STUDIES ON THE FUNCTIONAL CAPACITY OF A DENERVATED HOMOTRANSPLANTED KIDNEY IN AN IDENTICAL TWIN WITH PARALLEL OBSERVATIONS IN THE DONOR¹

By NEAL S. BRICKER,² WARREN R. GUILD,³ JOHN B. REARDAN,⁴ AND JOHN P. MERRILL⁵

(From the Department of Medicine, Peter Bent Brigham Hospital, Harvard Medical School, and the Howard Hughes Medical Institute, Boston, Mass.)

(Submitted for publication May 25, 1956; accepted August 10, 1956)

The successful transplantation of a human kidney between 24-year-old male identical twins has made possible the study of the function of a homo-transplanted kidney. The purposes of the study were twofold: 1) to evaluate the functional capacity of the transplanted kidney; 2) more specifically, to investigate the capacity of a transplanted, and therefore totally denervated, kidney to regulate renal hemodynamics and electrolyte and water excretion.

Studies were performed on both the recipient (R) and the donor (D). All but one of the experiments on R were performed after his own two kidneys had been surgically removed; thus, the majority of the data obtained specifically describes the function of the transplanted organ. Certain parallel studies were performed on D, who after transplantation possessed as his only source of renal function the mate of the transplanted kidney.

METHODS

Case material

The subjects were 24-year-old white male monozygous twins. The donor was clinically well and possessed normal renal function. The recipient was a victim of far advanced, inexorably progressive chronic glomerulonephritis of at least 16 months' duration and prior to transplantation presented the classic manifestations of uremia and malignant hypertension. After a period of

preliminary study, during which time the twins were shown to be identical, D's left kidney was transplanted retroperitoneally into the right iliac fossa of R. End to end anastomoses were effected between the renal artery of the transplanted organ and the recipient's right hypogastric artery and between the renal vein and the right common iliac vein. The ureter was implanted directly into the urinary bladder.

Clinical improvement began in the immediate post-operative period and continued until all the apparent stigmata of both uremia and hypertension regressed. Bilateral nephrectomy was performed in a two-stage procedure at three and at five and one-half months following transplantation, leaving R with only the transplanted organ. To date he has enjoyed over a year of total well being on an unrestricted regimen. Detailed accounts of the clinical course and operative procedure have been previously described (1).

Procedure

Twenty-three clearance studies and several miscellaneous experiments were performed over an eighteen-month period. Control studies were obtained on D prior to transplantation. The majority of observations on R was made during a four-month interval beginning six months after transplantation.

Except where indicated, all studies were performed in the morning with the subjects postprandial and recumbent. In ten studies (six on R and four on D) glomerular filtration rate (GFR) was measured by the clearance of inulin (C_{in}) using standard renal clearance techniques as previously described (2). In nine of these ten studies, effective renal plasma flow (ERPF) was measured by the clearance of p-aminohippurate (C_{PAH}). In six of the studies in which C_{in} was measured, urine was collected through an indwelling soft rubber multiholed catheter, and urine collection periods (15 to 20 minutes in duration) were concluded with two washouts of distilled water and two or more injections of air. In the control and early postoperative studies on D and the postoperative (left nephrectomy) and osmotic diuresis studies on R, bladder catheterization was not performed.

In an additional ten studies (six on R and four on D) endogenous creatinine clearance (C_{cr}) was employed to estimate trends in GFR. These studies were carried out using voided specimens. In the majority of individual

¹ This study was supported in part by grants from the John A. Hartford Foundation, Inc.; the Medical Research and Development Board, Office of the Surgeon General, Department of the Army; the U. S. Public Health Service; and the American Heart Association.

² Present address: Washington University School of Medicine, St. Louis, Missouri.

³ Life Insurance Medical Research Fellow.

⁴ U. S. Public Health Service Fellow.

⁵ Established Investigator of the American Heart Association.

TABLE I *
Serial measurements of C_{in} , C_{Cr} and C_{PAH} in recipient and donor

	Time, mos. after transplant.	C_{in} ml./min.	C_{Cr} ml./min.	C_{PAH} ml./min.	F.F. %	24 hr. C_{Cr} ml./min.
Donor						
Two-kidney control		147		477	33.0	
Recipient						
Before right nephrectomy	3	67		369	18.0	
After bilateral nephrectomy	6		84			
	6	65		460	14.2	
	6		82			
	7	71		378	18.7	
	7		86			
	7	59		391	15.0	
	7		73			
	8	61		362	16.7	
	8		78			
	9		96			
	9	65	94			
	9					65
	9					68
	9					67
Donor						
After removal of left kidney	1	68		389	17.6	
	7	74		413	17.9	
	7		92			
	7		77			
	8	84		420	20.0	
	8		76			
	8		93			

* C_{in} = inulin clearance; C_{Cr} = endogenous creatinine clearance; C_{PAH} = p-aminohippurate clearance; F.F. = filtration fraction.

clearance periods, urine flows exceeded five ml. per minute, and the collection periods were generally greater than 20 minutes in duration. Finally, in three studies (on the recipient) GFR was estimated by means of 24-hour C_{Cr} . The experiments which did not include estimation of GFR will be considered in the text.

Because of the diversified nature of the experiments performed, additional comments on individual experimental protocols will be included in the discussion of results.

Inulin was determined according to the method of Roe, Epstein, and Goldstein (3); PAH according to the method of Smith, Finkelstein, Aliminos, Crawford, and Graber (4); chloride according to the method of Van Slyke and Hiller (5); and creatinine according to the method of Bonsnes and Taussky (6). Sodium and potassium were analyzed on an internally compensated Barclay flame photometer; urine and plasma osmolalities were determined on a Fiske Osmometer; pH was determined on a Beckman pH meter; and CO_2 was determined manometrically (7).

Clearance values have not been corrected to standard body surface area. For purposes of such correction, the body surface area of the recipient was 1.71 sq.m., and of the donor 1.80 sq.m.

RESULTS

I. Serial Measurements of GFR and ERPF; Concentration and Dilution; Acidification and Alkalinization

A. Serial measurements of C_{in} and C_{PAH} (Table I)

Each datum is the mean of three clearance periods. The pretransplantation two-kidney control values in D were C_{in} = 147 and C_{PAH} = 477 ml. per minute.

Recipient: C_{in} after left nephrectomy but prior to right nephrectomy was 67 ml. per minute. Serial values for C_{in} following bilateral nephrectomy failed to reveal a consistent trend, and the average value for the five studies was 64 ml. per minute. C_{PAH} ranged from 369 to 460 ml. per minute, but again no trend was apparent. Filtration fractions varied in an irregular manner from 14.2 to 18 per cent.

