Papers and Originals

Renal Homotransplantation in 24 Patients *

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There are now in the world about 30 patients who have lived longer than one year after homotransplantation from donors other than identical twins (Murray, personal communication, 1964). Several centres in Europe and the United States have made outstanding contributions to the clinical field, and encouraging results have been reported by Hume *et al.* (1963), Merrill *et al.* (1963), Shackman *et al.* (1963), Woodruff *et al.* (1963), and Starzl *et al.* (1964a). Results obtained at the present time indicate that useful prolongation of life is possible in from 30 to 50% of patients having terminal renal failure.

Between January 1963 and June 1964 27 renal transplantations were performed on 24 patients at the Cleveland Clinic (Table I). Six cases have been reported in detail (Figueroa *et al.*, 1964). As this is a rapidly advancing field we believe it is appropriate to analyse our results and draw preliminary conclusions for future guidance.

Methods

Pre-operative Treatment.—All patients had terminal renal failure; the nature of the disease is indicated in Table I. Seven patients had been maintained on a chronic haemodialysis programme (Brandon *et al.*, 1962) from 6 to 18 months and had received from 72 to 138 haemodialyses. Since December 1963 dialysis was used mainly to prepare patients for transplantation. Bilateral nephrectomy was performed about two weeks before living-donor-kidney transplantations and about 10 to 14 days after cadaver-kidney transplantations. Splenectomy was performed in eight patients and thymectomy in nine.

Choice of Donors.—Close blood relatives served as living donors and an unrelated living donor (brother-in-law) was used only once. A general medical examination, tests of renal function, and renal arteriography were carried out on all living donors. Donors with young children or having family responsibilities were avoided. Cadaver donors with a history of renal disease or hypertension were not used.

Operative Details

Cadaver donors were heparinized after death, an infusion of low-molecular-weight dextran[1] was given, and closed chest cardiac massage and artificial respiration were performed until the kidneys were removed (Nakamoto *et al.*, 1964). Initially the cadaver kidneys were cooled to only 8 to 10° C. in saline solution. Since November 1963 they have been first flushed out with about 100 ml. of a warm perfusing solution (temperature 28° C.) until the venous return becomes clear. This is followed by perfusion with 100 ml. of cold solution (temperature 10° C.). The kidneys were then kept in cold isotonic saline (temperature 10° C.). The composition of the perfusing fluid is indicated in Table II. The kidneys were transplanted into the iliac fossa as first performed by Kuss and described by Murray and Harrison (1963). Both kidneys from one cadaver were transplanted in one patient (Case 1).

Since January 1964 the ureter has been implanted into the bladder through a submucous tunnel. An infusion of mannitol (50 g.) was started at the time of completion of the vascular anastomosis. Most patients received azathioprine (Imuran), from 2 to 4 mg./kg. of body-weight starting on the day before the operation, but in a few patients the administration of the azathioprine was begun one week before transplantation. The subsequent maintenance dose of azathioprine has varied from 25 to 250 mg./day, depending on the white-cell count. We have tried to keep the white-cell count above 5,000/c.mm. Prednisone, from 100 to 200 mg. daily, was started on the day of operation, the dose being gradually reduced. Seven patients received actinomycin C, 200 μg. weekly, and four patients received local irradiation to the graft as described by Hume *et al.* (1963) (dose 4×150 r) in addition to the other drugs.

Post-operative Course

A profuse diuresis was usually observed post-operatively when kidneys from living donors were used. One patient (Case 10) produced 33 litres of urine on the first day after transplantation. Fluid losses were usually replaced with 5% dextrose in 1/4-strength saline solution. Frequent estimations of blood and urine electrolytes were made during the diuretic phase and losses replaced accordingly. There was a tendency for the patients to develop hyperkalaemia after cadaver-kidney transplantation, and cation-exchange resins were often given prophylactically (Kayexalate,[2] 30 g. daily by enema). Blood used for transfusions was first run through potassium exchange resin columns.[3] An infusion containing glucose 20%, insulin 20 units, calcium gluconate 4 g./l., and sodium lactate 80 mEq/l. in normal saline was used to prevent the effects of severe hyperkalaemia (Kolff, 1955). Haemodialysis was performed after every cadaver-kidney transplantation and after

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[1] Rheomacrodex, supplied by Pharmacia Laboratories, Rochester, Minnesota.

[2] Winthrop Laboratories, New York, N.Y.

[3] Fenwal Laboratories, Morton Grove, Illinois.

two living-donor-kidney transplantations (Cases 8a and 17). Prophylactic antibiotics were given in most cases.

The patients were nursed in an intensive-care unit for the first few days post-operatively. They were transferred later to single rooms, where reverse isolation nursing care was practised. The urethral catheter placed at the time of surgery was, at first, removed in the second week after transplantation; more recently it has been removed on the third day. Patients whose post-operative course was without complications were discharged from hospital after two weeks and seen thereafter as out-patients. Daily white-cell counts, urinalysis, and weekly tests of renal function were done during the first few weeks. Later investigations were performed less frequently. Patients were encouraged to have normal diets and to return to work as soon as they were fit.

