Movement Disorders
Vol. 14, No. 4, 1999, pp. 545–550

Controversies

Penicillamine: The Treatment of First Choice for Patients With Wilson's Disease

J. M. Walshe

The Reta Lila Weston Institute of Neurological Studies, University College, London, U.K.

"Wilson's disease is one of the very few forms of serious hepatic, neurological or psychiatric disease for which specific, effective pharmacological therapy is available. In virtually every patient who is asymptomatic, and in any of those who are ill, decoppering therapy can maintain or restore to normal health and longevity, despite the genetic abnormality these patients possess."[1]

The physician, when confronted with a new patient with Wilson's disease nowadays, has a wide variety of therapies from which to choose. Listed chronologically these are dimercaptopropanol (BAL),[2] diemethyl cyteine (penicillamine),[3] dimercaptopropane sulphonate (Unithiol),[4] zinc sulphate (or acetate),[5] triethylene tetramine 2HCI (Trientine),[6] and ammonium tetrathio molybdate.[7] Liver transplantation needs to be considered as a first treatment only in those patients with hemolysis and acute hepatic failure.[8] It is interesting to note that none of the pharmacologic agents listed was introduced by one of the giant pharmaceutical companies; all have resulted from the work of individual researchers.

It is probably true to say that in clinical medicine there is no substitute for experience. Scheinberg and Steinlieb, who must have treated more patients with Wilson's disease than others in this field, have stated "Treatment which must begin when (and only when) the diagnosis is certain, consists in the vast majority of patients of daily oral administration of capsules or tablets of penicillamine . . . ."[1] Similarly, Walshe and Yealland,[9] when describing their experience of 137 patients with neurologic Wilson's disease, wrote "Penicillamine still remains the drug of choice for the treatment of Wilson's disease although it has acquired, perhaps undeservedly, a reputation for unacceptable toxicity." While the great majority of these patients made an excellent recovery, 11 failed to respond to penicillamine or any other treatment. In 10 of these patients, the liver copper concentration had been reduced to below that found in heterozygotes, suggesting adequate "decoppering," but in four patients in whom the brain copper was determined, all showed significant retention of the metal into the toxic range, that is, above 40 μg/g wet weight.[10]

Returning to the initial question, when choosing the drug of first choice for a newly diagnosed patient with Wilson's disease, it is worth considering the mechanism of action of the various therapies.

Dimercaprol (BAL) and its orally active derivative the sulphonate (Unithiol): Both have two sulphydrol groups that form a tight five-membered ring with copper, probably the strongest available bond. The former has the additional advantage of being a nonpolar molecule that can readily cross the blood–brain barrier. Dimercaptropropanol, and probably the sulphonate, is subject to tachyphylaxis, probably as a result of auto-oxidation of the two sulphydryls to the disulphide as a result of enzyme induction in the liver. Furthermore, the parent compound has to be administered by painful intramuscular injection and is therefore not suitable for long-term management, although it still has a place in early treatment of the dystonic patient.[1]

Penicillamine, a cleavage product to the penicillin molecule, has a single sulphydryl group and an amino group, which potentially can form a ring compound with copper, but the available evidence suggests that the penicillamine–copper bond is more complex.[11]

Zinc salts do not bind copper or promote its urinary excretion but act by inducing metalothionein formation

Received November 23, 1998. Accepted November 27, 1998.
Address correspondence and reprint requests to Dr. J. M. Walshe, Broom Lodge, 58 High St., Hemingford Grey, Huntingdon, Cambs PE18 9 BN, U.K.

