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## PATHOLOGICAL CHANGES IN SIX TREATED BABOON-TO-MAN RENAL HETEROTRANSPLANTS

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PRIOR to 1925 several renal heterotransplants were performed between various species. Most of these either failed to function or excreted for only brief periods and those that were examined microscopically showed acute tubular necrosis or infarction. During this time the only heterotransplants said to have survived for long periods were two feline kidneys transferred to dogs (Avramovici, 1924); but when these eventually failed they were not examined microscopically. In recent years very few renal heterotransplants have been recorded and those that have been seem to have undergone progressive vasoconstriction within a few minutes; when removed after a few hours they have shown congestion and interstitial hæmorrhages (Calne, 1961 *a*).

Since the introduction in 1961 of moderately effective methods for altering and partially suppressing the homograft reaction, based on the use of the drugs 6-(1-methyl-4-nitro-5-imidazolyl), thiopurine ("Imuran"), prednisone and actinomycin C (Calne, 1961 *b*; Murray *et al.*, 1962), there has been a great renewal of clinical interest in the homotransplantation of organs, particularly kidneys (*Transplantation*, 1964). However, while the use of volunteers as kidney donors has obvious moral and legal drawbacks, the use of cadaveric donors is handicapped by the uncertainty of the supply and the difficulty of ensuring that the organ transplanted is healthy.

Because of this dilemma there has, in the last year, been a re-exploration of renal heterotransplantation in man using sub-human primates as donors. In this period at least twenty-two such transplants have been performed: thirteen from chimpanzees (Hume, 1964; Reemtsma *et al.*, 1964, *a, b*, and *c*; Reemtsma, 1965), eight from baboons (Hitchcock *et al.*, 1964; Starzl *et al.*, 1964; Wolcott, 1964) and one from a rhesus monkey (Reemtsma *et al.*, 1964 *a*).

Six of the baboon-to-man renal heterotransplants were performed at the University of Colorado Medical Center between 20th December 1963, and 17th January 1964. In this paper the pathological changes they underwent are described.

### MATERIALS AND METHODS

*Baboons.*—These were obtained from the Southwest Foundation for Research and Education, San Antonio, Texas. They were all adults of the species *Papio doguera* (olive or dog face baboon) and came originally from Kenya. They had all been in captivity for at least one year, during which time their freedom from disease had been ascertained and they had been vaccinated and given prophylactic antibiotics and anti-parasitic agents. After the kidneys had been removed the animals were autopsied and infections, infestations, and other abnormalities sought. In the liver of the animal used in Case 1 an encapsulated pocket of *Hepaticystis (Plasmodium) kochi* in megalo-schizont form was found. The other five males were free from disease.

The baboons were blood grouped, but because the red cell antigens of this animal do not react with specific human isoagglutinins, two indirect methods of identification were used: firstly, the ability of the animal's saliva to inhibit the activity of specific antisera; and secondly, the power of the animal's serum to agglutinate human erythrocytes (Moor-Jankowski *et al.*, 1964).

*Renal Heterotransplantation.*—All the donor kidneys, with one exception, were removed *en bloc* with the aorta and inferior vena cava and transplanted to the right iliac fossa of the patient, where anastomoses were made with the external iliac artery and vein (Starzl *et al.*, 1964). The

ureters were implanted into the bladder. The exception was SD1 where the baboon kidneys were removed separately and transplanted one into each iliac fossa. The donor kidneys were perfused with cold 10 per cent. low molecular weight dextran in normal saline to which heparin and procaine chloride had been added.

*Treatment of Recipients.*—In all cases splenectomy and bilateral nephrectomy were performed at the time of renal heterotransplantation. Treatment with Imuran 150 to 200 mg. per day was started two to five days pre-operatively and with prednisone 150 mg. per day two to five days before transplantation. After operation the administration of these drugs was continued in high dosage. In addition 200 to 400  $\mu$ g. per day of intravenous actinomycin C, and local X-irradiation to the transplant, 150 r every other day for three or four doses, were given either prophylactically or for the treatment of rejection.

*Histological Studies.*—Sections were stained routinely with hæmatoxylin and eosin, periodic acid-Schiff reagent, Weigert's for elastic counterstained with hæmatoxylin and van Gieson, picro-Mallory 5, Martius yellow-scarlet-blue (Lendrum *et al.*, 1962), Mallory's phosphotungstic acid hæmatoxylin (PTAH) and methyl green pyronin. The Feulgen reaction and special stains such as Sudan 3 and Masson 44/41 (Lendrum *et al.*, 1962) were used when indicated.

### CASE REPORTS

**SD1.**—The recipient was a 40-year-old man, blood group A rhesus-positive, who was suffering from terminal uræmia due to chronic glomerulonephritis. The donor was a 20.9 kg. male baboon of blood type A. Heterotransplantation was carried out on 20th December 1963, and during the procedure the right kidney was ischaemic for twenty-nine minutes and the left for thirty-seven minutes. The baboon kidneys excreted 8.7 litres of urine in the first twenty-four hours and from then onwards urinary excretion was 2 to 4 litres per day. The blood urea nitrogen (BUN) which was 212 mg. per cent. just before operation, fell to 45 mg. per cent. and the endogenous creatinine clearance (CrCl) rose to 65 ml. per minute. Prophylactic actinomycin C and local X-irradiation were given. On the fifth, ninth, and sixteenth days pulmonary emboli occurred. Heparin therapy was begun after the second embolus; at the time of the third, as the thrombi seemed to be coming from the left calf, the femoral vein on that side was tied. However, the patient developed a pneumonia and died twenty-three days after renal transplantation.

