

PROTEIN METABOLISM IN ADDISON'S DISEASE

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Although Addison's disease is one very closely connected with a gland which must have important functions regulating metabolism, since associated with tuberculosis of this organ are general weakness, loss in weight and a marked pigmentation of the skin and the mucous membranes, nevertheless the amount of chemical work which has been done in an attempt to throw light on the process is not large.

Those investigators who have taken up the cases from the point of view of protein metabolism have in the main contented themselves with a study of the nitrogen balance, and these observations have been extended further to a simultaneous determination of the effect of the administration of adrenal gland substance on the protein breakdown.

Even here the results are not uniform, for Senator¹ believes that the physiologic effect of the gland substance in case of Addison's disease is to lead to increase in body weight and appetite and to produce a retention of nitrogen, but a slight minus balance in calcium. Both Kaufmann² and Pickhardt³ report increased nitrogen loss during the administration of the tablets, and to-day the use of the gland in the treatment of the condition has lapsed into disfavor.

Not all the cases of Addison's disease, however, show a loss of nitrogen, for in some it will be seen that nitrogen equilibrium may be maintained on a diet which is not only low in nitrogen, but much below the average in heat units. Marchetti and Stefanelli,⁴ on account of the way some of the patients react with this low nitrogen and caloric diets, advance the idea that the oxidative capacity of the organism is lowered.

Some isolated observations that have been made on the urine in Addison's disease lead one to suspect that the nitrogen and carbon metabolism may be abnormal. Leva⁵ reports the presence of acetic and formic acids in the urine, and taurocholic acid was also said to have been detected. Gerhardt and Reichardt also say that large amounts

1. Senator: *Charité-Ann.*, 1898, xxiii, 287.

2. Kaufmann: *Zentralbl. f. Stoffwechs. u. Verdauungskr.*, 1901, ii, 173.

3. Pickhardt: *Berl. klin. Wchnschr.*, 1898, xxxv, 727.

4. Marchetti and Stefanelli: *Riv. crit. di clin. med.*, 1901, ii, 773.

5. Leva: *Virchow's Arch. f. path. Anat.*, 1898, cxxv, 35.

of fatty acids were found in the urine, and the observation regarding taurocholic acid has been confirmed by Jacoby⁶ in what is admitted to be a doubtful case. Marchetti and Stefanelli and Maragliano lay considerable stress on the indicanuria, while Leva and Pickhardt, on what appear to be good grounds, criticize the view that indicanuria is a symptom due directly to disturbance of the adrenal function, and point out that the appearance of large amounts of indican in the urine is probably the effect of increased intestinal putrefaction, such as occurs in many cases with diarrhea, and diarrhea is common in this disease.

That the protein metabolism, especially the endogenous protein metabolism, is lower than usual is indicated by the estimations of Leva of the kreatinin output. This observer found the kreatinin distinctly lowered, while in a control case of icterus the excretion was normal.

With regard to the proportion in which the nitrogen and sulphur containing constituents of the urine are excreted, there is an absolute lack of information.

It is true that Varannini,⁷ Marchetti and Stefanelli and Leva all give the results of urea and uric acid estimations, but the methods employed can not be used to determine what the influence of the condition is on the nitrogen metabolism, so that these results will not be taken up in detail.

REPORT OF CASE

The case we report was that of a patient in Bellevue Hospital, and for the privilege of the examination we are indebted to the courtesy of Dr. Alexander Lambert.

The abstract from the notes of the case is as follows:

Patient.—M. M. male, aged 50, native of Ireland. There was no family history; no cancer or rheumatism. The patient drank beer, but seldom whiskey. He denied venereal disease.

History.—The patient had had no illness up to four years before coming under observation. He had to give up work on account of weakness and shortness of breath; was unable to walk without frequent stops for breath; had attacks of dizziness, with flashes before the eyes. About this time he noted that his skin was getting dark. This was first observed on the hands and face; later on other parts of the body. About two years later, he noticed that his legs were swollen. He arose two or three times in the night to urinate. He often had attacks of palpitation, but no fainting. His appetite was always good; he never had any gastro-intestinal disturbance. For two years he had pain and stiffness of the limbs after exposure to wet and cold. His chief complaint was general weakness.

