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THE RENAL EXCRETION OF SODIUM AND POTASSIUM IN THE DOG*

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25 February 1949

*Sub-project under Studies of Body Reactions and Requirements under Varied Environmental and Climatic Conditions. Approved 31 May 1946. M.D.F.R.L. Project No. 6-64-12-06-(17).

Project No. 6-64-12-06
Sub-project MDFRL 06-(17)
MEDEA

25 February 1949

ABSTRACT

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OBJECT

Studies were carried out on unanesthetized dogs to determine some of the factors controlling the fraction of filtered sodium and potassium reabsorbed by the renal tubules. The interference with the reabsorption of each of these ions by the other and the phenomenon of tubular secretion of potassium were investigated. Filtration rate (as measured by inulin and creatinine clearance) and effective renal plasma flow (as measured by sodium para-aminohippurate clearance) were determined before and during the intravenous infusion of 0.9% NaCl, 10% NaCl and 1.2% KCl solutions. The percentage of filtered electrolyte reabsorbed for both sodium and potassium was measured, and the serum concentration of each ion was allowed to vary over wide ranges while that of the other ion remained at normal levels. 1.2% KCl solution was also infused into dogs previously fed KCl for a week.

RESULTS AND CONCLUSIONS

The percentage of filtered sodium which is reabsorbed by the tubules is functionally related to the serum sodium concentration. The percentage of filtered potassium which is reabsorbed by the tubules is related to the rate of filtration of potassium. The presence of the chloride salt of each ion in the glomerular filtrate depresses the reabsorption of the other ion. The ingestion of potassium chloride prior to the infusion of this salt augments the depression of potassium reabsorption which normally follows an increased filtration of potassium.

RECOMMENDATIONS

Investigations should be carried out to determine the other factors which regulate the fraction of filtered sodium reabsorbed by the renal tubules. The mechanism of tubular secretion of potassium should be studied further.

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THE RENAL EXCRETION OF SODIUM AND POTASSIUM IN THE DOG

I. INTRODUCTION

The observation that the intravenous infusion of 10% sodium chloride solution produced in the dog a marked potassium diuresis led to this investigation. Such an observation is by no means unique. Wolf (17) has shown in man that the intravenous infusion of hypertonic sodium chloride solution effected a greater potassium excretion than the infusion of hypotonic solution. Stewart and Rourke (13), studying the effects of intravenous infusions in man, have shown that 0.9% saline solution produced a greater excretion of potassium than 5% glucose solution. Simply by the ingestion of sodium chloride, the rate of potassium excretion in man is increased, as pointed out by Gamble (5). Conversely, the infusion of potassium sulfate solution has been shown by Schwartz, Smith and Winkler (12), to produce a diuresis of sodium in dogs.

All these phenomena are not confined to the cations. Pitts and Lotspeich (11) have clearly demonstrated the significance of a similar relationship among anions in the regulation of the acid base balance. The increased reabsorption of chloride lowers the capacity of the renal tubules to reabsorb bicarbonate and produces an increased excretion of this ion. Conversely, the increased reabsorption of bicarbonate diminishes the tubular reabsorption of chloride. Schwartz, Smith and Winkler (12) have claimed that increased excretion of sulfate will increase the tubular reabsorption of chloride in spite of a rising serum chloride concentration. Their evidence shows that chloride excretion is repressed by sulfate excretion. Lotspeich (8) has demonstrated evidence in dogs of a tubular maximum for sulfate reabsorption by injecting sodium sulfate solution intravenously, elevating the plasma sulfate concentration, and saturating the renal tubules with this ion. When hypertonic sodium chloride was added to the sodium sulfate infusions, the rate of tubular reabsorption of sulfate was markedly reduced from the maximum values attained with sodium sulfate alone. Maximum levels of tubular reabsorption have also been demonstrated for phosphate (7, 10). The rate of reabsorption of these ions cannot be increased beyond these maximum levels by increasing the filtered load.

In exploratory experiments, in this laboratory, the rates of tubular reabsorption of sodium and potassium were found to vary widely when different concentrations of sodium chloride and potassium chloride were infused intravenously in dogs. No obvious pattern of reabsorption was apparent. Consequently, the premise was adopted that for any given quantity of sodium or potassium filtered by the glomeruli per unit time, the fraction reabsorbed could be predicted, provided the factors regulating this fraction were known.

The purpose of this investigation was to determine some of the factors controlling the fractional reabsorption of sodium and potassium. Evidence of maximum tubular reabsorption of sodium and potassium was sought, and the mutual interference with reabsorption by these ions was investigated. The percentage of filtered electrolyte reabsorbed for both sodium and potassium was measured, and the serum concentration of each ion was allowed to vary over wide ranges while that of the other ion remained at normal or nearly normal levels. Renal plasma flow was measured in addition to filtration rate in an attempt to demonstrate qualitative changes in renal hemodynamics following the infusion of sodium and potassium chloride.

It also proved necessary to study the phenomenon of tubular secretion of potassium in order to formulate valid conclusions as to the effect of sodium chloride upon the reabsorption of potassium. It appeared reasonable to believe that undetermined potassium secretion might well invalidate any estimations of potassium reabsorption.

II. EXPERIMENTAL

A. Methods

A series of 28 experiments was carried out on 6 trained unanesthetized female dogs. These were used in a post-absorptive state and were lightly restrained, supine on a dog-board. Following the withdrawal of a blood sample, subsequently to be used as a blank in the various chemical analyses, a mixture containing 0.2 ml. of a 20% sodium para-aminohippurate solution and 2.5 ml. of a 10% inulin solution, each per kilogram of body weight, was injected into the loose, areolar tissue of the axillae. Inulin was used exclusively to measure filtration rate in the first 12 experiments. After inulin and creatinine clearances had been determined simultaneously in 3 experiments, and it was established that the inulin/creatinine clearance ratios consistently ranged between 0.92 and 1.00, creatinine was substituted for inulin. Purified creatinine (0.25 gm. per kilogram body weight) was dissolved in 30.0 ml. of distilled water, and para-aminohippurate solution was added before injection. After a 20-minute period, 25 ml. of water per kilogram body weight were administered by stomach tube, followed by the installation of a silk-woven catheter into the bladder.

One or more control experiments without infusion were carried out on each of the 6 dogs. Intravenous infusions were started in every instance from 5 to 10 minutes before zero time which was established as 30 minutes after the subcutaneous injection. The solutions of NaCl and KCl were administered according to the following schedule:

10% NaCl: Continuous intravenous infusion of a 10% solution at a rate of 2 to 5 ml./min.

0.9% NaCl: Continuous intravenous infusion of a 0.9% NaCl solution at a rate of 1 to 3 ml./min.

1.2% KCl: Continuous intravenous infusion at rates ranging from 2.5 to 6.0 ml./min., varying the rate with individual experiments and from period to period.

1.2% KCl following KCl feeding: Continuous intravenous infusion as above, following the administration in the diet of 5 grams of potassium chloride given twice a day for one week.

Following the initiation of the infusion, 3 to 8 consecutive clearance periods of 15 to 20 minutes in length were measured. Clearance periods and the drawing of blood samples were timed to the nearest tenth of a minute. Blood samples were drawn from the external jugular veins at a time approximately 2½ minutes before the midpoint of the anticipated length of the period for which these amounts were timed. The bladder was washed at the end of each period with 20 ml. of distilled water followed by the injection and withdrawal of 20 ml. of air. After the period had been timed, an exact moment 2½ minutes before the midperiod was calculated; and at the conclusion of the analyses the actual plasma and serum concentrations at these times were obtained by interpolation. Inasmuch as the plasma concentrations of all substances studied changed at small and fairly uniform rates, the values used in the calculations properly represent the composition of the blood from which each urine sample was formed.

Analyses for inulin and para-aminohippurate (PAH) were carried out on heparinized plasma and diluted urine samples according to the methods of Harrison (6) and Smith et al. (14), and for creatinine according to the modified alkaline picrate procedure of Brod and Sirota (2). Sodium and potassium determinations were made on diluted serum and urine samples with a Perkin-Elmer Flame Photometer (Model 52-A) utilizing an internal lithium standard of 20 mEq/L. Blood for serum analyses was collected under mineral oil and centrifuged shortly after clotting. The serum was diluted 100 times with distilled water. Urine samples were diluted from 5 to 200 times depending upon the anticipated concentration of the cation. A maximum sodium standard of 2 mEq/L was used throughout for both serum and urine samples. Maximum potassium standard utilized for sera was 0.1 mEq/L; for urine 0.4 mEq/L. Studies with urine and serum samples revealed an accuracy of about 1% for sodium determinations, about 4% for serum potassium, and about 2% for urine potassium determinations.

The data were corrected for surface area according to the formula 0.112 x weight $(kg.)^{2/3}$, in order to minimize partly the differences inherent in the use of dogs of different size.

