Diet Discontinuation Policies and Practices of PKU Clinics in the United States

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Abstract: Marked diversity in policies and practices for discontinuation of the PKU diet in the U.S. was found in a nationwide survey. Seventy-two of the 78 identified clinical centers treating PKU provided data. No clinicians are currently considering diet discontinuation at ages earlier than their present policy or practice. A definite trend toward later discontinuation of diet was identified. A few clinicians have always recommended indefinite diet continuation while many clinics have experience with children ages 9–12 who have discontinued the diet. Clinics with seven or more children off diet in this age range are significantly more likely than smaller clinics to be considering a later age for diet discontinuation.

There were 151 children approximately age 10 or older, who remain on a low phenylalanine diet. These children are followed by 29 clinics, but over one-half of them are followed by five clinics which have had long-standing policies of indefinite diet continuation. Factors associated with success in long-term management are a firm clinic policy supporting continued diet treatment; frequent, supportive contacts with the family; open discussion by staff with families and establishment of a trusting relationship; teaching children to accept responsibility for diet management from an early age. (*Am J Public Health* 70:498–503, 1980.)

Introduction

The age for discontinuing dietary treatment of phenylketonuria (PKU) has been a worldwide source of controversy for many years. Because of the rigidity and severe limitations of the low phenylalanine diet, it has seemed desirable by many clinicians to terminate diet as early as possible, in spite of limited and conflicting evidence on the consequences.

Although brain size does not increase dramatically after age 6, it has been known since 1907[1] that myelination continues through the teens, and possibly through 40 years of age. Yakovlev and Lecours[2] have pointed out that the timing of brain myelination differs markedly in different tracts and nuclei. The effect of high phenylalanine levels on continued development of the brain after age 6 is not known.

Johnson[3] found no behavioral deterioration when diet was discontinued at an early age. Pueschel, et al,[4] found that mealtimes were less stressful although many children were not enthusiastic about new foods; many parents reported improvements in behavior. Holtzman, et al,[5] showed a statistically insignificant intelligence quotient (IQ) drop between ages 4 and 6 years for five PKU children who went off diet compared with five who remained on diet. The National Collaborative Study of Children Treated for PKU reported a significantly lower IQ at age 8 in children who had discontinued diet at age 6 when compared with children who had continued the diet after age 6.[6]

Brown and Warner[7] summarized the published reports on discontinuation of diet and found that most of the data were based on follow-up of children on a normal diet for a relatively short period of time. Generally these reports showed no harmful effects, but a few studies showed drops in intelligence quotients after diet discontinuation. Their own study found a decrease in the rate of mental gain of 11 children discontinued from diet at 6–10 years of age, while 17 children of similar age remaining on diet and 26 control children continued their mental gains at the previous rate. Within the on-diet group, those with lower plasma phenylalanine levels showed a significantly greater rate of mental gain than those with higher plasma phenylalanine levels.

A similar relationship with plasma phenylalanine levels while on diet was found by Bickel and Kaiser-Grubel[8] in Germany in a group of treated children with PKU who had average IQs of 70 at the beginning of the study. A later study from England and Germany[9] of treated children with normal intelligence also showed dropping IQs following complete or partial diet discontinuation; the IQs dropped faster in those children with higher plasma phenylalanine levels. Berry, et al,[10] found a strong negative correlation ($P < 0.01$) between early serum phenylalanine levels and later IQ scores. Cabalska, et al,[11] in Poland showed drops in IQ scores for

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early-treated children of normal intelligence two years after diet had been discontinued at age 5.

There are a few reports of children being returned to diet. Murphy[12] in Ieland reported one child returned to diet after deterioration of mental development following discontinuation of diet at age 3 with behavioral improvement and an increase in IQ after diet was re-instituted. Robertson, et al,[13] described a child in Australia who resumed dietary treatment after a significant drop in IQ and appearance of difficult-to-manage behavior following diet discontinuation at age 5; the behavior improved markedly but IQ increased only slightly. In both cases described, the children had been returned to diet for less than 18 months.

The aim of this paper is to describe the diet discontinuation policies and practices of clinicians involved in the long-term management of children with PKU in the United States and to describe any discernible trends in those policies and practices.

