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PHENYLKETONURIA

Richard Koch

Division of Medical Genetics, Childrens Hospital of Los Angeles, Los Angeles, California 90054-0700; and University of Southern California, Los Angeles, California 90033

Elizabeth Wenz

Division of Medical Genetics, Childrens Hospital of Los Angeles, Los Angeles, California 90054-0700

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INTRODUCTION

It is now some 50 years since Äsborn Fölling identified the first case of phenylketonuria (PKU) in Norway (16). In 1953, Bickel et al (6) initiated

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dietary treatment by phenylalanine restriction (6). In 1963, Gruter noted the improvement in behavior and motor development in children when the restricted diet was initiated. "The change is always in the direction of normalization; the hyperactive children became quiet and the apathetic children became more active" (21). Since the 1960s, screening of newborns has changed the clinical outcome remarkably. Data from the National Collaborative Study of Children Treated for PKU has demonstrated that early diagnosis and treatment result in normal development (56). The major unsolved clinical problem relates to the length of treatment (54). Initially it was thought that the phenylalanine-restricted diet could be discontinued at 4–6 years of age (25). In fact in one reported series the phenylalanine-restricted diet was discontinued at age 2 years (10).

Today it seems clear that maintaining the restricted diet is preferable (26), but there is still disagreement as to how long that is necessary (24). The purpose of this review is to present the current procedures for diagnosing and managing children with phenylketonuria and to present the latest results from the National Collaborative Study of Children Treated for PKU.

COLLABORATIVE STUDY OF CHILDREN TREATED FOR PKU

The first results from dietary treatment were challenged (5) in the 1960s because these early reports were based on small sample sizes and were not controlled for placebo effect. To counter these criticisms and to delineate more clearly the treatment modalities, the need for a longitudinal study was discussed among clinicians at PKU centers in 1965 and 1966. The National Collaborative Study of Children Treated for PKU was initiated in 1967, and from 1968 to 1972, 216 infants identified on newborn screening in 19 PKU clinics across the country were enrolled. The natural protein challenge providing 180 mg/phenylalanine/kg/day for three days at three months and one year after diagnosis was utilized to discriminate classical PKU children from the variant group (7). Twenty-nine of these children were subsequently excluded from the study because they did not meet the criteria for a confirmed diagnosis of classical PKU (41). The remaining 166 children have been followed; however, more children have since been excluded because of moving, noncompliance, or death. Complete data at age 6 years is available on 134 children (29). The most recent data reported by Holtzman et al (24) show clearly that intellectual ability and academic achievement in school are affected adversely when blood phenylalanine levels are persistently greater than 15 mg/dL before the age of six years.

DIAGNOSIS OF PKU

The Collaborative Study for the Treatment of Children with PKU accepted the three following biochemical parameters, each of which must be met, as diagnostic: (*a*) two measurements of blood phenylalanine levels greater than 20 mg/dL, made 24 hours apart while the patient is on a normal diet; (*b*) blood tyrosine levels of less than 5 mg/dL; and (*c*) the presence of metabolic excretion products of phenylalanine in the urine (55). In an effort to improve early diagnosis other techniques such as (*a*) the oral phenylalanine challenge, (*b*) liver phenylalanine hydroxylase measurement, and (*c*) deuterated phenylalanine loading have been devised and studied. Despite these efforts, it is clear that a group of infants who fit the initial biochemical parameters of classical PKU do not indeed have this condition and are not as much at risk for neurological damage as the child with classical untreated phenylketonuria. This is true for the commonly accepted methods for making this diagnosis (53). Most recently the work of Woo and his associates has provided molecular genetic methods for gene analysis; however, this technique is still not in general use at present (58). These various approaches are well described elsewhere, but because of the technical aspects, oral protein challenge remains the simplest and easiest to administer and interpret and therefore is described here in more detail.

The oral protein challenge is defined as feeding protein to equal 180 mg phenylalanine per kilogram of body weight (mg phe/kg). The challenge can be done at home with cooperative competent families; otherwise hospitalization is necessary to obtain accurate data for interpretation. Baseline studies consist of blood phenylalanine and tyrosine determinations while on the restricted diet and studies for the usual metabolites of phenylalanine excreted in the urine such as orthohydroxyphenylacetic acid, phenylactic acid, phenylacetic acid, phenylpyruvic acid, and phenylacetylglutamine. After baseline specimens are obtained, the subject is fed a diet containing 180 mg/kg/day of phenylalanine in natural protein for 72 hours (49). During this three-day period, blood phenylalanine levels are obtained daily. Repeat measurements of blood tyrosine and urine for metabolites are obtained on the third day of challenge. Accurate intake for phenylalanine, protein, and calories is calculated for the baseline day and the three following days of the challenge. Sometimes a diet change such as utilized in the challenge will cause vomiting and irritability, but in the majority of patients it is well tolerated. If the goal of 180 mg phe/kg is not achieved because of the volume of the food prescribed, an intake of 150 mg phe/kg/day is usually sufficient to cause the anticipated increase in blood phenylalanine concentration.

