sulfur excretion after cysteine injection was relatively slow, recovering about 50% of the sulfur of the amino acid in the urine during 36 hours following the injection. In contrast to the results with cysteine the major portion of the methionine sulfur was excreted in the neutral sulfur fraction. The post-injection urines gave a positive reaction with Grote's[7] test for C-S-S-C compounds. The Sullivan test for cystine, as described by Brand, Harris and Biloon[8] gave questionable results. The presence of acetone bodies in the urine prevented the interpretation of the usual sodium cyanide-sodium nitroprusside test for S-S compounds.

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On the Mechanism of Sodium Depletion in Addison's Disease.

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The authors have made the following observations in relation to the development of acute adrenal insufficiency in Addison's disease: 1. There is a marked decrease in the concentration of sodium in the blood serum.[1] 2. The withdrawal of salt from the diet of a patient suffering from Addison's disease promptly induces symptoms of severe insufficiency.[2] 3. The administration of NaCl in large amounts brings about striking clinical improvement which may be correlated with a return of the Na content of the blood to a normal level.[1, 2] These findings have recently been confirmed by Harrop and his coworkers.[3, 4] 4. Sodium is lost from the body of adrenalectomized dogs as a result of augmented renal excretion of this element.[5] This observation has also been substantiated by Harrop.[6]

[7] Grote, I. W., *J. Biol. Chem.*, 1931, **93**, 25.

[8] Brand, E., Harris, M. M., and Biloon, S., *J. Biol. Chem.*, 1930, **86**, 315.

[1] Loeb, R. F., *Science*, 1932, **76**, 420.

[2] Loeb, R. F., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 808.

[3] Harrop, G. A., Weinstein, A., Soffer, L. J., Trescher, J. H., *J. Am. Med. Assn.*, 1933, **100**, 1850.

[4] Harrop, G. A., *J. Am. Med. Assn.*, 1933, **101**, 388.

[5] Loeb, R. F., Atchley, D. W., Benedict, E. M., Leland, J., *J. Exp. Med.*, 1933, **57**, 775.

[6] Harrop, G. A., Soffer, L. J., Ellsworth, R., and Trescher, J. H., *J. Exp. Med.*, 1933, **58**, 17.

The writers have suggested that the adrenal glands play an important rôle in the regulation of sodium metabolism, and that the sodium depletion occurring in adrenal insufficiency is dependent therefore upon a disturbance of this function. This idea gains support from the fact that in adrenal insufficiency there is a loss of sodium without change in potassium excretion, whereas in other clinical states associated with base loss, such as ketogenic acidosis due to starvation[7] or diabetes,[8] NH_4Cl acidosis,[9] and severe diabetic glycosuria,[8] sodium depletion is accompanied by a parallel loss of potassium. The foregoing facts suggest that the kidney is the locus of action of the sodium regulatory mechanism of the adrenal gland.

It remained to be shown, however, that sodium is not lost from the body in adrenal insufficiency as the result of an acidosis due to the formation and excretion of some undetermined organic acid. For this reason we have studied the excretion of ammonia and titratable acid in a patient suffering from Addison's disease, in whom acute adrenal insufficiency was induced by salt withdrawal and in whom "compensation" was reestablished by salt administration. Since it has been shown[8] in diabetic ketosis that the NH_3 excretion increases 10 fold, reaching more than 225 m. eq. in 24 hours and the titratable acid of the urine is correspondingly augmented, a complete balance study was not considered essential for the observations here presented, particularly as the decrease in sodium concentration in the blood in acute adrenal insufficiency is even greater than that found in severe acidosis.

The patient, E. F., was a white woman of 38 whose past history was irrelevant except for tuberculosis of the hip and pleurisy with effusion. For 2 years before admission she had irregular abdominal pains and occasional vomiting spells. For the past year there had been rapidly increasing brown pigmentation of the whole body, and for 6 months she had had dyspnoea on exertion and definite but not marked weakness. Physical examination was entirely negative except for extensive generalized brown pigmentation. There were, however, no patches in the buccal mucous membranes. Her blood pressure varied between 112/80 and 76/50 during her stay in the hospital.

The patient was given a regular diet and was allowed to eat salt as she desired, for eighteen days, during which time the patient

[7] Gamble, J. L., Ross, G. S., Tisdall, F. F., *J. Biol. Chem.*, 1923, **57**, 633.

[8] Atchley, D. W., Loeb, R. F., Richards, D. W., Jr., Benedict, E. M., and Driscoll, M. E., *J. Clin. Invest.*, 1932, **12**, 297.

