STATEMENT ON TREATMENT OF PHENYLKETONURIA

COMMITTEE ON THE HANDICAPPED CHILD

In response to many requests from individuals and agencies, the following statement on the present status of treatment of phenylketonuria (PKU) has been prepared. The Committee on Fetus and Newborn has reviewed the present status of neonatal screening for inborn errors of metabolism (e.g., PKU and related problems) and is reporting separately.

There is considerable discrepancy of opinion regarding the treatment of phenylketonuria. The enthusiasts say that with adequate mass screening, diagnosis, and early treatment, phenylketonuria can be eliminated as a cause of mental retardation; the doubters believe that there is need to improve screening procedures and that the efficacy of treatment leaves much to be desired.

AREAS OF AGREEMENT ON TREATMENT

In spite of discrepancies in the available data, certain facts appear to warrant acceptance, namely:

1. If PKU is detected early, and the infant is started on the proper diet before 6 months of age, and then is “adequately” maintained, the child usually will demonstrate borderline to average intelligence at 5 years of age. The earlier treatment is begun, in general, the better the result.

2. For the infant being treated with a diet low in phenylalanine, the acceptable concentration of phenylalanine in the serum probably lies above 3 mg/100 ml and below 8 mg/100 ml. Some insist that it be kept below 4-6 mg/100 ml. Concentrations over 12 mg/100 ml are almost certainly too high to achieve best results.

3. For optimum results the diet must be maintained rigidly and constantly, and at the same time the parents must also offer the child the usual affection, stimulation, discipline, and security necessary for normal behavioral development.

4. Wide individual variations exist in the dietary intake of phenylalanine (20-40 mg/lb in the newborn, and 8-20 mg/lb in the older child) which will result in acceptable levels of phenylalanine in the serum.

5. Frequent accurate determinations of the concentration of phenylalanine in the serum appears to be an integral part of management in order to maintain phenylalanine at a level which will permit normal physical growth without interfering with the development and function of the brain. Such determinations may be needed daily at the onset, then weekly or monthly, depending on the parents’ ability to carry out prescribed dietary therapy.

Because of these and other problems of diagnosis and management, most clinics attempting optimal service to children with PKU utilize a multidisciplinary team. The co-ordination of pediatric, social work, psychological, nutritional, and nursing skills in such a team, together with the assistance of a qualified biochemical laboratory, facilitates good care of these children as well as studies of possible improvements in diagnosis and treatment. Since many pediatricians complete their training without ever seeing a case, and/or without the oppor-
tunity to supervise the care of children with the disorder over a period of time, it is recommended where possible that physicians take advantage of centers combining these multidisciplinary skills for assistance in diagnosis, treatment, follow-up care, and study of patients with phenylketonuria.

REASONS FOR CONFUSION ABOUT TREATMENT

Because an adequate and reliable diet first became available in this country only in late 1958 and because early screening tests have only recently come into general use, only a few patients have been discovered within the first month of life. Even they have been treated for less than 6 years, and this period of time is inadequate for assessing child development and projecting eventual intellectual ability on optimum treatment. The picture is further confused by the fact that there are rare individuals who biochemically have PKU (i.e., have an elevated concentration of phenylalanine in the blood, or fail adequately to convert a load of phenylalanine to tyrosine as compared to both normals and carriers) and yet are of normal intelligence. Intelligence quotients in twelve such patients so far reported ranged between 96 and 120. At least one infant, identified at birth and placed on the diet for only one year, probably falls into this category. Possibly he would have been entirely normal without any therapy. Although serum levels of phenylalanine in early life are undoubtedly critical, information about them is not available in most reports of such cases. Lack of recognition of the infrequency of such cases may lead to false conclusions that the diet may never be necessary or helpful.