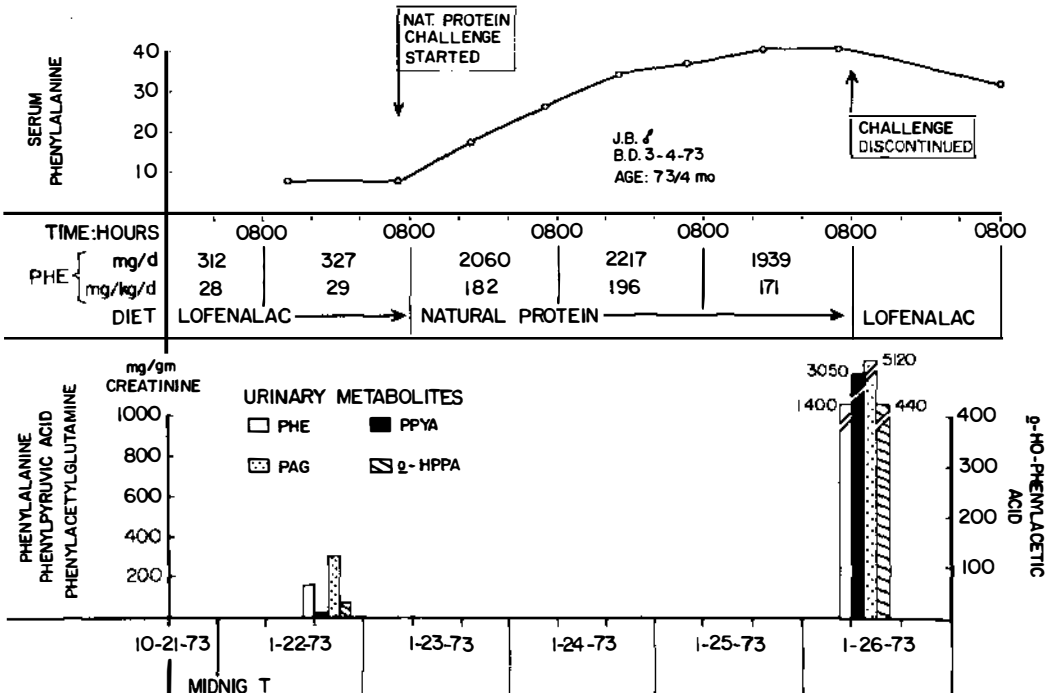

Figure 1 Natural protein challenge demonstrating the sharp rise in blood phenylalanine characteristic of an infant with classical phenylketonuria.

Figure 1 shows the response in a child with classical PKU. Note the sharp rise in blood phenylalanine and concomitant rise in urinary metabolites of phenylalanine. The tyrosine level remains unchanged and may even decrease a bit. Such infants have little or no phenylalanine hydroxylase activity in their liver (<1%).

Figure 2 shows the characteristics of a variant. The response is easily differentiated from classical PKU. In addition, urinary metabolites of phenylalanine are usually present in diminished amounts and the blood tyrosine level usually increases. These subjects have significant amounts of phenylalanine hydroxylase present in liver (5–10%). Variants exhibit elevated blood phenylalanine levels of 10–15 mg/dL throughout their lives, whereas those with classical PKU on an unrestricted diet typically exhibit levels greater than 15 mg/dL. There are other subjects who initially exhibit elevated blood phenylalanine levels but these drop to <4 mg/dL by adolescence. Occasionally a child will not demonstrate one of these responses and cannot be categorized, but this is rare in our experience.

All subjects with classical PKU should be treated with the phenylalanine-restricted diet through adolescence. It is our practice to treat variants with a phenylalanine-restricted diet if their phenylalanine blood levels persistently range above 12 mg/dL. Subjects with persistent levels below 10 mg on an unrestricted diet are not treated.