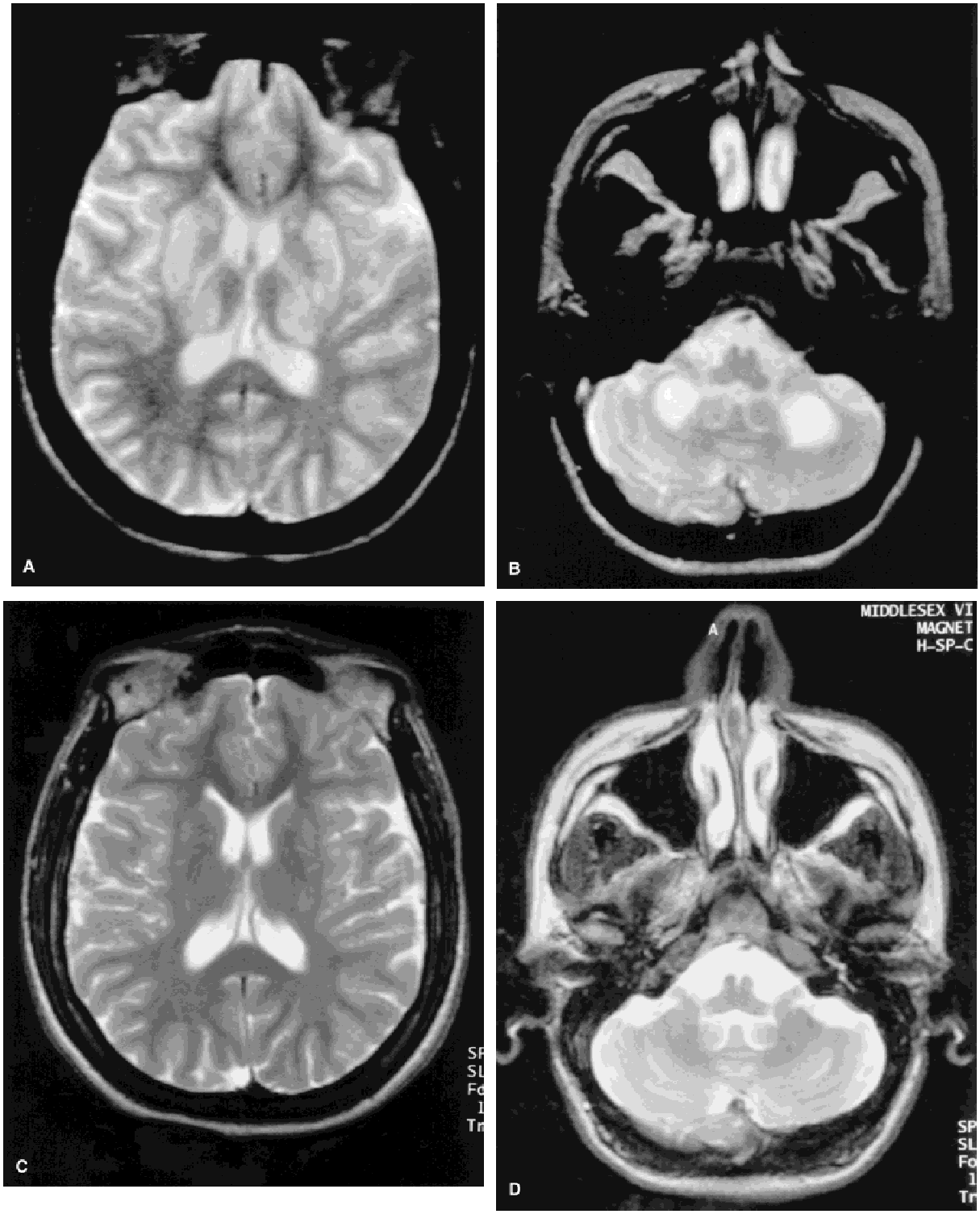

FIG. 1. First MRI brain scan of a 19-year-old woman with advanced neurologic Wilson's disease. Second scan at age 24 when she was virtually symptom-free. (**A** and **B**) First scan: "Extensively high T2-weighted signal involving the basal ganglia and thalami, dentate nuclei and cerebellum . . . ." (**C** and **D**) Second scan. "There has been a marked degree of improvement in the T2 high signal changes in the basal ganglia and thalami. The abnormal high T2 signal in the cerebellar white matter and dentate nuclei has almost disappeared on treatment."

