Renal Heterotransplantation in Man *

KEITH REEMTSMA, M.D., MED. SC. D., B. H. MCCRACKEN, M.D., M.R.C.P., J. U. SCHLEGEL, M.D., PH.D., M.A. PEARL, M.D., C. W. PEARCE, M.D., C. W. DEWITT, PH.D., P. E. SMITH, M.D., R. L. HEWITT, M.D., R. L. FLINNER, M.D., OSCAR CREECH, JR., M.D.

From the Departments of Surgery, Medicine, Microbiology and Pathology, Tulane University School of Medicine, and the Tulane Surgical Service, Charity Hospital, New Orleans

THE CONCEPT of cross-species transplantation has intrigued the mind of man for as long as he has recorded his myths and his history. Daedelus, who grafted bird feathers to his arms, was perhaps the first to transplant across the species barrier successfully; a similar experiment by his son, Icarus, ended in acute graft rejection when he flew too close to the sun.[1]

Scientific reports on renal heterotransplantation into man appeared early in this century. In 1905 Princeteau [2] inserted slices of rabbit kidney into a nephrotomy on a child with renal insufficiency. "The immediate results were excellent," he wrote. "The volume of urine increased; vomiting stopped. . . . On the 16th day the child died of pulmonary congestion . . ." (Fig. 1). In the following year, 1906, Jaboulay [3] on two occasions attempted renal heterotransplantation into man using vascular anastomoses. The heterografts, one from a pig and another from a goat, were inserted into the antecubital spaces. Neither graft functioned, and failure was attributed to vascular thromboses (Fig. 2).

In 1910 Unger [4] described his attempt at transplantation of kidneys from a non-human primate into man. The patient died 32 hours after transplantation, and autopsy showed venous thromboses (Fig. 3). Neuhof,[5] in 1923, attempted treatment of a patient with mercury bichloride poisoning by renal heterotransplantation. When he was unable to obtain a human kidney, he transplanted the kidney of a lamb into the patient. The patient died nine days later, but Neuhof was not totally discouraged. He

V. **Greffe rénale.** Record I ✓ first [illegible]

M. PRINCETEAU présente les deux reins d'un enfant de son service et fait part à la Société de l'observation suivante :

Un enfant atteint d'ostéomyélite de l'extrémité supérieure du fémur droit ayant fusé dans l'os iliaque entre à l'hôpital des Enfants dans un état très grave, ayant de l'albumine dans les urines et un anasarque très marqué. Immédiatement il fit une grande incision, nettoya le foyer principal et après quatre interventions successives l'état de l'enfant s'était amélioré. Subitement, en fin août, cet enfant fit de la paralysie faciale et un œdème généralisé, vomissant tout ce qu'il prenait et urinant à peine 20 grammes de liquide par jour.

Devant de si graves symptômes, M. Princeteau fit une néphrotomie à gauche et inclut dans le rein deux tranches de rein d'un lapin. Les résultats immédiats furent excellents, l'urine augmenta, les vomissements cessèrent; quinze jours après l'intervention la quantité d'urine était de un litre par jour. Le seizième jour, l'enfant succombait à une congestion pulmonaire.

A l'autopsie, on trouva les deux reins gros et blancs, un foie muscade et la rate extrêmement ramollie. Quant aux inclusions de tranches de rein de lapin, elles paraissaient greffées, mais un examen histologique est nécessaire pour montrer la nature de l'adhérence. J. M.

FIG. 1. Princeteau, M.: Greffe rénale. J. Méd. Bordeaux, 26:549, 1905.

* Presented by title before the American Surgical Association Meeting, Hot Springs, Virginia, April 1–3, 1964.

This study was supported in part by Office of Naval Research Grant No. Nonr-475-07 and U.S.P.H.S. Grants HE-09178-01 and AM-5911-03 NTN.

wrote "(this case) proves, however, that a heterografted kidney in a human being does not necessarily become gangrenous and the procedure is, therefore, not necessarily a dangerous one, as had been supposed. It also demonstrates that thrombosis or hemorrhage at the anastomosis is not inevitable. I believe that this case report should turn attention anew . . ." (Fig. 4).

However, scientific interest in transplantation declined when the immunologic basis of the rejection process was established. With the demonstration of effectiveness of immunosuppressive drugs,[6-11] there has been renewed interest in transplantation. An accelerated effort in renal homotransplantation has been accompanied by problems in procuring organs. Ethical consider-

BULLETIN.

BULLETIN DU LYON MEDICAL

GREFFE DE REINS AU PLI DU COUDE PAR SOUDURES ARTÉRIELLES ET VEINEUSES.

J'ai pratiqué la greffe rénale par sutures vasculaires, deux fois, le 24 janvier et le 9 avril de cette année; je me proposais d'établir une suppléance fonctionnelle pour la sécrétion urinaire, en installant un rein étranger mais sain, pouvant venir en aide aux organes naturels qui étaient atteints de maladies incurables.

La première fois c'était chez une femme de 48 ans, brightique, présentant une forte hypertension, avec céphalalgie, diminution de la vue et de l'ouïe, et qui n'émettait par jour que 500 cc. environ d'une urine albumineuse et ne contenant que 4 gr. d'urée. Un rein de porc qui avait été tué trois heures avant, mis immédiatement après son extraction dans du sérum artificiel tiède, fut anastomosé par ses vaisseaux aux vaisseaux du pli du coude de la malade. C'était le rein gauche et le pli du coude gauche. Une incision longitudinale, faite suivant la direction de l'artère humérale à ce niveau, mit à nu d'abord la veine médiane céphalique qui fut disséquée, puis profondément l'artère avant sa bifurcation. Une bande d'Esmarch avait été placée à la racine du bras, une ligature ayant été mise sur la portion des vaisseaux qui devait être leur bout périphérique, ceux-ci furent sectionnés, montrant leur bout central vide de sang. Alors le rein fut fixé dans cette plaie, la face antérieure en avant et non recouverte, l'uretère occupant le plan profond et dirigé vers le bord interne du pli du coude. L'artère rénale fut soudée au bout central de l'artère humérale, la veine rénale au bout central de la veine médiane céphalique, de la façon suivante: chacun des vaisseaux de la malade était introduit dans la lumière d'une virole métallique, de dimensions appropriées, puis retournée à l'extrémité de cette virole jusqu'à une rigole circulaire où il était fixé par un fil circulaire; la paroi interne du vaisseau, endartère ou endoveine, devenait ainsi externe et pouvait être coaptée avec la

FIG. 2. Jaboulay, M.: Greffe de reins au pli de coude par soudures artérielles et veineuses. Lyon Med., 107:575, 1906.

Aus der experimentell-biologischen Abteilung des Königl. pathologischen Instituts der Universität Berlin und aus der Privatklinik Dr. Ernst Unger.

Nierentransplantationen.

(II. Mitteilung.)

Von

Dr. Ernst Unger-Berlin.

(Nach einem am 2. März 1910 in der Berliner medizinischen Gesellschaft gehaltenen Vortrage.)

M. H.! Im April 1909 hatte ich mir erlaubt, Ihnen über Nierentransplantationen zu berichten. Carrel und Guthrie ge-

FIG. 3. Unger, E.: Nierentransplantationen. Klin. Wschr., 47:573, 1910.

THE TRANSPLANTATION OF TISSUES

BY

HAROLD NEUHOF, M.D.

INSTRUCTOR IN SURGERY, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS; ASSOCIATE SURGEON TO BELLEVUE, MOUNT SINAI, AND MONTEFIORE HOSPITALS; ATTENDING NEUROLOGICAL SURGEON, CENTRAL AND NEUROLOGICAL HOSPITAL

WITH THE COLLABORATION OF

SAMUEL HIRSHFELD, M.D.

ADJUNCT SURGEON, MOUNT SINAI HOSPITAL

SURGICAL MONOGRAPHS

UNDER THE EDITORIAL SUPERVISION OF

DEAN LEWIS, A.B., M.D.
PROFESSOR OF SURGERY, RUSH MEDICAL COLLEGE

EUGENE H. POOL, A.B., M.D.
ATTENDING SURGEON, NEW YORK HOSPITAL

ARTHUR W. ELTING, A.B., M.D.
PROFESSOR OF SURGERY, ALBANY MEDICAL COLLEGE

D. APPLETON AND COMPANY
NEW YORK LONDON
1923

FIG. 4. Neuhof, H.: Transplantation of Tissues. New York: Appleton and Co., 1923, p. 260.

TABLE 1

	Donor			Recipient	
Name	ABO	Rh	MN	Patient	ABO
Adam	$A_{1,2}$	ccD-	M	1. J. D.	A_1
Dave	O	ccD-	MN	2. P. R.	O
Butch	O	ccD-	*	3. E. P.	B
Topeka	$A_{1,2}$	ccD-	M	4. D. P.	O
Fred	O	ccD-	MN	4. D. P.	O
Vickie	A_2	ccD-	M	5. A. A.	A_2
James	A_2	ccD-	*	6. O. S.	A_1

* Not done.

ations have posed difficult problems, particularly in the use of volunteer human donors. The use of organs harvested from human cadavers has depended on rapid transfer or preservation and has imposed restrictions of supply, selection and scheduling.

In our renal homografting program we had increasing difficulty obtaining donor organs. Attempts to use cadaveric kidneys met with no prolonged success, and the supply of expended kidneys was inadequate. We were reluctant to press the use of volunteer humans for ethical, scientific and legal reasons.

As this impasse was developing we decided to explore the use of non-human sources for clinical renal transplantation. This decision was prompted, in part, by clinical urgency. Additionally, a regional primate center in this vicinity brought scientists experienced in primatology. Furthermore, an active program in transplantation immunology had been developed to give an added base to the study.

The fact that no significant, sustained success had accompanied any previous attempt [2-5, 12, 13] at renal heterotransplantation into man was disquieting but hardly conclusive that failure was inevitable. Much recent evidence had suggested that graft-rejection is not always a simple, all-or-none process, but rather is a spectrum of phenomena, varying from organ to organ and species to species. Furthermore, the pessimism which has beclouded heterotransplantation had been derived largely from skin-grafting studies between widely disparate species. It seemed unwarranted to project these findings into the field of renal transplantation among primates, one of whom is man.

Our basic conjecture was that kidneys from non-human sources closely related to man would respond similarly to human kidneys following transplantation into man. The problem of more strenuous immune suppression was balanced against the advantages in the use of a non-human donor.

In practice, all patients were terminal uremics, maintained on dialysis, who were presented the following alternatives:

1) Supporting treatment only, 2) Homograft from a human volunteer, with the word "volunteer" defined in the strictest sense, 3) Cadaveric homograft, if and when available, or 4) Heterograft.

The risks, the uncertainties, the experimental nature of the work were discussed with the patients and their families. If they chose to procede with transplantation and had no volunteer donor, a search was made for a cadaveric kidney. If no suitable cadaver kidney became available in a stated period of time, a heterograft was used, with the patient's understanding and consent.

The chimpanzee was selected as the donor in heterografting studies for several reasons. This species is considered taxonomically closely related to man. The range of size of chimpanzees approximates that of man, a factor which might have significance in the transplantation of other organs in addition to kidneys. Furthermore, renal function of chimpanzees corresponds closely to that of man.[14] Additionally, chimpanzees have been found to be of blood types A and O,[15] thereby offering the possibility of the *universal donor* from the standpoint of blood groups.

Case Reports

Between November 5, 1963 and February 10, 1964 six patients received renal heterotransplants from chimpanzees. All patients were in terminal uremia necessitating dialysis and all patients received pre-transplantation treatment of azathioprine, actinomycin C and steroids. Selection of the donor was based on body size and blood typing of donor and recipient (Table 1). In each instance the donor received general endotracheal anesthesia, with monitoring of blood pressure, electrocardiogram and body temperature. Creatinine clearance was determined in each donor. At moderate hypothermia (about 30° C.) the entire renal complex, including both kidneys and ureters, aorta, and vena cava, was removed *en bloc* after anticoagulation and was irrigated. Patients were prepared simultaneously by extraperitoneal exposure of the external iliac artery and vein. In each instance the aorta and vena cava of the graft were anastomosed to the recipient's external iliac artery and vein, respectively, in an end-to-side fashion (Fig. 5). The periods of ischemia, from the time of vessel clamping in the donor until blood flow was restored through the graft in the recipient, varied from 36 to 43 minutes. All patients received postoperative azathioprine, actinomycin C, steroids and x-radiation to the transplant.

