The Partition of Nitrogen in the Urine of Malnourished Jamaican Infants

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According to the principle put forward by Folin in 1905, the distribution of nitrogen in urine among urea and other nitrogenous constituents depends upon the absolute amount of nitrogen present. Phansalkar and Patwardhan[1] studied the partition of urinary nitrogen in Indian adults on low protein diets, and showed that Folin's concept held true at all levels of nitrogen metabolism, regardless of the source of the dietary protein (animal or vegetable). Moreover, the quantitative relationship between urea nitrogen and total nitrogen was the same in the Indian subjects as in those studied nearly fifty years before by Folin.

The object of the present work was to see whether the same principle holds true in malnourished children, or whether the state of malnutrition alters the pattern of nitrogen excretion. Our main interest was in the quantitative aspect of urea excretion, and no attempt was made to analyze separately all the nitrogenous constituents of the urine. Measurements were made of urea, ammonia, creatinine and "residual nitrogen," which includes creatine, uric acid, amino acids and undetermined nitrogen.

SUBJECTS AND METHODS

The subjects were twenty-four malnourished male Jamaican infants, ranging in age from six months to two years. The clinical characteristics of protein-calorie malnutrition as it is seen in Jamaica have been described previously.[2,3] The patients in the present series represent an average selection. In fifteen children twenty-four–hour urine samples were obtained within two days of admission to the hospital; in four others the first collection was made within a week of admission; and in the remaining five the study was not begun until the children were recovering. Further twenty-four–hour specimens were collected at intervals up to three months. Urine samples at twenty-four or forty-eight hours were also obtained from five other children who died within a few days of admission.

The urine specimens were acidified with sulphuric acid. Total nitrogen was measured by the micro-Kjeldahl method; urea and ammonia by Conway's method[4]; and creatinine by Jaffe's method.[5] The residual nitrogen, which includes creatine, uric acid, amino acids and unidentified nitrogen, was calculated by difference.

So that a comparison can be made among different patients, the absolute amounts of nitrogen excreted are expressed as milligrams of nitrogen per kilogram of body weight per twenty-four hours.

RESULTS

Urea

The results at different periods of time after admission to the hospital are summarized in Table I. In the early days total nitrogen outputs were low because the babies took little food; at these low levels, the proportion of urea nitrogen was reduced, but not more than is to be expected from Folin's rule. This is evident from Figure 1, in which urea nitrogen (y) is plotted against total urinary nitrogen (x). The regression equation of y upon x is $y = 1.003x - 56.9$ (correlation coefficient 0.965). This is in close agreement with the results obtained by Phansalkar and Patwardhan[1] in Indian adults. If it is assumed that the Indian subjects had an average body weight of 50 kg., the regression equation for their results is $y = 0.971x - 32$, where y (urea nitrogen) and x (total urinary nitrogen) are both expressed

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TABLE I

Partition of Urinary Nitrogen in Malnourished Infants at Different Stages After Admission to Hospital

Group	Days After Admission	No. of Subjects	Mean Body Weight (% of Standard)	Absolute Output (mg./kg./day)			Percentage of Total Nitrogen			Creatinine (mg./kg./day)
				Total Nitrogen	Ammonia	Residual	Urea	Ammonia	Residual	
I	0–2	15	57.0	109	19	22	58	18	21	10.1
II	3–5	5	54.0	96	27	24	42	28	25	11.7
III	6–10	7	57.0	128	23	34	51	18	27	12.7
IV	11–15	6	57.0	186	27	33	65	14	18	12.2
V	16–20	5	57.0	248	26	36	73	10	15	11.0
VI	21–25	7	61.5	250	30	17	79	11	7	10.9
VII	26–35	10	61.5	243	26	24	78	12	10	10.4
VIII	36–45	8	64.0	340	29	23	83	8	7	13.4
IX	45+	7	76.0	428	32	34	83	7	8	14.5
Fatal cases	...	5	...	87	...	35	62		33.5	...

as milligram per kilogram of body weight per twenty-four hours. It appears, therefore, that if a comparison is made between these severely malnourished children and healthy adults, not only does the same general rule govern the proportion of nitrogen excreted as urea, but there is also an almost identical numerical relationship.

