Phenylketonuria

Some Current Problems

A circular from the Department of Health and Social Security has recommended the adoption of the Guthrie Bacterial Inhibition screening test for phenylketonuria in place of Phenistix testing of the urine. The specimen to be examined is blood taken from a heel-prick between the 6th and 14th days of life, preferably at the beginning rather than at the end of this period. The responsibility for the collection of the blood samples is divided between the maternity hospitals, the Medical Officer of Health, and the general practitioner, depending on the place of birth (hospital, home, or nursing home) and the length of stay in hospital.

Before a decision is made to embark on such an undertaking it is essential that satisfactory answers can be given to questions concerning the reliability and simplicity of the recommended test, and the efficiency of the administrative arrangements for the collection and transport of specimens to the laboratory and for the retesting of all doubtful cases. It is essential to know the cost of the operation and to decide whether it is a justifiable charge on the community. Most important of all, the treatment offered to the individuals concerned must be effective and free from risk.

There are other reliable and economic techniques available for the detection of phenylketonuria in addition to the Guthrie Bacterial Inhibition test mentioned earlier. One-dimensional chromatography and fluorimetric examination of blood have been tried extensively and shown to be entirely reliable. The administrative arrangements for the collection and transport of blood are similar to those for Guthrie testing except that the blood is collected in heparinized microcapillary tubes. These arrangements have been studied and shown to present no real problems. The cost of each of the three techniques is relatively small, providing that large numbers of babies are tested in one centre so that the best use can be made of the equipment and the staff. However, there is a significant capital outlay in respect of fluorimetry. In addition to the laboratory screening arrangement, there must be

an experienced and well-equipped unit to provide the clinical and biochemical support. In this way the diagnosis would be reliably confirmed before the start of any treatment.

At the present time the only available treatment for phenylketonuria is the introduction of a diet low in phenylalanine but containing enough protein, growth factor, and vitamins to permit normal growth. This treatment has been criticized on two accounts; the first on the grounds of overtreatment, when the children have failed to thrive and have developed skin rashes around the mouth, on the face, and around the anus and in some instances, megaloblastic anaemia. Sudden death has also been reported. In addition, it has been pointed out that protein deprivation in early infancy may in itself give rise to mental retardation. These complications are not seen today when the patients are referred to a special centre for biochemical evaluation and where experienced dietetic advice is available. The second criticism relates to the outcome of the treatment: several writers have emphasized the lack of scientifically controlled observations on the outcome of diet, and have suggested that many children might have developed normally without any phenylalanine restriction and that there is no real proof that the diet has helped these children. This question has to a considerable extent been answered by Dr. Hudson and his colleagues in the current number of the *Archives*. They have analysed the progress of 169 phenylketonuric children diagnosed and treated within the first four months of life in their own clinic, in conjunction with 169 similar cases from other reliable sources. The most important figures are those obtained on children over 2½ years of age. The intelligence scores in 97 out of 184 such children ranged between 50 and 125, with an average intelligence quotient of 90·4, compared with 105 for parents and unaffected sibs, and 53 for the affected sibs, both treated and untreated. Unfortunately there are no details about the latter children in respect of birth rank, the proportion

