

Papers and Originals**OBLITERATIVE VASCULAR CHANGES IN FOUR HUMAN KIDNEY HOMOTRANSPLANTS**

BY

K. A. PORTER, M.D., D.Sc.
*Senior Lecturer in Pathology***W. B. THOMSON, M.D., B.Sc., M.R.C.P.**
*Senior Registrar in Medicine***K. OWEN, M.S., F.R.C.S.**
*Consultant Surgeon***J. R. KENYON, B.Sc., F.R.C.S., F.R.C.S.Ed.**
*Assistant Director, Surgical Unit***J. F. MOWBRAY, M.B., B.Chir., M.R.C.P.**
*Lecturer in Medicine***W. S. PEART, M.D., F.R.C.P.**
*Professor of Medicine**St. Mary's Hospital, London, W.2*

[WITH SPECIAL PLATE]

In the first large series of well-documented human renal homotransplants Hume *et al.* (1955) recorded one case where a kidney from a cadaver survived and functioned for six months in a young man suffering from chronic glomerulonephritis. At post-mortem examination the large and medium-sized arteries of the transplant showed "a severe degree of arteriosclerosis." Similar arterial changes have since been mentioned in several other renal homotransplants, the majority of which have been into hypertensive recipients. The opinion has been expressed that the changes have occurred because the vessels of the transplant, accustomed to a normal blood-pressure, have suddenly been exposed to a considerably higher pressure.

In this paper we report a further four cases where after transplantation of a cadaver kidney the homotransplant has developed severe obliterative vascular lesions. We present evidence that these changes are not caused by high blood-pressure but are probably part of that immunological rejection process which we know as the homograft reaction.

Methods

In each of the patients a kidney from a cadaver was transplanted into an iliac fossa—usually the right, but the left was used in Case 2. The renal artery was anastomosed end-to-end with the internal iliac artery, and the renal vein end-to-side with the external iliac vein. The ureter was inserted into the bladder through an oblique tunnel with mucosa-to-mucosa anastomosis and was drained for the first 12–30 days by a separate indwelling catheter.

All four patients were given, post-operatively, 6-mercaptopurine ("puri-nethol") or 6-(1-methyl-4-nitro-5-imidazolyl) thiopurine ("imuran"), together with some actinomycin C ("sanamycin"), and one or more of the hydrocortisone-like steroids. Two of the patients (Cases 3 and 4) were given in addition chlorambucil ("leukeran") post-operatively and either 6-mercaptopurine or chlorambucil pre-operatively.

Several transfusions of stored blood of the same ABO and Rh groups as the recipient were given to each patient. Case 1 was given 8.64 litres in the three months before transplantation and 1.62 litres in the first week after transplantation; Case 2 received 8.64 litres in the five months before and 3.78 litres in the two months after kidney transplantation; Case 3 was given 3.24 litres in the month before and 10.8 litres in the three months after transplantation; and Case 4 received 2.16 litres in the two weeks before and 3.78 litres in the two months after transplantation.

Case 1 (No. 484708)

A woman aged 46 (weight 60 kg.) developed bilateral ankle oedema and heavy proteinuria in July, 1960. Renal biopsy showed this to be due to the lobular form of Ellis's type 2 glomerulonephritis. Her blood-pressure at this time was 190/95 mm. Hg. By September, 1962, she had severe rapidly progressing renal failure, and on November 10 received a kidney transplant from a normal 16-year-old boy who had died in another hospital from a head injury. His blood groups are compared with those of the recipient in Table I. The kidney was placed in saline surrounded by ice while awaiting transplantation and was ischaemic for 2 hours 20 minutes. Urine flow began from the transplant almost immediately and over 2 litres was excreted in the first 24 hours. The patient was given 6-mercaptopurine 5 mg./kg./day orally, and high doses of hydrocortisone intramuscularly (for details see Chart 1). Early progress was good and the blood urea began to fall rapidly, but on the 15th day, when the cortisone dose was being reduced and 6-mercaptopurine had been withdrawn because of leucopenia, the patient developed fever, tachycardia, and anorexia. By the 17th day the urine volume and urine urea output were falling and the blood urea was rising.

A biopsy of the transplant, taken at the 21st day, showed interstitial oedema and a fairly heavy, very patchy cellular infiltration consisting mainly of small lymphocytes, but 10% were plasma cells and 2% larger pyroninophilic cells. Most of the proximal and many of the distal tubules showed evidence of regeneration of their epithelium. There was some swelling of

TABLE I.—Erythrocyte Groups of Donors and Recipients

| Case No. | Subject | ABO | Rh | | MN | S | P ₁ | Lu ^a | K | Le ^a | Le ^b | Fy ^a |
|----------|-----------|----------------|-----------|-------------------|----|---|----------------|-----------------|---|-----------------|-----------------|-----------------|
| | | | Phenotype | Probable Genotype | | | | | | | | |
| 2 | Recipient | AB | CcDee | CDe cde | MN | — | — | — | — | — | — | — |
| | Donor | A | ccDEe | cDE cde | MN | + | — | — | — | — | — | — |
| 3 | Recipient | A | ccDee | cDe cde | M | + | — | — | — | + | — | + |
| | Donor | A ₁ | CcDEe | CDe cDE | M | + | — | — | — | — | + | — |
| 4 | Recipient | O | CcDee | CDe cde | MN | + | ++ | — | — | — | — | + |
| | Donor | O | CcDee | CDe cde | MN | + | ++ | — | — | — | — | + |

the endothelial cells lining the arterioles and interlobular arteries. The glomeruli appeared normal (Special Plate, Fig. 1). It seemed that the kidney was undergoing rejection and high doses of hydrocortisone (800 mg. daily) were again given. This was associated with a rapid return of body temperature and heart rate to normal and a feeling of well-being. The rise in

decrease in the numbers of small lymphocytes in the lymph nodes and spleen, although plasma cells and larger pyroninophilic cells were still plentiful. Some lymph nodes contained small areas of necrosis. The patient's own kidneys were of normal size, but showed apparently total glomerular destruction by type 2 nephritis. There was some fibrous intimal thickening of the walls of the arcuate and interlobular arteries with elastic increase.

The transplanted kidney was enlarged (200 g.). The main renal vessels and ureter were unobstructed and normal, but many of the interlobar, arcuate, and interlobular arteries within the graft showed obliterative changes. In most of the vessels there was general thickening of the intima by loose, very cellular fibroblastic tissue. Sometimes the intimal thickening was confined to only part of the circumference of the artery; on other occasions it had caused complete obliteration of the lumen. It was often accompanied by some medial atrophy and either reduplication or fragmentation of the internal elastic lamina (Special Plate, Fig. 3). Histiocytes laden with fat were present in variable numbers in the deeper layers of the thickened intima, adjacent to the media. Some of the arterioles showed thickening of their walls, and in occasional glomeruli there was thickening of the capillary basement membranes. Most of the tubules were normal, but a few were still undergoing repair. There was slight interstitial fibrosis and a few small foci of infiltrating lymphoid cells (Special Plate, Fig. 4).

Case 2 (No. 557629)

A boy aged 11 (weight 37 kg.) had a 10-year history of recurrent pyelonephritis. Severe progressive renal failure began in 1960. In June, 1962, he received a kidney from an adult male who had been killed in an accident, but kinking of the renal artery led to necrosis of the transplant, which was removed after eight days. In the next few months his blood pressure rose and had to be controlled by methylodopa and intramuscular reserpine; with this treatment it averaged 160/110 mm. Hg.

