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PATHOLOGICAL CHANGES IN 37 HUMAN RENAL HOMOTRANSPLANTS TREATED WITH IMMUNOSUPPRESSIVE DRUGS

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WITH the advent of the treatment of human renal homotransplants by immunosuppressive drugs (Murray *et al.*, 1962), many such kidneys have now functioned for several months (Hume *et al.*, 1963; Murray *et al.*, 1963; Starzl *et al.*, 1963; Woodruff *et al.*, 1963); and several have survived beyond one year (Merrill *et al.*, 1963; Goldman *et al.*, 1964; Hume *et al.*, 1964; Murray *et al.*, 1964; Starzl *et al.*, 1964; Dunea *et al.*, 1965). Most of these transplants, even those between non-identical twins, have at some time during their stay in the recipient undergone one or more episodes of rejection. Recently serial biopsies have shown that acute fibrinoid necrosis of the vasculature of the transplant, with or without much cellular infiltration, may occur during these crises (Porter *et al.*, 1964 *b*). Further, even after treatment has apparently halted or reversed the rejection process, the vascular lesions may progress to fibrous intimal thickening with narrowing or obliteration of the interlobular arteries (Porter *et al.*, 1964 *b*). It is not known how frequently this progression occurs in transplants that survive a rejection episode. If fibrous intimal thickening is a common event then many of the renal homotransplants functioning to-day are likely to fail within a few years from ischæmic damage.

In this paper the pathological changes in thirty-seven human renal homotransplants from the Denver series are analysed with two main objects in mind. Firstly, to try and assess just how common vasculonecrotic lesions are in transplants that are clinically in a rejection phase; secondly, to determine how many of the transplants that survive such an episode show residual vascular damage.

MATERIALS AND METHODS

Between 24th November 1962 and 30th March 1964, seventy-five human kidneys were homotransplanted at the University of Colorado Medical Center: of these seventy-two came from living and three from cadaveric donors (Table I). By 1st June 1965, in thirty-nine instances either the patient had died or the transplant had been removed surgically because of failure to function or some other complication. Thirty-seven of these kidneys were examined and it is upon this material that the present report is based.

Each kidney was transplanted into either the left or right iliac fossa and the ureter implanted into the bladder. In one of the cadaveric cases (CD3) two kidneys were transplanted at the same operation, one into each iliac fossa: this pair of kidneys is counted as one transplant in Table I. In eight patients, after the primary homotransplant or heterotransplant had failed, a second kidney was inserted into the opposite iliac fossa and the primary transplant removed. Case LD57, however, was an exception in that the first transplant, which never functioned, was left in the recipient. The period of ischæmia each kidney underwent is shown in Tables II, IV and VI. In all cases except LD5, LD7 and LD43 bilateral nephrectomy and splenectomy were performed at or before the time of transplantation. In LD5 neither of the patient's own kidneys was removed; in LD7 the right kidney was not removed until seventy-three days after renal transplantation and in LD43 left nephrectomy was never performed. In

addition to this treatment four patients (LD4, LD5, LD9, and LD11) underwent thymectomy thirteen to eighty-five days before renal homotransplantation.

All the patients were treated with 6-(1-methyl-4-nitro-5-imidazolyl) thiopurine (" Imuran "), starting one to nineteen days before transplantation, in a dosage of 3 to 8 mg. per kg. per day. On the day of surgery and for the first three days after transplantation the dosage was increased to 6 to 15 mg. per kg. per day, but after this the dosage was reduced to 3 to 6 mg. per kg. per day and regulated daily according to the total white cell counts in an attempt to avoid the production of severe leukopenia. In most of the patients steroids were withheld until the onset of rejection, but in nine patients (LD4, LD46, LD56, LD57, LD59, LD61, LD62, LD64, and SD3) prednisone 30 to 100 mg. per day was started two days before transplantation and administered continuously thereafter.

TABLE I

Number of Kidneys Homotransplanted, Recipients still Alive and Transplants Examined Pathologically in the Denver Series

Kidneys Homotransplanted between 24th November 1962 and 30th March 1964				Outcome by 1st June 1965			
				Patients		Transplants	
				Alive	Dead	Failed and Replaced by Second Transplant	Examined Pathologically
75	72 from living donors	64 primary renal transplants		35	23*	...	22
				...	...	6	6
		8 secondary renal transplants	2 into patients who had previous primary baboon renal hetero-transplants	...	2*	...	1
			6 into patients who had previous primary human renal homotransplants	1	5	...	5
	3 from cadaveric donors			...	3	...	3
75				36	33	6	37

* Permission for necropsy refused in one case.

When rejection was recognised, prednisone 150 to 400 mg. per day was given. Actinomycin C, 200 to 400 micrograms intravenously, was also started and repeated every five to seven days. In ten of the patients one or more courses of local X-irradiation were given to the transplant. Each course consisted of three or four doses of 150 *r* given every other day. Once reversal of the rejection phase was achieved prednisone was slowly reduced to a maintenance dose of 10 to 20 mg. per day.

Material from the kidney transplants was stained routinely with hæmatoxylin and eosin, periodic acid Schiff reagent (PAS), Weigert's for elastic tissue counter-stained with hæmatoxylin and van Gieson, picro-Mallory 5, Martius yellow-scarlet-blue (MSB), Mallory's phosphotungstic acid hæmatoxylin (PTAH), and methyl green pyronin. Other special stains such as Sudan 3 and Masson 44-41 (Lendrum *et al.*, 1962) were used when indicated.

RESULTS

The thirty-seven renal homotransplants fell into four main groups :—

1. Those from patients who were in a rejection phase.
2. Those from patients who died after one or more rejection episodes had been recognised and apparently treated successfully.
3. Those from patients who had not at any time experienced a clearly recognisable clinical episode of rejection.
4. Those which either did not function or developed some complication necessitating their early removal.

Transplants from Patients who were in a Rejection Phase.—Fifteen kidneys were examined after their removal from patients who were in or just starting to recover from a clinical episode of rejection.

The onset of rejection was assumed when, after a period of normal renal function, the patient became oliguric and developed hypertension and fluid retention, followed shortly afterwards by fever, tachycardia, proteinuria, elevation of the blood urea nitrogen (BUN) and creatinine, depression of the creatinine clearance (CrCl) and urinary sodium excretion, swelling and tenderness of the transplant, and sometimes by the appearance of lymphocytes in the urine (Starzl *et al.*, 1963). The development of this syndrome varied in rapidity from a few hours to many days and was not always complete. When the second episode of rejection occurred in transplant LD10, which had been functioning for more than seven months, the appearance of signs and symptoms was insidious and it was difficult to be certain about the day of onset (Starzl *et al.*, 1964).

The clinical course of all the recipients in this group and, in those who died, the cause of death and some of the post-mortem findings, are listed in Table II. Two of the renal homotransplants had come from cadaveric donors (CD1 and CD2) and one was a second transplant (LD29); the others were primary renal homotransplants from living donors.

Gross Appearances.—Most of these renal homotransplants were enlarged, the mean weight being 241 g. with a range of 148 to 350 g. (The kidneys of the normal adult man weigh from 125 to 170 g. each; those of the female weigh 115 to 155 g. each.) The capsule was usually thickened, and in all but one of the cases stripped easily leaving a smooth cortical surface which in five of the transplants was speckled with petechial hæmorrhages. When cut the cortex was pale and bulged; in two of the kidneys the medulla was deeply congested. A few of the transplants showed tiny cortical areas of infarction. The main renal vessels were patent, and in all except LD35 the ureters were unobstructed. In this latter case there was blockage of the ureter with debris at its junction with the bladder, and a rupture 1 cm. in diameter on the anterior wall of the pelvis. In another patient, LD61, the ureter had been re-implanted six days before the patient's death because of obstruction at the ureterovesical junction. The ureteric walls were thickened in the majority of the transplants in this group.

Microscopical Appearances (Table III).—*Glomeruli.*—No striking changes were present. Two cases showed slight thickening of the basement membranes of the tuft capillaries by PAS-positive material. The glomeruli were hypertrophied in the transplant that had functioned for 295 days (Fig. 1). In five of the kidneys there had been extension of fibrinoid necrosis from affected afferent arterioles into the walls of the glomerular capillaries (Fig. 2). Fibrosis of a few tufts and periglomerular fibrosis were present alone or together in six of the transplants. Only one case showed hyperplasia of the juxtaglomerular body with increased granularity of the juxtaglomerular cells.

