Phenylketonuria (PKU) was first described and defined biochemically in 1934 by Folling, and deficiency of the enzyme phenylalanine hydroxylase (PAH) was determined to be its cause in 1953 by Jervis. When efforts to purify PAH were undertaken by Kaufman, he discovered that all activity lost at a single purification step could be restored simply by mixing the two separated protein fractions. He subsequently showed that the missing factor was dihydropteridine reductase, the deficiency of which was later found to lead to hyperphenylalaninemia that did not respond clinically to reduction of the blood phenylalanine with diet. The work of the Swiss group, now ably led by Blau, developed the use of tetrahydrobiopterin (BH₄) to treat this family of disorders, which were all characterized by BH₄ deficiency. BH₄ treatment has been in use for more than a generation with excellent results in the patients and with no demonstrably harmful adverse effects. The prevailing view was that the hyperphenylalaninemas were bifurcated in two groups, those caused by varying degrees of deficiency of the apoenzyme, PAH, and those caused by varying degrees of deficiency of one of the several enzymes that were required for the biosynthesis of biopterin and the enzyme required for the reduction of dihydrobiopterin to BH₄.

This understanding lasted until 1999, when Kure et al published the results of a study that demonstrated that a fraction of patients who are PAH deficient responded to treatment with BH₄ with a dramatic lowering of plasma phenylalanine levels without any dietary alteration. Initially thought to be a response to higher BH₄ at the active site of PAH, it has been shown subsequently to be caused by stabilization of mutant PAH that was associated with a variety of different missense mutations in the gene. That other factors played a role was demonstrated by a disparity in response between siblings and other patients with identical mutations in the PAH gene. Suddenly, the neat bifurcation between the two types of hyperphenylalaninemia became blurred, with patients with PAH-deficiency responding to BH₄.

Then the uses of BH₄ expanded. Until patients with PKU were shown to be candidates for BH₄ treatment, the rare patient with BH₄ dependency (approximately 1% of all patients with hyperphenylalaninemia in the United States) received the product from a little known pharmaceutical company in Switzerland under individual compassionate-use investigative new drugs from the US Food and Drug Administration. With this larger market looming, Biomarin (Novato, California), an American company, in partnership with Merck-Serono (Darmstadt, Germany), developed the product and undertook the rigorous testing necessary to get US Food and Drug Administration approval for use in PKU. This was greeted with much fanfare by the PKU community and was the first non-dietary option for some patients with PAH deficiency ever developed. Unfortunately, the cost of the product is very high and would exceed $100 000 a year for most adults who benefited from it. Despite this, resistance from third-party payers has not been high and is a lesser problem faced by the PKU community. What many programs are demanding, however, is that this expenditure be accompanied by some quantifiable evidence of fall in plasma phenylalanine levels or, in some instances, a demonstrable increase in the permissible protein intake per day and an accompanying improvement in the quality of life. Many programs do insist that phenylalanine levels in plasma be maintained in a “therapeutic range” of <600 μM or better.

When one considers the multiplicity of mutations involved and other inter-individual variations, it is no great surprise that determining who is a responder and who is not is a rather messy business. When taken as groups and using a 30% fall in plasma phenylalanine when on a stable diet, approximately 10% of patients described as having “classical PKU,” with untreated plasma phenylalanine levels >1200 μM, respond; approximately 50% of patients with plasma phenylalanine levels between 600 and 1200 μM respond; and approximately 90% of patients with levels <600 μM (who ordinarily don’t receive dietary treatment) are considered responders. Occasionally, the responses are sufficiently dramatic to eliminate the need for any dietary restriction of protein. When assessed individually as outpatients, the responses, especially partial ones, are harder to quantify. Diets vary daily, some patients become more careless at the prospect of reducing their dietary protein limitation, and the resultados of the study, even when done as carefully as described by Burton et al in this issue of The Journal, are uninterpretable. This has led to the uncertainty that will be discussed.

The study by Burton et al is important in several other respects as well. They do demonstrate, albeit in a limited number of patients in a relatively short period, that the medication can be used safely in patients younger than the 4 years of age specified in the US Food and Drug

BH₄ Tetrahydrobiopterin
PAH Phenylalanine hydroxylase
PKU Phenylketonuria

S.C. has received research funding from and has served as an advisor to Biomarin, the manufacturer of Kuvan. He has not, nor will he in the future, derive any personal financial gain from these efforts.

