Hyperammonaemia

A Variant Type of Deficiency of Liver Ornithine Transcarbamylase

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The specific syndrome arising from an absent or low hepatic ornithine transcarbamylase activity has been termed hyperammonaemia (Russell *et al.*, 1962; Levin and Russell, 1967; Levin, 1968). In the previous communication (Levin *et al.*, 1969) 2 cases occurring in mother and child are described. In this article, we record an infant who during the course of an investigation for the cause of his vomiting had an unexplained episode of illness in which he became lethargic, drowsy, and finally comatose, with convulsions. He was found to have a high plasma and CSF ammonia, and the diagnosis of hyperammonaemia was confirmed by assay of the urea cycle enzymes of the liver.

Studies of the properties of the liver ornithine transcarbamylase in this patient suggest that he represents a variant type of deficiency of this enzyme. This may be correlated with the relative mildness of his condition, and the rapidity and completeness of clinical recovery. The effect of citric acid, glutamic acid, alanine, and arginine on plasma ammonia levels was also studied.

Case Report

A male, born on August 8, 1966, was the first child of unrelated parents in whom there was no family history of fits, mental defect, or other metabolic diseases on either side. The mother developed toxæmia during pregnancy which was terminated by induction at 36 weeks. The infant was normal but slightly immature, weighing 2.4 kg. He was breast-fed at first, then bottle-fed, and was apparently well for 6 months, growing steadily along the 3rd centile for weight (Fig. 1). At 6 months he was admitted to Southend General Hospital on account of bronchiolitis. No other abnormality was noted at this time, and the milestones were normal. He weighed 6.5 kg. and took his milk and weaning diet well.

Very soon after discharge he began vomiting occasionally. It was effortless and unassociated with

malaise, anorexia, or constipation. However, it became increasingly troublesome and he ceased to gain weight. He was treated with atropine methonitrate ('eumydrine'), with no improvement, and at 8½ months was readmitted for investigation. He was then a thin, lively infant weighing 7 kg. There were no abnormal physical signs, and the blood chemistry, urine microscopy, and chromatogram were normal. Radiological examination showed no abnormality of the oesophagus, stomach, or upper bowel. The vomiting continued in hospital, occurring mainly in the evening, and often contained much of the day's food.

During the first week he was quite lively, but subsequently became drowsy and increasingly difficult to rouse in the morning. His temperature rose to 39.4 °C., the pulse to 136 per minute, and the liver, on which no comment had been made when he was examined earlier for possible pyloric stenosis, was now enlarged to 3 cm. below the costal margin. His condition deteriorated rapidly. CSF obtained by lumbar puncture gave normal results by the usual tests. Immediately after the lumbar puncture he collapsed and became semicomatose, with twitching. It was thought possible that the procedure had led to coning and medullary pressure consequent upon an intracranial space-occupying lesion, and 2 months after his first admission, May 7, 1967, he was transferred to the London Hospital for neurological investigation. He arrived deeply comatose and convulsing, remaining in this condition for over 36 hours. The fontanelle was tense and bulging. A further lumbar puncture produced a blood-stained fluid containing no excess of white cells and a normal protein content. The liver was now still further enlarged, to 6 cm. below the costal margin. Numerous biochemical investigations, including blood urea (22 mg./100 ml.), gave normal results. The EEG was grossly abnormal and reported as showing 'probably severe structural damage possibly due to severe electrolyte disturbance'. The echogram showed no mid-line shift and an air ventriculogram no abnormality.