Newborn Siblings of PKU Children

Since the disease is transmitted as an autosomal recessive disorder, familial recurrence is common. In 20 sibling pairs, seen at the PKU clinic at Childrens Hospital of Los Angeles from 1960 to 1978, phenylalanine levels during the neonatal period were studied (28). In addition to the mandatory screening procedure, blood specimens were obtained at birth (cord blood) and on days 1, 2, and 3. The amount of phenylalanine ingested during this time was estimated from the intake of breast milk, commercial formula, or evaporated milk formula. Dietary treatment was initiated in the younger of the sibling pairs based on the rise in blood phenylalanine. The data showed that the phenylalanine level in affected children rose sharply during the first 24 hours of life. In our PKU center at the present time, the newborn sibling in a family with an identified PKU child is fed a combination of Lofenalac and infant formula adequate in phenylalanine, protein, and calories or maintained on breast milk until the diagnostic blood and urine specimens are obtained and interpreted. The rate of increase in blood phenylalanine concentration compared with phenylalanine intake demonstrates if the phenylalanine-restricted diet is indicated.

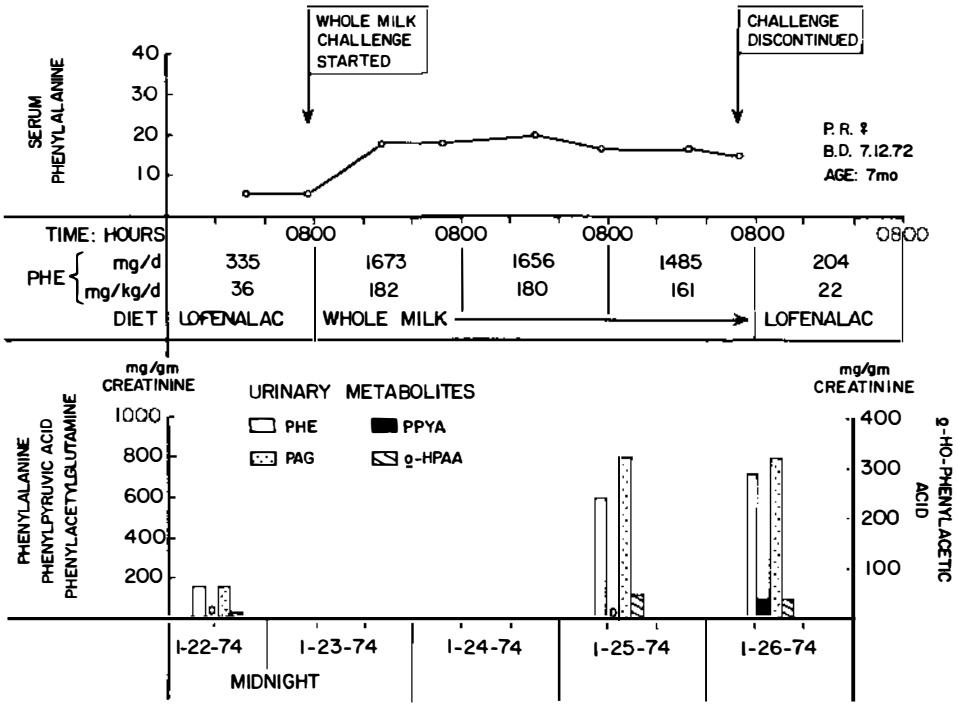

Figure 2 Natural protein challenge demonstrating the slight rise in blood phenylalanine characteristic of an infant with variant phenylketonuria.

DEFINITION OF HYPERPHENYLALANINEMIA CATEGORIES

Hyperphenylalaninemia (HPA) is clinically and biochemically a heterogeneous condition. The most severe form is referred to as classical phenylketonuria (PKU), and the most benign form, which requires no treatment, is referred to as benign hyperphenylalaninemia. The disorder involving the enzyme, phenylalanine (phe) hydroxylase, has been operationally defined according to the three categories described below.

Classical Phenylketonuria

Persons with classical PKU exhibit blood phe concentrations of $\geq$ 20 mg/dL, normal levels of tyrosine (tyr), and excessive phe metabolites in the urine while on a normal diet. Little or no hydroxylase activity is present.

Variant PKU

Generally persons with variant PKU have blood phe concentrations between 10 and 20 mg/dL but may not have phe metabolites present in their urine, unless ingesting excessive amounts of protein in their diet. Tyrosine levels are normal, and hydroxylase activity is definitely present.

