Chapter 39

Phenylketonuria and Maternal Phenylketonuria

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I remember when she was only 3 months old she lay in her basket on the sun deck of a ship. I had taken her there for the morning air. The people who promenaded on deck often stopped to look at her, and my pride grew as they spoke of her unusual beauty and of the intelligent look of her deep, blue eyes. I do not know at what moment the growth of her intelligence stopped, nor to this day why it did.

Pearl Buck about her daughter Carol
in *The Child Who Never Grew*

Phenylketonuria (PKU) may be the most thoroughly studied inherited metabolic disorder, a disorder in which the consequences can be multigenerational and can have significantly different outcomes. A neonate may be born with PKU or may be an offspring of a woman with maternal phenylketonuria (MPKU). The neonate with PKU will require long-term treatment to prevent developmental problems, while the pregnant woman with PKU must maintain exquisite control of her metabolic disorder to prevent harmful effects on her unborn child (Fig. 39–1).

Phenylketonuria was first described by a Norwegian physician, Asbjörn Fölling, in 1934, after a persistent and observant mother asked him to determine the cause of mental retardation in her two children. He noted a peculiar clinging odor about the children and suspected that it might be a clue to their mental retardation. After testing the urine of each child for a possible infection and finding none, he tested some acidified urine with an aqueous ferric chloride solution, expecting to find the red-brown color characteristic of ketones. Instead, he observed a dark green color now known to be characteristic of phenylpyruvic acid,[1] a metabolite of phenylalanine. Phenylketonuria remained a somewhat obscure biochemical curiosity for nearly 20 years. In 1951 Woolf and Vulliamy suggested that there might be a relation between excess phenylalanine and brain damage.[2] At about the same time, Armstrong and Tyler in the United States[3] began studies on the effects of phenylalanine-restricted diets, and Bickel et al. published the first report in 1953[4] describing marked clinical improvement after use of a phenylalanine-restricted diet. However, these initial attempts at therapy showed that initiation of treatment after recognition of developmental delay was futile in reversing the established cognitive damage. In contrast, initiation of therapy in affected newborns born into families known to be at high risk for PKU established the principle that diet could prevent cognitive damage.

The need for an effective means of testing newborns on a population basis led to programs for testing urine at the time of the 6-week well-child visit, using the same ferric chloride indicator used by Fölling. Although this program was logistically more feasible in the late 1950s than can even be imagined today, it was still far from ideal. Simple, cost-effective mass screening for PKU became a reality in the 1960s when Robert Guthrie devised the bacterial inhibition method for testing phenylalanine levels in dried blood collected on filter paper.

Phenylketonuria is inherited in an autosomal recessive manner and has an incidence of 1:10,000 live births in persons of European descent.[5] In Western Europe and North America, most PKU is due to mutations in the gene for phenylalanine hydroxylase, and over 400 disease-causing mutations have been identified.[5] This gene is located on human chromosome 12, band region q22–q24.1.[6] Defects in the genes coding for enzymes involved in the synthesis or recycling of the required biopterin cofactor are responsible for a minority of European cases of PKU but have increasing importance in the Middle East. Cofactor-dependent PKU affects neurotransmitter synthesis in a more global manner than the phenylalanine hydroxylase (PAH)–deficient type of PKU and requires a complex medical regimen in addition to a phenylalanine-restricted diet. Characteristic features of untreated individuals with PKU include mental retardation, diminished pigmentation, eczema, hypertonicity, seizures, and an unusual body odor.[7] Untreated adults with PKU may also develop behavioral problems such as hyperactivity, aggressiveness, self-inflicted injury, and negative mood swings.[8] However, many individuals with elevated phenylalanine levels have mild or absent cognitive and behavioral manifestations, so the disease spectrum has been expanded to include individuals with mild or benign hyperphenylalaninemia.

The phenylalanine-restricted diet proved effective in reducing serum phenylalanine levels and in promoting improved growth and development. The duration of the modified diet was not known, but the consensus was that the diet could be terminated at about 5 years of age, by which time an individual's brain has almost fully developed. Also not known was the optimal range for maintaining serum phenylalanine levels. In 1967 the PKU Collaborative Study was initiated, and infants identified by newborn screening as having PKU were enrolled.[9] The study lasted for 6 years, and infants were randomly placed in one of two ranges of phenylalanine concentrations. At 6 years of age they were randomly selected to discontinue or continue the diet, although their parents could request a preference. By the time the children reached 10–12 years of age, it was abundantly clear that those who stayed on the diet were developing much better than those for whom the diet had been stopped.[9] Although several major centers in the United States never willingly discontinued the diet, this study played a significant role in changing attitudes about stopping the diet. This phase of the PKU Collaborative Study continued until 1983.

