

ON DIURNAL AND NOCTURNAL VARIATIONS IN THE EXCRETION OF URIC ACID. BY J. B. LEATHES.

IN studying certain aspects of nitrogenous metabolism the following procedure was adopted. A diet of sufficient caloric value was taken, which was distributed over six meals, all of which were identically the same, taken at regular intervals of three hours from seven in the morning till ten at night. This diet contained no purine derivatives in any form. The regular distribution of such a number of small meals was designed to eliminate as far as possible the irregularities in excretion which are caused by the digestion and assimilation of nitrogenous food-stuffs. And with the same object in view, not only were diuretic drinks such as tea and coffee omitted entirely from the diet, but the volume of fluid taken at each meal was the same throughout, as well as the amount and nature of the dissolved or solid foods. Between the hours of ten p.m. and seven a.m. it is true there was no intake either of solids or liquids: for the greater part of this time was taken up in sleep. But for eighteen hours out of the twenty-four the conditions were in many important respects the same.

The urine was collected at the hours at which the meals were taken and another sample was obtained, or sometimes two, during the night. Each sample was measured and analysed, and from the analytical results the rate was calculated at which each of the substances for which the data were obtained had been excreted in each of the periods of the day. In that way curves could be drawn indicating the variations in these rates; and it is these curves that sum up the substance of this paper.

The analyses were carried out as follows: (1) two samples were taken for the estimation of the total nitrogen by Kjeldahl's method.

(2) The creatinine was estimated colorimetrically by a method which in essentials is that described by Folin¹. Both these determinations were carried out on the same day as, or at any rate within twenty-four hours of, the collection of the samples.

¹ Folin. *Zeits. für physiol. Chem.* xli. p. 223. 1904.

(3) 50 c.c. or when possible 100 or 150 c.c. were measured off into stoppered bottles containing 10, 20 or 30 grs. of ammonium chloride and put aside for the estimation of uric acid at the end of the experiment. This was then done according to the modification of Hopkins' method suggested by Wörner¹.

The first experiment began on the 11th of August and ended on the 23rd. During this time the food taken each day consisted of 2 quarts (2.28 litres) of milk, obtained from a large dairy supplying a product of nearly constant composition, 600 g. of bread and 110 g. of butter. The heat equivalent of this diet was calculated to be about 3500 cal. or just over 50 cal. per kg. of bodyweight. The daily nitrogen intake was about 21.5 g. and the daily output in the urine from the fourth day on when the variations began to be insignificant was about 19 g. on an average. The total nitrogen and creatinine was estimated in the urine of each period of all these days, the uric acid similarly only during the last week. In the following table the figures, calculated from the results of the analyses, represent the amount of uric acid excreted in each hour of the period ending at the time indicated at the top of the column.

TABLE I.

Observed rates of uric acid excretion, in mg. per hour, during the periods ending at the hour of:

	3 a.m. ¹	7 a.m.	10 a.m.	1 p.m.	4 p.m.	7 p.m.	10 p.m.
Aug. 16	—	—	—	39.6	35.5	—	20.4
17	24.7	23.5	25.7 (some loss)	37.2	30.3	26.6	27.2
18	19.0	25.5	35.6	28.1	31.0	29.3	24.9
19	18.5	23.0	34.7	30.7	25.7	27.6	20.6
20	19.1	19.0	31.9	35.9	—	25.4	25.1
21	21.0	21.0	29.6	37.0	34.7	26.5	19.9
22	21.8	22.2	—	25.5	27.2	26.9	23.9
23	22.9	23.4	26.6	26.4	—	—	—

Calculated averages from the above observed rates:

21.0	22.5	31.3	32.5	30.7	27.0	23.1
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¹ The hour at which the samples in this column were collected varied on the different days.

