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Dietary Treatment of Homocystinuria

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Homocystinuria was described in 1962 by Field, Carson, Cusworth, Dent, and Neill and later in the same year by Gerritsen, Vaughn, and Waisman. A further case was reported by Komrower and Wilson (1963); in this case and the ones described by Field *et al.*, the patients presented a characteristic picture of congenital bilateral dislocation of the eye lens, iridodenesis, genu valgum, pes planum, and kyphoscoliosis. They had fair brittle hair (though some later cases lack this feature (Schimke, McKusick, Huang, and Pollack, 1965), a high malar flush, and showed evidence of poor peripheral blood circulation. Vascular thromboses have been reported by several observers and we have seen three examples of this complication; two children died following operations to relieve intraocular tension and were found, at necropsy, to have a pulmonary embolism. All of the early cases showed mental retardation, but several cases reported by Schimke *et al.* have normal intelligence.

Carson, Cusworth, Dent, Field, Neill, and Westall (1963) studied the first reported case in more detail and carried out biochemical investigations, showing that there was an increased level of methionine and a readily detectable level of homocystine in the blood plasma, and an increased excretion of these sulphur-containing amino acids in the urine. Moreover, the urinary homocystine was isolated in crystalline form and subjected to chemical analysis to confirm its identity. Gerritsen and Waisman (1964) reported on the absence of cystathionine in the brain of their first patient who had died of the disease and this observation was confirmed by Brenton, Cusworth, and Gaull (1965) who examined the brain in a further fatal case. As a result of these observations it was suggested that the clinical picture of the disease arose from a failure to convert methionine to cystine, due to the lack of a specific enzyme. Mudd, Finkelstein, Irreverre, and Laster (1964) demonstrated extremely low activity of cystathionine synthetase in liver tissue obtained by percutaneous biopsy from two affected patients, and compared these results with those obtained from relatives of the homocystinuric patients and from normal controls (Finkelstein, Mudd, Irreverre, and Laster, 1964). Further evidence for the existence of an enzymic block preventing the conversion of methionine to cystine has recently been provided by Brenton, Cusworth, Dent, and Jones (1966) who showed clearly that a homocystinuric child under dietetic control required cystine as an essential amino acid, and could not be maintained in positive nitrogen balance on a diet providing methionine but no cystine.

When homocystinuric patients are fed a normal diet they accumulate methionine in their body fluids and tissues: there is an abnormal amount of circulating homocystine and a lack of cystathionine in certain tissues. In devising a form of therapy for these patients it seemed justifiable to approach the question of diet in one of two ways. The first would be to reduce the methionine intake to minimal requirements and to supplement the diet with additional cystine, on the assumption that either excess methionine or homocystine is detrimental to the subject and gives rise to the clinical picture previously described. The second approach would be based on the assumption that the disease is due to a deficiency of cystathionine and not to the raised plasma levels of methionine and homocystine, and to supply to the patient cystathionine, an amino acid which is not a constituent of a normal diet. Cystathionine is very expensive and is rapidly excreted in the urine; moreover, no known function has been found for this compound. For these reasons we decided that a low methionine—high cystine diet should be tried first. The opportunity to test this form of therapy arose in 1964 and we are reporting on the condition of a homocystinuric child, now 2 years and 3 months old, who has been on this dietary régime since the age of 2 weeks. Perry, Dunn, Hansen, MacDougall, and Warrington (1966) have recently reported on their experience after feeding a homocystinuric child for six months on a similar diet with the same objective.

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Case History

In February 1964, two children aged 13½ years and 7 years, respectively, were referred by Dr. R. M. Forrester; they showed the clinical signs of homocystinuria and were proved to be so following biochemical investigations. There were also two normal children in the family, both girls aged 8 and nearly 11 years. An eldest child had died at 6½ months, the cause being diagnosed as pneumonia. While these investigations were in progress, the mother gave birth to her sixth child, P.W., on April 14, 1964. This child was delivered by normal, vertex presentation, weighing 2·9 kg., length 49 cm. Initial examination was normal and blood was taken and urine collected at 9 hours for examination (Table I). The baby was transferred to the Royal Manchester Children's Hospital where she was given evaporated milk feeding. The urine was examined on alternate days and blood was taken on day 3 and day 9. On day 3 the plasma methionine was 1·5 mg./100 ml. and homocystine 0·4 mg./100 ml., a trace of homocystine being detected in the urine. Methionine (500 μg./mg. creatinine) and homocystine (740 μg./mg. creatinine) were detected in the urine on day 5, and on day 9 the plasma methionine and homocystine levels were significantly raised to 26·8 and 1·2 mg./100 ml., respectively. We considered that these figures justified a biochemical diagnosis of homocystinuria. The child was immediately placed on the low methionine diet which she has received with continuing modification ever since (Table II).