On November 26 a second kidney was transplanted, this time into the left iliac fossa. The donor was a 52-year-old man who had died at another hospital from a subarachnoid haemorrhage from an inoperable cerebral-artery aneurysm. His blood groups and those of the recipient are shown in Table I. Although at the time it was thought there was no previous history of hypertension, this proved incorrect. Examination of

blood urea was halted and the urine urea output increased. The 24-hour creatinine clearance, which had fallen, again rose. Urine output did not increase immediately, probably because of the pronounced sodium-retaining effect of the large doses of hydrocortisone, and the patient became oedematous. When the hydrocortisone dose was reduced to 325 mg. daily the urine volume rose and the oedema cleared. The blood urea returned to normal levels on the 33rd day. The urinary protein loss fell from 5 g./24 hours on the 17th day to less than 1 g./24 hours on the 58th day.

The patient again developed fever and tachycardia on the 38th day, this time while she was receiving both hydrocortisone and 6-mercaptopurine. There was no evidence of infection. Biopsy of the transplant on the 41st day showed less oedema and cellular infiltration than previously, but in one interlobular artery there was gross fibroblastic intimal thickening with some medial atrophy and fragmentation of the internal elastic lamina (Special Plate, Fig. 2). A few of the tubules were atrophic, but most were now normal. The glomeruli were normal. There was no response to increasing the dose of steroids to the equivalent of 800 mg. of hydrocortisone daily, or to intravenous actinomycin C. Anorexia and the high steroid dosage made the patient weak and wasted and she was disinclined to get out of bed. On the 59th day she suddenly collapsed and died.

The blood-pressure in this case averaged 180/90 mm. Hg after transplantation until the last 21 days, when it fell to an average of 120/80 mm. Hg. The diastolic pressure never exceeded 100 mm. Hg, and no hypotensive drugs were used.

Post-mortem Examination

There was a massive pulmonary embolus, which had arisen from thrombus in the deep calf veins, and there were recent haemorrhagic infarcts in the lower lobes of both lungs. The heart was enlarged (530 g.) owing to left ventricular hypertrophy. The gall-bladder contained several small mixed stones, and the liver had many tiny focal necroses. There was a

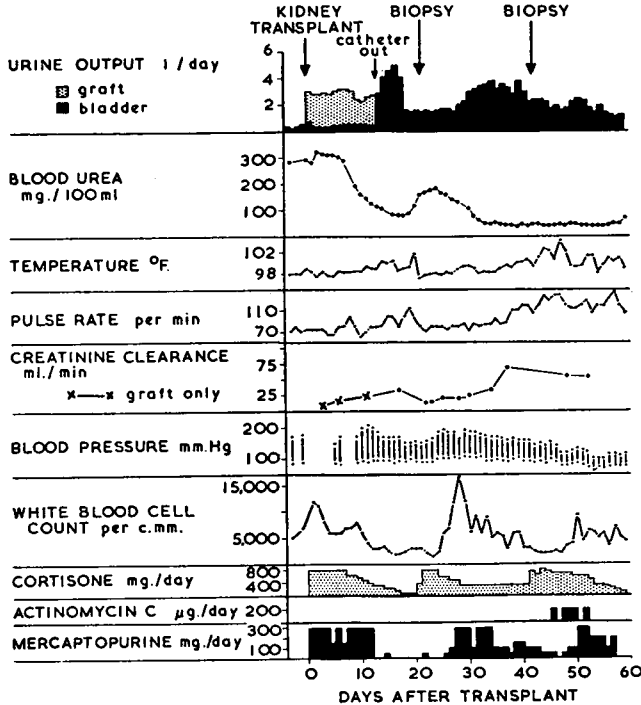


CHART 1.—Clinical course of Case 1.

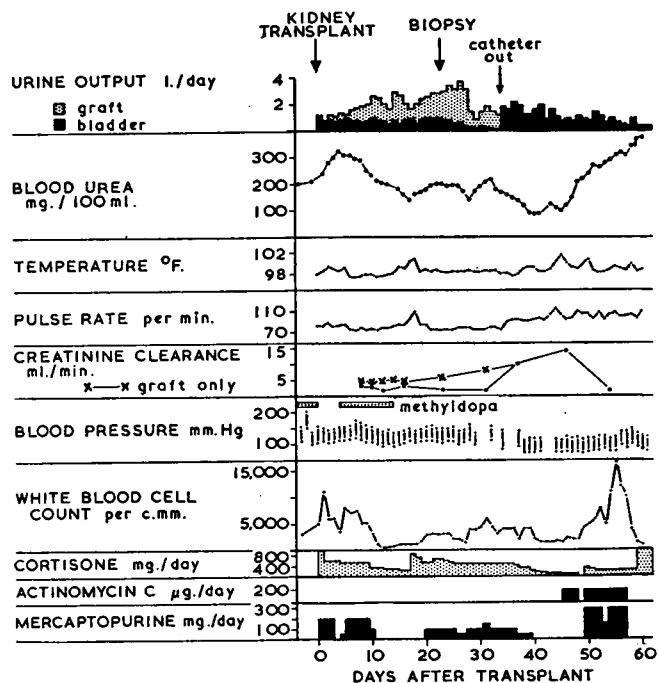


CHART 2.—Clinical course of Case 2.

K. A. PORTER *et al.*: VASCULAR CHANGES IN KIDNEY HOMOTRANSPLANTS

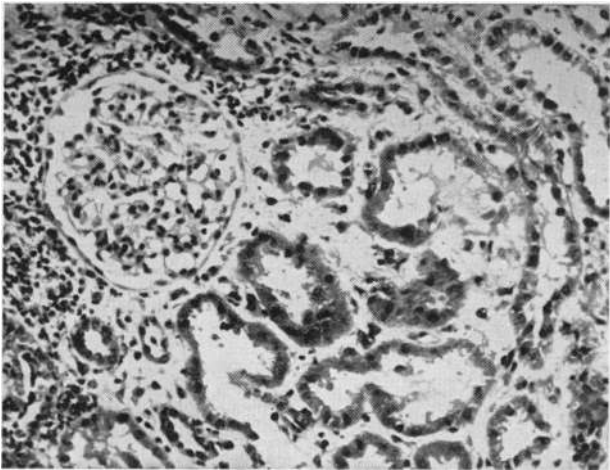


FIG. 1.—Case 1. Biopsy of graft at 21 days, showing interstitial oedema, patchy infiltration by lymphoid cells, and tubular damage and repair. (H. and E. $\times 200$.)

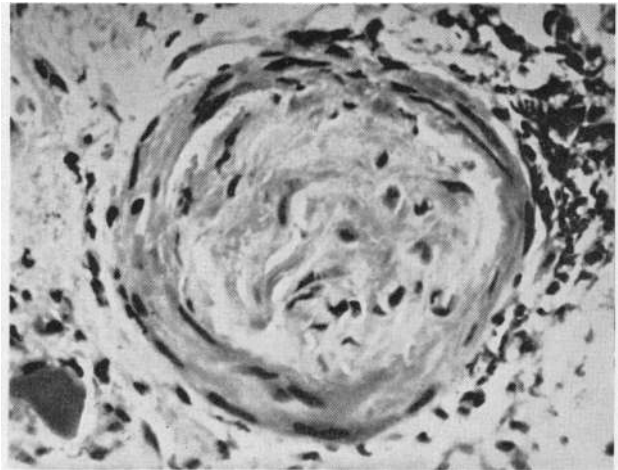


FIG. 2.—Case 1. Biopsy of graft at 41 days. An interlobular artery shows massive fibroblastic intimal thickening and some medial atrophy. (Elastic/van Gieson. $\times 400$.)

