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This Week's Citation Classic®

Sternlicb I & Scheinberg I H. Prevenlion of Wilson's disease in asymptomatic patients. *N. Engl. J. Med.* 278:352-9. 1968. [Albert Einslein College of Medicine and Bronx Municipal Hospital. Bronx. NY]

Forty-two subjects in whom the diagnosis of Wilson's disease was established based on biochemical criteria were treated with penicillamine. All remained asymptomatic during a period of observation of 142 patient-years. An estimate based on the natural history of Wilson's disease suggested that symptoms could have been expected to develop in at least eight of the subjects. [The *SCI®* indicates that this paper has been cited in more than 225 publications.]

Prevention of Wilson's Disease

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In 1947 Wilson's disease was a curious, neurological and hepatic syndrome that was diagnosable only by clinical examination and was invariably fatal by adolescence or soon thereafter. Over the next decade five discoveries led to diagnosability—by biochemical criteria alone; and treatability—by four pills daily.

First, in 1948, C.G. Holmberg and C.B. Laurell,[1] in Sweden, discovered a normal blue protein of plasma that contained several atoms of prosthetic copper. Second, in the same year J.N. Cumings,[2] in Britain, finding large excesses of copper in the brains and livers of patients, suggested that this copper was probably theetiologic agent that caused the disease and that its removal by British antilewisite might be therapeutic.

Third, in 1952,1.H. Scheinberg and D. Gitlin,[3] in the US, reported that deficiency of ceruloplasmin appeared to be diagnostic of Wilson's disease, though this deficiency alone soon proved not to be a sufficient diagnostic criterion. Fourth, as a result of G. Menghini's[4] development in Italy of a needle that made hepatic biopsy safe and feasible, a ceruloplasmin of <20 mg/dl *and* a hepatic copper >250 µg/g dry weight appeared to be a pair of criteria sufficient for the diagnosis—*even in the absence of symptoms.*

Finally, in 1956 J.M. Walshe,[5] working in the US and Britain, discovered that penicillamine was safe and effective oral therapy for Wilson's disease.

Over the next several years we realized that these discoveries might make it possible to prolong the asymptomatic state indefinitely. Indeed, by 1968 we thought we had proved that they could. We submitted our proof to the *New England Journal of Medicine.*

The *Journats* reviewing statisticians, however, said in effect that the paper was unpublishable because we had not proven that low ceruloplasmin and high copper are unequivocally diagnostic of Wilson's disease, and, therefore, we should have treated half of our patients with a placebo. But we hadn't even considered using patients as placebo controls when we began treating asymptomatic patients because we were convinced they were suffering from a disease that—without chelation therapy—had been proven to be unavoidably fatal by 36 years of clinical experience. Moreover, our certainty of the diagnosis of Wilson's disease in our patients was strengthened by the fact that almost all of them had a sibling whose Wilson's disease had been confirmed clinically or at autopsy.

We revised our manuscript three times to escape this impasse, but failed to satisfy the *Journal's* reviewers, or its editorial staff—except for Franz Ingelfinger, the editor. He overruled reviewers and staff, publishing the manuscript accompanied by an editorial—"Editor's Choice"[6]—that read, in part: "Sternlieb and Scheinberg's manuscript has been seen by at least four clinicians conversant with liver disease, by two expert epidemiologists and by three biostatisticians. It has been discussed repeatedly and at length by the editorial staff; one editor [Ingelfinger himself, a fact he omitted] even traveled to New York for a personal confrontation with one of the authors.... The *Journafs* advisers in matters epidemiologic and statistical, however, remained unconvinced... [and, Ingelfinger concluded]...it was high time to publish the manuscript. The critical reader must judge for himself."

Almost 25 years later Ingelfinger's choice has been proven wise. The pharmacologic prevention of symptomatic Wilson's disease is now generally accepted wisdom.[7]

1. **Holm hers C G & Laurell C B.** Investigations on scrum copper II Isolation of the copper containing protein and description of some of its properties *Acta Chem. Scand* 2:550-6. 1948 (Cited 435 times.)

2 **Cumings J N.** The copper and iron content of brain and liver in the normal and in hcpaloicnlicular degeneration *Brain* 71:410-6. 1948 (Cited 225 times.)

3. **Scheinberg I H & Gitlin D. Deficency** of ceruloplasmin in patients with hcpalolennticular degeneration. *Seience* 116:484-5. 1952 (Cited 280 times.)

4. **Menghini G.** One-second needle biopsy of the liver. Gastroemterology 35: 190-9. 1958 (Cited 255 times.)

5 **Walshe J M. P**enicillamine. a new oral therapy for Wilson's disease *Amrr J. Med* 21-487-95. 1950 (Cited 400 times.) [See also **Walshe J M.** Citation Classic. *Current Contents/Lite Science* 26(37):21. 12 September 1983.]

6 **Ingelfinger F. E**ditor's choice Wilson's disease N. Engl. *J Med* 278:392-5. 1968

7 **Walshe J M.** Diagnosis and treatment of presymplomaltc Wilson's disease Lancet 2:435-7. 1988

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