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Anemia
growth
hypoproteinemia
malnutrition
mental retardation
phenylalanine
phenylketonuria
rickets

Malnutrition with Early Treatment of Phenylketonuria

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Extract

Thirty-two children with phenylketonuria in whom dietary therapy was started prior to 6 months of age are reviewed. Evidence of profound malnutrition during year 1 of life, demonstrated by deficient growth, anemia, hypoproteinemia, roentgenographic bone changes, and various clinical symptoms, was found in three patients. In two of these patients, the malnutrition was quickly corrected; present intelligence levels in these patients are dull normal. The third patient, however, suffered prolonged malnutrition and the present IQ is only 50. Signs of less severe but prolonged malnutrition were found in 16 patients with phenylketonuria despite apparently adequate diets and adequate levels of phenylalanine in serum. Three of these are retarded, five are borderline, six are in the dull normal intelligence range, and two are normal.

In 13 recently diagnosed cases of phenylketonuria, more liberal amounts of phenylalanine and protein were given that resulted in moderate elevation of phenylalanine levels in serum. No evidence of malnutrition was found in these children and present IQ tests showed that none was testing retarded or borderline; four were rated as dull normal and nine were normal.

Speculation

The possibility is raised that mental retardation was produced by early malnutrition from too vigorous application of dietary therapy in phenylketonuria. It is suggested that more liberal diets would prevent this malnutrition and that despite moderate elevation of phenylalanine levels in serum, ultimate intellectual function will be improved.

Introduction

Many favorable reports have been published on the value of a low phenylalanine diet in the treatment of phenylketonuria (PKU) [2, 3, 8, 15, 20, 34, 38, 39, 41]. The enthusiasm of early workers has been tempered by more critical assessment of long-term results [5–7, 9, 24, 29, 37].

Mass screening of newborns for phenylketonuria now results in most patients beginning dietary treatment during the first few weeks of life. Little attention has been paid to the hazards of feeding a synthetic low phenylalanine diet to young infants although at least seven deaths [6, 21, 23, 24, 31, 48, 53] associated with, but not necessarily caused by, such diets have been reported. Various complications of dietary treatment have been described including peculiar roentgenographic bone changes [8, 25, 26, 44], vacuolization of

red cell precursors in the bone marrow [35, 57], megaloblastic anemia [53], hypoglycemia [21, 23], hypoproteinemia [32], 'phenylalanine deficiency syndrome' [11, 52, 63], poor weight gain [43, 63], cutaneous lesions [52, 63], and impaired antibody responses [62].

A number of authors admit that weight gain and linear growth of their treated patients has been retarded [1, 6, 13, 35, 41, 57], while others state that these indices have been maintained within the normal range [7, 8, 32, 61]. Though it has been reported that untreated patients with phenylketonuria are small in stature [27, 36, 45], no data have been presented to support this claim and others have even challenged this statement [26, 56].

ROUSE [52] described two infants, erroneously fed a low phenylalanine diet on the basis of false positive screening tests, who later developed the 'phenylalanine deficiency syndrome'. They were subsequently found not to have phenylketonuria and were returned to a normal diet. Despite improvement in nutritional status, their intellectual progress has so far remained slow.

In 1963–1965, a number of reports suggested that malnutrition in the first 6 months of life resulted in permanent subnormal mentality despite correction of the malnutrition [12, 17, 18, 55, 60]. Malnutrition in older children, however, did not induce this permanent brain damage. We became concerned that these findings might apply to our young (under 6 months) infants receiving dietary treatment for PKU.

Evidence that malnutrition in the first 6 months of life may produce permanent subnormal mentality continues to accumulate [67, 68].

In late 1965, we became dissatisfied with the progress of our patients who had received early treatment for phenylketonuria. Nearly all had poor weight gain and linear growth despite diets that maintained the phenylalanine levels in serum at concentrations considered adequate (table I). The intelligence quotients were not as high as expected. Three patients developed profound malnutrition before 6 months of age. We wondered if our treatment was producing permanent mental retardation due to malnutrition caused by too vigorous restriction of phenylalanine and protein during the early months of life.

This paper presents data on 32 patients in whom dietary therapy was started prior to 6 months of age and who are now 2 years of age or over.

