be transported against an *apparent* concentration gradient into a region where glucose is present at a different anomeric composition. This hypothetical passage of glucose is actually passive but would appear to be active when viewed as total glucose without considering the anomeric compositions of the glucose in the two compartments. There is no bar in the mutarotase hypothesis to the passive transfer of a nonmutarotating inhibitor through the mutarotase system since an inhibitor could possess the structural requirements for passage via this system. Mutarotation would be required only for the type of "uphill" transport exemplified by glucose in this instance. The mutarotation of a substance, therefore, may not be necessary for its transport via the mutarotase system. Carrier mechanisms for transport have been proposed by which both substrates and inhibitors may be transported (*15*). Widdas (*16*) has postulated that the entrance into the cell and active transport may be the result of two different systems, with only the active transport being energy dependent. In accordance with this view, to actively transport a nonmutarotating substance by way of mutarotase, a second step dependent on energy would be required.

Thus, it is possible to state that the sharing of all or a part of a common pathway by glucose and by an inhibitor of mutarotase, cannot of itself be used as an argument to rule out participation of mutarotase in such a common pathway. Obviously, these considerations also apply to a compound such as α-methyl glucoside which is actively transported (*17*) and inhibits mutarotase (*18*).

ALBERT S. KESTON
Institute for Medical Research and Studies, New York

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Heterotransplantation of the Kidney: Two Clinical Experiences

Abstract. *The field of heterotransplantation is now being explored because of success with immunosuppressive measures in homotransplantation, and because of the scarcity of suitable human organs. Two patients in terminal uremia, maintained on dialysis, received heterotransplants from nonhuman primates. In the first case a renal heterotransplant from a rhesus monkey implanted in a 32-year-old woman showed satisfactory immediate function but was removed after 10 days because of inadequate function. The second patient received a renal heterotransplant from a chimpanzee. A threatened rejection was reversed with immunosuppressive measures, but 2 months after transplantation the patient died of pneumonia. The transplanted kidneys showed no evidence of rejection.*

Heterotransplantation of the kidney was attempted early in this century (*1*) but no function of such grafts was documented. When the immunologic basis of the rejection process was defined, interest in heterotransplantation waned. New exploration of this field now seems warranted because of success with immunosuppressive measures in homografts (*2*) and because of difficulties in obtaining suitable human organs. In two patients in terminal uremia, renal heterografts from nonhuman primates were used when no homografts were available.

Case 1. A 32-year-old female with a documented history of hypertension and pyelonephritis during her seventh pregnancy in 1958 was admitted to Charity Hospital in March 1963 with symptoms of weakness, vomiting, weight loss, and abdominal pain. Examination showed a lethargic, chronically ill patient with blood pressure of 150/100. Laboratory studies included a hematocrit of 23 percent; urinalysis showed pyuria, albuminuria, and specific gravity of 1.007. Other studies included the following: blood urea nitrogen, 120 mg per 100 ml of blood; creatinine, 6 mg per 100 ml of serum; creatinine clearance, 14 ml/min; and urine culture, *aerobacter aerogenes*.

In May 1963, the patient was readmitted to Charity Hospital in uremic coma. Tracheostomy was performed. She improved with medical management but was readmitted in August 1963 because of congestive heart failure and progression of uremia. On admission she showed blood pressure of 180/100, ascites, and marked edema. Hematocrit upon admission was 21 percent; hemoglobin, 6.2; blood urea nitrogen, 160 mg per 100 ml; and creatinine, 17.2 mg per 100 ml of serum; urinalysis showed specific gravity of 1.008, albuminuria and pyuria.

Peritoneal dialysis was begun, and a search was made for a human kidney from either a volunteer or cadaver. Because of progressive deterioration and the lack of a homograft, a heterograft was used. On 8 October 1963, the donor, a rhesus monkey, was prepared with hypothermia and anticoagulation. Both kidneys, the aorta, and the vena cava were removed *en bloc* and transplanted into the right iliac fossa of the patient. The aorta and vena cava of the graft were anastomosed to the external iliac artery and vein, respectively, of the recipient. The ureters were implanted into the bladder through submucosal tunnels. The time of ischemia was 46 minutes. Immunosuppressive agents included azathioprine (Imuran), steroids, actinomycin C, and azaserine. Mannitol was given during and immediately after the operation.

Urine appeared in the ureteral orifices 10 minutes after completion of the anastomoses. Urinary output reached a maximum of 3500 ml on the 1st day and creatinine clearance rose to 24 ml/min. Additional laboratory data are given in Table 1.

On 13 October an episode of acute abdominal pain and tenderness prompt-

ed exploration of the wound. A small retroperitoneal hematoma was evacuated, but the kidneys appeared normal on gross examination. On 15 October oliguria was noted and the following day peritoneal dialysis was resumed. On 18 October the graft was removed. Despite dialyses, uremic coma and gastrointestinal bleeding occurred. Tracheostomy was performed on 20 October, and later that day the patient died.

