Hepatic glycogen synthetase deficiency

Sir,

The publication of the article 'Hepatic glycogen synthetase deficiency: further studies on a family', by J. R. W. Dykes and J. Spencer-Peet (1972), is very welcome. A further description of these patients will allow us to screen patients with idiopathic hypoglycaemia better. However, I want to take exception to Table VI, suggesting a system for differential diagnosis by various tests. As was described in your journal by Fernandes, Huijing, and van de Kamer (1969), there is a definite rise in blood lactate concentration in patients with a deficiency of the debranching enzyme system, as well as in patients with a phosphorylase (kinase) defect after administration of galactose. Furthermore, there is a normal response of the blood glucose in children with the phosphorylase kinase defect after glucagon administration.

Preliminary differential diagnosis of glycogen-storage disease has been made by numerous paediatricians all over the world on the basis of our screening technique outlined in our paper. These preliminary diagnoses have, with very few exceptions, been confirmed in our laboratory by enzyme assays. Exceptions are patients with idiopathic hyperlactic acidemia and Leigh's disease (Tang *et al.*, 1972; Grover, Auerbach and Patel, 1972), and defects in gluconeogenesis (Baker and Winegrad, 1970).

In my opinion the Table should read as shown. It can be seen that the various tests in patients with

debranching enzyme deficiency and with glycogen synthetase deficiency give the same results.

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Dr. J. R. W. Dykes and Dr. J. Spencer-Peet comment as follows:

While recognizing Professor Huijing's extensive experience with defects in the hepatic phosphorylase system, we would not support his contention that the blood glucose response to glucagon is always normal either in these patients or in those with debrancher

TABLE

Preliminary differential diagnosis of liver glycogen storage diseases by various tests

Enzyme defect	Fasting hypoglycaemia	Fasting blood lactate	Oral galactose load		Fasting glucagon test	
			Blood glucose	Blood lactate	Blood glucose	Blood lactate
Glucose 6-phosphatase	Severe	High	No rise	Marked rise	No rise	Marked rise
Debranching enzyme system	Moderate to severe	Normal	Rise	Marked rise	No rise when fasted (normal rise when fed)	No rise
Phosphorylase (kinase) (see Huijing, 1970)	Nil to moderate	Normal	Rise	Marked rise	Normal rise	No rise
Glycogen synthetase*	Severe	Normal	Rise	Marked rise	No rise when fasted (small rise when fed)	No rise
Normal children	Nil	Normal	Rise	No rise	Normal rise	No rise

*From Dykes and Spencer-Peet, 1972.

defects tested postprandially. Taking a blood glucose rise of more than 35 mg/100 ml as normal for this test, Spencer-Peet *et al.* (1971) found that 1 out of 3 children with low hepatic phosphorylase activity, and 4 out of 7 with deficiency of amylo-1, 6-glucosidase tested 3 hours after a meal gave only subnormal responses.

We are grateful to Professor Huijing for his comments regarding the changes in lactic acid levels after glucagon administration in phosphorylase and debrancher defects. The statement in our table was erroneous in that it did not represent the usual findings as reported by Fernandes, Huijing, and van de Kamer (1969). We do not, however, use this test in these two conditions, as a reliable preliminary diagnosis can be made from clinical features, the results of the glucagon test, and the finding of a raised erythrocyte glycogen. We trust that Professor Huijing would agree with us that a definitive diagnosis can only be made by assaying the relevant enzymes in suitable tissue samples.

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Globoid cell leucodystrophy

Sir,

In their article 'Galactocerebrosidase deficiency in globoid cell leucodystrophy of late onset' (*Archives of Disease in Childhood*, 1972, **47**, 449), Young, Wilson, Patrick, and Crome describe clinical heterogeneity of globoid cell leucodystrophy. There are increasing numbers of disorders that are clinically distinct, but which have been shown to result from a deficiency of the same enzyme, e.g. generalized gangliosidosis, Tay-Sachs disease, metachromatic leucodystrophy, and mucopolysaccharidosis I (Hurler and Scheie syndromes). If these multicomponent lysosomal enzymes are distinct,

based on a unique gene for the polypeptide core of each, then the deficiency of one and the same enzyme in several separate clinical states suggests mutations in different portions of the same gene. That is to say, such heterogeneity argues for allelism as its basis.

With one mutant allele for an enzyme, a single homozygous phenotype results with characteristic homogeneity of that phenotype. With 2 mutant alleles, 3 phenotypes are possible, i.e. phenotypes resulting from the distinct genotypes aa, aa', and a'a'. 3 mutant alleles would result in 6 possible phenotypes, and so on.

A mutation producing an autosomal recessive disorder may exist in the homozygous state, or in an allozygous state producing a phenotype called an allelic compound. The allozygous state exists when each member of a gene pair is replaced by a mutant gene, but not identical mutations as in the homozygous state. The term double heterozygote should be reserved for two mutant genes which occur at separate loci. This was aptly shown by McKusick *et al.* (1972) for mucopolysaccharidosis I. The Hurler disease (MPS I-H) is the result of a homozygous state for a mutation coding for α -L-iduronidase. The Scheie disease (MPS I-S) results from the homozygous state of a mutant allele for the same enzyme. The allozygous state (one chromosome carrying the Hurler allele and the homologue carrying the Scheie allele) results in an intermediate phenotype. If the frequency of mutant allele a is 0.01 and a second mutant allele a' is 0.0001, then excluding consanguinity, aa' is 100 times more likely to occur than a'a'. Thus a newly described 'variant' of a classical phenotype is statistically more likely to be an allelic compound than the homozygous state of a new second allele.

Invoking 2 mutant alleles for galactocerebrosidase would introduce sufficient heterogeneity to cover the cases reported and referred to by Young *et al.* Multiple mutant alleles resulting in allelic compounds as well as homozygous states make classification of similar diseases quite difficult. This is especially true where the diagnosis is dependent on a clinical phenotype and no biochemical markers exist.

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