



# This Week in the Journal

December 26, 2002

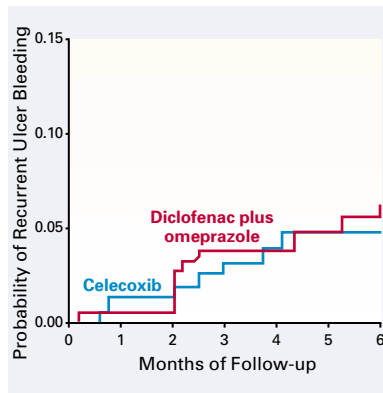
*“In the subtropics, influenza is an important cause of hospitalization among children.”*

## Hospitalizations of Children for Influenza

In Hong Kong, the seasons for influenza and respiratory syncytial virus (RSV) infection sometimes do not overlap, so that a relatively accurate estimate can be made of the effects of influenza-related acute respiratory disease in children. Using data from a well-defined population, these researchers found high rates of hospitalization attributable to influenza in children: 278.5 per 10,000 children younger than one year of age and 218.4 per 10,000 children one to less than two years of age in 1998.

*Influenza has substantial effects in children that are not widely appreciated. Findings such as these may prompt consideration of the need for influenza vaccination in children.*

see page 2097 (editorial, page 2159)



## Celecoxib versus Diclofenac plus Omeprazole to Reduce the Risk of Recurrent Ulcer Bleeding in Patients with Arthritis

This randomized, controlled trial compared treatment with celecoxib and treatment with diclofenac plus omeprazole in patients with arthritis and ulcer bleeding. The rates of recurrent ulcer bleeding during six months of follow-up were similar in the two groups (4.9 percent in the celecoxib group and 6.4 percent in the diclofenac-plus-omeprazole group).

*Treatment with a COX-2-selective NSAID was not inferior to treatment with the combination of a nonselective NSAID and a proton-pump inhibitor in reducing the risk of recurrent ulcer bleeding. However, the rates of recurrent ulcer bleeding were substantial in both groups.*

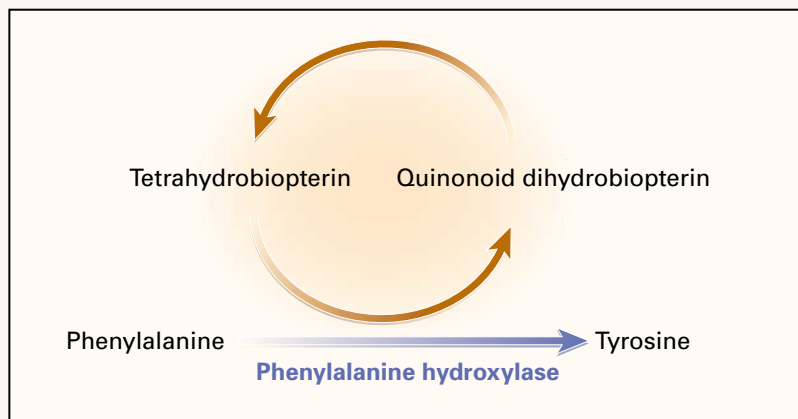
see page 2104 (editorial, page 2162)

## PERSPECTIVE

## Tetrahydrobiopterin and Dietary Restriction in Mild Phenylketonuria

Inherited disorders of intermediary metabolism are the prototypes for the treatment of genetic disorders. In each condition, accumulation of a metabolite results from a genetically determined abnormality in a metabolic pathway in which there is deficient biosynthesis either of an enzyme or of a cofactor necessary for the function of an enzyme, leading to abnormal activity of the enzyme. The outcome in patients identified by newborn-screening programs in the United States and around the world attests to the success of treatments based on an understanding of the pathophysiology of these disorders. Therapy spares children the ravages of severe illness, mental retardation, and even death. Treatments are designed to prevent accumulation of a toxic metabolite by restricting the intake of a precursor, such as an amino acid, or by enhancing the activity of the deficient pathway. However, successful treatment often requires stringent diets that have a substantial effect on the affected person's quality of life.

