Correspondence

Phenylalaninaemia

Sir,

The article on phenylalaninaemia by Blaskovics, Schaeffer, and Hack (1974) is timely in that it emphasizes the need for careful evaluation of all suspected cases of phenylketonuria; some patients may be in danger if treatment is too restrictive, others may not need any dietary treatment. The rather complex classification proposed by the authors receives some support from their own observations, but may need to be modified when improved techniques permit more accurate studies of enzyme activities. We prefer the simpler and more practical classification given by Scriver and Rosenbarg (1973). They cover 5 types described by Blaskovics et al., in three groups. (1) "Classical" phenylketonuria. (2) Phenylketonuria ('mild' variant with relaxed phenylalanine tolerance). (3) Phenylketonuria ('transient' variant).

This grouping is more helpful in the clinical context. The authors stress the importance of estimating the daily phenylalanine tolerance of patients on treatment; in the variant forms this is usually over 500 mg/day.

We estimated the daily phenylalanine intake required by 24 of our patients on a low phenylalanine diet at some point between the ages of 11 and 13 months, and at a time when the serum phenylalanine was at an acceptable level. In 18 cases the intake was between 275 and 450 mg/day (mean 365, 2 SD 120). They are all, to the best of our knowledge, cases of classical phenylketonuria. 5 patients were able to tolerate 500 to 600 mg phenylalanine/day. 4 of these returned to normal diet between the ages of 1 year 3 months and 3 years. On normal diet one patient maintains a serum phenylalanine level of 2–3 mg/100 ml in the other 3 the range is 7–13 mg/100 ml. These 5 children are all developing normally. All show impaired phenylalanine tolerance on a loading test, giving curves above that expected from a heterozygote, but below that of a child with classical phenylketonuria. Perhaps none needed treatment, yet at the time of diagnosis all but one had a serum phenylalanine above 20 mg/100 ml and metabolites of phenylalanine were detected in the urine. The fifth 'atypical' patient tolerated exactly 500 mg phenylalanine/day but was maintained on a diet for 7 years because she had 2 mentally retarded sibs.

Our present practice is to start treatment if the serum...
phenylalanine remains above 15 mg/100 ml whether or not metabolites are present in the urine. Some clinicians would put this level at 20 mg/100 ml, others at 8 or 10 mg/100 ml. A recent report (Angeli et al., 1974) describes 8 retarded microcephalic infants born to a mother with a serum phenylalanine of 18 mg/100 ml. if this level is harmful to the fetus, where dare we draw the line below which we can say there will be no harm to the neonate? After about 4 months of treatment we advise observing the effects of increasing the phenylalanine in the diet in the manner described by Blaskovics et al. At the age of one year we look at the total daily intake of phenylalanine. These two observations help to indicate the need for further strict dieting, or relaxation with a view to stopping treatment.

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Dr. Blaskovics comments as follows:

Dr. Hudson and Miss Clothier suggest that our proposed classification scheme may be modified when more precise enzymological methods are available. We would hope so, but because of adverse attitudes toward what is now considered 'unethical research', the final enzymological answers for clinical application may not be available for years to come. We may have to rely even more on various kinds of oral challenges to classify patients and our critics may 'allow' us to use natural foods as the least offensive agents to accomplish this.

Dr. Hudson and co-worker indicated that they preferred the classification scheme suggested by Drs. Scrivener and Rosenberg because it was simpler, more practical, and it embraced our 5 types. We believe fewer types are less desirable and firmly believe that every effort must be made to refine and subdivide our scheme further. To reduce the number of types because it is simpler would be comparable to returning to fewer types of glycogen storage diseases or maple syrup urine diseases.

They stress the importance of estimating the daily phenylalanine tolerance of patients while receiving dietary treatment. This is acceptable but with qualifications. Before starting standardized testing in our clinic (which we presume is not dissimilar from other clinics), we were complacently satisfied with a patient's dietary prescription when the serum phenylalanine was in an acceptable range. The tolerance could be estimated; however, we found that if less than the maximally tolerated phenylalanine intake was given, in addition to adequate calories and protein, the phenylalanine tolerance varied. For example, some children with types III and IV phenylalaninaemia were considered to have classical PKU because their initial diagnostic phenylalanine levels were quite high (between 20 and 37 mg/100 ml) and because their serum phenylalanine levels did not become subnormal while receiving 'usual intakes' for PKU infants and children. Furthermore, the serum phenylalanine levels in types III, IV, and V phenylalaninaemia will often fluctuate on a constant high phenylalanine intake. Depending upon how one defines PKU (and in most instances it is with an arbitrary fixed serum phenylalanine level and the presence of certain urinary metabolites which can be related to the serum phenylalanine levels), the diagnosis can and often will vary from day to day. Making a diagnosis in relation to the serum phenylalanine levels while the patient receives a 'normal' diet is also fraught with dangers. A normal diet varies considerably from country to country, with age, ethnicity, fads, religion, etc. We believe that the concept of a 'normal diet' has been a hindrance to progress and diagnosis.

Dr. Hudson provides the best evidence for not estimating tolerance but for using a standardized diagnostic challenge. To quote him: 'We estimated the daily phenylalanine intake required by 24 of our patients on a low phenylalanine diet at some point between the ages of 11 and 13 months, and at a time when the serum phenylalanine was at an acceptable level. In 18 cases the intake was between 275 and 450 mg/day (mean 365, 2 SD 120). They are all, to the best of our knowledge, cases of classical phenylketonuria. 5 patients were able to tolerate 500 to 600 mg phenylalanine/day. 4 of these returned to normal diet between the ages of 1 year 3 months and 3 years. On normal diet one patient maintains a serum phenylalanine level of 2-3 mg/100 ml, in the other 5 the range is 7-13 mg/100 ml'.

We do not believe that the difference between 450 mg/day and 500 mg/day is significant, and we find it extremely difficult to classify patients on the basis of a 50 mg/day difference in phenylalanine intake. The serum phenylalanine off diet in one patient (2 to 3 mg/100 ml) did not change from the on diet level (assumed by us), yet the phenylalanine intake must have doubled if not trebled on a normal diet. The same is probably true for the other 3 patients whose levels rose to 7 to 13 mg/100 ml on a normal diet.

Dr. Hudson and co-worker indicate that they increase the phenylalanine in the diet in the manner described by us after about 4 months of treatment. We would like to stress our conviction that an adequate diagnosis cannot be made on the basis of a single challenge. In our clinic and in other centres participating in the Collaborative Study of Children Treated for PKU, approximately 37 of 219 patients (16%) admitted to the study with serum phenylalanine levels >20 mg/100 ml on two occasions 24 hours apart, and with urinary metabolites consistent with PKU, failed to meet these same criteria when challenged later. Most failed to meet these criteria 3 months after the initial diagnosis had been made, but some who met these criteria during the first challenge failed at the one year challenge.

We would also make a plea for a diagnosis based on some form of standardized challenge before dietary discontinuation in all patients so that differences in response to the discontinuation may be appreciated. We believe that there are large numbers of children detected in neonatal screening programmes who have not been adequately diagnosed but will soon be eligible for termination of dietary restriction by virtue of age.
Letter: Phenylalaninaemia.

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