Benign Hyperphenylalaninemia

The term benign hyperphenylalaninemia is applied to persons with blood phe concentrations between 4 and 10 mg/dL. The urine is usually normal for metabolites of phenylalanine, and blood tyrosine values are normal. Hyperphenylalaninemics may be diagnosed by newborn screening, but because they are normal in intelligence and clinically asymptomatic they may escape detection. Hydroxylase activity is present in significant amounts.

CLINICAL PRESENTATION

Prior to the advent of newborn screening, mental retardation (30) was the most common phenotypic expression of children with untreated PKU. Decreased pigmentation and eczema, seizures, and neurological complications were common. Autistic activity occasionally was the major presenting symptom. Although body odor was often a predominant observation on physical examination, it seldom was the reason for seeking medical assistance.

The degree of mental retardation was related to age: the younger the child the less the degree of intellectual deficit. While it is realized that developmental testing with Gesell Scales does not equate directly with intelligence quotient, most of the children less than four years of age were not testable on Stanford-Binet Scales because they were nonverbal. The data

show that at one year of age the developmental quotient (DQ) has already dropped to about 50, demonstrating a loss of approximately one IQ point per week of nontreatment. By two years of age the DQ was even lower (27) and by three years of age it was approximately 30. The latter figure is less reliable because of the difficulty of testing very retarded children at such a young age. In addition to the severity of the mental retardation, these children often presented severe behavioral problems and sometimes mutism. The eczema was often resistant to the therapeutic measures and seizures, when present, more difficult to control (27). Laboratory results for blood counts, urinalyses, liver and renal function studies, and endocrine evaluations were usually normal. The diagnosis of PKU was often missed even by specialists. The diagnosis usually was not made until the child presented at a medical facility that was routinely screening for PKU with either blood or urine tests.

Historically, urine (ferric chloride) testing was available from the very first report of Fölling in 1934, whereas blood testing only became generally available in the late 1950s with the publication of the Guthrie test (22) and the McCaman & Robins method (37) for phenylalanine determination. While amino acid analyzers for running tests were available earlier, the cost was prohibitive.

The major breakthrough for newborn screening occurred with the development of the Bacterial Inhibition Assay (22). This simple inexpensive test revolutionized the approach to diagnosis and treatment (23). Because it utilized a dried blood spot as a collecting procedure, it could be used for routine newborn screening. While this method for phenylalanine determination is used primarily for screening, the correlation with the McCaman & Robins test is excellent and some PKU centers utilize it for monitoring as well. Earlier when PKU children presented with mental retardation, a neurologic work-up including electroencephalogram, skull x-rays, and cerebrospinal fluid examination was often performed. Today these procedures are seldom done.

The recent description of defects in biopterin metabolism causing hyperphenylalaninemia makes it mandatory to include urinary studies for these defects as well (39).

NUTRITIONAL THERAPY

Dietary treatment for phenylketonuria traditionally has been based on the restriction of dietary phenylalanine, while maintaining adequate protein and caloric intake. Adequate protein is defined as the ratio of total essential amino acids to phenylalanine, with adequate carbohydrate, essential fats, minerals, vitamins, and trace elements as well. The diet is planned to provide the majority of the amino acids, except for phenylalanine, as the phenylalanine-restricted protein products, and the allowed foods contain the amount of

phenylalanine tolerated. The diet must be calculated for all these nutrients to assure adequacy and bioavailability. The total fat content and sources of essential fatty acids may need to be considered because of the absence of lipids in some products and the specific fatty acids included in others.

Products available in North America are as follows: Lofenalac and Phenyl-free from Mead Johnson (42); PKU 1, PKU 2, and PKU 3 from Milupa Corporation (38); and Maxamaid and Maxamum from Scientific Hospital Supplies (48). Nutrient content is described in the *Final Report of the Task Force of the Dietary Management of Metabolic Disorders Commentary on Nutrition, American Academy of Pediatrics,* June 1985, or in the product information from the manufacturers.

These products are described as special dietary products and are exempt from "Requirements for Infant Formulas" of the Federal Foods, Drug & Cosmetic Act. These products are devoid of or deficient in phenylalanine and are not to be the sole source of nutrition for the infant or child (13).

Diet For The Infant

The diet is calculated using a restricted phenylalanine product combined with breast milk, infant formula, or evaporated cow's milk. The nutrient content of these milks is listed in Table 1.