Tubules.—Widespread recent tubular necrosis with active regeneration of the lining epithelium and casts of protein and cell debris was seen in four of the transplants. Patchy tubular damage was present in five others. Lymphocytes were found in the lumen of a few tubules, but only in

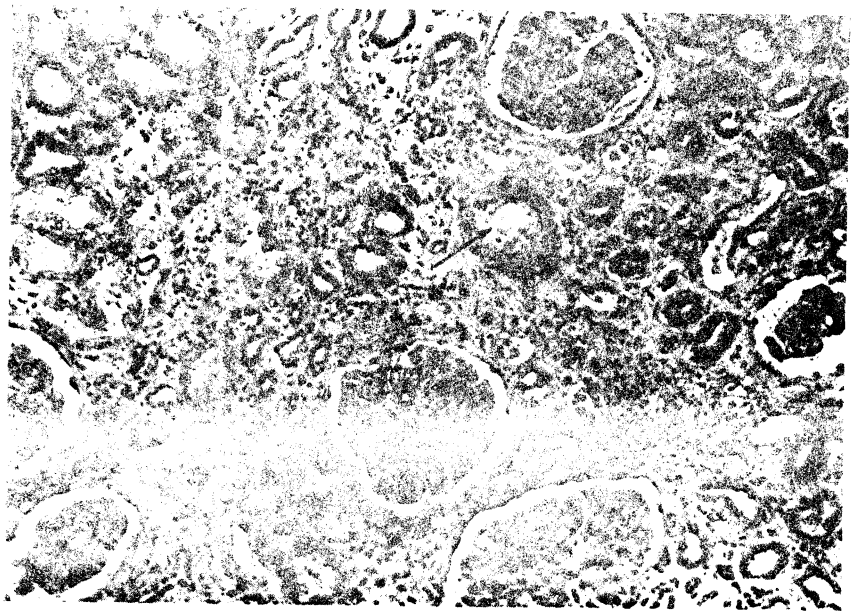

FIG. 1

Renal homotransplant from patient LD10 who died at 295 days in a rejection episode which had started sixty-seven days previously. The glomeruli are hypertrophied, many of the tubules are atrophic and the interstitium shows fibrosis, some œdema and a few small foci of infiltrating lymphoid cells. There is fibrous obliteration of an interlobular artery (arrow). (H. & E.) ×150.

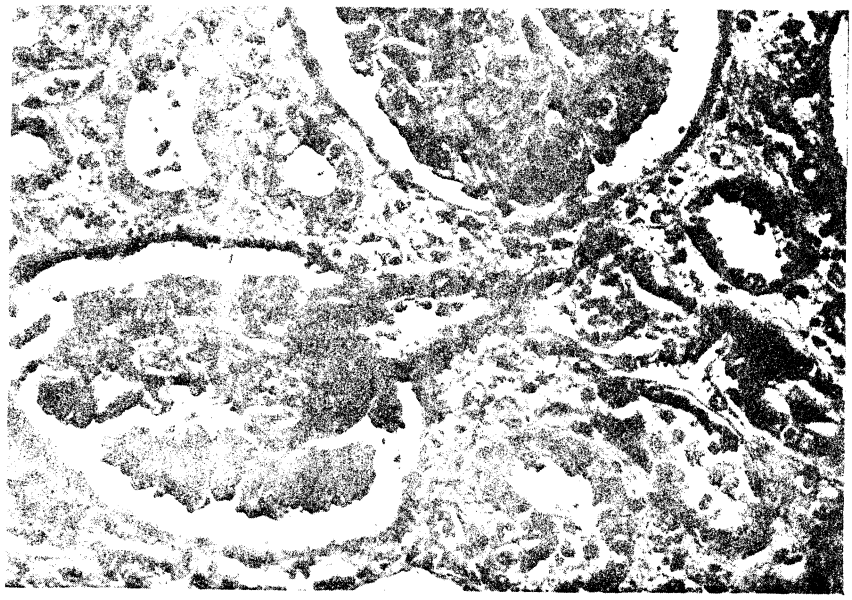

FIG. 2

Cadaveric renal homotransplant from patient CD1 who died at twenty-five days in a rejection episode which had started fifteen days earlier. There is fibrinoid necrosis of parts of the wall of an afferent arteriole which branches to supply two glomeruli. The vasculonecrotic process extends into the capillaries of both tufts. The tubules are damaged and the interstitium is œdematous. Infiltrating cells are scanty and confined to peritubular capillaries. (H. & E.) ×400.

TABLE II

Main Clinical and Necropsy Findings in Fifteen Cases of Human Renal Homotransplantation where the Transplant was Examined either during or shortly after a Rejection Episode

Case	Sex, Age, Blood Group: Donor	Recipient	Ischaemia (mins.)	Clinical Course	Cause of Death and Necropsy Findings
CD1	M32 A + Cadaver	O + M21	106	Only moderate early function. Best creatinine clearance 8·3 ml. per minute; best output 2,120 ml. per 24 hours. Irreversible rejection episode at 10 days during which blood pressure rose to 164/144. Died at 25 days	Septicæmia secondary to acute *Pseudomonas aeruginosa* pleurisy and pericarditis. Bone marrow aplasia. No fibrinoid necrosis of pancreatic and periadrenal arterioles
CD2	M47 A + Cadaver	A + M29	124	Oliguria from beginning. Best creatinine clearance 0·23 ml. per minute; best output 210 ml. per 24 hours. Blood pressure 170/100. Transplant removed after traumatic rupture at 12 days. Considered to be in rejection at time of removal. Course complicated by severe wound infections. Patient died at 41 days following hæmorrhage from dialysis shunt in arm	Staphylococcal pneumonia with abscess formation. Bone marrow hypoplasia. Left ventricular hypertrophy. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD10	M32 O + Unrelated	O + M46	38	Moderate early function. Series of complications including myocardial infarction, gastro-intestinal hæmorrhage and aseptic necrosis of first lumbar vertebra. Rejection episodes at 3 and 229 days; first was reversed, but second persisted until death. Hypertensive until 97 days, then normotensive until 275 days when hypertension recurred and was incompletely controlled by drugs. Died at 295 days	Uræmia and pneumonia
LD11	M32 O + Brother	O + M36	30	Good early function. Rejection episode at 2 days with marked oliguria for 14 days. Developed diffuse polyneuritis. Laparotomy at 7 days for suspected perforated peptic ulcer which was not found. Renal function slowly improved from 14 to 25 days. Blood pressure 160/120 throughout course except for brief spell of terminal hypotension. Died at 25 days	Congestive cardiac failure with massive œdema. Generalised atherosclerosis with myocardial fibrosis. Muscle wasting and decubitus ulcers secondary to polyneuritis. Parathyroid hyperplasia with extensive metastatic calcification. Bone marrow hypoplasia. Old nephrectomy wound infected with *Staph. pseudomonas* and *proteus*. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD24	M37 A + Unrelated	A + M42	23	Good early function. Rejection episodes at 2 and 24 days; first was reversed, but second persisted until death at 38 days. Blood pressure 130/80 on antihypertensive drugs. Hypotension during terminal 24 hours, following hæmorrhage from rectum	Pseudomonas and proteus septicæmia. Marrow aplasia with multiple hæmorrhages into skin, lungs, intestines and adrenals. Infarct upper lobe right lung. Œdema. No fibrinoid necrosis of pancreatic and periadrenal arterioles

LD28	F42 A — Sister	A	M49	34	Good early function. Rejection episode at 13 days which was being reversed when patient died at 25 days. Blood pressure 150/90 on hypotensive drugs. Developed cavity in right lung at 5 days. Terminally fever, pneumonia and hypotension	*E. coli* septicæmia. Pulmonary tuberculosis. Large left pulmonary embolus. Infarction of jejunum secondary to embolus. Abscess in tail of pancreas. Marrow aplasia. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD29	M27 AB — Unrelated	AB	M40	30	Second kidney. Good early function. Rejection episode with complete anuria at 2 days. Not reversed. Blood pressure 150/90 on hypotensive drugs. Died at 8 days	Parenchymal *E. coli* and *Pr. mirabilis* septicæmia. Uræmia. Marrow aplasia. Multiple pulmonary emboli. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD31	M32 A — Unrelated	A	M55	42	Good early function. Irreversible rejection episode at 5 days. Moderately severe hypertension despite drugs. Died at 14 days	Pulmonary embolus. Pseudomonas pneumonia. Marrow aplasia. Uræmia. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD32	M23 A — Brother	A	M20	33	Good early function. Rejection episode commenced at 11 days; anuria at 18 days. Function slowly improving at time of death. Hypertensive despite drugs. Died at 42 days	*Candida albicans* and *E. coli* septicæmia. Foci of moniliasis were present in the transplant, myocardium and intestine. Marrow aplasia. Organising pneumonia. Œdema. Petechial haemorrhages into skin and gut. Chronic venous congestion. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD35	M23 A — Unrelated	A	M38	27	Good early function. Rejection episode at 18 days associated with necrosis of renal pelvis. Transplant removed at 21 days. Normotensive throughout	Received second transplant (see Table VI) and died 9 days later
LD43	F57 O — Mother	O	M25	46	Poor early function. In rejection terminally, but time of onset uncertain. Blood pressure 200/110 despite drugs. Died at 38 days	*Strep. faecalis* septicæmia. *Aspergillus fumigatum* in lungs. *Candida albicans* in transplant. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD46	M29 O — Husband	O	F25	31	Excellent early function. Irreversible rejection episode at 31 days. Onset of rejection was associated with a blood pressure of 160/90. Died at 43 days	Septicæmia. Marrow aplasia. Uræmia. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD59	F44 B — Wife	B	M48	43	Excellent early function. Irreversible rejection episode at 37 days. Normotensive but on hypotensive drugs. Died at 45 days	Klebsiella pneumonia and lung abscesses. Marrow aplasia. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD61	F24 O — Mother	O	F5	30	Excellent early function. Rejection episodes at 3, 14, and 25 days. First two reversed, but third irreversible. Ureter re-implanted at 30 days because of stricture. Hemiparesis at 15 days. Hypertensive (150/100) until 15 days, then normotensive until last few days when hypotensive. Died at 35 days	*E. coli* septicæmia. Marrow aplasia. No gross changes found in brain. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD64	M33 O — Brother	O	M30	19	Good early function. Rejection episode commenced at 44 days. Very persistent but reversal almost complete when patient died at 65 days. Hypertensive (140/100) despite drugs	Septicæmia secondary to *Pseudomonas æruginosa* pneumonia. Pulmonary œdema. Bone marrow hypoplasia