Excreted electrolyte was calculated by multiplying the urine concentration of the ion by the actual urinary output per minute.

Filtered electrolyte or filtered load was calculated by multiplying the serum concentration by the inulin or creatinine clearance.

Reabsorbed electrolyte was calculated by subtracting the excreted electrolyte from the filtered electrolyte.

The percentage of filtered electrolyte that was reabsorbed, expressed by the function t/L, was obtained by dividing the t or reabsorbed electrolyte by the L, or filtered electrolyte and multiplying by 100. Negative values for the t/L function indicate a greater excreted electrolyte than a filtered electrolyte, with a resulting negative value for reabsorbed electrolyte.

B. Results

1. Control Data:

The control data comprised 42 clearance periods (measured on 6 female dogs). From these, the following observations were made (see Table 1 for control data on 2 of the dogs):

a. There were wide differences in the renal plasma flow. PAH clearance values corrected for surface area ranged from 124 to 295 ml./min., with mean values for all periods of 209.

b. Inulin or creatinine clearance values corrected for surface area ranged from 41.6 to 91.5 ml./min. with a mean value of 67.8.

c. Filtration fractions remained moderately constant, ranging from 0.24 to 0.36, and in no instance varied more than ± 0.04 during the course of a single control experiment.

d. Sodium filtered through the glomeruli was reabsorbed almost completely, the percentage of reabsorption (t/L Na) varying from 98.8% to 99.9% with a mean value of 99.6%.

e. The percentage of filtered potassium reabsorbed was less, ranging from 79.7% to 98.0%, with a mean value of 90.5%.

2. Sodium Injection:

a. 0.9% NaCl: Two experiments comprising a total of 8 clearance periods gave the following results (see Table 1):

(1) The intravenous infusion of 0.9% NaCl raised the mean value for renal plasma flow, although individual measurements were widely scattered. PAH clearances corrected for surface area rose to a range of 218 to 399 ml./min.

(2) The filtration rate rose to a range of 80.9 to 94.8 ml./min.

(3) The serum sodium concentration gradually rose to a range of 143 to 151 mEq/L.

(4) The percentage of filtered sodium reabsorbed (t/L Na) fell slightly in both experiments.

(5) The serum potassium concentration was slightly depressed.

(6) The percentage of filtered potassium reabsorbed (t/L K) was slightly depressed in both experiments by the end of the fourth clearance period, approximately 80 minutes after the beginning of the infusion.

TABLE 1

SODIUM EXPERIMENTS

Time	Period	C_{PAH}	C_I or C_{Cr}	F.F.	Urine Flow	SODIUM Serum	SODIUM Filtered	SODIUM Excreted	SODIUM Reabsorbed	SODIUM Clearance	SODIUM t/L	POTASSIUM Serum	POTASSIUM Filtered	POTASSIUM Excreted	POTASSIUM Reabsorbed	POTASSIUM Clearance	POTASSIUM t/L
min.		ml/min/ M^2	ml/min/ M^2		ml/min.	mEq/L	mEq/min/ M^2	mEq/min/ M^2	mEq/min/ M^2	ml/min/ M^2	%	mEq/L	mEq/min/ M^2	mEq/min/ M^2	mEq/min/ M^2	ml/min/ M^2	%
Dog A ----- Weight 15.9 kg. Surface area 0.71 M^2 ----- Experiment 1. Control																	
0 - 20	1	216	73.6	.34	3.1	135	9.94	0.04	9.90	0.30	99.6	4.8	0.35	0.037	0.31	7.71	89.5
20 - 38	2	229	76.0	.33	4.5	135	10.27	0.04	10.23	0.23	99.7	5.0	0.38	0.027	0.35	5.41	92.9
38 - 56	3	229	72.4	.32	4.5	135	9.78	0.02	9.76	0.16	99.8	5.0	0.36	0.023	0.34	4.60	93.8
56 - 72	4	250	77.9	.31	5.4	135	10.52	0.02	10.50	0.14	99.8	4.8	0.37	0.023	0.35	4.78	93.9
Dog A ----- Weight 13.2 kg. Surface area 0.62 M^2 ----- Experiment 2. 0.9% NaCl Solution																	
0 - 20	1	223	85.2	.38	6.0	149	12.70	0.17	12.53	1.11	98.7	4.9	0.42	0.039	0.38	7.97	90.7
20 - 40	2	219	90.2	.41	8.4	150	13.52	0.37	13.15	2.54	97.2	4.5	0.42	0.044	0.37	10.55	88.2
40 - 59	3	230	82.1	.36	7.4	151	12.42	0.43	11.99	2.83	96.5	4.6	0.38	0.041	0.34	8.91	89.3
59 - 79	4	218	80.9	.37	6.3	151	12.21	0.66	11.55	4.36	94.6	4.6	0.37	0.047	0.32	10.22	87.3
Dog A ----- Weight 13.5 kg. Surface area 0.64 M^2 ----- Experiment 3. 10.0% NaCl Solution												4.4					
0 - 21	1	253	81.8	.33	4.7	155	12.98	1.72	11.27	11.02	86.8	3.8	0.32	0.074	0.25	19.47	76.7
21 - 41	2	275	106.4	.39	9.5	163	17.34	3.17	14.17	19.35	81.9	4.0	0.43	0.119	0.31	29.75	72.0
41 - 61	3	361	117.7	.33	10.4	169	19.89	3.32	16.57	24.19	80.2	4.2	0.49	0.201	0.29	47.86	59.4
61 - 79	4	[illegible]	127.8	.32	10.4	173	22.06	4.37	17.69	25.11	80.3	4.6	0.59	0.252	0.34	54.76	57.1
Dog B ----- Weight 16.5 kg. Surface area 0.72 M^2 ----- Experiment 4. Control																	
0 - 19	1	245	77.2	.31	0.6	140	10.76	0.02	10.74	0.17	99.8	5.2	0.40	0.024	0.38	4.62	93.8
19 - 39	2	236	80.1	.34	2.1	140	11.17	0.02	11.15	0.17	99.8	4.8	0.38	0.024	0.36	5.00	94.2
Dog B ----- Weight 16.2 kg. Surface area 0.70 M^2 ----- Experiment 5. 1.9% NaCl Solution																	
0 - 19	1	325	94.3	.29	4.8	146	13.75	0.04	13.71	0.33	99.8	5.2	0.49	0.032	0.46	6.25	93.7
19 - 37	2	315	92.4	.29	6.2	143	13.21	0.04	13.17	0.25	99.7	4.8	0.44	0.028	0.41	5.53	93.6
37 - 59	3	336	90.3	.27	3.5	147	13.27	0.03	13.24	0.28	99.7	4.2	0.38	0.033	0.35	7.86	91.4
59 - 79	4	399	93.4	.23	3.4	148	13.82	0.11	13.71	0.67	99.3	4.3	0.39	0.048	0.34	11.43	87.7
Dog B ----- Weight 16.4 kg. Surface area 0.70 M^2 ----- Experiment 6. 10.0% NaCl Solution												3.6					
0 - 18	1	347	100.4	.28	3.3	157	15.76	1.04	14.72	6.66	93.4	3.5	0.35	0.061	0.29	17.43	82.7
18 - 37	2	402	[illegible]	[illegible]	[illegible]	[illegible]	16.71	2.18	14.53	15.63	86.7	4.4	0.48	0.093	0.39	[illegible]	80.8
37 - 56	3	446	130.6	.29	9.7	162	21.86	3.32	18.54	20.89	84.6	4.1	0.54	0.217	0.34	48.04	60.2
56 - 75	4	473	141.6	.32	9.5	168	25.37	3.64	21.73	24.64	85.7	4.2	0.60	0.262	0.36	62.30	57.7

(7) There was a significant increase in the rate of excretion of potassium, due both to the rise in filtration rate (serum K being constant) and to the fall in t/L K which approximated the simultaneous fall in t/L Na (see Table 1).

b. 10% NaCl: The effect of an infusion of 10% NaCl upon the excretion of sodium and potassium was studied in 5 experiments, comprising a total of 19 clearance periods. The data from 2 experiments are given in Table 1. From these data, the following observations were made:

(1) 10% NaCl raised the mean value for renal plasma flow considerably although individual measurements were widely scattered. PAH clearance values corrected for surface area tended to rise to a range of 192 to 473 ml./min.

(2) Filtration rate also tended to rise to a range of 74.8 to 151.0 ml./min.

(3) Parallel increases in both of these measurements maintained a relatively constant filtration fraction. In no instance did this vary more than ± 0.09 during the course of a single experiment.

(4) In all cases the increase in renal blood flow and in filtration rate roughly paralleled the increase in serum sodium concentration which reached a maximum in the last period of each experiment (see Figure 1).

(5) The filtration, reabsorption, and excretion of sodium and potassium were markedly increased by the infusion of 10% NaCl.