Another difficulty in attempting to interpret results lies in the complete lack of uniformity of opinion as to what constitutes adequate control of dietary intake and what blood levels of phenylalanine should be maintained. Resolution of this difficulty is not aided by inclusion in reports of results of dietary treatment, of patients discovered late, i.e., after approximately 9 months of age, and of those discovered earlier and treated with a “low phenylalanine diet” as prescribed by books and tables, but without benefit of frequent determinations of the concentration of phenylalanine in the blood. Even if one pooled all existing data, it is doubtful that there would be sufficient evidence to judge what level of phenylalanine in the serum constitutes satisfactory control. The available evidence strongly suggests that the correlation of amounts of dietary phenylalanine per pound of body weight with serum levels of amino acid varies not only from age to age in the same child, but from child to child within the same family, and even more so from case to case in unrelated children. It is not yet established whether the serum level of phenylalanine in a patient with PKU needs to be as low as that found in the average unaffected child or adult (i.e., below 4 mg/100 ml) or only in the range of the normal-appearing parent and sibling carriers which may vary between 8 and 12 mg/100 ml after a meal of high protein content.

Lastly, because of the difficulties of maintaining the diet, it is impossible to be sure in any particular patient that the diet was consistently maintained on a day-to-day basis or was merely resumed before known testing periods, so that the child regained the desired serum concentration for the test only.

PROBLEMS IN DIETARY TREATMENT

It is the experience of those working closely with this disease that maintenance of the diet is easy during the bottle-feeding period. Difficulties arise when the child, who should be eating all foods, begins to forage himself. Here is where parental guidance, discipline of the child, and knowledge of the nutritional content of foods and food substitutes become of crucial importance. Utilization of accurate data on the phenylalanine content of all foods is a necessity for easier and better management. A particular problem is that, as yet, there are no truly palatable bread substitutes with consistencies similar to actual bread or toast. Availability of satisfactory
bread substitutes would make maintenance of the diet a much simpler task for mothers. Other good food substitutes low in phenylalanine are also urgently needed. It is also generally agreed that severely retarded children first discovered to have PKU after the age of 2 years cannot be brought up to normal intelligence levels, but they usually can be helped. The changes wrought by the diet in these patients include amelioration of objectionable symptoms and behavior patterns, e.g., convulsions, irritability, destructiveness, short attention span, rocking, peculiar hand patterns, and eczema. It has been noted that some of the older children in the initial stages of treatment are temporarily made more hyperactive and difficult to manage, but this subsides and they ultimately become more tractable. The difficulty encountered in changing a child accustomed to eating what he wants, to a very restricted diet, as he simultaneously becomes more active and irritable, has led, in many cases, to the abandonment of the diet before beneficial effects have had a chance to manifest themselves. In older children, more than a year of therapy may be necessary before improvement is evident.

CONCLUDING COMMENT

Any objective evaluation of the results of dietary treatment of children with PKU must take into consideration a multiplicity of uncontrolled variables affecting the outcome. Included are the differing initial levels of intelligence and phenylalanine tolerance in each child, the differing heredities of each child (even in the same family), and the differing abilities and motivations of parents in maintaining the diet. However, it is clear, as stated earlier, that children with PKU can be helped if the problem is detected early enough and adequate treatment is begun promptly and maintained adequately.

This conclusion must not lead to unrealistic expectations or to over-enthusiastic application of treatment programs. Some parents are either unwilling or unable to maintain dietary treatment. Over-rigidity of dietary management has led to early death, presumably from insufficient protein intake or hypoglycemia. Over-hospitalization for rigid control has deprived children of the normal stimulation and affection of home and family, thus preventing normal psychological maturation. Exaggerated predictions for normal development regardless of the age of discovery and irrespective of the strictness of the diet or of the hereditary endowment have led to frustration and discouragement on the part of both pediatricians and parents. Much more data, taking into account all the known variables, must be accumulated and carefully analyzed before definitive statements can be advanced regarding the precise value of diet in preventing or ameliorating phenylketonuria. This will require considerable time. A collaborative study to evaluate management of this disease would be valuable.

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REFERENCES
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