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351
Administration approval. This comes as no surprise because of the experience outside the United States, but it serves to legitimize its use in this population in this country. It also raises, in a commendably restrained manner, the question of the appropriate patient population for the use of this very expensive treatment.

Kuvan has its “detractors” as well. They are concerned by the price, as we all are, and emphasize that the safety of the product has not been rigorously tested, even if it is a natural biological substance found in man. Less emphasized, but a subtlety, is that the availability of such a product undermines the long-standing basis for care of PKU, namely the dietary discipline that can maintain plasma phenylalanine in a demonstrably safe range. The difficulty in maintaining this discipline is illustrated by the problems in determining who is a responder, how to keep responders focused on the maintenance of a low plasma phenylalanine levels in the face of a “liberalized” diet, and the many, if not most, patients who lapse from ideal control as they grow older and become independent.

There are other uncertainties surrounding the use and effect of Kuvan in patients with PKU. Many practitioners define response quite liberally, and almost any fall in plasma phenylalanine is considered to be significant, in contrast to the 30% used by most careful studies and despite the difficulties aforementioned. A number of clinics report improvement in a variety of psychological and subjective performance areas, even with no fall in plasma phenylalanine level. These anecdotes have led to an underground belief that PKU patients may benefit from Kuvan therapy in the absence of a fall in plasma phenylalanine. This observation or belief occurs despite BH₄ not readily penetrating the central nervous system and never being postulated to have an effect on behavior independent of lowering of phenylalanine values. These claims fuel skepticism and might indicate a very expensive placebo effect. Finally, there is the issue of the patients with so-called “benign hyperphenylalaninemia.” These individuals with phenylalanine levels <600 μM are rarely treated and are largely indistinguishable from healthy individuals. However, no rigorous study has ever demonstrated that phenylalanine levels higher than reference range levels are safe and that the outcome in these individuals would not be better if their phenylalanine levels weren’t in the reference range. Studies published in 1985 suggest that quite subtle, but measurable, effects can be seen with phenylalanine levels higher than the reference range when careful neurocognitive testing is done. Almost all clinics have patients ordinarily defined as having benign hyperphenylalaninemia who are not performing at the expected level. Whether this is caused by high blood levels of phenylalanine or some other cause is usually not known. The availability of a product that can lower plasma phenylalanine levels in this population requires that we revisit this issue, now swept under the rug by me and other doctors.

Like so many clinics, we are delighted with the availability of Kuvan for the treatment of PKU. For our patients who respond and who have had well-controlled plasma phenylalanine levels, we have achieved either lower phenylalanine values or a striking change in phenylalanine dietary tolerance and an improvement in their quality of life. There are an equal number of patients whose lives have been, and remain, akimbo, and any judgment of their BH₄ responsiveness or improvement in their phenylalanine levels cannot be assumed to be accurate. It may be that testing for responsiveness is best carried in a double-masked fashion in the clinic, as it was during the clinical trials, even with the added burden to already overburdened clinical programs. We need, in addition, careful studies to assess changes in neurocognitive function, with or without a fall in phenylalanine levels, to answer once and for all the question of whether Kuvan can change neurocognitive outcome, especially when begun early in life, an approach empowered by the studies of Burton et al. Studies in older individuals may be too late to effect any change, and failure in this population cannot readily be used to predict the effect when started earlier, during the most fragile period of brain growth and development. Finally, a careful prospective study in patients with hyperphenylalaninemia who have levels <600 μM should be carried out. This is a radical idea, especially with patients who have a relatively good outcome, but that idea that they might do still better is at least plausible and needs to be addressed. This, too, will have to be a prospective study begun early in life, in part because of the difficulty in recruiting patients who have already been given a very favorable prognosis.

With the advent of BH₄ therapy and the testing of enzyme-replacement approaches, these are indeed, exciting times in PKU and the hyperphenylalaninemas, and data, rather than rhetoric, are the backbone of better patient care.

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