In the second experiment, which began on Sept. 13 and ended on Sept. 26, the food consisted of biscuits (Huntley and Palmer's plain arrowroot), butter and water. Of the biscuits six were taken at each meal, the weight of the daily ration being 540 g. with 36.5 g. of moisture. Three samples dried to constant weight contained 1.00, 1.15 and 0.97% of nitrogen, which gives a daily intake of nitrogen of about 5 g., or a little

¹ Wörner. *Ibid.* xxix. p. 70. 1900.

over 30 g. of proteid. The amount of butter taken in the day was the same as in the first experiment. This diet therefore contained less than a quarter of the amount of nitrogen contained in the diet of the earlier experiment, and in fact nitrogenous equilibrium was not attained on it. The heat equivalent also was very considerably lower than in the case of the earlier diet. Nevertheless the loss of weight was inconsiderable. The urine was collected and analysed as before and the following table is constructed similarly to the last.

TABLE II.

Observed rates of uric acid excretion, in mg. per hour, during the periods ending at the hour of:

	3 a.m.	7 a.m.	10 a.m.	1 p.m.	4 p.m.	7 p.m.	10 p.m.
Sept. 17	—	—	—	24·3	18·1	24·3	21·4
18	8·0	13·7	20·4	23·0	20·3	18·1	14·1
19	14·1	15·6	19·4	25·6	23·9	19·5	14·5
20	9·5	12·7	23·0	27·3	23·3	18·0	14·9
21	12·1	17·9	22·2	23·7	24·8	26·0	23·5
22	8·1	18·0	19·3	17·8	17·0	20·1	17·3
23	8·5	8·3	11·2	25·1	18·9	17·6	17·5
24	15·2	18·7	22·6	27·7	22·7	—	—

Calculated averages from the above observed rates:

10·8	15·0	19·7	24·3	21·1	20·5	17·6
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The average rates of uric acid excretion in the corresponding periods of the different days, which are given in the last line of Tables I and II, are laid out in the form of curves in Fig. 1, in which the upper curve is that given by the results of Exp. I and the lower by those of Exp. II. In order to show more clearly the form of the curve of diurnal variations, it is extended over a period of 48 hours. The curves for the creatinine, and for the total amount of nitrogen excreted, calculated as averages in a similar way, are given for comparison, the former above the uric acid curves in Fig. 1, the latter in Fig. 2.

It will be noticed that in the subject of these experiments at any rate there is a remarkable difference between the rate of uric acid excretion at different times in the day. It is very much slower at night than by day. The maximum is in the morning from ten to one. After this there is a steady decline till the minimum in the earlier part of the night, when the rate of excretion on the low nitrogen diet is less than half that found in the forenoon. In the first waking hours from seven to ten the rate is considerably increased, and in fact there is a fairly definite tendency for the rate to rise in the latter part of the night.

The very close agreement in the general form of the two curves obtained from the two experiments clearly shows that this variation in the different periods of the day is not merely accidental, but a general characteristic of the functions concerned. To prove however whether

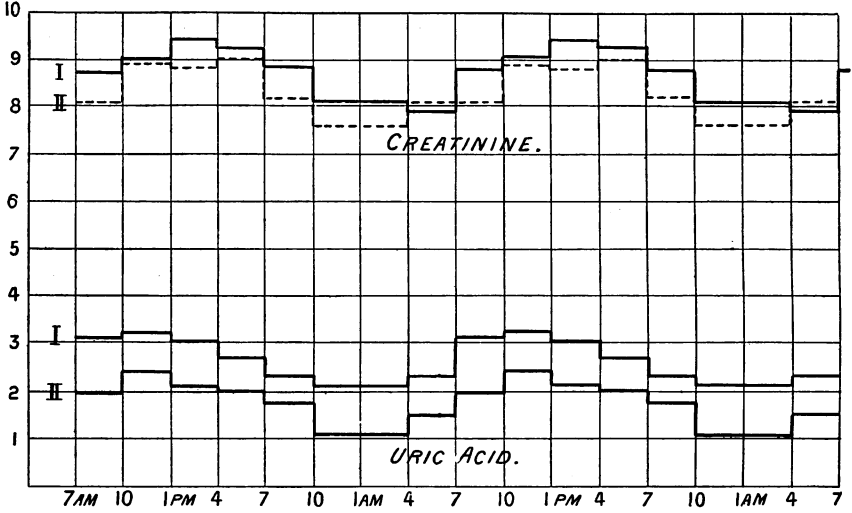


Fig. 1. In the figure the ordinates give the average rate of excretion of uric acid and creatinine in centigrams per hour for each of the periods indicated on the abscissa. The Roman numbers in the left-hand column refer to the number of the experiment.

