannot answer on the basis of these data, because, as you may remember, almost all of these kidneys functioned superbly from the beginning. Therefore, it would be difficult to make the kind of correlations that you suggest.

Splenectomy, as far as I'm concerned, is an unproven issue in the human, and probably is not provable on the basis of clinical investigation. If you believe in basic biology, there is plenty of evidence that splenectomy is a biologic immunosuppressive maneuver, but just what effect it has on transplant survival, I think is unanlyzable.

May I make one final comment before closing? This is the first American Surgical meeting that I have ever been to that was not graced by the presence of Dave Hume. It is strange to give a paper on Dave's favorite subject, realizing that his smiling face and swashbuckling emanations are not today, or ever again, going to be working their way to the podium—usually down that aisle (indicating)—to set up a lively but always good-natured duel.

I, for one, have no intention of forgetting our good friend simply because he is not with us today. Thank you.