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THE PROBLEMS AND PROGNOSIS OF THE CHRONICALLY SURVIVING PATIENT AFTER RENAL HOMOTRANSPLANTATION*

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On previous occasions, reports have been published on a consecutive group of 64 patients treated at the University of Colorado Medical Center with renal homografts obtained from living volunteer donors.[1,2] In the last of these communications,[2] prepared in May of 1965, the mortality was summarized. Late complications, homograft function, the results of retrospective antigen analysis (performed by Paul Terasaki), and pathologic studies were documented in detail. In addition, the possible role of thymectomy in promoting homograft acceptance was discussed.

The following is a further brief report on the same patients. In the intervening nine months two additional deaths have occurred, leaving a residua of 34 chronic survivors who are now from $22\frac{1}{2}$ to 39 months posttransplant.

Methods

The therapy provided and detailed accounts of each of the 64 cases have been described.[1,2]

Results

Mortality. Twenty-seven of the 30 deaths occurred during the first postoperative year (TABLE 1). Twenty-three patients died within 120 days of operation. Four more succumbed between the fourth and tenth months. One patient, previously reported,[2] died $13\frac{1}{2}$ months after transplantation from hepatitis and septicemia. Since May of 1965, two additional late deaths have occurred.

Case Reports

Case 1 (LD36). A 43-year-old man was first seen at the University of Colorado Medical Center on September 18, 1963. At age two, he had a "strep

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TABLE 1
SURVIVAL STATISTICS IN 64 CONSECUTIVE PATIENTS TREATED WITH RENAL HOMOGRAFTS FROM NOVEMBER, 1962 TO MARCH, 1964

Total No. Patients	Deaths Within First Year	Deaths After First Year	Survivors* at 2/16/66
64 (100%)	27(42.2%)	3(4.7%)	3—36-39 months
		(1—13-1/2 months	9—30-36 months
		1—22 months	17—24-30 months
		1—23-1/2 months)	5—22-1/2—24 months

*None of the surviving patients has had late retransplantation.

throat which settled in his kidneys." At age 21, he was rejected for military service because of proteinuria. Hypertension was first noted when he was 37. In November of 1962 his BUN had been 26 mg%, but in January of 1963 he first had uremic symptoms, including vomiting. A right retrograde pyelo-

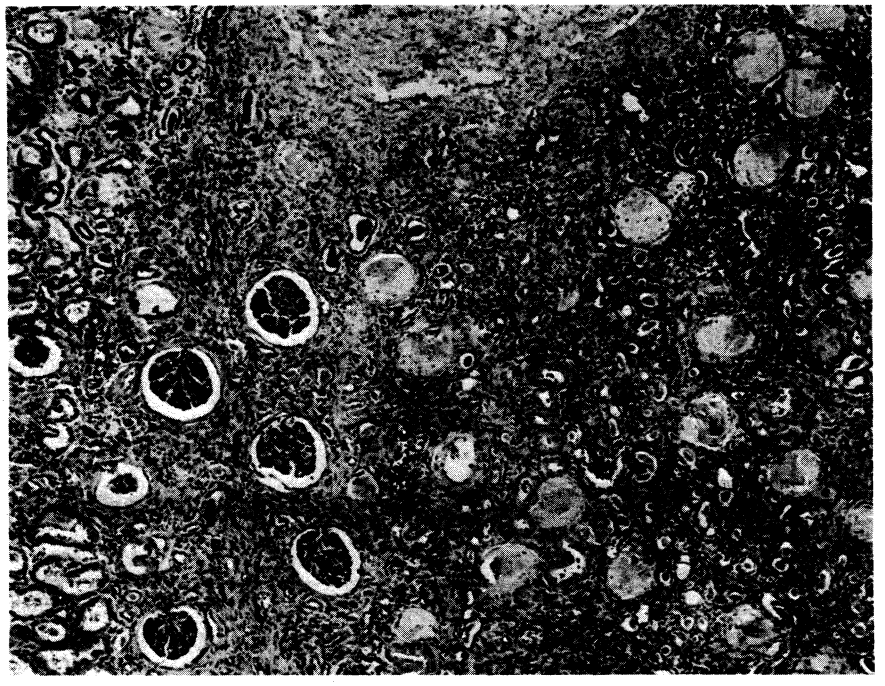

FIGURE 1. Own left kidney from Case 1 (LD36). On the right of the photomicrograph there is a chronic pyelonephritic scar in which the glomeruli are fibrosed, the tubules atrophic, and the interstitium densely infiltrated with lymphocytes. Relatively normal renal tissue is present on the left. H & E × 80.

gram at that time showed a normal calyceal system. At the time of his first admission to Colorado General Hospital BUN was 94 mg%, plasma creatinine was 15.2 mg% and his daily urine (average volume 1200 ml) contained 2.6 to 6.1 gm protein. Urine cultures were sterile. Conservative management was elected, but five days after discharge he was readmitted with vomiting, and an increase of BUN and creatinine to 125 mg% and 18.3 mg%, respectively. During the next ten days the BUN rose to 170 mg%. After hemodialysis he received bilateral nephrectomy, splenectomy, and renal homotransplantation on October 14, 1963. The homograft was donated by his wife; the blood groups were O+ to B+. Ischemia was 38 minutes. His own diseased kidneys were shrunken and coarsely scarred. Microscopically, the fibrosed areas were densely infiltrated by lymphocytes and showed glomerular destruction and tubular atrophy; elsewhere, there were a few hypertrophied glomeruli and hyperplastic tubules (FIGURE 1). These appearances were suggestive of chronic pyelonephritis rather than glomerulonephritis.