Immediately before renal heterotransplantation the patient's blood pressure was 140/95 mm. Hg; afterwards he became normotensive and remained so until his death. At no time did he develop a clearly recognisable rejection episode, but some impairment of renal function was apparent terminally.

*Necropsy Findings.*—The pulmonary artery supplying the right lower lobe of the lung was occluded by a septic thrombotic embolus which lay astride the first bifurcation. A large part of that lobe was necrotic and infected producing an abscess; the remainder of the lobe was affected by confluent pneumonia. Early bronchopneumonia involved the remainder of the right lung and all lobes of the left lung. The responsible organisms were *E. coli* and *Ps. aeruginosa*. There was mild inflammation of the tail of the pancreas with some adjacent fat necrosis. The source of the emboli was not found.

*Heterotransplanted Kidneys.*—The right kidney was surrounded by 400 ml. of blood clot. Both kidneys were enlarged (right, 65 g.; left, 70 g.); normal baboons of the age and weight of those used in this study have kidneys which weigh from 16 to 41 g. each. The renal capsules stripped easily leaving cortical surfaces that were lightly speckled with pin-point haemorrhages. The cut surfaces of the kidneys bulged. All the vessels, including the anastomoses, were free from thrombus, even though the vessels on the right appeared to be compressed by the haematoma. The ureters were patent.

Microscopically the glomeruli were normal except for prominence of the parietal cells of Bowman's capsule (Fig. 1). There was patchy recent necrosis of the proximal convoluted tubules and the lumina contained casts which stained positively with PAS. The oedematous interstitium was heavily infiltrated with cells which were diffusely scattered throughout the cortex of both kidneys (Fig. 1). Many of these cells were plasma cells and small lymphocytes; about 10 per cent. were larger lymphoid cells with pyroninophilic cytoplasm, a large pale nucleus and prominent nucleolus (Fig. 2); some were eosinophils and a few were mononuclears showing erythrophagocytosis. Several of the infiltrating cells were in mitosis, and some were still within peritubular capillaries. Double or treble nuclei were often seen in the plasma cells. Occasional small interstitial haemorrhages were present. Several interlobular arteries were blocked with fibrin, platelets, and lymphocytes; in others there was slight fibrous intimal thickening and duplication of the internal elastic lamina. The latter change was also seen in three control baboons of comparable weight who had been in captivity for similar periods to those used in this study. Many peritubular capillaries had been destroyed. A few tiny focal infarcts were present in the superficial cortex.

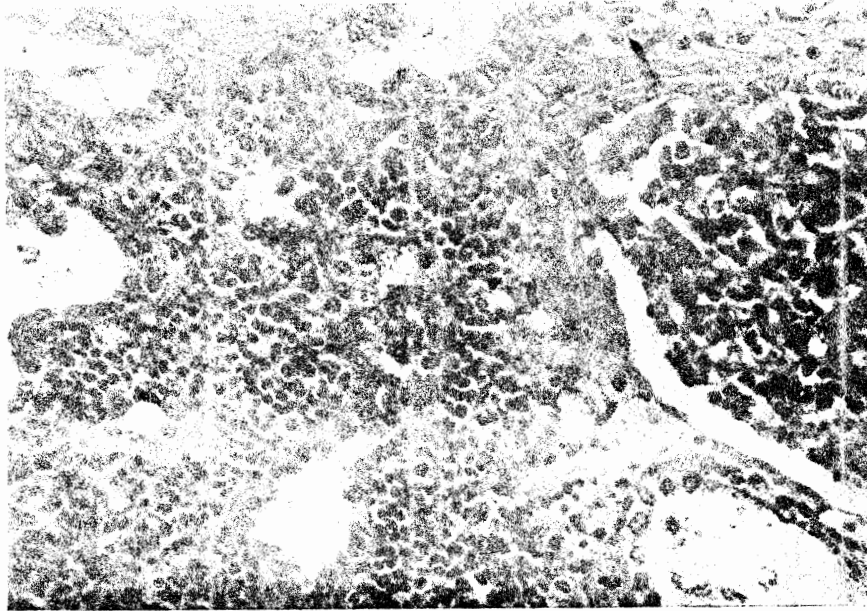


FIG. 1

Baboon renal heterotransplant from patient SD1 who died at twenty-three days as the result of a septic pulmonary embolus. This patient never experienced a definite rejection episode. The oedematous interstitium is heavily infiltrated with lymphoid and plasma cells. Note the swollen epithelial cells forming the parietal layer of Bowman's capsule. (H. & E.)  $\times 150$ .