Methods

In May of 1978, a questionnaire was sent to all identified programs involved in the treatment of PKU in the U.S.[14] Some of these programs had been previously identified through a variety of sources (programs collaborating in the National Collaborative Study of Children Treated for PKU or programs represented by visitors to the annual meetings of this group, unpublished lists of programs compiled by persons involved in the treatment of PKU, and programs known to the authors through nationwide distribution of PKU treatment materials). Additional clinics were located through telephone calls to universities, medical schools, and state health departments, and by asking each identified program to name nearby programs known to them.

Members of each program were requested to provide information on numbers and birthdates of individuals on diet and off diet, formula(s) used for treatment, source of funds for formula purchase, target goals for serum phenylalanine levels during treatment, frequency of blood level monitoring and diet analysis, frequency of clinic follow-up for on- and off-diet individuals, and clinic staffing patterns. Additionally, each program described its current practice/philosophy for discontinuation of the low phenylalanine diet by choosing the statement(s) which most closely defines it, from the following:

- We currently recommend diet discontinuation at a specific age.
  Age or Age Ranges Considered: _____
- We currently have no general recommendation for a specific age for dietary discontinuation.
- We are seriously considering recommending dietary treatment until a *later* age than is current practice.
  Age or Age Range Considered: _____
- We are seriously considering recommending dietary discontinuation at an *earlier* age than is current practice.
  Age or Age Range Considered: _____
- We do not recommend that the diet ever be discontinued.

The questionnaire was completed by staff members of given programs familiar with program content, usually the program director (physician), nutritionist, or nurse. Follow-up telephone calls were made as necessary to confirm and clarify data received.

Ninety programs involved in PKU treatment were finally identified. Private physicians not routinely treating PKU were excluded from this list. Fewer than 60 children with PKU were identified as being followed exclusively by private physicians. Four of the 90 programs are small non-specialty clinics involved in the treatment of fewer than 10 children; eight are decentralized programs coordinated by state health departments which were able to provide only fragmentary data and are involved in the treatment of fewer than 50 children. Data from these two types of programs were excluded from analysis.

The data reported are from information provided by 72 of the 78 remaining programs which are clinical centers located in 40 states where PKU is treated on a regular basis. The six clinics which did not provide adequate data for analysis within the data collection period were estimated to follow fewer than 25 children with PKU. The 72 centers represented in this report serve approximately 95 per cent of the reported individuals treated for PKU in the U.S.

In the Fall of 1979, follow-up telephone calls were made to seven clinics which had been identified as having a significant number of children continued on diet who were age 10 or over at the time of the original survey, for the purpose of further describing unique features of these clinics and delineating current policies with respect to dietary discontinuation.

A single definition for phenylketonuria has not been universally accepted because of the variable biochemical picture in individuals; however, the most widely held diagnostic criteria include any individual whose serum phenylalanine level exceeds 20 mg/100 ml, and whose serum tyrosine level is normal (1-2 mg/100 ml). Those responding to the questionnaire reported PKU caseload data on the basis of their individual clinic criteria for diagnosing PKU. It is probable that these data may include a few children who by some standards could be classified as having a variant form of PKU.

The individuals designated as "off diet" in this report are those who are consuming a non-restricted diet either as a result of parents' wishes, parents' or children's non-compliance with dietary recommendations, clinic policy, late diagnosis and unsuccessful diet management, or late-diagnosis and never treated. The individuals designated as "on diet" are those who are receiving a low phenylalanine protein substitute as part of the diet, in an attempt to keep serum phenylalanine levels low. "Early-treated" refers to those individuals treated prior to three months of age; "late-treated" refers to those treated after three months of age.

The progressively diminishing number of identified individuals with PKU who have birthdates prior to 1970 in comparison to those with birthdates after 1970 may be due to lack of clinic contact with off-diet individuals. The reported numbers of individuals on diet treatment are assumed to be fairly accurate.