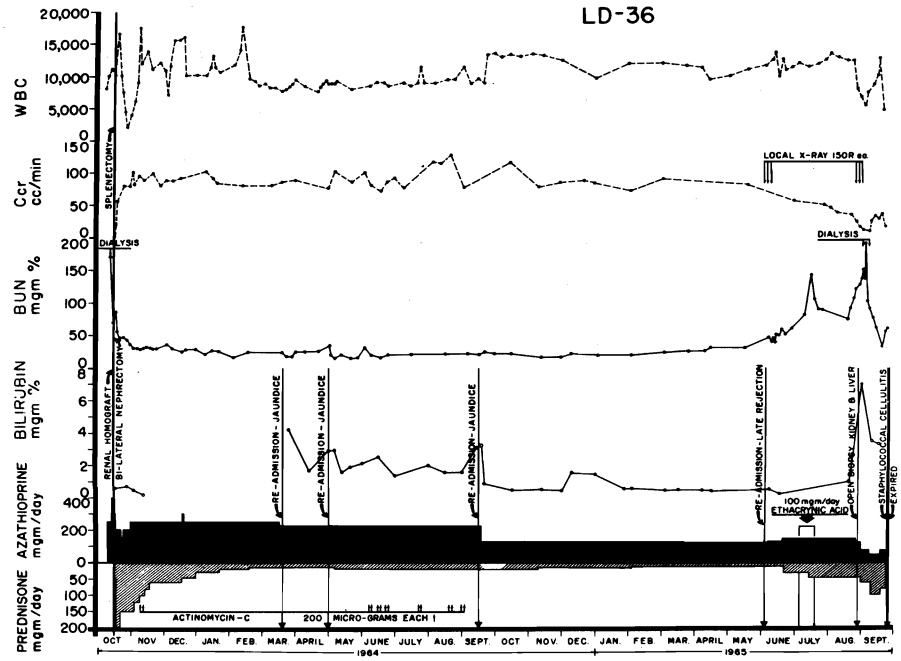

FIGURE 2. Course of a 43-year-old patient (LD36) who died 711 days after renal homotransplantation. His wife was the donor; blood group transfer was O+ to B+. Note the jaundice which was first observed five months after operation and which recurred intermittently until the time of death. The reduction in immunosuppression which was instituted because of the hepatic complications may have been responsible for the late homograft failure. Note also the temporary further impairment of renal function during a course of ethacrynic acid.

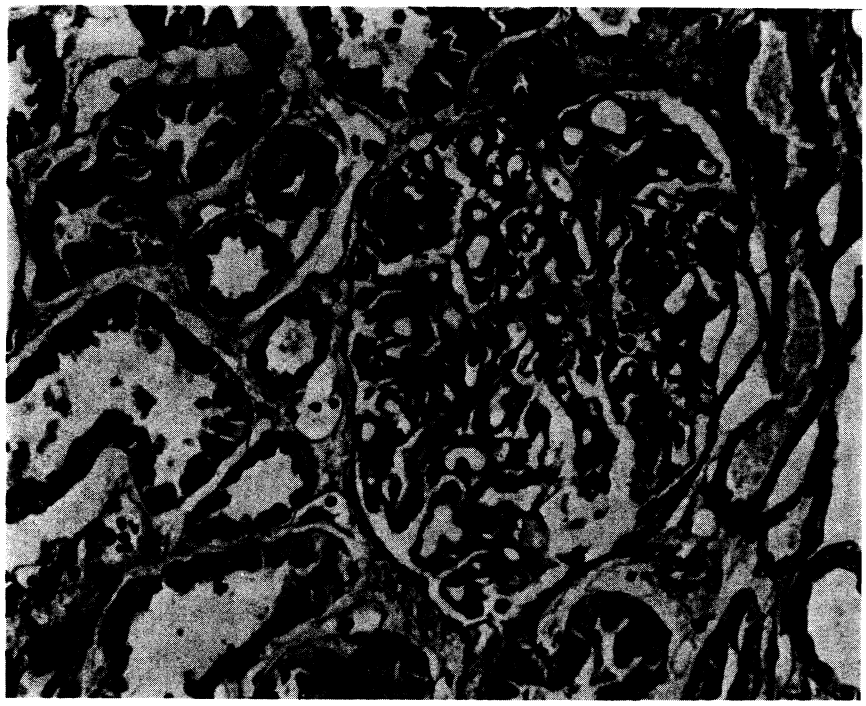

FIGURE 3. Biopsy of renal homograft from Case 1 (LD36) one year, ten months after transplantation. The glomerular capillary basement membranes are diffusely thickened. PAS × 400.

Rejection was diagnosed one day postoperatively and treated with the addition of 200 mg prednisone per day to the preexisting azathioprine therapy (FIGURE 2). Recovery was rapid thereafter. He was discharged from the hospital on November 20, 1963 with 60 mg/day prednisone, and 250 mg/day azathioprine; his BUN was 23 mg% and creatinine clearance was 85 ml/min. During the ensuing four months prednisone was lowered to 15 mg/day and azathioprine to 225 mg/day without change in renal function.