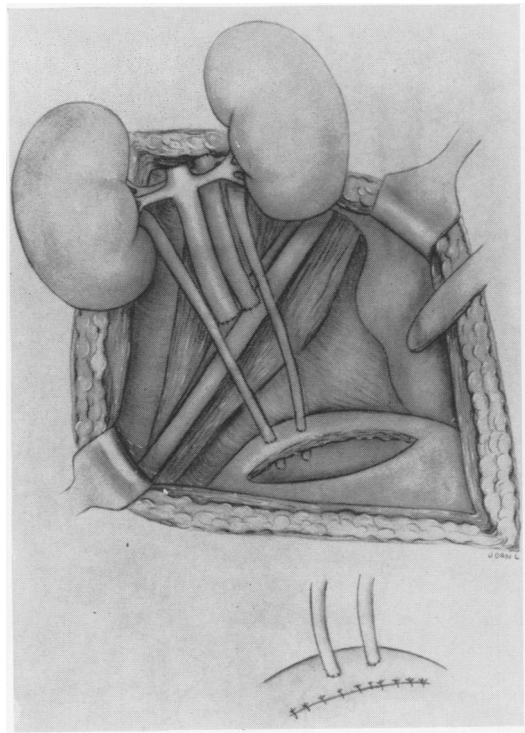


FIG. 5. Artist drawing of the operative field. The renal complex from the donor is implanted into the extra-peritoneal space in the recipient. The ends of the donor aorta and the vena cava are anastomosed to the sides of the external iliac artery and vein, respectively. The ureters are implanted into the bladder through sub-mucosal tunnels.

Case 1. This 43-year-old former dock worker with a history of hypertension since 1957, was admitted to the Veterans Administration Hospital, New Orleans, in 1959. Renal biopsies showed nephrosclerosis and chronic glomerulonephritis. He was treated with dietary management, including salt restriction. He was readmitted in June, 1963 because of progressive uremia, hypertension, and congestive heart failure. Laboratory studies included the following: BUN, 240 mg.%, creatinine, 14 mg.%, and creatinine clearance 8 ml./min. There was no improvement with dietary management, and peritoneal dialysis was required.

On November 5, 1963 he received a renal heterograft. During the first 14 hours after transplantation the urinary output was 6,700 cc. The BUN which was 112 mg.% on the day of operation, decreased to 39 mg.% by the fourth day following transplantation. The creatinine which was 11.2 mg.% on the day of operation fell to 1.5 mg.% 48 hours after transplantation. Four days after transplantation threatened rejection occurred but was reversed following local irradiation to the graft and increased doses of immunosuppressive drugs (Fig. 6). His early course has been reported previously in detail.[16] Function of the graft was confirmed by renograms, scans and intravenous urogram (Fig. 7).

On December 18th he was allowed to leave the hospital because he was asymptomatic and had normal renal function. He was readmitted on December 20th with a temperature of 39.4° C. and radiographic evidence of an infiltrate in the right middle lobe with pleural effusion. Culture of the sputum revealed *Aerobacter aerogenes*. The dosage of azathioprine was lowered because of leukopenia, but renal function continued satisfac-

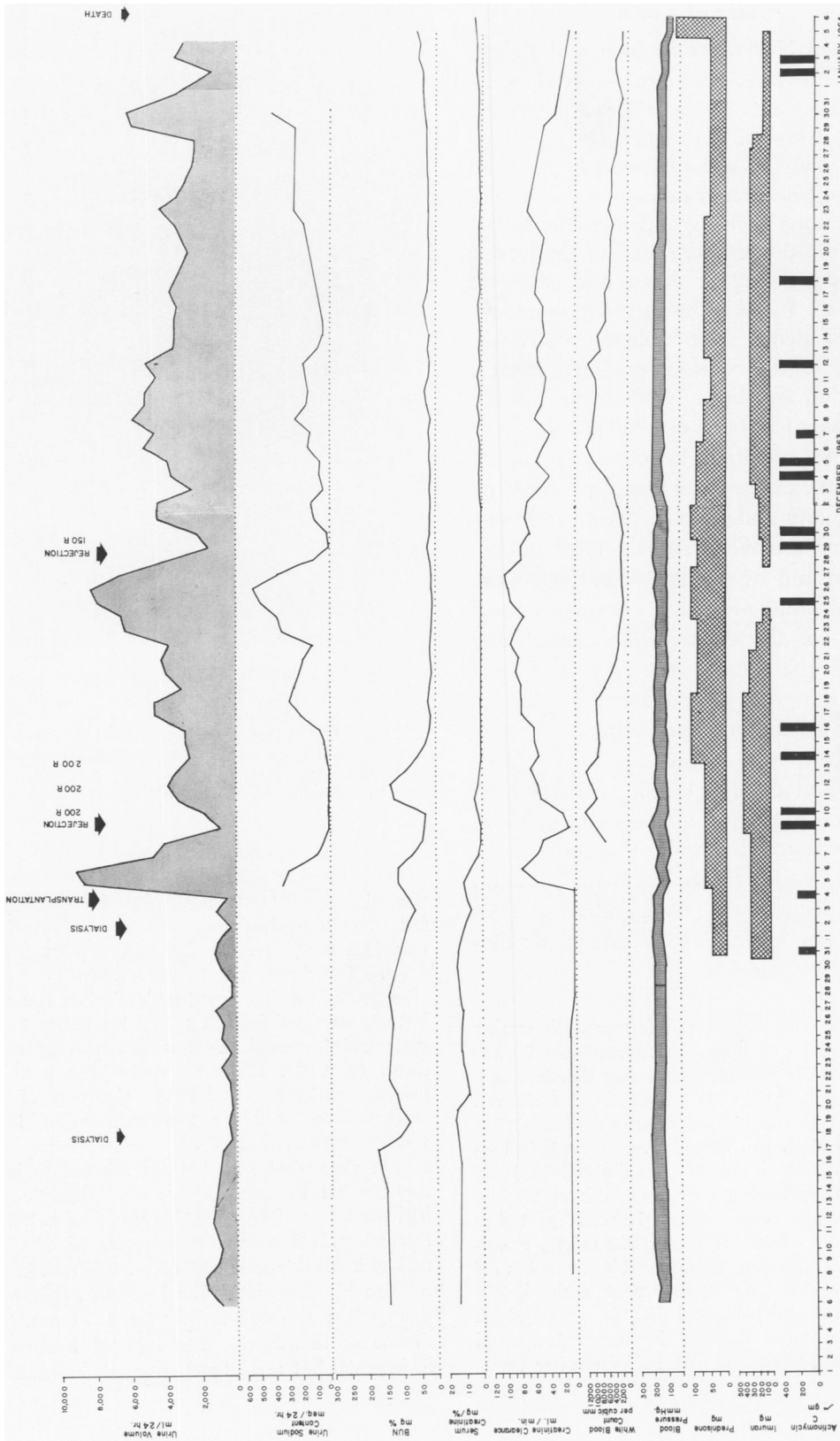


FIG. 6. Chart of Case 1 illustrating certain clinical features, laboratory studies, and drug treatment.

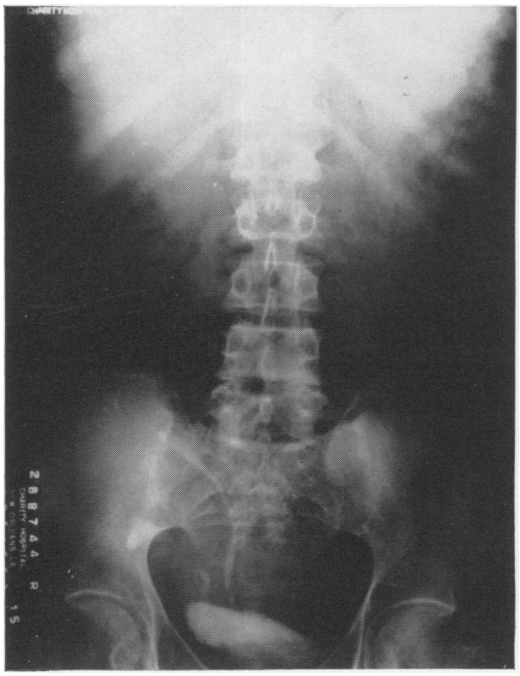


FIG. 7. Intravenous urogram in Case 1 performed ten days following transplantation. Film demonstrates contrast material in calyces of both transplanted kidneys and in both ureters.

tory. The patient's condition later deteriorated rapidly and he died 63 days after transplantation, following a period of shock apparently due to sepsis.

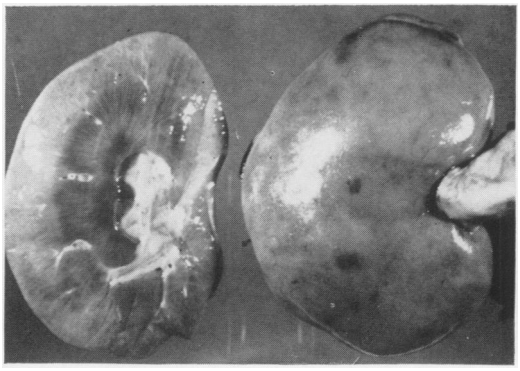


FIG. 8. Photograph of transplanted kidneys in Case 1. Arterial and venous anastomoses were patent.

Autopsy showed acute bronchopneumonia, right lower lobe; acute tracheobronchitis; resolving abscess, right middle lobe. The transplanted kidneys showed acute tubular necrosis, consistent with shock; there was no cellular infiltrate or changes in the blood vessels (Fig. 8, 9).

Serial renograms (Fig. 10) demonstrated a progressive delay in the appearance of the peak of uptake. Changes in the renogram, however, were not correlated with biochemical changes in renal function.

Hemagglutination studies (Fig. 11) demonstrated a precipitous rise in titer beginning on the fourth day following transplantation. This titer fell to pre-transplantation levels at the end of one month and remained at this level throughout the

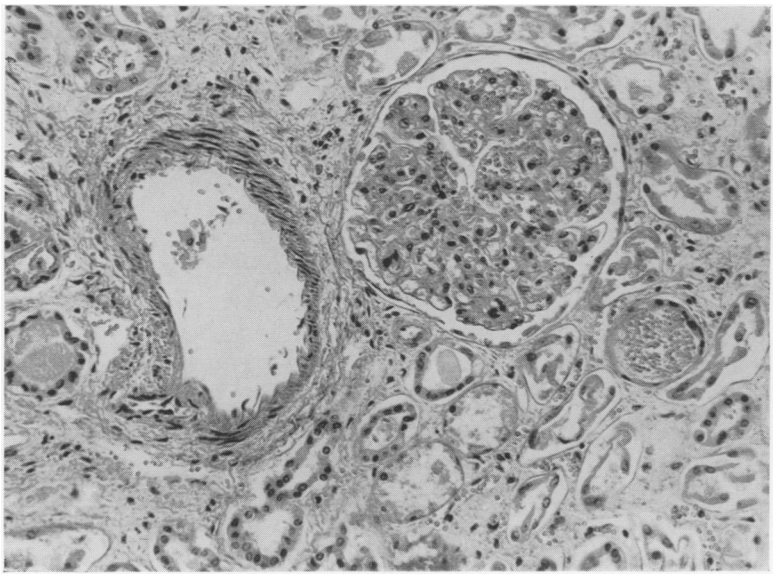


FIG. 9. Photomicrograph of transplanted kidney from Case 1. Sections show interstitial edema, tubular degeneration, normal glomerulus and intra-lobular artery.

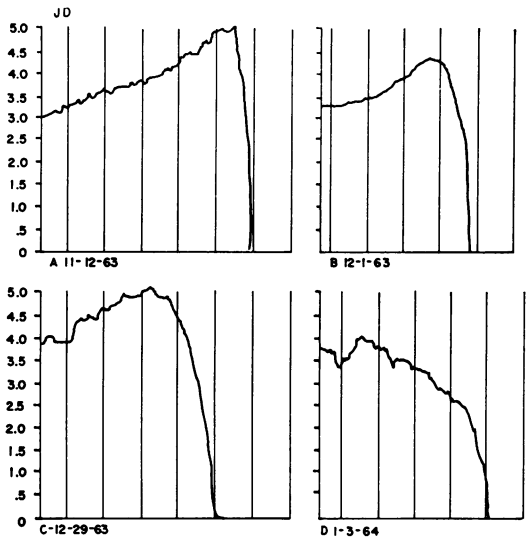


FIG. 10. Serial renograms in Case 1.

second month. Data on cytotoxicity studies are shown (Table 2).