Gross examination of the specimen showed several punctate hemorrhagic areas on the surface of the kidneys, patency of the main renal vessels, and thickening and obstruction of the distal ureters. On microscopic examination most glomeruli were normal but in a few instances showed some slight proliferations. Proximal and distal convoluted tubules showed degenerative changes with loss of epithelial cells, regenerative activity, and granular casts in the lumen. The interstitium showed mild to moderate edema and a sprinkling of inflammatory cells. There were scattered dense accumulations of inflammatory cells surrounding arterioles, venous sinusoids, and glomerular capsules. The cells were predominantly lymphocytes and histiocytes with an occasional plasma cell and neutrophile. Many of the arterioles showed severe fibrinoid necrosis surrounded by an infiltrate of neutrophiles and interstitial extravasation of erythrocytes. Larger arteries were normal. Sections of the ureters showed intact mucosa and extensive extravasation of erythrocytes throughout the wall.

Case 2. A 43-year-old male with a documented history of hypertension since 1957 underwent renal biopsy in 1959 which showed chronic glomerulonephritis. He was readmitted in June 1963 with congestive heart failure, and laboratory data included blood urea nitrogen of 135 mg and serum creatinine of 8 mg per 100 ml of blood. He was transferred from Veterans Administration Hospital to Charity Hospital. In preparation for transplantation, peritoneal dialysis was begun and azathioprine, actinomycin C, and steroids were given for 1 week. As no suitable human kidney became available, a heterograft was used.

The donor, a 41-kg male chimpanzee, was prepared with general anesthesia and endotracheal intubation. Body temperature was lowered to 30°C and after heparin was administered the entire renal complex, including both kidneys, ureters, aorta, and vena cava, was removed *en bloc*. Vascular continuity was restored by end-to-side anastomoses of donor aorta and vena cava to the recipient's external iliac artery and vein, respectively. Donor ureters were implanted into the patient's bladder through submucosal tunnels. The period of ischemia was 39 minutes. Mannitol was given during and immediately after implantation, and urine flow appeared approximately 10 minutes after completion of the vascular anastomoses.

Table 1. Clinical course and laboratory data in case 1.

Date (1963)	Urine volume (ml/24 hr)	Blood urea nitrogen (mg/100 ml)	Serum creatinine (mg/100 ml)	Creatinine clearance (ml/min)
31 Aug.	<400	160	17.2	
4 Sept.	<400	148	14.6	1.6
Dialysis				
21 Sept.	<200	103	12.8	
Dialysis				
7 Oct.	200	55	6.8	
Transplant				
8 Oct.	3500	55	6.7	24.3
9 Oct.	1950	69	5.7	13.5
10 Oct.	860	63	4.6	9.3
11 Oct.	1330	74	4.6	9.1
12 Oct.	1880	89	4.9	11.6
13 Oct.	1920		5.0	9.6
14 Oct.	930		5.1	6.0
15 Oct.	340	112	7.1	
16 Oct.	240	132	8.7	0.47
Dialysis				
17 Oct.	220	130	6.4	0.48
18 Oct.	100	100	4.8	0.64
Removal of transplant				
Dialysis				
19 Oct.	100	78	4.8	
Dialysis				
20 Oct.	10		5.0	
Dialysis				
Tracheostomy				
Death				

During the first 24 postoperative hours, urinary output was 7200 ml and creatinine clearance rose from a preoperative value of 3.7 to 78 ml/min. Additional laboratory data are included in Table 2.

On the 4th postoperative day, threatened rejection of the transplant was suspected when the patient's temperature rose to 103, when the urinary output declined sharply, and when the urinary sediment showed numerous lymphocytes. Treatment included increased doses of azathioprine, steroids,

Table 2. Clinical course and laboratory data in case 2.

Date (1963)	Urine volume (ml/24 hr)	Blood urea nitrogen (mg/100 ml)	Serum creatinine (mg/100 ml)	Creatinine clearance (ml/min)
17 Oct.	1850	176	16.0	8.22
Dialysis				
22 Oct.	1400	140	12.0	6.0
28 Oct.	1700	140	14.0	3.7
Dialysis				
4 Nov.	300	89	9.8	
Transplantation				
6 Nov.	7200	112	7.1	78.0
7 Nov.	4750	72	2.4	56.0
8 Nov.	4000	46	1.5	49.4
9 Nov.	878	39	1.5	11.9
Rejection				
10 Nov.	1750	34		21.9
Reversal of rejection				
11 Nov.	3300	124	3.0	50.4
12 Nov.	3900	136	2.4	55.4
13 Nov.	2500	92	1.5	66.0
14 Nov.	2900	61	1.2	56.9
15 Nov.	2870	33	0.8	60.0
16 Nov.	2940	30	1.3	61.6
17 Nov.	4640	20	1.2	78.4
18 Nov.		28	1.3	

and actinomycin C, as well as local radiation to the graft which was repeated on the 7th and 10th days after transplantation. Clinical findings and laboratory data suggest that the rejection was reversed.