He was at first fed by gavage with a milk mixture, but because of regurgitation and convulsions this was replaced by intravenous glucose 18 hours after admission. Shortly after starting this he rapidly improved and was out of coma within 24 hours. Paper chromatography of a specimen of urine taken shortly after

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FIG. 1.—Progress chart. Note improving weight and height gain on a low protein diet.

admission revealed an excess of glutamine and uracil, suggesting a possible high blood ammonia. This was confirmed when the plasma ammonia was found to be $182 \mu\text{g. NH}_3\text{-nitrogen/100 ml.}$ more than 48 hours after the start of the infusion. A provisional diagnosis of hyperammonaemia, possibly due to a congenital metabolic disorder, was made, and on May 12, he was transferred to the Queen Elizabeth Hospital for Children for further investigation. On arrival he was alert and hungry and able to smile, but seemed dazed, was hypotonic, and exhibited some indefinite ataxic movements of the arms. No abnormal physical signs were detected apart from the liver enlargement which had diminished. Enzyme assays on a biopsy specimen of the liver confirmed the presence of an enzyme defect of the urea cycle. Histologically there was a mild increase of fibrous tissue in the portal tracts but no evidence of cirrhosis.

Fasting levels of plasma ammonia ranged between 40 and $90 \mu\text{g. NH}_3\text{-N/100 ml.}$, i.e. up to twice the upper limit of normal, and rose to $160\text{--}250 \mu\text{g. NH}_3\text{-N/100 ml.}$ after ingestion of protein (see Table II). A low protein diet of SMA ('adapted' milk) in 5 equally spaced feeds was thereafter instituted. Later, egg yolk and rice were added. Within a few days of admission he seemed almost normal, except for persisting liver enlargement which gradually returned to normal during

the next 4 weeks. The EEG 4 days after admission showed only slight residual abnormality. All subsequent EEG's have been normal, both between meals and after protein ingestion. He was discharged a month after admission weighing 7.8 kg. and on a diet containing $13\text{--}14 \text{ g. protein per day.}$ He gained weight rapidly at home and resumed normal mental development. Within a few weeks he had lost all evidence of hypotonia and at 1 year old was beginning to stand and walk. At 15 months he weighed 9 kg. and was between the 3rd and 10th centile for height. He was then able to say a few words. Progress was so good that his protein intake was increased to 18.5 g. daily. However, within two months he had lost a little weight, possibly associated with an attack of bronchitis, and the plasma ammonia level rose. In consequence, though he showed no adverse symptoms, the intake of protein was reduced to about the previous level, at which he has since remained. At 21 months he remained in excellent health and he was walking, running, and talking in short sentences. When last seen, at 2 years of age, he was a normal boy and had grown from below the 3rd centile for weight and the 10th centile for height at 1 year to the 25th centile for both at 2 years (Fig. 1), while the bone age, which had been 6 months retarded at 1 year, was approximately at the chronological age at 2 years.

Results of Laboratory Investigations

The methods used are described in the previous paper (Levin *et al.*, 1969).

Biochemical investigations. Plasma sodium, potassium, chloride, standard bicarbonate, and pH determined on a number of occasions were all within normal limits. Serum calcium, magnesium, phosphorus, total protein, albumin, globulin, non-protein nitrogen, cholesterol, and uric acid were also normal. The blood urea ranged from 10 to 22 mg./100 ml. in random estimations, though occasionally levels up to 28 mg./100 ml. were reached 3 or 4 hours after a protein meal. The liver function tests were normal except for the serum GOT which was moderately raised during the acute episode and for a time thereafter. The alkaline phosphatase was also slightly raised.

There was only a slight increase in the urinary excretion of amino acids. Paper chromatography showed a prominent glutamine band. Quantitative analysis confirmed the increased glutamine excretion.

Ammonia levels in plasma and CSF. The plasma ammonia level estimated 4 days after the onset of coma was $182 \mu\text{g. NH}_3\text{-N/100 ml.}$ (normal $10\text{--}45 \mu\text{g. NH}_3\text{-N/100 ml.}$). Thereafter it was determined on many random occasions, the levels ranging from $40\text{--}237 \mu\text{g. NH}_3\text{-N/100 ml.}$, depending

TABLE I

Effect of Varying Protein Intakes on Plasma Ammonia; Levels at 3-hourly Intervals Throughout Day

