AZOTAEMIA IN INFANCY*

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It has long been known that infants with diarrhoea and vomiting show high levels of urea in their blood. Earlier investigators regarded this as due to dehydration (Schloss et al., 1918; Bessau et al., 1922) or to an attempt to retain at normal levels the blood osmotic pressure which was reduced as a result of salt loss (Hartmann and Smyth, 1926) while Wilmanns (1921) considered that the high blood urea arose from increased tissue protein breakdown due to passage of toxic products from the intestine into the circulation. The evidence presented in support of these theories was not satisfactory, and the conclusions were more or less a matter of surmise. More recently the approach to this problem has become clearer from studies on renal function in infancy (Young and McCance, 1942; Harrison et al., 1942) and from a closer understanding of extrarenal azotaemia in gastroduodenal haemorrhage. The latter work has been well summarized by Black (1942).

The present paper is an attempt to define the conditions under which azotaemia may develop in infancy and to explain its pathogenesis.

Material

The material for this study consists of all the sick infants under one year of age who on admission to the wards of this Department presented blood urea levels between 50 and 500 mg. per 100 ml. Forty-seven such cases were collected in a period of sixteen months. Another twenty sick infants, in whom the blood urea level was below 50 mg., have been studied as a control group.

Age Incidence

The age incidence is shown in fig. 1. The majority of cases occur during the first three months of life, when, moreover, the proportion of values over 150 mg. is much higher. The cause of this age incidence will be discussed later.

Factors Responsible for Azotaemia

As azotaemia is a symptom and not a clinical entity, an attempt was made to find a common link connecting all the forty-seven cases. A study was therefore made of the factors which might be responsible for the azotaemia.

URINE FINDINGS. Examination of a specimen of urine, collected as soon after admission as possible, yielded in most patients negative results. Slight albuminuria and a few pus and red cells, and/or occasional casts were noticed in some specimens,

but these findings, which are quite common in infants suffering from a variety of infective illnesses, were not constant. They were encountered with the same frequency in the control group, and they did not indicate a kidney lesion of sufficient severity to account for the increase in blood urea.

ETIOLOGY. The primary illness was: in twenty-nine infants, infective gastro-enteritis; in four pneumonia; in three, meningococcal meningitis; in one, septicaemia; in one, congenital heart disease; in two, pyloric stenosis; and in seven, an unknown infection (in five acute and in two of a more prolonged type). The etiology of the primary illness, varying so much, does not, therefore, offer the link connecting all these cases.

DIARRHOEA AND VOMITING. As extrarenal azotaemia in infancy has hitherto always been reported in connexion with primary or secondary gastro-enteritis, the presence or absence of diarrhoea and vomiting was studied. These symptoms were a prominent feature of thirty-nine cases, twenty-nine of primary gastro-enteritis, and ten in which diarrhoea and vomiting was due to parenteral infection. In the remaining eight cases (three of pneumonia, three of acute unknown infection, one of meningitis, and one of congenital heart disease) the azotaemia developed in the absence of any

FIG. 1.—Age incidence.

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gastro-intestinal symptoms. The azotaemia is not, therefore, necessarily connected with primary or secondary gastro-enteritis.

CLINICAL PICTURE. It was to be expected that the clinical picture of a group of cases of such varying etiology could not be the same. In spite of this a common factor, dehydration, was invariably present, under which general term are also included signs of circulatory embarrassment (collapse) due to dehydration of the intravascular compartment. The recognition of the importance of dehydration made a more accurate investigation necessary to see how far the degree of it was correlated with the degree of azotaemia.

MEASUREMENT OF DEHYDRATION. No objective method for the measurement of dehydration is absolutely reliable, but a fair idea of the amount of plasma loss may be gained by the careful interpretation of haematocrit values, and of the total loss of body water from changes in the infant's weight. Assuming that the total red-cell volume is constant during changes in hydration it can be shown that the amount of plasma loss in dehydration expressed as a percentage of the normal plasma volume equals

$$100 - \frac{100h}{h'} \quad \text{where}$$

h = haematocrit reading in normal hydration.

h' = " " " in the dehydrated stage.

For h' the haematocrit reading immediately after admission was taken, and for h the value after the infant seemed rehydrated clinically and the reading was practically the same in two successive days.