He was re-admitted to the hospital on March 18, May 1 and September 16 for "hepatitis." On each occasion he was jaundiced (FIGURE 2), had elevations in SGOT, SGPT, alkaline phosphatase and BSP retention, as well as depressions in serum protein. Because of the liver injury, the daily azathioprine dose was reduced to 125 mg/day. His condition remained stable until the last two weeks of May of 1965 when he developed massive proteinuria (as much as 35 gm/day); serum albumin was 2.3 gm%. His BUN rose to 45 mg% and creatinine clearance fell to 50 ml/min. Although he was not jaundiced, BSP retention was 31% and prothrombin time 50%. The subsequent azathioprine doses were 0–150 mg/day. Prednisone was increased from 12.5 to 45–

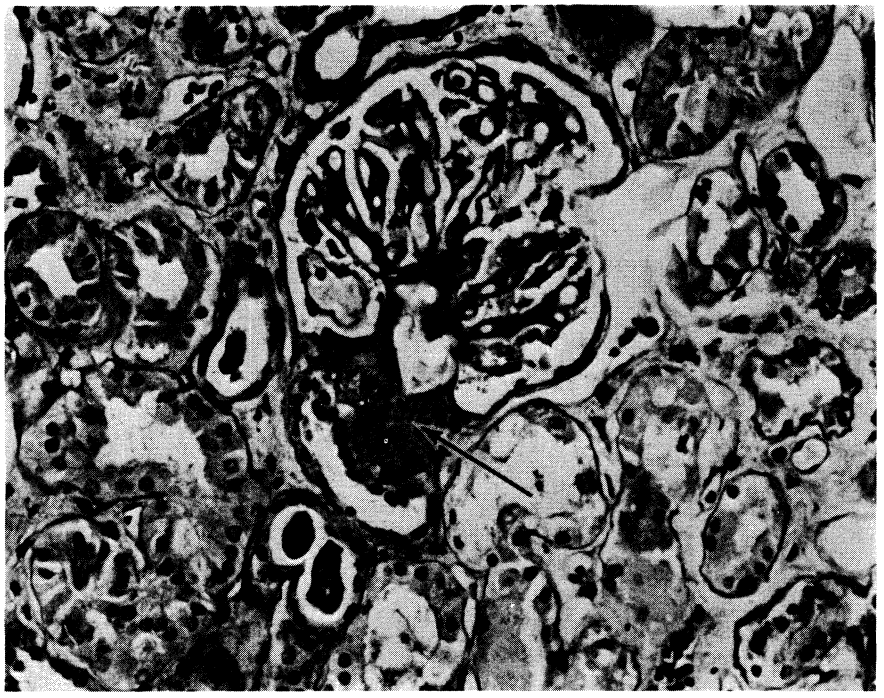

FIGURE 4. Biopsy of renal homograft from Case 1 (LD36). The juxtaglomerular apparatus, indicated by an arrow, is greatly enlarged. PAS × 400.

100 mg/day. In addition, two courses of local homograft irradiation were given in early June and late August (450R each time in three divided doses). The proteinuria decreased to 2–6 gm/day, but the BUN and creatinine clearance were not improved. A course of ethacrynic acid therapy (FIGURE 2) resulted in temporary further deterioration in renal function. After this, the BUN and creatinine clearance ranged 30–150 mg% and 10–40 ml/min respectively until two days before his death. Liver functions worsened with return of hyperbilirubinemia (maximum 7 mg%), and depression of total protein to 3.7 gm% with 1.3 gm% albumin; gamma globulin was normal (0.8 to 1.3 gm%). Open renal and liver biopsies were carried out on August 27.

The renal biopsy showed diffuse thickening of all the glomerular capillary walls and increase in the mesangial matrix caused by deposits of homogeneous material which stained positively with periodic-acid Schiff (PAS) reagent (FIGURE 3). The glomerular changes closely resembled those seen in diffuse membranous glomerulonephritis. The juxtaglomerular bodies were enlarged by hyperplasia both of the cells in the arteriolar walls and of the lacis cells, but the number of PAS-positive granules was not increased (FIGURE 4). The macula densa was prominent. Scattered areas of tubular atrophy and intersti-

tial fibrosis were present throughout the specimen but were particularly common just beneath the capsule. There were also several foci of infiltrating mononuclear cells, usually adjacent to small veins. About 40 percent of these cells were lymphoid and possessed cytoplasm which stained positively with methyl-green pyronin; similar cells were found in the peritubular capillaries. Large subendothelial deposits of homogeneous hyaline material were present in the walls of afferent and efferent arterioles. Many of the interlobular arteries were greatly narrowed or obstructed by fibrous thickening of the intima (FIGURE 5), a change sometimes accompanied by reduplication of the internal elastic lamina.

The liver biopsy showed condensation of reticulin and deposition of fibrous tissue around the central veins, together with portal fibrosis. Bands of connective tissue linked portal tracts one to the other (FIGURE 6). There was a moderately dense portal infiltration with mononuclear cells, most of which were lymphocytes and plasma cells. The centrilobular Kupffer cells contained hemosiderin and there were many fine fat droplets in the cytoplasm of the majority of the hepatocytes. There was no cholestasis.