Materials and Methods

Dietary treatment of phenylketonuria was started in our clinic in 1958; at present we have in our care 89 patients, the 32 reported in this paper, 46 in whom dietary treatment was not started until after 6 months of age, and 11 who are at present too young (under 2 years) for adequate DQ/IQ assessment. During the early stages of therapy, patients on diet therapy were seen in the clinic every 1 or 2 weeks. The interval was gradually extended to every 2 or 3 months in the older child, depending on their control and response to treatment.

Urine Phenistix [69] and Guthrie tests [28] using heel-prick blood, as well as determination of quantitative serum phenylalanine levels by the fluorometric method of MCCAMAN and ROBBINS [42] were performed at each visit (before 1963 the method of UDENFRIEND and COOPER [64, 65] was used). For the past 18 months, parents have cooperated by collecting blood specimens for Guthrie tests twice weekly at home. In addition, levels of hemoglobin and serum proteins were determined and long bone roentgenograms, and other appropriate investigations were performed at various intervals. The parents and patients were interviewed by a nurse, a dietitian, a psychologist, and a pediatrician during each visit. Psychological tests used were the Cattell, the Stanford-Binet, and the Wechsler scales [70].

From 1958 to 1963, the aim of our treatment was to maintain the fasting phenylalanine levels in serum within the normal range of 1–3 mg/100 ml; from 1963 to 1965 we allowed values up to 5 mg/100 ml. Early studies [46] had suggested that the intake of 25 mg phenylalanine/kg/24 h provided by Lofenalac [71] alone would be sufficient to maintain these levels and at the same time allow for optimal growth, but we found that at least 50 mg phenylalanine/kg/24 h, obtained by adding small amounts of whole milk, were always necessary in young infants. Despite monitoring the phenylalanine levels in serum every 1–2 weeks in the early months, great difficulty was found in preventing intermittent low phenylalanine readings. Growth was not satisfactory.

Because of our observations in these early patients, we changed our treatment in late 1965 to allow fasting phenylalanine levels in serum between 5 and 15 mg/100 ml. Most concentrations are now between 8 and 12 mg/100 ml. This was achieved by providing 50–100 mg phenylalanine/kg/24 h during year 1 of life.

Results

The 32 cases in this study can be considered conveniently in three groups (table I). Group 1, 3 infants who manifested profound malnutrition during the early treatment period; group 2, 16 infants, most of whom showed less severe but nevertheless definite and prolonged evidence of malnutrition; and group 3, 13 in-

Table I. Relation of age of diagnosis, IQ, phenylalanine values, and evidence of early malnutrition in 32 patients treated for phenylketonuria

