STUDIES ON THE NITROGEN AND SULPHUR METABOLISM IN "BRIGHT'S DISEASE": *I. The Retention of Nitrogen and Sulphur in "Nephrosis"*

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

I. The Retention of Nitrogen and Sulphur in "Nephrosis"[1]

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For many years the retention of the nonprotein nitrogen in the blood in Bright's disease has been studied in a variety of ways. In recent years the syndrome called "nephrosis" has been described and, by some, considered a clinical entity. For the purposes of the present study, this term has been used to designate patients who showed a syndrome characterized by edema, low basal metabolism, doubly, refractile fat in the urine, the excretion of large amounts of albumin, and the diminution of serum protein with a reversal of the albumin-globulin ratio. None of the patients studied had an increase in the nonprotein nitrogen in the blood. It has been shown that these patients do well on a high protein diet and that they may lose their edema under such conditions. When treated with such a diet they retain large quantities of nitrogen even when given in the form of crystalline urea (1). We have been able to study, over long periods, the metabolic reactions of five patients exhibiting this syndrome. In the present report, we wish to show the relationship between the nitrogen and sulphur retention in these patients.

The subjects of this, and succeeding studies to be reported, were on carefully weighed diets. The food intake was not analyzed, but standard 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

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essentially 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, 60, 100, and 150 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 only one period presented (number 10, fig. 1) was the patient on a weighed diet as little as four days and this patient had been on approximately the indicated dietary level for four weeks. In the remaining periods all patients had been on weighed diets of the

TABLE 1

Additional data on periods shown in figure 1

Period number	Dates of period	Patient number	Total serum protein	Serum albumin	Serum globulin	Blood cholesterol	Basal metabolic rate
			grams per 100 cc.	*grams per 100 cc.*	*grams per 100 cc.*	*mgm. per 100 cc.*	*per cent*
I	November 12–15, 1928	I	5.0	1.4	3.6		
II	November 19–22, 1928	I	5.1	1.9	3.2	454	−24
III	July 17–20, 1928	V					−11
IV	June 28–July 1, 1928	III	4.6	3.0	1.6	416	− 7
V	March 7–10, 1929	IV	3.7	0.4	3.3	471	
VI	March 4–7, 1929	IV	3.4	0.5	2.9	180	− 8
VII	July 11–14, 1928	V				290	
VIII	October 7–10, 1928	II	5.5	2.3	3.2	526	− 6
IX	June 28–July 1, 1928	V	3.6	1.7	1.9	200	− 6
X	May 13–18, 1928	III	5.3	2.5	2.8	312	−10

magnitude presented for at least ten days. All diets contained about 2000 calories made up largely by carbohydrate, as the fat intake never rose above 80 grams. The nitrogen, sulphur and phosphorus ran almost exactly parallel and the levels are sufficiently indicated in figure 1.

Analyses of the urine were done daily for creatinine by the Folin method (2), total nitrogen by the Folin modification of the Kjeldhal method (2) and total sulphur by Fiske's benzidine method (3). The nitrogen of the feces was determined in some experiments, but as this was found to make no significant difference it was not done always. For technical reasons the sulphur of the feces was not determined, but