Physical Examination.—The patient had a large frame, was well nourished, anemic, but did not seem to be acutely ill. The face and the upper part

6. Jacoby. *Charité-Ann.*, 1898, xxiii, 287.

7. Varannini: *Clin. med. ital.*, 1902, xli, 40.

of the body were deeply pigmented, with lighter streaks over the upper part of the face and forehead. The thighs and legs were lighter in color. The eyes were equal and reactive; to light normal; conjunctivæ very pale. The tongue was clean and moist; the dorsal surface showed patches of dark pigmentation. This pigmentation was also seen on the inner sides of the cheeks. The neck was thick, rounded and rigid.

Thorax: percussion, negative. Breath sounds, distant and indistinct. Posteriorly, crepitant rales over each base. Heart, not enlarged. Left border percussed 10 cm. to left of median line. Action fairly regular. Sounds clear. Systolic murmur heard best in the pulmonic area. Arteries thickened. Pulse small, low tension with quick upstroke.

Abdomen: liver and spleen not enlarged.

Extremities: slight clubbing of the fingers.

The patient was quite weak, and very anemic. His appetite was always very great. Except for weakness and great hunger, he complained of nothing.

TABLE 1.—BLOOD EXAMINATION

Date.	Hemoglobin.	Erythrocytes.	Leucocytes.	Polymorpho- nuclear.	Small Lymphocytes.	Large Lymphocytes.	Mononuclear.	Eosinophiles.	Basophiles.
April 11 . .	15	1,410,000	5000						
April 17 . . .	14	1,520,000	2500*	44.5	20.5	8.5	5.0	20.5	1.5
April 20			4700†	47.0	19.3	10.5	4.3	19.3	0.0
April 25 . .	18	1,764,000	5400‡	49.5	24.7	5.7	4.2	11.2	4.2
May 2 . . .	17	1,604,000	2300	52.3	22.3	8.6	3.6	10.6	2.3
May 19			6600	57.0					

* Normoblast.

† Normoblast (300 cells).

‡ Myelocyte (200 cells).

His bowels were very constipated until he was put on an oatmeal diet. The high eosinophile count which appears in the report on the blood findings remains unaccounted for. The stools were repeatedly examined for parasites and none found. Trichinosis was excluded by excising a piece of the pectoral muscle and examining for trichinæ. None were found.

Dynamometric Tests.—As general weakness is considered an important feature of Addison's disease, several dynamometric tests were made on the patient during his stay in the hospital. The results are as follows: R. and L. hands. April 8, R. 29.3 K.; L. 22.6 K.; April 16, R. 33.8 K.; L. 31.6 K.; April 17, R. 38.4 K.; L. 27.1 K.; April 25, R. 29.3 K.; L. 22.6 K.

Blood Pressure.—The blood pressure readings with the Janeway sphygmomanometer gave the following: April 17, R. 142; L. 138; April 25, 155; May 1, R. 116; L. 122; May 8, R. 107, L. 110; April 11 (Erlanger), Systolic, 128, Diastolic 90.

During the examination the temperature was subnormal, varying between 96 and 98 degrees. The pulse rate was between 76 and 92, and the respiration 20-24. The Calmette reaction was tried on several occasions with negative results.

HOSPITAL LABORATORY REPORTS

Urine.—April 4: Cloudy, amber; sp. gr. 1010; albumin, very faint trace; no sugar, few leucocytes, no casts, Cammidge's reaction absent.

Feces.—April 11: Light brown, semi-solid, normal odor, not fatty. Microscopic, few starch granules, many bacteria, no muscle fibers, no parasitic ova.

Blood.—See Table 1.

