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SYMPOSIUM ON 'DIETARY MANAGEMENT OF DISEASE'

The dietary management of phenylketonuria

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Phenylketonuria (PKU) is an inherited inborn error in the metabolism of phenylalanine. It is transmitted by an autosomal recessive gene and there is an incidence in the United Kingdom of about 1 in 10 000. Most untreated PKUs are mentally handicapped, with a mean I.Q. of about 50, they may be hyperactive, have epileptic fits and eczema. Untreated PKUs are often fair-haired and blue-eyed though not invariably, but they grow well and have a normal life expectancy. Babies born to PKU women are generally microcephalic and therefore mentally retarded; there is a high incidence of congenital defects in these infants (Pueschel *et al.* 1977).

In 1954 the results of the first attempts at regulating the phenylalanine intake of PKU children were reported (Bickel *et al.* 1954). The results of treatment were so encouraging that by 1960 the Ministry of Health were considering screening all infants. The first screening tests were ones depending on urine but these proved unreliable and tests using blood have been available to all newborn babies in Britain since the end of the 1960s. These tests are carried out by the health visitors or midwives between the 7th and 14th d of age. However, this is not the end of the story. Although we know that early diagnosis and institution of the correct diet will prevent mental retardation and produce children who attend normal schools and have the same prospects as other children in the family, we do not know what the long-term effect of discontinuing the diet will be nor if a PKU woman will improve her chances of having a normal child by being on a strict diet at the time she conceives.

Before a child found to have a raised phenylalanine level on screening is put on a diet the diagnosis must be confirmed. A diagnosis of classical PKU is made when blood level of phenylalanine is 1·8 mmol/l or more and the urine contains abnormally high levels of phenylalanine metabolites. Most clinicians will also treat cases of hyperphenylanaemia where the levels are consistently above 0·9 mmol/l on a normal diet.

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The principle of the dietary management is that the diet must provide enough protein and phenylalanine for growth while keeping the phenylalanine level in the blood at 2–3 times the value of the normal upper limit. The level should not be allowed to stay below 0·2 mmol/l as deprivation of phenylalanine will cause failure to thrive.

The regulation of phenylalanine intake

The amount of phenylalanine that an individual child will tolerate can only be determined by a process of trial and error. An initial intake of 200 mg phenylalanine (55–60 mg/kg body-weight for an infant) is given when the diet is started and this is adjusted in the light of weekly blood tests. The range of tolerance is 200–500 mg phenylalanine daily. A baby diagnosed as PKU as the result of screening would normally be stabilized by the age of 6 weeks. Once the tolerance level has been established the total amount the baby requires in a day will not alter much; it may be slightly reduced when the initial growth spurt is over at 6 months and rise again at other periods of rapid growth. The phenylalanine is provided by natural foods. At first pasteurized cow's milk is used (30 ml cow's milk is taken to provide 50 mg phenylalanine). After weaning the phenylalanine will be provided mainly by breakfast cereals and potatoes in various forms which are measured in portions containing 50 mg phenylalanine. Meat, fish, eggs and cheese which are very rich in protein, and therefore phenylalanine, are forbidden but most fruits and vegetables other than potatoes and pulses are usually allowed freely although they do contain some phenylalanine. If these 'free' fruits and vegetables are eaten regularly in large amounts and as a result the blood phenylalanine level is too high the number of portions of potato and cereal is reduced. The basic lists of foods which may be allowed freely and foods which should only be taken in specified amounts can be found in *Diets for Sick Children*, by Dorothy E. M. Francis (1974).

Meeting the requirements for protein

Because the amount of protein from natural food is limited by the phenylalanine tolerance to 4–10 g daily a phenylalanine-free protein supplement is needed to provide for normal growth. There are a number of preparations available or being developed. Some are based on a hydrolized protein such as casein, from which the phenylalanine has been removed, others are mixtures of pure amino acids in proportions similar to a protein of high biological value, such as human milk. All the preparations have added tyrosine since normally the body acquires much of its tyrosine from the breakdown of surplus phenylalanine. The products used for babies contain some carbohydrate and fat. Vitamins and minerals are given with the required amount of milk and some additional vitamin supplements to provide a complete diet. Children on these diets should have 3–4·5 g protein/kg body-weight per d in the first year reducing to about 2 g/kg per d thereafter. As the children get older they should have more solid food and therefore a concentrated protein supplement is used, such as one of the mixtures of pure amino acids.