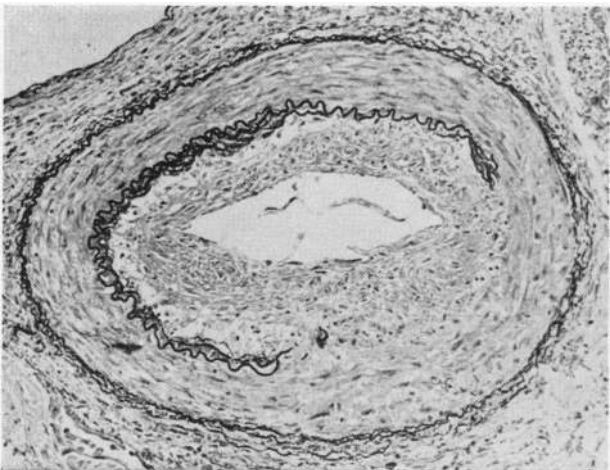


FIG. 3.—Case 1. Graft at 59 days. An arcuate artery shows intimal thickening and rupture of the internal elastic lamina. (Elastic/neutral red. $\times 35$.)

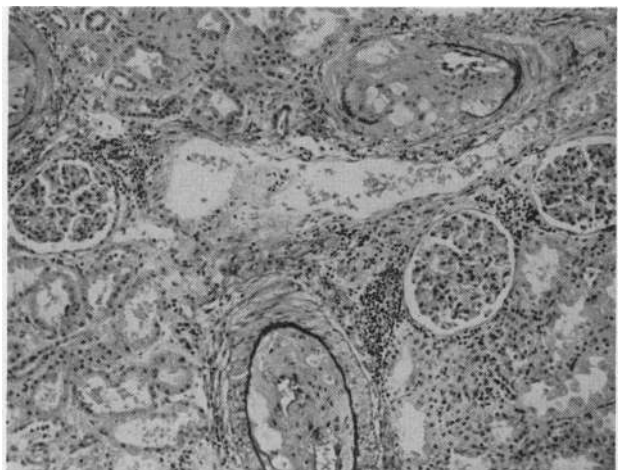


FIG. 4.—Case 1. Graft at 59 days, showing three obstructed interlobular arteries, a normal vein, normal glomeruli, and a few foci of lymphoid cells. (Elastic/neutral red. $\times 100$.)

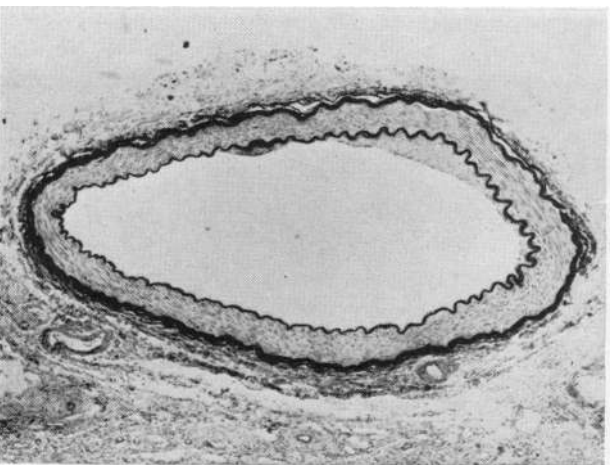


FIG. 5.—Contralateral kidney from hypertensive donor in Case 2. Interlobular artery showing small amount of intimal thickening and normal internal elastic lamina. (Elastic/van Gieson. $\times 20$.)

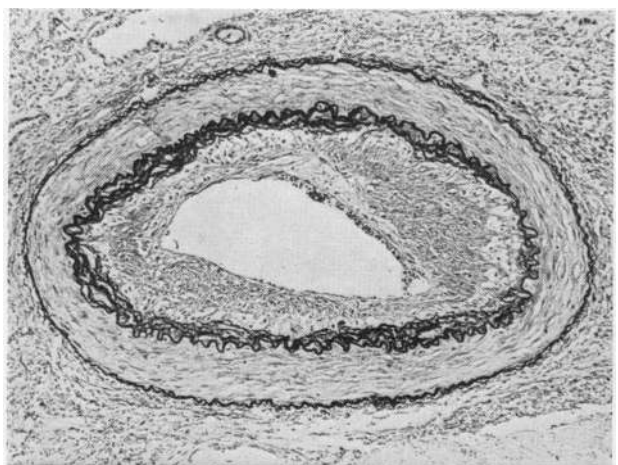


FIG. 6.—Case 2. Graft at 62 days, showing the changes which have occurred in intima and internal elastic lamina of an interlobular artery. Compare with Fig. 5. (Elastic/neutral red. $\times 20$.)

K. A. PORTER *et al.*: VASCULAR CHANGES IN KIDNEY HOMOTRANSPLANTS

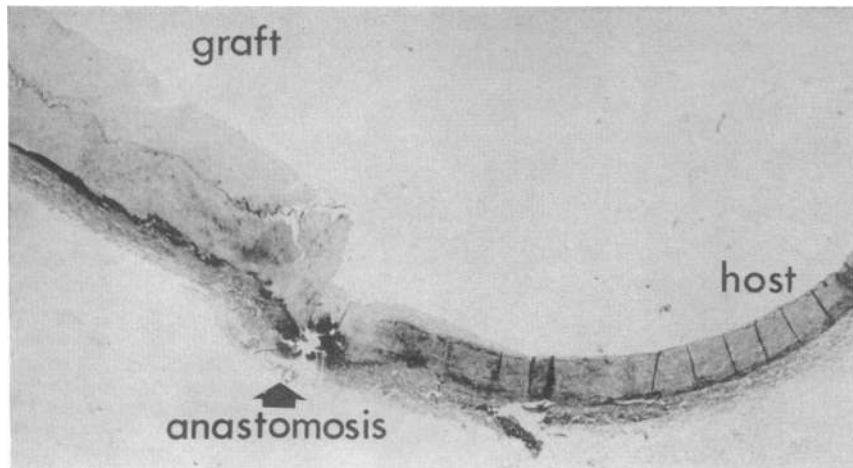


FIG. 7.—Case 2. Junction between renal artery of graft and internal iliac artery of host. Renal artery shows intimal thickening, rupture of internal elastic lamina, and medial necrosis, all starting abruptly at anastomosis with host vessel. (Elastic/van Gieson. $\times 10$.)

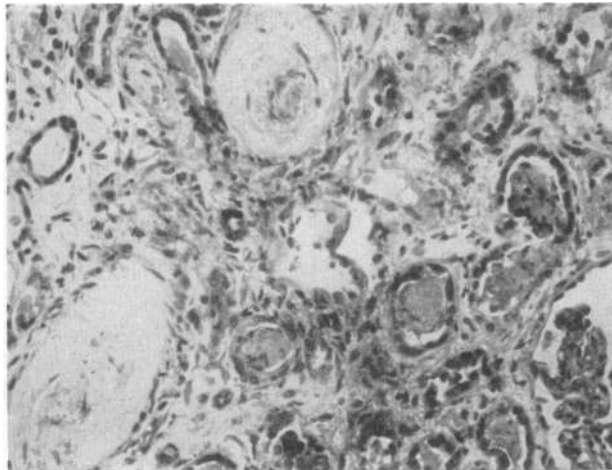


FIG. 8.—Case 3. Biopsy of graft at 52 days, showing widespread tubular atrophy, interstitial fibrosis, and two arterioles with thickened walls showing mucinous changes. (H. and E. $\times 400$.)

