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SOME EFFECTS OF VARIATION IN SODIUM INTAKE AND OF DIFFERENT SODIUM SALTS IN NORMAL SUBJECTS [1]

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In a separate paper (1) we have described effects resulting from variation of sodium intake in normal subjects, which we attribute to changes in adrenal cortical activity. It is the purpose of this paper to describe some additional effects of considerable physiological interest that were observed in the course of that study.

METHODS

Three normal young adults were maintained throughout the study on a constant diet adequate in calories and protein with a very low sodium (about 9 mEq.) and chloride (about 25 mEq.) content. At definite periods 480 mEq. of sodium were administered orally daily either as sodium chloride or as sodium citrate. The analytical methods and diet are described in detail in the previous report (1).

RESULTS

The complete data of this study were presented in a separate paper (1). Only data pertinent to the present discussions will be presented here.

Table I shows the weights of our three normal subjects for the three days before, during and following sodium administration. It is evident that with sodium chloride administration a much more marked gain of weight occurred than with sodium citrate. Each subject was on a maintenance caloric intake so that practically all weight changes occurring over such short periods as these are due to change in body fluid content.

Table II shows the changes in urinary sodium, chloride and potassium excretion that occurred before, during and following each period of sodium administration. No significant changes in fecal sodium, chloride, and potassium were noted and these are not recorded here. It is seen that with administration of sodium chloride there is in each case a parallel increase in both urinary sodium and chloride as would be expected. Following the

sodium citrate administration a similar increase in sodium excretion is noted; however, chloride excretion remains unchanged, or if anything, slightly decreases.

Table II shows further that with the sodium chloride administration no significant increase in potassium excretion occurred except in the case of M. L., whose urine potassium content rose from about 40 mEq. in 24 hours to 88 mEq. the first day of sodium chloride administration. In subjects W. C. and E. W. a significant decrease in potassium excretion occurred after cessation of sodium chloride administration. On the first day of sodium citrate administration, a very definite increase in potassium excretion took place in all subjects. This was followed, after omission of sodium citrate, by a decrease to unusually low levels of potassium excretion.

Table III shows the data we have collected re-

TABLE I

Nude, fasting body weights of subjects for the three days before, the three days of sodium administration and the three following days

W. C.	M. L.	E. W.	
75.005	68.285	64.650	Low sodium and chloride
74.950	68.620	64.920	Low sodium and chloride
74.565	68.640	64.805	Low sodium and chloride
76.830	70.370	66.840	Sodium chloride 479 mEq.
78.250	71.480	67.500	Sodium chloride 479 mEq.
77.748	71.270	67.660	Sodium chloride 479 mEq.
74.770	70.020	66.070	Low sodium and chloride
74.480	69.860	65.700	Low sodium and chloride
74.100	69.480	65.400	Low sodium and chloride
75.750	68.650	65.230	Low sodium and chloride
75.660	68.670	64.820	Low sodium and chloride
74.850	68.475	64.990	Low sodium and chloride
75.370	68.901	65.440	Sodium citrate 478 mEq.
75.830	69.010	65.730	Sodium citrate 478 mEq.
75.850	68.995	66.080	Sodium citrate 478 mEq.
75.330	68.650	65.340	Low sodium and chloride
75.030	68.230	65.110	Low sodium and chloride
75.150		65.450	Low sodium and chloride

Urinary sodium, chloride and potassium excretions of subjects for three days before, during, and three days following each three day period of sodium administration