who had dietary treatment, and the time of introduction of this diet. These figures are of great interest and underline the need for continuing a careful record of all diagnosed and treated phenylketonuric children and their families. Another significant communication is that of Menkes and Aeberhard (1969). These workers have made a detailed analysis of the chemical composition of cerebral lipids and of the fatty acid pattern of the major white matter and myelin glycolipids in a severely retarded heterozygote offspring of a phenylketonuric mother. The lipid abnormalities seen were comparable with those previously found in patients with phenylketonuria, suggesting a common aetiological factor, most probably phenylalanine. The quality of this circumstantial evidence gives considerable support to the contention that there is something of real therapeutic value to offer to the infant diagnosed as phenylketonuric. However, it is not possible to ignore the difficulties related to dietary treatment. The preparations used are unpalatable and the children often reject them when they reach the second and third years of life; in addition, they resent the restriction of food which they see eaten by other members of the family. These problems require the clinical unit to keep a regular and good contact with the families concerned in order to instruct and encourage them, and to improve, where necessary, any environmental deficiencies. In addition we need more information concerning the degree and period of dietary restriction: Hudson has suggested that serum phenylalanine levels below 12 mg./100 ml. are satisfactory for intellectual growth, but he makes no comments concerning the time to relax the dietary restriction. Hackney *et al.* (1968) reported a significant incidence of psychological disturbance in a large group of phenylketonuric children; this is in line with the experience of the Los Angeles and Manchester groups with children suffering from galactosaemia, and in both conditions the maintenance of a strict biochemical and dietary discipline may contribute to the emotional disturbance. It is, therefore, essential that these children should be cared for by a team (or special advisory centre) which includes a dietitian, a psychologist, and a social worker in addition to the clinical and biochemical staff who would share the subsequent supervision of the case with the family doctor and the local paediatrician. This special advisory centre should be responsible for the screening laboratory together with supporting and research activities. There would be work for seven or eight such units in the United Kingdom and Northern Ireland.

One or two of the recommendations contained in the Ministry circular are open to criticism. In the first place there is a request that the test should be carried out as near to Day 6 as possible though there is no evidence to indicate that early diagnosis with treatment within the first two weeks of life offers any better prognosis than treatment started within the first four to six weeks. There are other difficulties related to the time of testing: a significant proportion of the babies born in hospital return home after 48–72 hours, and in addition many babies are born at home or in small nursing homes. This means that several people are involved in testing: the hospital doctor, the general practitioner or midwife, and the health visitor, and inevitably there is an increasing risk of errors of omission. It seems advisable to place the responsibility with one person, the Medical Officer of Health of the area in which the family live, who could arrange for his health visitor to take the blood on the first visit to the home. This would mean that the majority of babies would be tested between Day 12 and Day 16, and it would only be necessary for the hospital authorities to test babies remaining as in-patients for more than 14 days. In this way a high percentage cover of the population should be obtained and the diagnosis could be confirmed and treatment started by the fourth week of life. This would not place any unreasonable demand on the time of the health visitors: where this arrangement has been in operation the health visitors have stated that they have spent less time than they did when testing by Phenistix.

Finally, it seems advisable to set up alternative screening methods to the Guthrie Bacterial Inhibition test in order to gain further experience, and to compare their accuracy and efficiency. One-dimensional chromatography has the immediate advantage that one can identify with ease a minimum of six amino acid disturbances: phenylketonuria, tyrosinaemia, homocystinuria (as methioninaemia), maple syrup urine disease, histidinaemia, and hyperprolinaemia. It has been used in Canada and this country with complete satisfaction. There is, however, one important proviso. This technique is more sophisticated than the Guthrie test, and the interpretation of the chromatogram should be carried out by two experienced observers. The employment of this technique in areas to cover 150,000–200,000 births a year would give useful information concerning the incidence of certain amino acid disorders other than phenylketonuria, and would allow us to add to our limited but encouraging experience of the dietary therapy.

Once again this must be undertaken by centres properly equipped to handle the biochemical problems and able to afford the cots and hospital facilities required for the supervision of these infants.

There is one outcome of successful detection and treatment with important implications for the future. Between 20 and 25 girls with this disorder are born each year in this country, and will grow up into adult life capable of marriage and of bearing children. There is increasing information about the fate of the heterozygote infants of such women; they are born with a lower birthweight and a smaller head circumference, and usually their men-

tal development is significantly retarded. It may be necessary to place these women on a low phenylalanine diet throughout the pregnancy. Alternatively, it might be better to discourage them from becoming pregnant.

G. M. KOMROWER

Royal Manchester Children's Hospital,

Pendlebury,

Nr. Manchester M27 1HA

REFERENCES

- Hackney, I. M., Hanley, W. B., Davidson, W., and Lindsay, L. (1968). Phenylketonuria: mental development, behavior, and termination of low phenylalanine diet. *Journal of Pediatrics*, **72**, 646.
 Menkes, J. H., and Aeberhard, E. (1969). Maternal phenylketonuria. *ibid.*, **74**, 924.