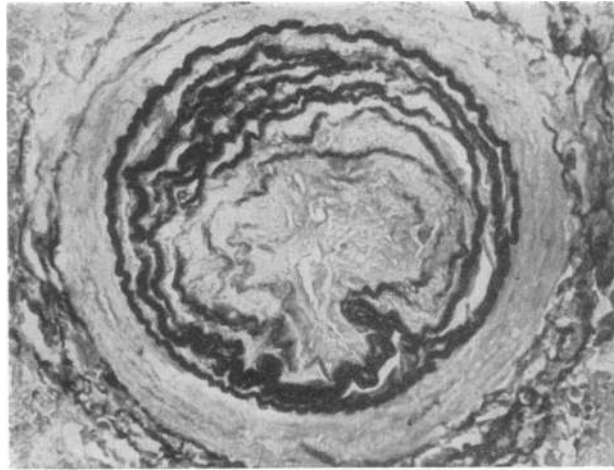


FIG. 9.—Case 4. Biopsy of graft at 52 days, showing an interlobular artery obstructed by intimal fibroblastic thickening. There is also marked elastic increase. (Elastic/van Gieson. $\times 250$.)

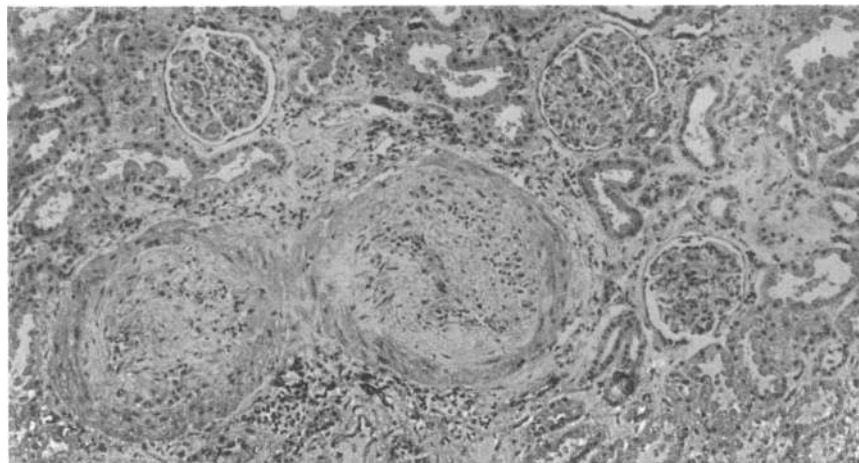


FIG. 10.—Case 4. Graft at 86 days, showing two completely obstructed interlobular arteries, some tubular atrophy, interstitial fibrosis, and a few infiltrating lymphoid cells. (H. and E. $\times 100$.)

the contralateral donor kidney showed malignant hypertensive changes with fibrinoid necrosis of the arterioles, but only slight fibrous intimal thickening of some interlobar, arcuate, and interlobular arteries (Special Plate, Fig. 5). The graft was kept in saline surrounded by ice while awaiting transplantation, and was ischaemic for 3 hours 30 minutes. The patient was given hydrocortisone 1 g. intramuscularly and 6-mercaptopurine 5 mg./kg. in the first 24 hours. Thereafter the dose of mercaptopurine was adjusted according to the white-cell count and the hydrocortisone was slowly reduced (see Chart 2). For the first four days the urine output was low, but after this it steadily increased and the blood urea fell. On the 15th day the patient developed fever and tachycardia. This was followed by a fall in urine output from the transplant, a rise in the blood urea, and an increase in protein loss in the urine from 0.3 to 0.9 g./24 hours.

A biopsy at 22 days showed interstitial oedema and widespread infiltration by lymphoid cells, 5% of which were plasma cells and 5% large pyroninophilic cells. Proximal and distal tubules showed active regeneration following widespread necrosis, and many contained doubly refractile oxalate crystals. Occasional arterioles showed fibrinoid necrosis as in the contralateral donor kidney. One afferent arteriole was thrombosed and the associated glomerulus infarcted. Other glomeruli were normal. The dose of hydrocortisone was increased to 900 mg./24 hours with a rapid fall in the temperature and pulse rate, and a slower fall in blood urea, and increase in urine output from the graft.

On the 38th day, when steroids were again being withdrawn, fever and tachycardia recurred, and from the 45th day the urine output fell and the blood urea rose. The urinary protein loss, which had fallen to 0.25 g./24 hours, rose sharply to 3.5 g./24 hours on the 50th day. Intravenous actinomycin C had no effect apart from producing severe ulceration of the fauces. The patient deteriorated and died in uraemia at 62 days.

After the second renal transplant the blood-pressure averaged 150/110 mm. Hg until the last 30 days, when it fell to an average of 125/90 mm. Hg. The diastolic pressure at no time exceeded 120 mm. Hg, but methylodopa treatment was necessary for the first two post-operative weeks.

Post-mortem Examination

The heart was enlarged (250 g.) owing to left ventricular hypertrophy. The liver was normal and the lymphoid tissues showed some loss of small lymphocytes. The patient's own kidneys were very small (4 and 37 g.) and showed chronic pyelonephritic scarring but in the intervening areas the interlobular and arcuate arteries were normal.

The transplanted kidney was swollen (300 g.); the subcapsular surface was speckled with haemorrhages and the cortex was mottled, deep-red zones of haemorrhagic infarction alternating with paler areas. The main renal vessels and ureter were unobstructed, but there was thickening of the intima of the arteries of the graft starting abruptly at the anastomosis with the host internal iliac artery (Special Plate, Fig. 7). This fibrous thickening, with patchy interruption of the underlying internal elastic lamina, extended throughout the interlobar arteries into the arcuate and interlobular arteries (Special Plate, Fig. 6). In the haemorrhagic areas veins of interlobular size and smaller were thrombosed. Cellular infiltration was not a feature, but a few interlobular arteries were cuffed with lymphocytes and plasma cells. Away from the infarcts the glomeruli showed some thickening of the tuft capillary basement membranes by homogeneous P.A.S.-positive material.

Case 3 (No. 580739)

A man aged 38 (weight 60 kg.) had an eight-year history of recurrent haematuria, proteinuria, and urinary infection with coliform organisms and was thought to have bilateral chronic pyelonephritis. When admitted to hospital he was in severe renal failure with a blood-pressure of 210/130 mm. Hg. The high blood-pressure was controlled by methylodopa.

Treatment with 6-mercaptopurine was commenced three weeks prior to transplantation of a kidney which was performed on

February 12, 1963. The donor was a 48-year-old man who died during operative repair of a rheumatic aortic incompetence. Perfusion of the donor was continued with blood containing heparin 3 mg./kg., supplemented by dextran and saline, until the renal bed in the recipient had been prepared. The transplant had two renal arteries; one was anastomosed end-to-side with the external iliac artery and the other end-to-end with the internal iliac artery. The kidney was ischaemic for 1 hour 9 minutes. A comparison of the blood groups of the donor and recipient are given in Table I. The post-operative course and treatment of this patient are summarized in Chart 3. At first urine output was very good and the blood urea fell rapidly, but on the ninth day the ureter of the transplant became necrotic at its lower end.