W. C.			M. L.			E. W.			
Na	Cl	K	Na	Cl	K	Na	Cl	K	
(mEq.)	(mEq.)	(mEq.)	(mEq.)	(mEq.)	(mEq.)	(mEq.)	(mEq.)	(mEq.)	
13.2	5.9	49.8	2.6	2.7	33.2	1.9	15.5	88.7	Low sodium and chloride
17.0	7.0	49.9	1.6	1.0	42.8	1.3	8.7	103.2	Low sodium and chloride
1.5	4.9	68.2	1.2	0.9	41.2	0.6	7.6	77.1	Low sodium and chloride
20.4	16.8	68.2	152.2	152.6	87.6	72.5	115.2	99.2	Sodium chloride 479 mEq.
250.2	267.2	81.0	371.2	411.2	76.0	361.6	395.0	102.2	Sodium chloride 479 mEq.
425.8	466.8	83.5	582.9	614.4	41.6	477.7	497.0	62.5	Sodium chloride 479 mEq.
292.9	300.7	78.4	201.9	188.4	30.4	254.0	238.5	47.1	Low sodium and chloride
53.4	57.2	33.8	53.5	62.8	67.6	108.9	94.3	42.8	Low sodium and chloride
70.5	63.2	34.5	31.0	42.8	66.8	86.0	87.4	69.0	Low sodium and chloride
4.2	14.4	71.8	6.4	8.4	66.4	3.72	25.1	91.3	Low sodium and chloride
5.4	11.2	79.7	5.7	7.8	60.4	1.78	20.7	103.3	Low sodium and chloride
7.1	16.8	84.4	4.5	9.2	66.4	2.52	17.1	83.4	Low sodium and chloride
284.7	13.2	147.6	305.0	9.8	159.6	214.6	2.8	217.7	Sodium citrate 478 mEq.
430.9	10.2	128.6	457.5	6.0	85.2	374.7	5.4	101.9	Sodium citrate 478 mEq.
439.0	12.0	66.6	454.5	3.5	78.8	434.6	4.1	58.3	Sodium citrate 478 mEq.
112.7	9.6	40.0	61.1	3.0	9.2	188.2	6.7	22.0	Low sodium and chloride
50.1	9.6	31.2	66.3		20.4	71.4	8.3	32.2	Low sodium and chloride
26.0	6.2	53.6				25.9	8.6	52.7	Low sodium and chloride

garding glomerular filtration rate and sodium and chloride excretion in these normal subjects. In subject E. W. the glomerular filtration rate is estimated from the 24 hour endogenous creatinine clearance (2, 3). In our other two subjects, glomerular filtration rate was determined by inulin clearances (4). The sodium and chloride excretions were obtained simultaneously with the filtration rates.

<center>DISCUSSION</center>

The discussion is organized about the four points we wish to stress:

I. *The importance of fixed anion as well as cation to the accumulation of extracellular fluid.*

As is well known, quantitatively the important cation of the extracellular fluids is sodium, and through renal regulation the concentration of sodium in the extracellular fluids is maintained within very narrow limits. Even in disease it is uncommon to find the serum sodium concentration varying more than 20 mEq./L from the normal value of about 140 mEq. Thus, it has come to be generally realized that extracellular fluid volume does not increase without available sodium

(5). This fact has become the central principle in the management of clinical edema by sodium restriction.

Furthermore it is true that the important anion of the extracellular fluid regarded quantitatively is chloride. Little, however, is mentioned regarding the role played by chloride in the accumulation of extracellular fluid. Table I and Figure 1, which show the changes in body weight that occurred with administration of equivalent amounts of sodium first as sodium chloride and then as sodium citrate, clearly indicate that weight gain is much greater following administration of sodium chloride. In short experiments of this type, change in weight is necessarily due almost entirely to changes in body fluid content. Calculation of predicted weight change from increase in chloride space following sodium chloride administration reveals that the weight gain is almost entirely due to increase in extracellular fluid. Figure 1 shows that the serum sodium and chloride concentrations in subject E. W. rose slightly and equally on administration of sodium chloride.

The inability to accumulate much extracellular fluid and gain weight when the same amount of sodium was administered as the citrate salt was

by any further reduction in urine chloride excretion. The slight weight gain that occurred was associated with the small expansion of extracellular fluid volume made permissible by the dilution of the existing chloride content of the extracellular fluid. Thus in the absence of fixed anion, administration of sodium, even in large amounts, does not increase extracellular fluid volume importantly.