Total body water loss was calculated from changes in weight. In some subjects the normal weight before the onset of the illness was available, but where this was not so the weight gained following rehydration was taken to represent the total body water loss.

The blood urea values are plotted in fig. 2 against plasma loss expressed as a percentage of the normal (sufficient data for calculation in forty-four cases), and in fig. 3 against total body water loss expressed in per cent. of body weight (sufficient data for calculation in thirty-seven cases).

It can be seen in fig. 2 that, except in two patients, with rising blood urea the minimum plasma loss also increased, so that all infants presenting a certain blood urea level had a plasma loss over a corresponding minimum. For example, in infants in whom the blood urea level had risen over 50 mg. there was a plasma loss of at least 10 per cent., while when the blood urea was over 150 mg. there was a plasma loss of at least 30 per cent. (The dotted line has been drawn to make this correlation more evident.)

In fig. 3 the same correlation exists between azotaemia and total water loss, and here the two striking exceptions in fig. 2 (high blood urea without plasma loss) fall well into the general rule. Both patients were chronically dehydrated infants in whom the plasma volume had returned to normal at the expense of the extravascular compartment,

FIG. 2.—Blood urea volumes plotted against plasma loss.

which was depleted by 13 and 14 per cent. respectively of body weight.

From a closer study of figs. 2 and 3 two further points emerge.

(a) The distribution of the values for infants under and over three months is the same; younger infants, therefore, given the same degree of dehydration, do not tend to develop higher blood-urea values and the higher incidence of azotaemia during the first three months of life is due to the well established fact that younger infants become more easily dehydrated.

(b) The distribution of the values for infants with and without diarrhoea and vomiting was the same.

While azotaemia has always developed in this series in connexion with a corresponding minimum water loss, the reverse, as can be seen in figs. 2 and 3, did not hold, and a certain water loss did not necessarily cause a corresponding degree of azotaemia. For example, in marked dehydration with a plasma loss of from 30 to 40 per cent. or a total water loss of from 8 to 10 per cent. of the

FIG. 3.—Blood urea volumes plotted against total water loss.

body weight, blood-urea values ranged as widely as from 70 to 300 mg.

An investigation, therefore, became necessary into the factors which, given a certain degree of dehydration, determine the ultimate rise in blood urea.

CONTRIBUTING FACTORS. As complete metabolic experiments were not possible, the following factors were studied.

1. Duration of the symptoms before admission. There was no direct correlation between duration of symptoms and height of blood urea.

2. Concentrating capacity of the kidney. Estimation of the urea content of a specimen of urine passed soon after admission gave values ranging from 1.08 to 4.65 per cent. The higher values were not necessarily obtained from the infants with the high values for blood urea, so that no relation existed between the height of the blood urea and the urea content of the urine. The response of the kidneys of sick infants to the stimulus of a high blood urea varies widely, therefore, in different individuals. This varying response is undoubtedly one of the factors determining the ultimate rise in blood urea in each case of dehydration.

3. Protein intake. It was impossible to assess the protein intake during the days preceding admission. The influence of protein intake on the blood urea was therefore studied after admission, during the period of rehydration.

Dehydration being the main cause of the azotaemia, it is natural to expect a fall in blood urea during rehydration; this was seen in twenty-eight cases out of the forty for which sufficient data were available, but in the remaining twelve cases there was a temporary but significant rise in the blood urea ranging from 20 to 70 mg. The protein intake of these two groups of cases, subdivided according to their age, is shown in table 1.

TABLE 1
EFFECT OF PROTEIN INTAKE (GRAMMES PER 100 ML. OF TOTAL FLUID INTAKE) UPON BLOOD UREA DURING REHYDRATION

Age group	Fall in blood urea (28 cases)	Rise in blood urea (12 cases)
0-3 months (25 cases)	17 cases protein intake less than 3.8%	8 cases protein intake 3.8-7.6%
4-12 months (15 cases)	11 cases protein intake less than 5.5%	4 cases protein intake 7-7.6%

It is evident from this table that all cases with rising blood urea were taking more than 3.8 g. of protein per 100 ml. of fluid intake if under three months of age, and more than 7 g. if older. It seems, therefore, that there exists a critical level in the protein intake, lower for young infants and higher for older, over which any excess may cause a rise in the blood urea. This critical level was

FIG. 4.—Changes in blood urea during rehydration (fall).

more constant when expressed, as in table 1, as a fraction of total fluid intake, than in relation to the unit of body weight.