Phenylketonuria is one of the first inborn errors of metabolism that could be diagnosed by newborn screening. Early treatment with a phenylalanine-restricted diet has succeeded for nearly 40 years. In phenylketonuria, the inability to metabolize the essential amino acid phenylalanine results in its accumulation, which is toxic to the brain. The conversion of phenylalanine to tyrosine requires the enzyme phenylalanine hydroxylase in a complex



The Conversion of Phenylalanine to Tyrosine.

hydroxylating system that requires a cofactor, tetrahydrobiopterin (see Figure). Deficiency in phenylalanine hydroxylase activity can arise from deficient biosynthesis of the enzyme or from deficient biosynthesis of the cofactor tetrahydrobiopterin. Deficiency of phenylalanine hydroxylase is the most common cause of phenylketonuria; more than 500 mutations have been recognized in the gene that encodes phenylalanine hydroxylase. The activity of this enzyme is distributed in a continuum, from less than 5 percent of normal activity in classic phenylketonuria to high levels of activity in persons with mild hyperphenylalaninemia. Other genes control the biosynthesis of tetrahydrobiopterin, and in some forms of phenylketonuria, mutations affecting those genes result in the inability to make this cofactor. In the small percentage of patients in whom tetrahydrobiopterin production is deficient, administration of tetrahydrobiopterin has been an effective treatment.

The pathways of intermediary metabolism are important intracellular processes in which the constituents of dietary protein, fat, and carbohydrate are catabolized to provide energy and substrates for other pathways and are ultimately degraded into waste products such as carbon dioxide, water, and urea.

They are complex pathways, involving multiple enzymes; many enzymes in the intermediary stages of metabolism require cofactors. Even when biosynthesis of a cofactor is normal, the activity of an enzyme can often be increased by the administration of pharmacologic amounts of the cofactor. Vitamin B<sub>12</sub>-responsive forms of methylmalonic acidemia, pyridoxine-responsive homocystinuria, and thiamine-responsive branched-chain ketonuria are disorders in which cofactor treatment enhances enzyme activity.

Therefore, it was natural to ask whether the deficient activity of phenylalanine hydroxylase in phenylketonuria could be enhanced by the administration of tetrahydrobiopterin, an approach that would not succeed if there was little or no expression of the involved enzyme. However, if the deficiency was less severe, such a strategy might succeed. In 1999, Kure and colleagues at Tohoku University School of Medicine, in Sendai, Japan, observed that serum phenylalanine concentrations gradually decreased in four patients given tetrahydrobiopterin in a loading test. Such a test is standard in parts of the world where deficient biopterin synthesis is an important cause of phenylketonuria. But the patients studied by Kure and colleagues did not have defi-



## Alkaptonuria

Alkaptonuria is caused by mutations in the *HGO* gene and a deficiency of homogentisate 1,2-dioxygenase, which lead to an accumulation of homogentisic acid (HGA), ochronosis, and connective-tissue destruction. There is no effective therapy for the disorder. This study of the natural history of alkaptonuria examines findings in 58 patients, 57 of whom had detectable *HGO* mutations. The data are intended to serve as a base line for future trials of therapy. Nitisinone, which inhibits the enzyme that produces HGA, was administered briefly in two patients; urinary HGA levels decreased and plasma tyrosine levels increased without apparent adverse effects.

*Although nitisinone reduced HGA production in two patients, the long-term safety and efficacy of this treatment are unknown.*

**see page 2111**

cient bioprotein synthesis. The mechanism of the response was unclear, but it did not seem to correlate precisely with a particular mutation in the gene encoding phenylalanine hydroxylase. A few other reports describing small numbers of cases followed. The correlation of responsiveness with specific mutations is not consistent in these reports, but most of the patients described apparently had mild forms of hyperphenylalaninemia. Hypotheses based on the relation between mutations in the gene encoding phenylalanine hydroxylase and the three-dimensional structure of the phenylalanine hydroxylase enzyme have been proposed to explain the observations.