II. *Dissociation of renal sodium and chloride excretion*

Table II clearly shows that when sodium chloride is administered there occurs a parallel increase in urinary excretion of sodium and chloride. With the administration of sodium citrate a similar increase in urinary sodium occurs but the urinary chloride continues to be small or even
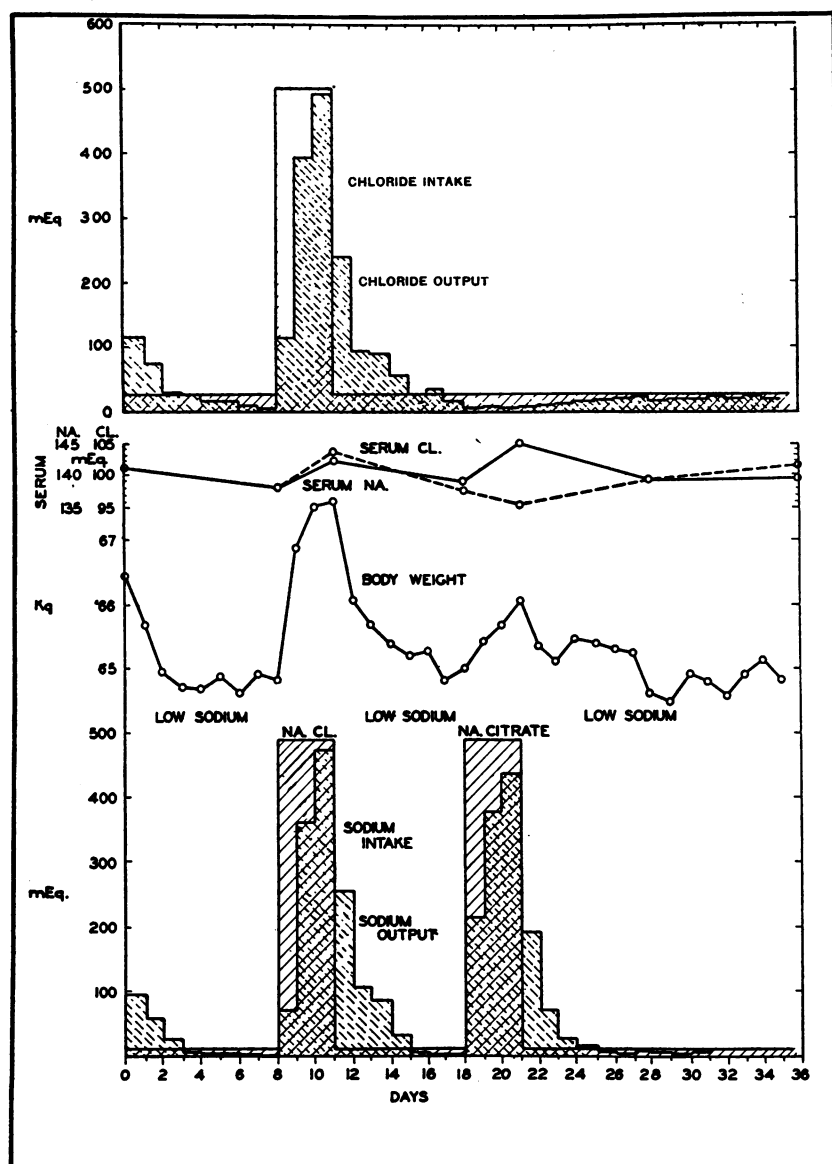

FIG. 1. To Show Changes in Body Weight, Serum Sodium and Chloride Concentrations Together with Sodium (Lower) and Chloride (Upper) Balances in Subject E. W.

Note especially the decreased chloride excretions occurring during the period of sodium citrate administration.

decreases below the base line. This is illustrated in Figure 1 for subject E. W.