Protein Intake (g./kg. body weight)	Plasma Ammonia ($\mu\text{g.NH}_3\text{-N}/100\text{ ml.}$)						
	0 hr.	3 hr.	6 hr.	9 hr.	12 hr.	15 hr.	18 hr.
1.8		64	65	171	126	111	
1.4		48	93	121	142	83	
1.2	46	41	68	77	57	88	68

presumably on the relation to the previous meal. The CSF ammonia level, measured only once, was $32\text{ }\mu\text{g.NH}_3\text{N}/100\text{ ml.}$ (normal up to $10\text{ }\mu\text{g.NH}_3\text{-N}/100\text{ ml.}$). This was $1\frac{1}{2}$ hours after a protein meal, when the plasma levels 30 minutes before and 30 minutes afterwards were 108 and $132\text{ }\mu\text{g.NH}_3\text{-N}/100\text{ ml.}$, respectively.

Dietary protein and plasma ammonia. The effect of different levels of protein intake was assessed by determining the plasma ammonia at 3-hourly intervals over a period of 15 hours during the day at different levels of protein intake. The results (Table I) show that in general the less the protein intake, the lower the ammonia levels. In two series, at two different age periods, in which though the total protein was unaltered, the intake calculated per kg. body weight was less as he grew older, plasma ammonia levels were lower with the lower intake per kg. This suggests that the apparent increase in protein tolerance with age may be related to a decreasing protein intake per kg. body weight.

TABLE II

Plasma Ammonia Levels After Protein Ingestion; Effect of Citric and Glutamic Acids

Protein Load	$\mu\text{g.NH}_3\text{-N}/100\text{ ml.}$				
	Fasting	Hours after Protein	Load		
		1	2	3	4
10 g.	45	108	132	163	152
10 g.	75	104	138	237	111
9 g. + 0.5 g. citric acid . .	87	123	145	251	223
10 g.	88	—	155	189	148
10 g. + 1.5 g. citric acid	71	86	94	200	167
10 g. + 2.0 g. glutamic acid	76	170	240	246	137
Urea mg./100 ml. }	(12)	(16)	(17)	(20)	(21)
10 g. alone	112	143	128	116	
Urea mg./100 ml. }	(14)	(15)	(17)	(18)	

Protein loading tests. Plasma ammonia levels were also determined after fasting and 1, 2, 3, and 4 hours after a protein feed. There was a marked rise, maximal at 3 or 4 hours after the meal, greatly in excess of the slight rise occurring in normal infants under similar conditions. This rise in plasma ammonia was not abolished or diminished by giving citric acid (0.5 g. or 1.5 g.) just before the protein meal, nor was glutamic acid (2 g.) any more effective (Table II).

FIG. 2.—Effect of ingestion of (a) L-alanine (0.6 g./kg.), (b) L-alanine (0.6 g./kg.) and arginine (0.125 g./kg.) together on plasma ammonia and blood urea levels. Note that the addition of arginine to L-alanine does not reduce the rise of plasma ammonia.

Effect of ingestion of alanine and arginine.

In some cases of protein intolerance associated with raised ammonia levels the latter are lowered by administration of arginine. Plasma ammonia and blood urea levels were therefore determined at hourly intervals for 4 hours after oral ingestion of L-alanine (0.6 g./kg.), and after L-arginine (0.125 g./kg.) given with alanine (0.6 g./kg.) The results are shown in Fig. 2. After alanine, the plasma ammonia rose to the high level of $338\text{ }\mu\text{g.NH}_3\text{-nitrogen}/100\text{ ml.}$ after 3 hours, with a relatively small increase in the blood urea. L-alanine and arginine together induced an identical rise in plasma ammonia, but the increase in blood urea was

TABLE III

Plasma Amino Acid Levels, Fasting and After Oral Ingestion of Protein or Amino Acids