P.W. was discharged home in August 1964, aged 4 months, and has been readmitted on 7 occasions for periods varying from 2 days to 1 month for recheck and further study. She is now 2 years and 3 months of age and is in excellent health (Fig. 1). She weighs 11·8 kg. and measures 86 cm., she walks, talks, feeds herself, and plays normally with other children. She has, as yet, not gained full control of her sphincters. Routine examination was normal apart from an occasional erythematous rash in the napkin area and some degree of genu valgum.

TABLE I

Blood Plasma Levels of Sulphur-containing Amino Acids (mg./100 ml.) in Patient

Age	Methionine	Cystine	Homocystine
1 dy.	0·8	1·0	ND
3 dy.	1·5	1·2	0·4
9 dy.	26·8	0·4	1·2
3 wk.	0·4	0·6	0·07
5 wk.	0·7	Tr.	ND
2 mth.	0·7	0·3	ND
3 mth.	0·4	0·8	Tr.
4 mth.	0·6	0·6	0·02
6 mth.	0·5	0·2	0·1
7 mth.	1·7	0·2	0·1
8 mth.	9·7	0·1	0·1
9 mth.	1·6	0·2	0·3
11 mth.	1·1	1·0	Tr.
13 mth.	4·5	0·5	ND
15 mth.	4·9	ND	2·9
16 mth.	13·2	ND	1·0
16½ mth.	1·3	0·8	0·5
16¾ mth.	0·2	1·9	ND
17 mth.	0·7	0·7	ND
19 mth.	0·5	1·5	ND
20 mth.	0·7	1·2	0·1
22 mth.	1·0	0·4	0·3
24 mth.	1·2	0·3	ND
26 mth.	0·8	0·2	0·6

Tr., trace; ND, none detected.

TABLE II

Diet Schedule

Age	3-4 wk.	4-10 wk.	3-5 mth.	6-7 mth.	1-12 mth.	12-15 mth.	15-20 mth.	2 yr.
Weight (kg.)	3·5	4·5	5-6	6-7	8-9	9-10	10-11	11-12
Amino acid (g./day)								
Gelatin	10·75	13·9	13·9	18·7	23·2	18·0	12·0	9·0
Leucine	0·195	0·248	0·248	0·344	0·643	1·100	1·260	1·220
Isoleucine	0·154	0·198	0·198	0·267	0·559	0·700	0·780	0·780
Lysine	—	—	—	—	—	0·300	0·540	0·540
Phenylalanine	0·116	0·347	0·347	0·500	0·476	0·500	0·620	0·680
Tyrosine	—	—	—	0·150	0·225	0·250	0·270	0·270
Cystine	0·081	0·329	0·329	0·590	0·850	0·850	0·850	0·850
Ca cystinate	—	—	—	—	0·500	0·475	0·475	0·475
Threonine	—	—	—	—	—	0·450	0·560	0·560
Tryptophan	0·116	0·149	0·149	0·300	0·250	0·250	0·250	0·250
Valine	0·077	0·099	0·099	0·134	0·389	0·700	0·830	0·830
Histidine	—	0·300	0·300	0·360	0·270	0·400	0·800	—
Milk (ml.)	—	50	50	250	100	100	60	60
Vegetable	—	—	3 tsp. carrot	3 tsp. carrot	Amounts equiv. to 5 mg. methionine	Amounts equiv. to 5 mg. methionine	Amounts equiv. to 10 mg. methionine	Amounts equiv. to 10 mg. methionine
Potato	—	—	—	—	170 g.	170 g.	170 g.	170 g.
Lentils	—	—	—	—	—	—	—	28 g.
Cereal	—	—	3 tsp. baby rice	3 tsp. baby rice	—	—	14 g. cornflakes	14 g. cornflakes
Fruit	—	—	Apple *purée*	Apple *purée*	Various in average amounts	Various in average amounts	Various in average amounts	Various in average amounts
Arachis oil (ml.)	28	36	40-48	48-56	40	45	50	—
Sucrose (g.)	45	58	65-78	78-90	100-110	110-120	120	—
Mineral mix	8	11	12	12	12	12	12	—