On September 23, 1965, he developed *Staphylococcus aureus* cellulitis

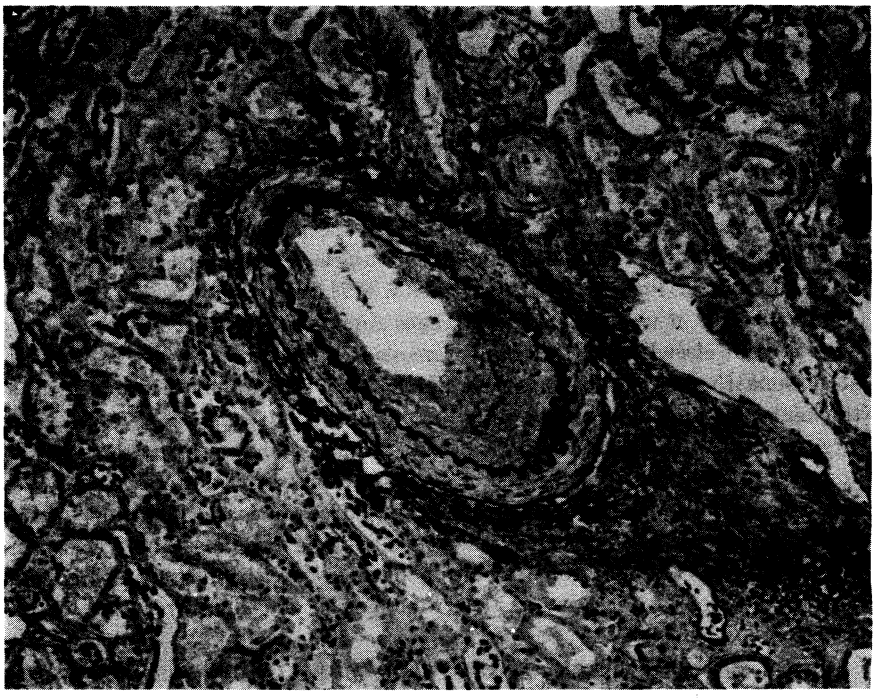

FIGURE 5. Biopsy of renal homograft from Case 1 (LD36). An arcuate artery is greatly narrowed by fibrous thickening of the intima. Weigert's elastic × 150.

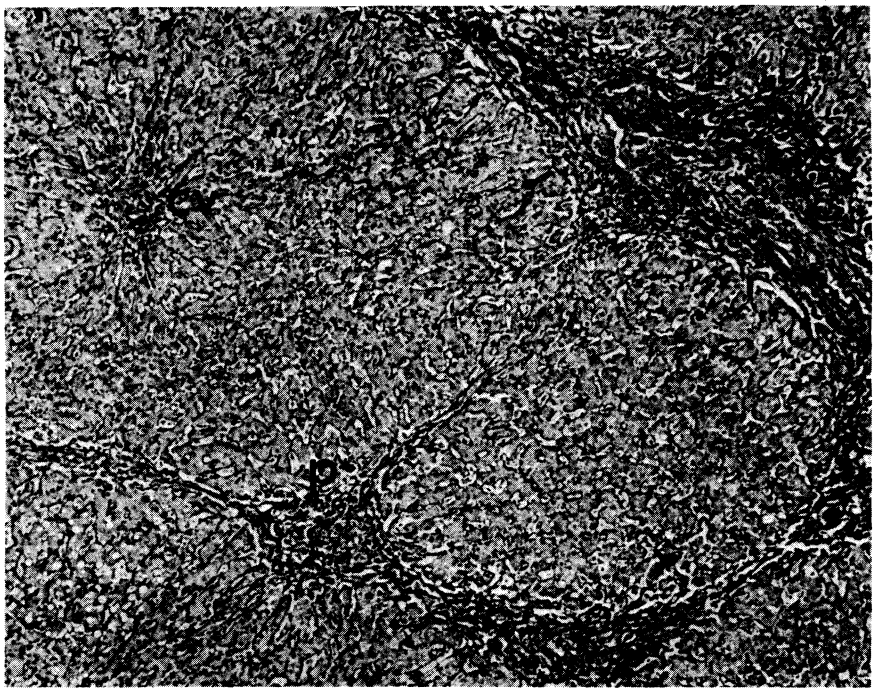

FIGURE 6. Liver biopsy from Case 1 (LD36). The lobular reticulin framework is collapsed and condensed around the central vein (cv) and there is portal fibrosis (P). Connective tissue bands link portal tracts. Reticulin stain × 80.

around a small ulcer on his sacrum. Despite specific antibiotic therapy, this spread within hours to involve the entire trunk and thorax, leading to death on September 25. Posttransplant survival was 711 days.

At autopsy, it was found that changes similar to those seen in the biopsy were present elsewhere in the renal transplant. The band of scarring immediately beneath the renal capsule was particularly prominent. Fibrous intimal thickening extended to the arcuate and interlobar arteries. Several of these larger vessels were completely obstructed. The anastomoses of the renal artery and vein to the iliac vessels were not stenosed. The hepatic findings were also confirmed at autopsy. In addition, widespread cytomegalic inclusion disease was found, particularly affecting the lungs and the adrenals. There was massive cellulitis of the skin and subcutaneous tissues with necrosis and edema, large collections of bacteria, and no evidence of a cellular reaction to the infection.

Case 2 (LD47). A 39-year-old man was admitted to Colorado General Hospital in November of 1963 with hypertension, azotemia, and congestive heart failure. His BUN was 150–200 mg% and plasma creatinine was 20 mg%. He was treated with multiple hemodialyses. After eight days of pretreatment

with azathioprine and two days of 200 mg/day prednisone, he received splenectomy, bilateral nephrectomy and renal transplantation on January 4, 1964. Both the patient and his fraternal donor were A+ blood type; ischemia time was 28 minutes. His own kidneys were almost completely destroyed by chronic Ellis[3] type 1 glomerulonephritis.

After excellent initial function, he had a rejection crisis on the 14th day. This was treated with local homograft irradiation (450 R). His subsequent course was uneventful and he was discharged from the hospital after six weeks with a BUN of 26 mg% and a Ccr of 86 ml/min (FIGURE 7). During the ensuing eight months, his prednisone dose was reduced to 10 mg/day. Two hundred and seventy days after operation he had a sudden late rejection which resulted in elevation of BUN to 80 mg% and a decrease in Ccr to 50 ml/min. Proteinuria of 1.5 to 7.0 gm/day persisted thereafter. He was treated with local homograft irradiation (450 R), actinomycin C and an increase in steroid dose to 100 mg/day. During the remaining 15 months of his life his renal function never again approached that which existed before the late rejection. On October 27, 1964, thymectomy was performed without demonstrable subsequent benefit. His BUN thereafter ranged from 50 to 85 mg% and the Ccr was 20–50 ml/min. until a few days before death.

Despite maintenance of reduced, though life-sustaining homograft function, his general condition deteriorated, requiring several hospitalizations for diffuse bone and abdominal pain. Since these were thought to be steroid complications, his prednisone dose was gradually reduced to 40 mg/day.