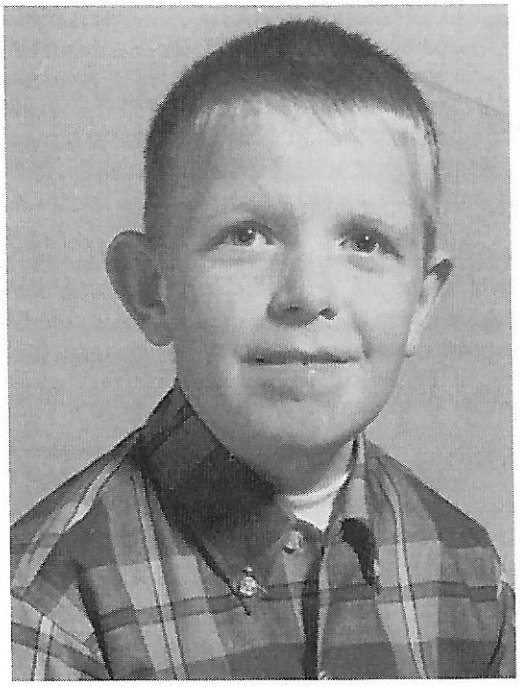

Figure 39–1. Phenylketonuria in this boy was recognized at age 3, when moderate retardation was noted. At age 8, he remains moderately retarded. Hospital Medical Center, Cincinnati Children's Division of Genetics. Used with permission.

In 1998, the PKU centers from the original PKU Collaborative Study agreed to evaluate the original subjects enrolled in the Collaborative Study from 1967 to 1983.[9] The goal was to ascertain their current psychological, medical, socioeconomic, and nutritional status. It was found that subjects whose diet had been discontinued had a much higher incidence of eczema, hyperactivity, hypoactivity, lethargy, headaches, mental disorders, surgery (not specified), asthma, and neurological signs than did those subjects for whom the diet had not been discontinued. It was noted that the subjects who remained on the diet had a higher incidence of hypertension and obesity[9] than did those who abandoned it. However, the numbers in this study were small. There were six times as many subjects in the discontinued-diet category as in the never-discontinued category, and the results observed may be an aberration. The NIH Consensus Development Conference was held in 2000. Based on the recommendations of an international committee, the participants concluded that neonates through age 12 years should have serum phenylalanine levels between 2 and 6 mg/dL (120–360 mol/L) and that adolescents and young adults should maintain levels between 2 and 15 mg/dL (120–900 mol/L).[10] Pregnant women with PKU must maintain serum phenylalanine levels below 6 mg/dL.

Phenylalanine Embryopathy, a Consequence of Maternal Phenylketonuria

The teratogenic consequences of elevated maternal phenylalanine during pregnancy were recognized and described first by C.E. Dent in 1956. Later by Mabry and coworkers and were among those who recognized the relationship of institutionalized retarded women with PKU and their institutionalized retarded children.[12] In 1963, they described three elderly women with PKU who together had seven mentally retarded children. Two of the women were sisters. One sister had an IQ of 82, and her only surviving child had an IQ of 30. The other sister had an IQ of 49 and had five living children with IQs ranging from 30 to 61. The third woman, born in Germany in 1913 and not recognized as having mental retardation until later in childhood, had an IQ of 27 and a daughter with an IQ of 24.

In 1980, Lenke and Levy described the full spectrum of effects of maternal PKU/hyperphenylalaninemia on the fetus.[13] This retrospective survey of the literature reviewed 524 pregnancies of 155 women with PKU or hyperphenylalaninemia who had 423 offspring and 101 spontaneous abortions. It revealed that an increased incidence of mental retardation, microcephaly, and congenital heart disease in offspring of women with untreated PKU during pregnancy correlated with elevated maternal serum phenylalanine levels.[13] Other features noted in these infants included thin upper lip, upturned nose, short nasal bridge, and/or epicanthal folds. In 1984, the National Institutes of Health funded a multicenter collaborative study to evaluate the efficacy of a phenylalanine-restricted diet during pregnancy. The study, which enrolled subjects from 1984 to 1995, conclusively showed that women who achieved control-range phenylalanine levels early in pregnancy and maintained those levels throughout pregnancy had very good physical and fetal outcomes.[14] Based on these findings, it is recommended that women with PKU maintain phenylalanine levels below 6 mg/dL before conception and throughout pregnancy.

Biochemical Abnormality

The biochemical defect in PKU is a functional deficiency of the liver enzyme, phenylalanine hydroxylase (PAH), which catalyzes the para-hydroxylation of phenylalanine to yield tyrosine.[5] The hydroxylase system requires a cofactor, tetrahydrobiopterin (BH4). A second enzyme, dihydropteridine reductase, recycles the pterin cofactor back to the active state.[5] In classical PKU, serum phenylalanine concentrations on an unrestricted diet are above 20 mg/dL, and the characteristic metabolites of phenylalanine (phenylpyruvic acid, phenylacetic acid, phenyllactic acid, 2-hydroxphenylacetic acid, and phenylethylamine) are excreted in the urine.[5] Phenylacetic acid[1] is responsible for the odor associated with untreated or poorly controlled PKU. In untreated individuals, pigment dilution in hair and skin is the consequence of defective transport of tyrosine, a precursor of melanin.