Case 2. This 12-year-old patient was admitted to Charity Hospital on September 9, 1963 with a history of enuresis and repeated bouts of urinary tract infection due to bladder neck obstruction. Previously bladder neck resections and left nephrostomy had been performed. Prior to admission he had several episodes of convulsions and coma, one of which left him with right-sided hemiparesis.

Physical examination revealed a chronically ill patient with a B.P. of 170/116. The abdomen showed scars of previous operations and a left nephrostomy. The clinical impression was chronic pyelonephritis, secondary to bladder neck obstruction, with terminal uremia.

Studies included serum creatinine of 15.4 mg.%, BUN 172 mg.%, hematocrit 19%. On 11-8-63, after preparation with peritoneal dialysis, bilateral nephrectomy and splenectomy were per-

TABLE 2. *Cytotoxicity Studies*

Case 1						
Days after transplantation	3	10				
Cytotoxicity: % loss viability	0	10				
Case 3						
Days after transplantation	0	22	36			
Cytotoxicity: % loss viability	0	24	16			
Case 6						
Days after transplantation	0	10	17	26	27	28
Cytotoxicity: % loss viability	0	1	28	12	25	26

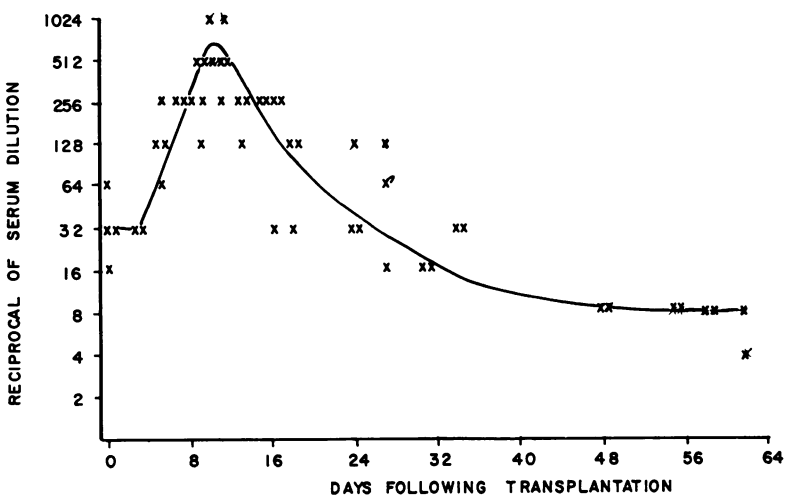


FIG. 11. Heterohemagglutinination studies in Case 1.

formed. Thereafter the patient was maintained on weekly hemodialysis, using a shunt in the right forearm. On 12-23-63, heterotransplantation was performed. The bladder was contracted, with a thickened wall. On 12-24-64 his urinary output dropped via the urethral catheter, and increased drainage of urine was noted from the lower end of the wound. On 12-25-63 cutaneous ureterostomies were performed. In the early postoperative period urinary collections were inadequate for technical reasons; however, urine volume remained 2,000–6,000 ml./day. Creatinine clearance immediately after operation was 60 cc./min. Three days after operation the BUN was 17 mg.% and serum creatinine was 0.7 mg.% (Fig. 12). On 12-28-63, spiking daily fevers of 104–105° F. developed.

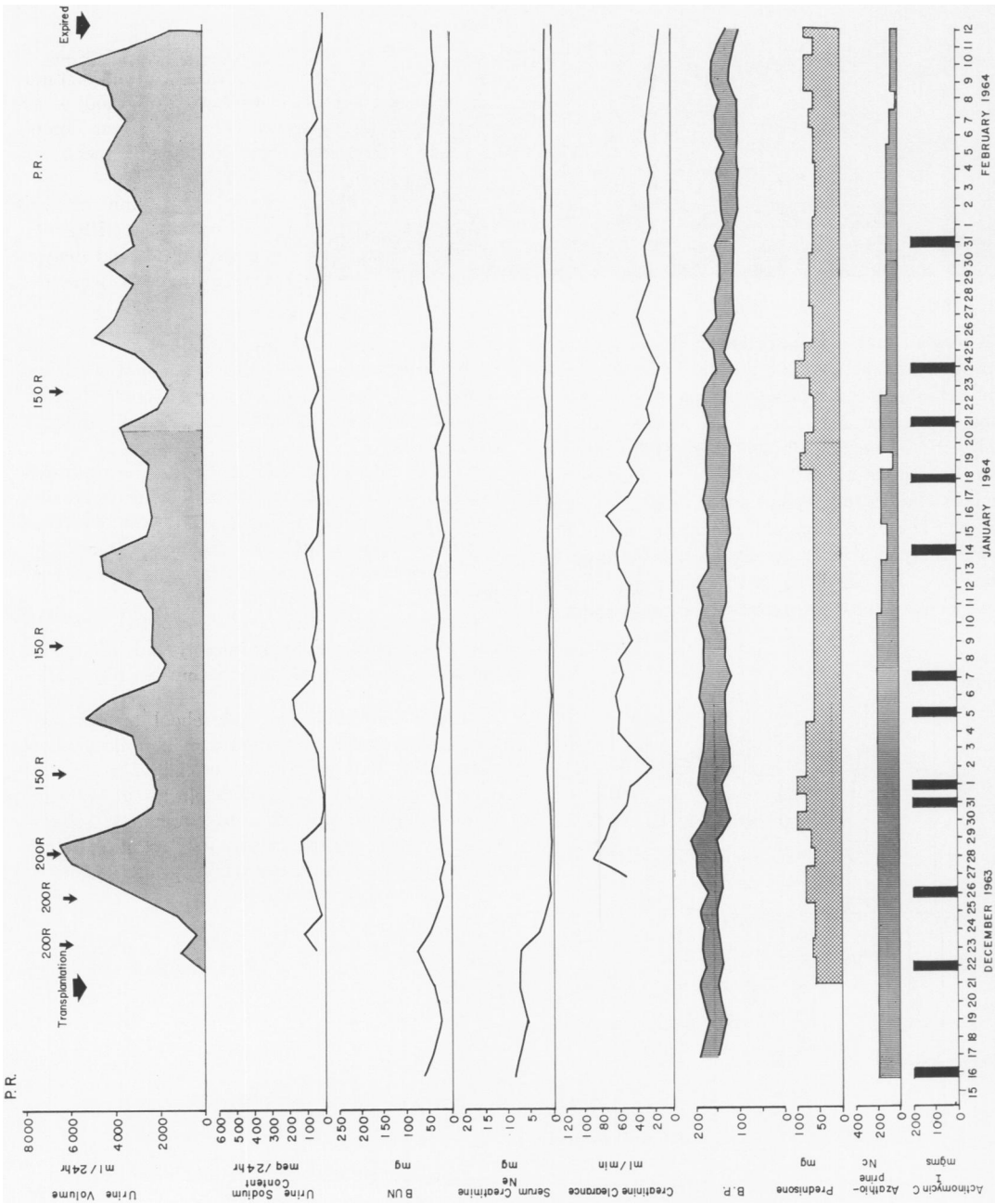


FIG. 12. Chart in Case 2 illustrating certain aspects of clinical course, laboratory studies, and drug treatment.

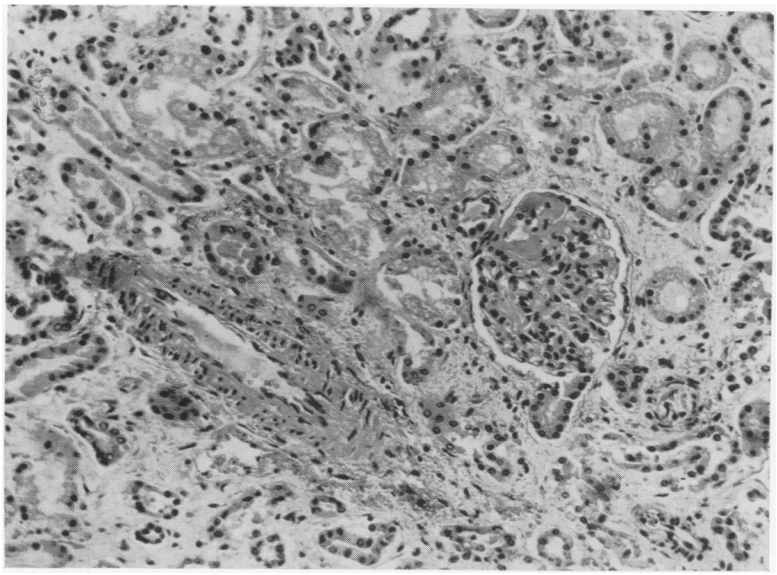


FIG. 13. Photomicrograph of transplanted kidneys from Case 2. Sections show interstitial edema, tubular degenerative changes, fibrin thrombi in the glomerular tufts and normal intralobular artery.

This was attributed to infection in the area of the transplant and in areas of the old operative incisions. During the last month of his life his white blood cell count and platelet count fell progressively; BUN remained in the range of 30–50 and serum creatinine 1.0–1.5 mg.%. His septic course, however, failed to respond to a variety of antibiotics. The predominant organism from the wound was *Aerobacter aerogenes,* not sensitive to antibiotics. He died on 2-13-64, approximately seven weeks after transplantation. Autopsy showed loculated pus around the transplant, at the site of nephrectomy, and in the abdominal incisions. Sections of the transplant showed acute tubular necrosis and edema without cellular infiltrate (Fig. 13).

Serial renograms (Fig. 14) demonstrated changes beginning in the second month following transplantation. These changes, however, were not closely correlated with the patient's clinical picture or chemical evidence of changes in renal function.

Agglutination studies demonstrated the absence of heteroagglutinans initially and throughout the entire post-transplantation course (Fig. 15).

Case 3. This 23-year-old school teacher was admitted in November, 1963 with chronic glomerulonephritis and progressive uremia. She had an episode of acute glomerulonephritis at 14 and persisting proteinuria. She had remained asymptomatic until approximately five months before admission when she noted weakness and dizziness.

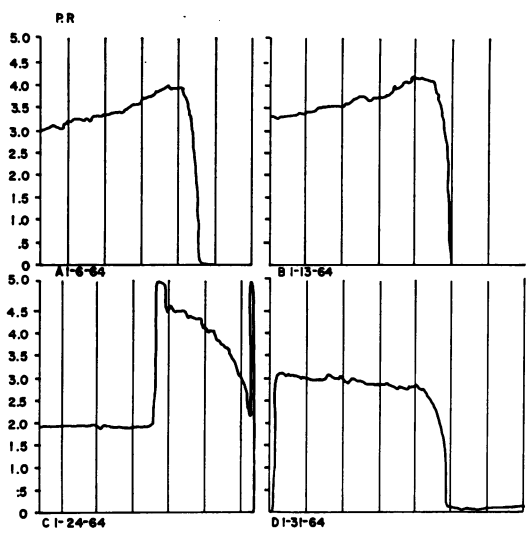


FIG. 14. Serial renograms in Case 2.

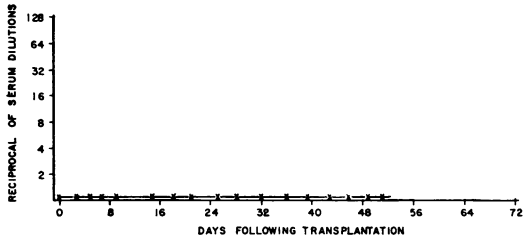


FIG. 15. Heterohemagglutininations studies in Case 2.

On admission her blood pressure was 190/120 and laboratory studies included BUN of 184 mg.%, creatinine of 40 mg.% and creatinine clearance of 4 ml./min. Rapid deterioration of her condition necessitated peritoneal dialysis.