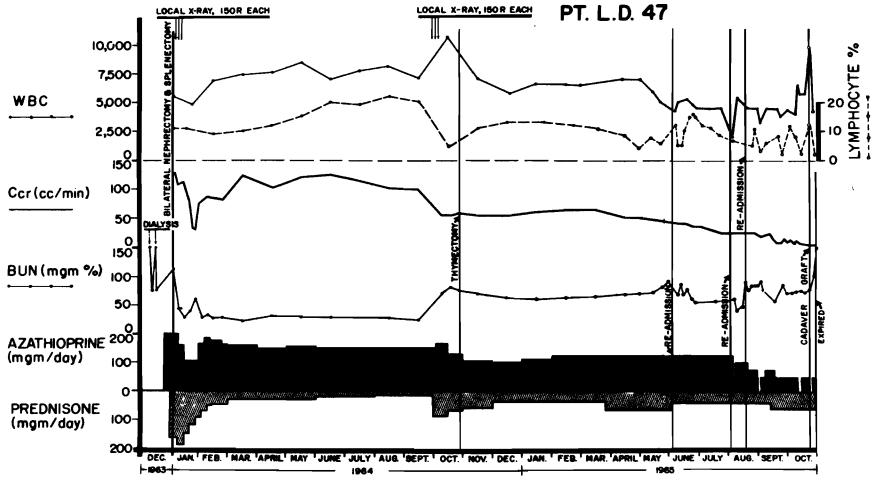

FIGURE 7. Course of a 37-year-old man (LD47) who received a kidney from his younger brother. Both were A+ blood type. Note the severe late rejection after nine months and the subsequent slow deterioration of renal function. The late thymectomy did not induce either lymphopenia or make the subsequent management easier; the post-thymectomy changes in lymphocyte counts were related to adjustments in steroid dosage.[2]

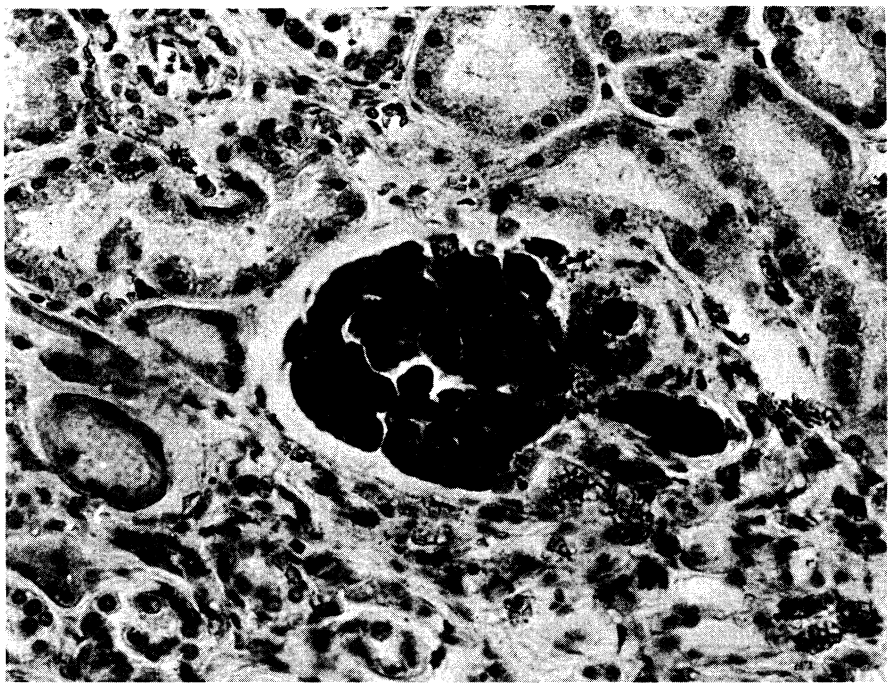

FIGURE 8. Renal homograft from Case 2 (LD47) at autopsy one year ten months after transplantation. Fat emboli, which appear black in the photomicrograph, are present in the glomerular tuft capillaries and in the afferent and efferent arterioles. Frozen section stained with oil red 0 × 400.

In August of 1965 a diffuse pulmonary infiltrate was noted by x-ray. Tracheal aspirate demonstrated *Pneumocystis carinii* which was treated with pyrimethamine and sulfadiazine. He became progressively hypoproteinemic, ultimately reaching a low of 4.1gm% total plasma protein with albumin of 1.5 gm%. His gamma globulins were not depressed. Numerous amylase determinations during the last two months of his life were elevated and progressive rises were observed in alkaline phosphatase (maximum 30.5 Bessey-Lowry units). He did not become jaundiced. He had a consistent fever during this time.

Terminally, renal function deteriorated markedly with Ccr's of 3–10 ml/min (FIGURE 7). Five days before his death, a kidney obtained from a cadaveric donor of the same blood type was transplanted to the retroperitoneal space of the opposite side. There was no evidence of function from the second homograft. The patient died five days later on October 31, 1965. His total survival was 665 days.

At autopsy, there was a great deal of scarring in the superficial cortex of the first renal homograft. Foci of interstitial fibrosis and tubular atrophy were

also distributed throughout the kidney. A few of these scars were infiltrated by mononuclear cells most of which were small lymphocytes, although about 5 percent were larger lymphoid cells with pyroninophilic cytoplasm. Fat emboli were present in the tuft capillaries of many glomeruli (FIGURE 8). In addition, several of the glomeruli showed focal thickening of the capillary basement membranes by PAS-positive material (FIGURE 9). A similar substance was deposited in the mesangium. There was moderate hyperplasia of all elements of the juxtaglomerular bodies. Many of the interlobular, arcuate and interlobar arteries were greatly narrowed by fibrous thickening of the intima (FIGURE 10), associated in several vessels with rupture of the internal elastic lamina. The arterioles, peritubular capillaries and veins were normal. The second renal homograft showed only acute tubular necrosis in the process of healing.