Accumulation of phenylalanine results in a series of direct and indirect biochemical changes that occur during early stages of development of the central nervous system and contribute to a pathogenic pattern that, without treatment, usually results in mental retardation by a still unknown mechanism. Among the hypothesized pathogenic mechanisms are monoamine depletion and impairment of brain protein synthesis through inhibition by phenylalanine or one of its by-products or through a relative deficiency of other essential amino acids. It is generally agreed that excess phenylalanine exerts a permanent deleterious effect on the brain during development and a reversible toxic effect subsequently.[5] Pathogenesis of the mental defect is probably the same whether infants are exposed to excess phenylalanine in utero or after birth, but the actual mechanism remains unclear. Possible explanations include competition for transport of large neutral amino acids (LNAA), inhibition of protein synthesis, interference with *N*-methyl-D-aspartic acid (NMDA) receptors, disturbance of myelin structure, and inhibition of neurotransmitter synthesis.[5] Active transport systems that carry phenylalanine across

membranes also carry other LNAA,[15] and when the transport system is overloaded by a single amino acid, the other amino acids are excluded from transport. This exclusion within the transport system can result in a disruption of growth and other processes.

Factors to Be Considered in Nutritional Evaluation

Specific Nutrients

The dietary treatment of PKU consists of providing a nutritionally balanced diet containing enough phenylalanine to meet the needs of an infant or growing child and to maintain the needs of the older child, adolescent, or adult without vastly exceeding that individual's limited capacity to utilize phenylalanine. As an essential amino acid, phenylalanine must be included in the diet in sufficient amounts to allow for protein synthesis. However, a safe and practical PKU diet virtually never returns the serum phenylalanine to normal levels. The diet includes a special-purpose medical food (a protein substitute, called a *formula*), natural foods to provide the requirement for phenylalanine, and commercially available amino acid–free products. The objective of treatment is to reduce serum phenylalanine to a control range of 2–6 mg/dL to promote normal growth and development during childhood and healthy neuropsychological function in all age groups.[16]

Phenylalanine requirements (per kilogram body weight), as initially defined by Holt and Snyderman,[17] are greatest during infancy and diminish significantly with age. Acosta and Yannicelli[18] recommends for infants 0 to 3 months old 25–70 mg/kg/day, for children 1 to 4 years old 200–400 mg/day (approximately 15–30 mg/kg), for adult women 220–700 mg/day (approximately 4–12 mg/kg), and for adult men 290–1200 mg/day (approximately 4–17 mg/kg). Limited amounts of natural foods provide the essential amino acid, phenylalanine, calories, and variety in the diet. Sufficient calories must be obtained from the diet to prevent catabolism of protein and to prevent weight loss.

The *protein requirement* is provided by a phenylalanine-free formula that provides close to 85% of the nitrogen in most prescriptions.[19] These products are composed of L-amino acids that are more rapidly absorbed than whole protein. Consequently, there is a more rapid rise in serum amino acid concentration than occurs with the usual digestion of whole protein, and the utilization of L-amino acids is different from that in whole protein.[20] When dietary phenylalanine is restricted, tyrosine becomes an essential amino acid and other essential amino acids must be present simultaneously. Occasionally, supplemental L-tyrosine will be required to maintain serum tyrosine levels within an acceptable range.[18] Based on the information published by Ross, infants need 250–350 mg tyrosine per kg/day, children 1–11 years old need 1.72–4.0 g/day, women over 11 years old require 3.4–5.0 g/day, and males of the same age need 3.4–6.5 g/day. Commercial phenylalanine-free formulas are well fortified with L-tyrosine, and typical formula prescriptions should meet the tyrosine requirement.

Energy needs of the individual may not be met by the formula and the limited amounts of natural foods permitted. Special low-protein foods and free foods such as sugar and fats may be used to provide needed calories. Part of the fat should be in the form of safflower, corn, or canola oil as a source of the essential fatty acid, linoleic acid. Requirements for thiamin, riboflavin, niacin, and folic acid increase significantly during times of rapid growth; vitamins A, C, and E are needed for development of the structural and functional properties of new cells; and vitamin D is needed for skeletal growth. Because foods of animal origin are seldom used, intake of vitamin B_{12}, iron, calcium, copper, selenium, zinc, and cholesterol may be inadequate. However, if the formula is consumed in an amount appropriate for the age of the individual, these nutrients, with the exception of cholesterol, should be adequately provided and a vitamin/mineral supplement should not be needed.[21]