On January 13, 1964 she received a renal heterotransplant. Diuresis occurred with a urinary output on the day of operation of 7,000 ml. By the third day following transplantation the BUN had fallen from a pre-transplant level of 116 mg.% to 12 mg.%, and the serum creatinine fell from a preoperative level of 21 mg.% to 0.9 mg.%. Creatinine clearance was 50 cc. per min. Her blood pressure fell to normotensive levels, 110/70. Her subsequent course demonstrated satisfactory renal function until the 23rd day following operation when threatened rejection was suspected (Fig. 16). Urinary output decreased to 1,000 ml./24 hours, and BUN and creatinine rose to 28 and 1.9 mg.%, respectively. Creatinine clearance fell to

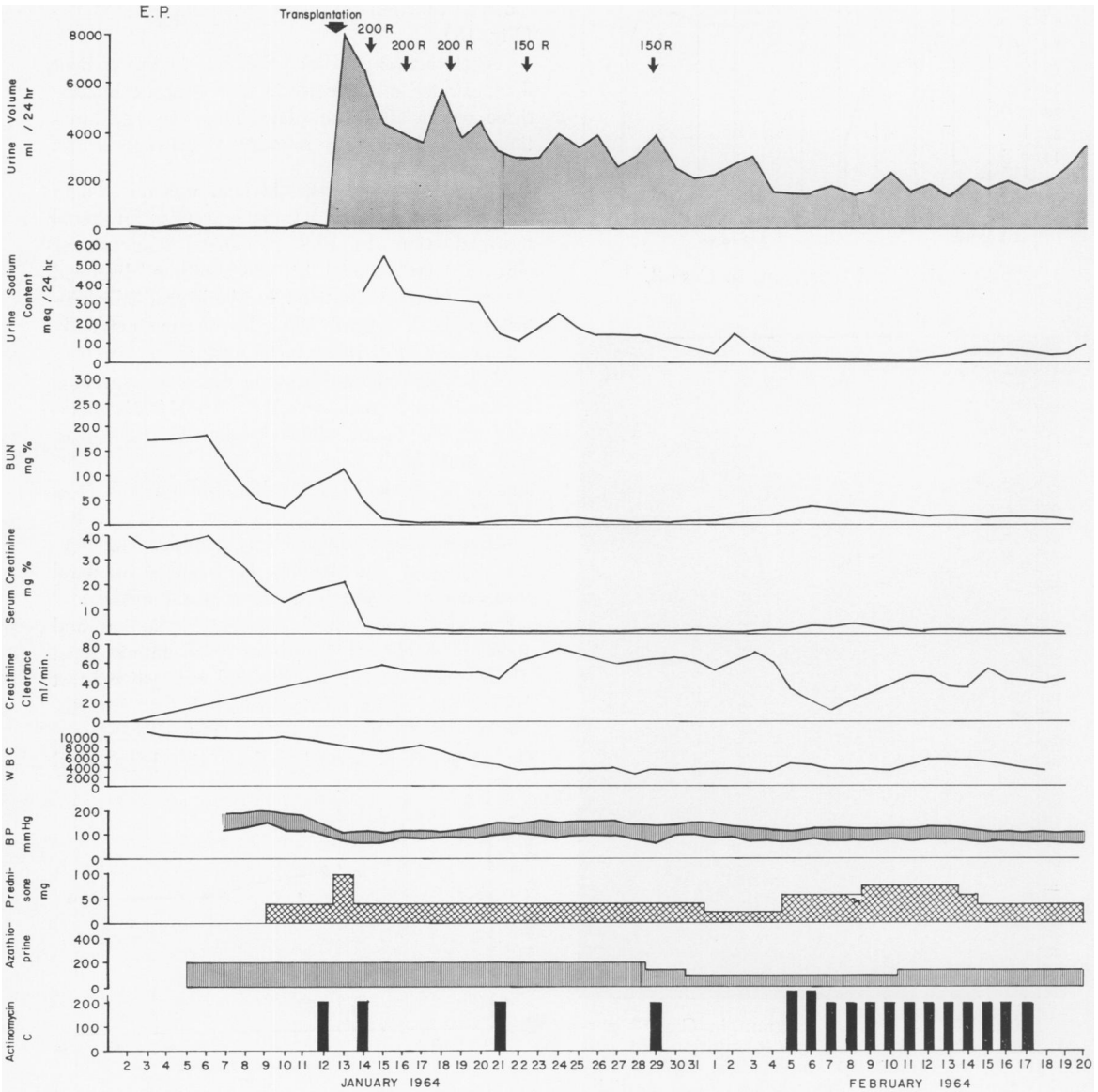


FIG. 16. Chart of Case 3 illustrating certain clinical features, laboratory studies, and drug treatment.

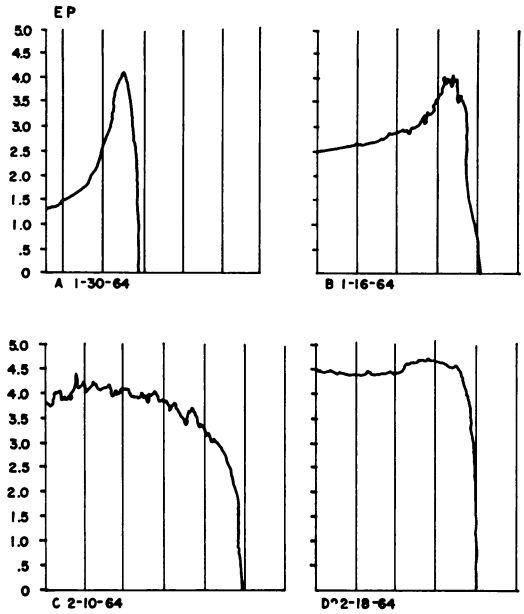


FIG. 17. Serial renograms in Case 3.

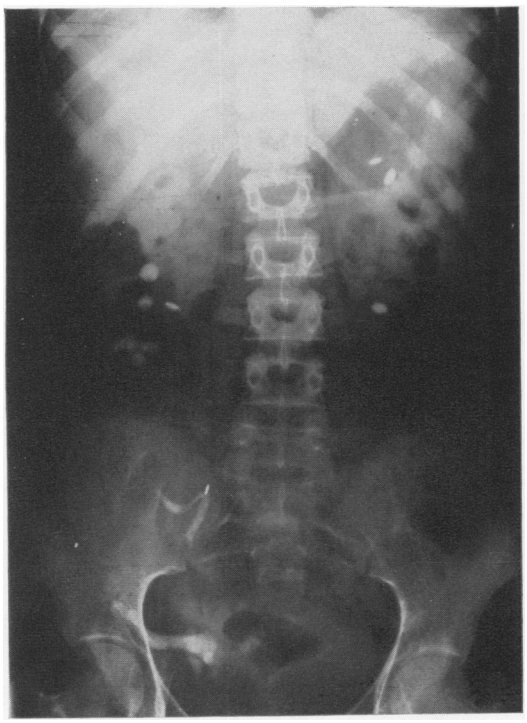


FIG. 18. Intravenous urogram in Case 3 performed 12 weeks after transplantation. In this case the transplant was inserted in such a way that the calyx of the upper kidney faces medially and the calyx of the lower kidney laterally. Contrast material is seen in both calyces and ureters.

31 ml. per min. and urinary sodium content to 11.6 mEq. for a 24-hour period. Gradual reversal of rejection occurred during the following two weeks, although unexplained fever persisted for 3 months. She is now asymptomatic and has normal renal function 6½ months after transplantation.

Serial renograms (Fig. 17) in this patient demonstrated a delay in peak activity which coincided with clinical and biochemical evidence of threatened rejection. Following reversal of rejection, the renogram resumed a more normal pattern. Intravenous urogram 12 weeks after transplantation showed function of both transplanted kidneys (Fig. 18).

Agglutination studies (Fig. 19) in this patient demonstrated a slight rise in titer at approximately three weeks after transplantation. The agglutination titer subsequently returned to previous levels.

Case 4. This 35-year-old man was referred to Charity Hospital in terminal uremia for renal transplantation. In 1955 a clinical diagnosis of chronic glomerulonephritis was confirmed by renal biopsy. Since that time he had gradually deteriorated. In August 1963, he became markedly uremic, his BUN rising to 250 mg.%.

Physical examination upon admission revealed a chronically ill man with B.P. 210/110. Examination of the thorax showed crepitant rales over both lung fields posteriorly. The heart was enlarged, a marked pericardial friction rub was heard over the entire pericardium, and a left ventricular gallop rhythm was audible. The liver was enlarged and tender. He showed bilateral costovertebral tenderness, edema of the ankles and sacral area, generalized muscular twitching and ataxia. The clinical impression was chronic renal disease with uremia, anemia and congestive heart failure. Studies on admission included an hematocrit of 16%, BUN 176 mg.% creatinine 16.8 mg.%. On 12-30-63 peritoneal dialysis was begun and

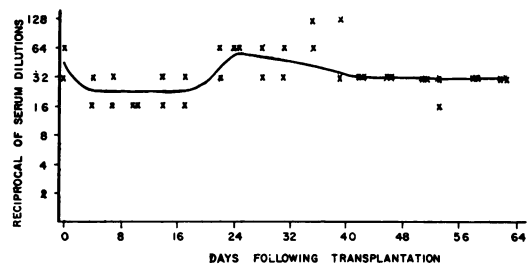


FIG. 19. Heterohemagglutinination studies in Case 3.

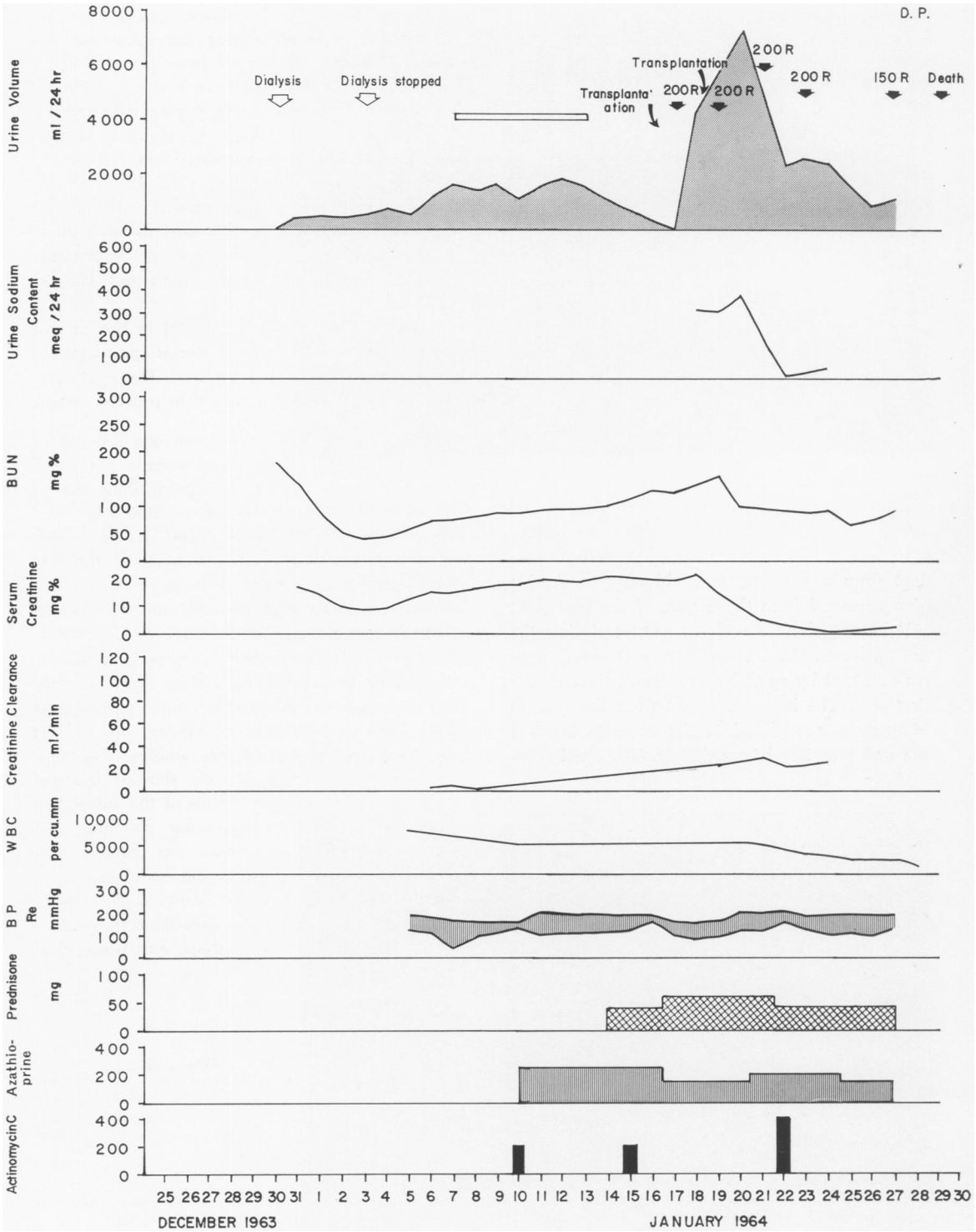


FIG. 20. Chart in Case 4 illustrating certain clinical features, laboratory studies, and drug treatment.