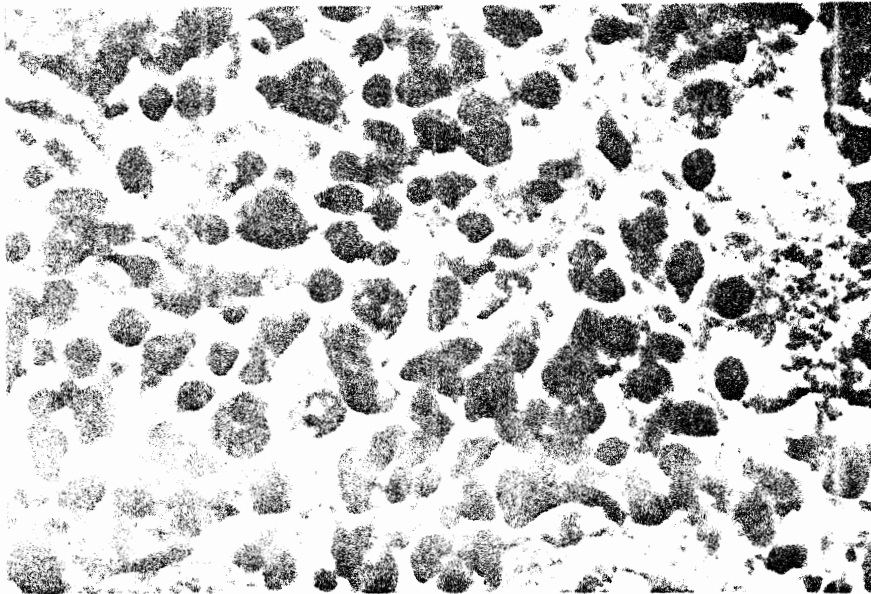


FIG. 2

High power view of heterotransplant from patient SD1. The cellular infiltrate is composed of small lymphocytes, plasma cells, larger pyroninophilic lymphoid cells and occasional eosinophils. (H. & E.)  $\times 550$ .

**SD1.**—The patient was a 46-year-old man, blood group O rhesus-negative, who was in terminal uræmia due to chronic glomerulonephritis. The donor was a 17.3 kg. male baboon of blood type B. Renal heterotransplantation was performed on 6th January 1964, with a renal ischaemia time of forty-four minutes. The baboon kidneys excreted 24.29 litres of urine in the first twenty-four hours, and the patient's BUN fell from 59 mg. to 18 mg. per cent. forty-two hours after transplantation. The CrCl ultimately rose to 117.7 ml. per minute. Three rejection episodes occurred. The first started at five days and was partially reversed by the administration of actinomycin C alone; the second started at nine days, was treated with actinomycin C and local X-irradiation, and was also partly reversed; the onset of the third was at fifteen days and this proved irreversible despite the use of actinomycin C and local X-irradiation. These rejection crises were similar to those seen in homotransplants in that at these times the urine volume, urinary sodium and chloride concentrations and the CrCl fell, whilst the BUN and serum creatinine rose. At these times the transplants were often swollen and tender. Early in this patient's course a septic embolus caused an infarct which later became a pulmonary abscess. Rupture of this abscess produced a bronchopleural fistula and an empyema which were treated at ten days by left lower lobectomy and lingulectomy.

Prior to heterotransplantation the patient's blood pressure was usually about 150/100 mm. Hg. Post-operatively chlorothiazide 1 g. per day was given and the blood pressure fell to normal levels and remained there until the onset of anuria when he again became hypertensive. The patient became anuric at twenty-five days and remained so until his death thirty-five days after renal heterotransplantation from uræmia and *Ps. aeruginosa* septicæmia.

*Necropsy Findings.*—There was fibrinous pericarditis and the heart was enlarged (520 g.) due to left ventricular hypertrophy. Confluent bronchopneumonia was present in both lungs due to *E. coli* and *Ps. aeruginosa*, and there was a septic infarct with a necrotic centre in the left upper lobe. The bone marrow was hypoplastic with depression of granulocytic precursors.

*Heterotransplanted Kidneys.*—Both kidneys were greatly enlarged (right, 180 g.; left, 150 g.) and their capsular surfaces were mottled with many large hæmorrhagic infarcts which on the cut surface extended deep into the medulla. The renal arteries and veins and their anastomoses with the iliac vessels were unobstructed and free from thrombus, but the blind pouch of baboon aorta contained laminated blood clot. The ureters were blocked by thrombus at their insertion into the bladder, and their walls were thickened and hæmorrhagic.

Microscopically much of the kidney was occupied by hæmorrhagic infarcts. Between these areas some of the glomerular tufts showed fibrinoid necrosis and there was extensive recent and rather older tubular damage with casts of cell debris and protein. Regeneration of tubular epithelium was occurring as witnessed by mitoses and new flattened basophilic cells. The very œdematous interstitium was infiltrated with the same sort of cells as were seen in SD1 but with a higher proportion of neutrophils and eosinophils. There were extensive hæmorrhages and some pools of fibrin. Fibrinoid necrosis of the walls of interlobular arteries and afferent arterioles was seen, and many of the interlobular arteries were blocked either by fibrin and platelet intimal deposits or by older fibrous intimal thickening. These changes were accompanied by multiplication of the internal elastic lamina in these vessels. There was some recent venous thrombosis.

**SD3.**—The patient was a 17-year-old man, blood group AB rhesus-positive, who was in terminal uræmia due to chronic glomerulonephritis. The donor was a 16.4 kg. male baboon of blood type B. Renal heterotransplantation was performed on 8th January 1964; the kidneys were ischaemic for 34.5 minutes. The baboon kidneys excreted 8.92 litres in the first twenty-four hours, and during the same period the BUN fell from 92 mg. to 67 mg. per cent. and the CrCl rose to 37 ml. per minute. A rejection episode started at five days but was partly reversed by local X-irradiation alone. Slow improvement occurred and by the eighteenth post-operative day the CrCl had risen to 55 ml. per minute, but the BUN remained elevated. A second rejection crisis started at the fiftieth day and was accompanied by swelling of the heterotransplants which produced massive œdema of the right lower leg. Partly because of this complication the baboon kidneys were removed sixty days after transplantation and replaced by a renal homotransplant. Before heterotransplantation the patient's blood pressure averaged 190/100 mm. Hg; immediately afterwards he was still hypertensive, but treatment with hydralazine, chlorothiazide and guanethidine slowly reduced the blood pressure to normal levels.