There was severe fatty infiltration of the liver, all the hepatocytes being heavily laden with large droplets of fat (FIGURE 11). The Kupffer cells contained a great deal of hemosiderin and there was some centrilobular cholestasis with bile "thrombi." Cytomegalic inclusion disease was found particularly af-

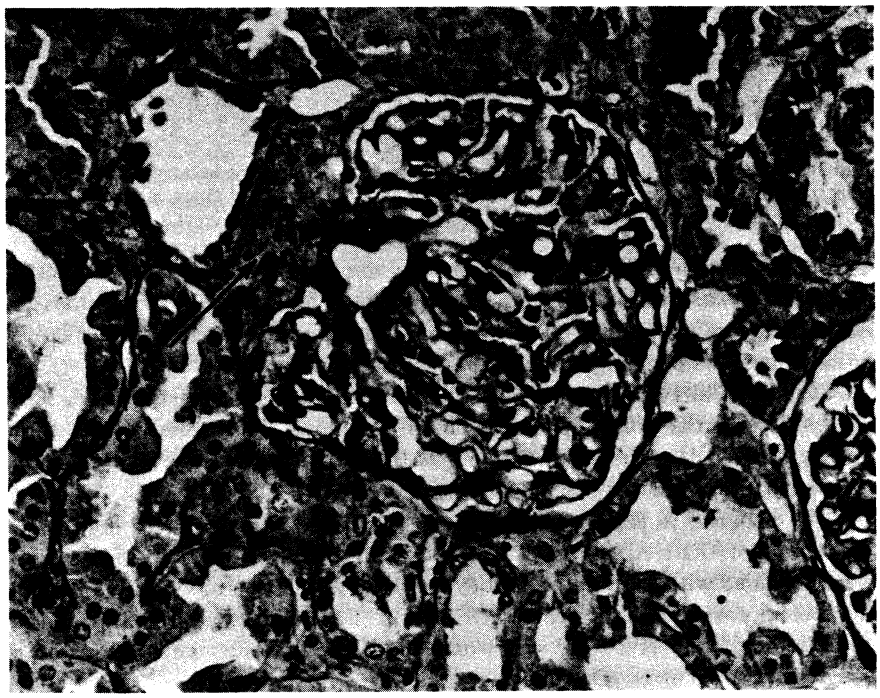

FIGURE 9. Renal homograft from Case 2 (LD47). There is hyperplasia of the juxtaglomerular apparatus, which is indicated by an arrow, and focal thickening of the glomerular capillary basement membranes. PAS × 400.

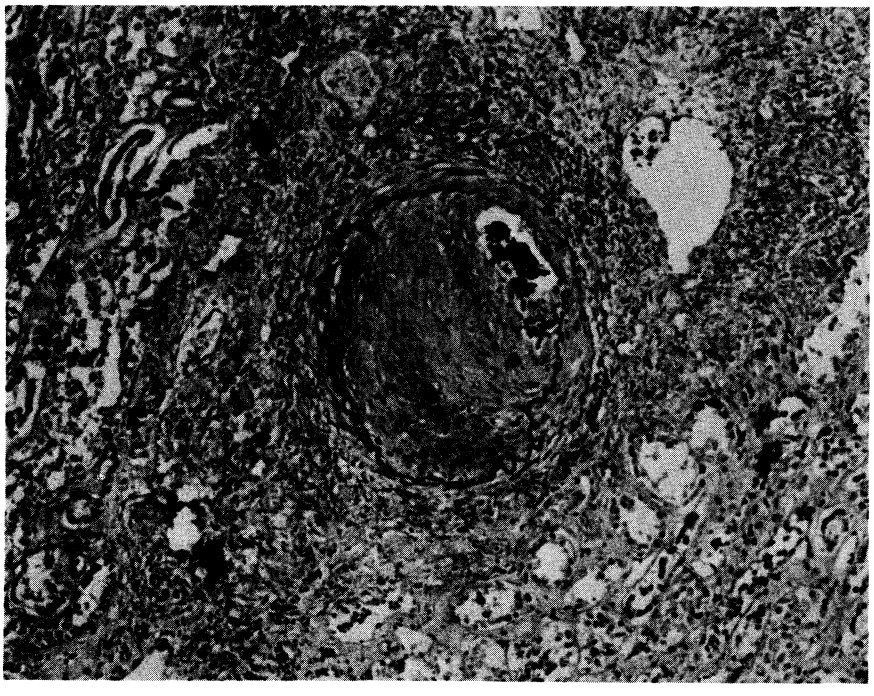

FIGURE 10. Renal homograft from Case 2 (LD47). An arcuate artery is almost obliterated by eccentric fibrous intimal thickening. Around the vessel there is tubular atrophy and interstitial fibrosis but very little cellular infiltration. Weigert's elastic × 150.

fecting the lungs and liver. The consolidated lungs were also diffusely infected by *Pneumocystis carinii* and contained necrotic foci filled with colonies of *Aspergillus fumigatum*. Fat emboli were present in many of the alveolar capillaries. There was pancreatitis accompanied by surrounding fat necrosis.

Survival. Thirty-four (53.1%) of the original patients are still alive, now $22\frac{1}{2}$ to 39 months posttransplant. Three are more than three years, nine are two and a half to three years, 17 are 24 to 30 months, and the other five are $22\frac{1}{2}$ to 24 months postoperative (TABLE 1).