A ureterostomy was performed and a biopsy taken of the transplant. This showed some tubular damage and repair, and a focal infiltration of the interstitium with lymphoid cells. Glomeruli and blood-vessels were normal. After this urine output from the transplant rose to 4 litres/day and the blood urea again fell, but infection of graft and bladder urine with *Escherichia freundii* and *Staphylococcus albus* necessitated a course of chloramphenicol and intramuscular colomycin. On the 19th day there was high fever, tachycardia, a fall in urine

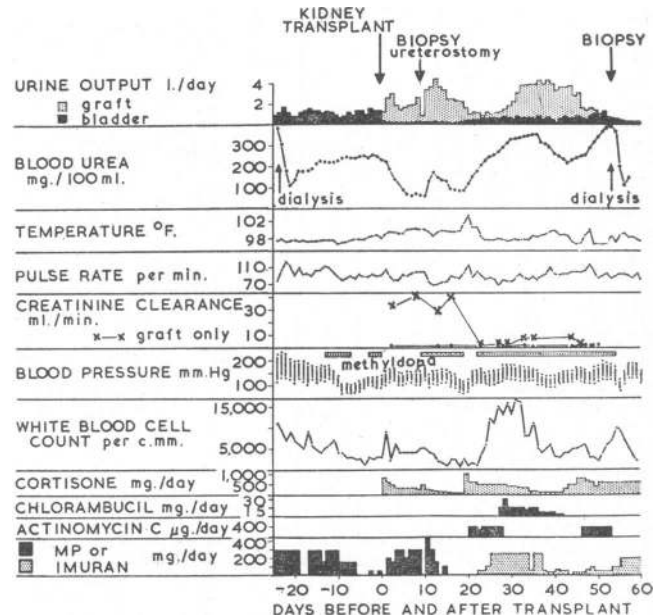


CHART 3.—Clinical course of Case 3.

output, a rise in the blood urea, and red cells and granular casts appeared in the graft urine. The dose of hydrocortisone was immediately increased to 1 g./24 hours and intravenous actinomycin C was given. The temperature and pulse rate fell and after a delay the urine volume began to increase, but on the 45th day there was again fever, tachycardia, a fall in urine output, and a rise in blood urea, unaffected by prednisone or actinomycin C. Protein losses in the urine from the transplant rose steadily after operation from 1 to 3 g./24 hours until the 42nd day, after which they fell rapidly. Protein losses from the patient's own kidneys remained roughly constant at 1 g./24 hours. On the 52nd day a biopsy of the transplant showed patchy haemorrhagic infarction associated with recent thrombosis of some small veins. Many of the interlobular arteries showed massive intimal thickening, but in this case several of the arteriolar walls were also grossly thickened by fibrous tissue which had undergone mucinous changes (Special Plate, Fig. 8). Between the areas of venous infarction there were normal glomeruli, widespread tubular atrophy, and foci of lymphocytic infiltration.

After kidney transplantation methylodopa had to be continued and the blood-pressure was kept at an average of 160/100 mm. Hg. The diastolic pressure never exceeded 120 mm. Hg. This patient is at present being maintained by dialysis.

Case 4 (No. 580594)

A man aged 44 (weight 58 kg.) was found to have proteinuria in 1948 and a duplex right kidney with a stone in the upper pole in 1955. A right renal biopsy showed changes consistent with chronic pyelonephritis. Progressive renal failure developed and when he was transferred to us in January, 1963, he required immediate peritoneal dialysis. The blood-pressure was controlled by methyl dopa and reserpine and averaged 170/100 mm. Hg. Chlorambucil 0.25 mg./kg./day was given by mouth for 17 days, then on February 12 he received a kidney transplant from the same cadaver that provided the kidney for Case 3. Blood groups of donor and recipient are compared in Table I. The transplant was ischaemic for 1 hour 25 minutes. Urine flow began at once from the transplant and there was a rapid fall of the blood urea to normal levels (see Chart 4). Post-operatively the patient was given hydrocortisone, chlorambucil, and 6-mercaptopurine.

All went well until the 38th day, when the patient developed fever and tachycardia and the blood urea began to rise. Large doses of prednisone, actinomycin C, and imuran produced a fall in his temperature and pulse rate, but the blood urea continued to rise rapidly, and from the 44th day there was a sharp and sustained increase in urinary protein from 1 to about 5 g./24 hours. A biopsy of the transplant on the 52nd day contained an interlobular artery which showed marked oblitera-

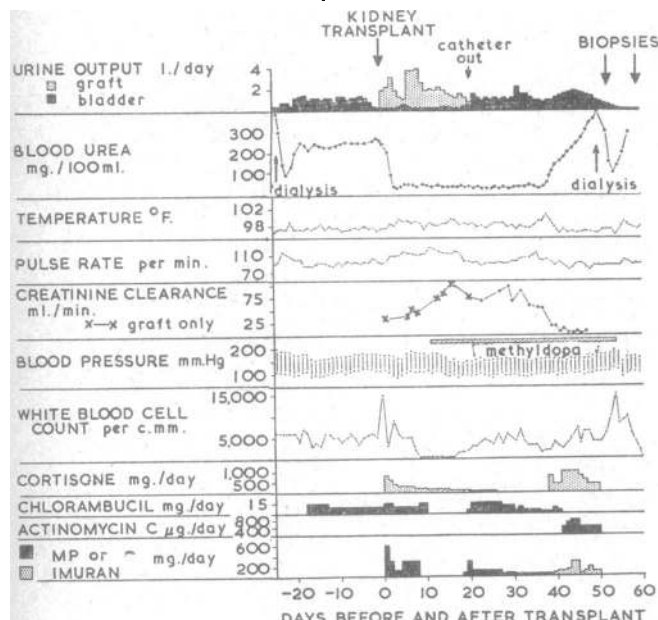


CHART 4.—Clinical course of Case 4.

tive fibrous intimal thickening with great increase of elastic tissue and some medial atrophy (Special Plate, Fig. 9). Otherwise the kidney seemed normal. A further biopsy, performed on the 59th day, again showed gross intimal thickening of the interlobular arteries with, in some, reduplication of the internal elastic lamina and obliteration of the lumen. However, there was now recent thrombosis of some of the veins with resulting patches of interstitial haemorrhage, and tubular and glomerular necrosis. Elsewhere the glomeruli were normal, but some of the tubules were atrophic and others regenerating, with mitoses in their lining cells. There were a few infiltrating lymphoid cells. For a time the patient was maintained by dialysis, but his condition worsened and he died in uraemia on the 86th day.

After operation the blood-pressure was controlled by methyl dopa at an average of 160/100 mm. Hg. The diastolic pressure at no time exceeded 110 mm. Hg.

Post-mortem Examination

The heart was enlarged (550 g.) owing to left ventricular hypertrophy, and there was a fibrous pericarditis. The liver contained a few tiny focal necroses. The lymphoid tissues showed some depletion of small lymphocytes. The patient's

own kidneys were small (60 and 55 g.) and scarred. The right kidney possessed two pelves and double ureters, and in the upper pole there was a spiny black calculus 1 cm. in diameter. Microscopically there were chronic pyelonephritic changes.

The transplanted kidney was swollen (230 g.) and showed the same deep red zones of haemorrhagic infarction alternating with paler areas that had been previously seen in Case 2. The main renal vessels and the ureter were unobstructed. Microscopically the appearances were essentially the same as those seen in the biopsy specimen taken 27 days previously (Special Plate, Fig. 10). Slight intimal thickening was present in the renal artery, but the main changes started in the interlobar arteries and spread peripherally into the arcuate and interlobular arteries. The arterioles were relatively unaffected. Between the areas of venous infarction there was marked interstitial fibrosis, slight patchy lymphoid infiltration, severe tubular atrophy, and some thickening of the basement membranes of the glomerular capillaries.

