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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