

Dr John Walshe and the treatment of Wilson's disease

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Background: Copper and Wilson's disease

1785: First description of copper intoxication (Thomas Percival, MD, FRS).

1912: 'Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver'. Wilson SAK, *Brain*, 1912, 34, 295.

1948: Elevated copper (and iron) levels found in brain and liver samples from Wilson's disease patients.

Significance of reducing copper levels in Wilson's disease patients realised.

1951: BAL (British Anti-Lewisite) suggested as a rational (chelation) therapy. Treatment of Wilson's disease with BAL reported by various investigators. (See John N. Cumings, *Heavy Metals and the Brain*, Blackwell, Oxford, 1959).

Dr John Walshe

Identifies **penicillamine** in urine of patients with liver injury receiving penicillin. (Walshe JM, *Q. J. Med.*, 1953, 22, 483).

First report of **D-penicillamine** as oral therapy for Wilson's disease. Walshe JM., *Am. J. Med.*, 1956, 21, 487-495; *Lancet*, 1956, 270, 25-26.

With Dr H. B. F. (Hal) Dixon, links known copper chelating properties of **trientine** and resemblance to endogenous polyamines; they suggest **trientine** could be used to treat Wilson's disease.

Details for the preparation of **trientine dihydrochloride** from technical grade triethylenetetramine published. (Hitherto only the tetrahydrochloride had been reported). Dixon HBF, Gibbs K, Walshe JM, *Lancet*, 1972, i, 853.

Problems concerning the analysis, supply, and Product Licence for **trientine** resolved.

Preliminary report of the use of **ammonium tetrathiomolybdate** for treating Wilson's disease. Walshe JM, *Orphan Diseases and Orphan Drugs*, eds. Scheinberg IH, Walshe JM., Manchester University Press, 1986, pp 76-85.

Background: Ligand chemistry

Penicillamine

Found to be a chemical degradation product of penicillins (1943)

Structure deduced by John Cornforth

Identified as the D-(or (S)-) isomer by Dorothy Crowfoot *et al.*

Triethylenetetramine (trientine)

First synthesis: A. W. Hofmann (1860)

Complex with cupric sulfate studied (1936)

Stability complex with Cu(II) measured (1950)

Chelate effect defined (1952)

Tetrathiomolybdate

First synthesis: J. J. Berzelius (1826)

Identified as a copper-binding agent following observations of depletion of copper levels in ruminants caused by dietary molybdenum (1943-1975)

1951 - 1954

1955

1956

1956-1970s

1968

1969

1972

1975

1975-1985

1982

1985

Suggests **D-penicillamine** (for the first time) as a potential metal chelating agent. In particular, for removing copper in a patient with Wilson's disease.

Difficulties with the supply of **D-penicillamine** overcome; manufacturing routes developed. Reviewed in *Angew. Chem., Int. Ed. Engl.* (1975).

First report of use of **trientine dihydrochloride** for treating Wilson's disease. Walshe JM., *Lancet*, 1969, ii, 1401-1402. Used initially for patients intolerant of **D-penicillamine**.

Expresses concerns about the supply of **trientine**. Walshe JM., *Br. Med. J.* (1975); *New Scientist* (1975).

Summarises use of **trientine** for treating Wilson's disease. Walshe JM, *Lancet*, 1982, i, 643-647.

Summary

Treatment of Wilson's disease was transformed in the 20th century by the introduction of four drugs, which could be administered orally: **D-penicillamine**, **triethylenetetramine (trientine) dihydrochloride**, **zinc acetate** and **ammonium tetrathiomolybdate**.

Three of these four oral treatments – **D-penicillamine**, **trientine** and **tetrathiomolybdate** – owe their provenance to the diligence, perspicacity and intuition of the English physician, **Dr John Walshe**.