The influence of high protein intake on the blood urea under normal conditions of hydration was studied in two infants of eleven and five months old respectively, the first with mental deficiency and the second with congenital hydrocephalus. They were kept for five days on a constant caloric and fluid intake while the daily protein intake varied from 1.5 to 7.6 and from 3 to 7.6 g. per 100 ml. of fluid intake. The results are presented in table 2, where it is shown that even under normal conditions of hydration high protein intake causes a rise in blood urea up to double the normal value. In assessing the value of these results it may be recalled that protein milk preparations may contain as much as 7.6 per cent. of protein.

The data of tables 1 and 2 were obtained during rehydration and under normal conditions of hydration.

There can be no doubt that during progressing dehydration an even lower protein intake may have the same effect on the urea level of the blood.

In very few cases was there reliable information about feeding during the days before admission. The impression from these cases is that infants put on a water diet presented lower urea values than similar patients kept on milk feeds.

Course

It has already been pointed out that the blood urea falls following satisfactory rehydration when the protein intake does not exceed a certain level. In fig. 4 a typical case is presented; it can be seen that the depleted plasma, as shown by the haematocrit, quickly returns to its normal volume, but that the blood urea requires a longer time to return to normal and that its fall roughly parallels the rise in weight. It seems, therefore, that during rehydration the replenishment of the

TABLE 2
EFFECTS OF HIGH PROTEIN INTAKE ON
BLOOD UREA UNDER NORMAL CONDITIONS
OF HYDRATION

Subject's age (months)	Day of experiment	Weight (g.)	Haematocrit	Protein intake*	Blood urea mg./100 ml.	Urine urea g./100 ml.
R. K. (11)	1	7,450	30	1.5	30	1.38
	2	7,440	28.5	7.6	60	3.07
	3	7,450	29	7.6	74	3.20
	4	7,480	29.5	7.6	76	
	5	7,540	28	1.5	40	
J. L. (5)	1	6,250	32	3	26	
	2	6,250	29	7.6	52	
	3	6,200	30	3	29	
	4	6,345	31	7.6	60	
	5	6,310	31	3	38	

* Protein intake is expressed as g. per 100 ml. fluid intake, for the twenty-four hours preceding the estimation of the corresponding values of weight, haematocrit, blood and urine urea.

intravascular compartment has first priority, after which any water administered is proportionately shared between the extravascular compartments (increase in weight) and the kidneys for excretion purposes (fall in blood urea).

In the cases with an initial temporary rise of blood urea due to high protein intake the subsequent course was similar if the rehydration was uncomplicated and after restriction of the amount of protein given.

Eleven of the infants of this series died, and autopsy was performed on nine of them. Of these nine, five died after their dehydration was corrected and their blood urea had fallen to normal or near normal levels, and in none of these five was a renal lesion found at autopsy; two died of pneumonia, one of meningococcal meningitis, one of *B. coli* septicaemia, and one of congenital heart disease.

In the remaining four cases the primary illness was gastro-enteritis and all had had one or more relapses. The blood urea in the late stages of their illness rose still higher, even during temporary improvement of their hydration, after intravenous administration of fluids. A typical example is given in fig. 5, where it can be seen that the significant fall in haematocrit, indicating successful relief of dehydration, was accompanied by a marked rise in the urea of the blood. In all four cases a renal lesion, called dehydration nephrosis by some, was found at autopsy. This lesion consisted in degenerative and regenerative changes of the tubular epithelium with deposition of calcium salts.

It seems, therefore, that a continuously rising blood urea in spite of rehydration indicates the development of an organic renal lesion and that it carries a bad prognosis. The causes and mode of development of this organic lesion are not clear. All four infants were very ill, and in three of them the illness lasted more than twenty days. As other infants with the same degree of severity finally

recovered, and as in one of these four patients the illness lasted for six days only, it seems as if severity and duration of the illness are not the only factors responsible for the organic renal lesion.