C_{Cr} ranged from 73 to 96 ml. per minute with a mean of 85. The C_{Cr}/C_{in} ratio (using composite

TABLE II
Solute and water excretion during mannitol and Pitressin® infusion in the recipient*

Per.	Time min.	C _{in} ml./min.	V ml./min.	U _{Na} V μEq./min.	U _{Na} V/FI %	U _{Cl} V μEq./min.	U _K V μEq./min.	Osm U/P	C _{osm} ml./min.	Tm ^a H ₂ O ml./min.	Tm ^a H ₂ O/C _{in} %
0	-154 to 0		0.27					2.8			
Prime: Inulin 2.8 gm.; Pitressin® 100 mU at -47 min.; Sustain: Inulin 22 mg./min.; Pitressin® 1 mU/min. in 0.9% saline at 8.8 ml./min. from -41 to 8 min.; Inulin 22 mg./min.; Pitressin® 1 mU/min.; Mannitol 1.1 gm./min. in 0.9% saline at 8.8 ml./min. from 8 to 147 min.											
1	0 to 41	74	1.3	102	0.99	103	21	2.3	2.9	1.6	2.2
2	41 to 74	63	4.0	232	2.7	253	41	1.7	6.6	2.6	4.1
3	74 to 97	58	5.7	305	4.0	340	56	1.5	8.6	3.0	5.1
4	97 to 118	57	7.3	430	5.8	458	65	1.5	10.6	3.3	5.8
5	118 to 137	52	7.5	450	6.7	487	74	1.4	10.5	3.0	5.8
6	137 to 147	59	9.4	526	6.9	582	90	1.4	12.8	3.4	5.8

* V = urine flow; UV = minute rate of excretion; FI = filtered load (uncorrected for Donnan equilibrium); Osm U/P = osmotic urine/plasma ratio; C_{osm} = osmolar clearance; Tm^aH₂O = maximum rate of solute free water removal. See preceding table for additional definitions.

mean values) was 1.33. C_{Or}/C_{in} when both clearances were measured concurrently was 1.44. Values for 24-hour C_{Or} during the administration of a 200 mg. sodium diet were 65, 68 and 67 ml. per minute, respectively.

Donor: C_{in} increased from 68 ml. per minute one week after transplantation to 84 ml. per minute eight months later. C_{PAH} increased from 389 to 420 over the same period. C_{Or} varied in an inconsistent manner between 76 and 93 ml. per minute. C_{Or}/C_{in} (using composite mean values for the same period of time) was 1.07.

B. Concentration and dilution (Table II)

Concentrating ability in R was assessed both by the maximal osmotic U/P ratio and by the maximal rate of solute-free water removal.⁶ Following withdrawal of water for 14 hours, R achieved a maximal osmotic U/P ratio of 2.78. During osmotic diuresis induced by mannitol infusion and under the influence of Pitressin® antidiuresis (100 mU administered intravenously as a single priming dose, and 1 mU per minute by constant infusion) the maximal value for solute-free water extraction (Tm^aH₂O) was 3.4 ml. per minute. The ratio

⁶ The concentration process in the normal subject is characterized by two limiting values. At low rates of urine flow, solute-free water may be reabsorbed to a maximal osmotic U/P ratio of approximately four. At high rates of urine flow, such as are obtained during osmotic diuresis, the removal of solute-free water under maximal ADH stimulation is governed by an upper limit (Tm^aH₂O). The normal value for Tm^aH₂O is 5.1 ± 1.5 per cent C_{in} (8). The osmotic U/P ratio in the normal subject during water diuresis does not typically decrease below 0.2.

Tm^aH₂O/C_{in} remained constant at 5.8 per cent during the final three clearance periods.

The diluting capacity of R was judged by means of his ability to elaborate a hypotonic urine following water loading.⁶ The minimal osmotic U/P ratio observed was 0.36.

The concentrating and diluting abilities of D were tested under conditions of water deprivation and water loading, respectively. The osmotic U/P ratios were of the same order of magnitude as those of the recipient.

C. Acidification and alkalization (Table III)

The recipient was given 4.0 gm. of non-enteric coated ammonium chloride in divided doses over the course of one day. On the following morning, voided urine samples were collected under oil at approximately 30-minute intervals. After a control period, 0.25 gm. of Diamox® (acetazolamide) was administered by mouth and five follow-up periods were obtained.

Following Diamox® administration, urinary pH rose from a control value of 5.33 to 7.63. Titratable acid disappeared within 30 minutes and bicarbonate and potassium excretion rates increased appreciably. Excretion rates of Na and Cl will be discussed below.

II. Experimental Alteration of Renal Hemodynamics

A. Intravenous Aminophylline

The influence of a single intravenous injection of 0.5 gm. of Aminophylline was examined in R

EFFECTS OF AMINOPHYLLINE

FIG. 1. THE INFLUENCE OF A SINGLE INTRAVENOUS INJECTION OF AMINOPHYLLINE ON RENAL HEMODYNAMICS, WATER AND ELECTROLYTE EXCRETION IN THE RECIPIENT

Aminophylline was injected over five minutes, and an additional five minutes was allowed before beginning the fourth period.

only (Figure 1). Subsequent to the administration of Aminophylline, C_{in} increased from a mean control value of 65 ml. per minute to a maximum of 82, whereas C_{PAH} showed a slight downward trend. Filtration fractions rose progressively from a mean control value of 14.2 to 18.4 per cent.

Urine flow and electrolyte excretion values will be considered below.

B. *L*-norepinephrine infusion

The response of both R and D to the infusion of *l*-norepinephrine at two dosage levels was ob-

FIG. 2. THE INFLUENCE OF CONTINUOUS INFUSION OF L-NOREPINEPHRINE ON RENAL HEMODYNAMICS AND ELECTROLYTE EXCRETION

Solid line = recipient; dashed line = donor.

served (Figure 2). After three control periods in each subject, *l*-norepinephrine was infused continuously at the rate of 2 μ g. per minute. Approximately 15 minutes was allowed for equilibration, and three clearance periods were then obtained. Thereafter, *l*-norepinephrine was administered at 10 μ g. per minute, and following stabilization of blood pressures (approximately 25 minutes) three final periods were obtained.

Blood pressure did not increase appreciably in either subject during the 2 μ g. dose, whereas rises of 30 to 40 mm. systolic and 20 to 25 mm. diastolic were produced by the larger dose. C_{in} remained constant throughout in both subjects. C_{PAH} , however, decreased strikingly during the infusion of the low dose, and following the increment in dosage a further decrease was demonstrable. Filtration fractions rose from a control value of 15 to 30 per cent in R and from 20 to 30 per cent in

D. Data on solute and water excretion will be discussed below.

C. Orthostatic hypotension

The results of this study in R are shown in Figure 3. The experiment was intended to assess the response to quiet standing; however, changing from the recumbent to the erect position on each of two occasions was attended by symptoms and signs of peripheral vascular collapse. In both instances return to the supine position was followed by prompt improvement. It was not possible to obtain measurements of blood pressure during the periods of maximal distress, but it is probable that the actual fall exceeded that recorded in Figure 3.

During the first clearance period following hypotension, C_{in} fell from the mean control value of 61 ml. per minute to 29, and thereafter increased slowly, ultimately exceeding the control level.