In another report (1) we present evidence to support the belief that the renal excretion of sodium in normal human subjects is regulated by adrenal cortical activity. Earlier studies by others of the action of adrenal cortical extracts and adrenal cortical hormones on sodium and chloride balance suggested a similar effect on both sodium and chloride (6–8). Such studies in the past have been conducted under conditions that might be expected to cause parallel changes in sodium and chloride balance, i.e., loss of sodium and chloride in the urine following adrenalectomy and retention of sodium and chloride on administration of adrenal cortical extract or adrenal cortical steroids to adrenalectomized animals. But when a definite need on the part of the body to conserve fixed anion, chiefly chloride, is created because of the presence of a large excess of sodium cation, a complete dissociation in the renal excretion of sodium and chloride is elicited. Our earlier studies (1) indicate that large intakes of sodium, either as the chloride or citrate salts, depress adrenal cortical activity. This would permit the large urinary excretion of sodium that followed the administration of sodium citrate; but accompanying this extensive removal of sodium there is no increased loss of chloride. In fact the urinary values for chloride fell below those of the control period. What it is that causes the kidneys to conserve chloride when excess base is administered, this study does not indicate. It is recognized, however, that such reduction of renal excretion of chloride serves a useful function in conserving fixed anion in the presence of the threat of alkalosis resulting from the sodium citrate administration— another example of the "wisdom" of the body.

III. Displacement of intracellular potassium by sodium

It was noted that each of our subjects showed a prompt and striking increase in urinary potassium excretion during the first 24 hours of sodium citrate administration. By the third day of the sodium citrate period the urinary potassium had dropped to or below the base line (see Table II). No such increase in urinary potassium content occurred with sodium chloride administration ex-

cept possibly for the much less striking increase in subject M. L. Figure 2 shows the theoretical potassium balance calculated from the actual nitrogen balance (grams nitrogen balance $\times 2.7 =$ mEq. theoretical potassium balance on the basis of changes in body protoplasm) and indicates that this potassium excretion was not the result of increased catabolism of tissues. Figure 2 also clearly shows that this marked potassium diuresis coincided with the markedly positive balance of sodium unaccompanied by fixed anion that resulted from the sodium citrate administration.

To learn more about the association of positive sodium and negative potassium balance the calculations shown in Table IV were made according to the method of Darrow (9) for the periods of sodium administration in each subject. The extracellular fluid volume was estimated as 20% [2] of the body weight on the morning of the first day of sodium administration. It is seen from Table IV that in each case with sodium citrate administration there is a positive intracellular sodium balance, definite in E. W. (222 mEq.) and M. L. (178 mEq.) and perhaps equivocal in subject W. C. (83 mEq.). This is associated with a negative

[2] Recent evidence by inulin space determinations (20) indicates that the extracellular fluid volume may be less than this per cent. Our subjects also had some shrinkage of extracellular volume as a result of the preceding restriction of sodium and chloride intake. However, the value taken for the initial extracellular fluid volume in these calculations, within reasonable limits, only insignificantly affects the results.

TABLE IV

Changes in intracellular sodium and potassium balances that occurred during the three-day periods of sodium chloride and sodium citrate administration *

	Total Na balance	Total K balance	Extra-cell-Na balance	Extra-cell-K balance	Intra-cell-Na balance	Intra-cell-K balance
	mEq.	mEq.	mEq.	mEq.	mEq.	mEq.
Subject E. W.						
after NaCl	+553	−9	+644	+13	−91	−22
after NaCit.	+436	−108	+214	+2	+222	−110
Subject M. L.						
after NaCl	+355	+46	+401	+11	−46	+35
after NaCit.	+236	−76	+58	+3	+178	−79
Subject W. C.						
after NaCl	+759	−60	+722		+37	
after NaCit.	+303	−133	+220	0	+83	−133

