Tetrahydrobiopterin and Mild Phenylketonuria

To the editor: The concept that phenylketonuria may be cured by tetrahydrobiopterin, the cofactor of phenylalanine hydroxylase, rather than by dietary protein restriction, has generated a number of therapeutic attempts. Muntau et al. (Dec. 26 issue)\(^1\) offer a more extensive study and claim that the majority of mild cases of phenylalanine hydroxylase deficiency are variably responsive to tetrahydrobiopterin. Major issues concerning the selection of patients and the experimental design, however, weaken the significance of their findings. Patients were classified according to their pretreatment plasma phenylalanine concentration instead of their phenylalanine tolerance, but only the latter permits the definite identification of the phenotype.\(^2\) The combined phenylalanine–tetrahydrobiopterin loading test was accomplished at variable basal phenylalanine concentrations, with a procedure that might lead to erratic results.\(^3\) Phenylalanine tolerance was reported to increase during long-term tetrahydrobiopterin administration from a mean value of 18.7 mg per kilogram of body weight to 61.4 mg per kilogram.

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Editor’s note: Dr. Rimm reports having received speaking fees from the Distilled Spirits Council and the National Beer Wholesalers Association.

per kilogram, but a phenylalanine tolerance above 100 mg per kilogram is characteristic of benign forms of phenylketonuria.2

The safest conclusion to be drawn from this study is that severe phenylketonuria is not responsive to tetrahydrobiopterin, whereas consistent phenylalanine hydroxylation after phenylalanine loading is shared by variants of phenylketonuria with high residual phenylalanine hydroxylase activity — points that have already been elucidated.2,4 Whatever activity might be exerted by tetrahydrobiopterin in individual cases of phenylketonuria awaits demonstration, notwithstanding the strong biopterin response elicited by acute or chronic hyperphenylalaninemia in patients with intact cofactor metabolism.5

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TO THE EDITOR: Currently, the standard treatment for patients with hyperphenylalaninemia is dietary protein restriction. This treatment is of paramount importance, especially during pregnancy, since high levels of phenylalanine may result in intrauterine retardation of brain development. Since a low-protein diet during pregnancy may result in retarded renal development, a subsequent reduction in the number of nephrons and, potentially, hypertension in adulthood, and since we treat pregnant women who have hyperphenylalaninemia with a protein-restricted diet, it would be interesting to know whether their offspring have an increased incidence of hypertension in adulthood due to a reduction in the number of nephrons. Patients with hyperphenylalaninemia are, in general, followed closely in metabolic clinics throughout the country and thus would be subjects for this type of analysis. Therefore, researchers who are interested in exploring further the concept of a low-protein diet during pregnancy with the potential consequence of reduced numbers of nephrons and the development of hypertension in adulthood might want to study this cohort of patients who are treated with protein

TO THE EDITOR: Muntau et al. infer that tetrahydrobiopterin may be an alternative treatment for certain variants of phenylketonuria related to phenylalanine hydroxylase deficiency but not for classic phenylketonuria. The distribution of phenylketonuria phenotypes they report is unusual. Most phenylketonuria treatment centers report that 50 to 70 percent of their patients have classic phenylketonuria and that the majority of the variants involve mild hyperphenylalaninemia. For example, Clemens et al.1 in Hamburg, Germany, report that of 14 consecutive patients with newly diagnosed phenylketonuria, 8 had classic phenylketonuria, 2 had mild phenylketonuria, and 4 had mild hyperphenylalaninemia. This difference in distribution suggests some selection bias in the study by Muntau et al. It is now clear that patients with mild hyperphenylalaninemia do not need treatment,2 possibly even during pregnancy.3 This conclusion leaves a small number of patients — those with mild phenylketonuria — who may be good candidates for therapy. It is of interest that Weglage et al.,4 in Münster, Germany, found that only 3 of 87 patients with newly diagnosed phenylketonuria had a response to tetrahydrobiopterin, and in these 3, the response was only temporary, necessitating the reintroduction of dietary therapy. Treatment with tetrahydrobiopterin is very expensive — as high as $30,000 per year for an adolescent or an adult, as compared with $6,000 for phenylalanine-restricted dietary therapy.

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restriction during pregnancy for hyperphenylalaninemia.

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THE AUTHORS REPLY: Ponzone et al. question our experimental design. The definite identification of the phenotype by a single method, which they request, is unachievable, considering the complexity and multifactorial nature of the condition.1 However, both pretreatment plasma phenylalanine concentrations and the dietary phenylalanine tolerance are widely accepted, albeit rough, measures of the metabolic phenotype.2 In any case, the choice of classification is unlikely to weaken our findings.

We deliberately deviated from previous loading-test protocols that have been standardized to detect tetrahydrobiopterin deficiencies — conditions that are entirely different from those we investigated. Notably, such tests failed to uncover the high prevalence of tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency, despite their application for decades. Only a recent reinterpretation of test results has permitted 70 percent of cases involving milder phenotypes to be tentatively reclassified as tetrahydrobiopterin-responsive.3 This proportion comes close to the 87 percent we found prospectively using a loading test specifically designed to detect tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. In addition, we cross-validated data by independent oxidation testing in vivo. Any hypothetical influence on enzyme activity by phenylalanine loading, as discussed by Ponzone et al., cannot explain the significant effects of supplemental tetrahydrobiopterin on phenylalanine oxidation that we observed. First, only minimal amounts of labeled phenylalanine were involved. Second, and more important, the criterion of sensitivity remains unaffected, since it was defined as the difference in the rate of phenylalanine oxidation between two separate tests, one performed without treatment and one during treatment. Full concordance between the loading and oxidation tests in 33 of 38 patients also validates our experimental procedures.

Our study was not designed to address Hanley’s question about the number of patients with tetrahydrobiopterin-responsive phenylketonuria in a representative cohort of all hyperphenylalaninemia phenotypes. We specifically aimed to evaluate tetrahydrobiopterin responsiveness in milder phenotypes, and seven patients with classic phenylketonuria were included only as controls. Some of them had a weak response that did not meet the study criteria for tetrahydrobiopterin responsiveness (Fig. 4 of our article). Accordingly, we explicitly stated that we cannot rule out a possible response in certain patients with classic phenylketonuria. The general statement by Ponzone et al. on this issue is premature and misleading.

We share Hanley’s concern about the compound’s prohibitive price. This and other obstacles outlined in our article suggest that we exercise caution with respect to this therapy at the present time.

D’agostino refers to pathologic mechanisms not yet investigated in maternal phenylketonuria. Hyperphenylalaninemia and inadequate intake of protein during pregnancy can act additively, resulting in congenital heart defects and low birth weight.4 If the safety issues can be resolved, tetrahydrobiopterin may complement preventive strategies for maternal phenylketonuria.

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Risk Factors for Retained Instruments and Sponges after Surgery

TO THE EDITOR: In explaining the association between increased body-mass index and a higher risk of retention of a surgical instrument or sponge, Gawande et al. (Jan. 16 issue)1 suggest that the increased risk may reflect “the amount of room there is in a patient in which to lose a sponge or instru-