Amino Acid	Fasting (mg./100 ml.)	3 hr. After Protein Load (mg./100 ml.)	Fasting (mg./100 ml.)	3 hr. After Alanine (6.2g.) (mg./100 ml.)	Fasting (mg./100 ml.)	2 hr. After Alanine (6.2g.) Arginine (1.26 g.) (mg./100 ml.)	15 Normal Adults (Fasting) (mg./100 ml.) Mean $\pm$ SD
Glutamine ..	20.0	23.0	17.2	18.5	15.3	22.1	10.8 $\pm$ 0.8
Glutamic acid ..	1.0	0.8	0.61	1.7	1.0	2.5	0.51 $\pm$ 0.22
Citrulline ..	0.10	0.10	0.08	Nil	0.10	0.16	0.45 $\pm$ 0.17
Ornithine ..	0.58	0.71	0.36	0.38	0.45	1.5	0.67 $\pm$ 0.09
Arginine ..	0.84	0.75	0.29	0.51	0.65	2.3	1.5 $\pm$ 0.42
Glycine ..	1.7	1.5	1.9	1.3	2.7	2.6	1.7 $\pm$ 0.27
Alanine ..	3.4	4.4	2.0	5.1	4.2	18.5	2.8 $\pm$ 0.63
Leucine ..	1.3	2.2	0.89	0.48	0.79	0.55	1.5 $\pm$ 0.22
Urea ..	14	17	12	16	13	20	14-50 (range)
Ammonia (μ g. NH_3 - N/100 ml.) ..	112	128	77	338	40	241	10-45 (range)

greater. The significance of these results is discussed below.

Plasma amino acid levels. These were also determined on a number of occasions, and some of the results are shown in Table III. As in the other cases of hyperammonaemia, fasting glutamine levels were very high, and glutamic acid was also raised. Both arginine and citrulline levels were low compared with the normal, whereas ornithine was within normal limits. After ingestion of protein, there was a marked rise in glutamine but little change in the other amino acids. Alanine ingestion resulted in a rise in plasma glutamine and glutamic acid, with little change in the other intermediates of the urea cycle. It also caused a marked rise in plasma alanine. The effect of alanine and arginine given together was similar to that of alanine alone. The rise in glutamine and, more marked, in glutamic acid, was consistent with the failure of arginine to reduce the rise in plasma ammonia resulting from the alanine. As expected, there was a rise in plasma alanine and arginine.

Amino acids in CSF. These were estimated on one occasion only, and the relevant levels are given in Table IV, together with those from normal children. Both glutamine and glutamic acid levels were higher than in the normal, whereas arginine was lower.

Urinary amino acids. These were determined quantitatively on a specimen of urine obtained during his initial episode while he was still having glucose electrolyte infusion, as well as on urine obtained just before a protein loading test and 4 hours after the ingestion. The results are shown

in Table V, together with those from normal urine for comparison. The increased glutamine and glutamic acid excretion confirmed the qualitative results of paper chromatography. In the first specimen examined, the excretion of ethanolamine was very high. No explanation can be given for this; in the other two urines, the level of ethanolamine appeared normal. Despite the low plasma arginine, the urinary concentration was normal in amount.

TABLE IV

Levels of Some Amino Acids in Cerebrospinal Fluid

Amino Acid	Patient (mg./100 ml.)	17 Controls 8 mth.-11 yr. (mg./100 ml.) Mean $\pm$ SD
Glutamine ..	14	8.3 $\pm$ 1.2
Glutamic acid ..	0.15	0.02 ($<$ 0.04)
Citrulline ..	0.02	0.015 ($<$ 0.035)
Ornithine ..	0.10	0.07 $\pm$ 0.05
Arginine ..	0.08	0.34 $\pm$ 0.10

TABLE V

Levels of Some Amino Acids in Urine

Amino Acid	During Episode of Illness (mg./g. N)	Fasting (mg./g. N)	After Protein Ingestion (mg./g. N)	Normal Children (mg./g. N)
Glutamine ..	110.0	67	38	16, 12
Glutamic acid ..	0.85	1.7	5.7	0.5, 0.2
Ornithine ..	0.53	0.3	0.62	0.15, 0.17
Arginine ..	0.23	0.58	0.82	0.22, 0.72
Ethanolamine ..	27.0	3.5	3.6	1.4, 1.3
Glycine ..	22.0	50.0	64.0	8.0, 5.7
Alanine ..	9.7	6.9	9.5	5.0, 2.2
Histidine ..	44.0	56.0	34.0	8.0, 12.0
Lysine ..	2.4	2.7	3.4	0.75, 2.1