In the patients who died, urea and ammonia were, unfortunately, not estimated separately. Together they accounted for 62 per cent of the urine nitrogen. This is lower than in any of the other groups, but not lower than would be expected with such a small output of total nitrogen.

Ammonia

When the children were most malnourished, i.e., in the first days after admission, the proportion of ammonia nitrogen was increased, and the ratio of ammonia nitrogen to urea nitrogen was very high; the absolute amount

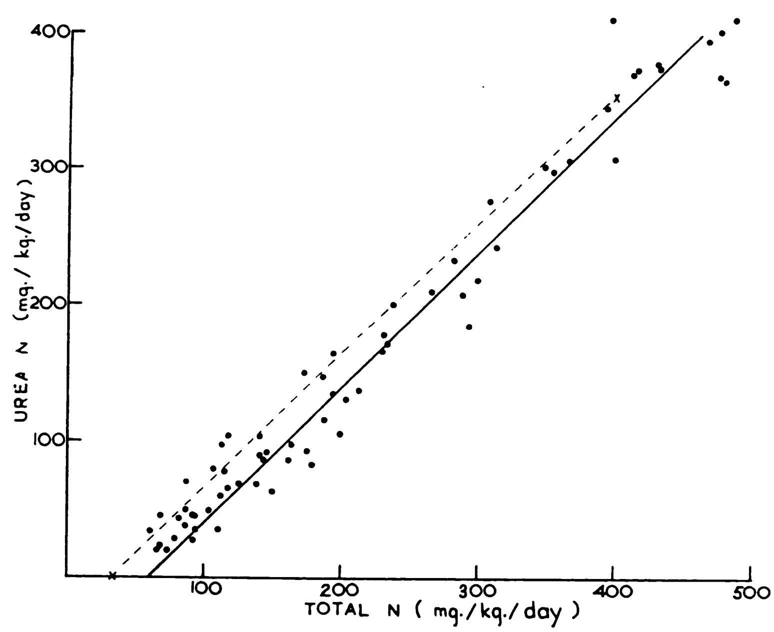

FIG. 1. The relation of urea nitrogen to total urinary nitrogen. ——, regression equation $y = 1.003x - 56.9$; ×- - -×, regression equation calculated from Phansalkar and Patwardhan's results[1] $y = 0.971x - 32$.

of ammonia nitrogen, however, was not increased and remained at much the same level throughout the hospital stay. There was, therefore, no confirmation of the claim by Platt and Heard[6] of an absolute as well as a relative increase in ammonia nitrogen in protein malnutrition. This result is a little surprising; some increase in ammonia nitrogen was expected in the early stages because the babies often had acidosis as a result of diarrhea. It may be, however, that the ability of the kidney to form ammonia is impaired. It has previously been shown that in these patients there is a defect in urinary acidification.[7]

Creatinine

The output of creatinine was often higher in the early stages than later—a phenomenon that has been observed previously.[8,9] It reached its minimum level in about the third week, and did not begin to rise significantly until about a month after admission when the body weight also began to increase steadily. These findings agree with the impression gained from animal experiments, that on recovery from malnutrition there is a lag in the rebuilding from muscle compared with that of liver.[10]

Residual Nitrogen

This fraction includes creatine, uric acid, amino acids and peptides, and undetermined nitrogen. Expressed as a percentage of the total urinary nitrogen, the residual nitrogen level was raised in the malnourished infant (Table I), and fell during the child's hospital stay. However, in absolute terms the residual nitrogen was not raised; if anything, it was a little low in the early stages. Even in the five children who died there was, on the average, no increase in the absolute amount of residual nitrogen. One of these patients survived for seven days. The residual nitrogen was high (72 mg. per kg.) during the first two days after admission, but fell to 29 mg. per kg. per twenty-four hours on the day before death.