Results

Twenty-seven homotransplantations were attempted on 24 patients. There were 14 cadaver-kidney and 13 living-donor-kidney transplantations. Of the 13 patients who are alive,

TABLE II.—*Composition of Kidney-perfusing Solution*

Factor	Content
Dextran	6 mEq/l.
Dextrose	2·5 mEq/l.
Mannitol	12·5 g./l.
Heparin	40 mg./l.
Electrolytes:	
Sodium	147 mEq/l.
Potassium	5 mEq/l.
Calcium	5 mEq/l.
Magnesium	1·6 mEq/l.
Chloride	136 mEq/l.
Bicarbonate	20 mEq/l.
Phosphate	1·6 mEq/l.

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TABLE I.—*Summary of Findings in 24 Patients who Underwent Renal Transplantation*

Case No.	Age, Yr.	Sex	Disease	No. Dialyses Before Transplantation	No. Dialyses After Transplantation	Date of Transplantation	Donor	Duration of Ischaemia Hr.	Duration of Ischaemia Min.	Period of Function	Outcome
1	48	F	Chronic glomerulonephritis	29	5	9.1.63	Cadaver, 27 yr., F. Both kidneys used. Renal artery stenosis endarterectomy	4 6	35 35	0	Non-viable kidneys. No urine produced. Died from sepsis, terminal agranulocytosis, 24.1.63
2	31	M	„ „	138	3	18.1.63	Cadaver, 37 yr., F. Coronary heart disease. Internal mammary artery implantation	3	50	0	Non-viable kidney. No urine produced. Cardiac arrest (hyperkalaemia). Died 23.1.63.
3	14	F	Chronic pyelonephritis and nephrocalcinosis	a 13 b 28	0 2	1.4.63 24.5.63	Mother, 40 yr. Cadaver, 59 yr., M. Repair of mitral stenosis	 3	32 34	11 mo. 11 days	Gradual decline in renal function (rejection). Transplant nephrectomy 4.3.64. Initial function. Died 5.6.64 from infection and neutropenia
4	21	M	Chronic glomerulonephritis	21	0	12.6.63	Father, 58 yr.		54	12 mo.+	Well, working. Blood urea 57 mg./100 ml. Creatinine clearance 80 ml./min.
5	41	M	„ „	26	0	16.7.63	Brother, 45 yr.		41	11 mo.+	Well, working. Blood urea 40 mg./100 ml Creatinine clearance 110 ml./min.
6	24	M	Chronic glomerulonephritis and pyelonephritis	16	0	9.7.63	Father, 50 yr.		50	11 mo.+	Well, working. Blood urea 33 mg./100 ml. Creatinine clearance 69 ml./min.
7	25	M	Primary hyperoxaluria and nephrocalcinosis	6	0	28.8.63	Mother, 56 yr.		34	10 mo.+	Anaemic (haemoglobin 7·7 mg./100 ml.) Renal function declining (recalcification of kidney). Blood urea 108 mg./100 ml. Creatinine clearance 23 ml./min.
8	37	M	Chronic glomerulonephritis	a 117 b 26	26 11	21.8.63	Brother, 39 yr. Cadaver, 60 yr., F. Reticulum-cell sarcoma (same as 12a)		48 19	5 days 0	Anuria on 5th day. Homograft necrotic when removed on 68th day Non-viable kidney. No urine produced. Homograft necrotic when removed, 5.11.63. Died, 4.12.63
9	34	M	Post-traumatic nephrectomy (Rt) hypoplastic kidney (Lt.)	14	3	24.8.63	Cadaver, 36 yr., F. Repair of aortic regurgitation	2	14	10 mo.+	Well, working. Creatinine clearance 23 ml./min. Blood urea 69 mg./100 ml.
10	25	M	Systemic lupus erythematosus	17	0	3.10.63	Mother, 56 yr.		41	6 wks.	Died from sepsis 15.11.63. Prostatic abscess. Good renal function until death (blood urea 69 mg./100 ml.)
11	41	F	Chronic pyelonephritis	39	0	9.10.63	Sister, 45 yr.		33	2 mo.	Good renal function until death. Developed ureteric fistula and died from sepsis 16.12.63
12	26	F	„ „	a 23 b 3	3 0	1.11.63 11.11.63	Cadaver, 60 yr., F. Reticulum-cell sarcoma Mother, 49 yr.	2	3 49	0 3 wk.	Non-viable kidney. No urine produced. Removed 11.11.63. Total necrosis Good renal function until death. Developed psychosis. Died from sepsis 4.12.63
13	56	M	„ „	114	1	17.11.63	Cadaver, 33 yr., F. Brain tumour Craniotomy	2	55	7 mo.+	Well. Blood urea 44 mg./100 ml. Creatinine clearance 44 ml./min.
14	44	F	„ „	72	13	18.11.63	Cadaver, 39 yr., M. Coronary heart disease. Omentopexy	2	10	1 hr.	Haemorrhage from kidney after decapsulation. Homograft removed on same day. Severe hepatitis. Died 17.12.63
15	20	M	Systemic lupus erythematosus	6	1	20.11.63	Cadaver, 47 yr., M. Subarachnoid haemorrhage. Craniotomy	2	1	7 wk.	Ureteral fistula. Good renal function until death. Died from sepsis 13.1.64
16	43	F	Polycystic kidneys	72	3	20.11.63	„ „ „	2	15	2 days	Oliguria. Died 30.11.63. Gangrene of small bowel. Normal-looking kidney at necropsy
17	47	M	Chronic glomerulonephritis	131	74	26.11.63	Mother, 68 yr.		50	5 days	Anuria on 6th day. Homograft necrotic when removed on 21st day. Maintained by periodic dialysis. Working
18	30	M	„ „	6	8	14.1.64	Cadaver, 44 yr., M.	2	10	5 mo.+	Well, working. Blood urea 54 mg./100 ml. Creatinine clearance 75 ml./min.
19	28	M	„ „	3	5	26.1.64	Cadaver, 39 yr., M. Subarachnoid haemorrhage. Craniotomy	2	6	5 mo.+	Well, working. Blood urea 40 mg./100 ml. Creatinine clearance 42 mg./min.
20	43	M	„ „	58	0	30.1.64	Unrelated living donor, 43 yr., M.		54	6 wk.	Died, 18.3.64. Septicaemia and agranulocytosis. Abscess close to lower pole of kidney. Good renal function until death
21	44	M	Nephrosclerosis, chronic pyelonephritis, gout	7	6	11.2.64	Cadaver, 49 yr., M. Subarachnoid haemorrhage. Craniotomy	2	7	4 mo.+	Well. Blood urea 60 mg./100 ml. Creatinine clearance 60 ml./min.
22	42	M	Rheumatoid arthritis (inactive), amyloidosis	20	10	6.4.64	Cadaver, 59 yr., M. Aortic valvotomy	2	47	2 mo.+	Well. Blood urea 60 mg./100 ml. Creatinine clearance 60 ml./min.
23	19	F	Chronic glomerulonephritis	24	0	29.4.64	Mother, 44 yr.		59	6 wk.+	Well. Blood urea 40 mg./100 ml. Creatinine clearance 120 ml./min.
24	16	M	„ „	16	0	18.5.64	Mother, 41 yr.		41	1 mo.+	Well. Has returned to school. Blood urea 34 mg./100 ml. Creatinine clearance 81 ml./min.

