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Editorial

Penicillamine as a Controversial Treatment for Wilson's Disease

Peter A. LeWitt, MD

Departments of Neurology and Psychiatry, Wayne State University School of Medicine, Detroit, Michigan, and the Clinical Neuroscience Center, Southfield, Michigan, U.S.A.

"Facts are the enemies of truth!" quipped a bewildered Don Quixote, a conclusion that readers of this "Controversies" section might well share. Professors Brewer and Walshe have each marshaled an army of facts in support of their personal "truths" on pencillamine's current role. Whereas management of Wilson's disease follows some of the most logical treatment strategies in all of clinical neurology, the optimal means for removing copper from the brain (and elsewhere) have not achieved consensus. Controversy seems to have arisen with each new generation of medications for Wilson's disease. Professor Brewer's work has given strong impetus to considering several alternatives to penicillamine, whereas Professor Walshe views the successes of his long experience with this drug as good enough to merit its continued use. All of the medications that chelate copper or stimulate hepatic metallothionen are far less risky than what might be regarded as the "gold standard" of Wilson's disease therapy, heterologous liver transplantation. However, the current pages of *Movement Disorders* tell us that the role of a drug now in its fifth decade of use, penicillamine, is still a matter of great controversy.

Professors Walshe and Brewer have both made substantial contributions to understanding the pathophysiology and clinical phenomena of Wilson's disease, and we owe them a great debt for their willingness to share their views on this important topic in *Movement Disorders.* Their clinical experience is as extensive as that of anyone who has ever treated Wilson's disease. Why, then, such disparity in conclusions that the use of penicillamine is "the treatment of first choice"[1] or "inexcusable now"[2]? The diversity in viewpoints may be attributable in part to difficulties inherent in the scientific study of this disorder. Anecdotal experience and small groups of cases have been especially influential on what is known about Wilson's disease because controlled clinical investigations have been difficult to conduct and interpret. Confronting the study of Wilson's disease therapeutics are the problems of its rarity, its clinical heterogeneity in distribution and extent of organ involvement, the marked variability in rate of clinical deterioration, and the inconsistent patterns of clinical response to various therapeutic interventions. Long-term study of patients is necessary to reach meaningful conclusions, even for patients who have undergone intensive study in metabolic research units.

Some of the most basic issues pertaining to Wilson's disease therapeutics do not square with attempts at a logical, simplistic view of the disorder. Few would argue with the notion that the primary goal of therapy is to rid the brain of excessive copper. However, assumptions that a copper chelator like penicillamine acts solely through this mechanism may not be the full story. For example, Hourapian and colleagues[3] reported on the autopsy results of nine patients with Wilson's disease treated chronically with penicillamine. Several of these patients achieved complete resolution of neurologic deficits. Despite this clinical outcome, eight of the brains showed markedly elevated copper concentrations and extensive pathologic changes. Furthermore, the severity of the neuropathologic lesions in these cases was minimally correlated with the regional cerebral content of copper. Improvements in a patient's brain imaging, as illustrated in Professor Walshe's article, are not necessarily the equivalent of effective decoppering or reversal of histologic damage. Clinicians can follow the diminution of Kayser-Fleischer rings or timed urinary copper excretion as guides to the outcome of therapy, but the neurologic course is not always correlated. The limitations of moni-

Address correspondence and reprint requests to Peter A. LeWitt, MD, Clinical Neuroscience Center, 26400 West Twelve Mile Road, Suite 110, Southfield, MI 48034, U.S.A.

toring tools may engender conservatism in accepting the reports of new therapeutic claims, as Professor Walshe seems to have done with the conclusions of Professor Brewer's extensive studies with tetrathiomolybdate and zinc. On the other hand, Professor Walshe readily acknowledges the toxicity and therapeutic limitations of penicillamine despite his long-term advocacy for this drug. Clinicians wanting to explain to their patients the pros and cons of all available treatments have a formidable task ahead of them. Fortunately, there is also the option of advocating participation in ongoing controlled clinical trials that currently are investigating optimal management of Wilson's disease.

In 2001, the Movement Disorder Society will sponsor a symposium on neurologic aspects of Wilson's disease. One aim of this symposium will be to foster consensus viewpoints for treating Wilson's disease amidst many controversies. The hard work ahead is to learn more about this disorder from the limited numbers of Wilson's disease cases around the world. Recent developments such as a homologous disorder of copper metabolism in the Long Evans Cinnamon rat[4,5] will be valuable at guiding future therapeutic strategies for Wilson's disease. Learning more about brain copper and its binding proteins may be important goals not only for the future study of Wilson's disease therapeutics but, possibly, for other neurodegenerative disorders as well.[6]

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