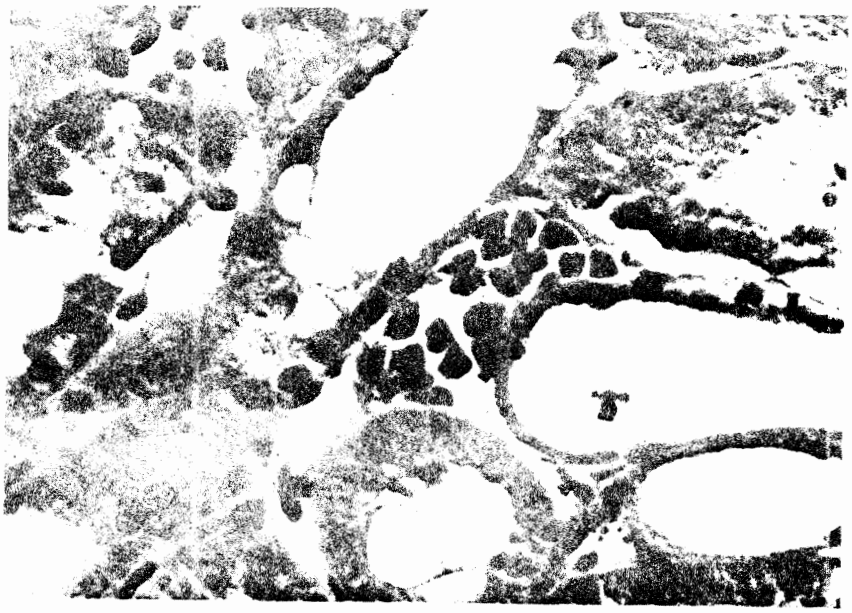

FIG. 3

Renal homotransplant which was removed surgically from patient LD35 at twenty-one days because of necrosis of the pelvis. Rejection had started three days previously. A group of infiltrating lymphoid and plasma cells are seen lying within two peritubular capillaries. The adjacent tubules are damaged. (H. & E.) × 500.

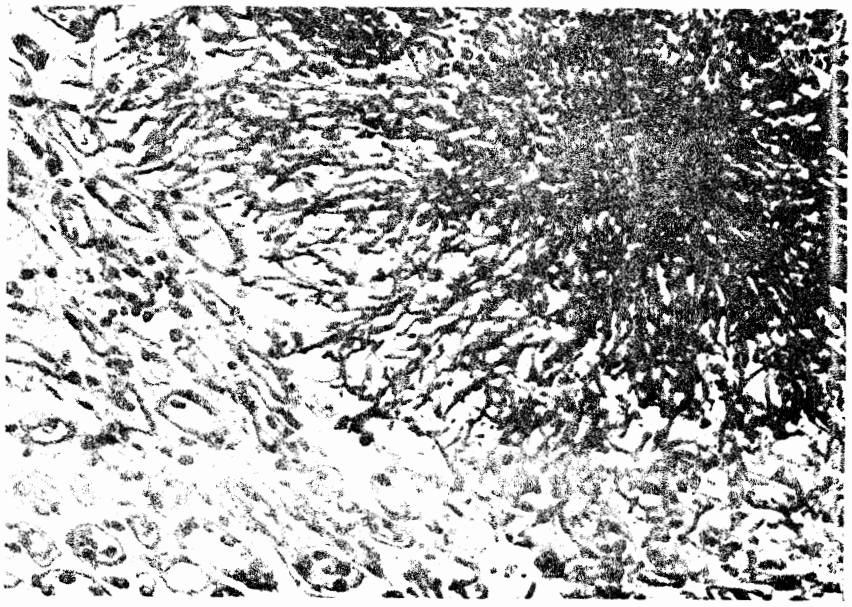

FIG. 4

Renal homotransplant from patient LD32 who died at forty-two days from systemic infection with *Candida albicans*. Recovery was occurring from a rejection episode which had started thirty-one days previously. A fungal colony growing in the medulla has elicited no cellular response. (Periodic acid-Schiff.) × 200.

TABLE III

Pathological Changes in Fifteen Treated Human Renal Homotransplants which were Examined during or just after a Rejection Episode *

Type of Lesion	Case Number														
	CD1	CD2	LD10	LD11	LD24	LD28	LD29 (ii)	LD31	LD32	LD33 (i)	LD43	LD46	LD59	LD61	LD64
Glomeruli—															
Hypertrophy	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Fibrinoid necrosis of tuft	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–
Thickening of capillary basement membranes	–	–	–	–	–	–	–	+	+	–	–	–	–	–	+
Tuft fibrosis	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+
Periglomerular fibrosis	–	–	+	–	+	–	–	–	–	–	–	–	–	–	+
Hyperplasia of juxtaglomerular body	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Tubules—															
Recent necrosis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Atrophy with evidence of regeneration	–	–	–	–	–	–	–	+	+	–	–	–	+	–	+
Casts	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Calcification	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Birefringent crystals	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Interstitium—															
Cellular infiltration	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Œdema	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Fibrosis	–	–	–	–	+	–	–	–	–	–	–	+	+	–	+
Hæmorrhage	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Fibrin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Blood vessels—															
Swelling of arteriolar endothelium	–	–	–	–	–	–	–	–	–	–	–	+	+	–	+
Destruction of peritubular capillaries	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+
Fibrinoid necrosis	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+
Intimal thickening—															
Fibrinous and platelet	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+
Fibrous	–	–	–	–	–	–	–	–	–	–	–	+	+	+	+
Internal elastic lamina—															
Rupture	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Multiplication	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Venous thrombosis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Arterial thrombosis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Patchy infarction	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

* –, lesions sought and not found; – to – – –, a comparative estimate of severity of particular lesion.

those cases with tubular damage and interstitial cellular infiltration. Birefringent calcium oxalate crystals were present in six of these kidneys.

Interstitium.—Cellular infiltration was present in all but two of the cases: although heavy in three it was generally light (Fig. 1) and consisted of occasional foci of small lymphocytes, plasma cells and larger cells with pyroninophilic cytoplasm, a large pale nucleus and prominent nucleolus. Often the cells were confined to peritubular capillaries (Fig. 3). Mitoses were not seen. Œdema was present in nine of the kidneys (Fig. 2) and there was interstitial fibrosis in six of the eight transplants which survived thirty-six days or longer (Fig. 1). Small hæmorrhages and collections of fibrin in the interstitium often accompanied arteriolar fibrinoid necroses. Monilial lesions were seen in two of the transplants. In patient LD32, who had systemic infection with *Candida albicans*, the lesions consisted of necrotic areas containing budding forms centrally and hyphæ peripherally but no cellular response (Fig. 4). Fragments of hyphæ of the same fungus were found in case LD43 surrounded and partly engulfed by giant cells.

Blood Vessels.—Foci of fibrinoid necrosis were seen in the walls of afferent arterioles and interlobular arteries in twelve of the fifteen homotransplants (Fig. 2). The damage was most widespread and severe in CD1, a cadaveric kidney in which transplantation was from a donor who was blood group A rhesus positive to an O positive recipient. The vasculonecrotic process generally involved the whole thickness of the arteriolar walls, but usually affected only the media and intima of the interlobular arteries. The vasa vasorum of arcuate and interlobular arteries sometimes showed these same necrotic changes. Swelling of the endothelial cells lining the arterioles was present in six of the cases, and obvious destruction of peritubular capillaries in ten. Fibrin and platelet deposits on the intima of damaged interlobular arteries (Fig. 5) were seen in nine of the kidneys and fibrous intimal thickening of these vessels in eight. This latter change was most severe in LD46 where many of the arcuate and interlobular arteries showed obliterative changes. In most of the vessels there was general thickening of the intima by fibroblastic tissue, covered on the luminal side by a thin layer of endothelial cells (Fig. 6). The intimal thickening was sometimes confined to only part of the circumference of the artery (Fig. 7); on other occasions it had caused complete obliteration of the lumen (Fig. 1). Deposits of fat of variable size were present in the deeper layers of the thickened intima immediately adjacent to the media (Fig. 7). Reduplication of the internal elastic lamina was present in eight cases and rupture of the same layer in six (Fig. 7). All the vascular lesions were more frequent and severe where arteries divided and gave rise to small side branches. Thrombosis of occasional small veins was found in four of the transplants and of damaged interlobular arteries in three. Tiny wedges of cortical infarction were present in four of these cases.

Ureter and Pelvis.—In those cases where the ureter was examined the transitional epithelium showed areas of ulceration (Fig. 8). There was œdema of the interstitial tissues and a focal, sometimes heavy infiltration with lymphoid and plasma cells. Swelling of the endothelial cells lining the small arteries and arterioles and fibrinoid necrosis of the walls of these same vessels (Fig. 8) with rupture of the internal elastic lamina was common. Fibrin and platelet deposition on the intima of affected vessels was also seen. In some, focal infarction and hæmorrhages into the ureteric interstitial tissues and into the peripelvic fat had occurred. These changes were prominent in the first transplant from patient LD35 where rupture of one of these infarcted areas in the pelvis had necessitated removal of the whole kidney.