Bilateral nephrectomy was performed in all patients with the exception of Cases 9, 14 and 16. Splenectomy was performed in Cases 3, 13 and 19–24. Thymectomy was performed in Cases 3–7, 12, and 22–24. Actinomycin C was given in Cases 3, 4, 6, 7, 10, 13 and 21. Local irradiation of the graft was performed in Cases 3 (a and b) 6, 13, and 21. Major blood groups were crossed in three patients (Cases 8b, A+ to O+; Case 10, AB+ to A+; Case 12a, A+ to O−).

seven received transplants from living donors, the longest period of function being 12 months; six patients received cadaver-kidney transplants, the longest period of function being 10 months. One patient who received a kidney transplant from a living donor is being maintained in the renoprival state by twice-weekly dialyses following surgical removal of the homograft (Case 17).

Causes of Failure and Complications

There were 15 failures in 12 patients. The main causes of failure were non-viability of cadaver kidneys at the time of transplantation, overwhelming infection, urine leakage with infection, and uncontrollable bleeding (Table III). Cessation of renal function in the first week after transplantation occurred in two patients who had received homografts from related living donors. In the absence of an obvious cause it may be that an acute vascular immune reaction had occurred. The homografts showed severe vascular occlusive lesions and large areas of focal necrosis (Cases 8a and 17). A recurrent form of rejection manifested by severe vascular occlusive lesions in one patient led to a gradual decline in renal function over the course of 11 months (Case 3). This patient, however, had led an almost normal life for the entire period following the relief of uraemia, anaemia, and malignant hypertension.

TABLE III.—*Causes of Failure of Renal Transplantation*

Cause	No. of Transplantations That Failed
Non-viable cadaver kidneys	4
Surgical factors	2
Sepsis secondary to ureteric fistula or wound infection	3
Septicaemia associated with severe terminal neutropenia	3
Possible acute rejection or unexplained non-function	2
Recurrent or chronic vascular rejection	1
	15

Most patients experienced a return of strength and well-being following successful transplantation. There was rapid gain in weight and some patients became overweight. Four patients (Cases 4, 5, 9, and 13) gained an average of 15 kg. each since discharge from hospital. One patient (Case 18) who had become profoundly emaciated gained 25 kg. since he received a cadaver-kidney transplant.

There was a tendency for the blood-pressure to fall after transplantation, sometimes over a period of from four to six weeks. Persisting hypertension was due to some complicating factor such as ligation of an accessory renal artery (Case 20) or rejection. Kolff *et al.* (1964) have shown that bilateral nephrectomy facilitated the control of severe hypertension in about 60% of patients so treated. There were seven patients with malignant hypertension in this series who had bilateral nephrectomy and renal transplantation and whose course could be followed for five months or longer (Fig. 1). Five of these seven became normotensive within six weeks and required no hypotensive therapy. One patient (Case 6) had two episodes of rejection accompanied by elevation of his blood-pressure. He became normotensive and was taken off hypotensive drugs, but required dietary sodium restriction. Hypertension recurred in one patient (Case 3) and required continuous antihypertensive treatment. Moreover, the blood-pressure rose sharply during episodes of rejection. Her renal function declined gradually. Transplant nephrectomy was carried out at 11 months because of persistent gross haematuria following a renal biopsy. The homograft showed severe thickening of the intima of large and small intrarenal arteries to the point of obliteration. The focal distribution of these lesions was unlike the more generalized intimal thickening seen in the arteriosclerosis commonly associated with hypertension. These vascular lesions are probably manifestations of a rejection process, as suggested by Porter *et al.* (1963), and the hypertension may have been produced by the vascular narrowing.