(6) The percentage of filtered electrolyte reabsorbed (t/L) fell markedly for both sodium and potassium; t/L Na values fell as low as 70.9% and t/L K values as low as 11.6%.

The rise in filtration rate increased the filtered load of potassium in spite of the fact that the serum potassium concentration was depressed to low values early during the infusion of hypertonic saline. This rise, coupled with the low values of the t/L K, effected a marked increase in the excretion of potassium. The increased excretion of sodium in no instance was accompanied by a depression of the t/L Na value equal to that of the t/L K.

Examination of Figure 1 reveals that the rise in serum sodium concentration was in most instances associated with a rise in the filtration rate. Although the serum sodium concentration rose as much as 50 mEq/L, and the sodium filtered load was doubled (see Table 1), the rate of reabsorption of sodium showed a continued rise. There was no evidence of the existence of a tubular maximum for sodium.

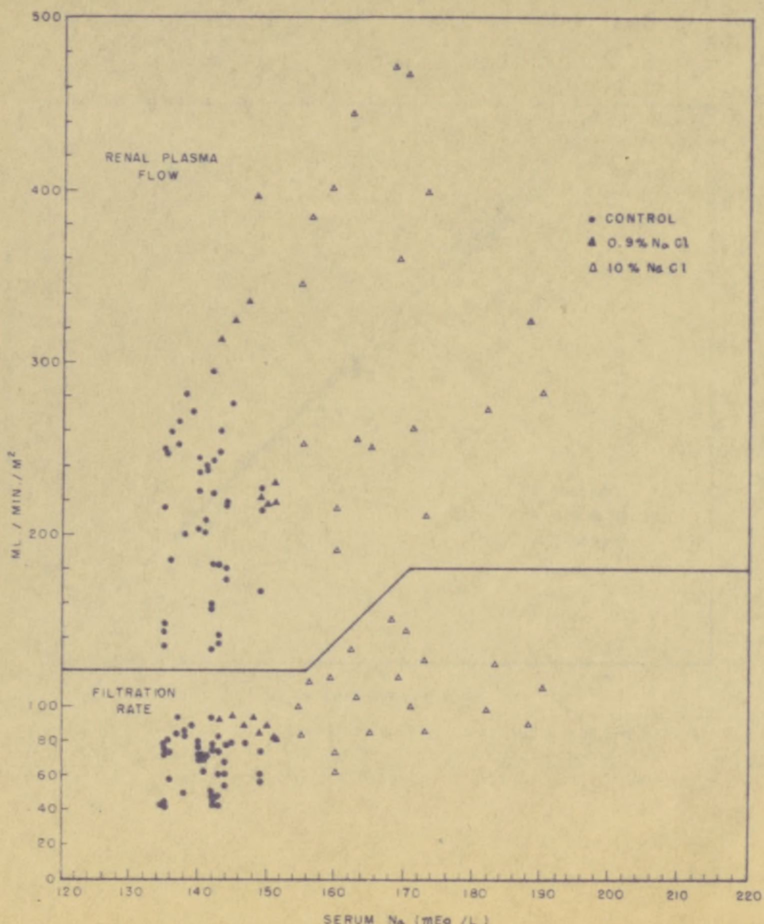

FIG 1 FILTRATION RATE AND RENAL PLASMA FLOW PLOTTED AS FUNCTIONS OF THE SERUM SODIUM CONCENTRATION. SERUM SODIUM CONCENTRATION WAS ELEVATED BY INFUSIONS OF 0.9% AND 10% SODIUM CHLORIDE

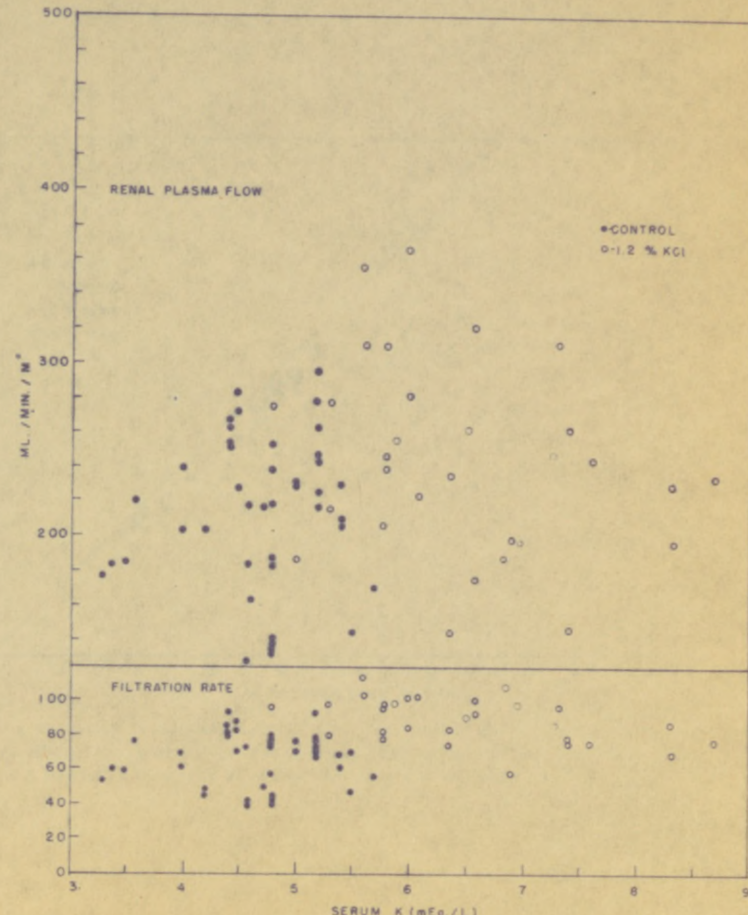

FIG 2 FILTRATION RATE AND RENAL PLASMA FLOW PLOTTED AS FUNCTIONS OF THE SERUM POTASSIUM CONCENTRATION. THE LACK OF CORRELATION OF THESE FUNCTIONS IS CLEAR

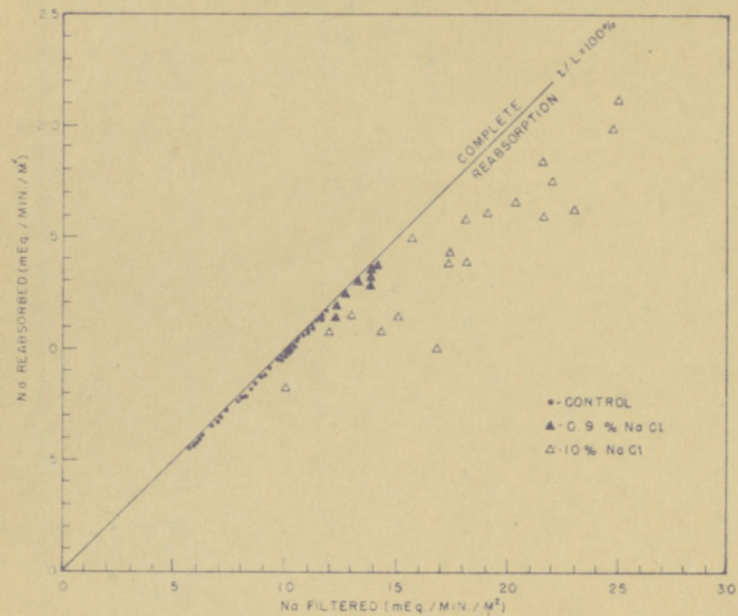

FIG. 3 THE RATE OF SODIUM REABSORPTION PLOTTED AS A FUNCTION OF THE RATE OF SODIUM FILTRATION. THE SCATTER OF 10% SALINE DATA IS CLEAR. THE DIAGONAL LINE MEASURES COMPLETE REABSORPTION, OR A t/L VALUE OF 100%.

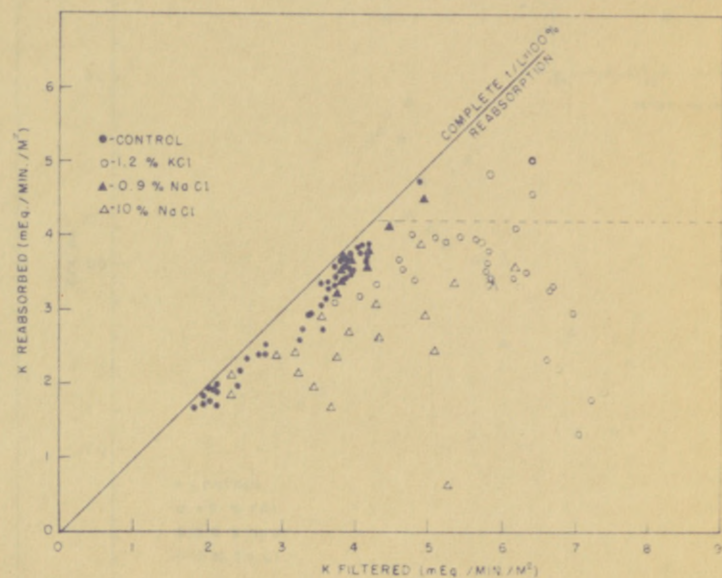

FIG. 4 POTASSIUM REABSORBED PLOTTED AS A FUNCTION OF THE POTASSIUM FILTERED. THE SCATTER OF THE INFUSION DATA IS CLEAR. THE DIAGONAL LINE MEASURES COMPLETE REABSORPTION, OR A t/L VALUE OF 100%.