The Collaborative Study of Children Treated for PKU obtained data suggesting a range of phenylalanine intake to maintain blood phenylalanine in

Table 1 Nutrient content of human milk and infant formulas

Formula	Formula per oz. as fed				
	Phenylalanine (mg)	Protein (g)	Carbohydrate (g)	Fat (g)	Energy (kcal)
Breast milk	12.3	0.27	2.04	1.35	21
Similac 20[a]	22	0.45	2.2	1.1	20
Similac 24[a]	32	0.66	2.55	1.3	24
Enfamil 20[b]	17	0.45	2.1	1.1	20
Enfamil-Pre[b] (Premature)	23	0.72	2.7	1.2	24
SMA 20[c]	24	0.24	2.2	1.1	20
SMA 24[c]	29	0.54	2.6	1.3	24
Isomil 20[a]	29	0.54	2.04	1.1	20
Prosobee 20[b]	29	0.6	2.07	1.1	20
Evaporated milk	104	2.1	3.2	2.4	42

[a] Ross Lab.
[b] Mead Johnson.
[c] Wyeth Lab.

Table 2 Recommended daily amounts of phenylalanine, protein, and energy for infants with PKU

Age (mos)	Phenylalanine ± s.d. (mg/kg/day)	Protein (g/kg/day)	Energy (kcal/kg/day)
0–3	58 ± 18	3.5	120
4–6	40 ± 10	3.3	115
7–9	32 ± 9	2.5	110
10–12	30 ± 8	2.5	105

the acceptable range of 2–10 mg/dL. Tolerance of phenylalanine varies with the individual (1), so the initial prescription is adjusted by monitoring blood phenylalanine concentrations and comparing them with intakes of phenylalanine and all nutrients.

Table 2 gives recommended prescriptions for the infant with PKU through the first year. Protein recommendations were adjusted for protein source; caloric (energy) recommendations are from the National Research Council Recommended Dietary Allowances 1980 (43).

A sample prescription using Lofenalac and a milk-based infant formula is calculated from the information in Tables 1 and 2, for a 4-kg infant, and is presented in Table 3.

The prescription for the infant with PKU can also be planned with a microcomputer program developed by Anderson, Kennedy & Acosta (4). The actual diet prescription is adjusted by the dietitian to correlate with blood phenylalanine concentrations.

In recent years, breast milk for the PKU infant has been used as the source of phenylalanine and additional protein and calories (12, 15). This procedure

Table 3 A sample prescription for a 4-kg infant

	Phenylalanine (mg)	Protein (g)	Calories
Lofenalac, 7 scoops[a] (67 g)	56	9.8	308
Infant formula, 10 oz. (ready to feed or 20 calories/oz[b])	180	4.5	200
Water, to equal total volume of 25 oz			
TOTALS	236	14.3	508
per kg	59	3.6	127
per oz	10	0.6	20

[a] One scoop (9.5 g) of Lofenalac contains 8 mg of phenylalanine, 1.4 g of protein, and 44 calories.

[b] Representative milk-based infant formulas, approximately 18 mg of phenylalanine per ounce.

requires more careful monitoring of weight, phenylalanine values, and other indications of nutritional adequacy of the diet for the infant. The infant may breast-feed in conjunction with the low-phenylalanine formula. If the phenylalanine-free product is used, each formula feeding must be followed by breast feeding to prevent hypophenylalaninemia. The phenylalanine-restricted formula is prepared to a dilution of 20 calories per ounce. One to three ounces of this formula is given prior to breast-feeding during the day. The amount of breast milk consumed is approximated using data in the literature (8, 11, 33). The infant is permitted to nurse during the night without being fed the low-phenylalanine formula if the serum phenylalanine concentrations continue in the treatment range. The nutritionist may need to counsel the mother if the infant consumes too little of the low-phenylalanine formula or is not gaining weight satisfactorily with a combination of breast-feeding and formula.

Initiation of Dietary Treatment

Currently, it is recommended that dietary restriction of phenylalanine begin when the blood phenylalanine exceeds 12 mg/dL. The maximum blood phenylalanine at the time of diagnosis is dependent on phenylalanine hydroxylase activity and the intake of phenylalanine. Individual tolerance for phenylalanine can then be estimated by calculating intake of breast milk or formula per kilogram of weight, compared with blood phenylalanine concentrations.