Transplants Examined some time after Reversal of a Rejection Episode.—Twelve kidneys came from patients whose last clearly recognisable rejection episode had been clinically reversed 14 to 160 days previously. Four of these cases had survived two rejection episodes and another two had encountered three such crises. The clinical course of these patients, the ultimate cause of their death and some of the post-mortem findings are listed in Table IV. All the renal homotransplants were from living donors; three were second transplants (LD19, LD23, and LD57).

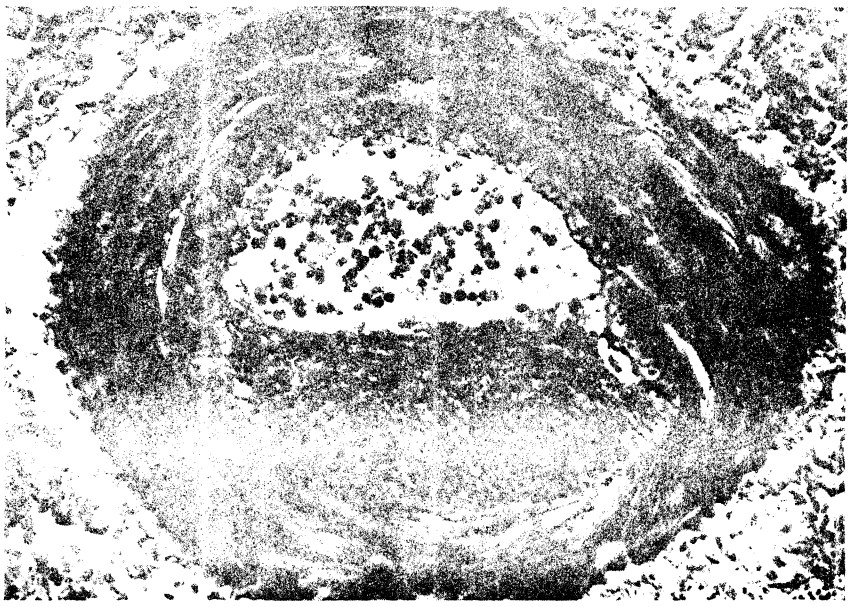

FIG. 5

Renal homotransplant from patient LD11 who died at twenty-five days whilst recovering from rejection episode which had started twenty-three days before. The intima of an arcuate artery is thickened eccentrically by a meshwork of fibrin and platelets.
(Lendrum's Martius yellow-scarlet-blue.) ×200.

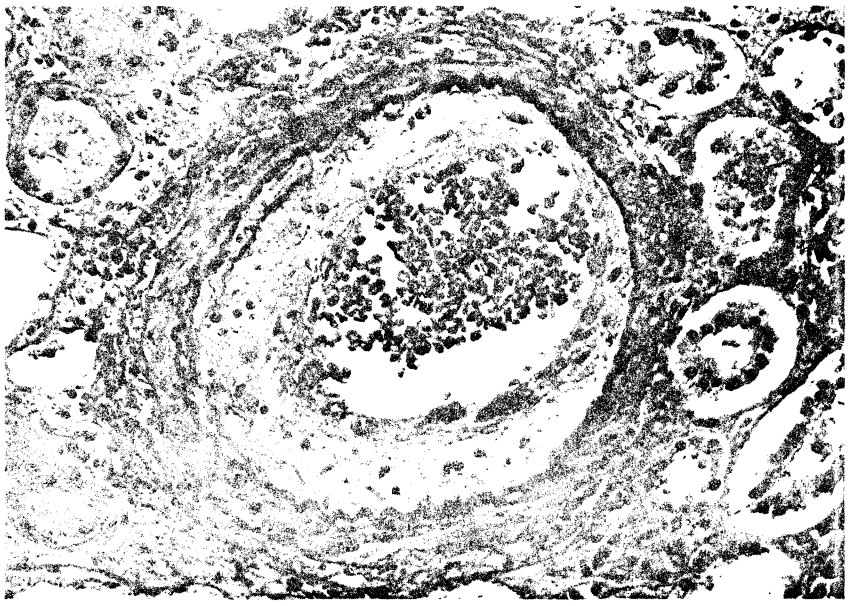

FIG. 6

Renal homotransplant from patient LD 46 who died at forty-three days in a rejection episode which had started twelve days previously. An arcuate artery is narrowed by concentric fibrous intimal thickening. (Elastic [redacted] van Gieson.) ×180.

TABLE IV

Main Clinical and Necropsy Findings in Twelve Cases of Human Renal Homotransplantation where the Transplant was Examined at least Fourteen Days after a Rejection Episode had been Reversed

Case	Sex, Age, Blood Group Donor	Recipient	Ischæmia (mins.)	Clinical Course	Cause of Death and Necropsy Findings
LD4	F30 A – Wife	AB – M34	36	Excellent early renal function. Rejection episodes at 17 and 42 days promptly reversed. Intestinal obstruction on day 32 relieved by operation. Massive pulmonary embolism on day 37 treated by embolectomy and vena caval plication. CrCl 45 to 60 ml. per minute thereafter but BUN normal. Wound abscess drained on day 69. Normotensive throughout. Died at 113 days	Pseudomonas septicæmia. *Staphylococcus aureus* subphrenic abscess, pneumonia and mediastinitis. Thrombosis of inferior vena cava and left common iliac vein. Some marrow hypoplasia
LD7	F32 O – Wife	A – M25	41	Early function good. Ureter reimplanted at 5 days because of urinary fistula. Rejection episode at 19 days promptly reversed. Hypertensive from 27 to 45 days; after this normotensive. Own right kidney removed at 73 days. Died at 79 days	Pseudomonas septicæmia. Staphylococci in wound. Multiple pulmonary emboli. Marrow hypoplasia
LD8	M20 O – Brother	O – M29	61	Moderate early function. Rejection episode at 4 days promptly reversed. Subsequent function excellent. Blood pressure averaged 150/100. The day before death vomited, became disorientated and then comatose. Convulsions started. Died at 62 days	Unexplained death. Slight pulmonary œdema and multiple old small emboli in lower lobe of right lung
LD9	M30 O – Dizygotic twin	A – M30	28	Immediate function good. Rejection episodes at 5, 34, and 71 days successfully reversed. Blood pressure maintained at 120/70 by hypotensive drugs. At 150 days developed monilial stomatitis which persisted. At 195 days melæna and hæmatemesis, but only gastritis found at laparotomy. After this renal function deteriorated; patient became lethargic, confused and hypotensive. Died at 207 days during peritoneal dialysis	*Pseudomonas æruginosa* septicæmia. Nocardial myocarditis and endocarditis with embolisation to adrenals, transplant and brain. *Candida albicans* and *kruzei* abscesses in lungs, brain adrenals and transplant. Marrow hypoplasia

LD16	M46 A — Brother	A	F41	23	Excellent early function. Rejection episodes at 5 and 29 days reversed with return of moderately good renal function. Normotensive throughout but on hypotensive drugs until 55 days. At 73 days acute abdomen. By 82 days serum amylase 800 units and hypotensive. Died at 83 days	Acute on chronic steroid pancreatitis with surrounding fat necrosis. Marked wasting. Slight bone marrow hypoplasia. No infection
LD19	M25 O — Unrelated	O	M17	26	Second homograft. Excellent early function. Rejection episode at 9 days reversed with good subsequent renal function. Normotensive throughout, but maintained on hypotensive drugs. After 3 months developed miliary type of bronchopneumonia with fever and cough. Died at 95 days	Pneumocystis carinii pneumonia. Cytomegalic inclusion disease affecting lungs, lymph nodes, gastric and salivary glands, pancreas and parathyroids
LD21	F40 O — Wife	A	M41	41	Good early function. Rejection episode at 4 days was reversed. Normotensive throughout but on hypotensive drugs. Emotionally depressed and mentally strange. At 68 days left lower lobe pneumonia with fever and cough. Died at 76 days	Disseminated *Candida stellatoides* infection affecting endocardium and intestine with abscesses in brain and lungs. Extensive generalised muscle wasting. Bone marrow aplastic. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD23	M30 O — Unrelated	O	M47	43	Second homograft. Excellent early function. Severe rejection episodes at 18 and 223 days were reversed but blood pressure rose to 190/110 late in course. Developed hepatitis. Died at 405 days	Hepatic necrosis and bone marrow aplasia
LD38	F44 A — Mother	A	M21	30	Good immediate function. Rejection episode at 3 days was reversed. Blood pressure controlled at 142/84 by hypotensive drugs. Developed pneumonia. Died at 38 days	Pulmonary œdema and pneumonia. Extensive generalised muscle wasting. Bone marrow hypoplastic. No fibrinoid necrosis of pancreatic and periadrenal arterioles
LD56	F47 A — Mother	A	F26	30	Good immediate function. Rejection episode at 7 days was reversed. About 145 days developed agranulocytosis, septicæmia and pneumonitis. Normotensive. Died at 155 days	Septicæmia and pneumocystis carinii pneumonia. Hepatic fibrosis. Marrow aplasia
LD57	M33 O — Unrelated	O	F36	35	Second transplant. Good early function. Rejection episodes at 2, 32, and 53 days. All apparently reversed. While at home suffered burn which became infected. Died at 71 days	*Pseudomonas æruginosa* septicæmia and pneumonia secondary to infected third degree burn
LD62	F36 O — Sister	A	M38	21	Good early function. Rejection episodes at 17 and 35 days successfully reversed. Multiple infected pulmonary emboli from about 60 days. Normotensive. Died at 116 days	Septicæmia. Multiple septic pulmonary infarcts and abscesses. Pneumocystis carinii pneumonia. Hepatic fibrosis. Marrow hypoplasia. Fibrinoid necrosis of pancreatic and periadrenal arterioles