A phenylalanine-restricted diet for *pregnant women* with PKU is similar to that prescribed for infants, children, adolescents, and adults. The diet during pregnancy should continue the control of serum phenylalanine begun before conception. The goal of treatment is to maintain serum phenylalanine levels between 2 and 6 mg/dL while providing adequate prenatal nutrition. The amount of phenylalanine needed during pregnancy increases with each trimester. Acosta and Yannicelli state that pregnant women with PKU need daily during the first trimester approximately 200–600 mg phenylalanine (4–12 g natural protein), during the second trimester 200–900 mg (4–18 g natural protein), and during the third trimester a woman may tolerate as much as 1200 mg (24 g natural protein).[18] A pregnant woman with PKU requires a higher intake of protein (70–75 g)[18] than the 60 g recommended by the 1989 Recommended Dietary Allowance. At all times, the amount of dietary phenylalanine recommended will be determined by serum phenylalanine levels and fetal growth. Supplemental L-tyrosine may be needed if serum tyrosine levels cannot be maintained within an acceptable control range. Pregnant women or those contemplating pregnancy should have an appropriate phenylalanine-restricted diet (including formula and thus multivitamins) and supplemental folic acid and vitamin B_{12}.[22]

In summary, requirements for essential amino acids, including phenylalanine and tyrosine, must be met for protein to be synthesized. For optimal utilization of other amino acids, phenylalanine intake should be distributed evenly throughout the waking hours. Calories in the form of fat and carbohydrate must be provided in sufficient amount to ensure that protein is not used as a source of energy. During pregnancy, care must be taken to ensure intake of sufficient calories to promote good fetal growth. An inadequate intake of essential amino acids from the formula or an inadequate amount of phenylalanine and tyrosine from food can be responsible for low weight gain. Optimal serum phenylalanine and tyrosine levels are maintained by adjusting the intake of natural foods.

Components of the Diet

The phenylalanine-free formula is the most important part of the dietary treatment for PKU. If an inadequate amount of formula is consumed, serum phenylalanine concentrations may increase due to tissue catabolism, growth will be inhibited, and mental development may be impaired. The first commercial product for treatment of PKU in the United States was Lofenalac, a casein hydrolysate, made by Mead Johnson. It was used from 1958 until it was discontinued in 2002. During the 1970s, phenylalanine-free products were introduced to the U.S. market. These products were concentrated sources of protein and contained fewer calories. The advantages of these products were recognized as important in the management of the older patient with PKU. Mead Johnson and, later, Ross Laboratories, Scientific Hospital Supplies, and Applied Nutrition developed similar products. By the turn of the twenty-first century, several major companies were

providing a variety of products with improved smell, taste, concentration of protein, enhanced vitamin and mineral composition, and fewer calories than the original products.

Many special-purpose medical foods are available. Each product is designed to meet nutritional needs and provides varying amounts of carbohydrate, amino acids (no phenylalanine), fat, vitamins, and minerals. All appropriate formulas used for treatment of PKU contain L-amino acids, simple sugars, and other nutrients. These products may have a high osmolarity if insufficiently diluted, and the practice of concentrating them to increase consumption exacerbates this problem. To compensate, the individual is encouraged to drink additional water or other fluids, which will also help to eliminate phenylalanine metabolites and may prevent symptoms associated with an overly concentrated formula, such as diarrhea, vomiting, and abdominal cramping. Natural foods include all edible foods, except formula, and provide essential amounts of phenylalanine, calories, vitamins, minerals, bulk, and a variety of textures and flavors. The formula and other foods should be offered within the same time frame for optimal use of all essential amino acids. Fruits and vegetables are important foods in the diet. Legumes, grains, and potatoes may be used, but in limited amounts because of their relatively high phenylalanine content. High-phenylalanine foods—meat, dairy products, and eggs—should be omitted or severely restricted. No food is strictly forbidden, but all foods are restricted to some degree. Only pure sugar and pure fat contain no phenylalanine.

Commercially available low-protein or protein-free products make the phenylalanine-restricted diet more palatable and interesting. Scientific Hospital Supplies (CamBrooke), (Ener-G Foods), Applied Nutrition, and Dietary Specialties are among the companies that provide specially designed foods. Low-protein recipes and phenylalanine food lists have been compiled into cookbooks and handbooks. These resources are an invaluable aid in managing a phenylalanine-restricted diet. Low-calorie foods warrant attention because many contain *Aspartame* (Equal; NutraSweet). Aspartame, under the brand name NutraSweet, is a dipeptide, L-aspartyl-L-phenylalanyl methyl ester that is metabolized to aspartic acid and phenylalanine. Any product that contains this sweetener should be avoided by individuals who have PKU. *Neotame* is a similar nonnutritive sweetener produced by the NutraSweet Company. Like Aspartame, NeoTame is composed of aspartic acid and phenylalanine, but the phenylalanine is not bioavailable because peptide bond cleavage is blocked by a 3,3-dimethylbutyl group.[23] The sweetness temporal profile of NeoTame may be modified by adding other substances, such as tyrosine or serine. It was approved for use in the United States, Australia, and New Zealand in 2002 and does not require any special labeling for individuals with PKU. *Alitame* is formed from L-aspartic acid and D-alanine[24] and thus is of no concern to individuals with PKU. It had not been approved by the Food and Drug Administration as of 2002.