Patient	How diagnosed[1]	Age treatment started	Present age	Present IQ	Deficient growth[2]	Hypoproteinemia	Anemia	Clinical signs[3]	Radiological changes: Spicules	Radiological changes: Osteoporosis	Radiological changes: Retarded bone age	Growth retardation lines	Serum Phenylalanine values in first 6 months of life: Serum, mg/100 ml <1	Serum, mg/100 ml 1–5	Serum, mg/100 ml 5–10	Serum, mg/100 ml >10	Guthrie, mg/100 ml <2	Guthrie, mg/100 ml 2–5	Guthrie, mg/100 ml 6–15	Guthrie, mg/100 ml >15
Group 1																				
DJ	Sc	2 wk	3.75 yr	86	+	+	+	+	—	Mod	—	—	3	14	8	2	–	–	–	–
CW	Sib	2 month	4 yr	80	+	+	+	+	+	Mild	+	+	3	4	2	1	–	–	–	–
TRu	Sib	5 day	6 yr	50	+	+	+	+	+	Mod	+	+	3	5	0	0	–	–	–	–
Group 2																				
PF[4]	Sib	4 month	7 yr	42	+	?	?	—	?[5]	?[5]	+	+	0	2	0	0	–	–	–	–
TRo	OS	5 month	6.5 yr	61	+	?	+	+	—	Mild	+	+	1	2	0	1	–	–	–	–
SC	OS	2 month	6 yr	73	+	+	+	+	+	Mild	+	+	1	4	0	0	–	–	–	–
GRu	OS	2 month	7 yr	74	+	?	+	—	—	Mild	—	+	1	3	0	0	–	–	–	–
MH	Sib	2 month	11 yr	85	—	?	+	—	?[5]	?[5]	—	+	0	4	0	0	–	–	–	–
AF	Sib	1 month	8.25 yr	91	+	?	?	—	—	—	—	—	2	1	0	0	–	–	–	–
DE	OS	2 month	5.25 yr	86	+	?	?	+	+	Mod	—	—	1	5	0	0	–	–	–	–
LB	Sib	2 wk	8 yr	86	+	+	+	+	—	Mod	—	+	1	0	2	0	–	–	–	–
BD	Sib	5 day	5.5 yr	84	+	?	+	+	+	Mod	+	—	2	5	0	0	–	–	–	–
GH	Sib	2 month	5 yr	72	+	—	—	+	—	Mild	—	—	1	7	0	0	–	–	–	–
RK	Sib	3.5 month	7.75 yr	84	+	?	+	—	?[5]	?[5]	—	+	1	1	0	0	–	–	–	–
KJ	Sib	5 day	3.5 yr	86	—	?	?	+	—	—	+	—	0	4	1	5	–	–	–	–
TC	Sib	4 day	5.5 yr	78	+	?	?	+	+	Mild	—	—	2	4	0	0	–	–	–	–
RC	Sib	5 day	4.75 yr	78	+	?	?	+	—	Mild	—	—	1	7	2	0	–	–	–	–
RS	Sib	5 day	4.5 yr	90	+	?	?	—	—	Mild	+	—	0	7	0	0	–	–	–	–
KiMc	Sc	2 wk	3 yr	86	—	—	—	—	—	—	—	—	0	7	1	1	–	–	–	–
Group 3																				
PT[6]	Sc	1 wk	26 month	80	—	—	—	—	—	—	—	—	1	3	1	0	8	28	3	0
KaMc	Sc	11 day	2.5 yr	94	—	—	—	—	—	—	—	—	1	5	1	1	2	10	14	1
JT[6]	Sc	1 wk	26 month	88	+	—	—	—	—	—	+	+	0	4	1	0	9	24	2	1

CWi	Sc	1 month	31 month	81	+	?	—	—	—	+	—	0	4	0	3	8	2	23	9
DG	Sc	2 month	25 month	102	—	—	—	—	—	—	—	0	1	0	2	2	10	19	6
SH	Sc	3 wk	2.5 yr	96	—	—	—	—	—	—	—	0	2	2	4	0	4	21	6
SeH	Sc	1 wk	2.5 yr	94	—	—	—	—	—	—	—	0	4	2	2	5	6	30	0
AK	Sib	1 month	24 month	85	—	—	+	—	—	—	—	0	1	2	1	6	7	19	5
SG	Sc	1 wk	2 yr	101	—	—	—	—	—	—	—	0	1	3	1	7	13	23	9
JF[6]	Sc	1 month	25 month	91	—	—	—	—	—	—	—	1	0	3	0	4	6	27	0
KK[6]	Sc	6 wk	25 month	121	—	—	—	—	—	—	—	0	1	1	1	5	23	5	0
JMacD	Sib	1 wk	3 yr	112	—	—	—	—	—	—	—	0	3	1	2	2	15	18	0
TMc	Sc	1 month	2.5 yr	103	—	—	—	—	—	—	—	0	2	2	0	8	13	10	0

[1] Sib, sib of known phenylketonuric; Sc, newborn screening (Guthrie); OS, office screening ($FeCl_3$).
[2] Deficient growth is defined as weight and height curves falling below the 3rd percentile during year 1 of life or a drop of more than 25 percentile points.
[3] Clinical signs are anorexia, vomiting, diarrhea, and fever of unknown origin.
[4] Mother had phenylketonuria.
[5] Roentgenograms not taken until patient was 2.5 years of age or older.
[6] Atypical phenylketonuria.

fants diagnosed within the past 3.5 years, who have been given more liberal allowances of phenylalanine and protein in their diets. In these we have found little evidence of malnutrition.

Group 1

Case no. 1 (DJ). This infant had a positive Guthrie screening test at 4 days of age; at 2 weeks of age, the phenylalanine level in serum was 82 mg/100 ml. She was fed a diet of Lofenalac and whole milk to provide 50 mg phenylalanine/kg/24 h and was discharged from the hospital at 1 month of age with a phenylalanine level of 9.6 mg/100 ml.