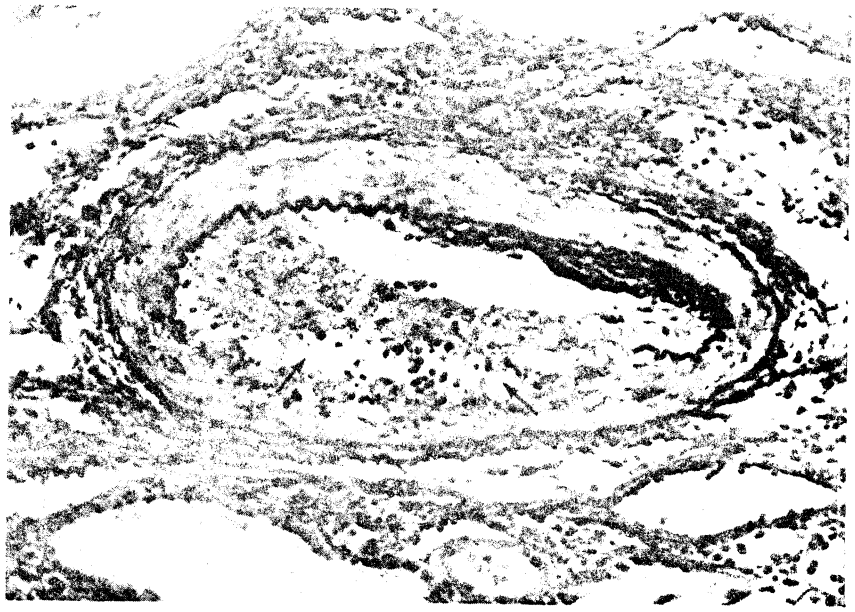

FIG. 7

Renal homotransplant from patient LD46 (*see* Fig. 6). An interlobular artery is greatly narrowed by eccentric fibrous intimal thickening. The internal elastic lamina is ruptured over the intimal plaque; there is multiplication of the elastic opposite this area. Fat spaces (arrows) can be seen in the deep layers of the thickened intima adjacent to the internal elastic layer. (Elastic—van Gieson.) ×300.

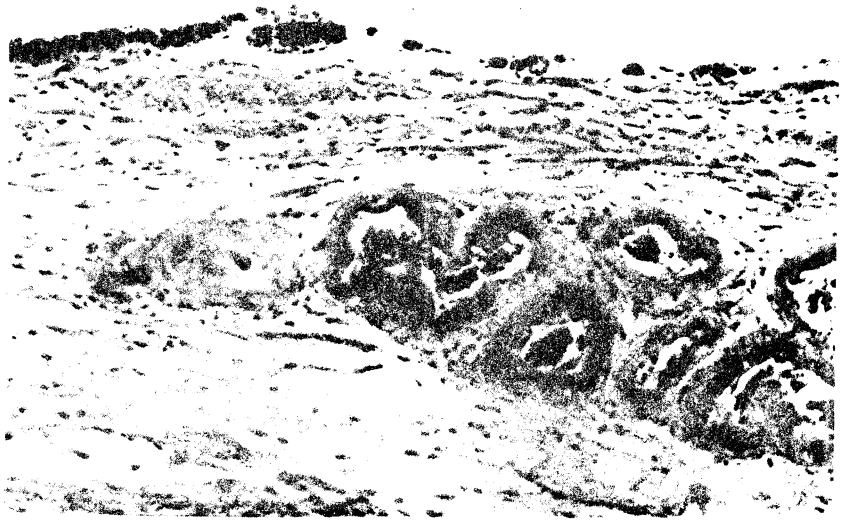

FIG. 8

Pelvis of renal homotransplant from patient LD61 who died at thirty-five days in a rejection episode which had started ten days previously. There is fibrinoid necrosis of the walls of several small arteries and arterioles lying in the œdematous peripelvic tissues. Fibrin and platelet deposits on the intima of some of the affected vessels can be seen. The transitional epithelial lining of the pelvis shows areas of ulceration. (H. & E.) 200.

Gross Appearances.—All the kidneys were enlarged, the mean weight being 199 g. with a range of 178 to 230 g. The capsule was thickened and stripped easily in all but case LD19, where there was an old superior polar infarct which had been caused by the ligation of a small accessory artery at the time of transplantation. The subcapsular surface was smooth, the cortex pale and the medulla reddish-brown. In patient LD4, where plication of the inferior vena cava had been performed following pulmonary embolectomy, the renal and right iliac veins and the lower part of the inferior vena cava were completely thrombosed, but in the other eight cases the renal vessels and their anastomoses were free from any obstruction. The ureters were unobstructed.

Microscopical Appearances (Table V).—*Glomeruli.*—Hypertrophy of the glomeruli was a feature in eight of the transplants. In one kidney there was a PAS-positive thickening of the tuft capillary basement membranes; in two others occasional tufts were fibrosed and there was periglomerular fibrosis. Two of the transplants showed hyperplasia of the juxtaglomerular body with vacuolation and increased granularity of the cells in the walls of the afferent arterioles.

Tubules.—Tubular damage was present in eight of these kidneys. In four it was recent necrosis affecting predominantly the proximal convoluted tubules; these transplants all came from patients who had been hypotensive terminally. In seven there were atrophic changes with evidence of active tubular repair, the tubules being lined by flattened epithelium and containing occasional mitotic figures. Tubular atrophy was most severe in two transplants which had functioned for 207 and 405 days respectively, the longest periods in this group (Fig. 9). Protein casts were present in six of these transplants, crystals of calcium oxalate in four and patchy calcification within tubular cells in five.

Interstitium.—In eight of the twelve transplants there was a very light, focal, cellular infiltration (Fig. 10). Often the cells were confined to peritubular capillaries. Most of the cells were small lymphocytes and plasma cells, but there were a few other larger cells with pyroninophilic cytoplasm. Œdema was present in only two cases; interstitial fibrosis was present in six (Fig. 9). In patient LD9 scattered *Candida hyphæ* and *Nocardia* were present with no surrounding cellular reaction.

Blood Vessels.—Fibrinoid necrosis was present in the arteriolar walls of three of the twelve transplants, and swelling of the arteriolar endothelial cells in only one. Seven of the twelve kidneys, however, showed intimal thickening of some of the interlobular arteries. In one of the transplants the new intimal layer consisted only of fibrin, platelets and a few lymphocytes; in two it was fibrous; in the other four both types of thickening were present. Multiplication of the internal elastic lamina of interlobular and arcuate arteries was present in nine of these kidneys; rupture of the same layer was present in only three. Thrombosis of the small intrarenal veins was present in three of the transplants, including the case where renal vein thrombosis was noted grossly.

Ureter and Pelvis.—In those cases where the ureter was examined the transitional epithelial lining was often thin and in places absent. There was an increase in submucosal fibrous tissue and strands of similar material separated the muscle bundles. In two the arteries supplying the ureter showed fibrous intimal thickening and either duplication or rupture of the internal elastic lamina.

Transplants from Patients who had not developed Clinical Evidence of a Rejection Episode.—Three renal homotransplants came from patients who, up to the time of their death, had shown no clinical signs and symptoms to indicate that they were rejecting their transplants. The clinical course of these patients (LD5, LD35 (ii), SD3 (ii)) and some of the necropsy findings are shown in Table VI. All the transplants were from living donors; two were second transplants (LD35 and SD3).

Gross Appearances.—Two of these kidneys appeared normal and weighed 150 and 180 g. respectively. The transplant from patient LD5 was pale, swollen and weighed 210 g.

Microscopical Appearances (Table VII).—*Glomeruli.*—The only abnormalities were in case

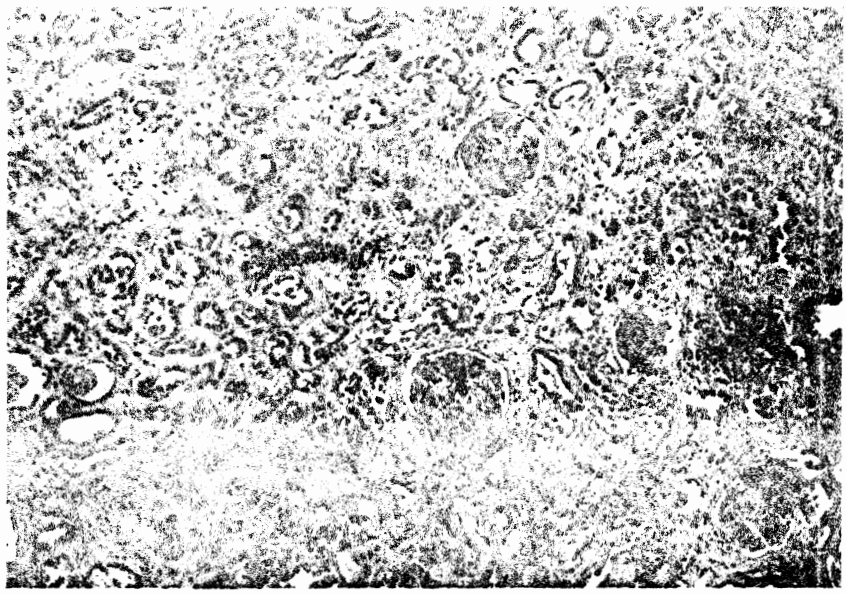

FIG. 9

Renal homotransplant from patient LD9 who died at 207 days from septicæmia, systemic nocardiasis and candidiasis. Rejection episodes at five, thirty-four, and seventy-one days had been successfully reversed. There is widespread tubular atrophy and interstitial fibrosis, but very little cellular infiltration. Many peritubular capillaries have been destroyed. (H. & E.) ×140.

