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STUDIES ON THE NITROGEN AND SULPHUR METABOLISM IN "BRIGHT'S DISEASE"

II. Observations on the Nitrogen and Sulphur Excretion in Patients without Renal Edema[1]

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In the course of the studies on the nitrogen and sulphur excretion in Bright's Disease, we early found one patient who seemed to be constantly in negative sulphur balance. While this patient was a moderately advanced nephritic at the time of study, he differed in no essential particular from other patients with Bright's Disease and nitrogen retention. A section of the experiment on this patient is shown in figure 1. During this entire period this patient was in positive nitrogen balance, was on a satisfactory diet in every possible respect, and was eating over two thousand calories. This led us to search the other records for evidence of a similar condition, and we have been able to find in every patient with chronic nephritis without renal edema, periods of actual negative sulphur balance, taking into account the urine alone. In many experiments on normals, the protocols of some of which are available in another publication (1), no such negative balance even for one day was ever encountered. In a patient studied later, we happened to find a period of transition from positive to negative sulphur balance. Nothing in the clinical condition of the patient could be found to account for this change. A portion of the experiment is shown in figure 2.

The plan of experiment was similar to that used in the previous study on patients with "nephrosis" (2). All these patients were on weighed diets. The food intake was not analyzed, but standard

[1] This work was done under a grant from the Proctor Fund for the Study of Chronic Disease of Harvard University.

tables of composition were employed to calculate the dietary constituents including the water in the food. To prevent a possible diuretic effect of water the total water intake, including the water in the food, was kept constant. Refusals of food were weighed on the ward and the total intake calculated by subtraction. The intake was essentially

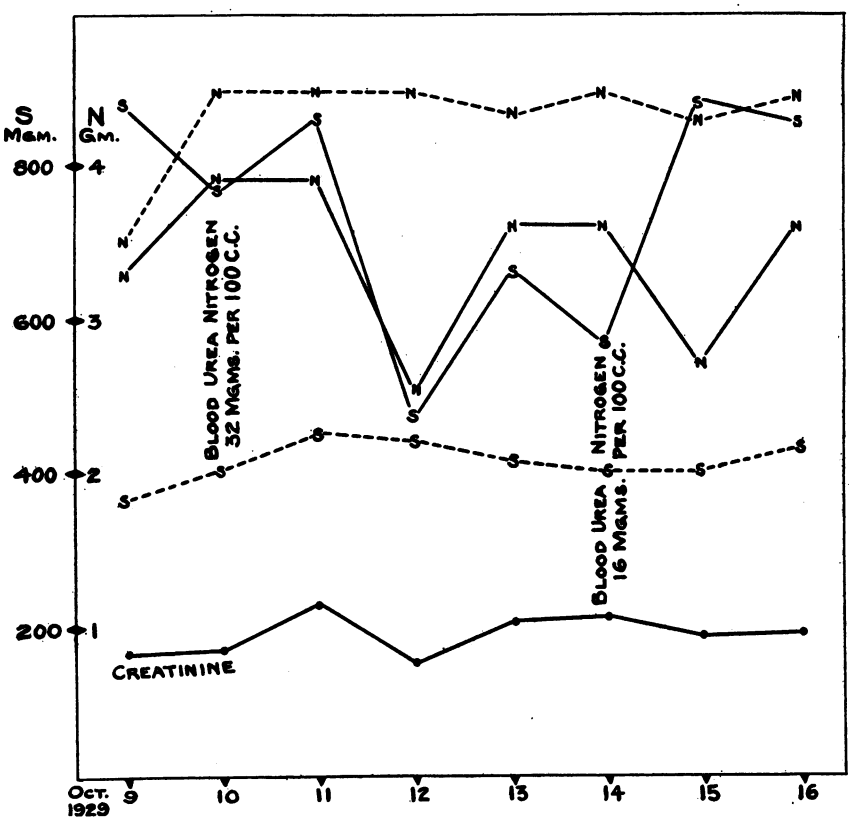

FIG. 1. CASE X. SHOWS CONSTANTLY NEGATIVE SULPHUR BALANCE
Solid lines show urinary output, dotted lines show intake

constant as to nitrogen, sulphur, phosphorus, calories and water. The diets were varied according to therapeutic necessity in the various patients, and corresponded to the standard hospital diets containing 28, 40 and 60 grams of protein. We thus had the advantage of keeping the patient on an approximate diet for a long time before the more

laborious process of carefully weighing the foods was commenced. In no period presented, was the patient on a weighed diet less than ten days. All diets contained about 2000 calories made up largely by carbohydrate, as the fat intake never rose above 80 grams. The

