

This Week's Citation Classic

Walshe J M. Penicillamine, a new oral therapy for Wilson's disease.

Amer. J. Med. 21:487-95, 1956.

[Thorndike Mem. Lab. and 2nd and 4th Med. Services, Boston City Hosp.:

Dept. Med., Harvard Med. Sch., Boston, MA; and Med. Unit, Univ. Coll. Hosp.

Med. Sch., London, England]

The ability of penicillamine to promote the excretion of a great excess of copper was first observed in a patient with Wilson's disease at the Boston City Hospital in May 1955. This observation led directly to the introduction of penicillamine for the treatment of Wilson's disease and other heavy metal intoxications. [The SC¹® indicates that this paper has been cited in over 255 publications since 1961.]

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"The introduction of a new drug into clinical medicine is, today, the business of the multinational pharmaceutical companies. The cost of such a venture is now in excess of 50 million dollars—research and development on this scale is far beyond the reach of the individual physician. Yet this is the story of exactly how such a task was initiated.

"In 1955, I was working on the liver unit of the Thorndike Memorial Laboratory at Boston City Hospital. One spring morning we were asked by Denny-Brown to see a patient, in the neurological unit, who was suffering from Wilson's disease, an inherited metabolic disorder in which excess copper accumulates in the liver and brain with disastrous effects on both organs. While returning to Thorndike it occurred to me that penicillamine, a derivative of penicillin, had the correct structural formula to bind copper and might well promote its elimination from the body. This notion was based on an earlier observation that patients treated with large doses of penicillin excreted penicillamine (some at least in the -SH state) in their

urine.¹ By good fortune, Charles Davidson, chief of the liver unit, was able to obtain a few grams of this rare compound, first from Merck Sharp & Dohme and later from John Sheehan, professor of chemistry at Massachusetts Institute of Technology. I took the first gram to prove this was safe and Denny-Brown's patient took the second. We both survived and I was rewarded by finding a tenfold increase in the urinary copper after these tests.

"Before returning to England, I bought all the available supplies of penicillamine in the Eastern US so that the project could be continued. I now had my next stroke of good fortune: further patients with such a rare condition as Wilson's disease might have been impossible to find had not my father been Britain's leading neurologist; he was able to persuade his colleagues to allow me to test this new treatment on their patients. In all cases it induced a spectacular increase in urinary copper excretion.

"This work was offered to and immediately accepted for publication by the *American Journal of Medicine*, but it only described the cupriuretic effects of penicillamine; it did no more than cautiously predict therapeutic benefit for the patients. Further, it suggested that the new drug might be of value in other heavy metal poisonings; its use in the management of cystinuria and rheumatoid arthritis was to be reported from other centres in the future.²

"If this work is frequently quoted in the literature (all too often it appears to be taken for granted), it is because it was the first description of a new therapy for a hitherto invariably fatal illness. It may be added that it was the first specific drug able to reverse any inherited metabolic disease and for the first time it became possible to reverse the course of a degenerative disease of the nervous system. A more recent account of the treatment of Wilson's disease with penicillamine can be found in *Metabolic and Deficiency Diseases of the Nervous System*.³

1. Walshe J M. Disturbances of aminoacid metabolism following liver injury. *Quart. J. Med.* 22:483-505, 1953.

2. Gordon D A, ed. Proceedings: International Symposium on Penicillamine, 8-9 May 1980. Miami, FL. (Whole issue.) *J. Rheumatology* 8(Suppl. 7), 1981. 181 p.

3. Vinken P J & Bruyn G W, eds. *Handbook of clinical neurology. Volume 27. Metabolic and deficiency diseases of the nervous system. Part I.* Amsterdam: North-Holland, 1976. 554 p.