Commentary

Treatment of Wilson’s disease: the historical background

J.M. WALSHE

From the Department of Neurology, The Middlesex Hospital, London, UK

When considering the management of patients with Wilson’s disease it is necessary to understand the basis on which present views are founded.

Wilson’s original description1 of the disease he called ‘hepato-lenticular degeneration’ was based on four patients he had seen and studied himself and six cases culled from the literature. He emphasized the predominantly neurological picture, and believed that the hepatic lesion did not affect the clinical outcome, even though one of his own patients actually died from variceal haemorrhage. Bramwell2 challenged this view when, in 1916, he suggested that some patients might present with liver failure before the nervous system became involved, a forme fruste of the disease. Despite Rumpel’s observation3 in 1913 that excess copper was present in the liver of a patient dying of this disease, its role in pathogenesis was not established until Cumings4 reported in 1948 that this metal was present in excess in both brain and liver of all patients dying of Wilson’s disease. Until this time the situation had been, quite simply, no pathogenesis, no treatment. In his seminal paper Cumings made the modest suggestion that removal of copper from the tissues of these patients with the recently discovered metal-binding agent5 then known as British antilewisite (BAL) and now marketed as Dimercaprol, might arrest the progress of this hitherto universally fatal disease. Cumings’s observation was the beginning of a therapeutic revolution.

In the early 1950s, both Cumings5 and Denny Brown6 published the first results of treatment with BAL and they were able to report a considerable improvement in symptoms. Unfortunately the use of BAL was associated with problems; it had to be given by painful intramuscular injection often associated with fever and leucopenia, haematuria and abscess formation. Its use was something of an ordeal for the patient, and each course of injections was followed by a lesser improvement. At some stage a sulphonic acid derivative of BAL (Unithiol, Dimival) which can be given by mouth was used in the Eastern block countries,7 but perhaps because of cost and lack of availability, found little favour in the West, although its use was successful in one patient.8 Thus, though it became clear that the course of the disease could be influenced by therapy, a search for more effective and less toxic treatments was set in train. An alternative chelating agent, EDTA, was tried but proved disappointing, as did the use of intravenous aminoacids.9 The finding, at this time, that caeruloplasmin was absent or deficient in most patients suggested that replacement of this protein should be the specific form of treatment. This also proved to be illusory.10 However, the situation was radically altered for the better when I reported11 that penicillamine, a degradation product of penicillin, was to be found in the -SH state in the urine of patients treated with penicillin. This aminoacid is able to mobilize large amounts of copper for excretion in the urine, in both patients and normals, when given by mouth.12 As a result of this observation, almost overnight, Wilson’s disease became one of the few inherited metabolic disease for which there was an effective therapy. So successful did this prove that Schouwink’s observation that zinc salts could block copper absorption from the gut and could be of therapeutic value passed virtually unnoticed.13 It was almost a decade later that Hoogenraad and his colleagues introduced this as an alternative approach to the management of patients with Wilson’s disease. Furthermore, they claimed that this avoided the problems of toxicity associated with penicillamine in some patients.14 A decade of penicillamine usage had indeed revealed a wide spectrum of toxic reactions varying from an early urticarial rash through skin damage, marrow depression to SLE and immune complex nephritis; one or other of these reactions

Address correspondence to Dr J.M. Walshe, Department of Neurology, The Middlesex Hospital, London W1A 8AA

© Oxford University Press 1996
being found in some 10% of cases.\textsuperscript{15} In addition to these side-effects, nearly a quarter of patients showed an increase in symptoms before improvement set in and a very few patients deteriorated dramatically without subsequent recovery.\textsuperscript{16} Unfortunately, in my experience, this is also true of zinc therapy. This led to a search for an additional orally active chelating agent. Having screened a large number of compounds,\textsuperscript{17} acting on a suggestion by Dr Henry Dixon of the Department of Biochemistry, University of Cambridge, I was able to show that triethylene tetramine, as the dihydrochloride (Trientine), could be used as a powerful 'decoppering agent' in patients with a heavy copper overload. However, it was less effective than penicillamine, at mobilising copper, in normals and patients who had been on long-term treatment.\textsuperscript{18} Follow-up studies have shown that this is a very effective treatment, and one with very few unwanted side-effects, but it has the disadvantage of being more expensive than penicillamine and, being poorly absorbed from the gut, it needs to be given in rather larger doses.\textsuperscript{19}

The discovery of three possible treatments for patients with Wilson's disease by 1970 did not mean that all problems were solved. Some patients only presented, or were diagnosed, at a time when terminal liver damage precluded any realistic hope of medical treatment. This led to the introduction of liver transplantation\textsuperscript{20} for such patients, and thanks to modern anti-rejection treatment, has become a standard procedure in this situation, for patients with both acute and chronic liver failure. Nevertheless, a small number of patients, whilst not meriting surgery still do not respond to the various medical remedies available or are subject to toxic reactions, so that the search for new treatments continues. In the 1950s, one compound used was ammonium molybdate.\textsuperscript{21} This was based on the observation that herba vores feeding on pastures contaminated with this metal developed serious copper deficiency; unfortunately molybdate did not have a similar action in man. The reason for this only became apparent later when it was found that molybdate was converted in the rumen into thiomolybdates; the tetramethyl compound having the most powerful 'anticopper' action. This led me to investigate the use of thiomolybdate as a potential treatment for Wilson's disease, first on myself and subsequently on patients with the disease who had proven to be intolerant of other more conventional treatments.\textsuperscript{22} Tetramethylmolybdate has proved to be a very useful tool in controlling copper balance in patients with Wilson's disease. Like zinc, it blocks intestinal absorption of the metal, probably rather more effectively, but it has the additional advantage of binding copper already present in the tissues in a tight metabolically inert
References

2. Bramwell B. Familial cirrhosis of the liver: four cases of acute fatal cirrhosis of the liver in the same family, the patients being respectively nine, ten, fourteen and fourteen years of age; suggested relationship to Wilson's progressive degeneration of the lenticular nucleus. *Edinb Med J* 1916; 17:90-9.