Dietary Management

An individualized prescription for phenylalanine, protein, and other nutrients is determined by either the metabolic dietitian or the metabolic physician. The phenylalanine prescription may be expressed by one of several available exchange systems or by counting milligrams of phenylalanine. Each method requires that the selection of desired foods remain within the specific prescription. Patients should be monitored frequently and adjustments made when necessary. Elevated or depressed serum phenylalanine levels may reflect an imbalance between the essential amino acids in the formula and phenylalanine from natural foods or insufficient protein and calories. An imbalance may result from an inadequate intake of formula, excessive intake of phenylalanine from natural foods, or illness (see Table 39–1).

Infancy

Early initiation of the diet is crucial if serum phenylalanine levels are to be lowered before irreversible brain damage occurs. Although study of adults with early treated PKU showed no effect on adult IQ if treatment was initiated in the first 30 days, it is recommended that phenylalanine be lowered to desired levels as quickly as possible once the diagnosis is confirmed. Many infants with classic PKU will have phenylalanine levels of 20–40 mg/dL at the time of diagnosis, and a brief *washout* is recommended during which phenylalanine-free formula is given with no supplemental phenylalanine. The formula should provide an appropriate number of calories and protein for the infant. An estimated duration can be determined from the recommendations of Acosta and Yannicelli,[18] and serum phenylalanine levels should be monitored daily during this period, which should not exceed 96 hours. At the end of the washout period, as serum phenylalanine levels approach 6–10 mg/dL, phenylalanine in the form of a standard infant formula must be added. The amount of regular formula will depend on residual phenylalanine activity. Acosta and Yannicelli recommend 25–70 mg phenylalanine per kilogram and use the initial serum phenylalanine level as a surrogate marker of residual phenylalanine activity to guide the initial prescription; *the higher the diagnostic level, the lower the phenylalanine prescription.* As growth slows in the latter months of infancy, the phenylalanine allowance decreases to 10–35 mg/kg at 9–12 months of age.[18] Prematurity and the associated increase in protein requirement modifies these recommendations toward the high side.

The infant with PKU should be considered as normal and healthy unless there is a reason to think otherwise. The infant will go through the same developmental stages as any other infant. As the infant grows, baby foods will be offered and the phenylalanine in these foods will gradually replace the phenylalanine in the regular infant formula. As the infant approaches 1 year of age, table foods will begin to replace baby foods. The infant should be encouraged to drink from a cup and to self-feed. However, the formula continues to be the most important element in the diet, and consideration must be given to its importance. The number of bottles and the volume of formula taken by the infant gradually decrease during the first year of life. This decrease in fluid intake is most prominent when an infant is weaned from bottle to cup feeding. Unless the formula is made more concentrated, an insufficient amount of formula will be consumed, with a corresponding rise in serum phenylalanine. Regardless of age, inadequate formula consumption requires a more concentrated formula plus supplemental fluids in the form of water, juice, or other beverages (Table 39–2).

Childhood

Each phase of development has its own idiosyncrasies. The toddler has expanded horizons beyond the high chair and often is more interested in things other than food. This becomes a chal-

Table 39–1. Method for Determining the Amount of Formula and Supplemental Phenylalanine Needed to Provide for Growth and Development

1. Based on the age of the child or adult, or the age and weight of the infant, determine the individual's protein needs as established by the Recommended Dietary Allowance (RDA) (see Dietary Reference Intake, Appendix 1). *Note:* Acosta and Yannicelli recommend significantly more protein per day than does the RDA.[18] Approximately 85% of the day's allowance for protein should come from formula.
2. Based on the age and weight of the infant or the age of an individual over 12 months of age determine the amount of phenylalanine required. *Note:* the amount permitted will ultimately be determined by the individual's serum phenylalanine level.
3. Based on the age and weight of the infant, determine calorie needs as established by the RDA.
4. Phenylalanine-free foods such as sugar or oil may be added to the formula to adjust calories if necessary.
5. Calculation of *formula:*

Example 1:

Age:	2 years
Protein:[18]	30 g
Phenylalanine:[18]	200–400 mg

Formula prescription: 11 TBS (88 g powder) Phenex-2 unflavored provides
361 calories 26.4 g protein 0 mg phenylalanine

Food: provides the allowed amount of phenylalanine, calories, and variety to the diet.

Example 2:

Age:	adult pregnant woman, second trimester
Protein:[18]	70 g
Phenylalanine:[18]	200–900 mg

Formula prescription: 17 TBS (153 g powder) XPhe Maxamum unflavored provides
461 calories 59.7 g protein 0 mg phenylalanine

Food: provides the allowed amount of phenylalanine, calories, and variety to the diet.