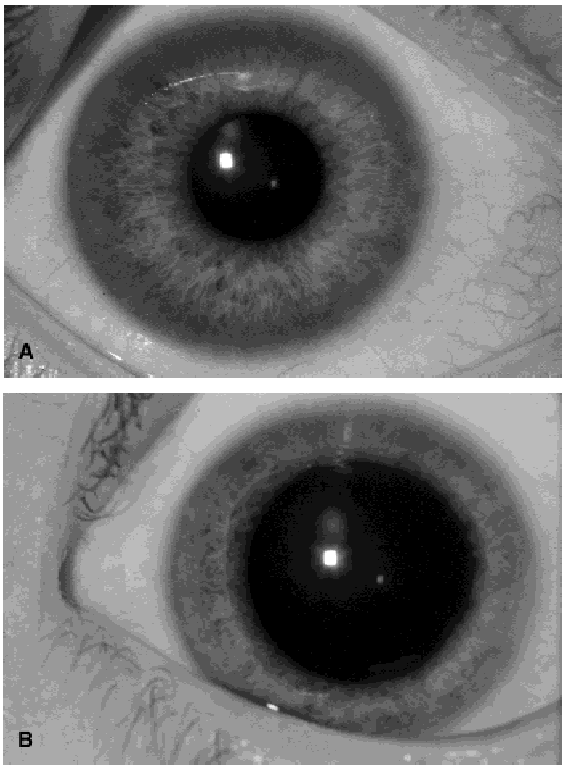

FIG. 2. Kayser Fleischer rings in a male with neurologic Wilson's disease. (**A**) June 1985, dense complete rings. (**B**) December 1986, complete clearing.

in the intestinal mucosa, thus preventing the absorption of copper from the gut.

Trientine, like penicillamine, promotes copper excretion in the urine; it has four amino groups that may form a ring compound with copper, but the nature of the bond had not been studied. It is poorly absorbed in the gut[12] and probably mobilizes copper from a different fluid compartment from penicillamine.[13]

Ammonium tetrathio molybdate is a powerful copper complexing agent, as has been known in the agricultural sciences since the early 1940s, but only introduced to Wilson's disease as recently as 1984. Not only does it combine with tissue copper forming a metabolically inert compound, but it also blocks copper absorption from the gut even more effectively than zinc.[14]

The evidence for the use of penicillamine as the initial therapy for patients with Wilson's disease rests on its impressive track record. It has been in use since 1955 and the first patient ever treated is still alive and well, having given birth to and raised up three children. There is a greater corpus of experience in the use of this drug than any other. It can reverse not only advanced clinical disabilities, but as demonstrated by computed tomography and magnetic resonance imaging scans,[15,16] can lead to apparent reversal of brain damage both in the basal ganglia and the brain stem (Fig. 1).

Kayser Fleischer rings will disappear completely in the majority of cases (Fig. 2) as will sunflower cataracts (Fig. 3). Manual dexterity will recover, as illustrated by handwriting examples in both parkinsonian and pseudosclerotic forms of the disease (Fig. 4). It has also been possible to demonstrate a reduction of the concentration of copper in the serum in patients on long-term penicillamine treatment[17] and improvement in the handling of radio-copper by the liver (Fig. 5).

Such remarkable evidence of benefit, both clinical, biochemical, and by imaging techniques has not been clearly documented for other forms of treatment. The improvement in the neurologic syndrome can be paralleled by improvement in hepatic Wilson's disease, apart from those presenting with acute hepatic–hemolytic disease. Such patients need immediate liver transplantation as a life-saving measure. The renal lesion of Wilson's disease can also show remarkable improvement with penicillamine treatment with reversal of the amnoaciduria and peptiduria[18] and recovery of the ability to acidify the urine[19]; psychiatric symptoms usually also improve.