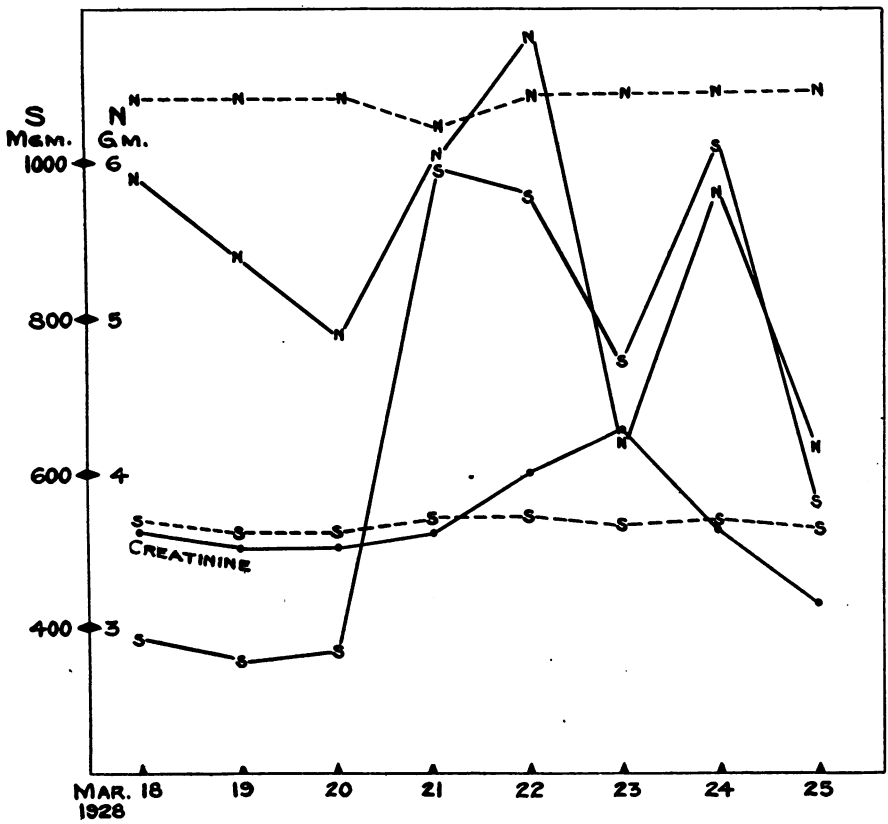

FIG. 2. CASE VI. SHOWS TRANSITION FROM POSITIVE TO NEGATIVE SULPHUR BALANCE

Solid lines show urinary output, dotted lines show intake

nitrogen, sulphur and phosphorus ran almost exactly parallel and the levels are sufficiently indicated in the figures.

Analyses of the urine were done daily for creatinine by the Folin method (3), total nitrogen by the Folin modification of the Kjeldahl method (3) and total sulphur by Fiske's benzidine method (4). For

technical reasons the sulphur and nitrogen of the feces was not determined. The addition of this figure would merely emphasize the negative sulphur balance and would increase the number of days in