TABLE VI

Levels of Enzymes of the Urea Cycle in Liver

	Patient (units)	Normal (mean and range) (units)
Carbamyl phosphate synthetase	250	320 (182-615)
Ornithine transcarbamylase at pH 7.0	1288	5183 (3950-6650)
at pH 8.0	4332	5787 (3900-9090)
ASA synthetase	13.5	37
ASA cleavage enzyme	115	177
Arginase	24,833	38,420 (24,600-56,300)

1 unit = 1 μ mole product formed/hr. per g. wet weight of tissue.
ASA = argininosuccinic acid.

Urea cycle enzymes in liver. These were assayed in a biopsy specimen of the liver obtained at open operation, and the results are shown in Table VI. Initially, ornithine transcarbamylase activity was measured by the method of Kulhánek and Vojtišková (1964), using a glycyl glycine buffer at pH 8.0, and the result was just within the normal range. However, when it was determined by the method of Brown and Cohen (1959), using a tris buffer, pH 7.0, as in some of the earlier cases of hyperammonaemia, the activity was only 25% of the mean normal value, and the ratio of enzyme activities at pH 8.0 and 7.0 was double the normal value. As the reduction in activity was smaller than in other instances of hyperammonaemia (Levin, 1968; Levin *et al.*, 1969), the Km values of the enzyme for its two substrates, ornithine and carbamyl phosphate, were determined (Table VII). The Km value for carbamyl phosphate was low, indicating a marked increase in the affinity for this substrate compared with the normal enzyme. The significance of these results is discussed later.

The activities of other enzymes of the cycle were within normal limits, except for that of argininosuccinic acid synthetase which was reduced to about 33% of a normal control.

Effect of enzyme block on pyrimidine synthesis. As in other instances of hyperammonaemia, there is an increased alternative utilization of ammonia to form orotic acid, uridine, and uracil, intermediates in the pathway of pyrimidine synthesis and breakdown (Levin, 1968; Levin *et al.*, 1969). The amount of these substances excreted daily varied according to the protein intake. Initially, when he was on a very low protein diet, 18 mg. orotic acid and 18 mg. uracil were excreted daily, the latter being the earliest indicator of the defect in the urea cycle; even greater amounts were found when the protein

TABLE VII

Properties of Ornithine Transcarbamylase

	Patient	Normal Controls
Km for ornithine	0.89 mM	1.26 mM (mean)
Km for carbamyl phosphate	0.34 mM	1.45; 0.95 mM (mean)
Activity at pH 7.0 (tris buffer)	1288 units*	5183 (mean)
at pH 8.0 (glycyl glycine buffer)	4332 units*	5787 (mean)
Ratio of the 2 activities ..	3.3	1.44 (mean)

* 1 unit = 1 μ mole product formed/hr. per g. wet weight of tissue.

intake was increased slightly. Uridine, which was absent from the urine when protein intake was very low, was also excreted in relatively high amount.

Discussion

The clinical course of this patient differed from that of other cases of hyperammonaemia presenting in infancy, in the relative mildness of the condition. Vomiting for no ascertainable cause together with failure to thrive from the age of 6 months were the only features until an acute episode of illness characterized by lethargy, drowsiness, and coma and again with no obvious cause. The similarity to the episodic stupor occurring in hyperammonaemia suggested the possible diagnosis, afterwards confirmed. In two other cases presenting in infancy (Russell *et al.*, 1962; Levin, 1968), severe brain damage was already apparent by the time they presented. In the present instance, there has been no evidence of this, and recovery on a low protein diet has, so far as can be judged, been complete.

Protein requirements. The treatment of this condition has been fully discussed elsewhere (Levin, 1967; Levin and Russell, 1967). Unlike the other cases of hyperammonaemia, neither citric acid nor glutamic acid appeared able to reduce post-prandial rise in plasma ammonia. The only effective method of treatment in this case was found to be a strictly controlled reduction of protein intake.