* The complete data from which these calculated values were derived are presented in our preceding paper (1).
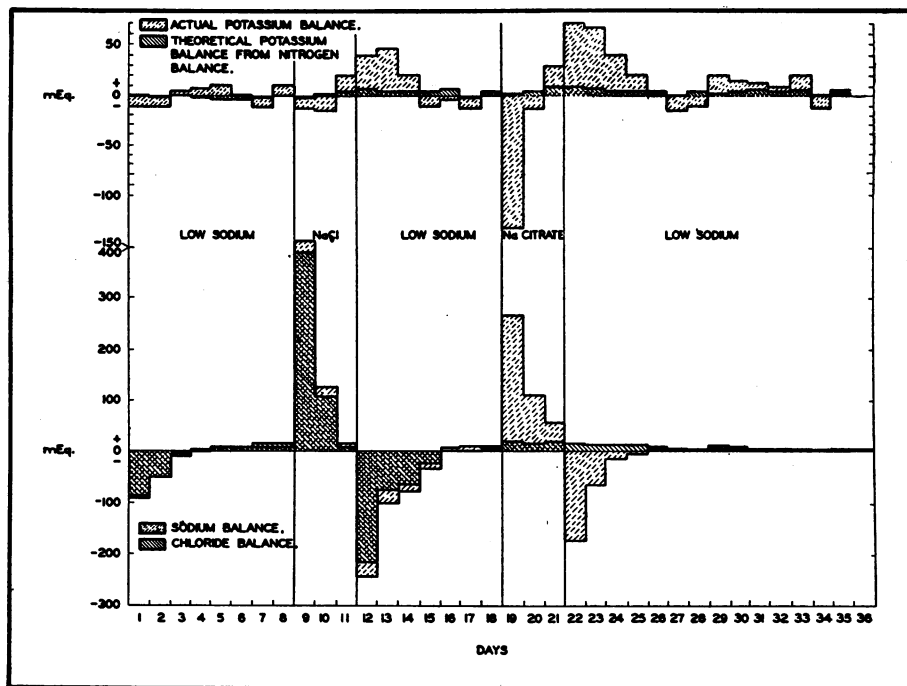
FIG. 2. THE ACTUAL AND THEORETICAL POTASSIUM BALANCES (UPPER) AND SODIUM
AND CHLORIDE BALANCES (LOWER) IN SUBJECT E. W.

Note that the sodium and chloride balances change together except during and following
the period of sodium citrate administration. The factor 2.7 was used to convert grams
of observed nitrogen balance to milli-equivalents of "theoretical potassium balance." The
values plotted are the difference between intake and urine plus fecal excretions. Note the
large negative potassium balance during the first day of sodium citrate administration.

intracellular potassium balance of − 110, − 79, and − 133 mEq. respectively for the three-day period.

This method of calculation originated by Darrow is based on the assumption that nearly all of the chloride of the body is restricted to the extracellular fluid compartment. The significant positive figures for "intracellular sodium balance" (or sodium that cannot be accounted for in the extracellular fluids of the body) clearly indicate that sodium has entered some part of the body unaccompanied by chloride. The coincident strongly negative potassium balance is good evidence that this sodium entered the intracellular compartment without chloride, displacing potassium, in so doing. We make no attempt to quantitate the intracellular sodium gain with the potassium loss, as extraneous factors, such as increase in tonicity of the extracellular fluid that occurred with the sodium administration and which might require changes in the total cation concentration within the cells, invalidate such attempts.

Administration of the sodium cation with fixed anion as sodium chloride resulted in no such gain in intracellular sodium. The total gain in body sodium was associated with nearly an equivalent gain of chloride. The sodium gain was accounted for by the increase in chloride space—expanded extracellular fluid volume. There was no occasion for sodium to pass into the cells. Hence no displacement of potassium occurred.