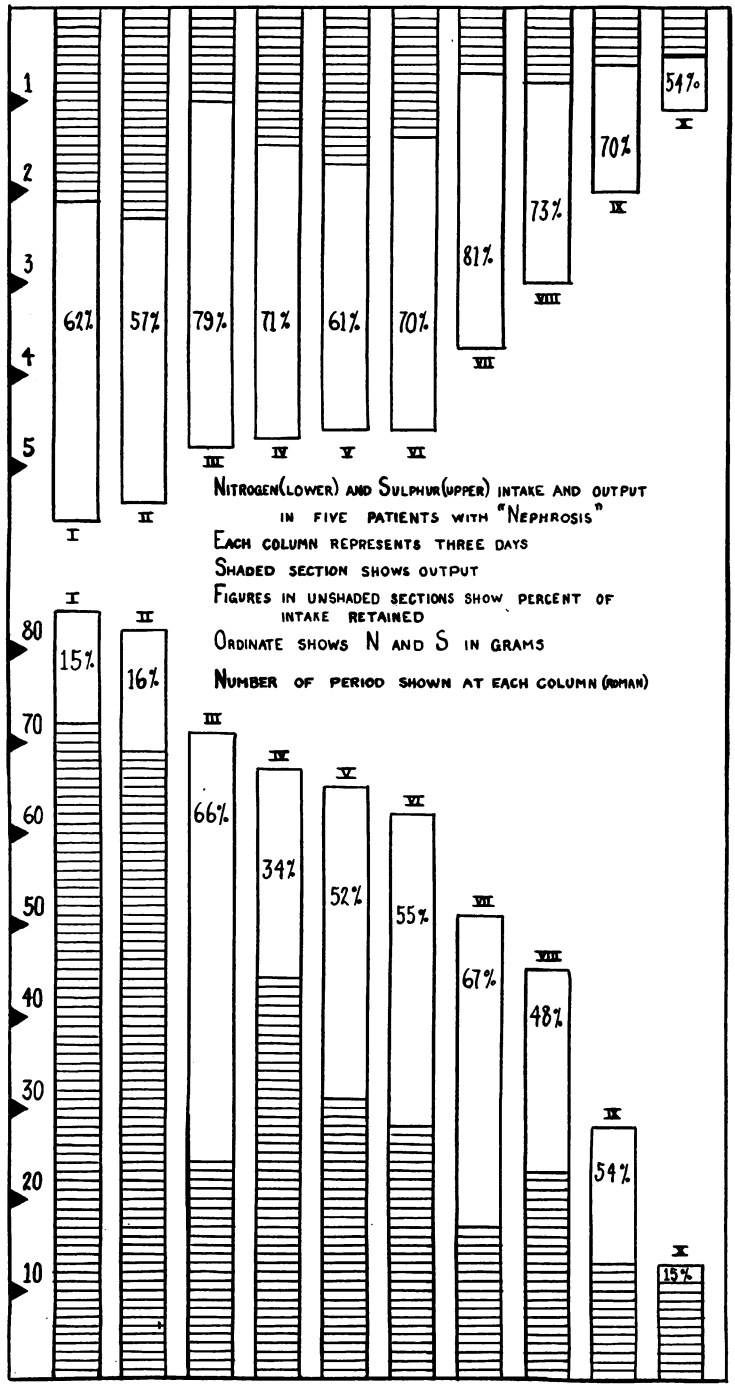

FIG. 1. NITROGEN AND SULPHUR INTAKE AND OUTPUT FOR THE 10 PERIODS SHOWN IN TABLE 1

it has been shown to be insignificant on high protein diets and to run parallel to the nitrogen. In order to minimize day to day variations we have chosen three days as the unit for comparison. All our experiments have been done on this basis. For the present study we have selected ten such periods free from any influences such as changes in diet or others to be reported later. In table 1 the periods presented in figure 1 are correlated with certain chemical findings and from the dates given in this table the general clinical condition of the patient may be ascertained by reference to the brief histories appended. In this connection it is interesting to point out that these periods of study included both edematous and nonedematous subjects.