It is interesting that the average figure for residual nitrogen in these malnourished and recovering infants (27.9 mg. per kg. per twenty-four hours) is almost identical with that found by Macy[11] for the sum of the corresponding

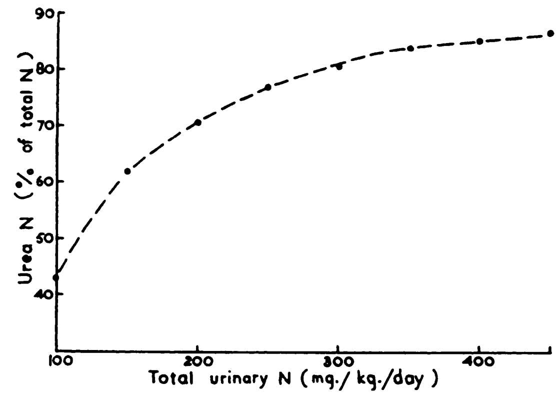

FIG. 2. The relation between the proportion of urea and total urinary nitrogen.

fractions in normal children (29.5 mg. per kg. per twenty-four hours).

COMMENTS

These results suggest that there is nothing abnormal about the gross partition of urinary nitrogen in the malnourished Jamaican child. The output of urea is no lower than would be expected at low levels of intake and total urinary nitrogen. Ammonia nitrogen and residual nitrogen, expressed as milligram per kilogram of body weight per day, were relatively constant, and no higher during malnutrition than after recovery. Studies of much the same kind have been made in other parts of the world. The figures given by Edozien et al.[12] for the partition of urinary nitrogen in subjects with kwashiorkor in Nigeria are urea 41 per cent, ammonia 20 per cent, creatinine 4 per cent, remainder 35 per cent. These are not very different from the results obtained during this study in the first days after admission (Table I). Edozien did not claim to have found absolute increases in components other than urea, as total outputs were not measured. However, two-thirds of the residual nitrogen was amino acid nitrogen; this figure is so high that it must represent an absolute as well as a relative increase in urinary amino acids. Other workers have also described some degree of aminoaciduria in kwashiorkor.[13]

In Uganda, Dean[14] found that in severe, but not in less severe, kwashiorkor there

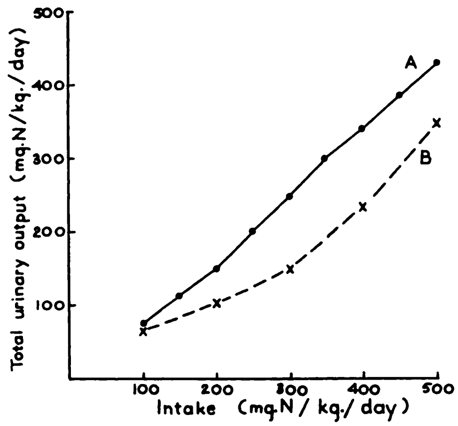

FIG. 3. The relation of nitrogen output to nitrogen intake. A, in the normal child. B, in the malnourished child.

was an increase in the absolute as well as in the relative amount of "undetermined nitrogen" in the urine, after allowing for urea, ammonia, creatinine, creatine, uric acid and α-amino nitrogen. The greater part of the undetermined nitrogen was thought to consist of purine-like substances, one of which was later shown to be imidazole acrylic acid.[15]

In the Jamaican babies, although the gross partition of urinary nitrogen was normal, there may well have been qualitative abnormalities which were not looked for. But in Uganda there was also an absolute increase in undetermined nitrogen. Why should the results be different in Jamaica? Judging by the mortality rate, body weights, and the like, the state of malnutrition is probably just as severe in Jamaica as it is in Uganda. I believe that very often there is also an element of tissue breakdown, manifested by increased outputs of creatinine, potassium and phosphorus, and raised serum transaminase levels in some patients.[16] It seems possible that this element of tissue destruction, perhaps related to infection, is more severe in Africa. Whatever the cause, the discrepancy with Dean's findings represents a regional difference in the picture of malnutrition which is worth further exploration.