Table 39–2. A Sample Menu for an Older Infant

	Non-PKU Diet	Phenylalaine (mg)	PKU Diet	Phenylalaine (mg)
Breakfast	2 T barley cereal, dry	28	2 T rice cereal, dry	16
	3 T banana/tapioca, jr.	12	3 T banana/tapioca, jr.	12
	2 T egg yolk, str.	108	2 T grits/egg yolk, str.	30
	1 oz milk	204	Prescribed formula	*
		352		58
Lunch	4 T creamed corn, jr.	40	4 T carrots, jr.	12
	2 T plums/tapioca, jr.	4	2 T plums/tapioca, jr.	4
	2 T chocolate custard, jr.	28	2 T dutch apple dessert, jr.	2
	4 oz milk	204	Prescribed formula	*
		276		18
Snack	2 animal cookies	16	2 animal cookies	16
	2 oz. apple-grape juice	4	2 oz apple-grape juice	4
		20		20
Dinner	2 T turkey, jr.	188	1 T turkey, jr.	94
	2 T green beans, str.	18	2 T green beans, str.	18
	3 T peaches, jr.	12	3 T peaches, jr.	12
	4 oz milk	204	Prescribed formula	*
		422		124
Bedtime	4 oz of milk	204	Prescribed formula	*
	Total for the day:	1,274	*Total for the day:*	220

*Supplemental phenylalanine may need to be added to the prescribed formula. Usually, the supplemental phenylalanine is in the form of homogenized milk. The amount varies according to need, but must be considered as part of the total phenylalanine requirement.
PKU, phenylketonuria.

From Hunt, M.M., ed. *Phenylalanine, Protein and Calorie Content of Selected Foods.* Cincinnati: The Children's Hospital Research Foundation; 1977. Used with permission.

lenge for the parent or caregiver who knows the importance of providing a specific amount of phenylalanine from natural foods and the importance of getting the child to take the prescribed amount of formula. Children learn at a very early age how to manipulate a parent, particularly where food is concerned. The preschooler and the young school-age child are relatively easy to manage. They are still within the confines of the home, and since growth velocity is slower, it is not difficult to satisfy their hunger. It is at this age that they are learning which foods they may eat, the amount allowed, and those foods that should be avoided altogether. This is also the time when families must include in their own diets the kinds of foods (i.e., fruits and vegetables) that are beneficial to the child with PKU.

Late Childhood and Adolescence

Hunger is a significant problem for patients in this age group. During the pubertal growth spurt, increased calorie and protein needs outstrip the small increase in phenylalanine allowance expected for body mass accretion. The result is a significant decrease in prescribed phenylalanine per kilogram of body weight. In addition, busy school and extracurricular schedules, as well as a desire to blend in with peers, makes dietary compliance challenging. The many special low-protein foods have been a tremendous boon to the phenylalanine-restricted diet but they are expensive, frequently inaccessible to the individual, and high in calories. Paradoxically, adolescence may reveal the first hints of obesity, especially in girls. At either end of the spectrum nutritional goals can be achieved, but it requires flexibility in the nutrition plan and significant patient motivation (see Table 39–1).

Adults

The diet for the adult is slightly less rigid. Adults should continue to take a prescribed amount of formula in order to meet protein and other nutrient needs. The intake of phenylalanine from natural foods should continue to be restricted, but the serum phenylalanine level is often maintained slightly above the control range of 2–6 mg/dL. The practical fact is that it is not necessary to eat much extra phenylalanine from natural foods to raise the serum phenylalanine level. The occasional personal decision to abstain from formula while restricting natural protein intake has resulted in significant nutrient deficiencies as well as poor serum phenylalanine control. Elevated serum phenylalanine levels affect individuals differently. Among the more common consequences of high phenylalanine levels are obesity, headaches, emotional instability, and fatigue[25] (Table 39–3).

Pregnancy

During the early years of treating PKU, a common practice was to discontinue the diet in childhood. Consequently, many women of childbearing age have been off the diet for years. These women need to be identified and the diet resumed if they are contemplating pregnancy or are pregnant. The woman with PKU who

Table 39–3. A Sample Menu for an Adult

	Non PKU Diet	Phenylalaine (mg)	PKU Diet	Phenylalaine (mg)
Breakfast	1 C Grape-Nuts Flakes	176	1/2 cup cornflakes	48
	1/4 lg. cantaloupe	35	1/4 lg. cantelope	35
	1 slice whole-wheat toast	117	1 slice low-protein toast	15
	2 t margarine	3	2 t margarine	3
	2 C coffee	—	1 C coffee	—
	4 oz 2% milk	204	Prescribed formula	*
		535		101
Lunch	1 hamburger bun	134	1 slice bread, regular	109
	4 oz hamburger	896	1 t margarine	2
	1 oz american cheese	351	1/2 small carrot, raw	10
	15 potato chips	75	1/2 C green beans	24
	1 peach, raw	30	1 peach, raw	30
	2 Oreo cookies	52	2 sugar wafer cookie	12
	12 oz Coke	—	Prescribed formula	*
		1,538		187
Dinner	1 1/2 C spagetti	384	2 rolls lo-pro spagetti	12
	1/2 C sauce/mushroom	160	1/4 C sauce/mushroom	80
	3 oz meatballs	672	1 med. tomato, sliced	46
	1 T parmesan cheese	135	1/2 T parmesan cheese	68
	1 slice garlic bread	100	1 slice garlic bread	100
	1 C lettuce salad	18	1 C lettuce salad	18
	2 T salad dressing	10	2 T salad dressing	10
	8 oz 2% milk	408	Prescribed formula	*
		1,887		334
	Total for the day:	3,960	*Total for the day:*	622

*Supplemental phenylalanine is seldom added to the prescribed formula for an adult or adolescent. However, if it is added, the supplemental phenylalanine, usually in the form of milk, must be considered part of the total phenylalanine requirement.
PKU, phenylketonuria.