These findings, namely, displacement of intracellular potassium on administration of sodium citrate,[3] strongly support the excellent studies of Darrow (8, 10–13) that the intracellular sodium plays a role in the defense of the normal extracellular pH.

The data presented in the preceding publication (1) offer an explanation of the lag in excretion of sodium on changing from low to high intake

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[3] One may anticipate exactly similar effects from sodium bicarbonate, acetate, lactate or other sodium salts having an associated anion that will be metabolized to bicarbonate in the body.

of sodium. Namely that the sharp restriction of sodium just before the administration of sodium citrate, resulted in maximal reabsorption of sodium in response to augmented adrenal cortical activity. This effect in decreasing amounts was continued for several days after the subjects had begun to take the sodium citrate. Thereafter, the adrenal drive relaxed and the large intake of sodium was accompanied by a plentiful excretion of sodium. During this lag in renal adjustment, the sodium cation passed into the cells of the body from the extracellular fluids, without accompanying fixed anion. This reduced the "available base" (or CO_2 content) of the extracellular fluids, and hence the extent of alkalosis that would have otherwise been produced by the sodium citrate administration. Had this shift of sodium into the cells failed to occur in subjects E. W. and M. L. an increase in the extracellular CO_2 content of 15 and 12 mM per liter, respectively, might have occurred with a resultant severe alkalosis.

The renal excretion of the potassium displaced from the cells was not impeded by the augmented adrenal cortical activity as was the sodium, since the potassium appeared in the urine. Desoxycorticosterone, the adrenal cortical salt-and-water-hormone par excellence, facilitates renal excretion of potassium while decreasing renal excretion of sodium (14). Hence the adrenal cortical activity during the lag in adjustment to the high sodium intake, though it prevented renal excretion of sodium, perhaps facilitated renal excretion of potassium. In subject E. W. the urine collection during the first 24 hours of sodium citrate administration was divided so that the urine passed during the first six hours of sodium citrate administration was collected separately and on analysis was found to contain only 1.4 mEq. of sodium (out of a total excretion of 215 mEq. for that 24 hour period) while it contained more than one-fourth of the total large potassium excretion of that day.

The negative intracellular sodium balance that followed the sodium chloride administration in subject E. W. is of sufficient magnitude to be interesting. The administration of large amounts of sodium chloride, which is "acid-producing" in that it contains equivalents of sodium and chloride (whereas the extracellular fluids normally contain sodium to chloride in the ration of 1.4 to 1), apparently caused a transfer of intracellular so-

dium to the extracellular fluids which would serve to help combat this effect of sodium chloride administration. Such a mechanism assisting in the prevention of acidosis has also been described by Darrow (11, 15).

It is realized that the type of calculation made above would include any extrarenal or extrafecal sodium loss from the body as a gain in "intracellular sodium." This possibility reduces itself to losses of sodium through the skin. The studies of Freyberg and Grant (16) of the insensible losses of sodium from the skin of normal adult subjects show that the daily sodium loss is less than 10 mEq. Hence in our normal subjects who avoided exertion and sweating, a cumulative loss of sodium through the skin over the three-day periods of about 30 mEq. would scarcely affect the positive balances recorded.

IV. Glomerular filtration, tubular reabsorption and the excretion of sodium

There has been considerable discussion in the current literature regarding the possible roles played by change in glomerular filtration rate and tubular reabsorption of sodium in the formation of edema (17–19). Because our studies involved very low and very high rates of sodium and chloride excretion resulting from the marked variations in sodium intake, observations were made to determine, if possible, how glomerular filtration and tubular reabsorption of sodium affected the excretion of sodium by normal subjects. Table III shows the simultaneous 24 hour endogenous creatinine clearance taken as a measure of glomerular filtration rate (2, 3) and the simultaneous 24 hour urine sodium and chloride content. Simultaneous inulin clearances and sodium excretions for subjects M. L. and W. C. are also recorded.