TABLE 1—Reported PKU Individuals by Year of Birth*

Year of Birth	Approximate Age Range (Years)	Number On Diet	Number Off Diet	Per Cent Off Diet
1978†	0-1/2	78	0	0
1977	1/2- 1 1/2	145	1	0.7
1976	1 1/2- 2 1/2	169	0	0
1975	2 1/2- 3 1/2	130	10	7.1
1974	3 1/2- 4 1/2	136	9	6.2
1973	4 1/2- 5 1/2	134	26	16.2
1972	5 1/2- 6 1/2	94	53	36.0
1971	6 1/2- 7 1/2	65	81	55.5
1970	7 1/2- 8 1/2	46	79‡	63.2
1969	8 1/2- 9 1/2	43	90‡	67.7
1968	9 1/2-10 1/2	34	88‡	72.1
1967	10 1/2-11 1/2	23	99‡	81.1
1966	11 1/2-12 1/2	27	76‡	73.8
Prior to 1966	Over 12 1/2	67	340‡	83.5
Totals		1191	952	

*Data reported between June 1 and August 1, 1978.
†Data reported for about first half of 1978.
‡Off-diet individuals with birthdates prior to 1970 could be underreported since some centers do not keep in close contact with them.

Results

Table 1 shows that most children with PKU receive dietary treatment until age 5 or 6. However, 151 children (20 per cent of those born prior to 1969) are still on diet at approximately 10 years of age or older. This group of older children are followed by 29 of the 72 clinics responding, but 59 per cent of them are followed by only five clinics.

The data (Table 1) before 1966 are probably fragmentary for reported off-diet individuals since most mandatory state newborn screening laws were not enacted until 1965 or 1966[15] and many children born prior to that time were late-treated or untreated.

Although 86 per cent of the clinics surveyed reportedly tried to keep serum phenylalanine levels below 10 mg/100 ml, the remaining 14 per cent considered levels up to 12 or 15 mg/100 ml acceptable. A number of clinics indicated that diet is "liberalized" as children get older.

Current and anticipated diet discontinuation policies are displayed in Table 2. No regional patterns for diet discontinuation were identified, and there was little correlation between clinic directors' years of experience with management of metabolic diseases and clinic policy for diet discontinuation.

Although no specific question was asked about criteria for diet discontinuation, a number of comments were volun-

TABLE 2—Diet Discontinuation Policies of U.S. PKU Clinics

No. of Clinics	Current Clinic Policy	Anticipated Clinic Policy
0		Considering earlier age for diet discontinuation
21	Specific age recommended: *Age of Child (Years)*	Same as current policy
1	3	
5	4-5, 5	
11	5-6, 6, 5-7	
3	6-8, 8	
1	10	
9	Specific age recommended: *Age of Child (Years)*	Considering later age
2	5	
4	5-6, 6, 5-8, 6-7	
3	6-8, 6-10	
17	No specific age recommended	Same as current policy
9	No specific age recommended	Considering later age or never
16	Never recommend diet discontinuation	Same as current policy

TABLE 3—Clinics with Diet Discontinuation Experience and with No Definite Commitment to Long-term Diet Continuation

	Number of Clinics	Number of Clinics Considering Later Diet Discontinuation†	Number of Children Ages 9-12* In Each Clinic	
			Total	Median
Smaller Clinics	17	1	1-6	4
Larger Clinics	17	11	7-36	16

*Approximate ages (this includes children born in the years 1966 through 1969).

†$\chi^2 = 8.34$. $P < 0.01$. Similar results were obtained when only the numbers of off-diet children 9-12 years old were used rather than the total number in this age range.

teered. One clinic stated that if compliance with diet recommendations has been poor, the child is recommended to stay on diet, while another indicated that if compliance has been poor, the child is allowed to discontinue diet. Five clinics volunteered the information that a decision for discontinuing diet for any one child is made on an "individual" basis; seven stated that while males may be discontinued earlier, females would remain on diet, through childbearing years. There appears to be no uniformity among clinics regarding criteria for discontinuation of treatment.

Clinics included in Table 3 had not adopted a policy of prolonged diet continuation at the time of the survey and were following at least one child in the range of 9 to 12 years who had discontinued the diet. Twelve of the 34 clinics were considering a later age for diet discontinuation, and the larger clinics were significantly more likely to be considering a longer period of treatment. However, the two largest clinics discontinued the diet (at 3 years and 5 to 6 years of age respectively), and did not intend to change this procedure.

Clinics with Experience Treating Older Children

Only five clinics were confirmed to have had experience managing the diets of four or more children over the age of 10 years (Table 4). All these older children, whether early or late treated, have been on diet continuously, and none had discontinued the diet 15-18 months after the original survey was completed. All five clinics had a firm policy of indefinite continuation of treatment since inception, but one clinic did conduct limited trials with a liberalized diet and observed undesirable behavioral and IQ changes. All clinics with the exception of clinic D, have had the same director from the beginning of clinic operations.

