Phenylketonuria

Though phenylketonuria (PKU) is a rare condition, it is one of the few causes of mental retardation for which medical treatment is available. There are, however, those who doubt this statement, claiming that the evidence for it is not proven and suggesting that actual harm may be done by a low phenylalanine diet (Bessman, 1966; Birch and Tizard, 1967).

Much of the confusion that has arisen, firstly, from a failure to realize that hyperphenylalaninaemia can arise in a variety of ways and PKU of the type detected by Phenistix is only one of these. Secondly, the quality of the dietary and biochemical care has not been uniformly good, and, thirdly, the diet has been stated at a variety of ages, often when marked brain damage has already occurred.

During the past few years it has become apparent that the Phenistix test on urine for the detection of classical PKU is unsatisfactory. In October 1968 the Medical Research Council Working Party on Phenylketonuria reviewed some mass screening procedures and considered that the Guthrie test on blood (Guthrie, 1961) would be a suitable procedure although it was hoped that its introduction would not be a deterrent to the continued use and further study of other screening tests. As a result of this report the Department of Health and Social Security recommended in HM (69) 72 that Phenistix testing of infants should be replaced by the Guthrie test on blood. Since the Phenistix test does not become positive until significant quantities of phenylalanine metabolites are present in urine, the method only detected those children who had high phenylalanine levels in the blood and large quantities of metabolites in the urine. With the introduction of screening tests which detect raised levels of phenylalanine in blood (this includes the Guthrie test), greater numbers of children give a positive result and diagnosis has become increasingly complex.

Historically, the way in which PKU has been diagnosed has therefore undergone marked changes. Originally patients were found by screening populations of retarded patients in mental institutions. Later, some patients were still found in this way, but others were found by routine urine testing in infancy or by the screening of sibs of known cases. With the introduction of screening on blood samples, the net has been widened further.

Phenylalanine is an essential amino acid. It is mainly metabolized to tyrosine but catabolism also occurs to phenylpyruvic acid and subsequent conversion to other metabolites. Carpenter, Auerbach, and DiGeorge (1968) have discussed five enzymes which may be involved in the production of hyperphenylalaninaemia. These include phenylalanine hydroxylase, dihydropteridine reductase, phenylalanine transaminase, tyrosine transaminase, and p-hydroxyphenylpyruvic acid oxidase. The inhibiting effect of raised metabolites on one or more of these enzymatic mechanisms must also be considered.

In PKU of the kind recognized for a number of years now, there was a rapid rise in phenylalanine levels in the blood to high values, increased metabolites in the urine, and the development of severe mental retardation. In a few such patients direct measurement of phenylalanine hydroxylase activity in the liver has shown a deficiency (Justice, O’Flynn, and Hsia, 1967). Before the development of any dietary treatment almost all cases of PKU must have been of this type (classical PKU).

However, from screening techniques dependent on the detection of phenylalanine in blood, patients have been discovered with smaller increases in phenylalanine than seen in classical PKU. One group may be considered to have atypical PKU; during the neonatal period the plasma phenylalanine level rises more slowly and levels off below 30 mg./100 ml. Metabolites such as phenylpyruvic acid are present in smaller amounts, and these children can tolerate larger amounts of phenylalanine in their diet than those with classical PKU (Carpenter et al., 1968). Loading such patients with phenylalanine does not differentiate them from those with classical PKU, and few direct estimations of liver enzymes have been performed. Whether or not children of this type should really be treated with a low phenylalanine diet is not really known. In a further group of patients the phenylalanine level lies between 5 and 20 mg./100 ml.
plasma. There is no absolutely reliable evidence on which to base a decision as to whether diet should or should not be used, but probably this clinical situation is harmless (Carpenter et al., 1968).

High levels of phenylalanine may occur without excess phenylpyruvic acid in the urine. These findings are associated with a high intake of protein and are corrected when the intake is reduced. It is thought that the condition arises from an abnormality in the phenylalanine transaminating system (Auerbach, DiGeorge, and Carpenter, 1967). Occasionally an infant is born with delayed maturation of the enzymes necessary for the catabolism of phenylalanine. Such an infant presents all the biochemical features of PKU but on treatment he requires increasing amounts of phenylalanine to maintain a normal level in the blood. Such patients eventually grow out of the condition completely (Moncrieff and Wilkinson, 1961; Stephenson and McBean, 1967).

About a quarter of infants of low birthweight and some full-term ones show raised tyrosine levels of up to 20 mg./100 ml. plasma (British Medical Journal, 1968). It is quite usual to find associated raised levels of phenylalanine up to about 15 mg./100 ml. It is thought that the raised tyrosine or parahydroxyphenylpyruvic acid inhibits the phenylalanine hydroxylating system.

The cause of mental retardation in PKU is far from understood. There is incomplete myelinisation of the central nervous system (e.g. Malamud, 1966), and Menkes (1968) has suggested that there may be decreased synthesis of myelin. Certainly, animal experiments indicate that high doses of phenylalanine early in life can cause marked changes in the composition of the brain (Agrawal, Bone, and Davison, 1969; Chase and O'Brien, 1970). In addition, phenylalanine and its metabolites inhibit the transport and concentration of other amino acids in liver and brain, and they interfere with the activity of enzymes involved in the metabolism of amino acids (Neame, 1961; Tashian, 1961).

