

aspects of the interview this is often the most important and often the most neglected.

How many doctors use nurses in clinics as "nurses"? How many can find time to teach nurses in the clinic situation? How many in reality use nurses as chaperons? I suspect most. As Salmon indicates, wise delegation on sapiential lines could see that clinics could have access to either an expert path. technician or to a qualified S.E.N. or S.R.N. as required. Both these experts being unhampered by the straightforward activities, neither should have to act as a clinic hostess. In this way much mere efficient use could be made of nursing expertise in this area of the hospital.—I am, etc.,

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REFERENCE

<sup>1</sup> Report of the Committee on Senior Nursing Staff Structure, 1966. London, H.M.S.O.

### 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 other inborn errors of metabolism cannot be accepted. With regard to phenylketonuria, there seems to be little consensus that dietary therapy constitutes "satisfactory treatment."<sup>1-3</sup> Leaving aside considerations of experimental design, one may alternately conclude that dietary therapy is of minimal value<sup>4</sup> or may even be deleterious,<sup>5</sup> prevents most but not all of the mental retardation,<sup>6</sup> permits completely normal mental development,<sup>7</sup> or may even produce individuals with higher I.Q.s than their unaffected siblings.<sup>8</sup> 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 data.

(3) The ages of the population for whom dietary therapy seems the most beneficial (neonates), and those of the "control" groups differ markedly. The latter include phenylketonuric siblings or unrelated, affected infants, both treated at a later age,<sup>8</sup> and an institutionalized adult population.<sup>9</sup> These groups do not control the environmental factors attending the interactions of the medical team, parents, and phenylketonuric infants. Moreover, as emphasized by 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.).<sup>2, 7, 10</sup>

(4) No effort has been made to minimize environmental influences which might perpetuate a patient'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 good 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 hydroxylase activity) may not exclude other hyperphenylalaninaemic syndromes, such as those caused by variant, and less efficient, forms of phenylalanine hydroxylase.<sup>11</sup> The ability of these patients to hydroxylate phenylalanine, albeit decreased, may facilitate their biochemical control by diet. Since a significant proportion of such hyperphenylalaninaemic individuals are not mentally retarded,<sup>11</sup> 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 will we be truly able to determine the efficacy of this therapy.—I am, etc.,

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### 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, however, I think necessary to draw attention to some of the more positive aspects of this transaction. The Society will retain its unique and priceless collection of *Disertations*, 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 books of which there are 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 be entirely bereft 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, sad in some ways as it is, will ultimately add to the strength and prosperity of a flourishing and important institution.—I am, etc.,

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### Utilization of Folate in Man

SIR,—About 75% of derivatives of folic acid (pteroyl-L-mono-glutamic acid) in a normal diet are claimed to be heptaglutamates,<sup>1, 2</sup> but this may not be so.<sup>3</sup> These polyglutamates could be used by degradation of the heptaglutamate to the monoglutamate followed by absorption of the monoglutamate. The action of phenytoin in producing subnormal serum folate levels has been attributed to the inhibition of an intestinal conjugase converting heptaglutamate to the monoglutamate.<sup>4, 5</sup> Since the pH optimum of this enzyme is 4.6 and that of the intestinal lumen is from 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 polyglutamate forms 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 polyglutamate folates 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<sup>10</sup>-formyl derivative of either pteroylheptaglutamate or dihydropteroylheptaglutamate or both (possibly derived during the analysis from N<sup>10</sup>-formyl-5,6,7,8-tetrahydropteroylheptaglutamate) 63%; the N<sup>2</sup>-methyl derivative of dihydropteroylheptaglutamate or tetrahydropteroylglutamate or both 20%; and the N<sup>3</sup>-formyl derivative of tetrahydropteroylheptaglutamate 14%.<sup>6</sup> A similar complexity is found in the 3-5% of yeast folate present as the monoglutamate. Since the proportions of those forms of the mono and heptaglutamate with substituted reduced pteridine rings 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-mono-glutamic acid we found microbiological assay 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.<sup>7</sup> 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