She was readmitted at 3 months of age with anorexia, vomiting, diarrhea, and poor weight gain (fig. 1). At this time she was receiving 35 mg phenylalanine/kg/24 h. This was gradually increased to 60 mg/kg/24 h. She became dehydrated and was in a state of electrolyte imbalance. Protein levels in serum fell to 3.72 g/100 ml (albumin 1.14 g/100 ml, globulin 2.58 g/100 ml) and her hemoglobin level dropped to 9.5 g/100 ml despite supplemental iron. Long bone roentgenograms revealed osteoporosis, metaphyseal cupping with spicules, and marginal beaking. Her condition continued to deteriorate and at 4 months of age she was fed whole milk for a 2-week period. During this time phenylalanine concentration rose to 30 mg/100 ml, all clinical symptoms disappeared, and serum electrolyte, proteins, and hemoglobin levels gradually returned to normal.

Fig. 1. Weight curves of patients in group 1 (note that only *patient TRu* had evidence of prolonged malnutrition).

At the end of this period, a low phenylalanine diet was reinstituted providing 100 mg phenylalanine/kg/24 h. She has remained well and maintains phenylalanine concentrations in serum from 5 to 10 mg/100 ml. Her most recent IQ, at 3 years of age, was 86.

Case no. 2 (TRu). This patient, the sibling of a child with phenylketonuria, had phenylalanine levels in serum of 18 and 36 mg/100 ml on days 4 and 5 of life. He was fed a diet containing 25 mg phenylalanine/kg/24 h and 4 weeks later the phenylalanine was increased to 50 mg/kg/24 h. Despite this increase he did poorly. During the first 8 months of his life he suffered from recurrent febrile episodes and required hospitalization three times. At 6 months of age he was admitted with vomiting, diarrhea, lethargy, skin rash, anorexia, and edema. Protein levels in serum were 3.82 g/100 ml (albumin 1.49 g/100 ml, globulin 2.33 g/100 ml) and the hemoglobin level was 7.8 g/100 ml. Roentgenograms of hands, wrists, and knees showed mild osteoporosis, cupping and lipping, and metaphyseal spicule formation in the radius and ulna (fig. 2). When fed a diet containing 75 mg phenylalanine/kg/24 h he gradually improved. His most recent IQ, at 6 years of age, was 50. The home situation was poor in this family and may well have been an additional contributing factor to his poor development.

Case no. 3 (CW). Phenylketonuria was detected at 2 months of age and she was fed a diet providing 40 mg phenylalanine/kg/24 h. Her growth and development appeared satisfactory until 6 months of age when she suddenly developed a rash, edema, and failed to gain weight. Levels of protein in serum were 3.8 g/100 ml (albumin 1.5 g/100 ml, globulin 2.3 g/100 ml) and phenylalanine concentrations ranged from 1 to 1.8 mg/100 ml. She had hypochromic anemia with a hemoglobin of 6.5 g/100 ml. Roentgenograms revealed diffuse osteoporosis of radius and ulna with typical spicular changes. The dietary phenylalanine was increased to 75 mg and later to 100 mg /kg/24 h and at the end of 2 weeks the level of proteins in serum had risen to 5.2 g/100 ml and hemoglobin to 8.2 g/100 ml. She improved gradually and her most recent IQ, at 4 years of age, was 80.

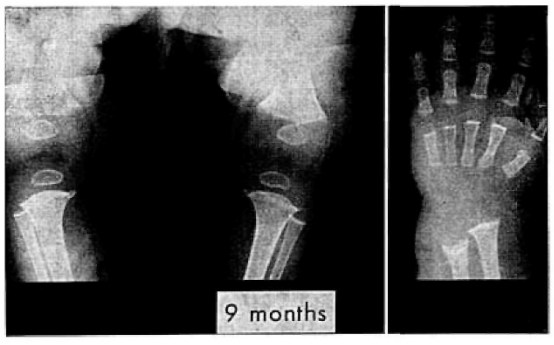

Fig. 2. Hand and knee roentgenograms of *patient TRu* (group 1) showing mild osteoporosis, cupping of the ulna and fibula, and marginal spur formation. Metaphyseal spicules are noted at the ends of the radius and ulna.

Group 2

These infants showed less profound but definite evidence of malnutrition; therefore, alerted by our experience with the infants of group 1, we looked, retrospectively, in 1965, at the remainder of our children with phenylketonuria in whom treatment was started early in life. Group 2 comprises the remaining 16 infants treated prior to 6 months of age up to late 1965.