Of the 24 children reported to be off diet in these clinics, 15 were late-treated and retarded; trial diets were either found to be not beneficial or unsuccessfully managed. Four children were determined to be PKU variants and five children discontinued therapy because of parental/child noncompliance and inability to cope with continued dietary restrictions.

Control of serum phenylalanine levels for these older children is reportedly variable. Although the clinic directors would like to keep blood levels below 10 mg/100 ml, this has been impossible to achieve in many cases.

Extensive use of Phenyl-Free® (Mead Johnson) or another phenylalanine-free formula by older children was reported only by two clinics. Lofenalac® (Mead Johnson) was consumed as the major dietary protein source for 57 per cent of the older children. Phenyl-Free was not used more extensively for a variety of reasons, including lack of interest by parents/child in replacing Lofenalac, poor acceptability, and cost in the absence of state funding or other financial support. There is no apparent relationship at present between use of a phenylalanine-free formula and successful continuation of the diet by these clinics. Successful continuation of diet management for these clinics was also not found to be contingent on public funding of formula.

Clinics represented in Table 4 are in contact with the on diet older children on a frequent basis (at least once per month), either through clinic visits or dietary monitoring, or both. Blood specimens are received at least monthly in contrast to the follow-up practices of seven of the 14 clinics (Table 3) which are treating only some of their older children; in these seven clinics, blood samples are obtained from treated older children three times a year or less.

TABLE 4—Clinics with Four or More On-Diet Children Over Age 10

Clinic	Date Clinic Began	Diet Discontinuation Policy	No. On-Diet Over Age 10	No. Off-Diet Over Age 10	Formula Use		Formula Funding Sources	Clinic Follow-up		
					Lofenalac	Phenyl-Free/ Combination*		Diet Records (No./Year)	Blood Specimens (No./Year)	Clinic Visits (No./Year)
A	1959	Never Discontinue	40	5	5	35	County, family, family insurance	3	12	12
B	1957	Never Discontinue	27	4	21	6	State, family, family insurance	3	24-52	6
C	1956	Never Discontinue	13	6	5	8	State	12	12	2
D	1964	Never Discontinue	5	7	4	1	State	12	12	6-8
E	1967	Never Discontinue	4	2	3	1	State (Lofenalac only)	12	12	3

*Combination of Phenyl-Free with Lofenalac or PKU-Aid ® (Milner Research, Ltd.).
PKU-Aid is used only by Clinic C in six cases, alone or in combination with Phenyl-Free.

All five clinics reported that the older children have made good emotional adjustments to dietary restrictions and had no significant problems. The children of normal intelligence take responsibility for keeping their own diet records and for their own diet management; they are reported to be, in general, comfortable with and committed to continued diet therapy. In one clinic, some children take their own blood specimens. Clinic staff commonly communicate directly with the child.

The five clinics reported that all of the early-treated older children are doing well in school, and are achieving according to family expectations in most cases. The oldest early-treated child on diet is followed by clinic A and was reported to be 20 years old.

Success in continuing diet therapy is attributed by these five clinics to a number of factors which can be summarized as follows:

- A firm clinic policy for indefinite diet management which is first communicated to parents when their child is very young, and is continually reinforced as the child grows;
- Supportive clinic staff and availability of staff for parental and child counseling; establishment of a trusting relationship between parents and staff;
- Frequent contact by clinic staff with families either through clinic visits, telephone contacts, or both;
- Open discussions by staff with families regarding data available on the risk/safety of diet discontinuation;
- Teaching children to accept responsibility for diet management from an early age.

Factors identified by these clinics as potential problems in continuing diet management include formula and special food cost when financial aid is unavailable, and family pressure to discontinue diet so that the child is not different from peers. Peer pressure, however, was not felt to be an outstanding problem.

Discussion

It is apparent that there is no agreement among clinicians involved in treatment of PKU regarding diet discontinuation policies. There is a trend among one-fourth of the clinics to consider diet discontinuation at an age later than has been current policy or practice. These clinics serve larger PKU populations than do those clinics not considering a later age. It seems possible that the 16 children reported to have been put back on diet had developed significant difficulties resulting from termination of diet. In any case, these children are all followed by clinics considering a later age for diet discontinuation.