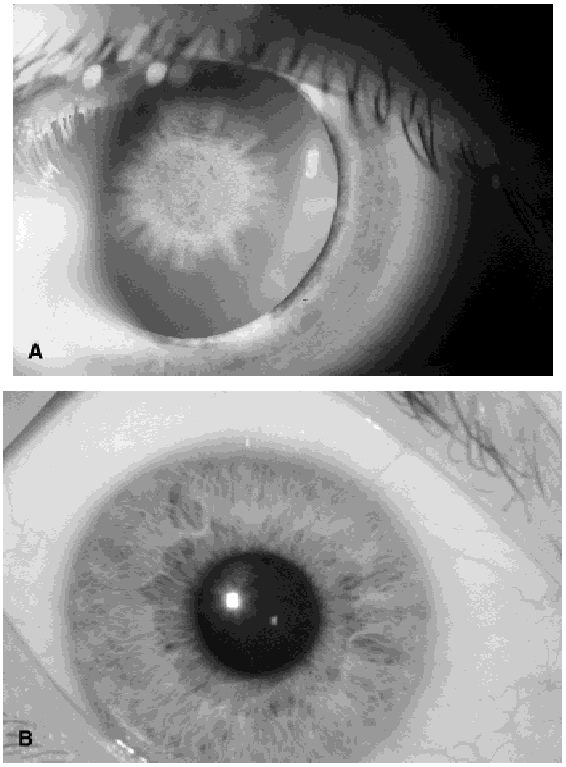

FIG. 3. Sunflower cataracts in a 13-year-old boy. Presymptomatic Wilson's disease but with a history of one epileptic seizure and abnormal liver tests. (**A**) Before treatment. (**B**) Clearance of cataracts after 18 months' treatment.