The disparity in results with related, as opposed to nonrelated, donors[2] is more evident than ever (TABLE 2). Only four (22.2%) of 18 patients who were provided with nonrelated kidneys are still alive, two having died during the second posttransplant year (FIGURE 12). By contrast, 30 (65.2%) of the 46 patients who received kidneys from blood relatives survive to date; only one death has occurred after one year (See Case 2).

Morbidity. Several late complications were reported in May of 1965 (TABLE 3). The most serious problem was delayed rejection, which usually seemed to follow a reduction in steroid dosage. Two of the nine patients previously

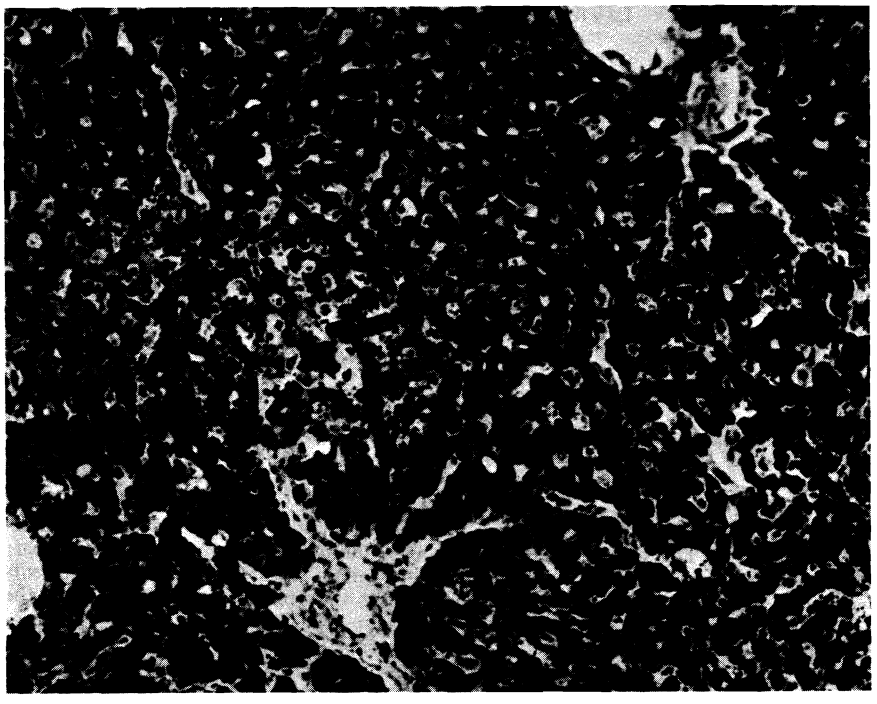

FIGURE 11. Liver from Case 2 (LD47). The majority of the hepatocytes are heavily laden with large fat droplets which appear black in the photomicrograph. Frozen section stained with oil red 0 × 150.

TABLE 2
EFFECT OF GENETIC RELATIONSHIP OF DONOR UPON ONE-YEAR SURVIVAL.

Donors	No.	Survival One Year
Unrelated donors:	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%)

*One of these patients died after 13-1/2 months, and another after 23-1/2 months.

†One patient died after 22 months.

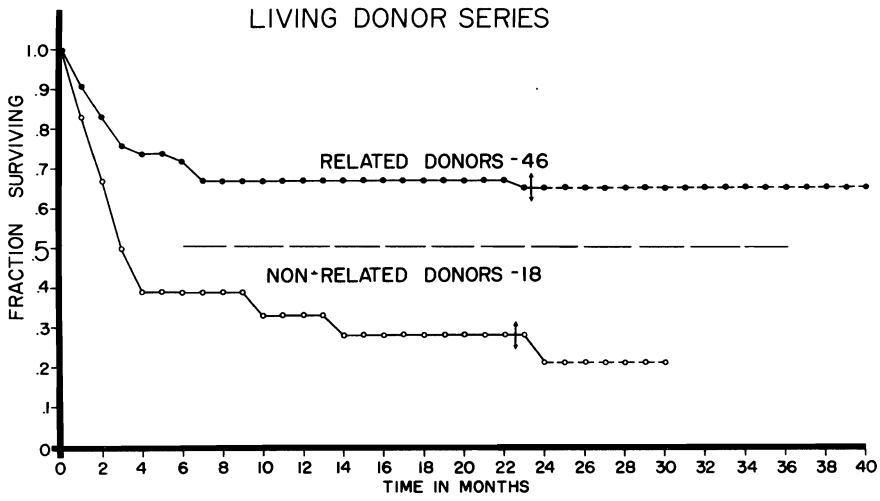

FIGURE 12. Life survival curves of related and nonrelated cases treated at the University of Colorado. The vertical arrows indicate the minimum follow-up for those patients still alive on February 16, 1966. The curve to the left of the arrows therefore represents survival data already achieved. The data to the right of the arrows are projected since the post-transplantation survival time in currently living patients ranges from $22\frac{1}{2}$ to 39 months. The 50 percent fractional survivorship is indicated by the centrally placed broken line (This graph is based upon life-survival computer analysis performed by Dr. M. R. Mickey of the University of California Center for the Health Sciences in Los Angeles).

TABLE 3
LATE COMPLICATIONS

Type of Complication	Number by May 1965	New examples by February 1966
Liver injury	3	2
Spontaneous bone fracture	5	0
Ureteral stenosis	4	0
Chronic pyelonephritis	1	0
Late rejection	9*	2†

*Two of these patients were already dead in May, 1965.[2] A third (LD47) subsequently died (Case Report 2).

†One of these patients (LD36) died (see Case 1).

reported had died by May of 1965; another of this group subsequently succumbed. (Case 2). An additional two examples have been seen in the ensuing nine months. One of these patients died of sepsis (Case 1); the other is still

alive and in good health, despite reduced function (BUN 40 mg%; Ccr 25–30 ml/min).