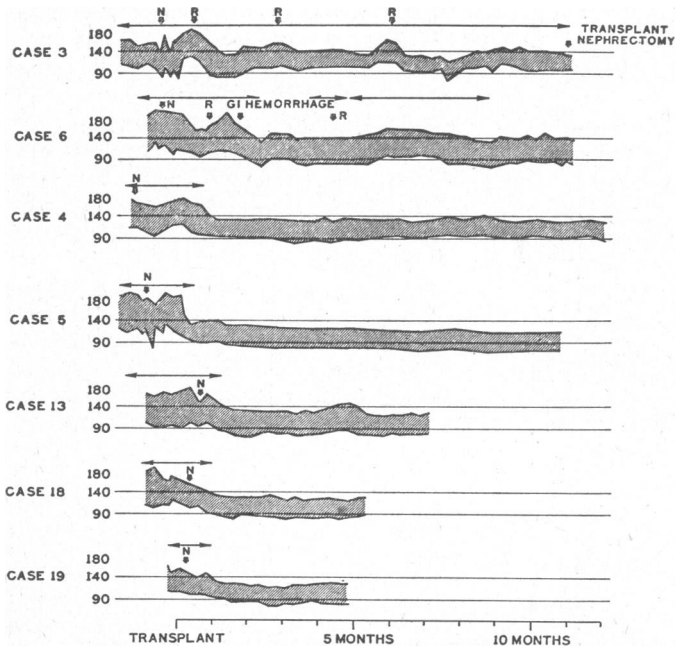

FIG. 1.—Effect of renal homotransplantation in seven patients with malignant hypertension. Five were cured. One patient (Case 6) became normotensive after two episodes of rejection. Patient 3 remained slightly hypertensive but severe hypertension occurred during rejection crises. N=Nephrectomy. R=Rejection. ⟷=Antihypertensive therapy.

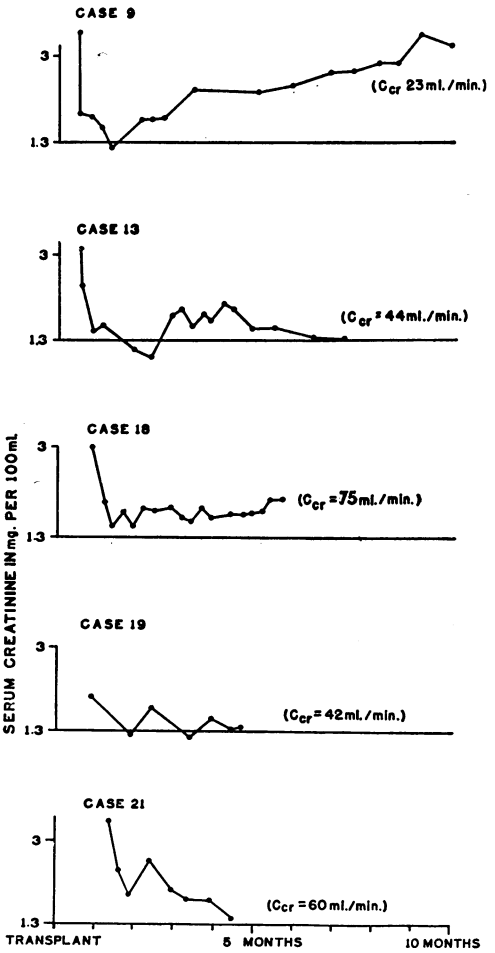

FIG. 2.—Renal function (serum creatinine levels in five patients) after cadaver-kidney transplantation. Renal function is fair in four patients. In one patient (Case 9) renal function has declined: however, the blood urea was 69 mg./100 ml., he felt well, and he was working full time.

Renal Shut-down

When cadaver kidneys are used there is usually a period of renal shut-down lasting for about 14 days. Sometimes the urinary output from the transplanted kidney is difficult to estimate, because patients who receive cadaver kidneys do not have their kidneys removed until after transplantation. The subsequent renal function of the cadaver-kidney transplants is shown in Fig. 2. One patient (Case 9), our longest-living patient with cadaver-kidney transplant, had impaired renal function after 10 months. His creatinine clearance fell from 75 to 23 ml./minute. The blood-pressure gradually rose from 110/70 to about 145/95 mm. Hg. However, his blood-urea concentration was 69 mg./100 ml., there was no anaemia, he was feeling fit, and was working full time. The other recipients of cadaver kidneys were maintaining fair renal function.

In the living-donor-kidney transplants (Fig. 3), deterioration of renal function occurred in two patients (Case 3, recurrent and chronic rejection ; and Case 7, primary hyperoxaluria). The latter patient (Case 7) had severe calcification of his own kidneys. The diagnosis of hyperoxaluria was made after transplantation. A needle biopsy of the homograft showed some deposition of oxalate crystals in the tubules as early as two weeks after transplantation. A second biopsy three months later showed no further increase in the calcification. His renal function, however, was declining and he remained anaemic.

Deterioration of renal function occurred in another patient (Case 6) during recurrent episodes of rejection. A renal biopsy taken at a time when he was thought to be rejecting the transplanted kidney showed cellular infiltration but no vascular lesions. The rejection process is apparently being controlled and his renal function is good (blood urea, 33 mg./100 ml. ; serum creatinine, 1.1 mg./100 ml. ; creatinine clearance, 69 ml./minute). The other patients have maintained good renal function.