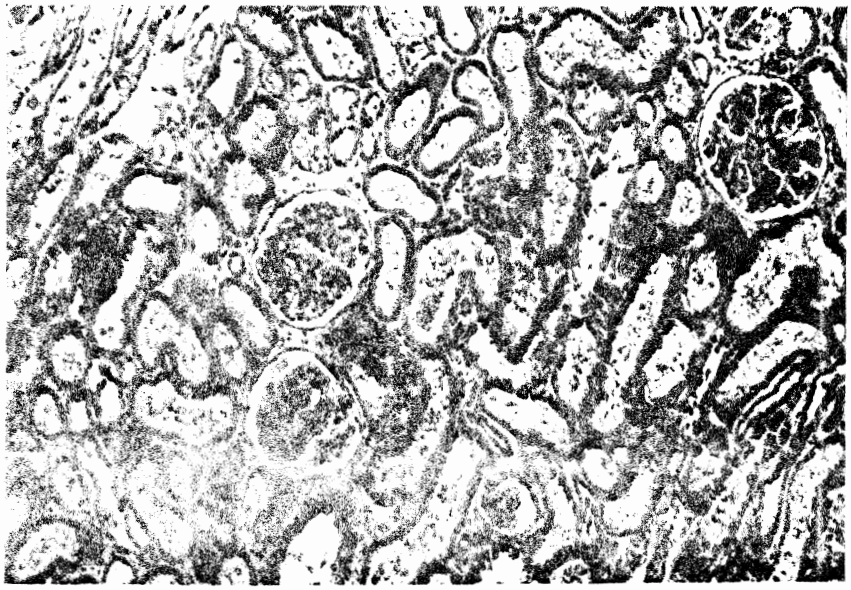

FIG. 10

Renal homotransplant from patient LD16 who died at eighty-three days from steroid pancreatitis. Rejection episodes at five and twenty-nine days had been successfully reversed. There are a very few infiltrating cells, all confined to peritubular capillaries. Glomeruli and tubules appear normal. (H. & E.) ×150.

TABLE V

Pathological Changes in Twelve Human Renal Homotransplants which were Examined at least Fourteen Days after a Rejection Episode had been Reversed *

Type of Lesion	Case Number											
	LD4	LD7	LD8	LD9	LD16	LD19 (ii)	LD21	LD23	LD38	LD56	LD57	LD62
Glomeruli—												
Hypertrophy	+	+	−	+	+	+	+	+	−	−	−	−
Fibrinoid necrosis of tuft	−	−	−	−	−	−	−	−	−	−	−	−
Thickening of capillary basement membranes	−	−	−	−	−	−	−	−	−	−	−	−
Tuft fibrosis	−	−	−	−	−	−	+	+	−	−	−	−
Periglomerular fibrosis	−	−	−	+	−	−	−	+	−	−	−	−
Hyperplasia of juxtaglomerular body	−	−	+	−	−	−	−	−	−	−	−	−
Tubules—												
Recent necrosis	−	+	+	−	−	−	−	−	+ +	−	+	−
Atrophy with evidence of regeneration	−	+	−	+ + +	−	−	+	+ +	−	−	+	−
Casts	+	+	−	−	−	+	+	+	−	−	+	−
Calcification	+	+	−	−	−	−	+	+	−	−	−	−
Birefringent crystals	−	−	−	+	−	−	+	−	−	−	−	−
Interstitium—												
Cellular infiltration	+	+	−	+	−	+	−	+	+	−	−	+
Œdema	−	+	−	−	−	−	−	−	−	−	−	+
Fibrosis	+	−	−	+ + +	+	−	−	+	+	−	+	+
Hæmorrhage	−	−	−	−	−	−	−	−	−	−	−	−
Fibrin	−	−	−	−	−	−	−	−	−	−	−	−
Blood vessels—												
Swelling of arteriolar endothelium	−	−	+	−	−	−	−	−	−	−	−	−
Destruction of peritubular capillaries	+	−	−	+ +	+	−	−	+	+	−	−	−
Fibrinoid necrosis	−	−	−	−	−	−	+	−	−	−	−	−
Intimal thickening—												
Fibrinous and platelet	+	−	−	−	−	−	−	−	−	−	−	−
Fibrous	−	−	−	−	+	−	−	+ +	+	−	+ +	+
Internal elastic lamina—												
Rupture	+	−	−	−	−	−	−	+	−	−	−	−
Multiplication	−	−	−	−	−	−	+	−	−	+	+ +	−
Venous thrombosis	+	−	+	−	−	−	−	−	−	−	−	−
Arterial thrombosis	−	−	−	−	−	−	−	−	−	−	−	−
Patchy infarction	−	−	−	−	−	−	−	−	−	−	−	−

* −, lesions sought and not found: + to + + +, a comparative estimate of severity of particular lesion.

SD3, where some of the glomeruli showed focal thickening of tuft capillary basement membranes by material which stained with Masson 44/41 as old fibrin (Lendrum *et al.*, 1962).

Tubules.—In LD5 where severe hypotension had been a post-operative complication there was widespread tubular necrosis with evidence of repair. Less severe older tubular damage was present in SD3. Many birefringent calcium oxalate crystals were present in LD5.

Interstitium.—Two of the homotransplants contained several foci of infiltrating lymphoid and plasma cells and interstitial œdema was present in two.

Blood Vessels.—Only the renal transplant from SD3 showed vascular changes. There was patchy replacement of arteriolar walls by material staining as old fibrin with Masson 44/41 and plugging of the lumens of a few of these vessels with similar material. Several of the interlobular arteries showed either fibrinous and platelet intimal thickening, or, more frequently, fibrous thickening of this layer, with damage to the internal elastic and narrowing of the lumen.

Transplants which either did not Function or Developed some Complication necessitating their Early Removal.—The seven transplants in this category could be subdivided into five small groups according to the main factor causing failure of the transplant or death of the recipient (Tables VI and VII).

1. *Technical Failure.*—In LD57, at the time of transplantation, one of the two veins draining the kidney was ligatured. After completion of the vascular anastomoses, however, it was found that the remaining vein was obstructed by the artery which crossed it. By the time this situation had been rectified the transplant had probably been at body temperature without venous drainage for about 120 minutes. The transplant never excreted urine but it was not examined until seventy-seven days later. By that time it weighed 190 g., showed complete hæmorrhagic infarction and there was old thrombosis of the main renal artery and both renal veins.

2. *Ischæmia.*—The first kidney to be transplanted into patient LD29 was supplied by two small arteries. The anastomosis of these to the recipient vessels produced a greater delay than usual and the transplant was ischæmic for eighty-four minutes. As it did not excrete urine it was removed at forty-eight hours and replaced by another transplant.

In the second case (CD3) both kidneys came from a man who had died from a myocardial infarct. The left kidney was ischæmic for 137 minutes and the right for 215 minutes; further, the donor had been hypotensive before death. Both kidneys failed to excrete urine and the patient died at four days.

All these transplants were pale and slightly swollen; the cortex was widened and the cortico-medullary junction blurred. The vessels were patent and the ureters unobstructed. Microscopically, there was massive recent tubular necrosis, affecting particularly the proximal part of the nephron (Fig. 11). The lumens of the tubules were filled with casts of protein and cell debris. There was evidence of active repair in the form of mitoses among surviving proximal tubular cells and the lining of tubules by new flattened epithelium. The interstitium was œdematous and contained scattered foci of small lymphocytes, plasma cells and occasional polymorphs, chiefly in relation to severely damaged tubules. The cellular infiltrate was heaviest in CD2. The glomeruli were normal in the transplant that had come from the living donor, but in the other case there was periglomerular fibrosis and a few fibrotic glomeruli. The cadaveric kidneys also showed fibrous intimal thickening of the interlobular and arcuate arteries.

3. *Blood Group Incompatibility.*—Two kidneys, which were incompatible on the basis of ABO blood groups, when transplanted into group O rhesus-positive recipients became cyanotic within a few minutes and failed to excrete urine. The first kidney (LD19) came from a group A positive donor and the second (LD23) was from a group B positive donor. Both transplants were removed within three hours of their insertion. They showed great distension of the afferent arterioles with erythrocytes and sludging of these same cells in the glomerular capillaries. There was interstitial œdema and hæmorrhages but no cellular infiltration.