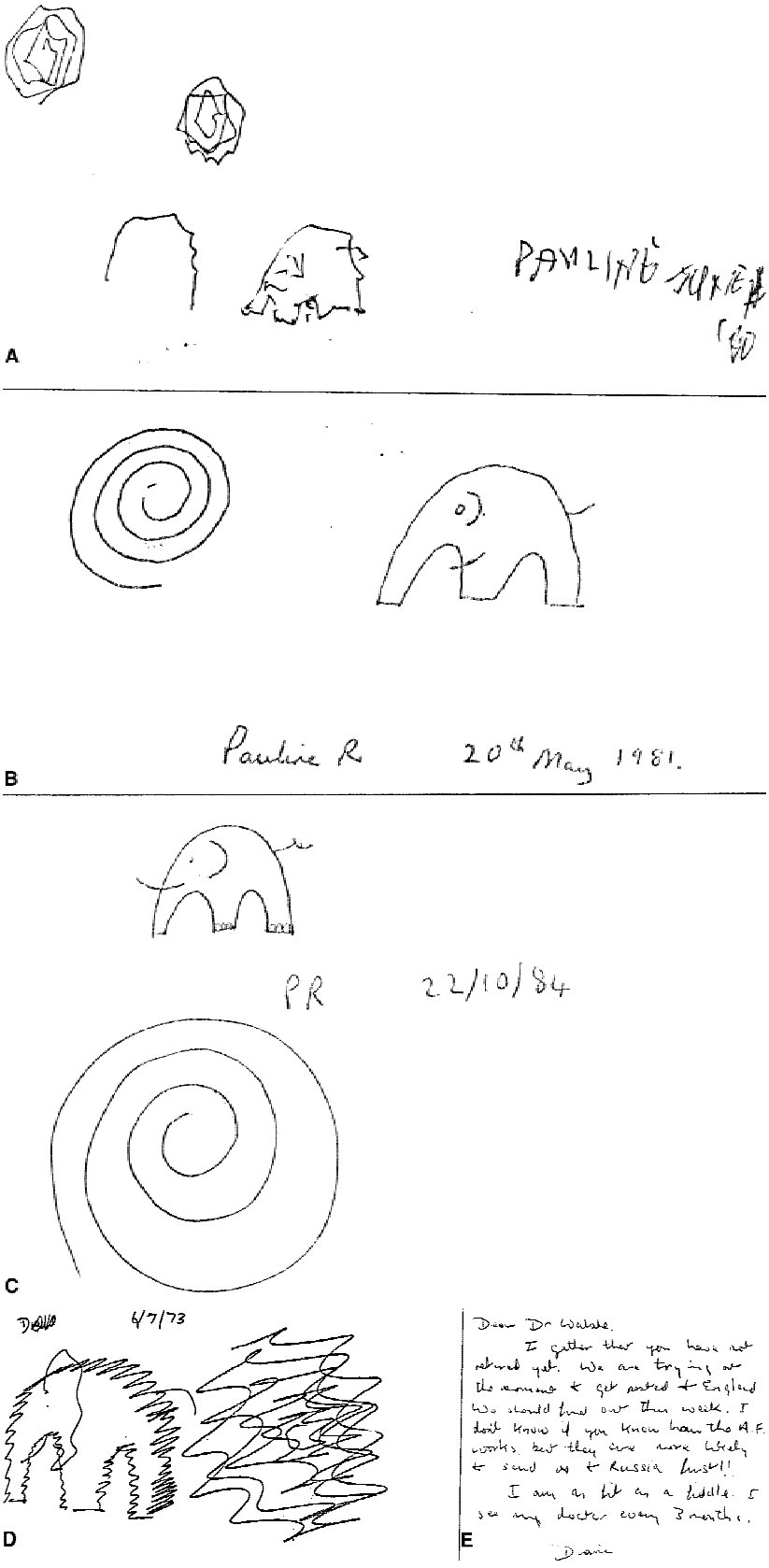

FIG. 4. Handwriting changes: A 20-year-old woman with severe parkinsonian Wilson's disease; (**A**) age 19 before treatment, (**B**) after 18 months', and (**C**) after 30 months' treatment. (**D**) A 23-year-old woman with severe pseudosclerotic Wilson's disease and (**E**) a letter from America 10 years later.