Studies over half a century on man's protein requirements have been largely concerned to establish optimal rather than minimal needs for the individual. For adults a daily intake of 1 g./kg., for growing children 2-3 g./kg., and for infants 3-4 g./kg. body weight have been widely accepted as optimal, allowing an adequate margin for individual variation and the varying biological

value of the available protein. It has long been appreciated, however, that an adult protein intake as low as 0.5 g./kg. is compatible with good health and adequate physical performance (Hegsted, 1968; Best and Taylor, 1961), and experimentally, nitrogen balance can be maintained on 18 g. protein daily, approximately 0.25 g./kg., using protein of 100% biological value (Hegsted, 1968). For infants under 1 year, the minimal requirement is not known, but, provided the biological value of the protein is high and absorption is not impaired, it is probably very much less than the 3.5 g./kg. per day accepted as optimal. For example, breast-fed infants will receive little more than 2 g./kg. body weight in the first few weeks of life, and less as they grow.

In our patient the daily protein intake, almost exclusively as milk and eggs, was kept below 1.5 g./kg. for over a year, except for a 7-week period, and this appeared to be sufficient to maintain good health, and physical and mental development. Weight, linear growth, and bone age all accelerated during the second year of life (Fig. 1). Plasma proteins and amino acids were normal.

Toxicity of ammonia. In hepatic failure the plasma ammonia level is commonly raised much above the normal range, and the levels above 250–300 $\mu\text{g.}/100\text{ ml.}$ are usually associated with neurological manifestations, such as confusion, tremors, and muscular twitchings, while in hepatic coma levels of 500–600 $\mu\text{g.}/100\text{ ml.}$ or over may be found (Sherlock, 1958). Correlation between plasma ammonia levels and signs and symptoms, however, is not close.

Little is known about the levels at which blood ammonia becomes toxic when hepatic failure is absent. However, observation from three separate sources suggests that concentrations considerably above the accepted normal range may be well tolerated at least by the adult. In studying the utilization of ammonia as a source of nitrogen in protein synthesis, Fürst, Josephson, and Vinnars (1968) administered ammonium acetate intravenously to volunteers, giving as much as 200 mEq within about 4 hours without observing any symptoms. The blood ammonia concentrations rose from an initial range of 50–80 $\mu\text{g.}$ to 150–300 $\mu\text{g. NH}_3\text{-nitrogen}/100\text{ ml.}$ Only when these limits were exceeded did the subjects begin to feel nauseated and dizzy, and some of them vomited.

In the dog the diversion of blood from the portal vein into the vena cava by an Eck fistula is known to be associated with the so-called 'meat intoxication', a neurological disorder of ataxia, convulsions,

and finally coma, usually occurring after the ingestion of meat, but sometimes spontaneously. McDermott and Adams (1954) made a similar fistula in a man of 69 years with carcinoma of the head of the pancreas in whom the liver was normal and portal hypertension or collateral circulation was absent. After his operation the patient suffered periodic episodes of confusion, with ataxia, stupor, and coma lasting 2 or 3 days, the only therapy being the parenteral administration of water, glucose, and electrolytes in adequate amounts. These episodes could be induced by giving a high protein diet, urea by mouth, or such substances as ammonium chloride or 'Resodec', an exchange resin containing ammonia. Even during periods when the patient was symptomless, mentally clear, and with a normal EEG tracing, blood ammonia levels were 50–75 $\mu\text{g. NH}_3\text{-N}/100\text{ ml.}$, higher than normal. When the symptoms were induced the plasma ammonia rose sharply, and at the height of the symptoms reached a level of 300–600 $\mu\text{g. NH}_3\text{-N}/100\text{ ml.}$, and the EEG became grossly abnormal. After such very high levels a normal mental state was not regained for several days. Finally, when he was given a diet in which the daily protein was limited to 40 g., the patient remained well for several months with only occasional episodes of mild confusion, and his blood ammonia levels during asymptomatic periods were around 150 $\mu\text{g. NH}_3\text{-N}/100\text{ ml.}$