*Heterotransplanted Kidneys.*—Both kidneys were greatly enlarged (right, 140 g.; left, 120 g.); the capsules stripped easily leaving cortical surfaces that were mottled with large hæmorrhages and yellowish infarcts. The renal vessels, the ureters and renal pelvis were all unobstructed.

Microscopically the glomeruli were hypertrophied, there was some thickening of the tuft capillary basement membranes, the cells forming the parietal layer of Bowman's capsule were cubical, and the juxtaglomerular granules were prominent, and their numbers increased (Figs. 3 and 4). There was much patchy recent tubular necrosis, affecting particularly the proximal convoluted tubules; many nephrons had been completely destroyed, active epithelial regeneration was occurring in many as shown by mitoses and new flat basophilic cells. In many tubules there were casts of protein and blood; some contained lymphocytes. The interstitium was grossly œdematous and newly infiltrated with lymphocytes, plasma cells, larger pyroninophilic lymphoid cells, and eosinophils (Fig. 5). Unlike the infiltration in SD1 the cells were distributed in a patchy fashion. Occasional mitoses were seen. In some areas there were small collections of neutrophils. Cells were also present which had engulfed large masses of deoxyribonucleic acid (as shown by a positive Feulgen reaction after application of ribonuclease); they closely resembled those seen in disseminated lupus erythematosus (LE cells). Many peritubular capillaries had been

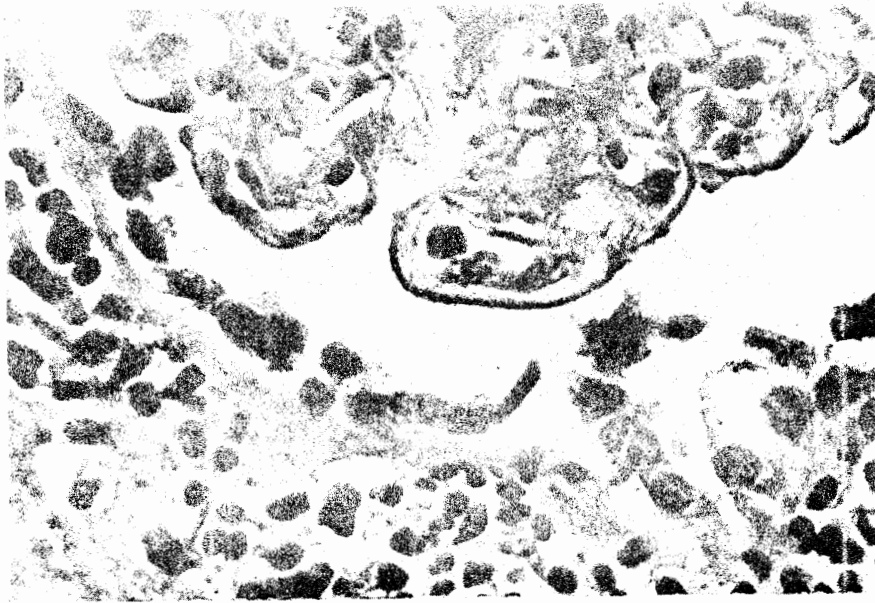


FIG. 3

Baboon renal heterotransplant removed at sixty days from patient SD3 who was in rejection for the second time. There is some thickening of the glomerular capillary basement membranes, the parietal cells lining Bowman's space are swollen and infiltrating host cells are present in the interstitium. Some peritubular capillaries are disrupted. (H. & E.)  $\times 450$ .

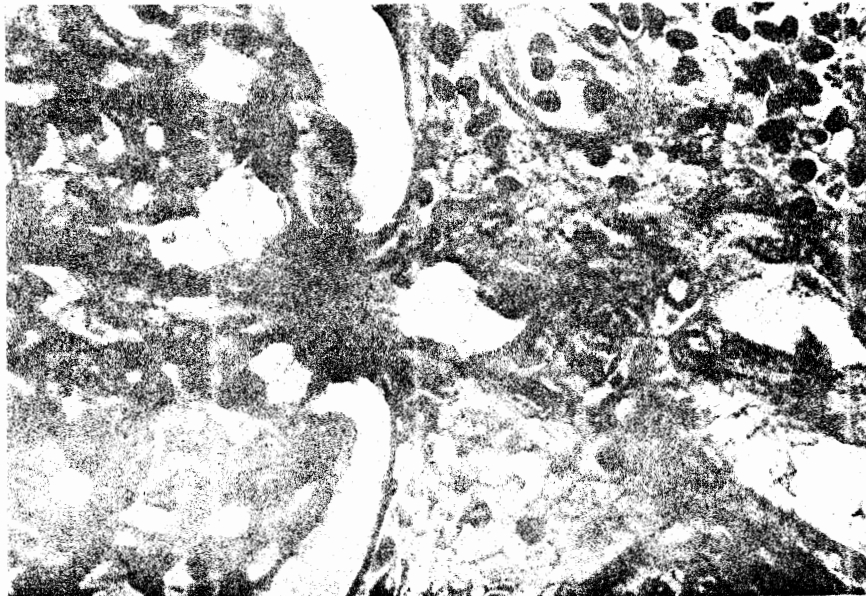


FIG. 4

Renal heterotransplant from patient SD3. The juxtaglomerular cells have vacuolated cytoplasm and contain an increased number of PAS-positive granules. (Periodic acid-Schiff.)  $\times 450$ .