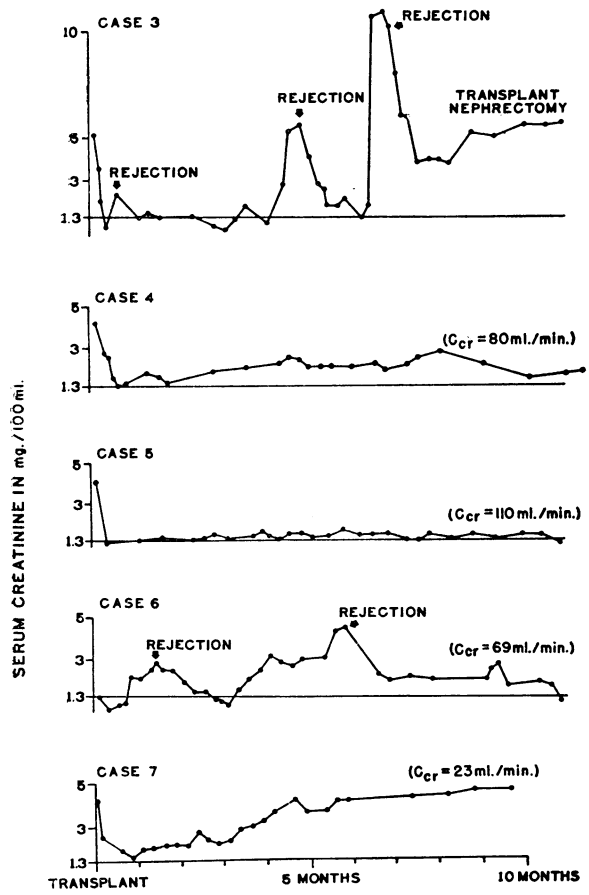

FIG. 3.—Renal function in five patients after living-donor-kidney transplantation. Renal function is good in three patients, but has declined in two (Case 3, re,ection ; and Case 7, hyperoxaluria).

Haemopoietic Function

Successful renal homotransplantation improved the anaemia in all but one patient (Fig. 4). The haemoglobin values ranged from 9 to 15 g./100 ml. in contrast to the profound anaemia before transplantation. In one patient (Case 3), following a dramatic rise in haemoglobin concentration after transplantation, the anaemia recurred as renal function began to decline. The fall in haemoglobin has also been parallel to the decline in renal function in the patient with primary hyperoxaluria (Case 7). At one time megaloblastic changes were noted in the bone-marrow, possibly related to the administration of azathioprine. In Case 6 it was possible to demonstrate large amounts of erythropoietin in the blood during an episode of gastro-intestinal bleeding in September 1963 (Hoffman *et al.*, 1964).

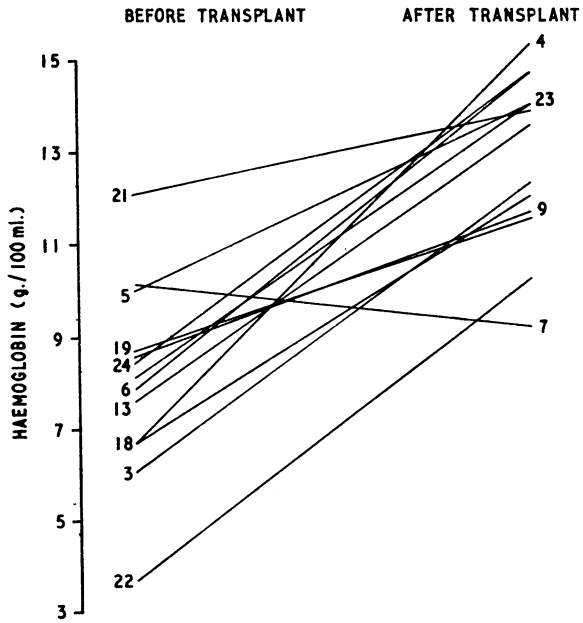

FIG. 4.—Effect of renal homotransplantation on anaemia. Most patients were anaemic before transplantation. "After transplant" indicates the latest blood-haemoglobin content ; in Case 3 the blood-haemoglobin level five months after transplantation is given ; anaemia developed as renal function declined. Patient 7 (primary hyperoxaluria) has remained anaemic.

Several patients have shown good ability to localize and overcome severe infections despite the immunosuppressive therapy. Empyemas, post-operative wound infections, pyelonephritis, and herpetic infections healed successfully.

Peripheral polyneuropathy has only recently been widely recognized as a crippling complication of uraemia, possibly because these patients now live longer than in the past. Regression of clinical signs and improvements in motor strength occurred in four patients after successful transplantation ; however, objective measurements have failed to show any improvement in the motor-nerve-conduction velocities (Versaci *et al.*, 1964).