In the dietary treatment, the aim has been to maintain the plasma phenylalanine levels at or slightly above the normal range. In the diet natural protein is largely replaced by artificial preparations low in phenylalanine. These are generally commercial preparations containing protein hydrolysate, and they have an unpleasant taste and are often bulky. Their actual phenylalanine content varies according to the preparation used, and with some of them it can be difficult to lower the plasma phenylalanine level and yet provide sufficient nitrogen intake. Recently a pure amino acid mixture instead of a hydrolysate has been used with considerable success (Bentovim et al., 1970); it allowed the inclusion in the diet of greater amounts of phenylalanine-free foods, and was more palatable and readily accepted. As a result food problems were greatly reduced.

The treatment given to children with PKU has been of a variable standard. The diet is undoubtedly difficult, particularly since phenylalanine is an essential amino acid. Extremely worrying side effects have been observed including anaemia (Royston and Parry, 1962), retardation of growth (Fisch, Gravem, and Feinberg, 1966), severe protein deficiency (Pitt, 1967), and even death (Dodge et al., 1959). There is evidence too that early infantile undernutrition can be detrimental to intellectual development (Davison and Dobbing, 1966). The use of the diet is, however, compatible with healthy physical growth, and the fact that in some children treatment has been poor is no reason for condemning it.

Where the care of a child with PKU has been good from the early weeks of life adequate intellectual development takes place (Clayton, Moncrieff, and Roberts, 1967; Baumeister, 1967; Fuller and Shuman, 1969; Hudson, Mordaunt, and Leahy, 1970). Though the mean intelligence quotient of these early treated patients tends to lie about 10 points below that of the normal population, they are educable at normal schools and differ strikingly from most untreated or late-treated PKU children whose mean intelligence quotient is about 50.

For good results these children should be treated in centres where there is a team comprising not only the paediatrician but a dentist, biochemist, psychiatrist, and psychologist. In this way the staff gain experience in caring for these children, laboratory facilities can be geared to their needs, and proper dietary supervision can be provided. Where a dietitian looks after numbers of these children she can provide the recipes and domestic 'know-how' so essential for the mothers. How to bake a low phenylalanine birthday cake is just as important as accurate phenylalanine levels or clinical care! In my experience the single PKU patient at a hospital does not in general get this type of care, and it is in this situation that disastrous effects of poor diet are liable to occur.

It is already known that the offspring of phenylketonuric mothers not on diet show a variety of abnormalities including defective growth, convulsions, microcephaly, and congenital heart defects. The literature on this has been reviewed recently (Yu and O'Halloran, 1970), and no less than 65 of 68 offspring were mentally retarded. These children
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did not have PKU but had been damaged in utero by circulating metabolites. In due course treated PKU mothers of normal intelligence will become pregnant, and this poses a new problem. The reintroduction of a low phenylalanine diet during pregnancy is essential but presents considerable difficulties. It is unpalatable and, since there is much that is poorly understood about dietary restrictions in pregnancy and amino acids are actively transported across the placenta, severe maternal dietary restrictions may be necessary. In addition, the diet should presumably be introduced before conception. Information is sparse, though Allan and Brown (1968) have described the successful use of diet in one pregnant subject. A number of treated patients are now in their teens. Some thought must be given to the way their care will be organized since the staff of maternity units have neither the experience nor facilities for providing the total care for such women. Since women of child-bearing age at present have not been screened for hyperphenylalaninaemia, the investigation of non-specific mental retardation in a child should include examination of the plasma amino acids of the mother.

Paediatricians with considerable experience of treating these children are generally in no doubt that intellectual deterioration can be prevented, provided the diet is begun early. Their experience is such that it would be unethical to conduct a randomized clinical trial of diet at this late stage. It may be that some hyperphenylalaninaemias are being treated unnecessarily, but with more accurate diagnostic criteria this may be avoided in the future.

Two problems face the paediatrician particularly at this stage: what plasma phenylalanine level should he try to maintain with diet and when can the diet be stopped?

In the light of past experience it is to be hoped that trials will be organized for metabolic disorders other than PKU now being recognized more frequently as a result of new screening procedures. In histidinaemia for example no less than half the subjects with the biochemical stigmata are mentally normal. In addition, within one family apparently identical biochemical findings may be associated with normal intellect in one sib and severe mental subnormality in another. The indiscriminate use of diet in every infant with a raised level of histidine in the plasma is therefore to be deprecated, and it is difficult to see how the problem can be solved with either a randomized clinical trial or very careful follow-up of untreated infants.

In spite of all the difficulties, the results for well-treated PKU patients in Britain are most encourag-
ing. With increasing knowledge and awareness of the problems still posed, the future looks hopeful.

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REFERENCES


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**Corrigendum**

Annotation: Genetics of Immunity Deficiency, Syndromes, by Kay, December 1970, Vol. 7, p. 310, in the section discussing IgA deficiency, column 2, lines 29–31 should read

... the analogy of fetal haemoglobin formation in trisomy-D (Patau’s syndrome). However in trisomy-E (Edwards’ syndrome) immunological abnormalities have not been...