It is obvious from a brief examination of these data that there is no correlation between glomerular filtration rate and renal excretion of sodium or chloride. Following the sodium chloride administration an increase in glomerular filtration rate is associated with an increased rate of excretion of sodium. However, no such increased rate is seen following the sodium citrate administration in spite of an equally large increase in the rate of sodium excretion. In another paper (1) we have suggested that the increased glomerular filtration rate

following sodium chloride administration is a non-specific response secondary to the resulting increased vascular volume. One certainly is not justified in interpreting it as a specific adjustment of the kidney for the purpose of increasing sodium excretion as has been postulated recently (18). Our findings in normal subjects are similar to those of Briggs et al. (19) who found no relation between glomerular filtration rates and sodium excretion in patients with congestive heart failure.

In what has just been said, mention of the serum sodium and chloride concentrations at the time of these clearance studies has been purposely avoided. Mokotoff et al. (18) have claimed that the tubular reabsorption of sodium is constant per unit of glomerular filtrate volume ("13.3 mM per 100 cc. of glomerular filtrate") and therefore varies directly with the glomerular filtration rate. These workers subtracted the sodium excreted in the urine from the product of the glomerular filtration rate and the serum sodium to obtain the rate of tubular reabsorption. As the quantity of sodium filtered is in nearly all cases tremendous in comparison with the quantity excreted such calculations are questionable. With a glomerular filtration rate of 160 liters in 24 hours and serum sodium of 140 mEq. per liter our subject E. W. was presenting approximately 22,400 mEq. of sodium to his renal tubules while the 24 hour urinary sodium excretion varied between 0.6 and 500 mEq. depending on the sodium intake. Thus as some 97% of the filtered sodium was always reabsorbed, the relatively large shift in urinary sodium must have occurred as a result of variations within this remaining 3% of the filtered sodium. In edematous cardiac and nephritic patients the glomerular filtration rate, though somewhat reduced (17–19), remains sufficiently large to still make the quantity of sodium excreted only a very small percentage of that filtered. Accordingly, the answer to the whole problem of the manner in which renal function is altered in certain cardiac and nephritic subjects making them unable to rid themselves of the usual daily sodium intake is hidden in the manner in which this very small fraction of the total filtered sodium is handled. However, methods such as the mannitol clearance with its unavoidable error of about 10% are much too crude to demonstrate these fine changes. One cannot detect changes of 3% in a function by using a measuring stick with a 10% error.

CONCLUSIONS

Sodium as the chloride and as the citrate salts was administered to normal subjects maintained on very low sodium and chloride diets. The effects on body weight, sodium, potassium, chloride and nitrogen balances were recorded. Simultaneous glomerular filtration rates and urinary excretions of sodium and chloride were obtained.

The gain in body weight with sodium chloride was strikingly greater than with sodium citrate. Ingestion of sodium as chloride caused parallel increases in urinary excretion of sodium and chloride, whereas sodium as citrate resulted in a similar increase in urinary sodium but the urinary chloride did not increase. Since in the previous paper (1) it was concluded that the desoxycorticosterone-like hormone activity of the adrenal cortex is depressed by sodium administration, this dissociation of sodium and chloride excretion demonstrates that some other factor causes renal conservation of chloride.

When sodium was administered as the citrate salt, a large increase in body sodium occurred accompanied by a large diuresis of potassium. Appropriate calculations indicate that significant amounts of sodium entered the cells, displacing large amounts of potassium.

The quantities of sodium appearing in the urine from 0.6 to 4.77 mEq. bore no relationship to the simultaneous volumes of glomerular filtrate. The sodium present in the urine is 3% or less of the sodium delivered to the tubules in the glomerular filtrate. Accordingly the relatively small variation in the amount of sodium not reabsorbed determines whether body sodium will be increased or decreased. Since the error inherent in the present methods is greater than the function to be measured, the exact role of filtration rate and tubular reabsorption in the excretion of sodium cannot at the present time be defined.

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