EFFECTS OF ORTHOSTATIC HYPOTENSION

FIG. 3. THE INFLUENCE OF ORTHOSTATIC HYPOTENSION ON C_{in} , WATER AND ELECTROLYTE EXCRETION IN THE RECIPIENT

C_{PAH} decreased from 362 ml. per minute to 162 and then rose to 437 during the fifth follow-up period. The electrolyte and water excretion rates will be referred to below.

III. Experimental Alteration of Salt and Water Excretion

A. Influence of drugs presumably having an intrarenal site of action

1. *Hydrocortisone*: Studies were performed on R only (Table IV). He was studied in the recumbent position⁷ and because of the long duration of the experiment was allowed light meals. Water diuresis was initiated by the preliminary ingestion of 750 ml. of water and maintained by

⁷ Subjects were allowed to stand during the brief intervals of voiding to facilitate bladder emptying in this and following experiments in which catheterization was not employed.

the administration of supplementary oral water and intravenous 5 per cent dextrose in water.

After three control periods, 134 mg. of hydrocortisone hemisuccinate (equivalent to 100 mg. of hydrocortisone) was administered by single intravenous injection, and 134 mg. was administered by constant infusion in 500 ml. of 0.9 per cent saline over a two-hour period. Observations were continued for 11 hours after completion of the infusion.

C_{Cr} decreased moderately during the period of drug administration, but thereafter returned to the control level. Urine flow, sodium excretion rate ($U_{Na}V$), and chloride excretion rate ($U_{Cl}V$) all increased initially; however, by the ninth clearance period, a decrease in each of these values was noted. During the tenth clearance period (340 minutes after the start of the infusion) $U_{Na}V$ had decreased to a minimum value of 27.5 μ Eq. per minute (control 83 to 115) and urinary sodium concentration was 5.5 mEq. per L. Potassium

TABLE III

*The effects of Diamox® on urinary pH, titratable acidity and electrolyte excretion in the recipient **

Per.	Time min.	V ml./min.	pH	TA μ Eq./min.	$U_{Na}V$ μ Eq./min.	$U_{Cl}V$ μ Eq./min.	U_KV μ Eq./min.	$U_{HCO_3}V$ μ mol./min.
4.0 gm. NH_4Cl day preceding study								
0	-30 to 0	1.7	5.33	18.7	99	125	40	2
0.25 gm. Diamox® orally								
1	0 to 30	3.3	5.83	10.5	107	132	48	4
2	30 to 60	4.0	7.25		284	239	114	34
3	60 to 90	4.4	7.35		326	251	172	185
4	90 to 120	2.4	7.63		224	138	126	159
5	120 to 168	3.2	7.53		252	169	125	164

* TA = titratable acidity. See preceding tables for additional definitions.

excretion rate (U_KV) increased markedly initially and ultimately levelled off at greater than twice the control value. Plasma electrolyte values remained constant.

2. *L-norepinephrine infusion*: The influence of *L-norepinephrine* on renal hemodynamics in both D and R has been discussed above. The effects on electrolyte and water excretion in R (Figure 2) were as follows: $U_{Na}V$ and $U_{Cl}V$ remained essentially unchanged throughout, and U_KV decreased modestly during the infusion of 10 μ g. per minute. Urine flow increased during the low dose, but returned toward control levels during the high dose.

3. *Intravenous Aminophylline*: The influence of 0.5 gm. of Aminophylline on renal hemodynamics in R has been discussed above. As shown in Figure 1, urine flow increased markedly, as did sodium and chloride excretion rates. The

chloride/inulin and sodium/inulin clearance ratios remained appreciably above control levels throughout the duration of observations.

4. *Diamox® administration* (Table III): Within 90 minutes after the oral administration of 0.25 gm. of Diamox® in R, urine flow increased from 1.7 to 4.4 ml. per minute, $U_{Na}V$ from 99 to 326 μ Eq. per minute, and $U_{Cl}V$ from 125 to 251 μ Eq. per minute. Additional effects of Diamox® have been discussed above.

5. *Osmotic diuresis*: The effects of the infusion of 12.5 per cent mannitol at 8.8 ml. per minute in R are shown in Table II. Urine flow increased from 0.3 to 9.4 ml. per minute, and osmolar clearance (C_{osm}) from 2.9 to 12.8 ml. per minute. $U_{Na}V$ rose from 102 to 526 μ Eq. per minute and C_{Na}/C_{in} increased progressively from 0.99 to 6.9 per cent.

TABLE IV

*The effects of intravenous hydrocortisone on C_{Cr} , solute and water excretion in the recipient **

Per.	Time min.	V ml./min.	C_{Cr} ml./min.	$U_{Na}V$ μ Eq./min.	$U_{Cl}V$ μ Eq./min.	U_KV μ Eq./min.	P_{Na} mEq./L.	P_{Cl} mEq./L.	P_K mEq./L.
1	0 to 51	5.1	95	115	138	31	139		4.3
2	51 to 79	6.2	97	92	94	26			
3	79 to 112	6.5	98	83	83	25	139	108	4.3
Hydrocortisone hemisuccinate: 134 mg. i.v. 127-139 min. and 134 mg. i.v. in 500 ml. 0.9% NaCl 139-250 min.									
4	112 to 140	6.1	85	70	61	32			
5	140 to 171	6.0	75	76	90	39			
6	171 to 230	6.8	83	107	147	70	140	108	4.3
7	230 to 290	7.6	95	105	180	114	140	108	4.4
8	290 to 350	7.5	91	74	155	115	139	108	4.4
9	350 to 410	3.7	64	33	80	65			
10	410 to 470	5.0	100	28	83	83			
11	470 to 560	4.4	99	37	88	92			
12	560 to 920	1.7	93	51	64	69			

* P = plasma. See preceding tables for additional definitions.

VENOUS CONGESTION OF LOWER EXTREMITIES

FIG. 4. THE INFLUENCE OF VENOUS CONGESTION OF LOWER EXTREMITIES ON RENAL HEMODYNAMICS AND ELECTROLYTE EXCRETION

Solid line = recipient; dashed line = donor.

B. Influence of alterations of extracellular fluid (ECF) volume and composition

1. Venous congestion of the lower extremities:

The normal supine human subject responds to the inflation of blood pressure cuffs around the thighs at subdiastolic pressures by decreasing the excretion rates of sodium and water and usually decreasing glomerular filtration rate (9, 10). However, $U_{Na}V$ and $U_{Cl}V$ usually do not decrease (and often increase) during the first clearance period of cuffing (9, 10).

Experiments were performed on both R and D (Figure 4). The subjects were water loaded and maintained in positive water balance throughout. After three control clearance periods, blood pressure cuffs were inflated to just below diastolic pressures and were so maintained for approximately an hour.