From Hunt, M.M., ed. *Phenylalanine, Protein and Calorie Content of Selected Foods.* Cincinnati: The Children's Hospital Research Foundation; 1977. Used with permission.

becomes pregnant must restrict her intake of phenylalanine from natural foods, and must achieve and maintain serum phenylalanine levels below 6 mg/dL. An excess of phenylalanine from natural foods will cause serum phenylalanine levels to increase, and the gradient of placental transfer exposes the fetus to even higher levels of phenylalanine than those reflected in maternal serum. Because of fetal growth and maternal physical changes, phenylalanine tolerance may increase during the second and third trimesters. Serum phenylalanine levels may rise if there are inadequate calories, inadequate total protein, and/or insufficient phenylalanine in the diet.

Return to Diet

Termination of the diet is no longer recommended at any age, and reinstating the diet is difficult. The underlying motivation for return to the diet has a significant effect on success, particularly over the long term. Women who are contemplating pregnancy or who are pregnant are usually motivated to follow the diet. Other adults may anticipate a significant improvement in physical or mental well-being. To return to the diet means that one must take a prescribed amount of formula, restrict the intake of phenylalanine from natural foods, and sustain this effort indefinitely. Implementation of a phenylalanine-restricted diet in a late-treated or never-treated individual is difficult and requires considerable structure in the environment. Several groups have reported significant benefits in terms of improved behavior,[8] but success is far from universal, and both food foraging and pica have been seen.

Illness

Illness and infections may elevate phenylalanine levels because of protein catabolism. Colds, sore throat, ear infections, fever, vomiting, and diarrhea are common illnesses that may result in a temporary biochemical imbalance. Appetite and formula consumption are affected by illness, and may require diet alterations. Although it is possible to design appropriate short-term solutions, as a practical matter departure from the diet for 2–3 days after a gastrointestinal illness or minor surgical procedure is not likely to cause harm. For significant illness, the metabolic dietitian should be consulted. An appropriate enteral nutrition plan can be constructed using conventional PKU products and appropriate whole-protein nutritional supplements, and custom intravenous amino acid mixtures are available for individuals who cannot be fed enterally for a prolonged period. An increasing number of medications, particularly suspensions and chewable tablets, are sweetened with Aspartame. The quantity of phenylalanine in these products varies and can be appreciable, but in most cases the benefit of the medication outweighs the increase in phenylalanine consumption, particularly for short-term courses of medication.

Follow-up and Outcome

Anthropometric measurements (linear growth and weight gain), periodic determination of serum amino acids (specifically phenylalanine and tyrosine), review of nutrient intake (formula and natural foods), and physical examinations are key components in the long-term management of PKU. Clinical well-being, adequate height and weight parameters, normal hemoglobin values, and appropriate serum amino acid levels indicate that nutritional requirements are being met. Periodic psychological assessments aid in assessing the overall development of the child or young adult.

Nutritional progress is monitored by determining serum phenylalanine levels and, if possible, the levels of other amino acids, especially tyrosine. The frequency of monitoring depends on the individual's needs and feasibility. However, the following recommendations are generally agreed to be reasonable: weekly during the first year of life; twice monthly for children 1–12 years of age; monthly for adolescents, adults, and nonpregnant women with PKU; and twice weekly during pregnancy.[10] The desired control range for serum phenylalanine is 2–6 mg/dL. This is not always an achievable range, and values slightly higher and reaching into the lows teens are acceptable for a nonpregnant older individual.

The individual diet prescription must be evaluated frequently by the metabolic dietitian to ensure that protein, phenylalanine, and calorie requirements are being met. The low-phenylalanine diet is fairly easy to maintain during periods of rapid growth in infancy and early childhood. However, dietary restriction of phenylalanine as a means of achieving and maintaining low serum phenylalanine concentrations becomes very difficult for the adolescent and adult because of significantly lower phenylalanine requirements and a declining growth rate. Termination of the low-phenylalanine diet is not recommended at any age. However, it does occur because an individual is either unwilling or unable to comply with the severe dietary restrictions.

Developing Therapies

> It seems most probable that the phenylalanine, or one of its breakdown products, circulating in the blood in concentrations much higher than normal, depresses the activity of the higher mental centres. Two possible methods of achieving this reduction seem worthy of investigation: restricting the phenylalanine intake in the diet to the basic minimum early in life and increasing the rate of excretion of phenylalanine by administering a substance which would competitively reduce tubular reabsorption.
>
> —Woolf and Vullamy's comment on the use of glutamic acid, 1951[2]

The severe restriction of natural protein and the poor organoleptic properties of the formula are barriers to long-term achievement of ideal PKU control. As a consequence, efforts have been made to develop new therapies for managing PKU.