Evidence of malnutrition in early infancy in these 16 patients was revealed by the following (table I): *1)* Growth retardation (defined here as weight and height curves dropping below the 3rd percentile in year 1 of life, or a drop of 25 or more percentile points during this period), exhibited by 13 of 16 patients in this group (fig. 3). *2)* Episodes of vomiting, diarrhea [10], anorexia, and unexplained fever found in 9 of the 16 children. *3)* Hypoproteinemia, in two of four patients studied. *4)* Seven of nine tested had refractory anemia. *5)* Fasting blood sugars were measured in four

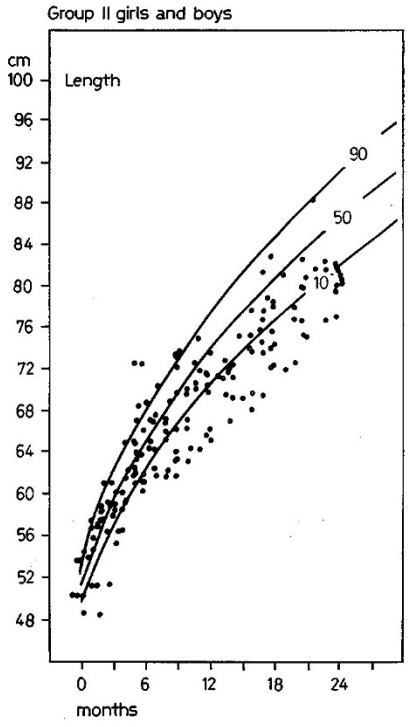

Fig. 3. Linear growth chart of patients in group 2.

infants on six occasions; all were normal. Extensive investigations neither of levels of serum proteins and amino acids nor of bone marrow were performed. *6)* The most striking and consistent findings aside from growth failure were the roentgenographic changes (fig. 4). In three children no roentgenograms were made until they were 2.5 years of age or older. At this time, X-ray films showed only lines of growth retardation in two, and retarded bone age in one. Of the remaining 13 patients, *a)* 4 had metaphyseal spicules [25, 26], *b)* 10 had osteoporosis, *c)* 4 had retarded bone age, *d)* 4 had lines of growth retardation, and *e)* X-ray films made at the time of diagnosis (i.e., before treatment) in 12 children were normal. In short, all but three of group 2 had roentgenographic evidence of osteoporosis with or without other bony changes during year 1 of life. Review of all phenylalanine determinations in serum during year 1 of life showed that 14% were less than 1 mg/100 ml; 66% were between 1 and 4 mg/100 ml; and 20% were over 4 mg/100 ml (also see table I).

When these moderately malnourished infants became older the problems of anemia, diarrhea, and vomiting resolved without special treatment and the roentgenographic changes gradually disappeared. Weight gain and linear growth improved, so that by 2 years of age most had reached at least the lower range of normal for age. Phenylalanine requirements changed at age 18–24 months to 25–30 mg/kg/24 h.

At present, the 16 patients of group 2 are 3–11 years old and recent IQ testing has shown 2 to be in the normal range, 6 dull normal, 5 borderline and 3 retarded (table II). The diagnosis of phenylketonuria was delayed in two (*PF* and *TRo*) of the three retarded children. One child *(PF)*, in whom the condition was not diagnosed until 4 months of age, now has an IQ of 40. He may have suffered intrauterine brain damage as his mother is a homozygous phenylketonuric.

Group 3

As a result of the findings in groups 1 and 2, we changed our treatment in late 1965 to allow fasting phenylalanine levels in serum to be maintained between 5 and 15 mg/100 ml. This required the provision of 50–100 mg phenylalanine/kg/24 h during year 1 of life.

With this more liberal diet, 2 of the 13 patients in group 3 have shown roentgenographic changes but none have had hypoproteinemia or anemia. Two have had brief episodes of deficient growth and one has had episodes of diarrhea and anorexia quickly corrected by dietary adjustments (usually made by adding more whole milk to the formula preparation).

Intelligence quotient testing of patients in group 3, at age 25–36 months, show nine normal, four dull normal, no borderline, and no retarded children (table II).