Discussion and Conclusions

The collected data may help in answering some of the following questions.

1. Is this form of azotaemia extrarenal? Against the presence of an organic renal lesion are: (a) the absence of constant and significant urine findings, (b) the rapid fall of the blood urea in the majority of the cases after uncomplicated rehydration, and (c) the absence of kidney lesion in cases which shortly before death presented this form of azotaemia (five cases in the present series and similar cases of previous authors).

It has already been mentioned that in four cases of this series an organic renal lesion was found at autopsy; a similar though not identical histological picture has been reported in infants by Schloss (1918), Lightwood (1935), and Butler et al. (1936). How can these organic renal lesions be accounted for? Gsell (1935) and Rohland (1936) suggested that the azotaemia in dehydration is at first always functional, but that if the dehydration lasts for a long time without being relieved irreversible changes may take place in the tubular epithelium. It has been suggested (Butler et al., 1936) that this lesion is due to physicochemical changes which take place in dehydration, but the mode of development is not clear. It has been pointed out already that the duration and severity of symptoms are not the only factors responsible for the development of the renal lesion described.

2. How does azotaemia develop in dehydration? There are two theoretical possibilities; increase in the amount of urea formed in the body, or interference with its excretion.

The first can play only a secondary role, because the amount of urea formed in the body as a result of dehydration (Black et al., 1943-44) is minute compared with the urea formed and excreted under normal conditions. The well known fact that in dehydration the urine volume is diminished strongly suggests that interference with the excretion of urea is the preponderant mechanism.

But how does dehydration interfere with the urea excretion? A critical review of the work done and the theories advanced was made by Kerpel-Fronius

FIG. 5.—Changes in blood urea during rehydration (rise before death).

(1936) for extrarenal azotaemia in general, and by Black (1942) for extrarenal azotaemia following gastro-duodenal haemorrhage. Schoenthal et al. (1933) found a diminished urea clearance in dehydrated infants.

In order to find out if haemodynamic factors (reduction of blood volume, fall of blood pressure, increase in colloid osmotic pressure and blood viscosity) or general dehydration are more important the cases of the present series were divided into three groups: (A) cases in which plasma volume was reduced relatively more than total body water (predominance of haemodynamic factors); (B) cases in which total body water was reduced relatively more than plasma volume; and (C) cases in which intra- and extravascular compartments were equally dehydrated.

As can be seen from figs. 2 and 3, the dehydration was confined to one (extravascular) compartment in two infants only. From the other thirty-two cases for which sufficient data were available for such a classification, eleven belonged to group A, sixteen to group B, and seven to group C.

As each group contains a fair number of cases, and as dehydration confined to one compartment only is rare, it seems that interference with the excretion of urea is due in most cases of the present series to a combination of two groups of factors. The one group consists of haemodynamic factors, the importance of which was experimentally shown by Goemoeri et al. (1939). The other factor is general reduction of the total body water (tissue dehydration), as a result of which there is not enough water available for urine formation. It is of interest to notice that a slight rise of the blood urea within normal limits occurs in the first few days of life (McCance and Widdowson, 1947) and that this is thought to be due to a temporary physiological dehydration.

3. What are the other factors, which with a given degree of dehydration determine the ultimate rise in blood urea? Such factors may be:

(a) The concentrating capacity of the kidney. As already mentioned there are great individual variations, and Young and McCance (1942) have clearly proved the great variability of the urea clearance in normal and dehydrated infants. When the urine volume is reduced as a result of dehydration, the infant whose kidneys have lower concentrating capacity, will, other things being equal, develop a higher blood-urea level.

(b) Infection. The increased tissue protein breakdown and consequently increased urea formation during infection is a well established fact. But in the present series infection acting in this way could not be held responsible for the azotaemia because (1) dehydration without infection as in cases of pyloric stenosis has caused blood urea levels as high as 190 mg., and (2) infection without dehydration in the control series has never been the cause of azotaemia. But infection may be indirectly responsible for azotaemia since it was often the cause of dehydration.