Condition of Survivors

Most patients were able to lead normal lives after successful renal homotransplantation and six have returned to work. One patient (Case 4) was working 60 hours a week and was reluctant to accept our advice to defer marriage. Another (Case 5) returned to his previous occupation as a travelling salesman, and another (Case 6) was working as a laboratory assistant in

the hospital. One patient (Case 18) returned to his home town in another State and drove in every two weeks for follow-up. One boy (Case 24) returned to school one month after transplantation. One patient (Case 13) had been admitted to the hospital following an episode of hypertensive encephalopathy. He was in coma and had severe uraemia and pericarditis. He was maintained by periodic haemodialyses for 13 months, and during that period developed a peripheral neuropathy, cardiac tamponade, and a left-sided empyema. In November 1963 a cadaver kidney was transplanted. Despite a period of ischaemia of two hours and 55 minutes he excreted urine promptly and showed no evidence of renal shut-down. Seven months later he was in good health, with a blood-urea content of 55 mg./100 ml. He has become normotensive. He returned to his home in another State and visited the hospital fortnightly for review. The failure of a transplanted kidney to function and its subsequent removal need not end the patient's useful existence. One patient (Case 17) received a kidney transplant after bilateral nephrectomy. The homograft never functioned well and was removed after 21 days. The patient continued to be maintained by periodic haemodialysis, and as vice-president of a company earns a good income for his family. He has received 205 dialyses over a period of 22 months.

The first few weeks after transplantation are the most critical period. After the first two months the prognosis improves to the extent that the patient stands a good chance of surviving for at least one year.

Discussion

Difficult Problems

The treatment of a condition as hopeless as terminal renal insufficiency raises unusual problems. Difficult and sometimes arbitrary decisions have to be made not only in initiating treatment by dialysis and performing a transplantation but also in acknowledging defeat and withholding further treatment. It is essential not to perform a renal transplantation while some usefulness of the patient's own kidneys remains, since the period of function of a renal homograft cannot be predicted. This often entails an additional period of observation after improvement has been produced by dialysis. Undue procrastination, however, is expensive, and may also cost the patient his life.

We prefer to perform transplantation in stable, responsible young patients without systemic disease, but we find it hard to deny patients already under our care the only chance of recovery, however small this may be. Patients are certainly entitled to that chance when a cadaver kidney is involved. We have been encouraged by our recent results with cadaver-kidney transplantations. Five of our last six cadaver-kidney transplants have been successful so far. So long as the ultimate outcome remains uncertain many ethical problems are avoided if cadaver kidneys are used. Further work will have to be done to obtain cadaver kidneys immediately after death, to decrease the period of ischaemia at the time of transplantation, and to devise a satisfactory method of cadaver-kidney preservation. It is planned in the future to use both kidneys from one cadaver for two recipients.

Haemodialysis

The maintenance of the recipients by adequate dialysis is an important aspect of the transplantation programme, particularly when cadaver kidneys are used. It is useful to have a small pool of potential recipients of different blood groups while awaiting a suitable cadaver kidney. We prefer to perform renal transplantation on fit subjects and we have not operated when clinical signs and symptoms of uraemia were present. Patients who receive kidneys from cadavers may have to be maintained by dialysis for periods of from two to five weeks during recovery from acute tubular necrosis. Failure to control uraemia at this critical stage favours infection and delays wound healing.

Blood-group Incompatibility

The importance of blood-group compatibility between donors and recipients is not proved, but it is probably safer not to cross major blood groups. It has been stated that the combinations A to non-A, B to non-B, and AB to non-AB, carry a higher risk (Starzl *et al.*, 1964b). We have crossed major blood groups on three occasions (Cases 8, 10, and 12a), but the final fatal outcome of these patients was due to other factors. Rejection did not occur in the six instances where the donors were Rh-positive and the recipients Rh-negative. Woodruff (1963) has stated that blood transfusions are potentially dangerous in the preparation of recipients for transplantation and that there is a risk of sensitization. Most of our patients had received numerous haemodialyses in which at least two units of blood were used per dialysis. Since December 1963 we have taken the precaution to remove the buffy coat from the blood before the transfusion. The abrupt cessation of renal function in two patients (Cases 8 and 17) in the absence of any obvious cause may have resulted from acute vascular rejection. This, however, is not proved and failure of function shortly after transplantation is not always caused by an immunological process (Dempster, 1963 ; Calne, 1964).

Immunosuppressive Therapy

Most workers have reported frequent episodes of clinical rejection in their series. We have seen clinical episodes of rejection in only three patients (Cases 3, 6, and 21), if the two patients who developed anuria in the first week after transplantation are excluded. The continuous administration of azathioprine and the use of large doses of steroids seem to be responsible for the rarity of episodes of rejection. It has been our practice to give an initial dose of from 100 to 150 mg. of prednisone and to reduce the dose slowly. Most patients take about 50 mg. after one month, and the eventual maintenance dose is from 2.5 to 15 mg. We have not attempted to discontinue all immunosuppressive therapy in our patients, although evidence from animal experiments points to this possibility (Pierce and Varco, 1963). We have found azathioprine to be a relatively safe drug, but on several occasions leucopenia forced us to reduce the dosage to a point where it probably ceased to be effective (Case 3a). We have observed severe neutropenia as a terminal event in six patients (Cases 1, 3b, 10, 11, 12, and 20). These patients died from a combination of sepsis and drug toxicity. The white-cell count fell precipitously within two to three days. Starzl *et al.* (1964c) has also encountered this syndrome in several patients. It appears to be one of the most common causes of death after transplantation. In our experience it is usually triggered by some technical problem, such as the use of non-viable or infected cadaver kidneys, breakdown of the ureterovesical anastomosis, partial ureteric obstruction, or ligation of an accessory renal artery.