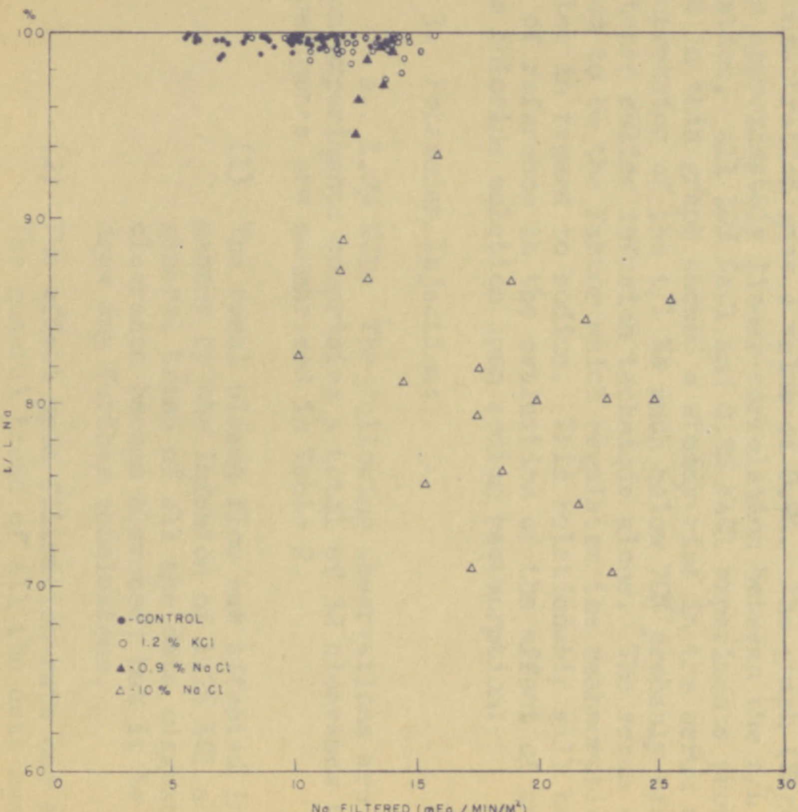

FIG. 5 THE PERCENTAGE OF FILTERED SODIUM REABSORBED (t/L Na) PLOTTED AS A FUNCTION OF SODIUM FILTERED. THE COMPLETE SCATTER OF THE SALINE INFUSION DATA IS CLEAR.

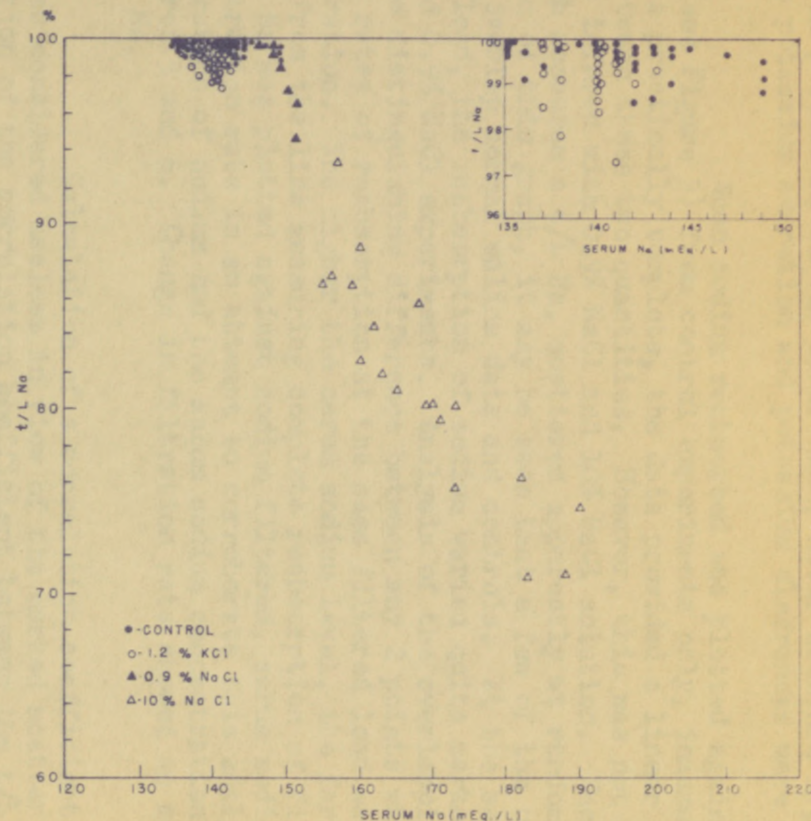

FIG. 6 THE PERCENTAGE OF FILTERED SODIUM REABSORBED (t/L Na) PLOTTED AS A FUNCTION OF THE SERUM SODIUM CONCENTRATION. AN APPROXIMATELY LINEAR RELATIONSHIP IS SHOWN. CORRELATION COEFFICIENT FOR 10% NaCl DATA = 0.94

As can be seen in Table 1, the rate of sodium excretion and sodium clearance became elevated as the serum sodium concentration rose. The serum potassium, on the other hand, never attained hyper-normal levels and yet potassium excretion and potassium clearances were also increased.

When sodium reabsorbed was plotted against sodium filtered (see Figure 3) from control experiments only, inasmuch as reabsorption was practically complete, the data provided a linear graphic relationship between these two quantities. However, this was not maintained in animals infused with 0.9% NaCl and 10% NaCl solution. These points, each of which measures a t/L Na, scattered apparently at random. Upon inspection of this graph, it may be seen that a few of the hypertonic saline points overlap normal saline data and controls. At the same filtered sodium load, the reabsorption of sodium varied quite markedly in the 10% NaCl and 0.9% NaCl experiments. Analysis of the overlapping data reveals that the distinguishing difference between any 2 points which represent unequal rates of reabsorption at the same filtered load was the serum sodium concentration. The higher the serum sodium level, the farther away were the points from the line measuring complete reabsorption of filtered sodium. The t/L Na was plotted against sodium filtered, serum sodium concentration and filtration rate in an attempt to corroborate this analysis. The rate of filtration of sodium and the serum sodium concentration are presented in Figures 5 and 6. Change in filtration rate showed no correlation with the t/L Na.

Calculation of a correlation coefficient for sodium filtered was considered useless in view of the marked scatter of the data. Calculation of the correlation coefficient between the t/L Na and the serum sodium concentration gave a value of 0.94. The graph (Figure 6) illustrates an approximately linear correlation between the t/L Na and the serum concentration. All 10% NaCl and 0.9% NaCl experiments providing the data portrayed in this graph showed a steady rise in the serum sodium concentration. Depression of the t/L Na much below 70% probably cannot be achieved by hypertonic saline infusion technique alone. The serum concentration is considered to be the factor which regulates the reabsorptive activity of the tubules in regard to sodium. This relationship will be used as a standard of reference in the evaluation of the effect of an infusion of potassium chloride solution upon sodium reabsorption.

3. Potassium Injection:

a. 1.2% KCl: The following observations are drawn from 7 infusion experiments comprising a total of 32 clearance periods. Two of these experiments are summarized in Table 2.

(1) The renal plasma flow was affected in an irregular manner by the infusion of 1.2% KCl solution. The general trend of all the data suggests that the PAH clearance became elevated; but it is impossible to draw any further conclusions.