Inflation of the blood pressure cuffs in R was attended by a fall in blood pressure and a con-

comitant decrease in C_{in} . By the third period of cuffing, blood pressure and filtration rate returned to control levels. An appreciable decrease in $U_{Na}V$ occurred only during the first period of cuffing, and the mean value for the three periods of cuffing was only 11 per cent below the mean control value. During the follow-up periods $U_{Na}V$ approximated control values. Chloride excretion rates paralleled those of sodium. A decrease in urine flow occurred, which was out of proportion to that of $U_{Na}V$ both in magnitude and duration. Values rose slightly after the cuffs were released. The urine flow response resembled that observed in the normal subject.

In D, C_{in} remained constant throughout. $U_{Na}V$ increased from the mean control value during the first period of cuffing, but fell during the succeeding two periods. During the follow-up periods, $U_{Na}V$ rose, eventually exceeding the control value. The decrease in $U_{Cl}V$ was greater in magnitude

TABLE V*
The effects of hypotonic saline infusion on C_{Cr} , solute and water excretion

Per.	Time min.	C_{Cr} ml./ min.	V ml./ min.	$U_{osm}V$ $\mu\text{osm.}/$ min.	$U_{Na}V$ $\mu\text{Eq.}/$ min.	$U_{Cl}V$ $\mu\text{Eq.}/$ min.	$U_{K}V$ $\mu\text{Eq.}/$ min.	Hct %	T.P. gm. %	P_{Na} mEq./L.	P_{Cl} mEq./L.	P_{K} mEq./L.	Wt. Kg.
A. Recipient													
1	-95 to -65	83	6.7	720	94	147	48	39.5	6.5	144	110	4.2	59.6
2	-65 to -35	81	6.8	738	92	143	42						
3	-35 to -5	82	7.1	717	99	142	41						
Two liters of hypotonic saline (Na 112 mEq./L.; Cl 90 mEq./L.; and HCO_3 22 mEq./L.) infused from 0 to 84 min.													
4	-5 to 25	81	6.7	737	90	115	32	36	5.8	131	104	4.2	
5	25 to 55	78	6.9	589	81	113	34						
6	55 to 85	75	7.3	632	80	113	39						
7	85 to 115	83	6.8	595	64	99	37	34.5	4.9	133	105	3.7	62.5
8	115 to 146	74	6.4	498	52	75	29						
9	146 to 175	71	6.2	424	50	67	28						
10	175 to 205	79	6.2	473	43	68	26	34	4.8	132	105	3.4	
11	205 to 235	75	6.2	475	43	67	26						
12	235 to 268	78	6.4	392	45	64	27	35	5.4	136	109	3.3	62.3
B. Recipient													
1	-105 to -75	90	10.0		310	300	111	44		140	108		
2	-75 to -45	84	9.8		255	259	88						
3	-45 to -15	79	9.0		212	213	95						
Two liters of less hypotonic saline (Na 126 mEq./L.; Cl 102 mEq./L.; and HCO_3 24 mEq./L.) infused from 0 to 73 min.													
4	-15 to 15	81	9.0		191	188	79	43		139	102		
5	15 to 45	75	8.7		184	182	73						
6	45 to 75	95	11.7		260	245	87						
7	75 to 105	75	9.3		197	178	61	39		139	105		
8	105 to 135	77	9.3		172	167	52						
9	135 to 165	76	8.3		141	129	43						
10	165 to 195	99	11.7		193	160	61	40		138	107		
11	195 to 225	77	8.7		139	135	43						
12	225 to 255	57	9.3		173	145	40	40		136	107		
C. Donor													
1	-92 to -63	79	6.6	831	164	194	76	47		139	100	4.1	66.7
2	-63 to -33	76	8.2	780	156	172	79						
3	-33 to -3	72	8.6	774	162	162	75						
Two liters of hypotonic saline (Na 112 mEq./L.; Cl 90 mEq./L.; and HCO_3 22 mEq./L.) infused from 0 to 94.5 min.													
4	-3 to 27.5	64	9.8	833	196	179	88	46	6.7	136	100	4.0	
5	27.5 to 57.5	76	10.9	970	240	222	104						
6	57.5 to 87	75	11.6	1,032	282	249	99						
7	87 to 117		12.6					44	5.8	135	101	3.6	70
8	117 to 147	75	11.6	1,009	313	268	80						
9	147 to 178	89	12.0	996	298	247	67						
10	178 to 208	85	11.6	974	319	240	57	42	5.8	132	98	3.8	
11	208 to 237	92	12.1	1,040	336	272	58						
12	237 to 277	100	10.7	877	294	230	39	41	5.3	131	100	3.5	69.6

* Hct = hematocrit; T.P. = total protein. See preceding tables for additional definitions.

and more sustained than that in $U_{Na}V$. Urine flow decreased markedly during the third period of cuffing, and increased slightly after the first recovery period.

2. *Systemic hypotension*: The effects of orthostatic hypotension on renal hemodynamics in R have been discussed above (Figure 3). Presumably, the fall in blood pressure was associated with

a transient decrease in effective circulating blood volume. Sodium and chloride excretion rates decreased following the onset of hypotension. However, rather than remaining depressed (as occurs in the normal subject), they increased with C_{in} , such that the sodium/inulin and chloride/inulin clearance ratios remained essentially constant throughout. Urine flow, on the other hand, de-

creased and remained depressed throughout the duration of the study.

3. *Hypotonic expansion of ECF*: The rapid infusion of two liters of hypotonic sodium chloride into a hydrated human subject in the supine position evokes an increase in $U_{Na}V$ despite a decrease in plasma sodium concentration (11).

The influence of hypotonic expansion of ECF was studied twice in R and once in D (Table V, A-C). The subjects were hydrated initially (500 ml. of water over a 30 to 60-minute period) and maintained in positive water balance thereafter. The control periods were begun after brisk water diuresis was in force.

In R (Table V-A) hypotonic expansion was associated with a progressive decrease in total solute, sodium and chloride excretion rates. Urine flow showed only minor changes and C_{Cr} decreased moderately. Plasma sodium concentration (P_{Na}) fell strikingly following hydration and increased modestly after completion of the infusion.

In a separate study (Table V-B), R's response to a less hypotonic solution was observed. The results were similar to those noted in the preceding experiment, despite the fact that the decrease in P_{Na} was of small magnitude.

The donor responded to hypotonic expansion in a manner characteristic of the normal subject (Table V-C). Thus, urine flow, total solute excretion, $U_{Na}V$, and $U_{Cl}V$ all increased appreciably subsequent to initiation of the infusion. C_{Cr} approximated control levels during expansion but rose during the follow-up periods.

4. *Isotonic expansion of ECF*: The normal human responds to the intravenous administration of isotonic saline by a moderate increase in the excretion rates of sodium and water and by the elaboration of an isotonic or hypertonic urine. When a single dose of two liters of water is administered 8 to 12 hours in advance of the saline infusion, the latter produces a copious excretion both of sodium and of water and the urine becomes hypotonic (12, 13).