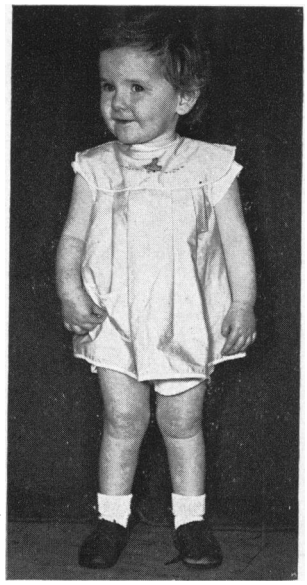

FIG. 1.—*P.W. aged 2 years.*

The last assessment of her intelligence (July 1966) gave a quotient of 97 (Stanford Binet). By the time she started the Stanford Binet test she was showing signs of tiredness and the psychologist commented on this and stated that, 'There is no doubt that Patricia continues to make normal progress, she is lively, talkative and active and plays well with materials that interest her. She is obviously accustomed to being the centre of attention and likes to have her own way. Her difficulties in the future may be more emotional than intellectual.' A careful ophthalmic review (March 1966) (Professor C. I. Phillips) revealed 'normal discs and fundi. No sign of dislocated lens or cataracts.' Skeletal radiographs did not show any abnormal bony changes and the estimated bone-age was approximately 2 years. The most recent blood platelet stickiness, measured by Dr. C. Bray of the London Hospital, was 72% and was considered to be well within the normal range of this technique (McDonald, Bray, Field, Love, and Davies, 1964). All the EEG examinations have been normal.

The urinary amino acid chromatograms were normal, but we have constantly noticed a degree of proteinuria, and electrophoretic examination of the urinary protein (carried out by Dr. H. S. Platt) showed this to be of tubular origin. A careful renal review was undertaken. There was no evidence of infection: after fasting for 20 hours the urinary specific gravity was 1016, and following a loading dose of ammonium chloride (100 mg./kg. body weight) the urine *p*H was 6·4, with an ammonia excretion of 17·5 μEq/min. This suggests some disturbance of renal tubular function. Liver function tests and serum electrolyte determinations were normal. At this time, the blood count showed Hb 8·2 g./100 ml., the white cell and differential count being normal.

Diet. The amino acid feed was based on the formula suggested by Westall (1963) for the dietary treatment of maple syrup urine disease. Gelatin, a protein which is deficient in methionine and branch chain amino acids, was the main constituent, to which were added certain essential amino acids and cystine but not methionine (see Appendix). Fat, carbohydrate, minerals, and a full complement of vitamins were also incorporated (Appendix). The initial feed provided 28 mg. methionine and 24 mg. cystine per kg. body weight. This diet quickly reduced the plasma methionine level to within normal range, and it was soon necessary to increase the methionine intake to 35 mg./kg. by the addition of 50 ml. milk each day. The plasma cystine levels remained low at this time, so the intake was increased from 24 to 76 mg./kg. This had little effect. We wondered whether this might be due to poor absorption of cystine in the gut because of its low solubility, so, at 6 months, the more soluble calcium cystinate (72% cystine equivalent) was given increasing the total cystine intake to 121 mg./kg. At this time, with the addition of 100 ml. of milk each day, the methionine intake was at its highest (42 mg./kg.).

The daily intake of the respective amino acids was in all cases, other than methionine, above the suggested intake necessary for growth (Table III), and at the 17th

TABLE III

Amino Acids Provided by Diet at Different Ages of Patient (mg./kg. body weight)

Amino Acid	Ages								Suggested Requirement*
	1 mth.	1-3 mth.	3-5 mth.	6-7 mth.	9-12 mth.	12-15 mth.	15-20 mth.	2 yr.	
Methionine	28	24	35	42	34	25	18	19	
Cystine	24	73	76	121	108	133	124	70	
Leucine	140	140	206	255	187	205	187	204	150
Isoleucine	86	86	124	160	116	128	112	142	119
Lysine	118	110	162	206	158	138	120	140	103
Phenylalanine	94	138	171	219	170	114	103	120	90
Threonine	56	56	83	112	79	103	93	103	87
Tryptophan	33	33	42	48	57	33	30	29	22
Valine	88	88	134	173	124	145	134	149	105
Histidine	20	87	98	108	60	65	80	70	34
Tyrosine	9	9	36	78	54	54	44	57	

* Holt and Snyderman (1965).