(2) The effect upon filtration rate was also unpredictable. The general trend of all the data again suggests that the infusion of KCl solution was accompanied by a gradual elevation of the creatinine clearance. The

TABLE 2

POTASSIUM EXPERIMENTS

Time	Period	C_{pah}	C_I or C_{Cr}	F. F.	Urine Flow	SODIUM Serum	SODIUM Filtered	SODIUM Excreted	SODIUM Reabsorbed	SODIUM Clearance	SODIUM t/L	POTASSIUM Serum	POTASSIUM Filtered	POTASSIUM Excreted	POTASSIUM Reabsorbed	POTASSIUM Clearance	POTASSIUM t/L
min.		ml/min/ M^2	ml/min/ M^2		ml/min.	mEq/L	mEq/min/ M^2	mEq/min/ M^2	mEq/min/ M^2	ml/min/ M^2	%	mEq/L	mEq/min/ M^2	mEq/min/ M^2	mEq/min/ M^2	ml/min/ M^2	%
Dog A ----- Weight 13.6 kg. Surface area 0.63 M^2 ----- Experiment 7. 1.2% KCl Solution																	
0 - 15	1	272	97.5	.36	1.2	141	13.75	0.04	13.71	0.26	99.7	4.8	0.47	0.11	0.36	22.93	76.5
15 - 29	2	274	98.8	.36	2.7	140	13.84	0.02	13.82	0.17	99.9	5.3	0.52	0.13	0.39	24.52	75.2
29 - 44	3	309	99.9	.32	6.0	141	14.08	0.06	14.02	0.40	99.6	5.8	0.58	0.24	0.34	41.38	59.2
44 - 59	4	309	95.6	.31	7.2	140	13.39	0.14	13.25	1.01	99.0	7.3	0.70	0.40	0.30	54.79	42.4
59 - 73	5	226	87.2	.39	4.9	140	12.21	0.19	12.02	1.37	98.4	8.3	0.72	0.54	0.18	65.06	24.5
Dog A ----- Weight 14.8 kg. Surface area 0.66 M^2 ----- Experiment 8. 1.2% KCl Solution following feeding KCl																	
0 - 20	1	160	86.8	.54	2.1	140	12.50	0.05	12.45	0.35	99.6	4.3	0.37	0.10	0.27	23.26	72.1
20 - 40	2	194	79.5	.41	5.6	138	11.13	0.03	11.10	0.25	99.7	4.9	0.39	0.13	0.26	26.53	66.1
40 - 59	3	262	86.8	.33	7.7	138	11.98	0.03	11.95	0.21	99.7	5.4	0.47	0.22	0.25	40.74	53.9
59 - 79	4	199	86.9	.44	6.8	140	12.00	0.07	11.93	0.52	99.4	5.9	0.51	0.35	0.16	59.26	31.8
79 - 98	5	193	84.9	.44	6.6	140	11.89	0.18	11.71	1.30	98.5	6.1	0.52	0.46	0.06	75.41	10.8
98 -118	6	180	86.6	.48	6.0	140	12.13	0.19	11.94	1.37	98.4	7.1	0.62	0.52	0.10	73.24	15.9
118-137	7	185	92.6	.50	5.0	142	13.15	0.24	12.91	1.69	98.2	7.0	0.65	0.62	0.03	88.57	3.9
137-157	8	182	99.9	.55	5.1	140	13.98	0.31	13.67	2.18	97.8	6.9	0.69	0.67	0.02	97.10	2.2
Dog C ----- Weight 14.5 kg. Surface area 0.67 M^2 ----- Experiment 9. 1.2% KCl Solution																	
0 - 15	1	213	81.0	.38	2.9	141	11.41	0.03	11.38	0.22	99.7	5.3	0.43	0.09	0.34	16.98	78.1
15 - 30	2	244	96.7	.40	4.1	141	13.63	0.04	13.59	0.27	99.7	5.8	0.56	0.16	0.40	27.59	71.1
30 - 45	3	220	103.3	.47	1.4	141	14.56	0.08	14.48	0.55	99.5	6.1	0.63	0.28	0.35	45.90	55.8
45 - 66	4	251	102.5	.41	2.5	140	14.34	0.18	14.16	1.30	98.7	6.4	0.66	0.43	0.23	67.19	35.9
66 - 82	5	367	103.0	.28	4.9	138	14.21	0.29	13.92	2.13	97.9	6.8	0.70	0.57	0.13	83.82	19.0
Dog C ----- Weight 16.4 kg. Surface area 0.72 M^2 ----- Experiment 10. 1.2% KCl Solution following feeding KCl																	
0 - 19	1	188	81.8	.44	4.7	142	11.62	0.01	11.61	0.08	99.9	5.2	0.43	0.12	0.31	23.08	72.3
19 - 39	2	221	79.7	.36	5.8	144	11.47	0.01	11.46	0.10	99.9	6.4	0.51	0.17	0.34	26.49	66.7
39 - 53	3	162	65.9	.41	2.2	144	9.49	0.02	9.47	0.14	99.8	6.1	0.40	0.20	0.20	32.79	49.5
53 - 71	4	174	66.9	.39	1.8	143	9.56	0.03	9.53	0.22	99.7	5.9	0.40	0.27	0.13	45.76	33.2
71 - 86	5	187	71.2	.38	1.7	144	10.25	0.03	10.22	0.18	99.7	6.2	0.44	0.37	0.07	59.66	16.6
86 -100	6	209	76.9	.37	2.5	144	11.07	0.05	11.02	0.38	99.5	6.0	0.46	0.45	0.01	75.00	1.9
100-130	7	219	81.5	.37	2.3	144	11.74	0.07	11.67	0.47	99.4	5.4	0.44	0.48	0.04	88.89	-8.0
130-151	8	189	79.7	.42	1.9	145	11.56	0.04	11.52	0.26	99.7	5.3	0.42	0.37	0.05	69.88	12.3

relationship of the serum potassium to renal plasma flow and filtration rate is portrayed in Figure 2. The poor correlation between these functions is evident.

(3) Although the serum potassium was significantly elevated, as seen in Table 2, in every experiment of this type, the serum sodium concentration was essentially unchanged.

(4) The t/L K and the t/L Na are depressed in every experiment. These values fell in one experiment from a control mean value of 92% to 19% for potassium and from 99.8% to 97.3% for sodium. The depression of the percentage of filtered sodium reabsorbed is slight but consistent in each experiment of the potassium infusion series, and the infusion of this solution produces in every experiment, an increase in the rate of excretion of sodium.

Winkler and Smith (16) have stressed the fact that the elevation of the serum potassium concentration relates to the rate of potassium excretion and the potassium clearance, and that potassium excretion is a somewhat different function of serum concentration at high than at low serum potassium concentrations. Upon plotting these relationships for the experiments on dogs reported here, a similar variation was found between experiments, and between individual clearance periods. Analysis of the data revealed that this variation was largely ascribable to variations from period to period, and day to day in the filtration rate. Table 3 reveals the importance of filtration rate in determining the rate of excretion of potassium:

TABLE 3
(Units as in Table 2)

DOG A

Exp. No.	Period	C_{Cr}*	Serum K	Filtered K	Excreted K	Reabsorbed K
7	2	98.8	5.3	0.52	0.13	0.39
11	3	84.0	6.4	0.54	0.14	0.40
7	3	99.9	5.8	0.58	0.24	0.34
11	4	78.0	7.4	0.57	0.22	0.35

*Creatinine clearance

Examining the data from two 1.2% KCl infusion experiments o on Dog A, it will be seen that when filtration rate differs widely, inverse values for serum potassium concentration may result in similar rates of potassium filtration, excretion and reabsorption. Attempts to relate the rate of potassium excretion solely to the serum concentration are not satisfactory. The filtration rate plays a major role in the regulation of potassium excretion. Only a poor correlation exists between serum potassium concentration and filtration rate (see Figure 2). Therefore, both serum potassium and filtration rate act practically independently in the regulation of the rate of excretion of potassium. An analysis of the conditions that regulate potassium excretion must include both of these factors.

It has been impossible to utilize, therefore, the relationship expressed by Winkler and Smith (16) as standards of reference from which one might differentiate the effect of sodium chloride upon potassium reabsorption.

Seeking evidence of a tubular maximum for potassium in the data (see Table 2), one is confronted with the observation that as the filtration of potassium increased, the rate of reabsorption rose and then rapidly fell in 5 out of 6 experiments. In no instance could a constant maximum rate of reabsorption be demonstrated although the serum potassium rose steadily in the course of each experiment, and the potassium filtered load approximately doubled in magnitude. The gradual depression of the rate of reabsorption of potassium in response to an increasing filtration of potassium appears to be unique in renal physiology. None of the other electrolytes behave in this fashion and neither do any of the organic substances such as glucose, ascorbic acid and the amino acids. The recent work of various investigators (1, 9) indicating the existence of the phenomenon of tubular secretion of potassium may lend clarity to an analysis of the data from these experiments. If the renal tubular system is capable of secreting potassium at the same time that it reabsorbs it, simultaneous potassium secretion will effect a pseudo-depression of reabsorption. Thus, potassium secretion will be deducted from actual potassium reabsorption. If tubular secretion attains sufficient magnitude, it may exceed reabsorption and effect negative values for computed reabsorption. The existence of a tubular reabsorptive maximum for potassium will be concealed by this process. The data reveal that a tubular maximum for potassium is possible, providing tubular secretion of potassium is postulated.