The response of both R and D to the infusion of 3,000 ml. of isotonic saline at 42 to 54 ml. per minute was observed. Each subject was studied twice, once in the hydropenic state (no water for 14 hours preceding the infusion), and again in the prehydrated state having ingested two liters of tap water ten hours before the infusion.

Recipient, hydropenic state: The results of this and the prehydration study on R are shown in

TABLE VI *
The effects of isotonic saline infusion on C_{Cr} , solute and water excretion in the recipient

Per.	Time	C_{Cr}	V	Osm U/P	C_{osm}	CH_2O	$U_{osm}V$	$U_{Na}V$	$U_{Cl}V$	$U_{K}V$
Hydropenic State										
Three liters of isotonic NaCl ($Na = 144$ mEq./L.) infused from 0 to 70 min.										
1	-8 to 21	67	0.9	2.1	1.9	-1.0	522	97	118	32
2	21 to 36	77	1.8	1.5	2.6	-0.8	729	135	173	52
3	36 to 51	76	3.0	0.84	2.5	0.5	699	135	203	59
4	51 to 70	63	3.4	0.59	2.0	1.8	571	89	226	63
5	70 to 82	88	5.9	0.47	2.8	3.1	781	113	187	86
6	82 to 99	67	5.8	0.38	2.2	3.5	628	92	147	73
7	99 to 117	67	6.3	0.36	2.3	4.1	646	89	152	74
8	117 to 137	59	5.4	0.37	2.0	3.4	578	108	151	63
Prehydrated State										
Three liters of isotonic NaCl ($Na = 143$ mEq./L.) infused from 0 to 56 min.										
1	-97 to -7	92	1.2	1.9	2.3	-1.1	644	172	168	23
2	-7 to 20	84	2.9	0.82	2.4	0.5	671	185	206	40
3	20 to 39	90	4.6	0.64	2.9	1.7	820	236	270	55
4	39 to 57	83	6.2	0.49	3.1	3.2	852	218	269	67
5	57 to 73	85	7.3	0.43	3.1	4.2	863	236	283	71
6	73 to 89	81	8.6	0.37	3.2	5.1	888	241	299	79
7	89 to 104	90	8.8	0.48	3.4	4.7	950	268	324	83
8	104 to 118	87	7.5	0.54	4.1	3.4	1,155	356	412	71

* CH_2O = free water clearance. See preceding tables for additional definitions.

TABLE VII *
The effects of isotonic saline infusion on C_{Cr} , solute and water excretion in the donor

Per.	Time	C_{Cr}	V	Osm U/P	C_{osm}	C_{H_2O}	$U_{osm}V$	$U_{Na}V$	$U_{O_2}V$	$U_{K}V$
Hydropenic State Three liters of isotonic NaCl (Na = 144 mEq./L.) infused from 0 to 61 min.										
1	-101 to -7	64	0.7	2.6	1.9	-1.2	548	118	132	23
2	-7 to 24	85	0.9	2.6	2.4	-1.5	683	150	172	30
3	24 to 41	83	1.5	2.0	3.0	-1.5	859	227	249	26
4	41 to 76	88	5.4	0.92	4.8	0.5	1,346	436	475	47
5	76 to 93	90	6.4	0.76	4.9	1.5	1,370	378	438	65
6	93 to 110	84	5.8	0.80	4.7	1.2	1,321	428	486	73
7	110 to 127	43	3.8	0.85	3.2	0.5	917	298	332	50
Prehydrated State Three liters of isotonic NaCl (Na = 138 mEq./L.) infused from 0 to 57 min.										
1	-45 to -8	90	2.1	1.0	2.2	-0.1	593	92	193	39
2	-8 to 19	94	4.1	0.61	2.5	1.6	701	131	166	47
3	19 to 41	91	6.1	0.46	2.8	3.3	797	162	197	52
4	41 to 58	91	8.4	0.40	3.4	4.9	977	263	300	54
5	58 to 73	86	7.8	0.43	3.4	4.5	952	273	318	61
6	73 to 103	98	9.2	0.44	4.1	5.2	1,136	280	380	94
7	103 to 118	94	5.0	0.49	4.3	0.7	1,205	338	409	109

* See preceding tables for definitions.

Table VI. C_{Cr} showed a slight initial increase followed by a delayed fall. Urine flow increased progressively, but this was due largely to an increase in free water clearance (C_{H_2O}). As a consequence, the urine became markedly hypotonic (osmotic U/P ratio = 0.36). Osmolar clearance (C_{osm}) and sodium excretion rates exhibited only minimal and unsustained increases.

Recipient, prehydrated state: The initial values for C_{Cr} , urine flow, and electrolyte excretion rates were all higher than those noted in the hydropenic study. C_{Cr} remained constant throughout. Urine flow exhibited a progressive increase, and in this experiment, C_{osm} contributed appreciably to this. C_{H_2O} also increased and osmotic U/P ratios reached a minimum value of 0.37. $U_{Na}V$ increased gradually but progressively throughout, reaching a peak value of 356 μ Eq. per minute as compared to the maximal value of 135 μ Eq. per minute noted during the hydropenic study.

Donor, hydropenic state: The results of this and the succeeding study on D are shown in Table VII. C_{Cr} , urine flow, C_{osm} , and C_{H_2O} all increased during the first five periods. Osmotic U/P ratios decreased to a minimum of 0.76. $U_{Na}V$ rose from 118 μ Eq. per minute to a maximal value of 436 during the third clearance period, and thereafter decreased.

Donor, prehydrated state: Prehydration did not appear to enhance electrolyte excretion. Thus, the increases in C_{osm} and $U_{Na}V$ were smaller than those noted in the hydropenic study. The increase in C_{H_2O} was of greater magnitude, however, and osmotic U/P ratios decreased to 0.43.

5. Infusion of hyperoncotic salt poor albumin: The intravenous administration of 25 per cent salt poor human albumin into normal supine subjects has been shown to evoke a decrease in the rates of solute and water excretion (14). When the albumin is infused rapidly (*e.g.*, 100 ml. in 15 to 20 minutes) the antidiuresis is more marked (15).

The responses of both R and D to the rapid infusion of 300 ml. of salt poor human albumin are shown in Tables VIII and IX. Water diuresis was induced by the preliminary ingestion of 1,500 ml. of water and maintained by the ingestion of water in quantities slightly exceeding the urinary volumes.