Diet.—For the purposes of an examination of his protein metabolism, the patient was put on a diet containing the following: Eggs, 280 grams; milk, 960 c. c.; sugar, 16 grams; white bread, 130 grams; butter, 20 grams; boiled rice, 480 grams; oatmeal boiled, 900 grams; tea, 480 c. c. As the diet varied slightly from day to day, the amount of nitrogen, fat and carbohydrate are

TABLE 2.—NITROGEN, FAT, CARBOHYDRATE AND CALORIC VALUE OF FOOD

Date.	Total Nitrogen.	Calories.	Fat.	Calories.	Carbo-hydrate.	Calories.	Total Calories.
April 29	16.01	410	95.8	890	293	1200	2500
April 30	15.51	398	88.9	825	277	1130	2353
May 1	15.51	398	88.1	820	277	1130	2353
May 2	15.51	398	89.8	835	277	1130	2368
May 3	15.51	398	88.9	825	277	1130	2358
May 4	15.51	398	88.9	825	277	1130	2358
May 5	15.02	385	91.4	840	246	1010	2235
May 6	14.22	364	84.3	785	236	968	2117
May 7	15.51	398	88.9	825	277	1130	2358

given in Table 2 with the individual and total heat units of the food. As the average weight of the patient was 72 kilos and the average caloric value of the food 2300 calories, the patient received on an average 32 calories per kilo.

The urines were collected in twenty-four hour periods, and the methods which have been used in the analysis have been given in the various papers of one of us.

Nitrogen Balance.—We were unfortunately unable to collect the feces quantitatively in this case, and thus are unable to give the nitrogen and sulphur balances. An examination of the difference between the nitrogen intake and the amount excreted in the urine leads one to believe that a minus balance of nitrogen was improbable. The total nitrogen intake during the period of experiment was 138.3 grams. Of this 97.6 grams were excreted through the urine. The patient's weight at the beginning of the experiment was 66.3 kilos and at the end 65.8 kilos, a net loss of 500 grams.

Volume of Urine.—As will be seen from the tables, exceptionally high volumes of urine are recorded, with a correspondingly low specific gravity. On one day only did the volume fall below 1500 c.c., and on two days over 2500 c.c. were passed. On the days on which the lower volumes were excreted there is a low nitrogen output. As the patient was exceedingly difficult to control it is possible, even with the care which was taken in watching him that some of the urine was lost. This is to a certain extent confirmed by the lower kreatinin elimination found on these days.

Amid Nitrogen.—On this fraction of the nitrogen we are inclined to lay some special stress as representing the desamidating capacity of the organism which appears to be at fault in some conditions of toxic character. The present case represents a type of disease in which desamidation has not suffered in the least. Comparing the ratios here obtained with those found in normal individ-

TABLE 3.—NITROGEN AND SULPHUR PARTITION IN ADDISON'S DISEASE

Date Received.	Volume. C.c.	Specific Gravity.	Total Nitrogen. Gms.	Gross Urea. Nitrogen. Gms.	Amid Nitrogen. Gms.	Urea Nitrogen. Gms.	Kreatinin. Nitrogen. Gms.	Uric Acid. Nitrogen. Gms.	Rest Nitrogen. Gms.	Gr. Urea. Per cent.	Ammonia. Per cent.	Urea. Per cent.	Kreatinin. Per cent.
April 30, '08...	2045	1007	11.220	10.210	0.916	9.294	0.382	0.074	0.554	91.00	8.17	82.83	3.41
May 1, '08...	2170	1007	12.484	11.320	1.138	10.182	0.384	0.074	0.702	90.70	9.15	81.55	3.08
May 2, '08...	1890	1008	9.090	8.320	0.800	7.520	0.274	0.060	0.436	91.50	8.80	82.70	3.01
May 3, '08...	2510	1008	11.780	10.820	0.980	9.840	0.340	0.083	0.537	91.90	8.38	83.52	2.89
May 4, '08...	2530	1008	11.740	10.728	0.860	9.868	0.329	0.056	0.627	91.38	7.32	84.06	2.80
May 5, '08...	2280	1007	11.628	10.579	0.889	9.690	0.315	0.059	0.675	90.96	7.65	83.31	2.71
May 6, '08...	1800	1008	10.980	10.135	0.918	9.217	0.333	0.032	0.480	92.28	8.36	83.92	3.03
May 7, '08	1360	1010	8.230	7.655	0.691	6.964	0.258	0.018	0.299	93.00	8.40	84.60	3.13
May 8, '08	1930	1009	10.500	9.726	0.965	8.761	0.310	0.027	0.437	92.65	9.23	83.42	2.95