When potassium reabsorbed was plotted against potassium filtered in control experiments only, the percentage reabsorption being practically constant, the data provided a roughly linear relationship between these two quantities (see Figure 4). However, this relationship was not maintained in animals infused with 10% NaCl and 1.2% KCl solutions. From Figure 4, it may be seen that when 10% NaCl was infused, the reabsorption of potassium varied widely for any filtered load and was depressed below control data. When 1.2% KCl solution was infused, there was a gradual rise in reabsorption accompanying a gradual increase in the potassium filtered load. With filtered loads of great magnitude, the rate of reabsorption of potassium became severely depressed.

Analysis of the data alone, revealed that the rate of excretion of potassium is determined by the combination of the serum concentration and the filtration rate. Each point on Figure 4 represents a t/L value. In an attempt to determine the factors responsible for this pattern in the t/L K, we have plotted t/L K as a function of filtration rate, serum potassium concentration and the rate of potassium filtration. Filtration rate alone appeared to have no relation to the changes manifested in the t/L K following the infusion of KCl. The graphs of serum potassium and filtered potassium are given in Figures 7 and 8. Calculations of the correlation ratios for the 2 graphs, analyzing statistically the 1.2% KCl data

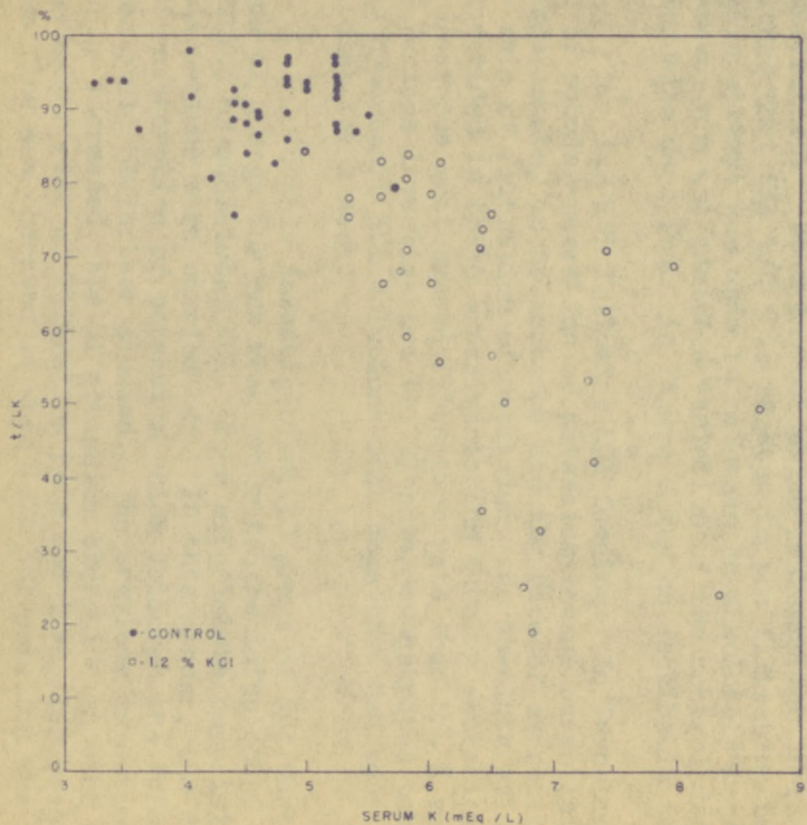

FIG. 7 THE PERCENTAGE OF FILTERED POTASSIUM REABSORBED (t/L K) PLOTTED AS A FUNCTION OF SERUM POTASSIUM CONCENTRATION. ONLY MINIMAL CORRELATION IS PRESENT. CORRELATION RATIO FOR KCl INFUSION DATA = 0.53.

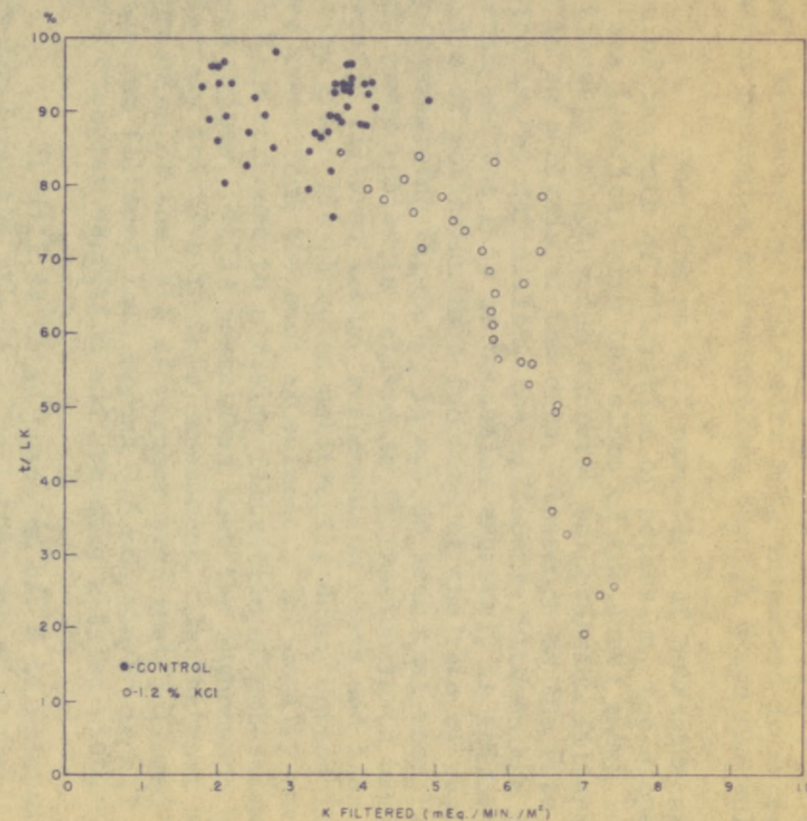

FIG. 8 THE PERCENTAGE OF FILTERED POTASSIUM REABSORBED (t/L K) PLOTTED AS A FUNCTION OF THE RATE OF POTASSIUM FILTRATION. EXCELLENT CORRELATION IS CLEAR. CORRELATION RATIO FOR KCL INFUSION DATA = 0.91.

only, revealed a value of 0.53 for the serum concentration and 0.91 for the filtered potassium graph. Analysis of Figure 7 revealed that the scatter is ascribable to the fact that the filtration rate had not been considered. Whenever the filtration rate increased in proportion to the rise in serum potassium concentration, the t/L K was markedly depressed.

When the rate of excretion of potassium was plotted as a function of the rate of filtration of potassium, the slope of the resulting curve was identical with the slope of the curve shown in Figure 8. This relationship of potassium excreted to potassium filtered was previously indicated in an analysis of the data. Inasmuch as the rate of potassium reabsorption is, by definition, the difference between the rate of potassium filtered and the rate of potassium excreted, it follows that the rate of filtration of potassium is a function of the rate of reabsorption of this ion. Upon reexamining Figure 4, it may be seen that when 1.2% KCl solution is infused, reabsorption is related to filtration in an unusual manner. With increasing filtered loads, reabsorption rises and then falls. Three points on the graph lie above an arbitrarily drawn dotted line. These t/L values were taken from the same experiment. The usually severe depression of the t/L K in response to a rising filtration of potassium was only slight in all these points. It is postulated that the phenomenon of tubular secretion was largely inactive in this experiment. In the rest of the data, the severe depression of the rate of reabsorption that followed the elevation of the potassium filtered load beyond 0.5 mEq/min/M^2 in all probability is ascribable to tubular secretion and presents a false picture of reabsorption.

It will be noted that the t/L K is related to a different variable factor than the t/L Na. The latter showed a correlation with the serum concentration. Studying potassium reabsorption in rats, Dicker (3) also concluded that the t/L K is related to the filtration of potassium. No exhaustive attempt was made to maintain an absolutely constant potassium dietary intake, and the admitted variation of the control data and potassium chloride infusion data found in Figure 8 may be ascribable to this fact.

b. 1.2 KCl following KCl feeding: An investigation of the phenomenon of tubular secretion of potassium became essential. With KCl infusion experiments, in no instance did the rate of excretion of potassium exceed the rate of filtration of potassium. No absolute evidence has therefore been provided in these experiments for tubular secretion of potassium. Potassium clearance must exceed filtration rate when t/L K values are negative. Various investigators (1, 9) have demonstrated tubular secretion by infusing hypertonic KCl solutions into dogs that had been fed additional KCl in the diet for a week.