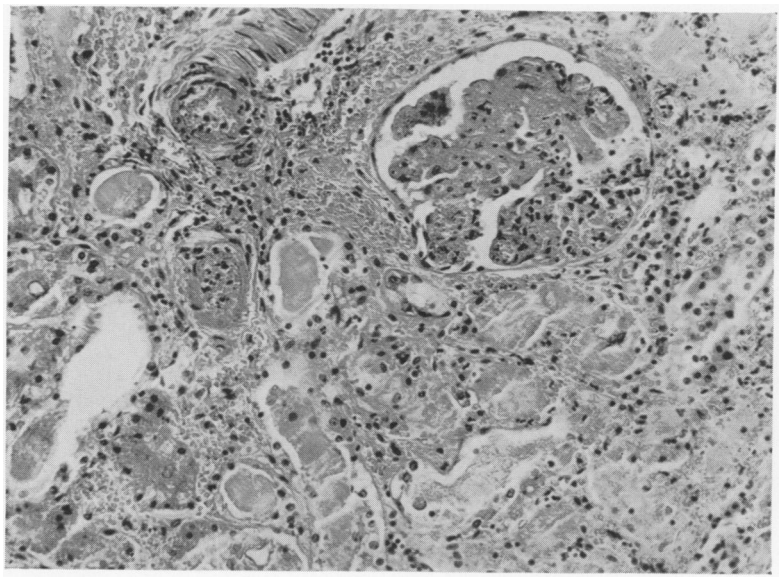


FIG. 21. Photomicrograph of the first transplant in Case 4, in which kidneys from a type A donor were implanted in a type O patient. Sections show severe tubular degeneration and interstitial edema, fibrin thrombi in a glomerulus, fibrinoid necrosis of blood vessels, and interstitial infiltration by lymphocytes and neutrophils.

continued for four days, with marked clinical and chemical improvement. On 1-16-64, the patient who was blood type O, received an heterotransplant from a chimpanzee of blood type A. No urine appeared from the ureters of the transplant and there was no significant output during the next 36 hours. On 1-18-64, a type O chimpanzee was obtained by special arrangement through the Air Force. The heterotransplant from the type O chimpanzee was placed in the opposite inguinal area and functioned immediately. The renal complex from the type A chimpanzee was removed. This wound was found to be grossly infected and was extensively drained. Examination of the removed specimen revealed it to be swollen and hemorrhagic. After operation, the patient ran an extremely septic course, and culture of his wound exudate and his blood grew out aerobacter which was resistent to all available antibiotics. His course after operation was marked by rapid deterioration to his death on 1-29-64, 11 days after the second transplantation. The creatinine clearance of the

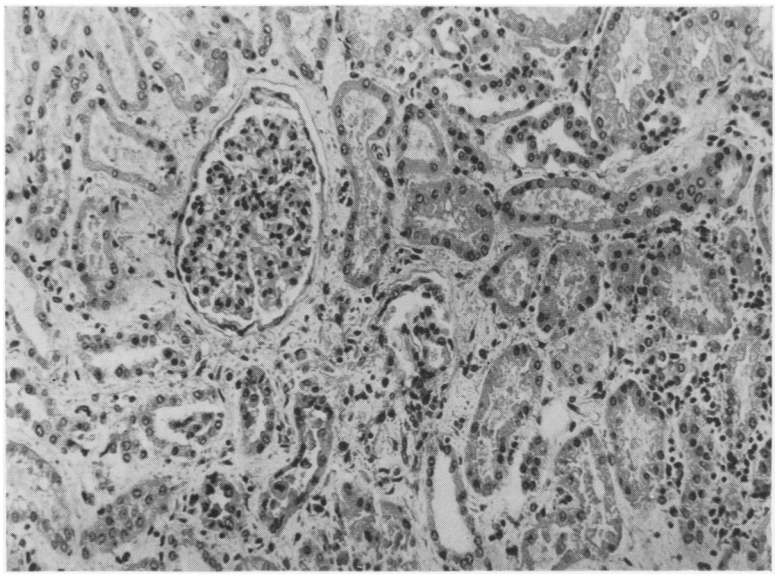


FIG. 22. Photomicrograph of kidneys following second transplantation in Case 4. These kidneys were from a donor of blood type O. Sections show normal glomerulus with interstitial edema, tubular degenerative changes, and slight lymphocytic infiltration.

transplant after operation ranged from 20–30 ml./ min. (Fig. 20). The serum creatinine during the early postoperative period fell rapidly to 2 mg.%. The BUN, however, which was 156 mg.% prior to operation never fell below 76 mg.%. There was a marked drop in his WBC to 1,000/cubic mm. and his platelet count dropped to 48,000. This was attributed to immunosuppressive drug therapy which was discontinued two days prior to death.

Pathologic studies of the transplant from the type A chimpanzee showed hypercellular glomeruli, tubular degeneration, edema, moderate cellular infiltration, and fibrinoid necrosis of blood vessels (Fig. 21). Sections of the graft from the type O donor showed normal glomeruli and vessels, with interstitial edema, tubular degenerative changes and slight cellular infiltration (Fig. 22). Hemagglutinin studies are illustrated (Fig. 23).

Case 5. This 46-year-old woman was admitted on 1-3-64 for evaluation for renal transplantation. Four years previously she was found to have polycystic renal disease, with hypertension, hematuria and back pain. During the six month period prior to admission she showed progressive renal failure and uremia.

Initial laboratory studies included blood urea nitrogen of 140 mg.%, serum creatinine, 14.8 mg.%, creatinine clearance, 5 ml./ min. Conservative treatment resulted in transient improvement, but subsequent deterioration and coma necessitated the initiation of peritoneal dialysis on 1-24-64.

On 2-4-64 she received a renal heterotransplant. Her early postoperative course was satisfactory with gradual improvement of renal function; creatinine clearance reached 80 ml./min. by the ninth postoperative day. However, on 2-14-64 she became febrile, and urine culture showed *Aerobacter aerogenes*. Marked leukopenia and thrombocytopenia developed (Fig. 24). On 2-22-64 threatened rejection was suspected and she was placed on higher doses of steroids and given additional local radiotherapy. Later that day she developed profound shock which failed to respond to the administration of steroids, antibiotics and vasopressors. Blood drawn just prior to her death grew *Aerobacter aerogenes*, and autopsy findings confirmed the impression of generalized sepsis.

Sections of the renal transplant showed normal glomeruli, marked tubular degeneration and edema, and perivascular infiltration with lymphocytes, and occasional plasma cells and histiocytes. An additional finding was fibrinoid necrosis of blood vessels (Fig. 25–28).

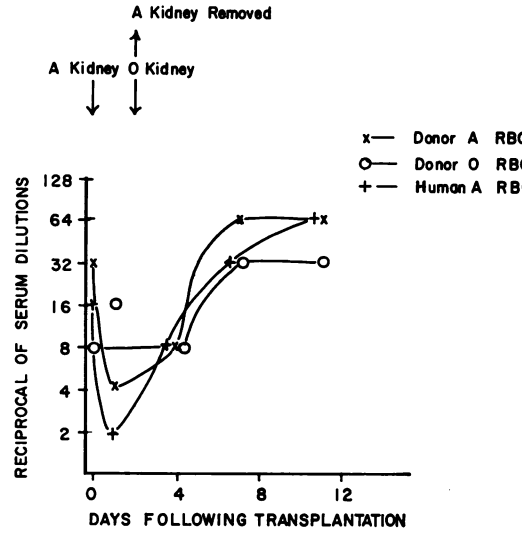


FIG. 23. Heterohemagglutinination studies in Case 4.

Agglutination studies showed an initial fall in titer followed by a rise on the fifth day and a subsequent decline. The alterations were not correlated with any obvious clinical or biochemical changes.

Case 6. This 16-year-old girl was admitted to Charity Hospital on 12-29-63 with a diagnosis of chronic glomerlonephritis and progressive uremia. For approximately one year she had noted dizziness, fatigability and intermittent periobital edema.

On admission laboratory studies included BUN 248 mg.%, creatinine 18.4 mg.% and creatinine clearance 4 ml./min. Peritoneal dialysis was begun on 12-30-63 and continued for one week.

On 2-10-64 she received a renal heterotransplant. The urinary output was 1,640 ml. and the creatinine clearance was 60 ml./min. on the first day following operation. Although the BUN and serum creatinine decreased to 22 mg.% and 0.6 mg.%, respectively, by the fourth day following operation, subsequently there was gradual increase of the BUN over the ensuing two-week period (Fig. 30). By 2-25-64 the BUN had reached a level of 112 mg.%, serum creatinine had increased to 4.1 mg.%, and creatinine clearance had diminished to less than 5 ml./min. despite vigorous immunosuppressive treatment.

A wound culture taken on 2-16-64 revealed *Aerobacter aerogenes*. On 2-29-64 the renal heterograft was considered nonfunctional and was removed. The wound was grossly infected and was drained. Despite peritoneal dialysis, and discontinuance of immunosuppressive drugs and treat-

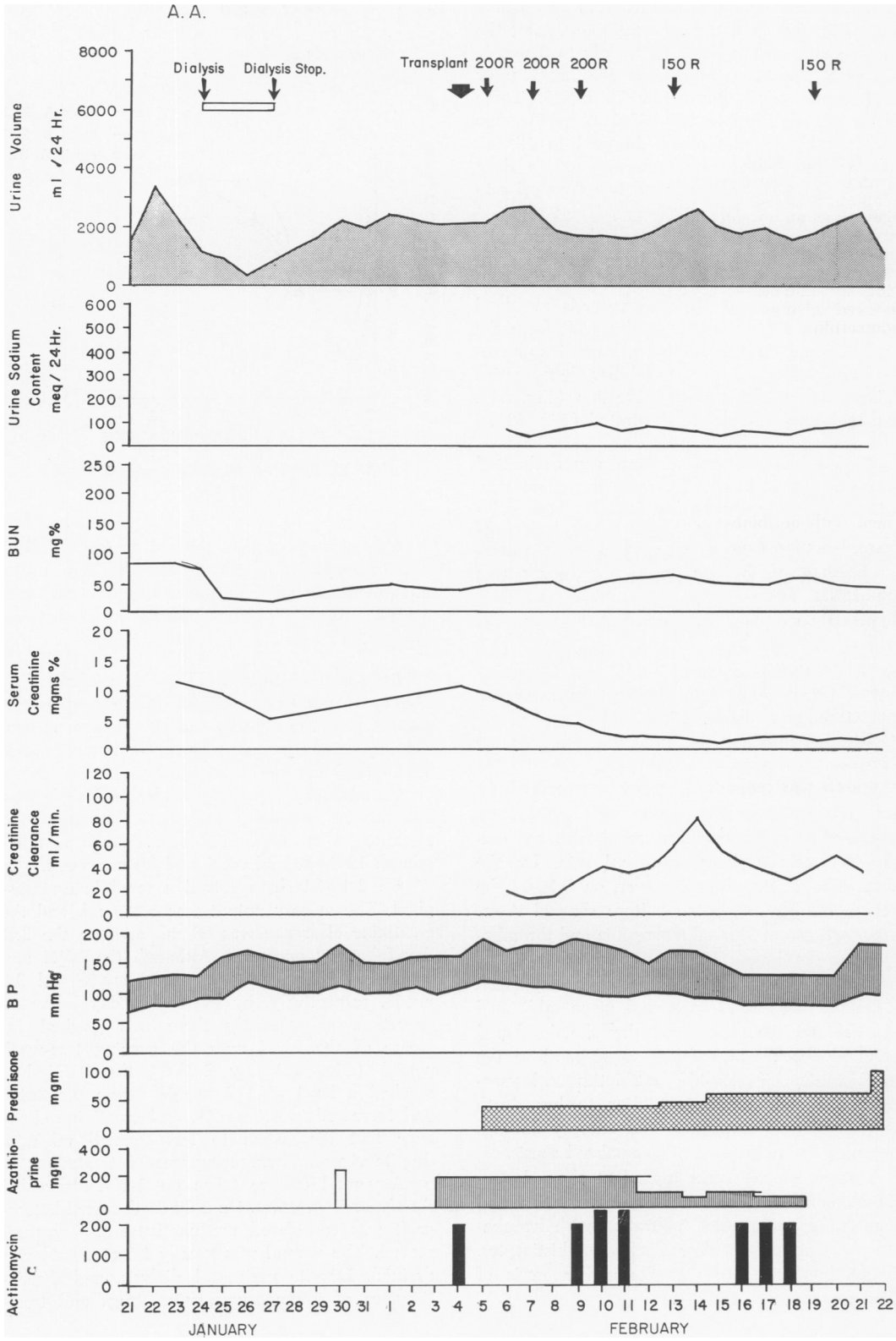


FIG. 24. Chart of case five illustrating certain clinical features, laboratory studies, and drug treatment.