[9] Folling, A., *Acta. Med. Skandinav.*, 1929, **71**, 221.

TABLE I

Date	Urine Analysis: Vol. cc.	Cl m. eq.	Titratable acid cc. N/10 acid	NH_3 m. eq.	Blood Analysis: Na m. eq. per l	K m. eq. per l	Cl m. eq. per l	HCO_3 m. eq. per l	Protein %	Non Protein N mg. per 100 cc.	Glucose gm. per l	Remarks
Aug. 18					135.3	4.6	100	25.3				Admission blood. Patient. quite well.
" 21-22	818	82.6	121	15.2								Regular diet until 9/5.
" 22-23	1667	124.0	172	15.5								
" 23-24	1790	136.9	221	18.1								
" 24-25	1240	112.5	174	13.9								
" 25-26	885	84.1	151	13.6								
" 26-27	1660	116.0	205	20.5								Catamenia
" 27-28	1615	129.5	183	23.2								"
" 28-29	1355	110.5	216	23.8								"
" 29-30	1210	92.6	219	18.7								"
" 30-31	1510	98.8	137	11.6								
Aug. 31-Sept. 1	2124	166.0	142	15.4								
Sept. 1- 2	1310	153.0	189	13.7								
" 2- 3	1610	147.5	100	10.3								
" 3- 4	2008	183.0	171	9.6								
" 4- 5	2310	159.0	213	11.0								Weaker than on admission
" 5- 6	1477	106.8	157	11.9	131.0	5.1	97.3	26.2	7.5	30.3	0.91	Salt poor diet started 9/5.
" 6- 7	965	55.0	129	13.3								Marked prostration. Unable to get out of bed.
" 7- 8	1847	178.0	190	11.2	123.4	5.6	88.9	25.9	7.8	26.7		Picture of severe adrenal insufficiency before salt administration, which started after blood was taken on 9/7.
" 8 -9	2034	352.0	214	14.5								
" 9-10	2160	290.5	221	20.5								
" 10-11	1710	350.1	241	19.6								
" 11-12	3605	376.0	316	23.7								
" 12-13	3290	320.0	285	26.2								
" 13-14	2844	417.0	270	26.7								
" 14-15	1760	300.7	214	20.7	138.1	4.9	105.0	25.7	5.6	22.7	0.81	"Feels perfectly well." Taking 10 gm. NaCl daily plus diet.

was up and about the ward, though she complained of nausea, occasional abdominal pain and slowly increasing weakness. She was then given a regular but salt-poor diet, containing less than 2.0 gm. of NaCl a day. Within 24 hours weakness and nausea increased, she felt dizzy, and had to remain in bed. The next day prostration was more marked, nausea was extreme and she vomited a total of 210 cc. in 48 hours. The patient's state of prostration did not justify continuation of the salt-poor regime, and in the next 24 hours she received a total of 20 gm. of NaCl by mouth and by rectum, in addition to the salt of her diet. Within 2 days she was up and about once more and was discharged 5 days later essentially symptom-free, taking 10 gm. of salt daily, in addition to that in her food.

The results are shown in the accompanying table. During the first 18 days of observation, while the patient ate salt as she desired, the sodium of the blood decreased from 135.3 m. eq. per liter to 131 m. eq. Coincident with this slow, steady loss of sodium, the NH_3 excretion and the titratable acidity of the urine were maintained at a normal level for the usual ward diet. During the next 48 hours when salt was withheld from the diet, the blood sodium fell abruptly to 123.4 m. eq. per liter, without increase in the excretion of ammonia or titratable acid. As sodium administration was forced (10 to 20 gm. of NaCl daily, in addition to salt of diet) the ammonia excretion increased slightly, but did not approach a level that would indicate significant acidosis. Furthermore, in this patient, the blood bicarbonate concentration was normal throughout the entire period of observation, in the presence of the marked fluctuations in the sodium level.

From this brief study it is apparent that the loss of sodium from the body in Addison's disease is not dependent upon the excretion of unusual quantities of acid as determined by the excretion of NH_3 and titratable acid, and hence it seems probable that we are dealing with a primary disturbance of the sodium regulatory mechanism, as the writers have previously suggested.[5] From the data now available, it may be inferred that the essential feature of this disturbance is an increase in the rate of sodium excretion by the kidney.

In this patient, as previously reported,[2] the clinical condition parallels the level of sodium in the blood, and the state of well-being is largely dependent upon the amount of sodium ingested, as might be predicted from the foregoing discussion.