The advantages of splenectomy and thymectomy are as yet unknown. We have encountered no complications from splenectomy or from thymectomy through a low cervical incision, as performed by Dr. George Crile, jun. We have observed, however, that the arteriovenous shunt used in haemodialysis (Scribner *et al.*, 1960) sometimes tends to thrombose after splenectomy. Four patients had a transient leucocytosis for periods of from two to six weeks after splenectomy. An increased dose of azathioprine could be given to three patients during that period. It is our impression that even when there was no rise in the white-cell count it was sometimes possible to administer a larger dose of azathioprine for a few weeks, without producing critical leucopenia.

The importance of technical factors in renal transplantations has been stressed recently. We have been impressed by the serious consequences of even minor deviations from a perfect surgical result. Leakage at the ureterovesical anastomosis is particularly dangerous and is often complicated by sepsis. Necrosis of the ureter usually means loss of the transplant, although we have recently been able to salvage a kidney following a plastic operation on the bladder to form a new pathway from the renal pelvis. The correct management of early post-transplantation anuria is important and ureteric obstruction must always be excluded. The assessment is more difficult when the patient has not had his own kidneys removed. We have suspected renal-artery occlusion on several occasions, but the major renal vessels were found to be normal on arteriography. The distinction between acute tubular necrosis, diffuse cortical infarction, and acute rejection is difficult, and at times a renal biopsy may be most informative.

Diagnosis of Homograft Rejection

The mechanism of homograft rejection remains poorly understood, but cellular, humoral, as well as vascular factors probably play a part (Dempster *et al.*, 1964). Some interstitial cellular infiltration has occurred in several patients without any reduction in renal function. Fibrinoid necrosis of small arteries in the two patients who became anuric in the first week after transplantation (Cases 8 and 17) may have been a manifestation of acute rejection such as has been described by Hamburger *et al.* (1962). The occurrence in the same patients of severe intimal thickening as early as the thirteenth day (Fig. 5) lends support to the suggestion by Porter *et al.* (1963) that the rejection phenomena may be localized in the blood-vessel walls. Intimal thickening was also seen three months after transplantation in one patient whose renal function has remained unimpaired since (Case 4). This finding has induced us to use actinomycin C in addition to azathioprine in the hope of preventing further vascular lesions in this patient. Gross obliterative vascular changes were found in a patient with declining renal function when the homograft was removed 11 months after transplantation because of uncontrollable bleeding following renal biopsy (Case 3a). It is probable that the vascular lesions represent one form of rejection and that the severe hypertension noted in this patient was due to intrarenal vascular occlusion (Kolff *et al.*, 1964). In this patient a low white-cell count did not permit the administration of full doses of azathioprine, and therefore one can only speculate on whether larger doses would have suppressed the rejection process.

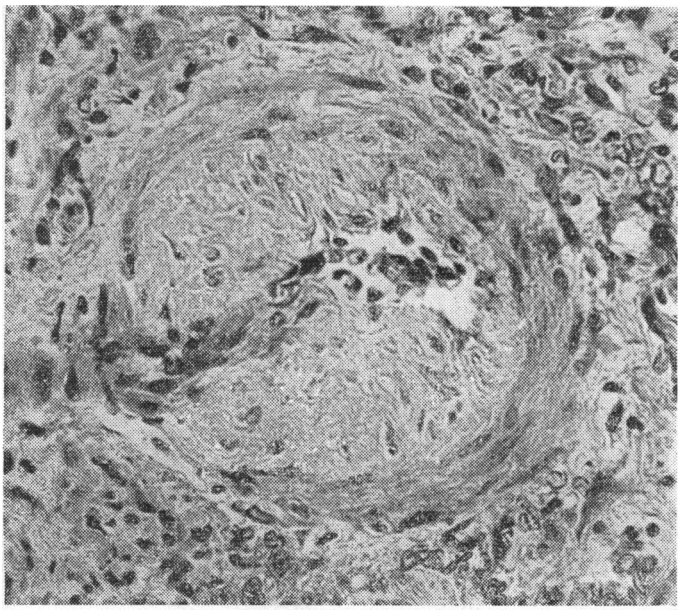

FIG. 5.—Case 8a. Biopsy specimen 13 days after transplantation showing intimal thickening, interruption of the internal elastic lamina, and severe narrowing of lumen of an artery. (Haematoxylin-eosin-methylene blue stain. ×430.)

The classical signs of homograft rejection are fever, oliguria, leucocytosis, increased excretion of protein and cells in the urine, swelling and tenderness of the renal homograft, hypertension, elevation of the blood urea, and the finding of cellular infiltration or obliterative vascular changes on renal biopsy. It is unusual, however, to encounter the full-blown rejection syndrome, and fever accompanied by some proteinuria is commoner. As the signs of infection, particularly of the urinary tract, are similar, the distinction between rejection and infection is often difficult. This is a serious therapeutic dilemma, because the treatment of these two conditions is quite opposite. It has been said that the appearance of lymphocytes in the urine is a reliable sign of rejection (Hume *et al.*, 1963), but we have found the differentiation between lymphocytes and small epithelial cells difficult. In retrospect, many transient episodes of fever were due to infection, even though rejection had been suspected at first. In two patients, however, no evidence of infection was found and the fever was suppressed by increasing the dose of prednisone.