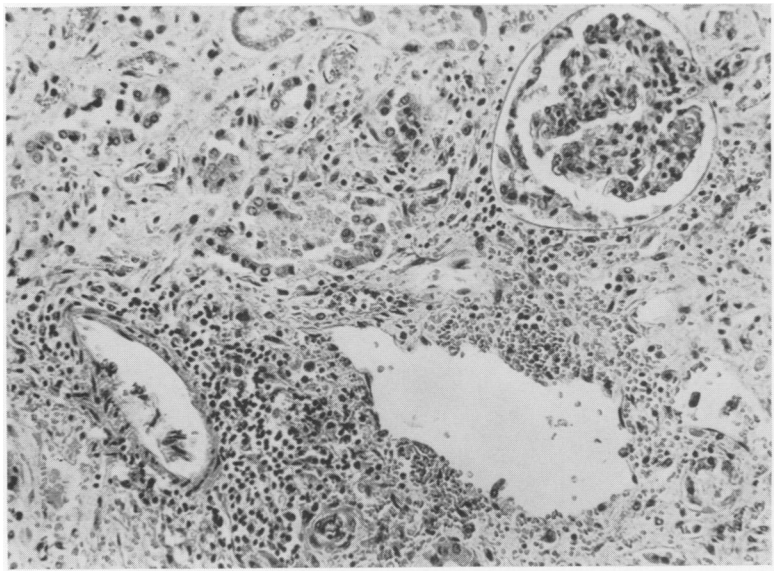


FIG. 25. Photomicrographs of transplanted kidneys in Case 5. Sections show an intralobular artery with peri-vascular cellular cuffing. There is marked tubular degeneration and edema, without marked changes of the glomerulus.

ment with antibiotics she died 27 days following transplantation from uremia and convulsions.

Sections of the transplanted kidneys showed interstitial edema, tubular necrosis, glomerular hypercellularity and mild cellular infiltration (Fig. 31).

Agglutination studies demonstrated a rise in titer beginning approximately one week after transplantation (Fig. 32). This change coincided with clinical evidence of rejection. The subsequent decline in titer occurred approximately at the time the graft was removed. Pre-rejection levels of agglutination titers were observed when the patient was maintained on dialysis and immunosuppressive agents were discontinued.

Discussion

Limitations of scope and time of this study do not permit precise definition of many aspects of renal heterotransplantation in man. Nevertheless, several observations on this small group of patients studied for short periods of time deserve comment.

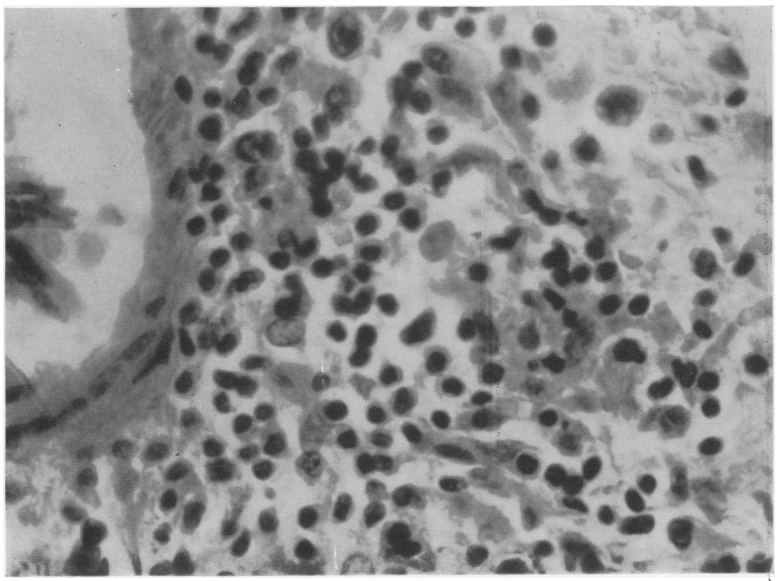


FIG. 26. High-power photomicrograph of perivascular cellular infiltrate showing lymphocytes with occasional plasma cells and histiocytes.

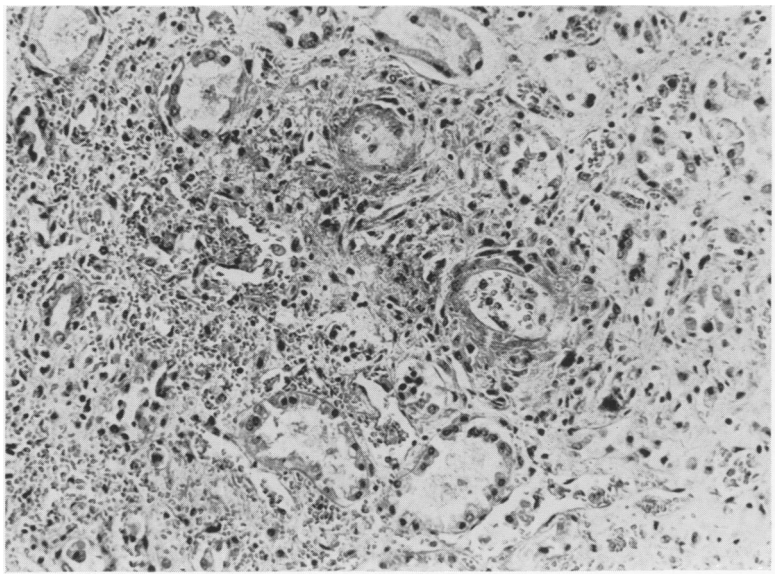


FIG. 27. Photomicrograph of transplanted kidneys in Case 5. Sections show fibrinoid necrosis of blood vessels, severe tubular degeneration and cellular infiltration.

Function of the transplant occurred in all cases with the exception of the instance in which major blood group incompatibility was challenged (Case 4, first transplant). The degrees of function varied considerably. Prompt diuresis and return toward normal of renal function often occurred, but in some instances this was delayed, perhaps due to tubular damage. In general, renal function has proved to be a lesser problem than infection attributed to immune suppression.

Initially an assumption was made that rejection of heterografts would be more immediate and severe than rejection of homografts. For this reason, strenuous immunosuppressive measures were used, including azathioprine, steroids, actinomycin

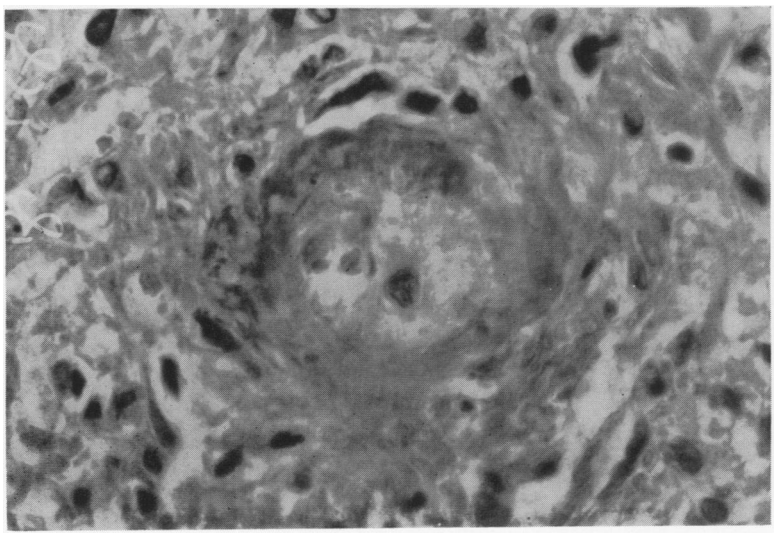


FIG. 28. High-power view of sections shown in Figure 27 from the transplanted kidneys in Case 5. There is severe fibrinoid necrosis of the blood vessel.

C and local irradiation. We have continued to use these modalities, but we have chosen to decrease our reliance on heavy doses of immunosuppressive drugs in view of our preponderant difficulties with infection compared with graft-rejection.

The interpretation of serial renograms has been difficult. A progressive delay in uptake of isotope has been observed, but such changes often were not associated with obvious alterations in renal function. In one instance (Case 3) a marked delay in uptake coincide with clinically apparent rejection. In this case the renogram returned toward a normal pattern after reversal of rejection.

Increasing effort has been placed on matching recipients and donors and on following the immunologic response in the recipient. All patients and donors have been typed for major blood groups, ABO, Rh and MN. Chimpanzees were found to show A_1, A_2, $A_{1,2}$ or O; uniformly ccD-Rh_o^{-ch}; and M or MN, erythrocytes with the corresponding complementary hemagglutinins occurring only in the ABO group. These results are in agreement with those of Wiener and Moor-Jankowski.[15] The designations A_1, A_2, or $A_{1,2}$ reflect differences in susceptibility to *Dolichos biflorus* extracts rather than identity with the human subgroups of A. All chimpanzee erythrocytes were agglutinated by rabbit anti-human M but showed partial or no agglutination in similar anti-N serum and are listed as MN or M on this basis. Furthermore, all chimpanzee red cells were strongly agglutinated in anti-C(hr') and anti-D (Rh_o) sera but failed to react with anti-C, anti-E or anti-e. Tests for other groups, such as Kk or Ss, which require the use of developing anti-human globulin anti-serum were not done because of the evident possibility of interference by human anti-chimpanzee hetero-hemagglutinins. These results can be interpreted to indicate strong similarities, but not identity, between human and chimpanzee Rh and MN isoantigens. Chimpanzee blood group A substance may be even more closely related to human A, in that one patient, (Case 4) responded to stimulus by a type A chimpanzee kidney with a specific increase in antihuman A_2.

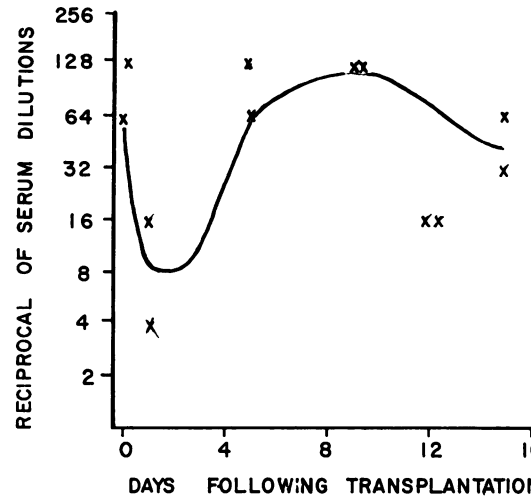


FIG. 29. Heterohemagglutinination studies in Case 5.

Cytotoxicity tests, performed by the trypan blue dye exclusion method were used to determine viability. Chimpanzee (type O) lymph node cells obtained at the time of transplantation were exposed to serum, washed, and then exposed to complement to eliminate any anti-comprementary effect of the serum. Earlier tests of the same samples were negative when this precaution was not taken. All sera reported were tested at the same time against one donor. No normal serum or pretransplant serum showed any activity, and viability in all control tubes was 90 per cent or greater throughout. Hemagglutinations were performed by standard technics using either chimpanzee donor erythrocytes or a battery of chimpanzee red cells of the same ABO type.