Vitamin and mineral supplementation of the diet

Care must be taken to see that the diet contains enough vitamins and appropriate supplements should be used. Unfortunately the protein supplements vary in their vitamin content so that it is necessary to check what vitamins are needed with the preparation chosen. The mineral content of the food supplement also varies, for example with one supplement it is necessary to add calcium, another requires extra iron and the pure amino acid preparations require a complete mineral supplement.

The importance of energy from non-protein sources

Ample energy from non-protein sources is also important, especially once the child has been weaned. Some protein supplements used for babies provide enough energy but some need to have carbohydrate added in the form of sucrose, glucose or glucose polymer and extra fat either as an emulsion of arachis oil or by using double cream for all or part of the phenylalanine allowance. Older children should have plenty of the special low-protein bread, pasta, cakes and biscuits made with protein-free flour.

It is important that the progress of these children should be carefully monitored. Frequent blood tests are needed, weekly for the first 6 months and then fortnightly until they start school, when a monthly test is adequate. In Manchester, blood is collected from a thumb or heel prick in the same way as for the original screening test. The blood is collected by the health visitor attached to the family's doctor or by a parent and posted to the laboratory. The children return to the clinic 6 weeks after confirmation of diagnosis and thereafter at three-monthly intervals. When the child attends the clinic, he is weighed and measured, a dietitian checks on his diet and a paediatrician examines the child physically. A venous blood sample is taken for a quantitative amino acid analysis and haemoglobin and serum protein levels are also checked. Between visits close contact is maintained with the families with the help of a liaison nurse.

Problems of dietary management at different stages of development

Alterations in the diet are not often needed once the tolerance of a particular child is known. In a normally well managed PKU child the phenylalanine level will rise for a number of reasons; the most likely is that the child has an infection, as any infection which puts the body into a catabolic state will produce a rise in the phenylalanine level which returns to normal when the infection has cleared. The phenylalanine level may also rise if the child is not growing because either he has been refusing the protein supplement for some time or if the energy intake is too low. If the child is not growing, he will not be laying down new tissue and therefore not using up the phenylalanine. If none of these explanations apply the child may be pinching forbidden foods or the mother may consistently be making a mistake such as giving the same weight of chips as boiled potatoes.

As the children get older we allow the blood level of phenylalanine to rise a little (Table 1). In most cases the larger helpings of 'free' food which the children eat as they get older mean a gradual increase in their phenylalanine intake which will automatically produce a rise in the phenylalanine blood level. Children who tolerate very little phenylalanine may have to have their allowance of measured foods reduced to compensate, while those who have a higher tolerance may actually be allowed an increase in the number of 50 mg phenylalanine portions. As the children get older they may be given exchange lists including previously forbidden foods such as chocolate, ordinary biscuits and tinned soups on the understanding that only one or two of these are taken on any one day. Children with a good tolerance for phenylalanine may be allowed to use up some of their allowance on eggs, meat or cheese when they are 8–10 years old. Exchange lists are not all issued at the beginning of this period as a small child can understand only a few simple rules and it is also helpful to be able to offer the child something new as he gets older, as a reward for keeping to the diet so far. Also, as the actual phenylalanine content of these manufactured foods is not known, the portions are calculated from the manufacturers' estimation of the protein content and the diet will be less accurate once these foods are included.