4. *Hæmorrhages.*—In case LD49 there were technical difficulties at the time of transplantation

which resulted in the kidney being ischæmic for fifty-eight minutes. Flow of urine from the homotransplant did not begin for two hours, but after this there was a daily excretion of 2 to 3 litres. However, the urine was heavily contaminated with blood. The hæmaturia persisted and, even after three explorations, no cause could be found: at four days the kidney was removed. Examination of the gross specimen showed blood in the pelvis but no bleeding point could be identified. Microscopically there were foci of proximal tubular damage and many crystals of calcium oxalate in the lumens, but no evidence of blood or pigment in any of the nephrons.

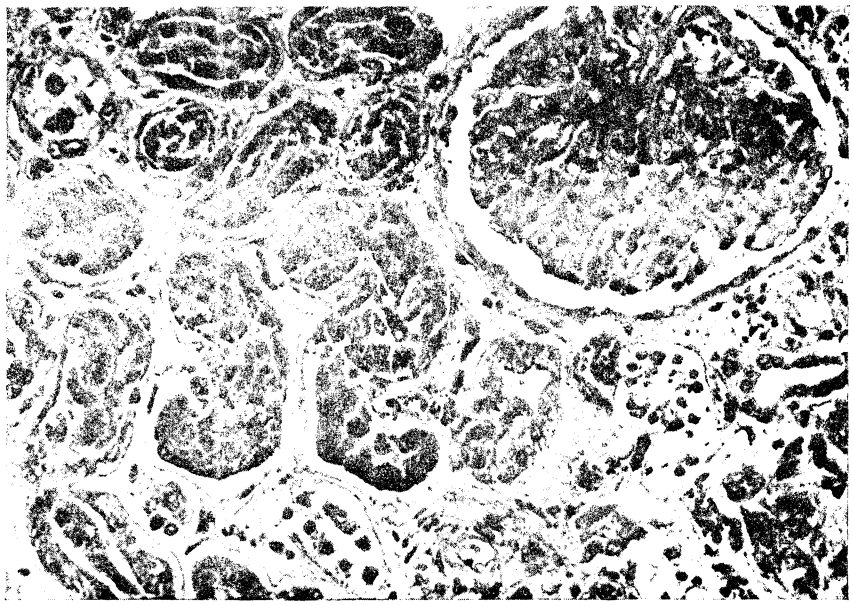

FIG. 11

Renal homotransplant which was removed surgically from patient LD29 at forty-eight hours because it had failed to excrete urine. There is marked tubular necrosis, affecting particularly the proximal parts of the nephrons, some interstitial œdema and occasional infiltrating host cells. (H. & E.) ×400.

There was no interstitial œdema, only minimal cellular infiltration and no evidence of inflammatory changes in the pelvis of the transplant. In the peripelvic fat there was a band of hæmorrhage and several small arteries were necrotic. There were many tiny foci of ulceration in the pelvic transitional epithelium and hæmorrhagic oozing into the pelvis had occurred over a wide area.

5. *Electrolyte Imbalance.*—One patient (LD26) died twelve hours after operation from hyponatræmia and hyperkalæmia during a massive post-operative diuresis in which urine output from the transplant averaged 1,320 ml. per hour. The immediate cause of death was cardiac arrest. At necropsy the homotransplanted kidney was a little swollen and pale. Microscopically the tubules and interstitium appeared normal, but some of the glomeruli were fibrosed and a few showed fibrous thickening of the capillary basement membranes associated with periglomerular fibrosis. There was hyalinisation of the walls of occasional afferent arterioles.

DISCUSSION

Swelling of the endothelial cells lining arterioles and fibrinoid necrosis of the walls of these vessels are now being recognised as important features of the acute homograft reaction in both human and canine renal homotransplants which have been modified by treatment (Parsons *et al.*,

TABLE VI

Main Clinical and Necropsy Findings in Ten Cases of Human Renal Homotransplantation where the Transplant was Examined at some time other than during or after a Clinical Rejection Episode

Case	Sex, Age, Blood Group Donor	Recipient	Ischæmia (mins.)	Clinical Course	Cause of Death and Necropsy Findings
LD5	M42 A – Unrelated	A M50	71	During transplantation cardiac arrest requiring open cardiac massage. Post-operatively patient hypotensive and renal function poor, although up to 3 litres of urine per day produced. Highest CrCl 28 ml. per min. Septicæmia developed and patient died at 11 days	Pseudomonas and hæmolytic *Staphylococcus aureus* septicæmia. Mediastinitis. Uræmia. Bone marrow hypoplastic
LD35	F27 A – Sister	A M38	28	Second homograft. Good renal function until death at 9 days. Output just before death 2,395 ml. per 24 hours; CrCl 69·6 ml. per minute. Mentally confused and disorientated. Convulsions at 7 days. Normotensive until last day when hypotensive	Bilateral pseudomonas pneumonia and septicæmia. Silicosis
SD3	M36 A – Unrelated	AB – M17	34	Second transplant. Early function was excellent. At 28 days a right lower lobe pneumonia developed which spread to involve both lungs. Sputum cultures grew *E. coli*, *Aspergillus fumigatus* and *Candida albicans*. Complicated by massive subcutaneous emphysema. Right-sided pneumothorax developed and patient died at 39 days. Terminally there was a decrease in urinary function. Normotensive throughout	Acute pulmonary insufficiency. Bilateral pneumonia due to *Aspergillus fumigatus* and pneumocystis carinii. Large fungal abscess in left side of brain
LD57	F54 O – Mother	O – F36	35	First homograft. Venous obstruction. Transplant did not function	Received second transplant (see Table IV) and died 71 days later
LD29	F39 AB – Sister	AB – M40	84	First homograft. Transplant did not function. Removed at 48 hours	Received second transplant (see Table II) and died 8 days later
CD3	M42 A – Cadaver	A – F42	L137 R215	The two cadaveric transplants did not function. Patient died 4 days later shortly after dialysis. Blood pressure 190/84	No immediate cause of death found
LD19	M31 A – Mother	O – M17	30	Transplant became cyanotic and soft within a few minutes after revascularisation. Removed at 1 hour	Received second transplant (see Table IV) and died 95 days later
LD23	M42 B – Brother	O – M47	58	Transplant became cyanotic and soft within a few minutes after revascularisation. Removed at 3 hours	Received second transplant (see Table IV) and died 405 days later
LD49	F41 O – Sister	A – M32	57	Early function good but persistent severe hæmaturia required 3 explorations culminating in nephrectomy at 7 days. Not hypertensive	Received second transplant and is still alive over 1 year later with good renal function
LD26	M49 A – Father	A – F16	23	Massive diuresis with an output of 1,320 ml. of urine per hour following transplantation. Electrolyte imbalance developed and patient died at 12 hours	Cardiac arrest due to hyperkalæmia. Moderate pulmonary œdema

TABLE VII

Pathological Changes in Ten Treated Human Renal Homotransplants which were at some time other than during or after a Clinical Rejection Episode*

Type of Lesion	Case Number									
	LD5	LD35 (ii)	SD3 (ii)	LD57 (i)	LD29 (i)	CD3	LD23 (i)	LD19 (i)	LD49 (i)	LD26
Glomeruli—										
Hypertrophy	—	—	—		—	—	—	—	—	—
Fibrinoid necrosis of tuft	—	—	—		—	—	—	—	—	—
Thickening of capillary basement membranes	—	—	+		—	—	—	—	—	—
Tuft fibrosis	—	—	—		—	+	—	—	—	—
Periglomerular fibrosis	—	—	—		—	+	—	—	—	—
Hyperplasia of juxtaglomerular body	—	—	—		—	—	—	—	—	—
Tubules—										
Recent necrosis	+	—	—		—	+ + +	—	—	—	—
Atrophy with evidence of regeneration	+	—	+		—	—	—	—	—	—
Casts	+	—	—		+	+ — +	—	—	—	—
Calcification	—	—	—		—	—	—	—	—	—
Birefringent crystals	+	—	—		—	—	—	—	+ +	—
Interstitium—										
Cellular infiltration	+	—	—		+	+	—	—	+	—
Œdema	+	+	—		—	+	—	—	—	—
Fibrosis	—	—	—		+	—	—	—	—	—
Hæmorrhage	+	—	—	Infarcted	—	—	+	—	—	—
Fibrin	—	—	—		—	—	—	—	—	—
Blood vessels—										
Swelling of arteriolar endothelium	—	—	—		+	—	—	—	—	—
Destruction of peritubular capillaries	—	—	—		—	—	—	—	—	—
Fibrinoid necrosis	—	—	—		—	—	—	—	—	—
Intimal thickening—										
Fibrinous and platelet	—	—	—		—	—	—	—	—	—
Fibrous	—	—	+		—	—	—	—	—	—
Internal elastic lamina—										
Rupture	—	—	+		—	—	—	—	—	—
Multiplication	—	—	—		—	+	—	—	—	—
Venous thrombosis	—	—	—		—	—	—	—	—	—
Arterial thrombosis	—	—	—		—	—	—	—	—	—
Patchy infarction	—	—	—		—	—	—	—	—	—
Congestion of arterioles and capillaries	—	—	—		—	—	+	+	—	—

* —, lesions sought and not found; + to + + +, a comparative estimate of severity of particular lesion.