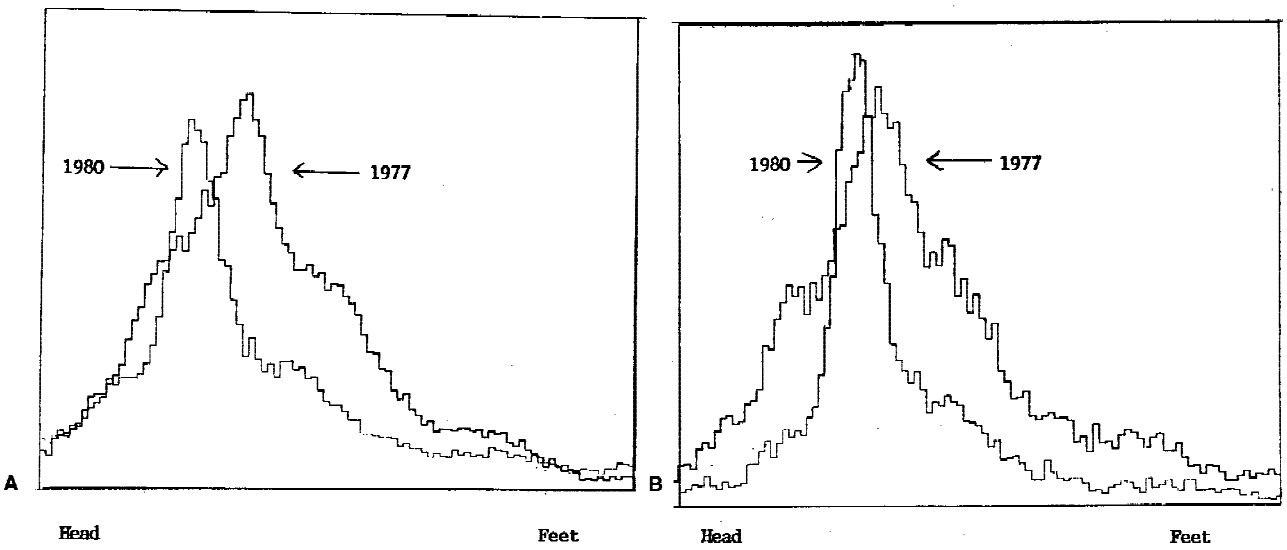

FIG. 5. Radiocopper studies to show improved liver uptake of copper after treatment. Radiocopper was given intravenously and the patient scanned from head to foot at regular intervals over 48 hours. Scans are shown for **(A)** 2 and **(B)** 24 hours after injection, before treatment, and 3 years later. The small lateral shift in the peak in each case is the result of slightly different positioning of the patient in the whole body monitor. It can be seen that in the 1979 scans, there has been poor localization of copper in the liver at both times, but 3 years later there is less extrahepatic activity and 24-hour scan shows increased localization over 2 hours. In neither case is there a secondary peak resulting from biliary excretion of copper as is seen in normal people.

It is a truism to state that all drugs that are pharmacologically active have unwanted side effects; it is also equally true that drugs that have no side effects are pharmacologically inert. Those who make claims to the contrary are not being realistic. The side effects of penicillamine can be serious, but in the hands of those experienced in the use of the drug this need not be the case. Here a distinction must be made between early- and late-onset toxicity; both the manifestations and the management are different. In my original account of the chelating properties of penicillamine,[3] I suggested that toxicity might arise as a result of interference with cysteine metabolism leading to liver necrosis and changes in skin and hair. Damage to the skin has been a problem in long-term management, but liver damage has not been reported. In practice, the major problems associated with penicillamine are immunologically induced: systemic lupus, both induced and precipitated, immune complex nephritis, Goodpasture's syndrome, epidermolysis bullosa, myasthenia gravis, and others.[20] Only the first two of these are at all common, can be easily spotted in carefully monitored patients, and occur in perhaps 5% of all patients.

The most common early complication is urticaria which may be severe. This can be managed relatively easily by stopping treatment and giving an antihistamine. Once the rash has cleared, penicillamine can be restarted in small doses and worked up slowly, perhaps under steroid cover. The really worrying problem is that of initial deterioration in neurologic signs, sometimes soon after starting treatment. This is unpredictable and is not peculiar to penicillamine but may occur in all therapies at present in use, although penicillamine has the worst reputation for this. In an earlier communication, Walshe and Yealland[9] noted an initial deterioration in 22% of patients treated but further showed that this did not alter the final outcome unfavorably. They also stated that it was not possible to predict, in terms of either the clinical or biochemical profile, how each patient will respond to treatment. It may be that when all the clinical syndromes associated with the various mutations on the Wilson's disease gene have been analyzed, it will be possible to select the optimum treatment for each patient.

It is of interest to note that in 50 patients personally seen since this series was published, none has suffered this unwanted response to treatment. In our total series, now in excess of 300 patients, three showed rapid deterioration which could not be reversed with any other available therapy. It has been suggested that this particular syndrome may be mediated by free radicals consequent on the sudden release of large amounts of copper by chelating agents; if this is the case, the administration of a free radical scavenger such as alpha tocopherol may be of help. It has been claimed that zinc salts do not lead to an increase of symptoms, but some reports suggest that this may not always be the case.[7,21–23] It must also be

noted that some patients reported as not responding to penicillamine treatment were incorrectly diagnosed.[24]

The evidence gathered here leaves no doubt that penicillamine is a powerful decoppering agent and at present, when used by an experienced physician, can offer patients with Wilson's disease a more reliable prospect of recovery than other therapies.