The maximum blood phenylalanine may be greater than 30 mg/dL in the first week of life, even on a relatively low protein intake. The goal of achieving a satisfactory blood phenylalanine concentration as quickly as possible is accomplished by prescribing protein and calories according to Table 2 and by restricting the phenylalanine intake to that supplied by the unsupplemented Lofenalac diluted to 20 calories per ounce. Medical supervision, daily serum phenylalanine determinations, and calculations of the infant's intake of phenylalanine, protein, and calories will prevent phenylalanine deficiency during this procedure.

Blood phenylalanine values in the range of 15–30 mg/dL at the time of diagnosis indicate that one half of the recommended phenylalanine in Table 2 be prescribed until the treatment range of 2–10 mg/dL is achieved.

Additions to the Diet for Infants

At age 4 to 6 months, infant foods are introduced to provide more of the required amount of phenylalanine. A meal plan is designed for the infant and serving lists of foods (3, 46) guide the parents under the supervision of the dietitian and physician. Adjustments in the diet prescription are made for blood phenylalanine concentrations, rate of growth, and physical activity.

When the child reaches an appropriate age, low-protein baked products and pastas along with phenylalanine-restricted recipes are recommended to increase caloric intake, variety, and palatability (44, 45, 47).

Adequacy of the Diet

The absence of fat in several of the low-phenylalanine products requires that linoleic and linolenic fatty acids be prescribed as 5% of the calories. Total fat content of the formula prescribed should be a minimum of 30 or 50% of the calories as it is in breast milk.

Nutrient needs for minerals, vitamins, and trace elements are usually met by the combination of low-phenylalanine-supplemented formula as prescribed. The infant with PKU has the same needs for these nutrients as does the non-PKU infant. Although the amino-acid-modified products have a vitamin-mineral component, laboratory tests are suggested to measure blood levels and thereby reveal any need for supplementation.

In the past few years, there have been reports of deficiencies in zinc, selenium, copper, and carnitine (2, 9, 18, 20, 51). The need for these nutrients during times of rapid growth is well documented, especially since inadequate diet therapy in PKU infants mimics clinically deficient states. Obtaining baseline data and monitoring blood values are indicated in the management of the infant with PKU.

CLINICAL RESULTS

Some years ago objections were raised regarding the adequacy of the beneficial effects of the phenylalanine-restricted diet; however, the evidence is now overwhelming that early diagnosis and proper dietary therapy are therapeutic and result in normal development for PKU children. Data from the Collaborative Study of Children Treated for PKU are conclusive and were recently reviewed by Holtzman et al (24).

Medically treated PKU children exhibit normal growth and development. The only significant medical finding noted in the Collaborative Study was the presence of pyloric stenosis in three male infants. This finding suggests that infants with pyloric stenosis should perhaps have a repeat blood phenylalanine test if their neonatal screening test was reported as normal.

An index of dietary control (IDC) was used to monitor dietary compliance in the Collaborative Study. The IDC value is the median blood phenylalanine level for individual 6-month periods through 6 years of age. The median values gradually increased to 12.5 mg/dL by 6 years of age for the total sample of 134 children.

Selected demographic variables were compared between families of children in adequate dietary control at age 6 ($<$15 mg/dL) and families of children in poor control. The children who were in poor dietary control at 6 years

(28%) came from families exhibiting a greater degree of marital instability and unemployment. Mothers, on the average, were younger and exhibited lower intellectual quotients on the Wechsler Adult Intelligence Scale (WAIS). Factors that were not related to dietary control included father's age and IQ, mother's employment status, and parents' education and socioeconomic status.

The total sample began dietary treatment at a mean age of 21 days. The range in age of first treatment was from 3 to 65 days. Thus, the study sample represented a group of PKU children treated very early. The PKU children scored an average of 98 compared with their non-PKU siblings, who had a mean IQ of 102. This difference was significant, but not highly so. Early-treated PKU children had significantly higher IQs than late-treated PKU children. Children who were treated in the second month of life scored a mean IQ of 85, whereas children who were treated in the first month of life scored a mean IQ of 95.

This finding stimulated additional analyses to investigate other predictors of eventual IQ. The results of these analyses demonstrated that the three most important predictors of 6-year IQ were mother's WAIS IQ (which explained 37% of the variance), age at which the subjects were first treated (7%), and how well the subjects adhered to the low-phenylalanine diet (4%) (29).