1963; Dempster *et al.*, 1964; Kincaid Smith, 1964; Porter *et al.*, 1964 *a*). In the present series fifteen transplants were examined at a time when the patient was either in or just recovering from a clinical rejection episode. Forty per cent. of these kidneys (Table III) showed arteriolar endothelial swelling and 80 per cent. showed necrotic lesions affecting the afferent arterioles and sometimes the vasa vasorum. Fibrinoid necrosis of the walls of interlobular arteries and fibrino-platelet and fibroblastic intimal thickening in these same vessels were also common.

Because of the close resemblance between some of these lesions and those seen in malignant phase hypertension, the possibility has to be considered that the vascular damage we have described resulted from exposure of the vessels of the transplant to a pressure higher than that to which they were accustomed. However, although many of the patients were or became hypertensive, the blood pressure in four patients (LD10, LD24, LD59, LD61) who developed florid vasculonecrotic lesions in their transplants was throughout controlled at normal levels with hypotensive drugs. Moreover, lesions were found in the renal transplant from one patient (LD35) who was not hypertensive at any time after transplantation. The damage was, therefore, not initiated by a raised blood pressure, but hypertension may have been a contributory factor when it reached high levels as, for example, in CD1 where the diastolic pressure was 144 mm. Hg. That it can never have been a major factor is witnessed by the lack at necropsy of fibrinoid necrotic lesions in vessels elsewhere in the recipients' tissues (Table III).

Neither can X-irradiation have been an important factor in the production of this vascular damage because only three of the transplants with lesions had been exposed to this treatment.

All the recipients were given corticosteroids, Imuran and actinomycin C, but it is improbable that any of these agents played a part in the production of the vessel changes because vasculo-necrotic lesions have occurred in renal homotransplants in both humans (Parsons *et al.*, 1963) and dogs (Porter *et al.*, 1964 *a*) treated with immunosuppressive drugs other than these. Even in normal untreated dogs, the arteries and arterioles within a renal homotransplant may show fibrinoid necrosis of their walls in the later stages of the rejection process (Simonsen *et al.*, 1953).

In a previous paper (Porter *et al.*, 1964 *b*) it was proposed that there are two important events which bring about failure of renal homotransplants. The first of these, disruption of peritubular capillaries (Kountz *et al.*, 1963), seems to be a major factor underlying the rejection of untreated kidneys transplanted into normal recipients; it is mediated by infiltrating host cells, which perhaps carry cell-bound antibody. The second, endothelial swelling and fibrinoid necrosis of the walls of arterioles and arteries, is a relatively unimportant terminal event in the rejection of untreated renal homotransplants which is perhaps mediated by circulating antibody. It was suggested that when survival of the transplant is prolonged by immunosuppressive drugs, this humoral aspect of the host's response may assume greater importance, in that during a rejection episode circulating antibody is rapidly produced. The resulting antigen-antibody reaction occurring in or on the arteriolar walls would cause swelling of the endothelial cells, and might induce spasm of the smooth muscle in the vessel. Later fibrinoid necrotic changes would appear in the damaged wall. Such lesions, widespread in a transplant, could explain the alterations in water, electrolyte and creatinine excretion that occur in a rejection crisis.

If the rejection episode is halted at the stage of endothelial swelling of arterioles there should be complete return of the vessels to normal. When fibrinoid necrosis of arterioles has occurred healing will result in hyaline changes in the walls of these vessels: if there is secondary thrombosis there will be fibrosis of the associated glomerulus. Once the damage has involved the interlobular arteries and intimal change has induced deposition of platelets and fibrin, ending the rejection phase will not prevent healing with replacement of the intimal deposits by fibroblasts. This progression has been clearly demonstrated by successive biopsies taken from a human renal homotransplant during and after treatment of a severe rejection episode (Porter *et al.*, 1964 *b*). Where the vessel wall has been appreciably weakened by the necrotic process, compensatory fibrous intimal thickening will also contribute to the narrowing of the lumen. If necrosis is initially widespread in the larger arteries, the healing process can produce obliterative collagenous

lesions throughout the renal arterial tree and many examples of this condition have now been recorded (Hume *et al.*, 1955; Küss *et al.*, 1962; Németh *et al.*, 1963; Parsons *et al.*, 1963; Porter *et al.*, 1963; Dempster *et al.*, 1964; Dunea *et al.*, 1964; Hopewell *et al.*, 1964). It is, however, not known how frequently fibrous arterial narrowing is likely to arise as a complication of a rejection episode which has been treated and apparently completely reversed with return of good renal function.

In the present series twelve transplants were examined after at least one rejection episode had been clinically reversed. Seven of these showed intimal thickening of interlobular arteries, but only in two were the lesions at all marked. Although this paucity of severe obliterative vascular lesions is encouraging, it should be noted that only one of the transplants was normal. A mild, focal cellular infiltration, tubular atrophy, and interstitial fibrosis were the other common changes. The tubular damage might have been due to a nephrotoxic effect from chronic administration of Imuran, but it is more probable that peritubular capillaries were continually being damaged on a small scale by host cells which resulted in a focal loss of tubules. Most of this tubular damage was probably corrected by regeneration and in the majority of these transplants there was evidence of active tubular repair. The three homografts which showed arteriolar fibrinoid necrosis were probably undergoing rejection which had not been recognised clinically.

During rejection focal proximal tubular necrosis was often seen and was probably secondary to disruption of peritubular capillaries. In those transplants which survived a rejection episode but developed narrowing of the interlobular arteries, severe tubular atrophy was usual, based on simple ischæmia as occurs in cases of renal artery stenosis. Transplants which were deprived of a blood supply for long periods during the actual procedure of transplantation suffered, as would be expected, severe proximal tubular necrosis.

In a few transplants there was enlargement and increased granularity of the juxtaglomerular cells: changes which are often seen when kidneys are ischæmic.

The glomerular and arterial lesions in the cadaveric transplant CD3 and the damaged arteriolar walls in LD26 were presumably present in the kidneys before they were transplanted.

Many of these renal homotransplants were enlarged. In those cases examined during or just after rejection the increase in weight was almost entirely due to interstitial œdema and cellular infiltration following damage to the fine vessels. In those kidneys which had existed for long periods in bilaterally nephrectomised recipients, compensatory hypertrophy was the main cause of the enlargement.

As would be expected the vessels of the transplanted ureters were also involved in the rejection process. Fibrinoid necrosis of the small arteries and arterioles was accompanied by focal infarction of the ureteric wall. Some of these changes have been previously well illustrated in a case described by Küss *et al.* in 1962. A point of particular interest that emerges from this study is that if, at the time of rejection, the ureter becomes blocked distally by debris due to tubular destruction resulting from the intrarenal vascular changes, then rupture of the necrotic ureteric or pelvic wall may occur as happened in LD35.

Four of this series of thirty-seven renal homotransplants showed some thickening of the glomerular tuft capillary basement membranes. More severe lesions have been encountered by Hamburger *et al.* (1963) in two human renal homotransplants seven and fifteen months after operation. Similar changes have been described in some of the transplants in dogs which have survived for long periods after treatment with immunosuppressive drugs (Porter *et al.*, 1964, *a* and *b*). The canine lesions were thought to have resulted from a combination of ischæmia and perhaps deposition of antigen-antibody complex. The renal lesions in Hamburger's cases were associated with splenomegaly and hypergammaglobulinæmia.

It has long been known that the degree of genetic similarity of donor and recipient is of great importance when considering the fate of homografts. This is borne out in the Denver series where nineteen (48·7 per cent.) of the thirty-nine renal homotransplants that failed by 1st

June 1965 were from an unrelated donor (cadaver, volunteer, wife or husband); whereas only five (13·9 per cent.) of the thirty-six homografts still functioning at this time were from such donors.

SUMMARY

Pathological changes in thirty-seven human renal homotransplants are described. All the patients had been treated with Imuran, prednisone and actinomycin C; ten had also received local X-irradiation to the transplant.

Fifteen of the transplants were from patients in a rejection phase. Most of these kidneys were enlarged because of interstitial œdema and several were speckled with petechial hæmorrhages. There was fibrinoid necrosis of afferent arterioles and interlobular arteries in twelve of the transplants, and the peritubular capillaries were disrupted in ten. Swelling of the arteriolar endothelial cells, fibrino-platelet and fibrous intimal thickening of interlobular arteries were also common. In most of the transplants there was a light infiltration with small lymphocytes, plasma cells and a few larger pyroninophilic cells. Similar changes were present in the pelvis and ureter.

Twelve of the transplants came from patients whose last rejection episode had been clinically reversed 14 to 117 days previously. All these kidneys were enlarged because of compensatory hypertrophy. Seven showed some intimal thickening of the interlobular arteries and in three there was fibrinoid necrosis of arteriolar walls. Tubular atrophy, interstitial fibrosis and a light cellular infiltration were also common changes. Only one kidney appeared normal.

Three transplants came from patients who had not experienced clinical evidence of a rejection episode. One showed acute tubular necrosis due to prolonged ischæmia at the time of transplantation; one was almost normal; the third showed vascular lesions suggestive of old unrecognised rejection.

Seven transplants had either not functioned or developed some complication necessitating their early removal. One of these was infarcted due to obstruction of the venous drainage; two showed massive acute tubular necrosis due to ischæmia; two, which were incompatible with their hosts on the basis of ABO blood groups, failed to excrete urine and showed distension of the arterioles and glomerular capillaries with erythrocytes; one bled uncontrollably from the pelvis; one came from a patient who died at twelve hours from hyperkalæmia and hyponatræmia during a massive post-operative diuresis.

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