In R, no trend in C_{Cr} was apparent subsequent to the initiation of the infusion. During the infusion, urine flow and C_{H_2O} decreased slightly; however, osmotic U/P ratios showed no consistent increase. C_{osm} remained constant during and following the albumin infusion, and although $U_{Na}V$ decreased progressively during the control periods,

TABLE VIII *

The effects of rapid infusion of 25% salt poor human albumin on C_{Cr} , solute and water excretion in the recipient

Per.	Time min.	C_{Cr} ml./min.	V ml./min.	C_{Osm} ml./min.	C_{H_2O} ml./min.	Osm U/P	$U_{Na}V$ μ Eq./min.	$U_{Cl}V$ μ Eq./min.	U_KV μ Eq./min.	P_{Na} mEq./L.	P_{Cl} mEq./L.	P_K mEq./L.
1,500 ml. of water ingested from -160 to -128 min.												
1	-176 to -128	91	2.7	2.6	0.1	0.99	178	202	53	140	105	4.0
2	-128 to -98	90	4.9	2.5	2.4	0.57	135	167	51			
3	-98 to -68	80	5.8	2.2	3.6	0.39	104	133	59	137	105	4.4
4	-68 to -39	77	5.7	2.0	3.7	0.35	74	104	57			
5	-39 to -8	76	5.8	2.0	3.8	0.34	73	99	52	135	105	3.8
300 ml. albumin infused from 0 to 75 min. (First 100 ml. infused from 0 to 23 min.)												
6	-8 to 21	76	5.5	1.9	3.6	0.34	64	83	52	128	105	3.9
7	21 to 53	88	5.2	1.9	3.3	0.37	63	61	68	131	101	3.7
8	53 to 83	82	6.3	2.2	4.1	0.34	91	69	73	136	100	3.4
9	83 to 113	79	6.1	2.0	4.1	0.33	74	57	60	135	99	3.9
10	113 to 143	81	6.6	1.9	4.7	0.29	69	64	50	136	100	3.6
11	143 to 173	78	6.2	1.9	4.3	0.30	65	68	45	134	101	3.3

* See preceding tables for definitions.

the lowest value noted subsequent to initiation of the infusion was only 10 μ Eq. per minute less than the last control value. $U_{Cl}V$ decreased throughout the control periods, and a moderate additional fall ensued after the onset of albumin infusion.

In D, C_{Cr} varied irregularly and no trend was apparent. Urine flow, C_{H_2O} , and C_{Osm} all decreased during the albumin infusion. Urine flow and C_{H_2O} increased toward control levels during the follow-up periods; however, C_{Osm} remained depressed throughout. Osmotic U/P ratios increased during the albumin infusion and decreased thereafter. Both sodium and chloride excretion rates decreased markedly during the infusion.

C. Influence of 200 mg. sodium intake (Table X)

On an *ad lib.* sodium chloride intake, R excreted 158 mEq. of sodium per 24 hours. While housed on a metabolic ward he ingested a diet containing 200 mg. of sodium for a three-day period. Urinary sodium excretion was 42 mEq. during the final 24-hour period. On the morning of the fourth day the sodium concentration of a casual urine specimen was 9 mEq. per L.

The recipient was subjected to a low sodium diet for a second time after an interval of eight months (eighteen months following transplantation). On the third day of sodium deprivation, the 24-hour sodium excretion totalled 61 mEq.

TABLE IX *

The effects of rapid infusion of 25% salt poor human albumin on C_{Cr} , solute and water excretion in the donor

Per.	Time min.	C_{Cr} ml./min.	V ml./min.	C_{Osm} ml./min.	C_{H_2O} ml./min.	Osm U/P	$U_{Na}V$ μ Eq./min.	$U_{Cl}V$ μ Eq./min.	U_KV μ Eq./min.	P_{Na} mEq./L.	P_{Cl} mEq./L.	P_K mEq./L.
1,500 ml. of water ingested from -154 to -131 min.												
1	-152 to -122	81	2.2	3.2	-1.0	1.5	242	276	37	140	114	3.9
2	-122 to -92	73	5.1	2.6	2.5	0.51	164	201	38			
3	-92 to -62	99	9.0	3.2	5.8	0.35	221	241	44	139	112	4.0
4	-62 to -32	91	9.1	3.0	6.1	0.33	194	209	46			
5	-32 to -2	88	9.2	2.9	6.3	0.31	193	147	52	139	111	4.0
300 ml. albumin infused from 0 to 40 min. (First 100 ml. infused from 0 to 9 min.)												
6	-2 to 28	79	6.9	2.5	4.4	0.36	144	106	70	134	112	4.1
7	28 to 59	84	6.3	2.3	4.0	0.37	112	59	96	136	110	3.8
8	59 to 89	92	7.7	2.4	5.3	0.31	119	74	72	137	109	3.8
9	89 to 118	90	7.8	2.3	5.5	0.30	131	79	46	137	110	3.6
10	118 to 148	97	7.9	2.3	5.6	0.29	149	93	37	136	108	3.8
11	148 to 178	84	7.9	2.4	5.5	0.31	162	108	31	136	109	3.8
12	178 to 208	87	7.7	2.4	5.3	0.31	158	110	36	136	109	3.5

* See preceding tables for definitions.

TABLE X

*The influence of a 200 mg. sodium intake on C_{cr} and electrolyte excretion rates in the recipient**

Day	24 hr. End C_{cr} ml./min.	$U_{Na}V$ mEq./24 hr.	$U_{Cl}V$ mEq./24 hr.	$U_{K}V$ mEq./24 hr.	P_{Na}	P_{Cl}	P_K
1	65	88	79	34	144	106	4.5
2	68	96	88	37	143	105	5.0
3	67	42	44	43	144	104	4.9

* See preceding tables for definitions.

DISCUSSION

The recipient twin represents an extraordinary experimental preparation in that his sole source of renal function is a transplanted kidney. Of additional interest is the fact that during the transplantation procedure the kidney became totally and irrefutably denervated. That the transplanted organ has maintained a considerable degree of functional integrity, and indeed that it functions in many respects in a normal manner is attested to by the following observations: 1) Its filtration rate approximates that of the donor's remaining kidney. 2) It has maintained its ability to concentrate urine. 3) It is able to dilute urine. 4) It is able to acidify urine. 5) It is able to alkalinize urine. 6) It is able both to increase and to decrease its rate of sodium excretion in response to varying stimuli. 7) It has the capacity to alter acutely both its filtration rate and renal plasma flow. 8) It has been able to maintain extracellular fluid volume and composition intact over a prolonged period of time despite widely varying dietary and climatic conditions.

Stability of glomerular filtration rate and renal plasma flow

In the recipient, serial studies (beginning six months after transplantation) showed neither a progressive rise nor a fall in either GFR or ERPF. It is probable, however, that some increase in clearance values occurred earlier in his course. This possibility receives indirect support from two sources: 1) Autotransplantation of a normal dog kidney to the iliac fossa using surgical techniques identical to those employed in the present subject is frequently attended by a marked initial decrease in clearance values with slow return toward control levels (16). 2) Clinical tests (including endogenous creatinine clearances) during

the initial two-month period suggested improvement in renal function (1).

Serial observations on the donor over an eight-month period following unilateral nephrectomy revealed a moderate rise in GFR and ERPF.

The sum of the values for C_{in} in recipient and donor eight months following transplantation was essentially equal to the two-kidney control value in the donor (145 vs. 147 ml. per minute). The combined value for C_{PAH} at eight months was appreciably greater than the control value (782 vs. 477). The degree to which the rise in C_{PAH} represents compensatory hypertrophy is obscured by the fact that the control value may have been inordinately low (filtration fraction 33 per cent) due to the donor's state of marked apprehension.