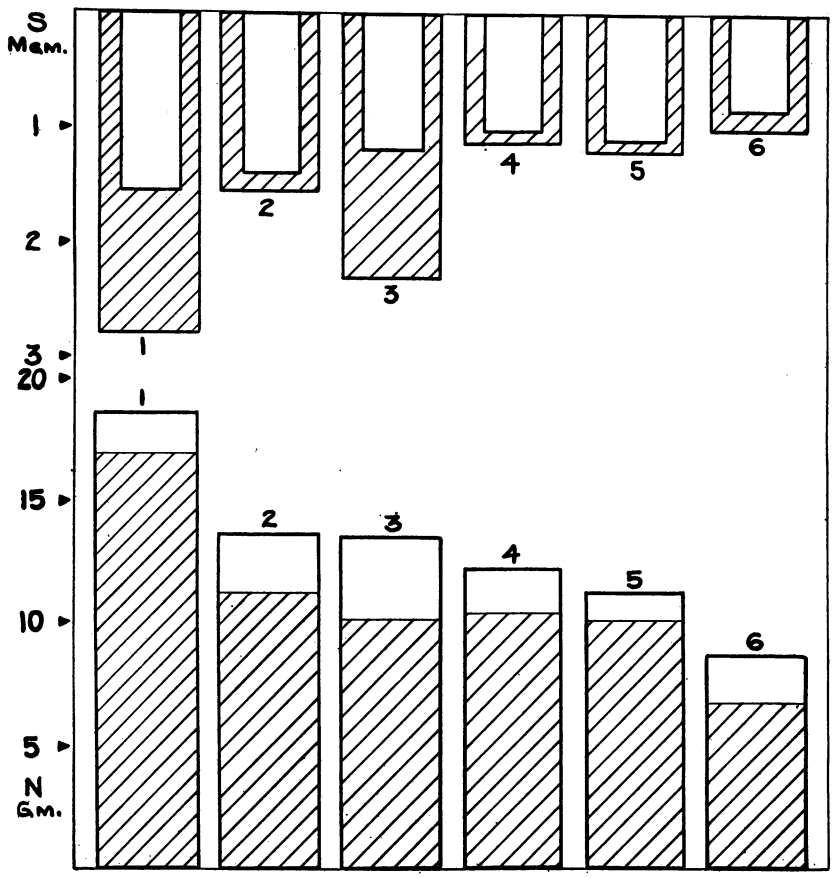

FIG. 3. NITROGEN (LOWER) AND SULPHUR (UPPER) INTAKE AND OUTPUT IN SIX PATIENTS WITH CHRONIC NEPHRITIS WITHOUT RENAL EDEMA

Each column represents three days. Shaded sections indicate output, unshaded intake. Number of period (cf. table 1) shown at each column.

which actual negative balance existed in the bodies of these patients, as there were a good many where the sulphur excretion in the urine alone was almost equal to the intake.

In figure 3 are shown the nitrogen and sulphur output and intake in selected periods from six patients with chronic nephritis, without renal edema. The shaded portion of the figure represents the output, the unshaded portion the intake. Each column represents a three day period. The dates of the periods of study are indicated in the table and correlation with the patient's clinical condition may be made by reference to the appended case histories. These are arranged, as were those previously presented (2), in a descending series according

TABLE 1

Additional data on periods shown in figure 3 and data on patients while in positive sulphur balance

Period on chart	Case number	Dates of period	$\frac{N}{S}$ intake	$\frac{N}{S}$ output	Blood urea nitrogen	Phenol-sulpon-phthalein test	Blood pressure	
							Systolic	Diastolic
					mgm. per 100 cc.	*per cent*	*mm. Hg.*	*mm. Hg.*
1	VI	March 22–25	11.8	6.0		40	110–144	62–86
2	XI	October 26–29	9.6	7.2	10	60	120	82
3	X	October 14–17	10.8	4.3	16	10	160–182	90–110
4	VII	April 7–10	11.9	9.1	7	22	160	114
5	IX	August 18–21	10.1	8.7	13	20	224	142
6	VIII	January 14–17	10.4	6.9	18	10	120	80
*	VI	March 13–14	12.8	13.8		42	120	80
	VI	March 20–21	12.6	13.1		40	120	80
	XII	March 2–3	12.6	10	15	14	223	162
	VII	April 4–5	13.6	11.5	7		160	114
	VII	March 31–April 1	12.5	13.4		32	150	108
	VIII	January 25–26	11.1	22.3	13	25	104	68
	IX	August 27–28	14.6	9.2	15	20	104	68

* These periods are not charted but indicate the $\frac{N}{S}$ ratio during positive sulphur balance.