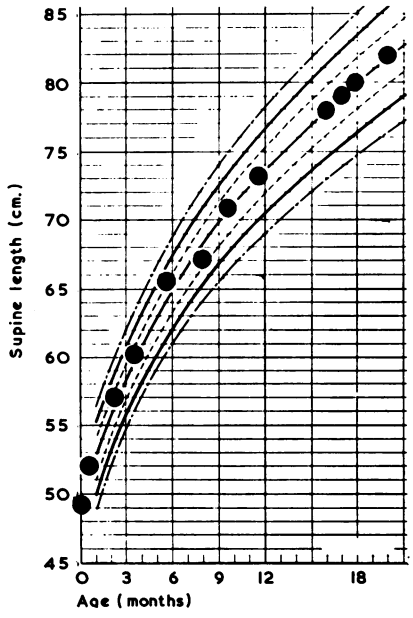

FIG. 2.—*Growth chart for first 20 months of life.*

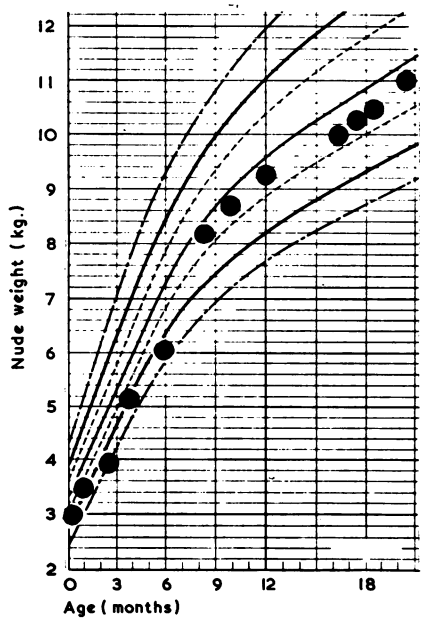

FIG. 3.—*Weight chart for same period.*

month, a three-day nitrogen balance was positive. (The balance was determined by making estimations of urinary nitrogen and then adding a further 10% of this amount in respect of faecal nitrogen.) During this time the diet was supplemented with milk, some baby rice, strained carrot, protein-free bread as produced for phenylketonuria, and apple *purée*. When she was 9 months of age P.W. began to reject the arachis oil in the mixture and on February 1, 1965, the daily amount was reduced to 4 ml./kg. and extra carbohydrate given in its place. The plasma level of methionine was generally within satisfactory limits, but there were unexplained rises which were hard to understand. We eventually found that a friend of the family, for reasons of compassion, was feeding P.W. with extra titbits.

During the earlier part of the second year it was evident that P.W.'s need for methionine was diminishing and an intake of about 20 mg./kg. was satisfactory. In November 1965 (P.W. aged 19 months) we stopped the vitamin and mineral mixtures hitherto given, and prescribed syrup Ketovite, 4 ml. b.d. and tablet Ketovite one b.d. This supplied all the previously administered vitamins and growth factors with the exception of p-amino benzoic acid. Effervescent calcium tablets containing 1 g. calcium daily were introduced at the same time: it was considered that the other minerals would be present in the more varied diet she was taking at this time. When she was 2 years old she began to show some resistance to taking her mixture in liquid form. A major dietary adjustment was made. The dry mixture was made up in the form of sugar-coated gelatin sweets flavoured with orange or black-currant. This was an extremely successful move, our only concern was to prevent the child consuming too many 'sweets'. In addition, the diet included milk 60 ml., cooked potato 180 g., vegetables 180 g., lentils 30 g., cornflakes 15 g., and protein-free rusks and bread, and fruit. A second nitrogen balance, carried out while on this régime, showed that she was in good positive balance. During a 48-hour period of observation the nitrogen intake was 8·3 g., and the retention was 3·36 g. This was a complete balance, including determination of both urine and stool nitrogen.

Comment

This two-year experience of feeding a low-methionine diet is encouraging. It has been possible to maintain satisfactory, if not ideal, control of the plasma levels of methionine and homocystine (Table II). Although the cystine levels were low for several months, the child has grown well (Fig. 2 and 3), and the more recent levels have been nearer the normal range. Her physical and mental development has been normal, and so far, apart from a tendency to show genu valgum, there are no signs of the more serious stigmata of homocystinuria. It was particularly gratifying to find that in her most recent test there was no sign of increased platelet stickiness. Her mother is convinced that P.W. at this age is much brighter than were her affected but untreated sibs and is very like her normal sisters. Nevertheless, one must remember that several of the children reported on earlier were apparently normal for the first few years of life (Komrower and Wilson,

1963) and for this reason considerable reservations must be made in respect of the long-term prognosis. We have been encouraged to try a modified diet in two cases where fits were a feature of the clinical picture, with encouraging results, as the fits were controlled more easily, and, in one case, the general development was noticeably advanced. At the present time, it is our intention to maintain this low-methionine diet indefinitely. We feel that the widespread physical disturbance, which would seem to be progressive in the absence of any dietary therapy, demands such an approach.