(c) Starvation. Here again the extra urea which may be formed as a result of increased protein breakdown is minute in comparison to the amount retained. Its insignificant role is well demonstrated by a quick fall in blood urea after rehydration on a water diet while the starvation still continues. If the excretion of urea is not, therefore, interfered with, any extra urea formed as a result of increased protein breakdown, either from infection or from starvation, can be easily eliminated through the kidneys.

(d) Protein intake. The influence of the protein intake on the blood urea level under abnormal and normal conditions has been demonstrated. It is of interest to notice that the best correspondence between protein intake and rise or fall in blood urea was obtained when the protein intake was expressed in relation to total fluid intake and not to body weight.

These results confirm Schiff's (1929) opinion on the importance of the protein intake in determining the water requirements of the body.

The high blood urea values in most cases in this series cannot be due to high protein intake alone, because the protein intake could not be very high before admission and because even very high protein intake (7.6 per cent. of total fluid intake) did not raise the urea to more than double the normal value if the hydration was normal. But, given a deficient excretion due to dehydration, it can very well be one of the most important factors determining the degree of azotaemia.

It is suggested that, dehydration being invariably present in extrarenal azotaemia, other factors determining the degree of azotaemia in each particular case are the concentrating capacity of the kidneys, the amount of protein intake, and, to a lesser degree, an increased tissue protein breakdown the causes of which are dehydration, starvation, and infection.

4. Has the increased urea harmful effects in itself and can it influence the course of the illness? Although an increased urea content of the body has been said to be harmful in various ways (Harrison and Mason, 1937), the existence of such harmful effects for the human body has not been clearly proved. Since in the present series azotaemia was always combined with dehydration and often also with infection, no conclusion could be drawn as to whether the increased urea was in itself harmful. But in a few cases there was a temporary hiatus between dehydration and azotaemia. These were the cases in which, because of high protein intake, the blood urea rose during rehydration. It seemed as if in some infants the increase in blood urea preceded a relapse in dehydration. A typical case is presented in fig. 6, where it can be seen that on the second day there was a rise in the blood urea due to a very high protein intake although the fall in haematocrit and the increase in weight showed a satisfactory progress of rehydration. The following day this progress had stopped, the weight had fallen, the haematocrit had risen again, and the infant was clinically more dehydrated. This relapse could not

FIG. 6.—Effect of high protein intake on blood urea and on rehydration.

be accounted for by any change in the number or character of the stools or by any recurrence of vomiting. The high protein intake was discontinued and a quick recovery followed.

McCance and Young (1943-44) demonstrated that intravenous injection of urea caused an increase in the output of water, and that this happened to some extent even during dehydration. The above mentioned relapse in dehydration may have been caused by the same mechanism, though direct proof is not available. The practical implication of this observation is that the use of therapeutic feeds of a high protein content (more than 4 per cent. for young infants and more than 6 per cent. for older) may cause a relapse of the dehydration. The use of such feeds is therefore not justified, particularly because the same therapeutic effects can be obtained with feeds of a normal protein content.

5. **Is the estimation of the blood urea in dehydrated infants helpful?** One estimation on admission simply indicates the presence and, roughly, the degree of dehydration. It is not, therefore, of any immediate practical value, as the presence of dehydration is easily detected on clinical examination and the degree may be more quickly and more directly estimated by other methods. Stransky (1920), on the basis of clinical observations, reached the same conclusion.

Successive estimations may be of greater help. A quick fall indicates a satisfactory rehydration and

is of good prognostic significance as regards the dehydration. A continuous rising or persistence in high levels, in spite of fall in haematocrit, makes the prognosis poor because it may indicate the development of irreversible changes in the renal tubules.

Summary

1. A study was undertaken of forty-seven sick infants presenting blood urea values of from 50 to 500 mg. per 100 ml. of blood.

2. An attempt was made to define the nature of this azotaemia and the conditions under which it may develop.

3. This azotaemia is always extrarenal at the beginning, and the basic condition necessary for its development is dehydration due to a variety of causes.

4. Contributory factors which may determine the degree of azotaemia are the amount of protein intake, the concentrating capacity of the kidney, and to a lesser degree increased tissue protein breakdown due to infection or starvation.

5. Persistence of high blood urea values in spite of rehydration is of bad prognostic significance as it indicates the development of irreversible changes in the renal tubules.

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