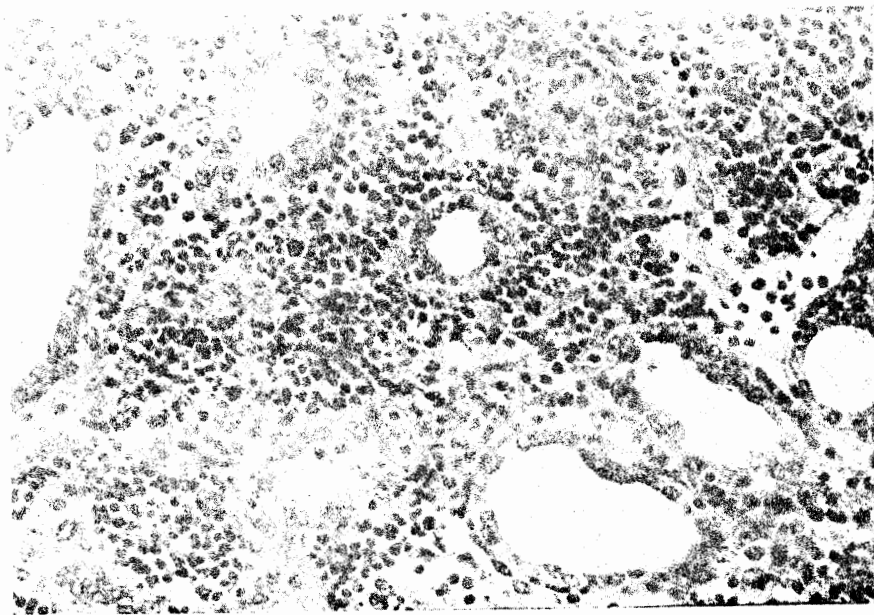


FIG. 5

Renal heterotransplant from patient SD3. The very oedematous interstitium is heavily infiltrated with plasma cells, eosinophils, and lymphoid cells. There is widespread tubular damage. (H. & E.)  $\times 225$ .

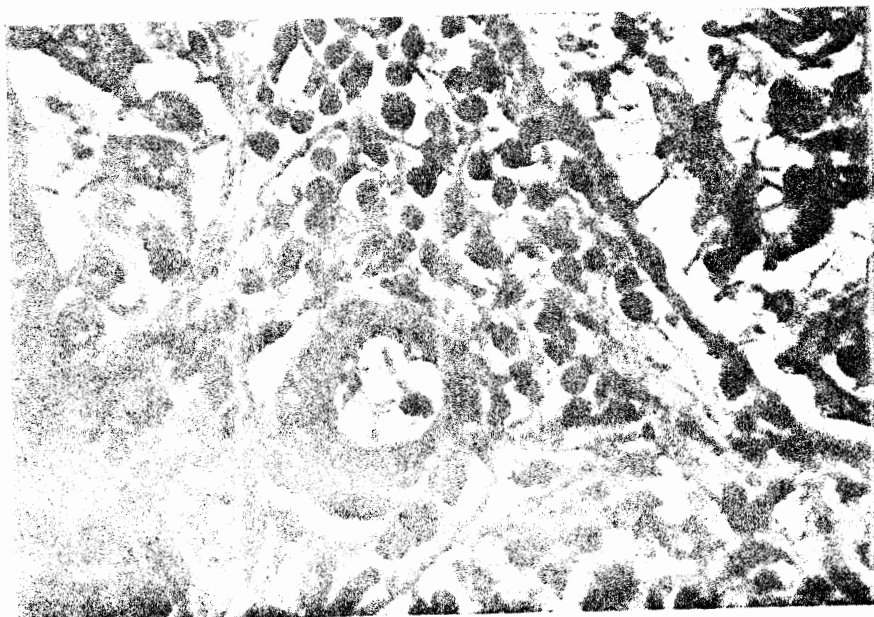


FIG. 6

Baboon kidney transplant from patient SD3. An arteriole shows marked fibrinoid necrosis of its wall. The surrounding interstitium is oedematous and infiltrated with lymphoid and plasma cells. (H. & E.)  $\times 450$ .

arteries (Fig. 6). Some of the afferent arterioles and interlobular arteries showed fibrinoid necrosis of their walls. Fibrinoid deposition of the internal elastic lamina, foam and platelet deposition on the intima was present in other interlobular arteries and in several had progressed to complete obliteration of the vessel. These vascular changes were accompanied by patchy infarction and many interstitial hemorrhages.

**SD3.**—The patient was an 18-year-old man, blood group B rhesus-negative, who was in terminal uræmia due to chronic glomerulonephritis. The donor was a 24.8 kg. male baboon of blood type B. Renal heterotransplantation was performed on 11th January 1964, with an ischemia time of twenty-nine minutes. The baboon kidneys excreted 20.25 litres of urine in the first twenty-four hours, and during the same period the patient's BUN fell from 132 mg. to 62 mg. per cent. and the CrCl rose to 58 ml. per minute. At the eighth day a rejection episode started which was treated with actinomycin C and two courses of local X-irradiation. Some improvement was obtained but a second rejection crisis occurred at thirty-seven days. This also was treated with actinomycin C and local X-irradiation, but with little effect, and forty-nine days after transplantation the baboon kidneys were removed and replaced by a renal homotransplant. Before heterotransplantation the patient's blood pressure averaged 150/130 mm. Hg. Afterwards the pressure fell to an average of 170/100 mm. Hg, but improved no further despite treatment with hydralazine, reserpine, chlorothiazide, and guanethidine.

