

fluence methylmercury absorption and neurotoxicity, which warrant investigation in humans.

Thus, perhaps the greatest contribution of this study is to highlight the potential of targeting heavily exposed immigrant groups in studies designed to assess the risks associated with environmental exposures. A prospective longitudinal study of Vancouver Chinese immigrants could provide valuable information to address the outstanding issues relating to the long-term developmental neurotoxicity of prenatal methylmercury exposure noted above. Other immigrant groups with unusually high exposures have also been identified, including Hmong and Laotian residents in the upper Midwest, who consume large quantities of locally caught environmentally contaminated fish, and migrant farm workers exposed to high doses of pesticides. Although the logistics of recruiting participants from poorly educated, non-English speaking groups, who may also be transient, is challenging, the payoff from the effort invested is likely to be considerable in terms of the valuable information to be gained regarding risks from low-level environmental exposures.

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A DEEPER LOOK INTO CYSTEAMINE ABSORPTION FOR THE TREATMENT OF CYSTINOSIS

Cystinosis, a rare autosomal recessive disorder of lysosomal cystine storage, can be treated successfully with oral cysteamine. Without treatment, patients experience deterioration of kidney function, and then other organs failures.¹ Cystine depleting therapy allows the delay or prevention of life-threatening renal and postrenal transplant complications of cystinosis.²⁻⁵ The once disastrous natural history of cystinosis, with death in childhood prompting physicians to dread making the diagnosis, has been changed to a favorable prognosis.

Cysteamine therapy, of course, is not as easy as it sounds. The free thiol smells and tastes awful, resembling the stench of rotten eggs, and it has to be taken assiduously every 6 hours⁶; some patients cannot tolerate cysteamine due to gastrointestinal side effects, that is, nausea and vomiting.⁷ Other problems in cystinosis include making the diagnosis, which even nowadays is missed quite often. Affected patients are completely normal at birth. They develop signs and symptoms of renal Fanconi syndrome, such as retarded growth, over the period of their first year of life. In fact, cystinosis is the single most common cause of renal Fanconi syndrome in

childhood. Therefore, any findings pointing to renal proximal tubular injury, such as generalized aminoaciduria, phosphaturia, glucosuria, low molecular weight proteinuria, metabolic acidosis, or rickets, should lead to a biochemical workup for cystinosis.

Typical crystals in the cornea can aid in making the diagnosis, but an experienced ophthalmologist is needed and the crystals might be absent before age 16 months.⁸ By then, the diagnosis has often been made. However, even in a setting of delayed diagnosis and treatment, cysteamine has proven beneficial.^{4,5} It should be continued after kidney

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transplantation, which does not cure the nonrenal components of this systemic disorder.

Nephropathic cystinosis requires treatment with cysteamine. Thus, any study in helping to understand the pharmacology of cysteamine can be of benefit. So far, pharmacological studies have addressed classic questions such as plasma levels and half-life times, but no studies in humans have determined where and how cysteamine is absorbed. Given the growing cystinosis community in the United States and abroad, studies like those of Dohil et al are most welcome.⁹ He and his team recruited six patients with cystinosis and eight controls under an institutional review board–approved protocol for the study of cysteamine absorption. To answer the question of where cysteamine is absorbed in the intestinal tract, they developed a special nasogastric tube, which enabled them to selectively apply cysteamine to specific parts of the intestinal tract.

They showed that cysteamine is absorbed in the small intestine much better than in the stomach or in the cecum. Cystine depletion, the biochemical measure for success of treatment, was also greatest following cysteamine delivery to the small intestine. It will be quite interesting to learn where the current drug preparation cysteamine bitartrate, Cystagon™, is absorbed. Based on these findings, enteric-coated cysteamine appears superior and should be studied in more detail in patients with cystinosis. Thus, the findings of this study might pave the way for different drug preparations with the prospect of increasing compliance for the treatment of cystinosis. A caveat for changing the current form of cysteamine into an enteric-coated form is the obligate need for a rapid increase of cysteamine blood levels to deplete the cell's lysosomes of cystine. Enteric coating could result in a slow release of cysteamine, which would abolish the desired pharmacological effect.⁶ We also do not know the certainty with which cysteamine can be predicted to be released from an enteric-coated preparation at a specific site in the intestine.

Dohil et al also measured gastrin levels in response to cysteamine administration. Their previous findings, suggesting the need for acid-suppression therapy with cysteamine treatment,^{10,11} have led to greater circumspection, with the finding that “not all cystinosis patients require acid-suppression therapy.” This finding is quite important for some cystinosis patients who already endure multidrug regimens. Furthermore, the device employed in this study, a custom-made nasogastric tube with

special features, offers the possibility to investigate other important aspects of pharmacodynamics and pharmacokinetics, particularly in children.

To go through the hurdles of clinical research in rare inborn errors of metabolism deserves respect and support. Parents of children with cystinosis and adults with cystinosis rely upon allies such as Dohil et al.

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