to the nitrogen intake. There it will be noted that the relationship of nitrogen in the urine to the intake is approximately that usually stated to be normal, whereas the sulphur output exceeded the intake distinctly and in two cases by a very considerable amount. It is perhaps worthwhile to call attention to the nitrogen-sulphur ratios in this experiment. It is obvious that they are very low indeed. We have also compared the ratios during this period of negative sulphur balance with the nitrogen-sulphur ratios during periods of more nor-

mal sulphur excretion (cf. table 1). We found that the tendency was, on the whole, for the nitrogen-sulphur ratios to be low or normal and in only one case were we able to find a high ratio comparable to those reported in patients with "nephrosis." The nitrogen-sulphur ratio of the intake, of course, was approximately the same. It is obvious that we have a striking contrast here, to the picture shown by patients with the nephrosis syndrome.

In the previous work, it was pointed out that the type of protein excreted during the nephrosis syndrome suggests a mobilization and excretion of deposit protein. Here the reverse appears to be the case. It seems unlikely that we are dealing only with a variation in the selective secretion of nitrogen and sulphur dependent solely on the kidney lesion. For example, in the first case charted, if the excretion of sulphur be taken to represent protein, we must account for the nitrogen left behind when this extra sulphur is excreted. Were this to be represented in the form of nonprotein nitrogen, the nonprotein nitrogen of this patient's blood should have risen on the average of 4 mgm. per 100 cc. per day during the period pictured on the chart. This did not occur. Of course, such nitrogen may be in the tissues or a type of deposit nitrogen may have been built up poor in sulphur. All this, however, is entirely hypothetical but the foregoing is presented as an example of what we must postulate if we assume that the phenomenon here presented is due to a selective excretion on the part of the kidney. It seems to us easier to consider this phenomenon and the related one in the nephrosis syndrome as evidence of a defect in the intermediary sulphur metabolism.

SUMMARY

1. The nitrogen and sulphur excretion of seven patients without renal edema were studied while these patients were on a diet constant as to nitrogen, sulphur, phosphorus, calories and water.

2. It is demonstrated that there is a strong tendency for these patients to go into negative sulphur balance while remaining in positive nitrogen balance.

3. The N:S ratio in the urine of such patients tends to be low even when they are in positive sulphur balance.

4. A contrast between the sulphur excretion in these patients and

those exhibiting the nephrosis syndrome suggests very strongly that there is a defect in the intermediary sulphur metabolism in patients with Bright's Disease.

CASE HISTORIES

Case VI. Medical number 31861, a white male, aged 17, was admitted to the hospital on January 19, 1928, with the complaint of edema. Past history is unimportant except for one attack of tonsillitis followed by a tonsillectomy eight years ago. The present illness began the middle of December, 1927 with general malaise, followed on January 3 by a swelling of the right knee with pain but without fever. The knee was not red. There was considerable abdominal pain and three days later, he noticed a swelling of the face. There have been no other symptoms. Physical examination showed normal fundi, a diastolic murmur in the third left interspace and the associated signs of aortic insufficiency. Blood pressure, 130 systolic and 74 diastolic. There was edema of the symphysis and sacrum and a definite fluid wave was made out. Hands and legs both showed edema. Hemoglobin was 85 per cent; red blood count, 5,000,000; white blood count, 12,450. Urine showed a large trace of albumin, a very large number of red blood cells and many granular and hyaline casts. Phthalein excretion was 50 per cent; blood urea nitrogen, 31 mgm. per 100 cc.; Wassermann, negative. He was put on a low protein diet and by January 30, had lost 11.4 kgm. Urine continued to show a large amount of albumin and many red cells. Blood pressure varied between 110 and 144 systolic, with a diastolic of 62 to 86. Phthalein excretion varied between 40 and 50 per cent. The red cells gradually cleared up, and he was discharged the middle of April.