**Heterotransplanted Kidneys.**—Both kidneys were enlarged (right, 96 g.; left, 92 g.) and their subcapsular surfaces were irregularly mottled with large hemorrhages and yellowish infarct. The renal vessels and their anastomoses were free from thrombus, and both ureters were patent.

Microscopically there was slight thickening of the glomerular capillary basement membranes, fibrinoid necrosis had extended into a few tufts from the walls of affected afferent arterioles and there was general hypertrophy of the proximal tubular apparatus. Patchy tubular necrosis was present but this was far less prominent and widespread than in SD3. A few protein casts were present. The interstitium was oedematous and there was a diffuse, but light, infiltration with plasma cells, larger pyroninophilic cells and lymphocytes. Two or three nuclei were common in the plasma cells. Many of the cells were still within peritubular capillaries and destruction of these vessels was widespread. Foci of hemorrhage were common. Many arterioles and some interlobular arteries showed fibrinoid necrosis of their walls accompanied by cellular infiltration giving a true arteritis (Fig. 7). Fibrino-platelet and fibrous intimal thickening together with rupture of the internal elastic lamina were seen in several interlobular and arcuate arteries. The fibrous intimal lesions were much more severe than any encountered in the three control animals (Fig. 8). Some vessels were completely obstructed. Focal infarcts were common.

**SD5.**—The patient was a 35-year-old man, blood group O rhesus-negative, who was in terminal uræmia secondary to chronic pyelonephritis. The donor was a 15.7 kg. female baboon of blood type AB. Renal heterotransplantation was performed on 14th January 1964, with a renal ischemia time of 27.5 minutes. The baboon kidneys excreted 12.35 litres of urine in the first twenty-four hours, and during the same period the patient's BUN fell from 81 mg. to 48 mg. per cent. and the CrCl rose to 34 ml. per minute. Rejection started at four days and was treated moderately successfully with local X-irradiation. A second rejection crisis started at seven days and was similarly treated with actinomycin C and increased doses of prednisone. This was ineffective and anuria occurred on the tenth day after transplantation. The patient died from uræmia nine days later.

Before heterotransplantation the patient's blood pressure averaged 160/100 mm. Hg; afterwards his pressure remained just as high despite treatment with reserpine, chlorothiazide,  $\alpha$ -methyl-dopa and hydralazine.

**Necropsy Findings.**—There was a sterile fibrinous pericarditis and a severe oesophagitis due to *Candida albicans*. The lungs contained areas of confluent bronchopneumonia.

**Heterotransplanted Kidneys.**—Both were greatly enlarged (right, 115 g.; left, 110 g.), uniform purplish-red and it was not possible on the cut surface to differentiate between cortex and medulla. The calyces, pelves, and ureters were filled with clotted blood. The main renal vessels and their anastomoses were free from ante-mortem thrombus.

Microscopically there was widespread hemorrhagic infarction. Many of the interlobular arteries were thrombosed and several showed rupture of their internal elastic layer. Fibrinoid necrosis of vessel walls was common.

**SD6.**—The patient was a 35-year-old man, blood group O rhesus-positive, who was in terminal uræmia due to chronic glomerulonephritis. The donor was a 16.4 kg. female baboon of blood type AB. Renal heterotransplantation was performed on 17th January 1964, with a renal ischemia time of thirty-seven minutes. The baboon kidneys excreted 24.0 litres of urine in the first twenty-four hours, and during the same period the patient's BUN fell from 111 mg. to 55 mg. per cent. and the CrCl rose to 61 ml. per minute. Three rejection episodes occurred. The first started at four days and was successfully treated with local X-irradiation; the second started at eighteen days and was less successfully treated with actinomycin C and local X-irradiation; the onset of the third was at forty-eight days but by this time pneumonia with multiple abscesses had developed, became uncontrollable and the patient died forty-nine days after transplantation. The clinical course was complicated by herpes zoster which appeared at twenty-three days. Before heterotransplantation the patient's blood pressure was 190/100 mm. Hg; afterwards this fell to 150/80 mm. Hg with the use of reserpine, hydralazine, and chlorothiazide.

**Necropsy Findings.**—There was severe bilateral pneumonia due to *Klebsiella aerobacter*.

**Heterotransplanted Kidneys.**—These were enlarged (right, 80 g.; left, 80 g.) and the subcapsular surfaces of both showed pale yellow infarcts and many irregular hemorrhages measuring 0.2 to 0.5 cm. in diameter. The main renal vessels and their anastomoses were free from thrombus and the ureters were patent.