Prolonged fever of uncertain origin occurred in four patients. Rejection was suspected at first and the doses of the immunosuppressive drugs were increased. There was no obvious site of infection and blood cultures were sterile. Antibiotics were administered in an empirical fashion. Two of these patients eventually died from pseudomonas septicaemia. Severe neutropenia had occurred as a terminal event (Cases 10 and 20). The focus of infection in one patient was an unrecognized abscess in the prostate and in the other an abscess near the lower pole of the transplanted kidney. One patient (Case 13) recovered after drainage of an unsuspected staphylococcal abscess originating in the pubic bone. Large doses of steroids suppressed the fever in the fourth patient (Case 21). Laparotomy disclosed no abnormality ; no diagnosis was made, but the patient recovered and was maintained on a small dose of prednisone (10 g./day) in addition to 150 mg. of azathioprine.

It is our impression that an increased sensitivity to cytotoxic agents occurs in the presence of sepsis. A therapeutic trial with an increased dose of prednisone is usually justified if in doubt and if no definite signs of infection are present. It is unwise, however, to increase the dose of azathioprine in the presence of relative leucopenia because there is a real danger of producing agranulocytosis. Treatment of obvious infections is less problematic, but infections of the urinary tract have been common and several patients have been plagued by large herpetic infections of the face, the mouth, and perhaps the oesophagus. Infection associated with extravasation of urine has caused the death of two patients (Cases 11 and 15). Relatively non-infected ureteral leaks have, however, been successfully corrected (Cases 3 and 22). Because of the danger of infection with resistant organisms we are now reconsidering our policy of placing a urethral catheter at the time of operation and of using broad-spectrum antibiotics as prophylaxis in the post-operative period. When nephrectomy precedes transplantation the anuric bladder may act as an asymptomatic reservoir of infection and irrigations with neomycin in the pre-operative period may be indicated.

One patient (Case 19) has had several episodes of haematuria. Cystoscopy revealed no abnormality. The patient later observed that this episode occurred after he had rested for some time with his feet up ; it may be that a mechanical factor such as compression of the homograft or of venous return was responsible.

Conclusion

The results obtained so far indicate that renal transplantation is now a feasible procedure. The failure rate is still high.

Most failures resulted from the use of non-viable kidneys, surgical factors, or infection, and may be avoidable in the future. These difficulties occurred during the first eight weeks after transplantation. We have noted an improvement in our results. In 1964 we have lost only two patients out of seven receiving homotransplants. We have been surprised by the relative success obtained with cadaver kidneys, and we have been impressed by the paucity of episodes of rejection when adequate immunosuppressive therapy was used.

While progress in basic immunological knowledge is likely to be slow, improved clinical results may be obtained with better management and surgical techniques, new methods of cadaver-kidney preservation, and improved immunosuppressive drugs. Renal homotransplantation may not yet be safe, reliable, or predictable. It has none the less provided several of our patients, who were in a desperate condition due to terminal uraemia, with a new lease of life.

Twelve patients of this series are alive after kidney transplantation, five of them for about 10 to 12 months. In addition, one girl (Case 3a) was given almost a year of happy life before surgical removal of the homograft.

Summary

The results of our first 27 cases of renal homotransplantation performed on 24 patients during a period of 18 months are reported. Of the 13 patients who are alive 12 have functioning homografts: six have received cadaver-kidney transplants, the longest period of function being 10 months, and six have received living-donor-kidney transplants, the longest period of function being over 12 months. The main causes of failure were use of non-viable cadaver kidneys (four cases), surgical factors (two cases), sepsis (six cases), and possible rejection (three cases).

All patients received azathioprine and prednisone as immunosuppressive therapy. In addition, seven were given actinomycin C and four received local irradiation to the graft. The spleen was removed in eight patients and the thymus in nine. Bilateral nephrectomy was performed in all but three patients, and facilitated the control of malignant hypertension. Haemodialysis played an important part in the preparation of patients before transplantation and in the maintenance of patients during the period of renal shut-down, especially in cadaver-kidney transplantation.

After successful transplantation patients were able to lead a normal life. Six patients have returned to work. Recovery from anaemia, malignant hypertension, and pruritus was the rule. Clinical improvement of uraemic neuropathy was noted in four patients. Clinical episodes of rejection were uncommon when continuous and adequate immunosuppressive therapy was used. Vascular changes occurred in four patients and were probably a manifestation of rejection. Leakage from the ureterovesical anastomosis has been successfully corrected in two patients but has caused a fatal septicaemia on two occasions.

Ureteric obstruction must always be excluded as a cause of post-transplantation anuria. Fever after transplantation may be due to infection or rejection, and a therapeutic trial with prednisone is justified in some cases. The use of cadaver kidneys avoids many social and ethical problems. Our early results with cadaver transplants are encouraging and we believe that no cadaver kidney should go to waste.

ADDENDUM.—Since this paper was prepared patients 13, 19, and 22 have died. The periods of function of the homograft were 11, 9, and 4 months respectively. Patient 13 died following late rejection of the homograft. The other two patients died from pneumonia. A further 15 patients received 19 homotransplants. There are now 19 patients who have functioning homografts (8 from living donors and 11 from cadavers). Five recipients have lived for over one year, the longest period of function being 19 months. The longest survival of a cadaver homotransplant so far is 15 months. Two patients are being maintained by periodic dialysis after removal of the homograft.

Dr. George Crile, jun., performed the thymectomies and splenectomies, and Dr. Eugene F. Poutasse headed the surgical team until January 1, 1964.

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