From the practical point of view, it is a useful finding that in the child as well as in the adult, in the malnourished as well as in the healthy, the proportion of urea depends only on the total urinary nitrogen, and hence on the intake. It has been suggested that this could form the basis of a test of protein nutritional status.[6] It would be more precise to describe it as a test of preceding protein intake. Working on these lines, Luyken and Luyken-Koning[17] measured the proportion of urea in the urine in a number of different racial groups of children in Surinam and in Holland. There was a general correlation between the urea content of the urine and the protein intake. The latter, however, was estimated only; no exact measurements were made.

For field surveys, the "urea index" (i.e., urea nitrogen as a percentage of total nitrogen), as it may be called, represents a particularly convenient tool, because measurements can be made on a single urine specimen, which does not have to be collected over a measured time interval. It is, however, most desirable that a quantitative relationship should be established between this index and the nitrogen intake.

In Figure 2 the percentage of urea is related to total urinary nitrogen. The curve is calculated from the regression equation of Figure 1, which describes the results in malnourished infants. An almost identical curve is obtained if one uses the data of Macy[11] on the output of ammonia plus creatinine plus creatine plus uric acid plus undetermined nitrogen in normal children, and assumes that this is constant at different levels of intake. From this curve, the total urinary nitrogen can be estimated from the proportion of urea; the estimate is most accurate in the region where the curve is falling most steeply, at outputs below 300 mg. nitrogen per kg. per day.

There is greater uncertainty about the relation of total nitrogen output to intake, because this depends on the nutritional state. Figure 3 shows two curves: A, the relation of nitrogen output to intake in the normal child, calculated on the assumptions that: (1) true absorption equals 95 per cent of intake; (2) fecal metabolic nitrogen equals 25 mg. per kg. per day; and (3) nitrogen retained equals 20 mg. per kg. per day,[11,18] down to an intake level of 200 mg. nitrogen per kg. per day, falling to 0 at an intake of 100 mg. per kg. per day. B, the relation of nitrogen output to intake in a malnourished child, calculated on the assumptions that (1) true absorption equals 90 per cent of intake; (2) fecal metabolic nitrogen equals 25 mg. per kg. per day; (3) that nitrogen retained equals 100 mg. per kg. per day, down to intake levels of 300 mg. nitrogen per kg. per day,[19] falling progressively to 0 at an intake of 100 mg. per kg. per day.

From Figures 2 and 3 a table can be constructed relating urea index to intake (see Table II).

Clearly there is much uncertainty about predicting the actual intake from the urea index. However, the index could perhaps be used as a screening test, and the level of 70 be taken as the dividing line between adequate and inadequate. In the normal child a urea index of 70 corresponds to an intake of 250 mg. nitrogen, or about 1.6 gm. protein per kg. per day. With a normal protein mixture, such an intake should be adequate for a child of two years or over.[20] In the malnourished child, the index of 70 would correspond to an intake of about 350 mg. nitrogen per kg. per day. Such a child, however, needs a larger intake than normal and, therefore, any lower value of the urea index should be regarded as unsatisfactory.

The urea index gives an estimate, albeit rough, of the quantity of protein intake. It gives no information about quality. If it is known from independent evidence that the quality is poor, a higher level of the index will have to be taken as the dividing line between adequate and inadequate. If the urea index is measured in a large number of subjects whose dietary intake is accurately known, it should be possible to establish whether or not it is of value as a screening test for inadequate or marginal intakes.

TABLE II
Relation of Urea Index to Intake

Intake (mg. nitrogen per kg. per day)	Urea Index	
	Normal Child	Malnourished Child
200	62	43
250	71	55
300	77	62
350	81	70

SUMMARY

Twenty-four–hour urine specimens were collected from malnourished Jamaican infants immediately after admission to the hospital, and at various stages of recovery. Measurements were made of urea, ammonia, creatinine and "residual nitrogen," which includes creatine, uric acid, amino acids and undetermined nitrogen.

The partition of urinary nitrogen agreed with Folin's concept of 1905; the proportion of urea nitrogen depended only on the amount of total nitrogen present.

The absolute amounts of ammonia nitrogen and residual nitrogen were relatively constant and no higher during malnutrition than after recovery. The urea nitrogen expressed as a percentage of the total nitrogen (i.e., the "urea index") may be useful for the assessment of protein intake.

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