Discussion

In these cases two crises were seen: the first starting 15 to 19 days after transplantation and the second at 38 to 45 days. Both were characterized clinically by fever, tachycardia, a fall in urine output, and a rise in blood urea. Histologically, at the time of the first episode the transplant showed interstitial oedema, focal infiltration by lymphoid and pyroninophilic cells, and tubular damage and repair; during the second episode there was intimal thickening of arteries, tubular atrophy, and interstitial fibrosis. By about the 60th day patchy venous thrombosis was, in some, an additional feature.

The lesions seen in the first clinical episode have often been described previously; sometimes, as in our patients, in association with signs and symptoms (Küss *et al.*, 1962; Hamburger *et al.*, 1962; Murray *et al.*, 1962, 1963); sometimes as an incidental finding in a transplant that was apparently functioning normally (Hamburger *et al.*, 1963). Electronmicroscopic examination of the infiltrating cells (Galle and de Montera, 1962) has shown that about 40% have an ultrastructure resembling that seen in immunologically competent cells in graft-versus-host reactions (Binet and Mathé, 1962). The acute rejection of kidneys by normal dogs (Dempster, 1953) and by humans not suffering from chronic uraemia (Michon *et al.*, 1953) is also characterized by interstitial oedema and by a similar though much heavier cellular infiltration. These facts make us think that the majority of the lymphoid and pyronin-positive cells and some of the oedema seen in the interstitium of our cases were part of an immunological rejection process mounted by the host against the renal transplant. The tubular necrosis was probably mainly due to the prolonged period of ischaemia inevitably associated with transplantation of a cadaveric kidney. Interference with tubular epithelial regeneration by the large doses of purine analogues and other drugs may partly account for the continued presence of active repair many weeks after transplantation.

In all four cases, by the time of the second clinical episode, cellular infiltration and oedema were less and striking vascular changes dominated the histological picture. Similar lesions were first described by Hume *et al.* (1955), who commented upon the extraordinary degree of intimal thickening in the intrarenal vessels of a kidney transplant which had survived and functioned for 180 days in an untreated patient suffering from chronic glomerulonephritis. Since then Goodwin *et al.* (1963) have mentioned similar arterial lesions in a kidney 144 days after its transplantation from mother to daughter. The recipient was treated with nitrogen mustard before the graft and cyclophosphamide

afterwards. Before the kidney was transplanted the patient had severe hypertension, but afterwards the blood-pressure fell. At the 40th day there was a pyrexial episode in which the transplant became swollen and oliguric, and on the 53rd day the patient again became hypertensive, the function of the transplant progressively deteriorated, and she eventually died in uraemia. At necropsy the kidney was grossly normal, but microscopically there was a "slight rejection reaction, marked arteriosclerosis, and glomerulitis."

Striking obliterative vascular lesions in a cadaveric transplant were recently described in another patient treated with cyclophosphamide (Parsons *et al.*, 1963). The kidney was oliguric until the 14th day but functioned reasonably from then until the 25th day, when function decreased, and the patient died on the 33rd day. At necropsy the kidney showed lesions affecting the whole arterial tree from the renal artery to the arterioles. The main features were extreme intimal thickening, and splitting and necrosis of the internal elastic lamina. The recipient's blood-pressure had been 180/120 mm. Hg.

In seeking an explanation for these arterial changes a number of possibilities can, we think, be excluded. X-irradiation and purine analogues cannot have been responsible, as they were not always used in patients reported to have shown such lesions. Indeed, no one drug or agent was common to all cases. Mural thrombus, when organized, may give intimal fibrous thickening. Prolonged vasoconstriction or chronic inflammatory changes around a vessel may be followed by endarteritis obliterans. However, none of these causes would produce lesions affecting the whole renal arterial tree, nor would there be medial changes or rupture of the internal elastic lamina. Total renal vascular occlusion in the rabbit for periods exceeding two hours causes severe damage to the arteries and arterioles; in the repair process intimal hyperplasia is prominent (Sheehan and Davis, 1959). Although some of the kidney homografts showing arterial changes were ischaemic for periods ranging up to 3 hours 30 minutes, this was not invariably so, and one case with severe lesions was ischaemic for only 42 minutes (Küss *et al.*, 1962).

Hypertension seemed the most likely explanation to Hume *et al.* (1955). As the blood-pressure in their case remained at about 240/140 mm. Hg there was every reason for accepting this view. However, although in our cases some individual arterial and arteriolar lesions resemble those seen in severe malignant hypertension, it is difficult to believe that the duration and degree of raised blood-pressure in Cases 1, 3, and 4 were sufficient to produce such dramatic changes. In Case 2 a kidney already accustomed to a hypertensive environment developed extensive vascular lesions after a stay of 62 days in a less hypertensive recipient. Finally, Küss *et al.* (1962) and M. Legrain (personal communication, 1963) have described the development of obliterative arteriolar and arterial changes in a kidney 57 days after transplantation into a patient with normal blood-pressure. While it thus seems clear that the vascular lesions are not initiated by a raised blood-pressure, any existing hypertension will probably further damage arterial walls already weakened by medial necrosis and elastic rupture. Where hypertension emerges late in the course of a renal homograft this may be due to ischaemia caused by the obstructive arterial lesions. For example, in the case of Küss *et al.* (1962) quoted above, the development of vascular changes in the transplant after 57 days in a normotensive environment was later followed by the onset of hypertension.

If the arterial lesions are not initiated by hypertension then an immunological cause becomes a strong possibility. Certainly vascular changes of this type have not been reported in kidney transplants between identical twins. It could be that, in patients receiving kidney homografts, chronic uraemia and treatment depress but do not halt the immune reaction by the host against the transplant. If this is so one would expect to find similar histological changes to those seen in acute canine renal rejection, but modified and spread over a longer period, the duration and severity being dependent upon the efficacy of the treatment and the genetic relationship between donor and recipient. In general this prediction appears correct. Practically all human kidney homografts surviving for more than a few days have shown some degree of infiltration by cells resembling those seen in the early stages of dog homografts. The infiltration has been maximal in those cases where chronic uraemia and treatment were lacking, or where genetic disparity was combined with ineffective treatment; and minimal where close genetic similarity was combined with vigorous treatment.

In the later stages of renal homograft rejection in the normal untreated dog there is swelling of the intimal endothelial cells of all the vessels from capillaries to large arteries, and the small and medium-sized arteries may show fibrinoid necrosis of the whole or part of the circumference of their walls, producing lesions resembling those seen in polyarteritis nodosa: ischaemia is the terminal event (Simonsen *et al.*, 1953). Two recent investigations, one using fluorescent antibody methods (Horowitz *et al.*, 1963) and the other utilizing renal-blood-flow measurements and electronmicroscopy (Kountz *et al.*, 1963), together show that this vascular damage occurs much earlier than was formerly thought and that it is one of the first and most important events in the rejection of canine renal homografts.

We believe that the vascular changes now being noticed in human renal transplants and those present in a dog kidney homograft after 64 days of treatment with a purine analogue (Porter and Calne, 1963) result from a similar process, albeit one that has been rendered chronic by uraemia and treatment so that compensatory intimal thickening features prominently. Where there is a close relationship between donor and recipient the homograft reaction will be weaker, and, if our view is correct, one would expect delay in the onset, and reduction in the severity, of any arterial changes in the transplant. Significantly in the one published case where lesions have been encountered in a transplant between dizygotic twin brothers they were not noticed until nearly eight months after transplantation, and even three years later the patient is still alive, though now needing hypotensive treatment (Hamburger *et al.*, 1962, 1963).