The improved results in these patients must be interpreted with caution for several reasons. The IQ of the patients in group 3, still only 25–36 months of

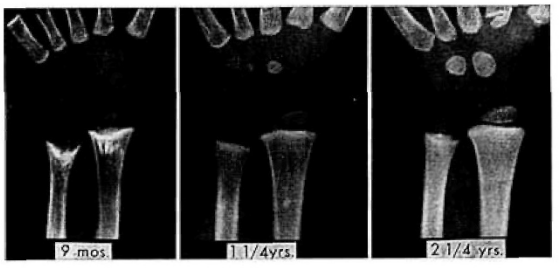

Fig. 4. Serial wrist roentgenograms of *patient DE* (group 2) showing osteoporosis, metaphyseal spicules, and cupping. Irregular linear densities in the metaphysis are present. All conditions improving with age.

Table II. Analysis of present IQ levels of infants fed the more restricted diets (groups 1 and 2) compared with those fed the more liberal diet (group 3)

IQ	Groups 1 and 2 (all classical PKU)		Group 3	
	Diagnosed before 2 months of age	Diagnosed after 2 months of age	Classic PKU	Atypical PKU
Normal, 90+	2	0	6	3
Dull normal, 80–89	8	1	2	2
Borderline, 70–79	5	0	0	0
Retarded, < 70	1	2	0	0
	19		13	

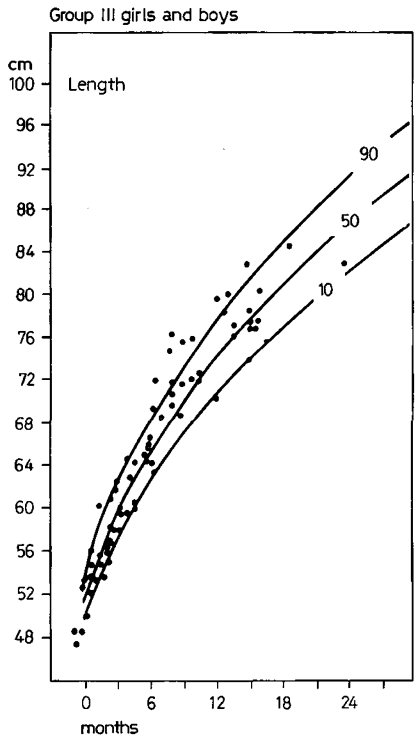

Fig. 5. Linear growth chart of patients in group 3.

age, may not be predictably valid. The average age of diagnosis of the patients in group 3 was less than those in groups 1 and 2, and 5 of the 13 infants in group 3 are mild (atypical) phenylketonurics needing only moderate dietary restriction. Indeed two of them, 25 and 33 months of age, respectively, are now fed an unrestricted diet, and have blood phenylalanine levels ranging from 8 to 18 mg/100 ml. These five mild 'atypical' patients, however, do not fulfill the present criteria for atypical PKU (i.e., initial phenylalanine values in serum of never over 20 mg/100 ml [32]) as their initial levels were all over 30 mg/100 ml (31.8–38.5 mg/100 ml).

Discussion

Of the three children showing major manifestations of malnutrition, two suffered only for relatively brief periods and malnutrition was quickly corrected. The subsequent progress of these two has been fairly satisfactory. Their intelligence so far is in the low normal range. The third patient in group 1, *TRu*, had a more prolonged and recurring problem (fig. 1) with malnutrition and at present has an IQ of 50, at 6 years of age. His sibling, in whom the diagnosis was made at 2 months of age, has an IQ of 74 at 7 years of age. Two similar cases have been described in the literature [4, 57].

The 16 infants in group 2, though less seriously affected, usually had evidences of prolonged nutritional deprivation shown chiefly in their growth charts and roentgenograms (figs. 2 and 3).

HOLT and ALLEN [30], in a study of 32 children who were treated for phenylketonuria, noted osteoporosis in one-half and retarded skeletal maturation in one-third. Twelve of their cases under 3 years of age had bony spicules, nine of these patients were under 1 year of age.

That malnutrition in early infancy causes permanent intellectual deficiency [12, 17, 18, 55, 60] is so far only speculation. We cannot prove that the malnourished state produced in the young infants we fed phenylalanine-restricted diets has been harmful. A false diagnosis of phenylketonuria in a number of infants led to their being fed low phenylalanine diets for periods of 12–24 months [4, 11, 16, 52, 54]. Mental development in some of these children has been retarded. It is possible that this is due to iatrogenic malnutrition in the early months of life.