The patient in Case 1 showed an abrupt rise in anti-A^{ch} rbc heterohemagglutinins at days 5–10 following transplantation, rising

FIG. 30. Chart in Case 6 illustrating certain clinical features, laboratory studies, and drug treatment.

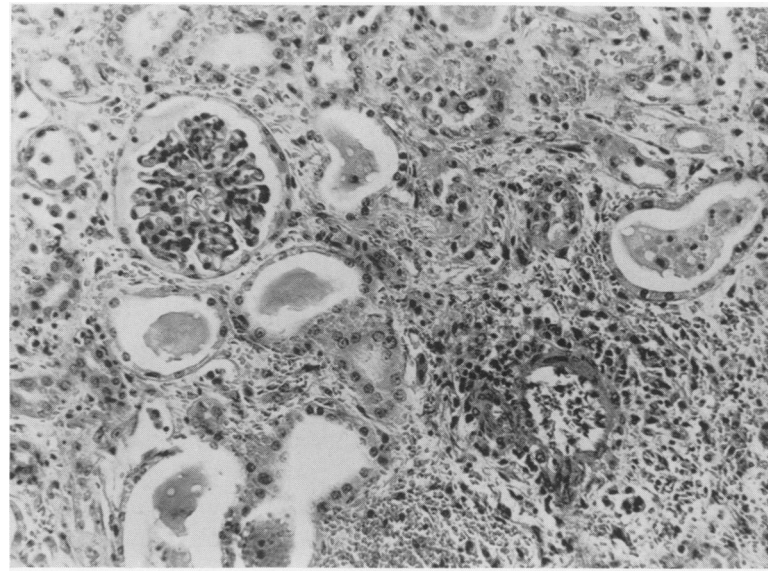


FIG. 31. Photomicrograph of transplanted kidneys in Case 6. Sections show hypercellularity of the glomerulus, interstitial edema, tubular degeneration and peri-vascular cellular infiltration.

from a pretransplant level of 1:32 to 1:1024. This gradually returned to pretransplant levels by day 30 and was below this at the time of death on day 63. Cytotoxicity tests show minimal and equivocal response on day 10. Other samples have not been tested as yet.

The patient in Case 2 showed a pretransplant natural anti-human A (A^h) titer of 1/8 which had decreased steadily to 1/2 by day 35. There was no natural anti-chimpanzee erythrocyte (Ch-rbc) titer before transplantation, nor did any appear later. Cytotoxicity tests through day nine were negative. This is the only patient that showed such a complete lack of response.

The patient in Case 3 showed a slight but significant rise in anti-O^{ch}rbc heterohemagglutinin titer following transplantation, but it did not appear until 23 days after transplantation in contrast to four other patients. This coincides in time with a delayed rejection crisis in this patient and may be correlated with it. There is other information, however, which contradicts this conclusion. The anti-A^{ch}rbc titer rose eight days after transplantation, in common with findings in the other patients. This did not change during the threatened rejection. Both titers had decreased by 40 days after transplantation despite retention of the functioning kidney. Cytotoxic antibody was present in high titer at day 23, and was still present, although waning, at day 36.

The patient in Case 4 showed two clearly separable responses in the hemagglutinine curve. First, immediately after transplantation of the incompatible type A kidney, both anti-A^{ch} and anti-A_2^{H} titers dropped precipitously, and rebounded past pretransplant levels after its removal. That the same antibody is being measured in the two tests and that it was adsorbed by the trans-

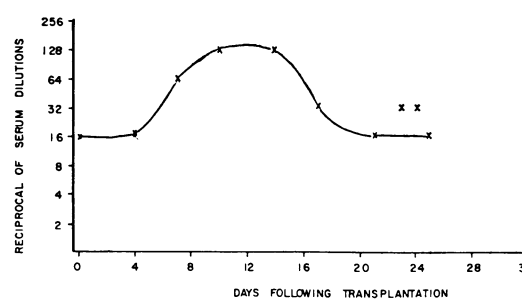


FIG. 32. Heterohemagglutinination studies in Case 6.

planted kidney is suggested by a) the failure of the kidney to function at any time, b) the reciprocal adsorption of the anti-A titer with H-rbc and ch-rbc and c) the adsorption of both the anti-A^{ch} and anti-A_2^h titer by chimpanzee lymph node cells and acetone-dried splenic tissue. Second, after transplantation of a type O kidney there was a rise in the anti-Ch heterohemagglutinin titer not adsorbable by A_2^H-rbc nor by chimpanzee node lymphocytes. No cytotoxic antibody was found at day 7.

The patient in Case 5 showed an abrupt drop in natural anti-Ch rbc titer immediately after transplantation with a return to pretransplant levels by day five. Little significance can be attached to the other changes as too few serum samples were available. Cytotoxicity tests were negative at days one and 15.

The patient in Case 6 showed a rise in anti-A^{ch}rbc heterohemagglutinin from a pretransplant level of 1/16 to 1/128 by day 10 with a decline to normal by day 20. The loss in titer occurred despite reduction of immunosuppressive therapy and retention of the kidney for three days. Cytotoxic antibody was present the day after azathioprine and actinomycin were discontinued and remained at approximately the same level for at least nine days after removal of the kidney. Whether this antibody appeared earlier is not known, but it was not found on day 10 which marked the height of the HA response and the day that a clinical rejection pattern appeared.

It is our interpretation that the normal human anti-chimpanzee heterohemagglutinin is directed against an antigen present only on the erythrocyte and that the rise in titer following transplantation is a secondary response to a single, minimal antigenic exposure to red blood cells left in the kidney despite perfusion. The failure to adsorb this antibody either from patient's sera or from normal human serum with chimpanzee buffy coat leukocytes or lymph node cells is the main supporting evidence. Other evidence is the drop in this titer in all patients and in spite of retention of the kidney in the absence of immunosuppressive therapy in one patient. This response, then, reflects the ability of the patient to respond to a secondary stimulus and is an anamnestic response. Presumably if there were other pre-existing heteroimmune systems directed against nucleated cells or against kidney tissue specifically, they too would be capable of stimulation in the presence of immunosuppressive therapy. The stimulation of anti-A response by transplantation of a kidney from a type A donor to an incompatible recipient falls in this class and this result was seen in one patient. The total HA response was composed of a minor component meeting the criteria outlined above and a larger response directed against A^h-rbc, A^{ch}-rbc and chimpanzee type A lymphoid tissue.

The presence of cytotoxic antibody in some of the patients may, on the other hand, directly reflect a tissue immunity. Whether it is responsible for the clinical signs of rejection is not known, but its appearance may coincide with a rejection crisis rather than with the heterohemagglutinin response. Its appearance in only some patients and then not before day 10 suggest that it is not a secondary response. More results must be obtained to examine this important point further, as it is apparent that the immunosuppressive therapy used was not successful in preventing the secondary response to Ch-rbc.

Pathologic studies have revealed no consistent pattern. Sections of the grafts from patients in Cases 1 and 2, who survived for approximately two months, showed interstitial edema and tubular necrosis, perhaps related to terminal shock and sepsis. There were minimal changes in the glomeruli and no significant cellular infiltration.

The sections of kidneys from the patient described in Case 4 showed various

changes. In the first transplant, in which kidneys were transplanted from a type A donor to a type O recipient, marked changes were seen, including interstitial cellular infiltration and edema, fibrinoid necrosis of blood vessels and fibrin thrombi in the glomeruli. In the second transplantation in Case 4, when kidneys from a group O donor were used, changes were less marked, with minimal cellular infiltration and normal glomeruli, but showing interstitial edema and tubular degenerative changes.

Pathologic studies of the transplant in Case 5 showed fibrinoid necrosis of blood vessels, tubular degeneration and moderate cellular infiltration. In Case 6, sections of the transplant showed increased cellularity of the glomerulus and moderate perivascular cellular infiltration.

Our tentative and preliminary over-all findings suggest that the heterografted kidney from chimpanzee to man may respond similarly to the homografted kidney from man to man. In a recent instance of renal homografting between sisters, threatened rejection occurred four days after transplantation, following a similar pattern to that seen in Case 1 reported here. There is similarity in time and degree of clinical and chemical changes seen in these two patients, in the initial response to transplantation, in the period of threatened rejection, and in reversal of rejection (Fig. 33).

Our further efforts will be directed toward defining the determinants of compatibility in matching of donor and recipient; toward adjusting of immunosuppressive measure to permit acceptance of renal heterografts; and toward studies of the long-term function of such grafts in man.

We would emphasize, however, that we regard this work as wholly experimental. Under these circumstances only the most stringent precautions will make such work justified and justifiable, and historic experience shows that the field of heterotransplantation may be abused flagrantly. The use of non-human kidneys in man removes the problems of the human donor, but the consequence of this exchange is increased difficulty imposed by cross-species transplantation. Whether heterografted kidneys will function often enough, well

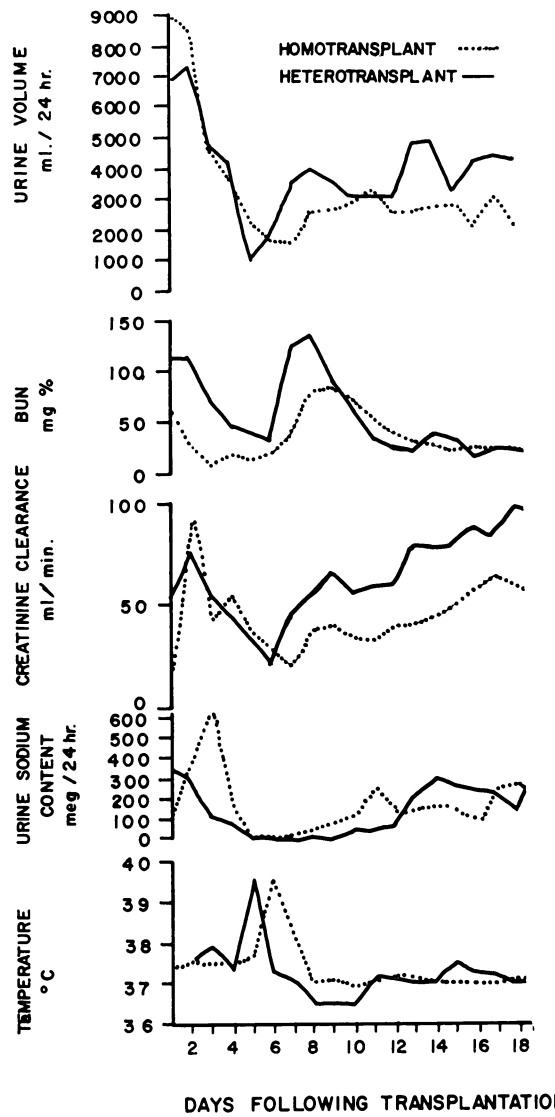
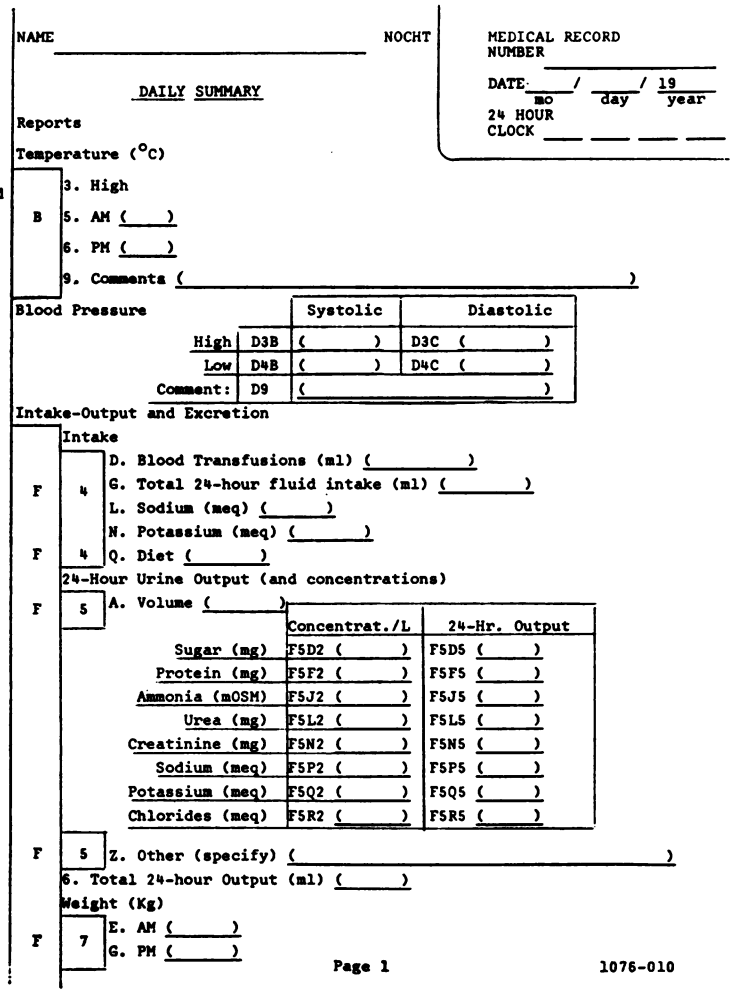


FIG. 33. Chart illustrating studies in two patients. The dotted line indicates studies in a patient receiving a homograft from her sister. The solid line indicates studies in the patient (Case 1) receiving an heterograft. Both patients underwent threatened rejection which was later reversed. These studies indicate certain similarities in time and degree of changes.