In this investigation, 10 grams of KCl were added to the diet of each of 4 dogs for one week prior to the infusion of an isotonic (1.2%) solution of additional KCl. Four experiments comprising a total of 28 clearance periods were carried out. In this manner, the depression of the rate of reabsorption of potassium which followed the infusion of 1.2% KCl solution could be further studied. The previous ingestion of KCl resulted in an increased rate of potassium excretion in each experiment. The same irregular rise of filtration rate and irregular response of the renal plasma flow was observed as when 1.2% KCl solution was infused without

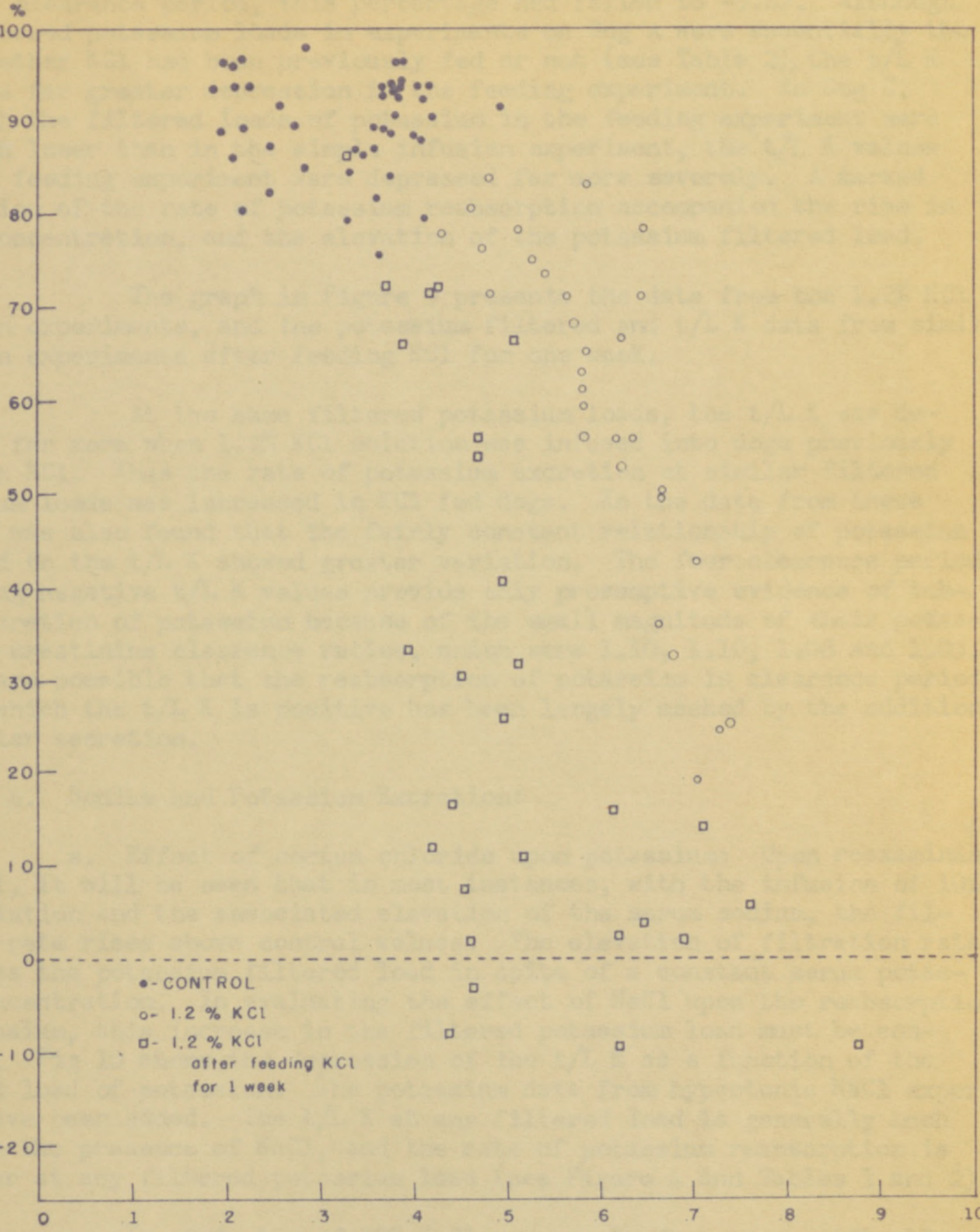

FIG. 9 THE PERCENTAGE OF FILTERED POTASSIUM REABSORBED (t/LK) PLOTTED AS A FUNCTION OF THE RATE OF POTASSIUM FILTRATION. INFUSION WITH 1.2% KCl SOLUTION WITH AND WITHOUT PREVIOUS FEEDING OF 10 GRAMS OF KCl DAILY FOR ONE WEEK

previous feeding, and the serum sodium concentration was again unchanged. The t/L Na showed the same slight depression in every experiment, falling in one clearance period to 97.6% during the infusion of KCl. However, the t/L K was greatly depressed. In one experiment by the end of the seventh clearance period, this percentage had fallen to -9.8%. Although the filtered potassium loads in experiments on Dog A were essentially the same whether KCl had been previously fed or not (see Table 2), the t/L K showed a far greater depression in the feeding experiment. In Dog C. although the filtered loads of potassium in the feeding experiment were all much lower than in the simple infusion experiment, the t/L K values for the feeding experiment were depressed far more severely. A marked depression of the rate of potassium reabsorption accompanied the rise in serum concentration, and the elevation of the potassium filtered load.

The graph in Figure 9 presents the data from the 1.2% KCl infusion experiments, and the potassium filtered and t/L K data from similar infusion experiments after feeding KCl for one week.

At the same filtered potassium loads, the t/L K was depressed far more when 1.2% KCl solution was infused into dogs previously fed with KCl. Thus the rate of potassium excretion at similar filtered potassium loads was increased in KCl fed dogs. In the data from these dogs it was also found that the fairly constant relationship of potassium filtered to the t/L K showed greater variation. The four clearance periods reporting negative t/L K values provide only presemptive evidence of tubular secretion of potassium because of the small magnitude of their potassium to creatinine clearance ratios, which were 1.10, 1.10, 1.08 and 1.03. It appears possible that the reabsorption of potassium in clearance periods during which the t/L K is positive has been largely masked by the addition of tubular secretion.

4. Sodium and Potassium Excretion:

a. Effect of sodium chloride upon potassium: Upon reexamining Figure 1, it will be seen that in most instances, with the infusion of 10% NaCl solution and the associated elevation of the serum sodium, the filtration rate rises above control values. The elevation of filtration rate increases the potassium filtered load in spite of a constant serum potassium concentration. In evaluating the effect of NaCl upon the reabsorption of potassium, this increase in the filtered potassium load must be considered. Fig 10 shows the depression of the t/L K as a function of the filtered load of potassium. The potassium data from hypertonic NaCl experiments have been added. The t/L K at any filtered load is generally much lower in the presence of NaCl, and the rate of potassium reabsorption is far lower at any filtered potassium load (see Figure 4 and Tables 1 and 2).

The infusion of 10% NaCl appears to depress specifically the reabsorption of potassium.

The effect of 10% NaCl upon potassium reabsorption was investigated further. Graphic analysis revealed that the serum sodium concentration appears to be more correlated with the t/L K than with sodium filtered, filtration rate or other sodium variables. This relationship is illustrated in Figure 11.

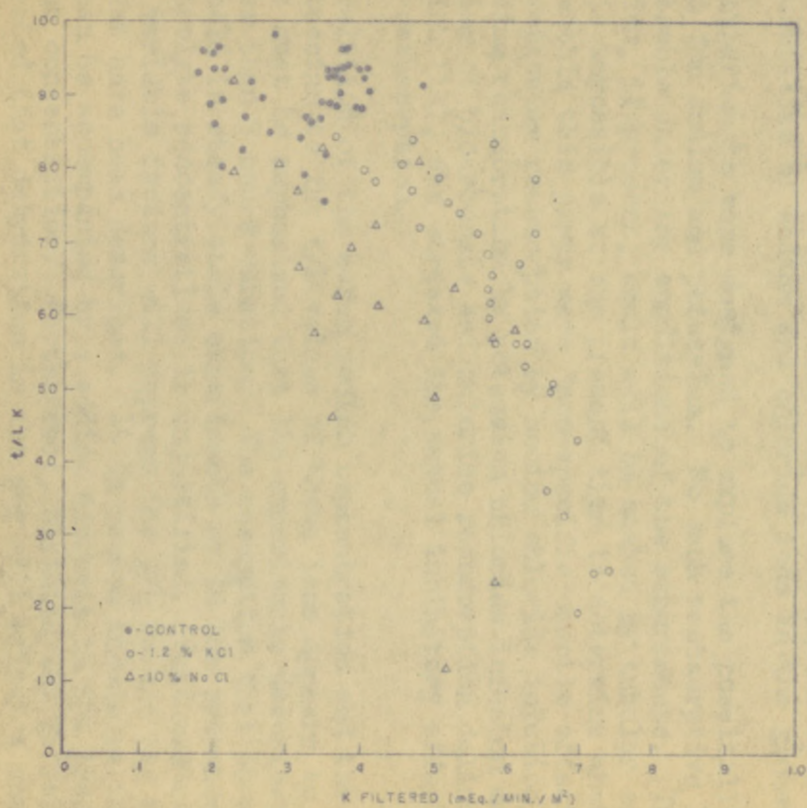

FIG. 10 THE PERCENTAGE OF FILTERED POTASSIUM REABSORBED (t/L K) PLOTTED AS A FUNCTION OF THE RATE OF POTASSIUM FILTRATION. DATA TAKEN FROM ALL 1.2 % KCl AND 10 % NaCl INFUSION EXPERIMENTS.