Additional evidence of graft function includes repeated normal renograms over the transplant without evidence of function of the patient's own kidneys and concentration of activity in the transplant by renal scanning. Intravenous urography demonstrated function of both transplanted kidneys on the 10th day after transplantation.

These cases illustrate that immediate function of the heterografts was satisfactory. Findings in the second case suggest that early rejection may be reversed by currently available immunosuppressive measures. The question of long-term function remains, of course, unanswered.

Note added in proof. The patient described in case 2 was readmitted with pneumonia on 20 December 1963. Despite treatment with antibiotics and reduction in dose levels of immunosuppressive drugs he showed progressive pulmonary infection and hypokalemia. He died on 6 January 1964. Autopsy showed acute bronchopneumonia in the right lower lobe, acute tracheobronchitis, and resolving abscess in the right middle lobe. Sections of the transplanted kidneys showed no evidence of rejection. The findings of acute tubular necrosis were interpreted as consistent with the state of shock, necessitating vasopressors for 36 hours before death; the transplant showed no cellular infiltrate and no changes in the blood vessels. Three patients treated subsequently by a similar method during the past month show satisfactory function of heterografts.

KEITH REEMTSMA
BRIAN H. MCCRACKEN
JORGEN U. SCHLEGEL
MAURICE PEARL
Tulane University School of Medicine, New Orleans, Louisiana

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20 November 1963

Intracranial Reward Delay and the Acquisition Rate of a Brightness Discrimination

Abstract. *An application of the techniques of intracranial self-stimulation to the study of delayed reward indicates that the rate of discrimination learning for stimulation of the hypothalamus is a decreasing function of the delay interval. The resulting delay-of-reward gradient does not appear to differ appreciably from other such gradients based on food reward.*

The demonstration that electrical stimulation of the brain can serve as an effective reward (*1*) has provided a new basis on which to approach the study of many reinforcement phenomena. Numerous investigators have, in fact, used these stimulation techniques to good advantage to study such factors as the brain structures involved in reward effects (*2*), the influence of various drive states on these central reward structures (*3*), and a variety of other related problems. Still another potentially useful application might be in studying the temporal parameters of reward and their relation to learning. Precise control of the duration of reinforcement or of the delay between the occurrence of a response and its reward is frequently complicated when food or water is the reward, since such factors are, in part, contingent upon the animal's behavior. In contrast, the techniques of electrical stimulation permit direct experimental control of such parameters and the use of a wider range of intervals than is normally possible with conventional reinforcers.

Evidence presently available indicates that brain stimulation is an effective reward in a learning situation. Rats will, for example, learn a multiple maze for such stimulation (*4*), and more recent evidence suggests that stimulation of certain areas of the hypothalamus is at least as effective a reward as food for the learning of a brightness discrimination (*5*). In the work reported here, this line of investigation was extended to study the rate of learning among groups reinforced by stimulation when there are differences in the stimulation along a temporal dimension. Delay of reward (stimulation of the hypothalamus) was the parameter chosen.

Male Sprague-Dawley rats were prepared for this experiment by permanent implantation of bipolar electrodes ("chronic electrodes") aimed at the same area of the posterior hypothalamus in all the animals. Subsequent histological examination of the brains of a sample of 12 of the 48 experimental animals revealed that the majority of these electrodes terminated in the dorsomedial and posterior hypothalamic nuclei, the remainder being distributed in the more lateral region of the hypothalamus or more posteriorly in the supramammillary area. Stimulation was provided by a biphasic rectangular waveform, with the parameters held constant throughout the experiment at the following values: peak current, 2 ma; frequency, 85 pulses per second; pulse duration, 0.175 msec; train duration, 0.5 second. Prior work with stimulation of essentially these same areas of the hypothalamus has indicated that effective reward is provided by these stimulus conditions (*6*).

The experimental compartment was a rectangular box containing two response bars; in the pretraining phase of the experiment the box was divided into two boxes, each with one bar, by the addition of a center panel. Under this latter condition each subject was first trained to press for stimulation on one or the other of the bars. A training session followed in which each response extinguished the house lights for a 10-second period and eliminated the opportunity for reinforcement until the lights came on again. Of each group of six animals completing 100 such trials on both sides of the box, one

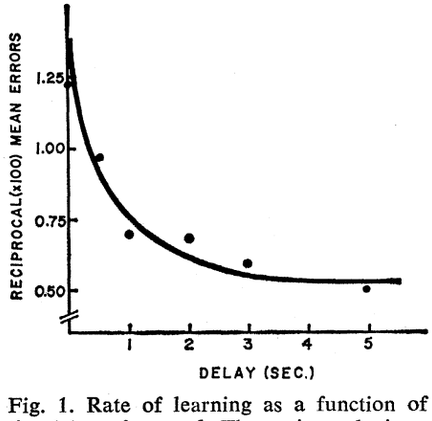

Fig. 1. Rate of learning as a function of the delay of reward. The reciprocal, times 100, of the mean number of errors in 500 trials is plotted against the delay interval. The curve has been visually fitted to the data points.