NAME _____ NOCHT

MEDICAL RECORD NUMBER _____

DAILY SUMMARY

DATE: ___/___/ 19___ (mo / day / year)

24 HOUR CLOCK ____ ____ ____ ____

Reports

Temperature (°C)

Field = M		
	B	3. High
		5. AM ( )
		6. PM ( )
		9. Comments ( )

Blood Pressure		Systolic	Diastolic
High	D3B	( )	D3C ( )
Low	D4B	( )	D4C ( )
Comment:	D9	( )	

Intake-Output and Excretion

Intake

		D. Blood Transfusions (ml) ( )
F	4	G. Total 24-hour fluid intake (ml) ( )
		L. Sodium (meq) ( )
		N. Potassium (meq) ( )
F	4	Q. Diet ( )

24-Hour Urine Output (and concentrations)

F	5	A. Volume ( )		
			Concentrat./L	24-Hr. Output
		Sugar (mg)	F5D2 ( )	F5D5 ( )
		Protein (mg)	F5F2 ( )	F5F5 ( )
		Ammonia (mOSM)	F5J2 ( )	F5J5 ( )
		Urea (mg)	F5L2 ( )	F5L5 ( )
		Creatinine (mg)	F5N2 ( )	F5N5 ( )
		Sodium (meq)	F5P2 ( )	F5P5 ( )
		Potassium (meq)	F5Q2 ( )	F5Q5 ( )
		Chlorides (meq)	F5R2 ( )	F5R5 ( )
F	5	Z. Other (specify) ( )		

6. Total 24-hour Output (ml) ( )

Weight (Kg)

F	7	E. AM ( )
		G. PM ( )

Page 1 1076-010

FIG. 34. Sample page from data-processing form for heterografting studies.

enough and long enough to warrant their continued use remains unanswered, but the present study suggests to us that further work in this area is indicated.

As work in heterotransplantation is beginning there is an opportunity to devise systems of data-processing using newly developed biomedical computer systems. A system is now in operation in which data are transferred from the standard clinical charts or flow sheets to data-processing forms (Fig. 34). These data are then coded and stored. The information then may be retrieved in various forms. Complete data, in the narrative form, may be printed out (Fig. 35), giving a record of complete information on a daily basis. Additionally selected data may be retrieved and recorded in a sequential form (Fig. 36), permitting analysis of trends in a single patient or among several patients. Such data collected from centers engaged in heterotransplantation will be processed and returned to the investigators, with summaries of all current work in heterotransplantation. Furthermore, all data from the various centers will be available to each investigator. Perhaps this rapid dissemination of data will aid in reducing the repetition of mistakes.

Summary

The use of chimpanzee kidneys in renal heterotransplantation into man is under investigation.

Recipients, all patients in terminal uremia who have been dialyzed, received grafts from donors selected on the bases of blood groups and body size.

Immunosuppressive measure included azathioprine, actinomycin C, steroids and local x-radiation.

Maximal functional survival of the transplant has been six months. Sepsis has proved to be a more frequent and lethal complication than rejection.

Immunologic response has been followed by heterohemagglutin titers and cytotoxicity studies. Pathologic studies have shown in general, tubular degeneration and interstitial edema without marked cellular infiltration or vascular changes.

The highly experimental nature of the study is emphasized, and caution is urged in clinical heterotransplantation.

In transplantation, a method for international cooperation in data-processing and data-sharing, using biomedical computers, is proposed.

Addendum

Six months after receiving an heterotransplant, the patient described in Case 3 is asymptomatic and is followed as an outpatient. Her renal function is normal and her white blood cell count ranges between 5,000 and 6,000. Immunosuppressive medications are azathioprine 75 mg. and prednisone 30 mg. daily.

```
I.D.NUMBER NOCHTT53108353                                    PAGE  9


      AM - 37.8
      PM - 37

     BLOOD PRESSURE
      HIGH
         SYSTOLIC - 140
         DIASTOLIC - 90
      LOW
         SYSTOLIC - 110
         DIASTOLIC - 70

     INTAKE-OUTPUT AND EXCRETION
      INTAKE
         TOTAL 24-HOUR FLUID INTAKE - ML - 4630
         DIET - BLAND
      24-HOUR URINE OUTPUT - AND CONCENTRATIONS
         VOLUME - 3700
         SODIUM - MEQ
            24-HOUR OUTPUT - 320
         POTASSIUM - MEQ
            24-HOUR OUTPUT - 184
      TOTAL 24-HOUR OUTPUT - ML - 3700
      WEIGHT - KG
         AM - 49

     HEMATOLOGY
      HEMATOCRIT - 35
      WBC - 5600
      PLATELETS - 158000

     BLOOD CHEMISTRY
      ELECTROLYTES
         SODIUM - MEQ/L - 147
         POTASSIUM - MEQ/L - 4.8
         CHLORIDE - MEQ/L - 101
         CARBON DIOXIDE - MEQ/L - 26.
      NON-ELECTROLYTES - MG PCT.
         BUN - 5
         CREATININE - 0.6

     URINALYSIS
      MICROSCOPIC - ABNORMAL QUANTITY PRESENT
         CELLS

TREATMENT

     DRUGS ORDERED
      PREDNISONE
         40 MG
      IMURAN
         200 MG
      ANTIBIOTIC - CHLOROMYCETIN 2 GMS PENICILLIN 2,400,000U
```

FIG. 35. Print-out form of a narrative type derived from data-processing forms.

```
                                IC NUM-NOCHTT53108353        DATE OF BIRTH-16- 2-40   SEX-F        PAGE  1

                          24-HOUR URINE OUTPUT                ELECTROLYTES                NON-ELECTROLYTES      CREAT.
  DATE          TIME      VOLUME     NA+      K+      HA+      K+      CL-      CO2      BUN      CREAT.     CLEARANCE
DY MO YR

13 01 64        0000        8000      N/A      N/A      137      5.7       93       18      116       21        N/A
14 01 64        0000        6465      353       71      143      4.2      108       26       47      2.7        N/A
15 01 64        0000        4320      547      196      144      3.7      105       30       12      0.9         59
16 01 64        0000        3970      352      184      145      3.4      100       29        9      0.9         55
17 01 64        0000        3500      340      180      143      2.7      104       29        5        1        N/A
18 01 64        0000        5700      320      185      148      3.4      102       29        5      0.9         54
19 01 64        0000        3700      320      184      147      4.8      101      26.        5      0.6        N/A
20 01 64        0000        4400      299      184      141      2.5       98       28        5      0.4         50
21 01 64        0000        3120      102      178      141      3.4       94       30        9      0.6         62
22 01 64        0000        2800      250      254      140      4.2       97       29      9.0      0.3         75
```

FIG. 36. Sample of selected daily values in one patient retrieved from data processed through the bio-medical computer center and printed in sequential form.

Acknowledgments

The work on primates was made possible by the efforts of Dr. Kenneth Burns and Dr. Arthur Riopelle. Anesthesia was supervised by Dr. John Adriani and the anesthesiologist participating in the primate work was Dr. David Scally. Radiotherapy was supervised by Dr. J. V. Schlosser. Renograms were made by Dr. Jack Mobley. We are indebted to the following for donations of chimpanzees: Major C. H. Kratochvil, USAF M.C., Commander, 6571st Aeromedical Research Laboratory, Holloman AFB, New Mexico; Major J. D. Marshall, Walter Reed Army Medical Center, Washington, D.C.; Mr. George Douglas, New Orleans Zoological Garden, New Orleans, Louisiana; and the Delta Regional Research Primate Center.

References

1. Ovid and Apollodorus, quoted by Edith Hamilton. Mythology. Boston. Little, Brown and Co., 1940.
2. Princeteau, M.: Greffe rénale. J. Méd. Bordeaux, **26**:549, 1905.
3. Jaboulay, M.: Greffe de reins au pli du coude par soudures artérielles et veineuses. Lyon Med., **107**:575, 1906.
4. Unger, E.: Nierentransplantationen. Klin. Wschr., **47**:573, 1910.
5. Neuhof, H.: Transplantation of Tissues. New York. Appleton and Co., 1923, p. 260.
6. Murray, J. E., *et al.:* Kidney Transplantation in Modified Recipients. Ann. Surg., **156**:337, 1962.
7. Murray, J. E., *et al.:* Reversibility of Kidney Homograft Rejection by Retransplantation and Drug Therapy. Ann. N. Y. Acad. Sci., **99**:743, 1962.
8. Murray, J. E., *et al.:* Prolonged Survival of Human-Kidney Homografts by Immunosuppressive Drug Therapy. New Engl. J. Med., **268**:1315, 1963.
9. Shackman, R., W. J. Dempster and O. M. Wrong: Kidney Homotransplantation in Human. Brit. J. Urol., **35**:222, 1963.
10. Hume, D. M., *et al.:* Renal Homotransplantation in Man in Modified Recipients. Ann. Surg., **158**:608, 1963.
11. Starzl, T. E., T. L. Marchioro and W. R. Waddell: Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance. Surg., Gynec. Obstet., **117**:385, 1963.
12. Hitchcock, C. R.: Personal communication.
13. Reemtsma, K., *et al.:* Heterotransplantation of the Kidney: Two Clinical Experiences. Science, **143**:700, 1964. (Case 1)
14. Gagnon, J. A. and R. W. Clarke: Renal Functions in the Chimpanzee. Am. J. Physiol., **190**:117, 1957.
15. Wiener, A. S. and J. Moor-Jankowski: Blood Groups in Anthropoid Apes and Baboons. Science, **142**:67, 1963.
16. Reemtsma, K., B. H. McCracken, J. U. Schlegel, M. A. Pearl, C. W. DeWitt and O. Creech, Jr.: Reversal of Early Graft Rejection After Renal Heterotransplantation in Man. J.A.M.A., **187**:691, 1964.

Discussion

Dr. Joseph Murray (Boston): Dr. Reemtsma's persistence in the study of heterotransplantation, although as yet not of clinical usefulness, has opened up this phase of transplantation biology for further experimental investigation. None of us one year ago would have guessed that any primate graft would have survived for 12 weeks. Certainly no one would have expected that any would have had a reversal of a rejection process, as has been so beautifully demonstrated by Dr. Reemtsma.

Primate grafts may in the future serve as a potential source of donor organs, and this possibility alone warrants further laboratory study in their use.

It is a tribute to Dr. Reemtsma's group that their initial failure did not dissuade them, as it has so many others in the past 50 years. Their persistence reflects an open-minded attitude so necessary for the accumulation of valid scientific data.

Dr. Reemtsma mentioned that we have established a registry of human kidney homotransplants under the aegis of the National Research Council and with the help of the Public Health Service. This registry is open to everybody performing or contemplating human kidney homotransplantation. We will send data sheets to anyone requesting them. All data will be tabulated, processed, and programmed on a semi-annual basis, and published in the journal *Transplantation* and all information will be available on request to all at any time.