Renal hemodynamic regulation

The recipient's responses to experimental events which typically induce changes in GFR and/or ERPF could not be distinguished from normal. Thus, following Aminophylline administration, C_{in} increased acutely with no increase in C_{PAH} ; during *l*-norepinephrine infusion C_{PAH} decreased markedly while C_{in} remained constant; and following orthostatic hypotension C_{in} and C_{PAH} both decreased sharply and remained depressed after blood pressure returned to normal. These data suggest 1) that both renal vasodilatation and renal vasoconstriction may occur in the absence of renal nerves, 2) that Aminophylline and *l*-norepinephrine may both act directly on the renal vessels, and 3) that renal vasoconstriction occurring in a denervated kidney may outlast systemic vasoconstriction. The results of these studies lend some support to the conviction that the regulation of renal hemodynamics in homeostasis is not dependent upon renal nerves.

Electrolyte excretion

Two general categories of experiments were employed to study electrolyte excretion by the transplanted kidney: 1) administration of drugs which are generally conceded to influence sodium excretion at the intrarenal level; and 2) alteration of extrarenal factors which are capable of modifying sodium excretion in the normal subject.

The results of the studies included in the first category were generally indistinguishable from the normal response. Thus, following Diamox® administration, a sodium, chloride, potassium, and bicarbonate diuresis occurred accompanied by a decrease in titratable acidity. Following mannitol infusion, a progressive increase in sodium, chloride, and potassium excretion rates was observed. Following Aminophylline, a brisk sodium and chloride diuresis occurred which persisted after the filtration rate returned to control levels. Finally, following intravenous hydrocortisone, a fall in $U_{Na}V$ and $U_{Cl}V$ occurred associated with a concurrent rise in U_KV . The infusion of *l*-nor-epinephrine was not attended by a decrease in sodium and chloride excretion rates. However, the consistency with which this phenomenon occurs in the normal has not yet been established (17, 18).

The recipient's responses to experiments in the second category were generally qualitatively or quantitatively abnormal. In four studies, ECF volume was expanded acutely. Following infusion of hypotonic saline on two occasions, a decrease in sodium excretion rate occurred rather than the increase observed in the normal subject. Following the infusion of isotonic saline in the hydropenic state, only a minimal and unsustained increase in sodium excretion rate occurred. Finally, following infusion of hyperoncotic albumin, only a negligible decrease in sodium excretion occurred and this could not definitely be related to the albumin infusion. During inflation of blood pressure cuffs around extremities, a stimulus which presumably results in a decrease in effective circulating blood volume, the only fall in sodium and chloride excretion rates occurred early in cuffing (when the normal frequently notes an increase). Moreover, the decrease was associated with a fall in blood pressure and C_{in} , and despite continuation of cuffing, $U_{Na}V$ and $U_{Cl}V$ returned

toward control levels. Following orthostatic hypotension, with its concomitant decrease in effective circulating blood volume, sodium and chloride excretion rates decreased only during the period of decreased filtration rate, and thereafter returned toward control levels with the rise in C_{in} . In the normal subject, temporary hypotension is followed by a decrease in urinary excretion of sodium and chloride which appreciably outlasts the decrease in GFR (19).

Water excretion

Three different stimuli employed in the recipient to study water excretion independent of the electrolyte excretion evoked changes: 1) infusion of Pitressin® produced a prompt antidiuresis; 2) alteration of plasma osmolality by water loading and hydropenia produced water diuresis and antidiuresis, respectively; and 3) expansion of ECF volume without change in tonicity (isotonic expansion in the hydropenic state) produced a water diuresis, and decrease in effective circulating blood volume (cuffing and orthostatic hypotension) evoked antidiureses out of proportion to the decreases in electrolyte excretion.

Consideration of abnormal responses in recipient

The only consistent deviations from normal were seen in the electrolyte excretion rates in those experiments in which ECF volume was acutely altered. Several variables should be considered when evaluating these abnormalities. First, the kidney was subjected to total anoxia for 90 minutes during the transplantation procedure. It is therefore conceivable that the defects in electrolyte excretion were due to a tubular lesion secondary to anoxemia. Somewhat against this explanation are 1) the prompt and normal response to drugs influencing sodium excretion at the intrarenal level, and 2) the many parameters of normal renal function observed including the near-normal concentrating ability.

The second consideration is that the failure to respond to volume changes was due to defective hormonal mechanisms. A deficient release of sodium-retaining hormones could also provide an explanation for the incomplete cutback in sodium excretion following ingestion of a 200 mg. sodium

diet. In this light it should be noted that the left adrenal gland was removed at the time of left nephrectomy. Evidence against the role of a hormonal abnormality is found in recent studies which suggest that Addisonian subjects respond in a normal manner to hypotonic saline (20), hyperoncotic albumin (15), and cuffing of the lower extremities (20). In addition, 24-hour excretion rates of 17-ketosteroids and 17-hydroxysteroids in the recipient were normal both in the control state and following an eight-hour ACTH infusion. Moreover, that the defect did not represent an inability of the kidney to respond to salt-retaining steroids is indicated by the normal response to intravenous hydrocortisone. The demonstration that prehydration facilitated the excretion of an administered load of isotonic saline (although to a lesser degree than that described in the two-kidney normal subject) may indicate the presence of a humoral influence on sodium excretion.

A third explanation for the defects observed in electrolyte excretion is that they were due to an abnormality in sodium transport which was present prior to transplantation of the kidney. The studies on the donor serve to minimize this possibility. Thus, his remaining kidney responded normally to hypotonic expansion of ECF, isotonic expansion of ECF in the hydropenic state, and hyperoncotic albumin infusion. The response to subdiastolic cuffing, although of small magnitude, was qualitatively and temporally normal. Finally, although the donor's response to isotonic saline infusion in the prehydrated state was abnormal, the recipient did not manifest the same abnormality.

The final and perhaps most intriguing possibility is that the recipient did not respond normally to acute changes in volume because denervation interrupted the efferent limb of a volume control system. Numerous observations in recent years have led to the belief that an extrarenal system exists which, in the interests of preserving constancy of ECF volume, is capable of influencing the renal excretion of both water and sodium. Changes in volume presumably affect water excretion by influencing the rate of release of anti-diuretic hormone. However, the mechanism by which the kidney is *notified* to change its rate of electrolyte excretion in response to volume changes

remains unknown. Both humoral and neurogenic pathways have been discussed (21).

That the recipient could adequately control volume on a chronic basis is attested to by his maintenance of normal body weight and plasma electrolyte concentrations over a period of many months. Moreover, that changes in volume without simultaneous changes in tonicity were capable of evoking changes in water excretion has been discussed above. There is some suggestion, however, that acute changes in volume did not evoke the changes in electrolyte excretion rates which are seen in normal subjects.

Although the present observations do not permit definitive evaluation of the possibility that renal nerves play a part in the efferent limb of the volume control system in man, the data presented are consistent with this interpretation.