Late-diagnosed children should also be treated. Gratifying results sometimes are seen even in severely retarded children. Figure 3 illustrates such a

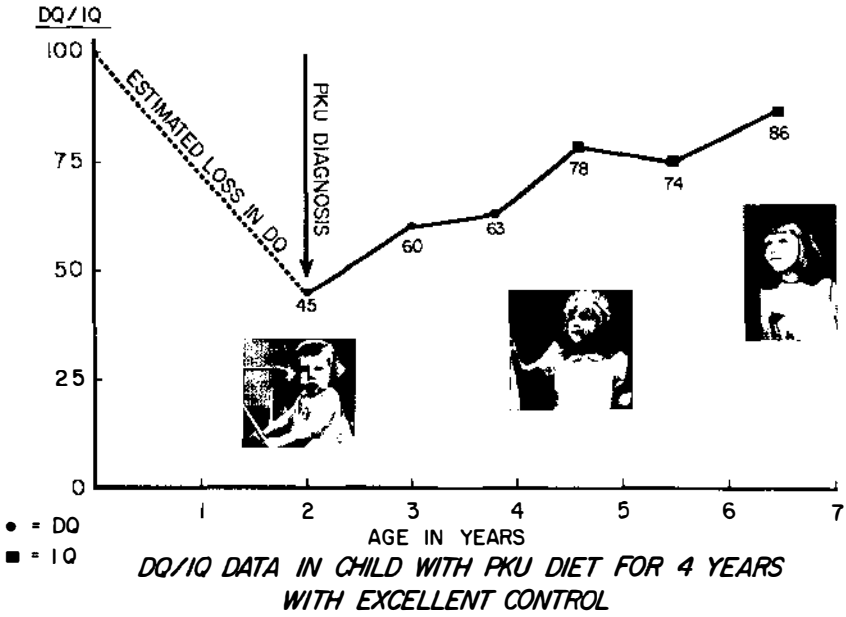

Figure 3 Gratifying response to dietary therapy in a late-diagnosed PKU child.

case. This child today is 26 years old; she has an IQ of 98 on a Wechsler Adult Intelligence Scale and is employed. She graduated from junior college and is planning to be married soon. She continues the phenylalanine-restricted diet utilizing an amino acid supplement.

DIET DISCONTINUATION

When and if to discontinue dietary restrictions is perhaps one of the most controversial aspects of PKU. Horner et al (25) were the first to report that perhaps discontinuation of dietary therapy was safe, but in recent years it has become clear that early diet discontinuation is harmful. The pioneering works of Cabalska et al (10) and of Smith, Bickel and colleagues (50) have now been corroborated by the results of the Collaborative Study.

The recent report by Holtzman et al (24) determined the effect on intellectual performance and behavior of the age at which dietary control was lost in 119 10-year-old children with phenylketonuria (PKU) who had started on a diet low in phenylalanine before the age of 65 days. The children's diets were considered to be out of control when their blood phenylalanine concentration persistently exceeded 15 mg/dL. The age at which control was lost was the best predictor of the child's IQ at the age of 8 or 10 years and of the deficit in the child's IQ as compared with those of his or her unaffected siblings or parents. The age at which control was lost was also the best predictor of the deficit in scores on the Wide Range Achievement Test (WRAT) of children with PKU at the age of eight in comparison with unaffected siblings. The greatest deficiencies in all of these outcomes were observed among children who were out of dietary control before the age of six years.

This review evaluated 12-year IQ (Table 4) and WRAT test scores for 95 PKUCS children, again grouped according to the age at which dietary control was lost. The differences between groups that were apparent at ages 8 and 10 persist throughout age 12 (Table 5). The group that maintained dietary control at least through 8 years of age, many of whom were still in good control at age 12, had the highest scores at age 12. The single exception was in the WRAT arithmetic, in which all groups of PKU children showed considerable deficit at age 12, regardless of dietary control.

Thus recent data indicate that the prudent course is to maintain dietary control through adolescence (57). This is difficult, but long-term control can be maintained by the physician by allowing "holidays" every two months beginning at age 10 years. A "holiday" is a day when the child can eat anything he or she wants and does not have to ingest the special formula. At age 12 the number of "holidays" is increased to one each month. This has allowed the children to eat and taste normal foods at parties and special celebrations. This approach is helpful and prolongs the period of dietary control.