Experimental work has shown that poor myelinization, one of the pathological findings resulting from malnutrition, can be produced by subjecting animals to minimal degrees of malnutrition during the period of maximum myelinization [19]. Also, nutritional deprivation during the early life of a rat is associated with a decreased synthesis of sulfatide (a component of myelin) and this decreased synthesis is not corrected by refeeding [14].

BESSMAN [6] has pointed out that a much larger number of untreated phenylketonurics than originally estimated may have normal intelligence. Since severe degrees of malnutrition in infancy may cause permanent intellectual deficit, care should be exercised in controlling the phenylalanine levels in serum to avoid producing malnutrition lest the treatment be as damaging as the disease.

During the early history of dietary therapy, some authors [46] suggested that 25 mg phenylalanine/kg/24 h were sufficient to maintain normal blood levels and also normal growth in young infants with phenylketonuria. This has proved fallacious and most workers now recommend an intake of at least 50 mg/kg/24 h in the early months of life. Our experience indicates that even this figure is often too low and that 50–100 mg/kg/24 h (and occasionally 125 mg) is necessary. These figures are similar to the minimal phenylalanine requirements for normal growth in nonphenylketonuric infants which were shown by SNYDERMAN and HOLT [58] to be 47–90 mg/kg/24 h. The average nor-

mal 5-kg infant actually receives about 300–350 mg phenylalanine/kg/24 h in the usual cows milk formula with added cereal and strained foods.

Infants fed on a wholly synthetic diet do not grow and thrive [58]. Cell growth is inhibited if the diet is low in any single essential amino acid [22]. Since whole milk must always be added to a Lofenalac diet during the first 6–12 months of life to maintain a good nutritional state, it is possible that this product is deficient in some yet undetermined nutrient.

There is some indirect evidence that levels of serum phenylalanine of up to 10–15 mg/100 ml may not be harmful to young infants. As yet, mental retardation in children with untreated transient hyperphenylalaninemia has not been reported. Gross disruption of related amino acids and metabolites does not occur until the phenylalanine levels in serum are over 12–15 mg/100 ml. Many of the untreated phenylketonurics with a high IQ have relatively low phenylalanine levels [33] and a number of these individuals have given birth to normal children.

For these reasons we have permitted phenylalanine levels in serum to reach 10–15 mg/100 ml without being concerned. Perhaps as PARTINGTON [49] suggests, the virtue of a low phenylalanine diet in the treatment of phenylketonuria lies not so much in maintaining normal levels of phenylalanine in the blood but in avoiding gross elevations.

In our 32 patients with phenylketonuria, diagnosed and treated prior to 6 months of age, we were unable, with the therapeutic diet used, to maintain the fasting phenylalanine levels at, or slightly above, the normal range and at the same time avoid definite clinical, laboratory, and radiological signs of malnutrition during year 1 of life. It is possible that permanent intellectual impairment was produced as a result of this malnutrition. We suggest that malnutrition can be avoided by allowing more liberal amounts of protein and phenylalanine in the diet and that the resulting moderate elevations of phenylalanine produced no impairment of intellect. We also suggest that it is most important to monitor the phenylalanine levels in serum once or twice weekly during the first 6–12 months of life, and also to watch for evidence of malnutrition in roentgenograms, serum protein levels, hemoglobin values, and growth and height gains.

More refined techniques for the evaluation of nutrition, such as measurements of hydroxyprolines in urine [66] and growth hormone studies [50], might also be of value in assessing the efficacy of the dietary treatment of this condition.

Summary

Studies of 32 patients with phenylketonuria, in whom dietary treatment was started before 6 months of age, are reported.

Evidence of profound malnutrition during year 1 of life was found in 3 cases, and less severe but prolonged malnutrition was found in most of the patients from a group of 16 despite phenylalanine levels in serum that were within the normal ranges.

In 13 cases that were recently diagnosed, more liberal amounts of phenlyalanine and protein were given that resulted in moderate elevations of phenylalanine levels. No evidence of malnutrition was found in these children, and their present IQ test scores are higher than those of the children who were fed the more restricted diets.

The possibility is raised that mental retardation was produced by early malnutrition from too vigorous application of dietary therapy.

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