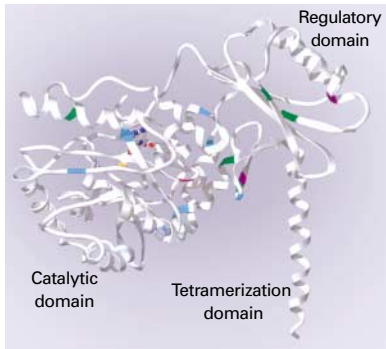
In this issue of the *Journal* (pages 2122–2132), Muntau and colleagues report on further studies designed to explore the therapeutic efficacy of tetrahydrobiopterin in patients with phenylketonuria. They show that tetrahydrobiopterin significantly lowered blood phen-

ylalanine levels in 27 of 31 patients with mild hyperphenylalaninemia or mild phenylketonuria. None of seven patients with classic phenylketonuria had a response. To assess the response, they performed an in vivo challenge with labeled phenylalanine. They also performed mutation analyses of the gene encoding phenylalanine hydroxylase and correlated the results with the response to tetrahydrobiopterin. These studies may help pave the way toward a method of predicting which patients will have a response and toward elucidation of the mechanism of that response. The observation that the mutations are in the catalytic domain and not the cofactor-binding domain of the protein raises further interesting questions about protein–cofactor interactions and the mechanism of the response.

The chief finding of the current report is that tetrahydrobiopterin treatment provides an improvement in phenylalanine tolerance. The ad-

vantages of such treatment would include decreased stringency and easier management of diet. In childhood, interactions with peers and school requirements make adherence to a restricted diet difficult. In adulthood, dietary restrictions complicate social and workplace activities. The management of pregnancy in women with phenylketonuria is a challenge that tetrahydrobiopterin treatment would ease, but its safety during pregnancy remains to be demonstrated. If treatment with tetrahydrobiopterin proves to have applicability in mild hyperphenylalaninemia, this treatment might translate into an improved quality of life for persons with mild phenylketonuria.

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### Tetrahydrobiopterin Responsiveness and Hyperphenylalaninemia

Patients with hyperphenylalaninemia due to phenylalanine hydroxylase deficiency require low-phenylalanine diets, even those with mild disease. This study explored the responsiveness of 38 such patients to the cofactor tetrahydrobiopterin. Tetrahydrobiopterin significantly lowered blood phenylalanine concentrations in most of the 10 patients with mild hyperphenylalaninemia and the 21 with mild phenylketonuria, but had no effect in the 7 with classic phenylketonuria. Seven mutations were probably and six were potentially associated with tetrahydrobiopterin responsiveness.

*Tetrahydrobiopterin responsiveness is common in patients with mild hyperphenylalaninemia phenotypes.*

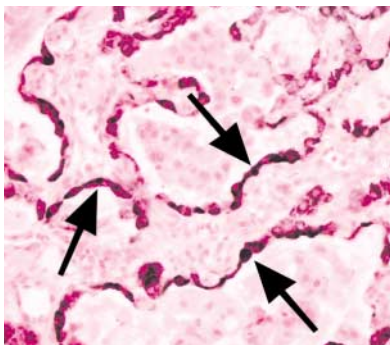
see page 2122 (Perspective, page 2094)

*“The consent forms contained detailed warnings about risks and did not overstate the prospect of benefit.”*

### Special Article: Descriptions of Benefits and Risks in Consent Forms for Phase I Oncology Trials

Phase I trials of chemotherapeutic agents have been criticized because it is believed that the consent forms investigators use promise benefits and ignore risks. This study of 272 consent forms obtained from 37 academic cancer centers and six large pharmaceutical companies does not bear out the concern that consent forms for studies of experimental treatments for cancer are inadequate or ethically flawed.

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### Mechanisms of Disease: Hydrophobic Surfactant Proteins in Lung Function and Disease

Pulmonary surfactants consist of phospholipids and the hydrophobic proteins surfactant protein B and surfactant protein C. These surfactants keep the alveoli in the lung open to the atmosphere. Mutations in the genes encoding these proteins cause a variety of pulmonary syndromes. The pulmonary diseases associated with some of these mutations exemplify the consequences of the accumulation of misfolded proteins in tissue.

see page 2141

*“The Moran decision clarifies the states’ authority and may allow physicians a larger say in decisions about managed-care coverage.”*

### Legal Issues in Medicine: Independent External Review of HMOs’ Medical-Necessity Decisions

A patient who was denied coverage for a specialized surgical procedure successfully sued her health maintenance organization (HMO). In its appeal to the U.S. Supreme Court, the HMO argued that as an ERISA plan (an employer health plan regulated by the federal Employee Retirement Income Security Act), it was exempt from an Illinois law requiring external review in disputes about the medical necessity of treatment. The Court ruled that the insurance aspects of ERISA plans are not exempt from state laws and that the HMO must offer external review.

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