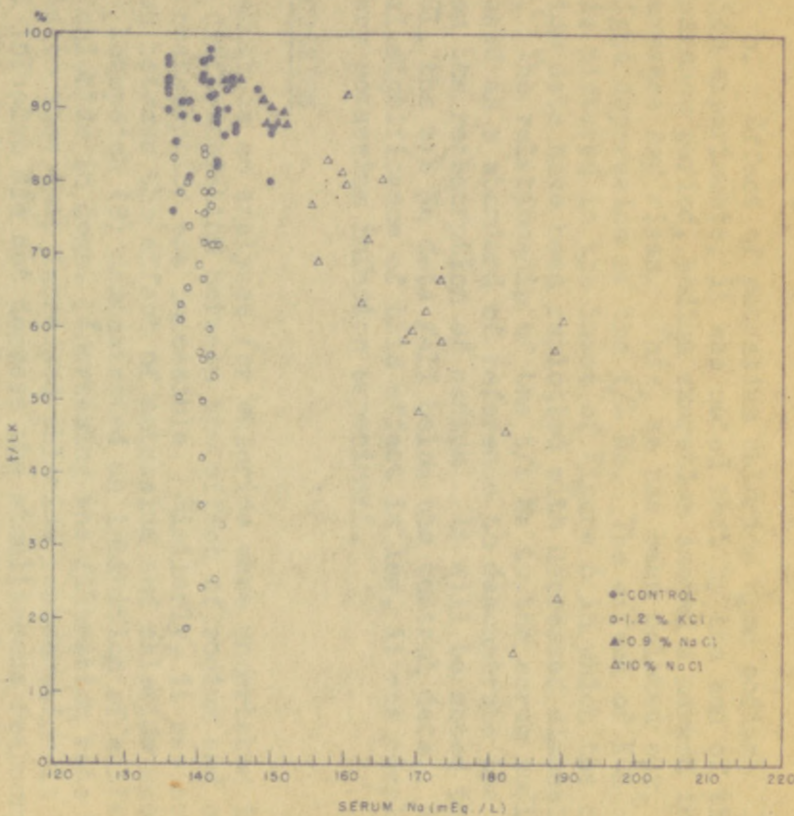

FIG. 11 THE PERCENTAGE OF FILTERED POTASSIUM REABSORBED (t/L K) PLOTTED AS A FUNCTION OF THE SERUM SODIUM CONCENTRATION. DATA TAKEN FROM ALL 1.2 % KCl, 0.9 % NaCl, AND 10 % NaCl INFUSION EXPERIMENTS.

The depression of the t/L K at normal serum sodium concentrations as seen in Figure 11 in the data from 1.2% KCl experiments, is effected by increasing the filtration of potassium.

b. Effect of potassium chloride upon sodium: In the 1.2% KCl infusion experiments, it was noted that by the end of the third or fourth clearance period, sodium excretion showed a marked increase and the sodium clearance had risen. This, as has been pointed out, was associated with a slight depression of the t/L Na. The effect of KCl on sodium reabsorption is pictured in the inset of Figure 6 in which the control and 1.2% KCl infusion data have been replotted with decreased dimensions of the coordinates. The relationship of the t/L Na to the serum sodium concentration has been used as a standard of reference to demonstrate the effect of KCl infusion on the reabsorption of sodium. It will be noted that in the presence of KCl, the t/L Na data fall below the control data. Although the statistical significance of this effect is low, it was completely consistent in every potassium infusion experiment.

III. DISCUSSION

Inasmuch as no analyses for chloride were undertaken in this investigation, a differentiation between the effect of sodium and of chloride upon potassium reabsorption was impossible. Similarly, it was not possible to distinguish between the effect of potassium and chloride upon sodium reabsorption. Lotspeich (8) demonstrated an inhibition of sulfate reabsorption by sodium chloride in dogs. Increasing the filtration rate by feeding meat, he was able to show that increased chloride reabsorption in the absence of a 10% NaCl infusion did not depress the simultaneous reabsorption of sulfate. He concluded that the decrease in the tubular reabsorption capacity for sulfate was a "non-specific osmotic effect" consequent upon the appearance of large quantities of sodium and chloride ions in the glomerular filtrate.

Our experiments were designed to explore the possibilities of a tubular maximum for sodium and potassium. No such reabsorptive limit for sodium was demonstrable under the conditions of the experiments. The tubular maximum for potassium, if present, could well be masked by tubular secretion of potassium. It is impossible at the present time to determine whether the effects portrayed within this paper were "non-specific osmotic effects". The inhibition of potassium reabsorption by sodium chloride infusion and the inhibition of sodium reabsorption by potassium chloride infusion may well exemplify the mechanism of bicarbonate and chloride reabsorption delineated by Pitts and Lotspeich (11), who stressed the mutual inhibitory effect of these ions in tubular reabsorption.

The relation of the serum sodium concentration and the rate of filtration of potassium to the t/L values of these ions appears to be consistent. However, it must be emphasized that the experiments described in this report were of less than 3 hours duration. The assumption that these relationships will also hold in steady state experiments or in the presence of falling serum electrolyte concentrations is unjustified. Furthermore, it is clear that many other variable factors will depress the t/L Na and the t/L K in addition to those that have been described. It is common knowledge that the state of alkalosis can be accompanied by a sodium diuresis in the presence of a normal serum sodium concentration. Furthermore, Elkinton and Taffel (4) have clearly demonstrated that dehydration in the dog will effect a sharp increase in the serum sodium concentration associated with a rise in potassium excretion and the virtual absence of sodium in the urine.

Wesson, Anslow and Smith (15) strengthened the concept of the obligatory and the facultative reabsorption of water and sodium. The use of the t/L function parallels their concepts of a constant 85% proximal tubular reabsorption of sodium and a varying distal reabsorption. They have supported the concept that the tubular reabsorption of sodium is functionally related to the filtration rate because an approximately constant fraction of the filtered sodium is reabsorbed by the proximal tubule and thin limb regardless of the filtration rate. It has not been possible to evaluate the investigations described in this report in terms of their concept primarily because of the introduction of the variable factor of a massive NaCl infusion. By this means, the overall percentage of filtered sodium reabsorbed was consistently depressed below the 85% reabsorption of the proximal tubule and thin limb. The meaning of the added mechanism involved is obscure at the present time. Furthermore, the role of the serum sodium concentration appears important in the regulation of the reabsorption of filtered sodium. In justification of the proposal that the serum sodium concentration regulates tubular reabsorption, these investigations are complementary to the concepts expressed by Gamble (5) in regard to the preservation of the normal total ionic level within the body.

No explanation is forthcoming at the present time for the mechanism underlying these factors or for the mechanism involved in the activation of tubular secretion of potassium. Apparently the excretion of potassium by the kidney is controlled by a different mechanism than the excretion of sodium.

IV. CONCLUSIONS

A. The renal tubular reabsorption of sodium and potassium has been studied in 6 unanesthetized dogs in 28 experiments comprising 129 clearance periods. The serum concentration of the two ions was elevated progressively over wide ranges by continued intravenous infusion of solutions of the corresponding chloride salts.

B. The percentage of filtered sodium which is reabsorbed by the tubules is functionally related to the serum sodium concentration.

C. The percentage of filtered potassium which is reabsorbed by the tubules and the rate of excretion of potassium are closely related to the rate of filtration of potassium.

D. The infusion of hypertonic sodium chloride depresses the fractional tubular reabsorption of potassium in excess of that ascribable to the simultaneous increase of the potassium filtered load.

E. The infusion of potassium chloride solution depresses the tubular reabsorption of sodium at normal serum sodium concentrations.

F. The ingestion of potassium chloride prior to the infusion of this salt markedly augments the depression of tubular reabsorption of potassium ascribable to the increased potassium filtered load. Presumptive evidence indicates that tubular secretion of potassium was in part responsible for this apparent depression.

G. The reabsorption of sodium is not limited by a tubular maximum.

H. The possibility is presented that a tubular maximum for potassium is concealed in our experiments by the simultaneous secretion of potassium by the renal tubules.

I. During the infusion of sodium chloride solution, the rise in serum sodium concentration is roughly paralleled by the rise in renal plasma flow and filtration rate. During the infusion of potassium chloride solution, the rise in serum potassium concentration shows no such correlation.

V. RECOMMENDATION

Investigations should be carried out to determine the other factors which regulate the fraction of filtered sodium reabsorbed by the renal tubules. The mechanism of tubular secretion of potassium should be studied further.

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