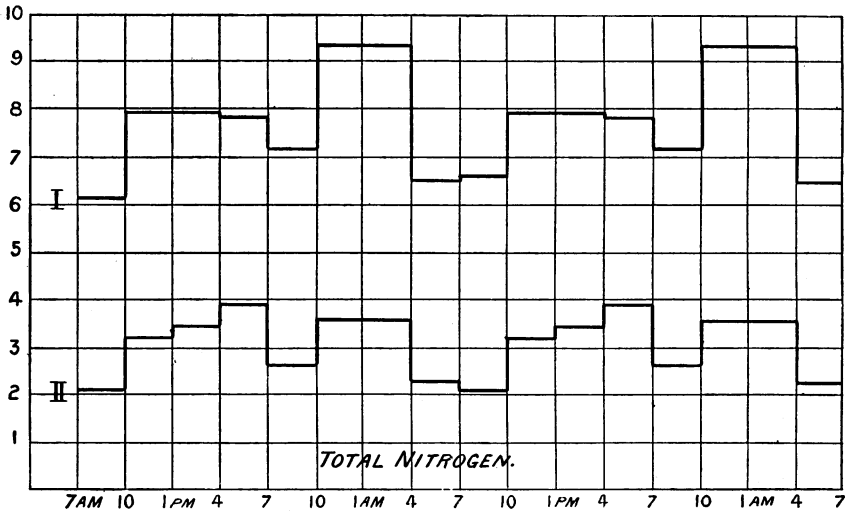


Fig. 2. The figure constructed like Fig. 1 gives for the two experiments the rate of excretion of nitrogen in all forms expressed in diagrams per hour.

it is due to idiosyncrasy, or whether it indicates a physiological law of more general interest, experiments are being carried out on other subjects. These, together with experiments bearing on the interpretation of the phenomenon will form the subject of a second paper which is in preparation, and for which will be reserved the full discussion of this and of other facts which are summed up in the curves of the rates of excretion of creatinine and total nitrogen which are also given in Table III.

For the present it will be sufficient to point out that the diminution of the rate of excretion of uric acid during the night, like the similar though less striking diminution in the rate of excretion of creatinine, cannot be explained as simply the result of diminished renal activity during sleep. For the accompanying curves indicating the variations in the rate of total nitrogen excretion show that the kidneys, on a full nitrogen diet at any rate, are more active during sleep than during the waking hours of the day, and even on the low nitrogen diet of the second experiment are almost at their maximum activity in the night. The low output of uric acid and creatinine during the night must be the expression of a diminished functional activity in some other organ or organs than the kidney. Now does it seem probable for the same reason that the explanation is to be found in diminished blood-pressure. The experiments now being carried out with a view to identifying the functions associated with the output of uric acid will be described shortly.

One other point may be noted here: the results of the experiments are in agreement with those of Folin in giving a lower absolute uric acid value on a low nitrogen diet, although the percentage of the total nitrogen excretion formed by the nitrogen of the uric acid is increased. The opposite result obtained by Burian and Schur, which led them to enunciate the law of constant uric acid excretion on a diet free from purine derivatives, has had evidence advanced in support of it by Walker Hall and others, and before Folin's results were published had found general acceptance. The divergence of the evidence on this point will be explained when it is possible to give a satisfactory account of the significance of uric acid among the nitrogenous excreta on such diets.

CONCLUSIONS.

1. In these experiments it was found that, when a uniform purine-free diet is taken, the excretion of uric acid is most active in the early waking hours and very much less active at night.

2. This is not a sign of variations in renal activity for the excretion of nitrogenous substances in general is as high during the night as during the day, or even higher.

3. It is a sign rather that there are corresponding variations in the formation of uric acid in the body at different periods in the day.

4. Similar though less marked variations were found in the rate at which creatinine is excreted.