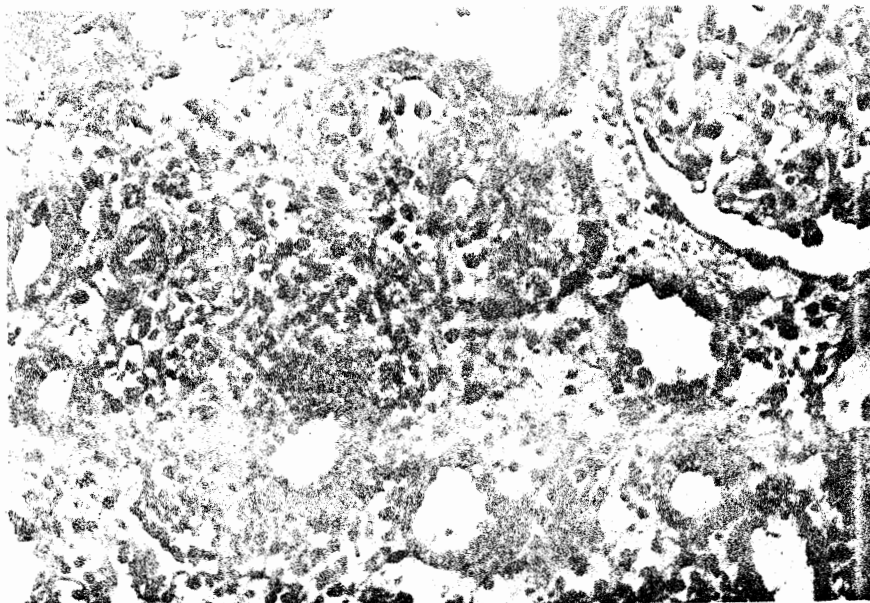


FIG. 7

Baboon renal heterotransplant removed at forty-nine days from patient SD4 who was in rejection for the second time. An interlobular artery shows fibrinoid necrosis and cellular infiltration of part of its wall accompanied by rupture of the internal elastic lamina. The interstitium is edematous and there is a focus of infiltrating host cells. (Weigert's elastic ■ van Gieson.)  $\times 265$ .

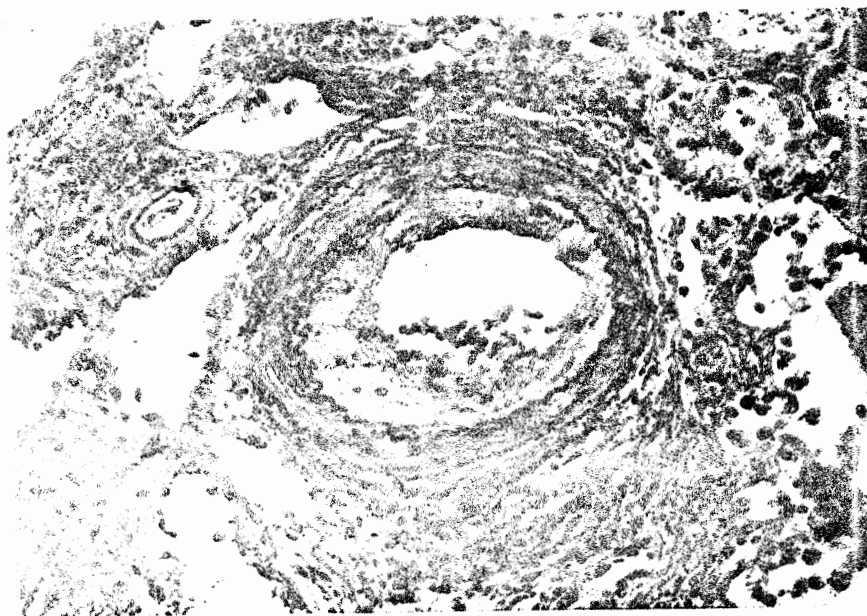


FIG. 8

Baboon renal heterotransplant from patient SD4. An arcuate artery shows fibrous intimal thickening and some slight elastic increase. (Weigert's elastic ■ van Gieson.)  $\times 265$ .

Microscopically, away from the infarcts the glomeruli were normal. There was widespread recent tubular necrosis with casts of protein and of blood in the lumens. Evidence of regeneration of tubular epithelium was also conspicuous. The interstitium was slightly oedematous and contained large areas of haemorrhage and a moderately heavy focal cellular infiltration. This differed a little from that seen in the other cases in being composed mainly

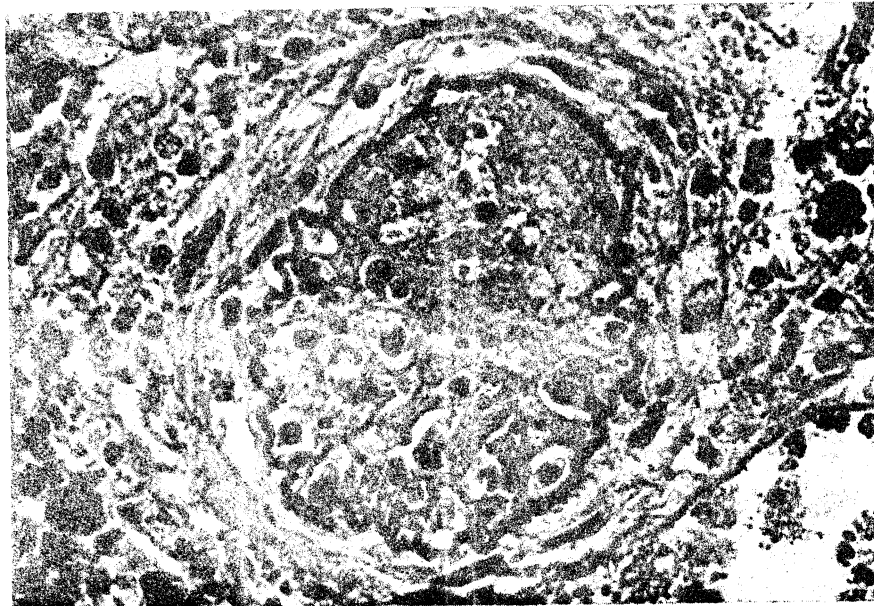


FIG. 9

Renal heterotransplant from patient SD6 who died at forty-nine days whilst in a third rejection crisis. An interlobular artery is completely blocked by fibrin, platelets and a few lymphoid cells. (H. & E. stain)  $\times 450$ .