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Appendix: A Suggested Low-methionine Diet for a Newborn Homocystinuric Child and Instructions for Preparing the Feed

Amino acid mixture	mg./kg. supplies
Gelatin 560 g. +	
Leucine 10 g.	160
Isoleucine 10 g.	105
Valine 4 g.	100
Phenylalanine 6 g.	105
Tryptophan 6 g.	36
Threonine, none	66
Lysine, none	127
Methionine, none	23
Cystine 10 g. / Calcium cystinate 10 g.	94
Calcium pantothenate 0·56 g.	

All the above substances are very carefully mixed together and are fed at the rate of 3·3 g. per day for each kilogram body weight.

Mineral mixture

Calcium lactate 450 g., calcium chloride ($CaCl_2$, $2H_2O$) 30 g., dipotassium hydrogen phosphate 150 g., disodium hydrogen phosphate 100 g., magnesium sulphate 80 g., potash alum 3 mg., sodium molybdate 3 mg., ferrous sulphate 2 g., copper sulphate 200 mg., zinc chloride 200 mg., manganese sulphate 200 mg., potassium iodide 8 mg., and cobalt sulphate 3 mg.

After very careful mixing the mineral mixture is fed at the rate of 2·5 g. per day for each kilogram body weight.

In addition, per kilogram body weight; Arachis oil 8 ml.; sucrose 13 g.; vitamin mixture 1 Abidec 0·6 ml.; and vitamin mixture 2 1·0 ml., as follows: folic acid 25 mg.; choline chloride 3·75 g.; p-amino-benzoic acid 50 mg.; inositol 50 mg., biotin 2·5 mg., vitamin B12 500 μg., all dissolved in 50 ml. of water and kept unfrozen in a refrigerator.

Alternative to vitamin mixture (1) and (2): syr. Ketovite 4 ml. b.d. and tab. Ketovite, 1 crushed tablet daily.

When mineral mixture is stopped calcium must be added to the diet. Calcium Sandoz effervescent 1 tab. t.d.s. will provide 1·14 g. elemental calcium and 50 mg. vitamin C.

Amino acid and gelatin 'sweets'. (See Table II). (Miss J. Coutts, S.R.D., Royal Manchester Children's Hospital). For each 10 g. gelatin in mixture, 25 ml. well-flavoured syrup, e.g. 20 ml. Ribena + 5 ml. water, or 20 ml. concentrated orange squash + 5 g. sugar.

Method. Put the gelatin + amino acid mixture in a small pan with the required amount of syrup, bring it to the boil, stirring continuously, and allow it to boil for a moment. Withdraw the pan from the heat and cool it, stirring the contents occasionally to keep the undissolved amino acids in suspension until the mixture starts to thicken, when it should be poured into a tray or small moulds such as foil bottle tops. When set turn the jelly

on to sugar and divide it into appropriate doses, making sure that each 'sweet' is covered with sugar.

Directions for preparing the diet. Assuming that the infant weighs 3 kg. Quantities to be increased as the child's weight increases (see diet sheet).

Equipment: 1 ½-pint pyrex measure
1 100 ml. measuring cylinder
1 Dropper - marked to 1 ml. in 0·2 ml. graduations
1 5 in. glass funnel
1 glass storage bottle (1 litre)
1 food mixer (Kenmix or similar)

Ingredients: 24 ml. arachis oil
40 g. sucrose
1 teaspoon acacia powder
10 g. Amino-acid mixture
7·5 g. Mineral mixture
*0·6 ml. Vitamin solution 1 (Abidec)
*1·0 ml. Vitamin solution 2

Method. Place in ½-pint measure—the measured quantity of arachis oil, the acacia powder, and about 150 ml. (5 oz.) of boiling water. Stir and pour into mixer. Switch to half speed and run for about ½-1 min. Place in ½-pint measure—the Amino acid mixture, the Mineral mixture, and fill to the ½-pint mark with boiled water. Stir until the solids are mostly dissolved and pour into the mixer and run at half speed for 1 min. Pour the contents of the mixer into the stock bottle and add boiled water to a final volume of 500 ml.

When cool add the vitamin solutions and shake to mix. Store in refrigerator. Give as feeds, 100 ml. × 5. Warm before feeding.

* The amounts of the vitamin solutions need not be increased as are the other components of the mixture as the infant increases in weight.