SUMMARY AND CONCLUSIONS

Studies have been performed on a subject with a homotransplanted and therefore denervated kidney. The majority of experiments were performed after the subject's own two kidneys had been surgically removed, and the data therefore describe the function of the transplanted organ. Certain parallel observations were made on the donor who possessed as his only kidney the mate of the transplanted organ. The filtration rate in the donor prior to transplantation was 147 ml. per minute. Following transplantation GFR varied in the recipient between 60 to 70 ml. per minute, whereas in the donor it rose slightly from 68 to 84. Manifestations of the functional integrity of the transplanted kidney were multiple and included the abilities to concentrate, dilute, acidify and alkalinize the urine, the capacity to respond normally to experimental conditions which typically evoke acute alterations in GFR and/or ERPF, the capacity to respond normally to a sodium retaining adrenal steroid and to different diuretic agents, and the ability to maintain ECF volume and composition intact over a prolonged period of time.

Abnormalities in sodium excretion of a qualitative and/or quantitative nature were observed following acute alterations of extracellular volume. Experiments in this category included: 1) hypotonic expansion of ECF, 2) isotonic expansion of ECF in the hydropenic state, 3) hyperoncotic al-

bumin infusion, 4) venous congestion of the lower extremities, and 5) orthostatic hypotension. Four of these experiments were repeated on the donor and the response in each instance was normal.

Changes in water excretion in the recipient occurred following intravenous Pitressin®, changes in plasma osmolality, and changes in extracellular fluid volume. As examples of the latter, a marked rise in free water clearance occurred following isotonic expansion of ECF, and antidiuresis occurred in association with venous congestion of the lower extremities.

It is concluded: 1) That a transplanted kidney in an identical twin host may function normally in most respects and may not only sustain life but may maintain normality. 2) That both renal vasoconstriction and renal vasodilatation may occur in the absence of renal nerves, and that renal nerves are probably not necessary for the regulation of renal hemodynamics. 3) That renal nerves are not necessary for the acute changes in electrolyte excretion occurring after administration of either diuretic agents (carbonic anhydrase inhibitor, xanthine derivative, or osmotically active non-electrolytic solute) or a sodium-retaining adrenal steroid. 4) That renal nerves are not necessary for changes in water excretion following intravenous Pitressin®, changes in osmotic pressure, or changes in extracellular fluid volume. 5) That renal nerves are not necessary for the chronic regulation of extracellular fluid volume or composition.

The possibility exists that the abnormalities in sodium excretion noted in the recipient following acute alteration of ECF volume occurred because denervation interrupted the efferent limb of a volume control system.

ACKNOWLEDGMENTS

The authors wish to thank Mrs. Antoinette d'Angelo, Miss Virginia Tsiknas, Robert Mossman, John MacNaughton, and Marjorie Grady, R.N., for technical assistance, and Dr. Ralph Straffon for reading the manuscript. Finally, we gratefully acknowledge the recipient and donor for their dedicated spirit of co-operation.

REFERENCES

1. Merrill, J. P., Murray, J. E., Harrison, J. H., and Guild, W. R., Successful homotransplantation of

- the human kidney between identical twins. *J. A. M. A.*, 1956, **160**, 277.
2. Bricker, N. S., and Hlad, C. J., Jr., Observations on the mechanism of the renal clearance of I¹³¹. *J. Clin. Invest.*, 1955, **34**, 1057.
3. Roe, J. H., Epstein, J. H., and Goldstein, N. P., A photometric method for the determination of inulin in plasma and urine. *J. Biol. Chem.*, 1949, **178**, 839.
4. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M., The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J. Clin. Invest.*, 1945, **24**, 388.
5. Van Slyke, D. D., and Hiller, A., Application of Sendroy's iodometric chloride titration to protein-containing fluids. *J. Biol. Chem.*, 1947, **167**, 107.
6. Bonsnes, R. W., and Taussky, H. H., On the colorimetric determination of creatinine by the Jaffe reaction. *J. Biol. Chem.*, 1945, **158**, 581.
7. Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry*. Vol. II. Methods. Baltimore, Williams and Wilkins Co., 1932.
8. Baldwin, D. S., Berman, H. J., Heinemann, H. O., and Smith, H. W., The elaboration of osmotically concentrated urine in renal disease. *J. Clin. Invest.*, 1955, **34**, 800.
9. Fitzhugh, F. W., Jr., McWhorter, R. L., Jr., Estes, E. H., Jr., Warren, J. V., and Merrill, A. J., The effect of application of tourniquets to the legs on cardiac output and renal function in normal human subjects. *J. Clin. Invest.*, 1953, **32**, 1163.
10. Wilkins, R. W., Tinsley, C. M., Culbertson, J. W., Burrows, B. A., Judson, W. E., and Burnett, C. H., The effects of venous congestion of the limbs upon renal clearances and the excretion of water and salt. I. Studies in normal subjects and in hypertensive patients before and after splanchnicectomy. *J. Clin. Invest.*, 1953, **32**, 1101.
11. Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. C., Production of increased renal sodium excretion by the hypotonic expansion of extracellular fluid volume in recumbent subjects. *J. Clin. Invest.*, 1952, **31**, 80.
12. Ladd, M., The effect of prehydration on the response to saline infusion in man. *J. Applied Physiol.*, 1951, **3**, 379.
13. Ladd, M., Effect of prehydration upon renal excretion of sodium in man. *J. Applied Physiol.*, 1951, **3**, 603.
14. Goodyer, A. V. N., Peterson, E. R., and Relman, A. S., Some effects of albumin infusions on renal function and electrolyte excretion in normal man. *J. Applied Physiol.*, 1949, **1**, 671.
15. Petersdorf, R. G., and Welt, L. G., The effect of an infusion of hyperoncotic albumin on the excretion of water and solutes. *J. Clin. Invest.*, 1953, **32**, 283.

16. Bricker, N. S., and Straffon, R. A., Unpublished observations.
17. Smythe, C. McC., Nickel, J. R., and Bradley, S. E., The effect of epinephrine (USP), *l*-epinephrine, and *l*-norepinephrine on glomerular filtration rate, renal plasma flow, and the urinary excretion of sodium, potassium, and water in normal man. *J. Clin. Invest.*, 1952, **31**, 499.
18. Kaplan, S. A., Fomon, S. J., and Rapoport, S., Effects of epinephrine and *l*-norepinephrine on renal excretion of solutes during mannitol diuresis in the hydropenic dog. *Am. J. Physiol.*, 1952, **169**, 588.
19. Bricker, N. S., Unpublished observations.
20. Rosenbaum, J. D., Papper, S., and Ashley, M. M., Variations in renal excretion of sodium independent of change in adrenocortical hormone dosage in patients with Addison's disease. *J. Clin. Endocrinol.*, 1955, **15**, 1459.
21. Selkurt, E. E., Sodium excretion by the mammalian kidney. *Physiol. Rev.*, 1954, **34**, 287.