uals, it will be seen that the average, 91.7 per cent, is quite as high as that which is found in healthy persons (88.5 per cent Shaffer*) and ratios higher have only been found by Schondörff and by one of us in animals receiving a large amount of meat.

Ammonia Nitrogen.—Both relatively and absolutely compared with urines of normal individuals on a similar diet, the ammonia nitrogen is high. This is interesting in view of the fact that other investigators have drawn attention to the presence of unusual acid products in the urine. While these were not tested for in the present case, the fact that no acetone was found in any of the samples of urine tested probably excludes the presence of acetoacetic and beta-oxybutyric acids. Despite this fact, one must admit a very considerable

8. Shaffer: Am. Jour. Physiol., 1908, xxii, 445.

degree of acidosis, not dependent on the character of the food intake. We hope at some future time to take up the study of this interesting feature of the case.

Urea Nitrogen.—Although the ammonia ratio is so much beyond that found in normal individuals, the high amid nitrogen ratio allows the urea ratio still to be quite within normal limits. The average for the entire series of analysis is 83.3 per cent, while Shaffer found for a similar diet 84.3 per cent. His ammonia ratio was however 4.3 per cent against our 8.3 per cent.

Kreatinin.—As an index of the total endogenous metabolism, it was of considerable importance to determine what the output of kreatinin was. As will be seen from the comparison with the normal figures the kreatinin is low. The patient weighed 72 kilos. The average output of kreatinin nitrogen during the time of examination was 0.32 grams. Per kilo body weight this gives a "kreatinin nitrogen coefficient" of $0.32 \div 72 = 4.4$. Even with the highest output

TABLE 3.—NITROGEN AND SULPHUR PARTITION IN ADDISON'S DISEASE—Continued

Date Received.	Uric Acid. Per cent.	Rest Nitrogen. Per cent.	Total Sulphur. Gms.	Total Sulphate. Gms.	Alk. Sulphate. Gms.	Ethereal Sulphate. Gms.	Neutral Sulphur. Gms.	Total Sulphate. Per cent.	Alk. Sulphate. Per cent.	Ethereal Sulphate. Per cent.	Neutral Sulphur. Per cent.	100 Total Sulphur. Total Nitrogen.	Phosphorus. Gms.	Chlorin. Gms.
April 30, '08.	0.70	5.29	1.022	0.866	0.807	0.059	0.156	84.80	79.00	5.80	15.20	9.1	1.000	0.454
May 1, '08.	0.59	5.63	1.024	0.836	0.783	0.053	0.188	81.56	76.40	5.16	18.44	8.2	1.048	0.527
May 2, '08.	0.66	4.83	0.733	0.578	0.536	0.042	0.155	78.85	73.13	5.72	21.15	8.1	0.760	0.516
May 3, '08.	0.70	4.51	0.956	0.783	0.670	0.113	0.173	81.90	70.09	11.81	18.10	8.1	1.052	0.831
May 4, '08.	0.48	5.34	1.017	0.853	0.736	0.117	0.164	83.84	72.40	11.44	16.16	8.6	0.971	0.822
May 5, '08.	0.51	5.82	0.930	0.798	0.707	0.091	0.132	85.77	75.98	9.79	14.23	8.0	1.015	0.565
May 6, '08.	0.30	4.39	0.967	0.817	0.751	0.066	0.150	84.53	77.64	6.89	15.47	8.8	0.945	0.423
May 7, '08.	0.22	3.65	0.722	0.598	0.558	0.040	0.124	82.88	77.22	5.66	17.12	8.8	0.851	0.302
May 8, '08.	0.26	4.14	0.917	0.737	0.658	0.079	0.179	80.42	71.80	8.62	19.58	8.7	1.044	0.440

All urines acid. No kreatin. No acetone.

kreatinin nitrogen, viz., 0.384 grams, the coefficient is still considerably below that which Shaffer considers normal. The coefficient in Shaffer's normal cases ranges from 11.7 to 5.4. Hence, in Addison's disease, a condition usually associated with a considerable degree of muscular weakness, the coefficient, as one might be led to expect from Shaffer's results, is low, and compares with what this observer found in diabetes and similar affections.

