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NTBC and Alkaptonuria

To the Editor:

La Du (1998) sounds an appropriate note of caution in posing the editorial question, "Are we ready to try to cure alkaptonuria?" (i.e., with homogentisate 1,2-dioxygenase [HGO] gene-replacement therapy). He suggests that localization of recombinant HGO to certain tissues might lead to accumulation of reactive intermediates of the tyrosine catabolic pathway. We would like to point out an alternative therapy for alkaptonuria (La Du 1995; MIM 203500) that obviates the problem of gene localization.

The potential treatment consists of oral administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or NTBC, in combination with some dietary restriction of phenylalanine and tyrosine. NTBC is a member of the triketone class of herbicides, which cause plants to bleach. The triketone herbicides are inhibitors of 4-hydroxyphenylpyruvate dioxygenase (HPPD) (Schulz et al. 1993), the enzyme that produces homogentisic acid (HA). Hence, NTBC should prevent the production of HA, which is believed to cause the signs and symptoms of alkaptonuria. NTBC binds to 4-HPPD in a rapid and avid (inhibitory concentration $[IC]_{50}$ = 40 nM), but reversible, fashion and inhibits both rat and human liver HPPD (Lindstedt et al. 1992; Schulz et al. 1993).

NTBC is the first effective drug therapy for the fatal hereditary disease tyrosinemia type I (Mitchell et al. 1997), which results from fumarylacetoacetate hydrolase deficiency. By reducing the supply of HA, NTBC partially blocks the formation of fumarylacetoacetate and thus lowers the concentration of oxidizing metabolites, which cause severe liver disease, hepatocellular carcinoma, and renal tubular dysfunction in infants and children with tyrosinemia type I (Mitchell et al. 1997). Early studies have shown both biochemical and clinical efficacy of NTBC (Lindstedt et al. 1992), and case reports indicate improvement in peripheral neuropathy (Gibbs et al. 1993) and renal disease (Pronicka et al. 1996). A murine model of tyrosinemia type I was treated with NTBC and responded with increased longevity, improved liver function, and partially normalized expression of hepatic mRNAs (Grompe et al. 1995). The only side effect was liver steatosis.

In humans, NTBC appears to be well tolerated for short and midterm administration and has been used at least since 1992 (Lindstedt et al. 1992). Complications—namely, photophobia and the presence of corneal crystals—have been observed in only one NTBC-treated child. These findings disappeared within 48 h, when a phenylalanine and tyrosine-restricted diet was introduced, and did not recur subsequently (Mitchell et al. 1997). Theoretically, NTBC therapy could result in neurological problems associated with tyrosinemia type II (tyrosine aminotransferase deficiency) or with tyrosinemia type III (4-HPPD deficiency) (Mitchell et al. 1997). Tyrosinemia type III has been diagnosed in only two patients, both of whom were ascertained because of neurological problems. One patient had mild ataxia, and the other had seizures and cerebral atrophy. Since these patients were evaluated because of their neurological symptoms, a causal relationship between their biochemical abnormalities and neurological symptoms cannot be determined. Patients treated with NTBC have not been reported to experience neurological problems, but dietary restriction of tyrosine and phenylalanine may be important for the prevention of any neurological, ophthalmological, and dermatological side effects of high tyrosine levels.

Because NTBC side effects have been reported for only a few patients, it may be prudent to await a more-detailed analysis of the entire group of tyrosinemia type I patients who have been treated with NTBC. However,

in anticipation that the side effects will prove to be minimal, we propose to evaluate the safety and efficacy of NTBC for alkaptonuria patients. With the cooperation of Dr. C. Ronald Scott of the University of Washington, we now are attempting to secure NTBC for use in the treatment of alkaptonuria.

Whereas gene therapy generally involves specific tissue localization, pharmacotherapy routinely employs a wide range of targets. For many metabolic disorders, this provides a distinct advantage. For example, in the treatment of cystinosis, cysteamine has beneficial effects upon a variety of organs and tissues (Gahl et al. 1995), including the kidney, muscle, cornea, and thyroid (Kimonis et al. 1995). NTBC could have multisystemic salutary effects as well, meaning that we really *are* ready to try to cure alkaptonuria.

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Gene Localization for Aculeiform Cataract, on Chromosome 2q33-35

To the Editor:

Aculeiform cataract (MIM 115700) is a form of congenital crystalline cataract that originally was described by Vogt in 1922 and was referred to as "Spiesskatarakt" (Vogt 1922). Since its original description, this entity also has been referred to as "frosted cataract," "needle-shaped cataract," or "fasciculiform cataract" (Parker 1956). This phenotype is characterized by fiberglasslike or needlelike crystals projecting in different directions, through or close to the axial region of the lens (fig. 1). Some crystals may be >1 mm in length, and their biochemical composition is not known. This type of cataract is considered to be different from the corraliform cataract, which does not show the needlelike projections. This opacity does not appear to respect the sutures or the direction of the lens fibers (François 1963) and appears to originate from the fetal and postnatal nuclei, suggesting a congenital origin with some postnatal progression, if any. The opacity causes a variable degree of