Phenylketonuria: Therapeutic Problems

Sir,—The assertion in your leading article "Screening Tests for Phenylketonuria" (5 October, 1968) that successful dietary therapy exists for patients with phenylketonuria and a better inborn error of metabolism cannot be accepted. With regard to phenylketonuria, there seems to be little consensus that dietary therapy constitutes “satisfactory treatment.” Leaving aside considerations of experimental design, it may alternatively conclude that dietary therapy is of minimal value or may even be deleterious, prevents most but not all of the mental retardation, permits completely normal mental development, or may even produce individuals with higher IQs than their unaffected siblings. Moreover, the following serious defects of experimental design exist in all studies of the dietary therapy of phenylketonuria:

(1) Each study involves a small number of patients with exceedingly heterogeneous characteristics. It is impossible to compare in sufficient numbers the intellectual performance of patients who are matched in all but one variable—for example, length of therapy.

(2) Marked differences among studies frequently prevent valid comparisons of results.

(3) The ages of the population for whom dietary therapy seems the most beneficial (neonates), and of those of the "control" groups differ markedly. The latter include phenylketonuric siblings or unrelated, affected infants, both treated at a later age, and an institutionalized adult population. These groups do not control the environmental factors attending the interactions of the medical team, parents, and phenylketonuria. Moreover, emphasis is placed on others, the results of tests of mental development of infants (D.Q. or I.Q.) cannot be validly compared with those of tests in older children (I.Q.)

(4) No effort has been made to minimize environmental influences which might perpetuate a parent's trend of development. Since the phenylketonuric infant under treatment is highly dependent on the physician (and the parents), his response to therapy may be influenced by the attitude of these adults (perhaps the result of their ability to achieve proper dietary control, etc.). None of the studies are sufficiently controlled to separate the effects on mental development of such reinforcement from those of reduced serum phenylalanine concentrations.

(5) The criteria employed routinely for the diagnosis of "true" phenylketonuria (that is, absence of phenylalanine hydrolase activity) may not exclude other hyperphenylalaninemic syndromes, such as those caused by variant, and less efficient, forms of phenylalanine hydroxylase. The ability of these particular patients to hydrolyse phenylalanine, albeit decreased, may facilitate their biochemical control by diet. Since a significant proportion of such hyperphenylalaninemic individuals are mentally retarded, their inclusion in these studies may skew the results of well-controlled dietary therapy in favour of normal mental development and function.

(6) Lack of knowledge regarding the natural history of phenylketonuria, and particularly the interaction of environment with genotype, preclude valid conclusions from the available studies of dietary therapy.

Your desire to adopt the best screening tests for phenylketonuria and other inborn errors of metabolism is certainly justified. It is hoped, however, that the Guthrie test will be used, with other more definitive tests, to select a group of patients with true phenylketonuria, on whom a controlled trial of dietary therapy may be conducted. Only by this means we will be truly able to determine the efficacy of this therapy.—I am, etc.,

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REFERENCES


4 Hackney, J. M., Hanley, W. B., Davidson, W., and Lindsay, L., J. Pediatr., 1969, 72, 646.


Library Sale in Edinburgh

Sir,—As a former Librarian of the Royal Medical Society I welcome the interest and sympathy expressed in your leading article (1 February, p. 269) on the sale at Sotheby's of a large part of our collection.

It is hoped that this advertisement may draw attention to some of the more positive aspects of this transaction. The Society will retain its unique and priceless collection of Disserations, and in addition to this has selected over 150 volumes of particular domestic interest to represent in nuclear form the library which it formerly possessed. The Society has also taken steps to ensure that it will not sell any copies of which there may not already copies in one or other of Edinburgh's medical libraries.

The decisions which have led to this sale have not been easy to make and they have not been taken lightly. As you rightly imply, the burden of caring properly for such an enormous asset has become too much for the resources of an undergraduate society. Nevertheless, we will not entirely shift of our tangible links with the past, and what we do retain should increase in value by being better preserved and more readily accessible.

I firmly believe that this radical step, and in some respects irreversible, is in the interests of the strength and prosperity of a flourishing and important institution.—I am, etc.,

EDINBURGH.

JACK CORMACK.

Utilization of Folate in Man

Sir,—About 75% of derivatives of folic acid (pteroyl-L-monoglutamic acid) in a normal diet may be assimilated by the liver, much of this being excreted in urine or expired in the breath. These polyglutamates may, however, be completely hydrolysed in the colon. Polyglutamate excretion in the stool could not be entirely accounted for by the urinary losses of the same acid. The polyglutamates could be used by degradation of the heptaglutamate to the monoglutamate followed by absorption of the monoglutamate. The absorption of phenylalanine is limited and serum folate levels have been attributed to the inhibition of an intestinal conjugating enzyme resulting in the production of polyglutamates. Since the pH optimum of this enzyme is 5.6 and that of the intestinal fluid is 6.5 to 7.0, unless this enzyme has an unusually wide range of activity it should be ineffective.

Dr. I. Chanarin and Miss Janet Perry (30 November, p. 546) claim that the polyglutamates of folate are absorbed and utilized to about one-third of the extent of the monoglutamate forms. Examination of the data suggests that this is not so, and that in these experiments the dietary folate levels in yeast were not absorbed. Dr. Chanarin and Miss Perry describe the heptaglutamate form present in yeast as the pteroyl-L-heptaglutamate. Analysis of the folates present in yeast shows little of this form present. The forms present are the N'"-formyl derivative of either pteroylheptaglutamate or dihydropyroheptaglutamate or both (possibly derived during the analysis from the N"-formyl, L, 5,6,7,8-tetrahydropteroylheptaglutamate (63%); the N'-methyl derivative of dihydropyroheptaglutamate or tetrahydropteroylglutamate or both 20% and the N"-formyl derivative of tetrahydroxyheptaglutamate 14%. The activity is found in the 3-5% of yeast folate present as the monoglutamate. Since the proportions of these forms of the mono and heptaglutamate with substituted reduced pteroylglutamates may vary with the foodstuff and diet it seems impossible to extrapolate Dr.Chanarin and Miss Perry's results with yeast into a general statement about dietary folates.

Dr. Chanarin and Miss Perry use microbiological assay with Lactobacillus casei and Str. faecalis to assess the amount of folates present and in some cases to identify them. Using standard solutions of pteroyl-L-monoglutamic acid we find monoglutamate is assayed with Str. faecalis gave results in good agreement with the chemical standard, while L. casei gave results which varied as much as 50% from the standard. Any scientific deductions drawn from small variations in the response of L. casei or in small differential responses between L. casei and Str. faecalis are therefore probably invalid.

The major part of the paper by Dr. Chanarin and Miss Perry determines the utilization of polyglutamate by short-term studies using urinary excretion of folates, and