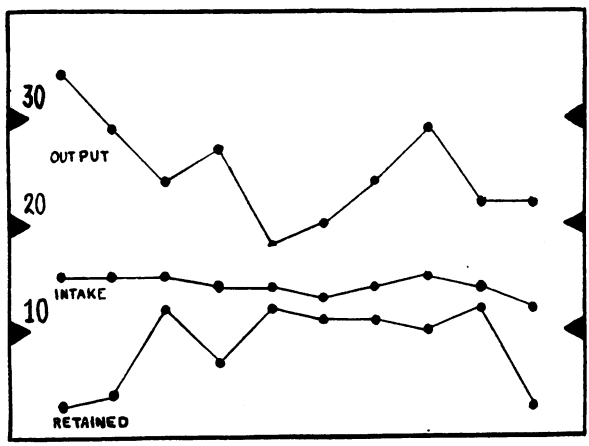

FIG. 2. THE TEN COLUMNS OF RATIOS ARE CALCULATED FROM THE TEN PERIODS SHOWN IN FIGURE 1

The results of this particular study are shown in the accompanying charts. Figure 1 summarizes the intake and output of nitrogen and sulphur of ten three-day periods from five patients on a varying level of protein intake. They are arranged from left to right in a descending series. The columns represent the intake while the shaded portion represents the output. The percentage figures in each column indicate the amount of the intake retained. It is immediately apparent that the percentage of retention of sulphur is greater under any of the circumstances than that of nitrogen. This is contrary to the usual

experience that sulphur is excreted more readily and earlier than nitrogen when protein is added to the diet (4). Blood sulphur determinations were not made, but Wakefield and Keith (5) have shown that in such patients there is no increase in the blood sulphur. The retention of sulphur on the lower dietary levels taken in conjunction with Keith's findings, demonstrate that this retention is not due to a failure of excretion on the part of the kidney.

In this connection, the nitrogen-sulphur ratios are of interest and are shown in figure 2, taken from the results presented in figure 1. It will be noted that the nitrogen-sulphur ratio of the diet corresponds roughly to that in starvation which is about 14 to 1, and this has been assumed to be the ratio in muscle protein (6). It is to be noted, that regardless of the level of the diet, the ratio in the intake remained practically constant. The nitrogen-sulphur ratio in the urine varied considerably, from period to period, but in every case, was significantly higher than that of the intake, and in certain cases yielded very high figures indeed. If we attempt to calculate the nitrogen-sulphur ratio of the "protein" retained, we get the lowest curve on the chart, indicating that such retained protein is rich in sulphur. It will be noted that except at the extremes of dietary intake, the N:S ratio of the retained protein appears to run at a fairly constant level, always below that of the intake. It may be that the variation of the output indicates an attempt to maintain the optimum level in the retained protein.

It is interesting to compare the sulphur-poor nitrogen excretion in these experiments with the descriptions of deposit protein, which is said to be poor in sulphur (4), suggesting that "deposit protein" may be the most important source of the N excreted in these patients. Boothby (7) found comparably high N:S ratios in the urine in patients with myxedema under treatment by thyroxin, and previous work (8) has shown that similar protein may be mobilized in normal individuals by the administration of iodides. It seems undesirable to erect an hypothesis on the basis of the evidence here presented, but these data suggest very strongly that the problem of the nephrosis syndrome may be concerned more with the intermediary sulphur metabolism than with the kidney itself. As to the exact phase of the metabolism involved we have no clue at the present time.

SUMMARY

1. The nitrogen and sulphur excretion of five patients exhibiting the nephrosis syndrome were studied while these patients were on a diet constant as to N, S, P, calories and water.

2. As in other studies a large retention of nitrogen occurred.

3. The retention of sulphur was greater than that of nitrogen regardless of the level of dietary nitrogen.

4. The N:S ratio in the urine was high.

5. The N:S ratio of the "retained protein" was low.

It is a pleasure to acknowledge the assistance of the diet kitchen in these experiments and especially that of Miss Mary Robertson.

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CASE HISTORIES

Case I. O'C. (Medical number 33490), a single, white male of 24 years, first entered the hospital on November 7, 1926 complaining of edema of the legs. His past history was unimportant except that in the preceding 20 months he had had

three periods of edema of the legs, the last occurring in April, 1925. This edema cleared up with dietary treatment alone. The treatment was apparently a low protein diet. At this admission he showed a large soft edema of the legs and a secondary anemia; hemoglobin 50 per cent, red blood cells 4,700,000. The urine showed large amounts of albumin and constantly contained red blood cells. Phthalein excretion was 55 per cent. Blood pressure 135/80. Blood cholesterol was elevated and basal metabolic rate minus 14 per cent. He was treated with desiccated thyroid in large doses without success but improved rapidly on a high protein diet (150 grams). He was readmitted in November, 1927, following a period in which he reduced his diet and again in October, 1928, when edema recurred following a comparatively slight cold. The blood analyses and urine analyses showed no essential change, though the secondary anemia was much improved. Blood pressure remained within normal limits and the phthalein excretion was 45 per cent. Blood urea nitrogen was at all times within normal limits. He was edema free by November 1, 1928.