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of small lymphocytes with fewer plasma cells and the larger type of pyroninophilic cells. Eosinophils were scanty. Many peritubular capillaries had been destroyed and there was fibrinoid necrosis of the walls of afferent arterioles and interlobular arteries. Several of these latter vessels were blocked by fibrin and platelet deposits on the intima (Fig. 9). Some small veins were thrombosed. These vascular changes were accompanied by many focal infarcts.

#### DISCUSSION

All the heterotransplanted baboon kidneys were enlarged. This was mainly due to interstitial oedema and was least apparent in the patient (SD1) who never experienced a clinical episode of rejection. Human homotransplanted kidneys are also usually swollen during rejection for the same reason (Porter *et al.*, 1965). However, whereas homotransplanted kidneys may be speckled with petechiae, they never show the dramatic blotchiness due to large haemorrhages and infarcts that were seen in the baboon heterotransplants. Haemorrhages were also a feature of two rhesus monkey kidneys which were transplanted into a woman, but in the account of this case no mention is made of infarcts (Reemtsma *et al.*, 1964 *a*). The chimpanzee-to-man renal heterotransplants seem to have shown only the range of gross changes that are customarily met with in human renal homotransplants (Reemtsma *et al.*, 1964 *c*).

Microscopically the heavy cellular infiltration was reminiscent of that seen in some untreated canine renal homotransplants, and it would appear that this was also a feature of the rhesus monkey kidneys that were heterotransplanted into a woman (Reemtsma *et al.*, 1964 *a*). Adequately treated human renal homotransplants rarely show anything approaching this degree of cellular invasion (Porter *et al.*, 1965), and a much milder infiltration seems also to be the rule in chimpanzee

renal heterotransplants (Reemtsma *et al.*, 1964 *c*). Eosinophils were common in the baboon kidneys. "LE" type cells were found and erythrophagocytosis was seen. These are not features of human renal homotransplants (although infiltration of canine kidneys by eosinophils does sometimes occur), nor have they been mentioned in the descriptions of the other simian renal heterotransplants. Mitoses were occasionally seen in SD1, an unusual finding in treated human renal homotransplants (Porter *et al.*, 1965). Although bizarre plasma cells with up to three nuclei are sometimes seen in all treated renal transplants, they seemed particularly plentiful in the baboon kidneys.

Just as in other simian renal transplants (Reemtsma *et al.*, 1964 *a, c*), canine homotransplants (Porter *et al.*, 1964) and human homotransplants (Porter *et al.*, 1965) from treated recipients in a rejection phase, fibrinoid necrosis of the walls of afferent arterioles and interlobular arteries was frequent. However, there was a tendency for the necrotic walls to be infiltrated with lymphoid and sometimes granulocytic cells producing a histological picture similar to that seen in acute polyarteritis nodosa. This is not usually a feature of rejecting human renal homotransplants (Porter *et al.*, 1965). All the baboon kidneys received one or more courses of local X-irradiation and, although the blood pressure of humans and baboons is similar, three of the pairs of baboon kidneys were exposed to a high blood pressure in the human recipient. These facts taken in isolation would make it difficult to support any claim that the vasculonecrotic lesions had arisen on an immunological basis. However, when the same type of lesion is known also to occur in both treated and untreated human and canine homotransplants, even where the recipient remains normotensive, it seems more reasonable to suggest an antigen-antibody reaction as the possible cause. The arguments against the arterial and arteriolar lesions encountered in human renal homotransplants being due to hypertension, X-irradiation or the administration of various drugs, have been given elsewhere (Porter *et al.*, 1964, 1965) and the largely circumstantial evidence pointing to an immunological cause has also been considered (Porter *et al.*, 1964). In the cases of chimpanzee-to-man renal heterotransplantation there was some suggestion of a rise in circulating cytotoxic antibody occurring during rejection, a time when vasculonecrotic lesions were also being found (Reemtsma *et al.*, 1964 *c*).

Two of the baboon renal heterotransplants showed thickening of the glomerular capillary basement membranes by PAS-positive material. As there was evidence of absorption of anti-baboon erythrocyte heteroagglutinins by the renal cells (Starzl *et al.*, 1964) this thickening could just possibly have been due to deposition of antigen-antibody complex.

### SUMMARY

Six baboon-to-man renal heterotransplants, each consisting of a pair of kidneys, were examined. Two had been removed from their recipients at forty-nine and sixty days after transplantation because of the ever-increasing doses of immunosuppressive drugs needed to control rejection; the other four pairs of kidneys were examined after death of the recipients at nineteen, twenty-three, thirty-five, and forty-nine days.

All the kidneys were enlarged. On the subcapsular surfaces of one pair there were petechiae; four were mottled with irregular haemorrhages and infarcts; one pair had undergone almost complete haemorrhagic infarction.

The transplants were heavily infiltrated with plasma cells, lymphocytes, large pyroninophilic lymphoid cells and eosinophils. Mitoses, "LE" cells and erythrophagocytosis were seen. Associated with this infiltration there was rupture of peritubular capillaries, interstitial oedema and widespread tubular damage.

Fibrinoid necrosis of the walls of arterioles and interlobular arteries, with narrowing and obstruction of some vessels by fibrin and platelet deposits on the intima were common in all except one pair of kidneys. Associated with these vascular lesions there were focal infarcts and extensive interstitial haemorrhages.

All the histological changes were more severe than those seen either in treated human renal homografts or in a comparable series of chimpanzee-to-man renal heterografts where cellular infiltration was slight and vascular lesions only present at the height of rejection.

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