Three patients in the presently reported series of chronic survivors were previously reported[2] to have developed jaundice. One had already died by May of 1965. The two others had exhibited improvement in liver function after reduction of the daily azathioprine dose. One of these latter patients (Case 1) subsequently developed late rejection and died with a combination of advancing renal failure, liver malfunction and bacterial sepsis. The third patient is still alive without jaundice, although there has been persistent hepatic dysfunction for 28 of the $31\frac{1}{2}$ months since homotransplantation.

Two new observations of liver injury have been made. Patient LD37 received a renal transplant on October 18, 1963. Jaundice was first noted in May of 1965. His azathioprine dose, which had been 175 mg or more since operation, was reduced to 75 mg/day. He is currently not jaundiced but does have elevations in SGPT, SGOT and alkaline phosphatase and depressions of prothrombin time and BSP excretion. The other new example is documented in Case 2.

There have been no new examples of the other major causes of late morbidity (TABLE 3).

Renal function. Creatinine clearances, BUN's and examinations of urine sediments are carried out on all patients at frequent intervals. In all but nine cases, PAH and inulin clearances, and concentration dilution capacity were measured on one or more occasions. Thirty-two of the 36 patients who were alive in May of 1965 have the same or improved function nine months later (TABLE 4). Of the four whose function deteriorated subsequent to May of 1965, two have died. Three of these four patients had received kidneys from nonrelated donors.

Pretransplant thymectomy. The four longest survivors in this series, now 34 to 39 months posttransplantation, had thymectomy prior to the homografting procedure. The benignancy of their late course has been the subject of considerable interest. These four patients have now been off steroids from 18 months to almost three years without any evidence of homograft functional instability. The evidence for and against the concept that thymectomy may have been of benefit in these cases has recently been reviewed.[2]

TABLE 4
TREND OF RENAL FUNCTION OF THE 36 PATIENTS
WHO WERE STILL ALIVE IN MAY, 1965.

Worse	4*
Same	31
Better	1

*Two of these patients (See Cases 1 & 2) are dead. The other two both received nonrelated kidneys.

Discussion

The late failures reported in the present study, in which death was ultimately due to a combination of factors, probably represent a prototype that will be observed with increasing frequency. These two patients as well as a third[2] who died after $13\frac{1}{2}$ months had experienced late homograft rejection with consequent permanent impairment of homograft function.

In each case, intensification of immunosuppressive therapy was necessary to maintain life-sustaining renal function. In each case, extra-renal complications ensued to which the immunosuppression apparently contributed. The increased susceptibility to septic complications caused by bacteria or unusual opportunistic organisms, under these special circumstances, is not unexpected. Similarly, the pancreatitis which was seen in the two most recent deaths is not surprising, since this complication is often associated with either uremia[4] or steroid therapy.[5]

The explanation for the late hepatic complications is less clear. In the present series, all three patients who died after one year had severe liver injury and two other long-term survivors also have chronic hepatic dysfunction. It is tempting to ascribe such complications to the hepatotoxicity of azathioprine, in view of the consistent parenchymal injury which this drug causes in the canine liver.[6] However, a similar specific toxicity has not been well demonstrated in man.[7] Furthermore, the clinical course and histopathologic studies in at least two of these five patients have been more consistent with the diagnosis of viral hepatitis. It is probable that these complications are due to more than one etiologic factor. In this connection, the widespread fat emboli in one of the late homografts (Case 2) may have originated from a steroid-induced fatty liver, as has recently been reported by Jones.[8]

With more complete information on the late morbidity and mortality after renal homotransplantation, both in this and in other series,[9-16] it has become possible to speculate more authoritatively about the future of these patients. Up to the present time, the late death rate in related cases has conformed remarkably well to the optimistic pattern predicted in Barnes' life-survival curves[17] which were prepared more than a year ago from the pooled National Academy of Sciences Registry. In the present series, the recipients of kidneys from blood relatives have fared extremely well, only one death having occurred from the seventh month onward; 65 per cent of the original group have now lived for 23 to 39 months. Furthermore, none of these survivors has had any diminution in homograft function for the last year. The benefit to these patients has already been substantial and can be expected to continue for long intervals in spite of the histologic abnormalities present at two years in many of the homografts.[18]

By contrast, it seems clear that the long-term prognosis of recipients of randomly selected unrelated homografts is extremely guarded. In the present series, only six of 18 such patients lived for as long as one year. Two subse-

quently died during the second postoperative year, and homograft function in two of the remaining four has declined significantly in the last 12 months. Furthermore, the degree of histologic injury in the nonrelated homografts studied after one year has been severe.[18] The observations emphasize that development of better immunosuppressive regimens and/or perfection of tissue typing techniques will be necessary before even moderately satisfactory long-term results can be expected within the unrelated donor-recipient human population.

Summary

Sixty-four patients were treated, from November, 1962 to March, 1964, with renal homografts from living volunteer donors. After one year, 37 patients were still alive. There have been three subsequent deaths after $13\frac{1}{2}$, 22 and $23\frac{1}{2}$ months. The fatalities were due to a combination of reduced renal function and multiple extra-renal complications. The other 34 patients are still alive, now $22\frac{1}{2}$ to 39 months postoperatively.

The outlook, after homotransplantation of kidneys from related donors, remains favorable. Thirty of the original 46 patients are still alive; only one death has occurred after seven months. Moreover, the 30 survivors have all had stable renal function for the past year or longer.

Both early and late results have been poor with nonrelated donor-recipient combinations. Only six of 18 such recipients lived for one year. Two have subsequently died during the second postoperative year, and two of the remaining four have had substantial declines in renal function during the latter interval.

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