Case VII. Medical number 32195, a single white female of 24 years, entered the hospital on March 8, 1928 complaining of blurring of vision. She had had scarlet fever at 5, and 6 years ago following a severe cold, was admitted to the Massachusetts General Hospital complaining of edema of the ankles. She was there for 6 weeks, and since then has been free of symptoms. Three weeks ago, she first noted blurring vision following a cold in the chest, and at the same time had a sharply localized headache relieved by vomiting. The disturbance of vision has gradually improved. When seen in the hospital, blood pressure was 175 systolic, 125 diastolic. There was a marked albuminuric retinitis, heart was enlarged but regular. Hemoglobin, 80 per cent; red blood count, 4,620,000. The urine showed a trace of albumin, large number of casts of all kinds. Blood urea nitrogen was 8.4. There was practically no change in the urinary picture. The blood urea nitrogen never rose during this admission. Blood pressure fell somewhat, but rose just before discharge to 168 systolic, 122 diastolic. Phthalein excretion varied between 15 per cent shortly after admission to 32 per cent on discharge. She was discharged on April 23 and died September 10, 1929.

Case VIII. Medical number 31781, a white female of 15 years, was admitted to the hospital on January 10, 1928. She was first seen in the Out-Door Department on December 30, with a hemoglobin of 50 per cent, the urine showing a large trace of albumin. She had always been well up to three years ago, when she noticed a sudden swelling and puffiness about both eyes and ankles. She had no respiratory infection. She went to the Boston City Hospital for a two weeks' stay, then left, but the edema returned 3 months later, in February, 1925 when she again went to the Boston City Hospital and remained there for 4 weeks. The edema returned 2 weeks after this admission, but gradually disappeared, and from September, 1926 to August, 1928 she was free of edema. At that time, 5 months before admission, she began to lose weight and it was noticed that she was getting paler. On admission, hemoglobin was 35 per cent; red blood count, 3,160,000; white blood count, 6300. Blood pressure, 120 systolic, 80 diastolic. Urine showed a large trace of albumin, a moderate number of red cells, but no casts. Phthalein excretion was 10 per cent, blood urea nitrogen 18. Blood pressure remained low. Phthalein excretion rose to 32 per cent on February 13. Red cells in the urine diminished and numerous hyaline and granular casts appeared. January 19 her hemoglobin had risen to 60 per cent but her red blood count was 2,980,000. She left the hospital on February 14.

Case IX. Medical number 35349, a white female of 47 years, entered the hospital on August 5, 1929 complaining of edema. She had noticed this for 3 years becoming progressively worse. She had pain under her left breast at times, which did not radiate, but she had attacks of a sense of pressure in her chest, especially at night. She had become progressively weaker and had shown some loss of weight in the past 3 years. Lately swelling of the legs and ankles and headaches have developed, together with nausea and anorexia. Eleven months ago she noticed that her vision was beginning to fail. Physical examination showed very extensive retinal changes with sclerosis of the vessels, and exudate and hemorrhages. Heart was enlarged as was the aortic dullness; the rhythm was regular and no significant murmurs were heard. Blood pressure, 225 systolic, 140 diastolic. Urine showed small amount of albumin, many red cells and a great many casts of all kinds. She was digitalized. Hemoglobin was 62 per cent; red blood count, 4,700,000; blood urea nitrogen, 28 mgm. and phthalein excretion, 40 per cent. By August 13 blood urea nitrogen had fallen to normal figures, blood pressure remained at about the admission level, phthalein excretion became stabilized at 25 per cent and edema had disappeared. The urine showed much the same picture except that fat appeared in the urine on August 23. She was discharged on September 3, blood urea nitrogen, 11; phthalein excretion, 25 per cent. She re-entered on December 18, 1929 with the typical picture of congestive heart failure. By December 24, renal insufficiency complicated the picture, the phthalein excretion being 5 per cent, blood urea nitrogen having risen to 25. She died in uremia January 7, 1930.