Table 1. *Acceptable phenylalanine blood levels at different ages in children with phenylketonuria*

Age group (years)	Phenylalanine (mmol/l)
0–2	0·2–0·4
2–4	Up to 0·5
4–8	Up to 0·6
8–10	Up to 1·0
Over 10	Up to 1·2

When a blood test shows a rise in phenylalanine level an explanation for this rise should be sought before the phenylalanine intake is altered. If tests are being carried out frequently and the increase is not very great, it is quite safe to wait to see what the next sample shows before taking action. With experience one learns which families are careless about the diet and need pulling up and which are over anxious and will only have their anxiety unnecessarily increased if they are informed every time there is a slight rise in phenylalanine levels. In case of illness parents are advised that neither the phenylalanine allowance nor protein supplement should be forced. If the infection is gastric and the treatment would normally be 24 h on clear fluids, this is what the PKU child should have; if it is a febrile illness about half the daily phenylalanine allowance should be given, probably as milk with plenty of high-energy drinks. The protein supplement should be offered in order to maintain the routine but no attempt should be made to force the child to take it whilst he is still ill. The children can be given any medicine that is necessary to clear the infection so that the normal dietary routine can be re-established quickly, as a break in routine is often the start of a period of rebellion against the diet.

PKU children who have been treated from infancy should develop normally and it is important that they should be treated as normal whenever possible. School meals can present a problem; some of the authorities are very helpful and will weigh out the correct amount of potato and vegetable and give fruit for a dessert, others will reheat a meal provided by the mother. If the school meals service will not take on this responsibility a packed lunch is the only alternative to going home for lunch. Self-catering holidays are the easiest especially with small children but it is quite possible for a PKU child to eat in a restaurant or hotel if he sticks to potato and vegetables and fruit. Holidays abroad are also possible and the children should be able to go away with their school. As the children get older, short periods when the diet may not be as carefully followed as it normally should, are not harmful. It could be much more damaging to exclude the PKU child from school outings and Scout camps and give him cause to feel resentful.

The need for support of families with phenylketonuric children

The principles of the dietary management of PKU should be readily understood by dietitians and most parents will grasp at least a simplified explanation but putting principles into practice is another matter. I am sure that unless one has lived with a child on such a diet, one cannot readily appreciate the strain it must be constantly watching to see that the child is not eating a forbidden food and knowing that three times a day an unpleasant foul tasting supplement has to be administered and that you cannot offer a chocolate as a reward for taking it without deducting something from the allowance of phenylalanine (Clothier, 1977). We try to help the families feel less isolated by bringing them to clinics with other PKU families and having two or three meetings a year for them, one of which is a Christmas party for PKU children and their unaffected siblings at which all the food is low protein, the others are evening meetings for parents, health visitors and now for some of the older children, at which we have had cookery demonstrations and talks from doctors on subjects such as current research, coming off the diet, genetics and intelligence tests. The talk or demonstration is really the excuse for giving the parents a chance to meet over a cup of coffee and to talk to people who can really understand their problems.

Dietary management of phenylketonuria in pregnancy

As the children grow up it is vital that the girls and their parents are well informed of the implications of PKU in pregnancy. Should a girl decide she wants a family in spite of the risks she must return to a strict diet and the blood levels should be kept in the region of 0·4 mmol phenylalanine/l. Once she is pregnant, all the dietary requirements of pregnancy must be met. A generous protein intake is important; we have given 100 g phenylalanine free amino acid supplement from the 10th week of pregnancy. Blood levels need careful monitoring as the phenylalanine requirements will be greater than normal during pregnancy with a sudden increase at about 20 weeks gestation. The phenylalanine requirement may more than double from the 20th week to the end of the pregnancy. The energy

intake is extremely important and women who are obese should try to lose their excess weight before they become pregnant as it is difficult to keep the phenylalanine levels down on a low-energy diet (Komrower *et al.* 1979).

In spite of the problems encountered in the management of this condition it is a very rewarding one to treat. Twenty years ago, with a few exceptions, the only PKUs who had a chance of developing normally were those born into families known to be at risk because an older child was mentally retarded and had been diagnosed as PKU. Today, unless by some tragic slip in screening, there should be no children who are severely handicapped because of PKU. Even in the families where the control is poor the children should be educatable, albeit at special schools, when 20 years ago they would have had to be put into institutions for the mentally handicapped.

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