REFERENCES

1. Scheinberg I, Sternleib I. *Major Problems in Internal Medicine XXIII. Wilson's Disease.* Philadelphia, PA: WB Saunders, 1984: 126–155.
2. Cumings JN. Effects of BAL in hepatolenticular degeneration. *Brain* 1951;74:10–22.
3. Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med* 1956;21:487–495.
4. Konovalov NV, Mittelstedt AA, Bauman LK, Gotovzeva EV. The metabolism of copper in hepatolenticular degeneration and treatment with thiols. *Zh Nevrol Psikhiatr Im S S Korsakova* 1958;58: 897–906.
5. Schouwink G. *De hepatocerebrale degeneratie, met een onderzoek naar de zinkstofwisseling.* MD thesis, Amsterdam University, Van der Wiel, Arnhem, 1961.
6. Walshe JM. Management of penicillamine nephropathy in Wilson's disease: a new chelating agent. *Lancet* 1969;1:1401–1402.
7. Walshe JM. Copper: its role in the pathogenesis of liver disease. *Semin Liver Dis* 1984;4:252–263.
8. Dubois RS, Giles G, Rodgerson DO, et al. Orthotopic liver transplantation for Wilson's disease. *Lancet* 1971;1:505–508.
9. Walshe JM, Yealland M. Chelation treatment of neurological Wilson's disease. *Quart J Med* 1993;86:197–204.
10. Walshe JM. Brain copper in Wilson's disease. *Lancet* 1987;2: 1030.
11. Laurie SH, Prime DM. the formation and nature of the mixed valence copper-D-penicillamine-chloride cluster in aqueous solution and its relevance to the treatment of Wilson's disease. *J Inorg Biochem* 1979;11:229–239.
12. Gibbs KR, Walshe JM. The metabolism of trientine: animal studies. In: Scheinberg IH, Walshe JM, eds. *Orphan Diseases and Orphan Drugs.* Manchester: Manchester University Press, 1986: 33–42.
13. Walshe JM. Copper chelation in patients with Wilson's disease. *Quart J Med* 1973;42:441–452.
14. Walshe JM. Tetrathiomolybdate (MoS4) as an 'anti-copper' agent in man. In: Scheinberg IH, Walshe JM, eds. *Orphan Disease, Orphan Drugs.* Manchester: Manchester University Press, 1986: 76–85.
15. Williams JFB, Walshe JM. Wilson's disease. An analysis of the cranial computerized tomographic appearances found in 60 patients and the changes in response to treatment with chelating agents. *Brain* 1981,104:735–752.
16. King AD, Walshe JM, Kendall BE, et al. Cranial MRI imaging in Wilson's disease. *Am J Roentgenol* 1996;167:1579–1584.
17. Walshe JM. Endogenous copper clearance in Wilson's disease: a study of the mode of action of penicillamine. *Clin Sci* (*Colch*) 1964;26:461–469.
18. Asatoor AM, Milne MD, Walshe JM. The effect of chelation therapy on the aminoaciduria and peptiduria of Wilson's disease. *J Roy Coll Physicians London* 1983;17:122–125.
19. Walshe JM. Effect of penicillamine on failure of renal acidification in Wilson's disease. *Lancet* 1968;1:775–779.
20. Walshe JM. Penicillamine and the SLE syndrome. *J Rheumatol* 1981;8(suppl 7):155–160.
21. Walshe JM. Treatment of Wilson's disease with zinc sulphate. *BMJ* 1984;289:558–559.
22. Stremmel W. Wilson's disease. In: Czlonkowska A, Van den Hamer CJA, eds. *Proceedings of the Fifth Symposium.* Delft: Technical University, 1991:184–186.
23. Lang CJG, Rabas-Kolominsky AE, Konras G, Konig HI. Fatal deterioration of Wilson's disease after institution of oral zinc therapy. *Arch Neurol* 1993;50:1007–1008.
24. Walshe JM, Yealland M. Not Wilson's disease: a review of misdiagnosed cases. *Quart J Med* 1995;88:55–59.