There is a striking similarity between these findings in a 69-year-old man with an Eck fistula, and our own and other cases with a disturbance of the urea cycle (Levin, 1968; Levin *et al.*, 1969). The evidence suggests that at least in the adult, and probably in children beyond the age of infancy, plasma ammonia levels of about 100 $\mu\text{g. NH}_3\text{-N}/100\text{ ml.}$ and for short periods possibly up to 150–200 $\mu\text{g. NH}_3\text{-N}/100\text{ ml.}$, are compatible with good health and may give rise to no symptoms or changes in the EEG. The experience gained from this case confirms that this may also be true in infants at least after the first six months of life.

Protein intolerance and raised blood ammonia. A condition of familial protein intolerance associated with a raised blood ammonia has recently been described by Perheentupa and co-workers (Perheentupa and Visakorpi, 1965; Kekomäki *et al.*, 1967). They suggested that it was caused by an inherited defect of transport of basic amino acids, which resulted in a deficient absorption and excessive excretion of arginine and ornithine. As a result, the conversion of ammonia to urea was defective. In their cases,

oral administration of arginine reduced blood ammonia levels, induced better growth, and increased the protein tolerance. In our case, however, the high plasma ammonia was not affected by oral arginine, and the excretion of arginine and ornithine was normal.

Nature of enzyme defect. It is now becoming apparent that more than one genetic variation of an enzyme can occur, giving rise to syndromes which, though similar, are not identical (LaDu, 1967). Such variation has been demonstrated in G6PD deficiency (Marks, 1964), heterogeneity of the aberrant enzyme being proved by differences in enzyme activity, substrate affinities, pH optima, stability, and electrophoretic mobility. It has also been postulated to occur in hyperphenylalaninaemia (Auerbach, diGeorge, and Carpenter, 1967), histidinaemia (Auerbach *et al.*, 1967), and fructosaemia (Levin *et al.*, 1968), and in other conditions.

In our patient also the liver ornithine transcarbamylase appears different from the normal one and from that found in the other cases of hyperammonaemia. There is a smaller reduction in its activity (Levin, 1968; Levin *et al.*, 1969), and this only became apparent when the activity was measured using tris buffer at pH 7.0, being just within normal limits when measured at pH 8.0 (Table VII). In addition, the substrate affinities were quite different compared with those obtained in normal liver. These results suggest that the liver ornithine transcarbamylase in this patient is a variant form differing from that in the other cases of hyperammonaemia.

Genetics. Plasma ammonia, glutamine, and glutamic acid levels were normal in the mother, both in the fasting state and after protein ingestion. No investigations were performed in the father, but there was no history of protein intolerance. It is therefore likely that the condition in this child is inherited as a recessive. In the other cases of hyperammonaemia, a dominant mode of expression has been suggested (Levin, 1968). This difference in the mode of inheritance would be explicable if the present case were, as postulated, a variant type due to a different mutation of the gene involved.

Summary

A new instance of hyperammonaemia is described. He is an infant who began vomiting and failed to thrive from the age of 6 months, and who had an unexplained acute episode of illness with lethargy, drowsiness, and coma at 8½ months of

age. He was found to have high levels of plasma ammonia, high urinary glutamine, and a characteristic pattern of plasma amino acid levels. The liver ornithine transcarbamylase activity was decreased to 25% of the normal, compared with 5–7% in other cases. Investigations of other properties of the enzyme showed differences from the normal.

Severe limitations of protein intake resulted in resumption of growth, and the child is now normal with no mental retardation. Plasma ammonia levels fell with restriction of protein, but are still above the normal. The requirements for protein and the relation of symptoms to plasma ammonia levels are discussed.

It is postulated that, because of the unusual properties of the enzyme as well as the relative mildness of his condition, this child represents a variant type of liver ornithine transcarbamylase deficiency, due to a different mutation of the gene involved from that found in other cases.

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