Kreatin.—The question of the presence or absence of kreatin from the urine has seemed to one of us from results which he has obtained to be of very considerable pathologic importance. Its presence in the urine is associated by some investigators invariably with loss of body protein, although this is assuredly not always the case. Others attribute its excretion to an impaired function of the liver. In any case, its appearance in the urine, when the factor

of starvation can be successfully eliminated, is probably of pathologic significance. In this case, as will be seen from the tables, kreatin is absent from the urine, and in the experience of one of us, it is the first important disease, associated with general weakness, in which no kreatin has been found. More information regarding the behavior of other cases of Addison's disease in this particular is earnestly desired.

Uric Acid Nitrogen.—On comparison with the data obtained from normal subjects, the uric acid nitrogen appears to be distinctly low, and this is especially the case towards the end of the experiment, when on one day only 0.018 grams were excreted. As an index of endogenous metabolism this corresponds with what was found in the kreatinin excretion. It is worthy of note that the low uric acid excretion is found on that day on which the lowest kreatinin output was observed. These results do not correspond with those of Marchetti and Stefanelli, who obtained on some days as much as a gram of uric acid, corresponding roughly to 0.3 grams of uric acid nitrogen.

Rest Nitrogen.—The absolute amount of rest nitrogen corresponds closely with what has been found in normal urines. The ratio moreover is not only within the normal limits, but is even below the values usually obtained.

THE PARTITION OF SULPHUR

Total Sulphur.—The impression which one obtains from an examination of the excretion of total sulphur is that it is high, and this is confirmed when one considers the relation which this component of the urine bears to the total nitrogen output. Shaffer's last determinations of the values in normal individuals give a ratio of 7.2. In this series of analyses the ratio is more than 1 per cent higher. While this is perhaps not of pathologic significance, one often sees in cases with the pathologic destruction of protein that apparently a type of protein is katabolized which is high in sulphur.

Sulphate Sulphur.—Comparing the results here obtained with those of Folin and Shaffer in normal subjects it will be seen that the oxidation of the sulphur part of the protein molecule has proceeded in every respect like that of a normal individual. There is certainly no deficiency in oxidation in so far as the sulphur group is concerned as has been asserted by the Italian investigators of this disease.

Ethereal Sulphate Sulphur.—In view of the importance which was at one time attached to the excretion of indican in Addison's disease it is interesting to examine the output of ethereal sulphur. The figures uniformly are somewhat high, especially on two days in the middle of the experiment, but an examination of the metabolites in normal individuals will disclose amounts of ethereal sulphur almost as high as those found here, so that one cannot assign to this any pathological importance.

Neutral Sulphur.—Neither relatively nor absolutely is the neutral sulphur increased above that found in normal subjects. As the sulphur of taurocholic acid would be found in this fraction, it is unlikely that the amount of taurocholic acid in these urines would be increased as some observers have claimed.

We are indebted to Mr. Emil Osterberg for much help in performing the chemical analyses described in this paper.

SUMMARY

The nitrogen and sulphur metabolism in a case of Addison's disease has been examined on a purin-free diet. The desamidating capacity of the patient and his capacity to transform the sulphur of the cystin

group into sulphuric acid were absolutely comparable to that of normal individuals. A considerable degree of acidosis was observed which is not accounted for by any factor which was found in this examination. The endogenous metabolism of the patient, as represented by the krea-
tinin and uric acid outputs was below that of normal subjects.