When cadaveric kidneys are used genetic similarity between host and donor is unlikely and a powerful homograft reaction can be expected. If this immune reaction is not adequately controlled in its early stages it is possible that severe vascular lesions rapidly occur. Failure to restrain the immune response of our recipients is clearly shown by the clinical crises and cellular infiltration of the transplants at about 20 days. A cadaveric kidney was also used by Parsons *et al.* (1930), who encountered similar, even earlier, obliterative arterial changes. Insufficient information is given in their preliminary report to decide whether there was clinical evidence of inadequate suppression of the homograft reaction in the first three weeks, but the drug they were employing, cyclophosphamide, is now known to be not particularly effective in dogs (Reams,

1963). Once obliterative vascular lesions have begun, tubular atrophy, interstitial fibrosis, and glomerular changes will inevitably follow. The recent reports of "glomerulonephritis" in some of the long-surviving human-kidney homografts, associated with splenomegaly and hypergammaglobulinaemia (Hamburger *et al.*, 1963), further support our thesis of a modified but continuing host-against-graft immunological reaction.

It is difficult to assess the frequency with which these specific vascular lesions occur in transplanted kidneys. The four cases we have described are the only ones which have shown such changes in a series of 17 cadaveric kidney homotransplants performed at St. Mary's Hospital since 1959 (see Table II). (The other 13 cases will be described in detail elsewhere.) When the published cases of renal transplantation are surveyed it is found that vascular

TABLE II.—Seventeen Cases of Cadaveric Renal Homotransplantation Performed at St. Mary's Hospital between August 13, 1959, and June 3, 1963

| Treatment | Case No. Sex, Age | Date of Trans- plant | Ischaemia Time (min.) | Donor | | Recipient | | Outcome |
|---|------------------------|----------------------------|-----------------------------|---|----------------|----------------|--|---|
| | | | | Sex, Age, Disease | Blood Group | Blood Group | Disease | |
| None | 519920 F 54 | 17/10/59 | 175 | M 46 Head injury | B+ | O+ | Chronic pyelonephritis | Transplant excreted up to 80 ml./24 hr. during first 6 days. Biopsy 9th day—infarction. Necropsy at 30 days—renal artery thrombosis. Transplant excreted up to 99 ml./24 hr. until 5th day. Patient died at 6 days from uraemia and pulmonary haemorrhages. Transplant showed same glomerulonephritic changes as host. Transplant excreted up to 80 ml./24 hr. until 3rd day. Patient died at 5 days from gangrene of left leg and aortic thrombosis. Transplant excreted 30 ml. hr. Patient died at 20 hours from bleeding duodenal ulcers. Necropsy—proximal tubular necrosis of transplant |
| | 531183 M 18 | 1/1/60 | 106 | F 36 Head injury | A+ | O+ | Rapidly progres- sive type 1 glomerulo- nephritis | |
| | 535461 F 3/12 | 1/4/60 | 110 | M 18 Head injury | O+ | O+ | Congenital microcystic disease | |
| | 501332 M 54 | 2/5/60 | 135 | M 21 CO poisoning | A+ | AB+ | Primary malignant hypertension | |
| Whole body X-irradiation in divided dosage after transplant | 480865 M 24 | 13/8/59 | 162 | M 46 Cerebral tumour | A+ | O+ | Chronic type 1 glomerulo- nephritis | Transplant excreted up to 120 ml./day for 19 days, then about 4 litres/day until death. Biopsy at 11 days showed heavy cellular infiltration and widespread tubular damage. Biopsy at 26 days showed repair of most of tubular damage and less cellular infiltration. Patient died at 39 days from pulmonary haemorrhage. No obliterative vascular lesions in transplant. No function. Necropsy at 8 days—transplant necrotic with renal artery thrombosis. Excreted up to 1 litre/day for first 5 days, then failing function and death of patient from uraemia and intra-alveolar haemorrhages on 12th day. At necropsy necrotic kidney with thrombosis of renal artery. Function of transplant uncertain because no ureteric catheter, but biopsy of medulla at 8 days normal. Patient died at 31 days from uraemia, bronchopneumonia, and intra-alveolar haemorrhages. Transplant necrotic. Renal artery thrombosed |
| | 550r 539031 M 21 | 24/6/60 | 109 | M 50 Coronary thrombosis | A+ | O+ | Chronic type 1 glomerulo- nephritis | |
| | 450r 470388 M 30 | 6/12/60 | 65 | F 44 Cerebral infarction | A+ | O+ | Chronic pyelonephritis | |
| | 400r 453385 M 70 | 24/6/60 | 185 | M 50 Coronary thrombosis | A+ | O+ | Late type 2 glomerulo- nephritis | |
| Whole body X-irradiation before transplant | 300r 483776 M 35 | 1/10/61 | 170 | M 43 Cerebral tumour | O+ | O+ | Chronic pyelonephritis | Transplant excreted up to 330 ml./24 hr. for 3 days. Patient died at 4 days from cardiac arrest during dialysis. At necropsy transplant showed several focal infarcts but main vessels unobstructed |
| MP after transplant | 555660 F 40 | 5/5/62 | 90 | M 40 Cerebral haemorrhage | A+ | A+ | Chronic pyelonephritis | Transplant excreted 5 ml./hr. Patient died at 24 hours from peritonitis from infected dialysis button. At necropsy transplant showed proximal tubular necrosis |
| Imuran after transplant | 557629† M 11 | 10/6/62 | 100 | M 54 Head injury | A+ | A+ | Chronic pyelonephritis | No function. Removed at 8th day. Kinking of renal artery |
| Imuran + actinomycin C after transplant | 557765 M 35 | 29/3/62 | 104 | M 57 Haemorrhage from oesophageal varices | O+ | O+ | Chronic type 1 glomerulo- nephritis | Transplant excreted up to 1,450 ml./24 hr. for first 4 days. Abrupt fall on 5th day. Patient died on 12th day from pulmonary oedema and peritoneal abscess at site of dialyses. At necropsy kidney transplant showed healing acute tubular necrosis with slight cellular infiltration |
| MP + actinomycin C after transplant | 484708† F 46 | 10/11/62 | 140 | M 16 Head injury | A+ | AB+ | Late type 2 glomerulo- nephritis | Transplant functioned well until death of patient from pulmonary embolus at 59 days. Crises at 15th and 38th days. Obliterative vascular lesions first seen in transplant at 41 days. After the 4th day the transplant excreted well until the 45th day, when function deteriorated. Crises at 15th and 38th days. Patient died in uraemia at 62 days. At necropsy obliterative vascular lesions were present in the transplant |
| | 557629† M 11 | 26/11/62 | 210 | M 52 Cerebral aneurysm and hyper- tension | A+ | A+ | Chronic pyelonephritis | |
| MP before transplant + MP, imuran, chloram- bucil, and actinomycin C after transplant | 580739† M 38 | 12/2/63 | 69 | M 48 Rheumatic aortic in- competence | O+ | A+ | " " | Transplant functioned well until 9th day, when ureter became necrotic and ureterostomy had to be performed. After this function improved until 45th day, but then deteriorated. Crises at 19th and 45th days. Obliterative vascular lesions first seen in transplant at 52 days |
| Chlorambucil before transplant + MP, imuran, chlorambucil, and actinomycin C after transplant | 580594† M 44 | 12/2/63 | 85 | M 48 Rheumatic aortic in- competence | O+ | O+ | " " | Transplant functioned well until 38th day, after which it deteriorated with death of patient in uraemia at 86th day. Crisis at 38 days. Obliterative vascular lesions first seen in transplant at 52 days |
| Imuran, actinomycin C, and irradiation to kidney, all after transplantation | 584487 F27 | 3/6/63 | 180 | M 34 Sub- arachnoid haemorrhage | O+ | O+ | " " | Transplant functioned well until 36th day, when crisis. This was treated with Co-irradiation to transplant. Alive with functioning graft at 56 days |