Large neutral amino acids. The LNAA, phenylalanine, tyrosine, leucine, isoleucine, methionine, tryptophan, histidine, valine, and threonine, are known to share a common receptor for transport across the blood–brain barrier. The presence in plasma of high levels of any one amino acid with appreciable affinity for the carrier reduces the rate of transport for the other amino acids using the same carrier. Thus, high phenylalanine in serum reduces the uptake by brain of other LNAA and may increase sequestration of these amino acids in peripheral tissues. Conversely, increasing the concentration of LNAA should decrease the number of sites available for phenylalanine transport and reduce entry of phenylalanine into brain.[5]

Butcher and Vorhees developed a PKU animal model[26] in the early 1970s. Phenylketonuria was experimentally induced in these animals by the combined feeding of a moderate excess (3%) of phenylalanine in the diet and an inhibitor of phenylalanine hydroxylase, *p*-chlorophenylalanine. A supplement of valine, isoleucine, and leucine (VIL) given together with the PKU-in-

ducing diet reduced the brain/blood ratio of phenylalanine, prevented the reduction of brain weight, and prevented the behavioral deficits found postnatally in offspring of rats with maternal PKU. Using a similar PAH inhibition model, Anderson and Avins[27] administered phenylalanine or LNAA plus phenylalanine to rat pups. As expected, the serum phenylalanine increased in both groups compared to baseline, but the LNAA group had lower brain phenylalanine LNAA.

Based on the success of early animal studies, Berry et al. added a supplement of VIL to the low-phenylalanine diet of children under treatment for PKU. They showed improved performance in a series of tests of motor skill and coordination during periods of VIL supplementation that was not sustained off the supplement.[26] In a subsequent double-blind, placebo-control crossover trial,[28] improved performance was demonstrated using the Attention Diagnostic Method. More recently, Pietz et al.[15] used quantitative ^{1}H magnetic resonance spectroscopy to measure phenylalanine influx after an oral phenylalanine challenge with and without LNAA supplementation, and demonstrated a beneficial effect of LNAA in blocking phenylalanine entry into the brain. The J.F.K. Institute in Denmark developed PreKUnil in the mid-1980s. This product[27] contains a spectrum of LNAA with an emphasis on tyrosine and tryptophan. Tyrosine is an important precursor of the neurotransmitters dopamine and noradrenaline. Tryptophan is a precursor of serotonin. In a limited clinical trial, Koch et al. demonstrated a decrease in brain phenylalanine, with patient-reported improvement in overall well-being.[29] As of 2003, it had not been approved for use in the United States.

Enzyme Therapy

Phenylalanine hydroxylase enzyme. Phenylalanine Hydroxylase Enzyme (PAH) is not a good candidate for protein replacement therapy, since its catalytic activity requires the presence of an active cofactor. Gene therapy offers more hope of delivering an active enzyme to an appropriate cellular destination, most likely the hepatocyte. Proof of the principle has been demonstrated in the very rare PKU patient who received a liver transplant for other reasons. Transient expression of PAH was shown in mice given an adenovirus/PAH vector. However, gene therapy vectors are not yet ready for use in humans, particularly for diseases with effective alternative therapies.

Phenylalanine ammonia lyase. Phenylalanine ammonia lyase (PAL) is a bacterial enzyme that converts phenylalanine to transcinnamic acid. It is unsuitable for infusion, but can be administered orally and remains catalytically active in the gut and requires no cofactor. A recombinant enzyme has been produced. Sarkissian et al.[30] demonstrated partial efficacy in a PAH-deficient mouse model. It is doubtful whether PAL can obviate the need for a modified diet, but it could liberalize the allowed phenylalanine intake. A disadvantage to PAL is its prohibitive cost.

Tetrahydrobiopterin (Cofactor). Tetrahydrobiopterin (BH4) is the cofactor used to treat some forms of cofactor-dependent PKU, a genetically distinct variant of hyperphenylalaninemia.[31] Recently, several investigators demonstrated BH4 responsiveness in a subset of patients with PAH mutations. Selection of appropriate patients requires departure from conventional diagnostic pathways. Trefz et al. advocate biopterin challenge to determine in vivo responsiveness. They conclude that BH4 supplementation instead of dietary modification for those who are BH4 responsive will result in better compliance with treatment.[32] However, BH4 is not readily available in the United States, making this strategy unfeasible.

Erlandsen and Stevens proposed that certain PAH mutations predict responsiveness. They demonstrated that oral administration of excess BH4 could promote the L-phenylalanine hydroxylation reaction in these patients.[33] In a study combining mutation analysis, short-term challenge, and long-term treatment, Muntau et al. demonstrated BH4 responsiveness in nonclassical PKU patients but found no responders among classical patients.[34] Tetrahydrobiopterin tablets are more easily administered than a phenylalanine-restricted diet, but at this time they cost significantly more than formula. They are available in the United States only for investigational use in a few cofactor-dependent patients and, unfortunately, have no efficacy in classical PKU patients.

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