Table 4 Summary of 12-year *PKUCS* IQ data (mean ± s.d. by age at loss of dietary control)

IQ	Age at loss of dietary control (mo.) ≤71 (*N* = 23)	72–95 (*N* = 42)	≥96 (*N* = 30)
6-yr Stanford Binet	91 ± 15	100 ± 14	102 ± 14
7-yr Stanford Binet	93 ± 12	98 ± 13	103 ± 14
8-yr Wisc—verbal	92 ± 12	98 ± 14	103 ± 12
—performance	93 ± 15	100 ± 14	103 ± 12
—full scale	92 ± 13	99 ± 14	103 ± 12
10-yr Wisc—verbal	91 ± 12	98 ± 12	103 ± 12
—performance	96 ± 16	100 ± 13	105 ± 12
—full scale	92 ± 14	99 ± 13	105 ± 12
12-yr Wisc—verbal	85 ± 15	94 ± 14	100 ± 10
-R—performance	92 ± 15	98 ± 13	101 ± 11
—full scale	87 ± 14	95 ± 14	101 ± 10

MATERNAL PKU

It is well established that untreated phenylketonuric women with blood phenylalanine levels exceeding 20 mg/dL during pregnancy invariably give birth to defective offspring with a wide variety of congenital anomalies, including microcephaly and congenital heart disease (14, 17, 19, 35, 36).

Deleterious effects are less well defined when the pregnant woman has blood phenylalanine levels between 4 and 15 mg/dL, the so-called hyperphenylalaninemic variant range (59). Variant women have normal intelligence and generally have not been considered at risk for having seriously defective offspring. Nonetheless, Mabry (34) has emphasized the increased risk to their offspring as well.

Lenke & Levy (32) collected data on 524 pregnancies in 155 PKU women of whom only 34 were treated on low-phenylalanine diet after, or shortly before, conception. Among the untreated pregnancies the frequency of mental retardation associated with microcephaly in their offspring was greatly increased over that of the children born to mothers with normal phenylalanine levels. Ninety-five percent of mothers with blood phenylalanine levels over 20 mg/dL produced a mentally retarded child. Since the data concerning treated pregnancies was conflicting and often incomplete, it was not possible to conclude that dietary therapy initiated after conception was effective. Ideally, starting the phenylalanine-restricted diet before conception is recommended (31, 40).

Our experience suggests that maternal phenylalanine levels of 4–8 mg/dL

Table 5 Summary of 12-year PKUCS IQ data (mean ± s.d. by age at loss of dietary control)

	Age at loss of dietary control (mo.)		
WRAT	≤71 (N = 22)	72–95 (N = 41)	≥96 (N = 25)
6-yr—reading	99 ± 20	106 ± 17	106 ± 15
—spelling	91 ± 23	99 ± 15	100 ± 15
—arithmetic	92 ± 17	99 ± 13	100 ± 9
8-yr—reading	94 ± 14	101 ± 15	109 ± 14
—spelling	93 ± 17	100 ± 14	105 ± 16
—arithmetic	92 ± 12	95 ± 13	96 ± 10
10-yr—reading	96 ± 15	101 ± 12	107 ± 12
—spelling	93 ± 17	101 ± 13	104 ± 14
—arithmetic	91 ± 12	91 ± 10	94 ± 7
12-yr—reading	92 ± 13	96 ± 11	104 ± 11
—spelling	87 ± 17	91 ± 13	98 ± 15
—arithmetic	80 ± 11	82 ± 11	83 ± 10

are not detrimental to fetal outcome. Four mothers with levels in this range gave birth to children with normal intelligence. On the other hand, four PKU women with levels above 12 mg/dL all had retarded children. Thus, restriction of the phenylalanine level in early pregnancy is essential for a healthy offspring. It is important to note that the phenylalanine level will be higher in the embryo than in the mother because of the positive transplacental gradient.

The social and psychological aspects play important roles in the management of these women (52). Providing the pregnant phenylketonuric mother with a knowledge of her disease and alerting her to the implications for her unborn infant are prime prerequisites for the positive rapport needed to initiate appropriate dietary treatment.

Close supervision of the diet and frequent assays of serum phenylalanine levels throughout the pregnancy are essential. A cooperative arrangement between the obstetrician and the nearest medical center offering PKU evaluation and service is the most advantageous type of supervision during this period.

CONCLUSION

While much has been learned in the past 50 years about phenylketonuria, the vexing problem of how long to treat these persons with a restricted phenylalanine diet remains. Accumulating evidence suggests continuing dietary therapy into adulthood may be required. Perhaps the molecular biologist may shed

some light on this perplexing problem. It is evident that in some way it is the elevation of phenylalanine or its by-products that induces the serious cerebral dysfunction seen in this disease.

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