Case II. Sp. (Medical number 32897), a married white male of 43 years, entered the hospital on July 5, 1928 complaining of swelling of the face and ankles of two weeks duration. On examination there was also found fluid in the abdomen together with enlargement of the spleen and liver. The circulatory system was normal; blood pressure 135/85. Urine showed large amounts of albumin with no pathological elements in the urinary sediment except doubly refractile fat granules. Phthalein excretion was 50 per cent; basal metabolic rate ranged from minus 6 per cent to minus 25 per cent and only on the first examination was the albumin of the blood greater than the globulin. Blood cholesterol was persistently elevated. On high protein diet his edema decreased but did not disappear. Thyroid therapy did not reduce the edema. It was finally found that he remained most free of edema on a diet of 100 grams of protein. In October, 1928, he developed a very slight secondary anemia. He left the hospital in December and re-entered in 1929 with hypertension, and retinal hemorrhages comparatively free of edema. During the period of this study he was only showing puffiness of the eyes in the morning and had slight pitting edema of the shins.

Case III. Z. (Medical number 32464), a single, white female of 23 years, entered the hospital April 21, 1928, complaining of edema of the legs. The onset was insidious beginning with weakness and the edema was first noted 8 months before. Later, edema spread from feet to legs and subocular edema was noted; then nocturia, palpitation and dyspnea on exertion developed. On entry, the patient was pale and there was slight edema of the legs and over the sacrum. Blood pressure 98/70. Wassermann reaction positive. She was treated with a low protein diet and given active antiluetic therapy without amelioration of her symptoms until on June 9th she was given a high protein diet. The urine showed large amounts of albumin with a moderate number of casts in the sediment.

Phthalein excretion 55 per cent; basal metabolic rate, minus 6 per cent to minus 10 per cent; blood urea nitrogen, 9 mgm. per 100 cc. The serum proteins showed the usual reversed ratio of albumin to globulin. She was practically edema free during period IV and had slight edema during period X.

Case IV. Alg. (Medical number 34316) a married, white female of 26 years, entered the hospital on February 12, 1929, complaining of edema and shortness of breath. The onset was in September, 1928, six weeks after a cold and sore throat. She had been treated at home with digitalis and low protein diet. Examination revealed fluid in both pleural cavities and in the abdomen, edema of the legs and over the sacrum, some pharyngeal inflammation, large amounts of albumin in the urine and reversal of the serum protein ratio. The urinary sediment was not remarkable. Blood pressure 125/85; blood urea nitrogen 11 to 15 mgm. per 100 cc.; blood cholesterol elevated; basal metabolic rate minus 8 per cent. After two days on the Karrell diet she was treated with a high protein diet without much improvement. On April 1st, she developed a sharp pain in the upper abdomen and died on April 4th of a fulminating septicemia.

Case V. R. (Medical number 32820) a married, white female of 38 years, entered the hospital on June 21, 1928, complaining of swelling of the ankles. She had had chorea in childhood and had been known to have rheumatic valvular heart disease since that time. This involved both the mitral and aortic valves. The onset of the present edema was 8 months ago and for the past month she had been in the Boston City Hospital where she was completely digitalized without relief. On entry there were the expected cardiac signs, a fluid wave in the abdomen and pitting edema over the ankles. Vital capacity, 45 per cent; blood pressure, 180/80; phthalein, 10 per cent. The urine contained large amounts of albumin and a moderate number of granular casts. There was severe secondary anemia; red blood cells, 2,500,000; basal metabolic rate minus 6 per cent. Serum proteins showed reversed ratio and blood cholesterol was elevated. She became edema free on August 13th after thorough digitalization and high protein diet. Infected teeth were removed on July 21st. This was followed by oliguria until the condition of the mouth again permited the mastication of the high protein diet on August 1st. She died months after this period with the signs of renal failure.