Case X. Medical number 35649. A white male, aged 35, admitted to the hospital on September 28, 1929 complaining of headaches and vomiting spells. He had been known to have "kidney trouble" since 1908, when his feet and legs were swollen for a month. About a year ago, he noticed a feeling of ill-health and an increase in his headaches, which he had had during this period, vomiting became more severe and of longer duration and has been almost constant in the last 4 months. Eight years ago he had an attack of what was called infantile paralysis with almost complete bilateral facial paralysis with only slight symptoms in the arms and legs. The facial paralysis lasted 6 months. Physical examination showed only a slightly enlarged heart, hemorrhagic retinitis; blood pressure, 182 systolic, 110 diastolic; phthalein excretion was only a trace; hemoglobin, 30 per cent; red blood count, 3,200,000; blood urea nitrogen, 52; basal metabolic rate, minus three per cent. He improved symptomatically. Urine showed a low specific gravity, a slight trace of albumin and no formed elements of importance in the sediment. On October 10, his phthalein excretion was less than 5 per cent; blood urea nitrogen, 32 mgm. per 100 cc.; hemoglobin, 50 per cent; red blood count, 3,750,000. On October 14, his blood urea nitrogen fell to 16 and his phthalein excretion rose to 10 per cent. A week later blood urea nitrogen was again 53 mgm., the urine showed a slight trace of albumin and many coarsely granular casts. His blood urea nitrogen varied between 50 and 27 and his phthalein excretion between 10 and 15 per cent. By the 31st of October, red blood cells had appeared in the sediment which persisted. On November 7, total blood protein was 7.6 per cent, albumin 5, globulin 2.6. He was discharged and readmitted in January, 1930 and died on April 22, 1930. He died in uremia with a blood urea nitrogen of 273. At autopsy the right kidney was contracted, weighing only 60 grams, and the left kidney was almost entirely replaced by a cystic degeneration.

Case XI. Medical number 35758, a white female, aged 16 years, admitted to the hospital on October 17, 1929, complaining of swelling of the ankles and puffiness of the eyes and headaches for 5 years. The onset was sudden 5 years ago. During the last 2 years, has had at intervals of 6 weeks to 2 months, attacks of nausea and vomiting. Physical examination, at entrance, showed a hemoglobin of 80 per cent; red blood count, 5,200,000. There was a slight pitting edema of the ankles; heart was not enlarged; blood pressure, 150 systolic, 100 diastolic. Urine showed many casts and slight trace of albumin. Phthalein excretion, 50 per cent; blood urea nitrogen, 13. On October 24 basal metabolic rate was minus ten per cent, and on October 25, total protein was 7.8, albumin 5.6, globulin 2.2, cholesterol, 153. The urine continued to show slight trace to a large trace of albumin, with many casts. Blood urea nitrogen ranged around 10 mgm. per 100 cc. and blood pressure had fallen until at discharge it was 122 systolic, 88 diastolic. Patient was discharged on November 15, 1929.

Case XII. Medical number 34368, a white male, aged 49 years, admitted to the hospital February 21, 1929 complaining of exhaustion and head pains. During

the past year, the patient has felt generally tired but he has been able to rest and has been refreshed in the morning. Has been working extremely hard and has explained his general weakness on that basis. About the latter part of December, 1928 patient had a mild winter infection, following which he was extremely weak and was kept in bed 2 weeks. Since that time, his sleep has been interrupted and broken, and he has had extreme nocturia which he had attributed to nervousness. For the last 6 weeks there has been a persistent sense of weakness and generalized headache which has been present part of each day. There have been no other symptoms except that he has blown repeated clots of blood from the nostrils during the last week. No true epistaxis. Physical examination shows no enlargement of the heart, which is regular. Retinal vessels show edema of both nerve-heads and the retinal vessels are very tortuous, veins dilated, and some recent hemorrhages are seen. Blood pressure, 236 systolic, 156 diastolic. Gradually improved on rest in bed, blood pressure at one time being as low as 200 systolic, 128 diastolic. The edema of the retinae subsided and his headaches diminished in intensity. Urine constantly showed a trace to a large trace of albumin, and some fixation of specific gravity. Phthalein excretion on admission was 12 per cent. There were constantly numerous casts of all sorts in his urine. Hemoglobin was 80 per cent; red blood count, 4,900,000 on March 19. On March 1, total protein was 4.2, albumin 3.1, globulin 1.1. Blood urea on March 12 was 15 mgm., blood uric acid 6.6. Blood creatinin on March 15 was 3 mgm., blood uric acid 5.6. On March 19, the blood nonprotein nitrogen was 39 mgm. per 100 cc. Patient was discharged on March 20. Blood pressure had returned to level of 224 systolic, 150 diastolic. He died April 23, 1929.

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