In the five clinics with the largest number of older children on diet and in which very few children are off diet, clinic policy was established before comparative reports were available on diet discontinuation vs continuation. The experience of these clinics demonstrates that it is possible to keep children on diet beyond the age of 10 years when there is a strong commitment to a policy of diet continuation.

Conflicting published reports may make each clinic depend mainly on its own experience in deciding on a clinic policy. Some of the clinics which recommend discontinuation of diet at pre-school or elementary school ages have had no experience with off-diet children; others have only a small number of children who have been taken off diet and major difficulties with diet discontinuation may not have occurred. However, even some large clinics apparently are satisfied with the progress of children off diet.

Follow-up in clinics with children off diet is variable. Even if problems exist, psychological and neurological evaluations may be sporadic and subtle trends may be missed. One clinic indicated that off-diet children are dismissed from follow-up altogether.

If there are adverse off-diet consequences, another reason why these might not be detected is related to the normal variability of 10–20 points in measured IQ from year to year in any one child.[7, 16] Such variations in tested IQ could mask losses in children discontinued from diet, or indicate losses when no real loss due to PKU was present.

An additional reason for not identifying problems which may have been caused by early diet discontinuation is that the adverse effects seem to be variable. In the authors' own experience, one adolescent developed severe bleeding eczema on his extremities and an abnormal EEG after nine years on an unrestricted diet. Another child, after diet discontinuation at age 6, began having severe behavior problems (hyperactivity, short attention span, and aggressiveness) and showed a drop of more than 20 IQ points at age 8. Reinstitution of diet in both cases has reversed these difficulties.

It is clear from the literature and the authors' own experience that some children do develop problems after discontinuing diet, but there are no current criteria which can be used to predict which children will develop significant problems after diet is discontinued.

Are there criteria to individualize a decision to discontinue or continue the diet? Criteria which have been used include quality of compliance to the diet, IQ, and the family's desire to continue or discontinue diet treatment. The last criterion may not be in the best interest of the child, while the first two have been interpreted in exactly opposite ways in different clinics.

A specific age, which has been commonly used as a basis for recommending diet discontinuation, does not take into account the variability in children's development. A more useful criterion may be the physical maturity of the child. Changes in inner cranial width and presumably brain size parallel those of peak height growth.[17] This might mean that children at the same stage of physical development in relation to peak height growth might be at a comparable stage of brain development. This assumes a much later age for dietary discontinuation than the common age of six years, and would result in treating most males longer than most females. However, no data are presently available on effects of stopping the diet at these older ages, and we do not want to imply that it is ever safe to discontinue the diet.

For some clinicians, the possible detrimental emotional effects of a strict diet in a food-oriented society has consti-

tuted reason to risk diet discontinuation. Possible small emotional effects of PKU on children have been described but not in relation to continuation or discontinuation of diet in controlled studies.[18, 19] These emotional effects need to be examined in relation to dietary changes.

The financial burden of an expensive formula may also be a reason for considering early discontinuation. Formula may cost up to several thousand dollars per year (depending on the child's age and consumption). Although 35 centers in at least 18 states reported that the state health department pays 100 per cent of the cost of formula, and at 26 additional centers the state pays a percentage of the cost, at 28 centers families may pay all or part of the cost of formula.[14] It is of interest to note, however, that in several of the clinics which follow the largest number of on-diet children 10 years of age or older, families may pay all or a significant part of the formula cost.

It is to be hoped that as more experience is gained over time, consensus on diet discontinuation will be achieved. At present, however, the situation can only be described as one of uncertainty and contradiction.

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Seek the Highest Degree of Probability

To believe that ethical judgments are absolute is to become indifferent to doubts in regard to them, and thus to encourage the many unconscionable and cruel prejudices which history shows to have paraded as moral imperatives throughout the ages. If our moral judgments rest on experience and can only attain a higher degree of probability, then it is up to us to do our utmost to examine the facts carefully and to attain the highest degree of probability that is humanly possible.

Morris R. Cohen: *A Preface to Logic*, Henry Holt & Co., NY, 1944 (reprinted 1977 by Dover Publications, NY)