† Cases described in detail in present report. MP = 6-mercaptopurine.

changes apparently similar to those that interest us have been recorded on seven previous occasions, always in transplants that have functioned for 32 days or longer (Hume *et al.*, 1955, Case G.W.; Küss *et al.*, 1962, Case Gén; Hamburger *et al.*, 1962, Cases G.S. and P.Y.; Goodwin *et al.*, 1963, Case D.M.; Parsons *et al.*, 1963, Case 1; Murray *et al.*, 1963, Case T.G.). Including our cases, only 29 kidney homotransplants have excreted urine for such a period, and 11 of these kidneys have developed obliterative vascular changes. The incidence of this complication may well be higher than these figures suggest, because interlobular and larger arteries are frequently not present for examination in biopsies of renal transplants and necropsy details are not available in all fatal cases.

The development of vascular changes in our transplants was neither prevented nor reversed by the treatment used. Experience in dogs and humans (Murray *et al.*, 1962, 1963) would suggest that if we had maintained a continuous moderate dosage of purine analogue and not been so concerned about keeping the peripheral white blood cell count low we might have been more successful. On the contrary, the assumed early rejection at 15 to 19 days did appear to be reversed by large doses of hydrocortisone-like steroids. This was shown by the fall in temperature, pulse rate, and blood urea, accompanied by a rise in urine volume and urine urea concentration. A similar experience was reported by Goodwin *et al.* (1963).

Summary

Four human cadaveric kidney homotransplants are described. The patients were treated with drugs intended to suppress the immunological rejection processes.

Three showed clinical evidence of rejection of the transplant at 15 to 19 days, apparently reversed by large doses of hydrocortisone-like steroids. All four developed further clinical evidence of rejection at 38 to 45 days.

Histologically the first rejection episode was associated with interstitial oedema and infiltration of the transplant by lymphoid and pyroninophilic cells. The second episode was characterized by marked intimal thickening and medial changes throughout the whole renal arterial tree leading to obliteration of many vessels and ischaemia of the transplant.

Evidence is presented that these striking vascular lesions are not due to hypertension but have an immunological basis. It is suggested that both the early cellular infiltration and the arterial changes represent different phases of a homograft reaction which has been modified but not halted by treatment.

We wish to thank Mr. Wylie McKissock, Mr. John Garfield, Mr. Felix Eastcott, Mr. Archie Carter, Mr. Roy Calne, and Mr. Lance Bromley for surgical help; Dr. Max Hulbert for the irradiation; Sister Drew and her staff for devoted nursing care; Miss Jane Rendall for expert technical assistance; Miss Paddy Baker for much general aid; and the Board of Governors of St. Mary's Hospital for financial help. One of us (K.P.) received a grant for expenses from the Medical Research Council.

REFERENCES

- Binet, J. L., and Mathé, G. (1962). *Nature (Lond.)*, **193**, 992.
 Dempster, W. J. (1953). *Brit. J. Surg.*, **40**, 447.
 Galle, P., and Montera, H. de (1962). *Rev. franç. Étud. clin. biol.*, **7**, 40.
 Goodwin, W. E., Kaufman, J. J., Mims, M. M., Turner, R. D., Glassock, R., Goldman, R., and Maxwell, M. M. (1963). *J. Urol.*, **89**, 13.
 Hamburger, J., Vaysse, J., Crosnier, J., Auvert, J., and Dormont, J. (1963). *Bull. Soc. méd. Hôp. Paris*, **114**, 225.
 ———, ———, Lalanne, C.-M., and Hopper, J. (1962). *Amer. J. Med.*, **32**, 854.
 Horowitz, R. E., Burrows, L., Paronetto, F., and Wildstein, W. (1963). *Fed. Proc.*, **22**, Part 1, 274.
 Hume, D. M., Merrill, J. P., Miller, B. F., and Thorn, G. W. (1955). *J. clin. Invest.*, **34**, 327.
 Kountz, S. L., Williams, M. A., Williams, P. L., Kapros, C., and Dempster, W. J. (1963). *Nature (Lond.)*, **199**, 257.
 Küss, R., Legrain, M., Mathé, G., Nedej, R., and Camey, M. (1962). *Rev. franç. Étud. clin. biol.*, **7**, 1048.
 Michon, L., Hamburger, J., Oeconomos, N., Delinotte, P., Richet, G., Vaysse, J., and Antoine, B. (1953). *Presse méd.*, **61**, 1419.
 Murray, J. E., Merrill, J. P., Dammin, G. J., Dealy, J. B., Alexandre, G. W., and Harrison, J. H. (1962). *Ann. Surg.*, **156**, 337.
 ———, Harrison, J. H., Wilson, R. E., and Dammin, G. J. (1963). *New Engl. J. Med.*, **268**, 1315.
 Parsons, F. M., Markland, C., Raper, F. P., and Fox, M. (1963). *Brit. med. J.*, **1**, 930.
 Porter, K. A., and Calne, R. Y. (1963). To be published.
 Reams, G. B. (1963). *Nature (Lond.)*, **197**, 713.
 Sheehan, H. L., and Davis, J. C. (1959). *J. Path. Bact.*, **78**, 351.
 Simonsen, M., Buemann, J., Gammeltoft, A., Jensen, F., and Jørgensen, K. (1953). *Acta path. microbiol. scand.*, **32**, 1.

RENAL TRANSPLANTATION IN MAN

A REPORT OF FIVE CASES, USING CADAVERIC DONORS

BY

R. Y. CALNE, M.S., F.R.C.S.

Hon. Consultant and Senior Lecturer in Surgery

LAVINIA W. LOUGHRIDGE, M.B., M.R.C.P.

Lecturer in Medicine

J. B. MacGILLIVRAY, M.B., Ch.B., D.C.P.

Lecturer in Morbid Anatomy

JOAN F. ZILVA, M.D., B.Sc., M.R.C.P.

Hon. Consultant and Senior Lecturer in Chemical Pathology

AND

A. J. LEVI, M.B., M.R.C.P., M.R.C.P.Ed.

Medical Registrar

From Westminster Hospital, London

[WITH SPECIAL PLATE]

The first successful cadaveric renal transplantations in man were reported by Hume and his colleagues (1955). In one of their cases the transplant functioned for five and a half months, although no attempt was made to modify either donor or recipient to prevent immunological rejection. Since that time there have been several further attempts at cadaveric renal transplantation, but most of these have been unsuccessful. It is the purpose of this communication to report five further cases in which an attempt has been made to prevent immunological rejection by direct application of experimental methods which had had encouraging results in dogs with homologous transplants (Calne, 1963a). We have used the drugs "imuran," actinomycin C, and prednisone.

Only patients in the terminal stages of chronic uraemia were considered for transplantation. It was felt desirable to exclude those with pre-existing infection. The experimental nature of the procedure was explained to them, and only those who were anxious to risk the operation were selected; it was not until all other conventional therapy had failed that the decision was made. Thus all the patients were gravely ill at the time of operation.

Selection of donors proved to be very difficult. Many patients dying in hospital are unsatisfactory for this purpose, since it is desirable to exclude those dying with