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 description 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. Bramwell 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 observation 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 Cumings 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 agent 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 Cumings and Denny Brown 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, but perhaps because of cost and lack of availability, found little favour in the West, although its use was successful in one patient. 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 intra-venous aminoacids. 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. However, the situation was radically altered for the better when I reported 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. 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. 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. 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...
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 meritng 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 herbivores 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 tetrathio compound having the most powerful `anticopper' action. This led me to investigate the use of tetrathiomolybdate 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} Tetrathiomolybdate 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 linkage probably involving albumin. Its effectiveness has subsequently been confirmed by both Danks\textsuperscript{23} and Brewer.\textsuperscript{24} But like all powerful chemicals, it has toxic side-effects. It can induce narrow depression\textsuperscript{25} and, in growing animals, it can induce bony deformities in the epiphyses. Its use in children must therefore be limited to short courses only.

Thus, in the course of some 30 years Wilson's disease has moved from being 100% fatal to a condition with a wide variety of effective possible treatments: two orally active chelating agents, penicillamine and trientine; two metal to metal antagonists, zinc and tetrathiomolybdate, and finally for terminal liver failure, hepatic transplantation. A word must be said here for BAL; when all else fails it is sometimes of value when used with one of the orally active chelating agents. Being a nonpolar compound it is better able to cross the blood-brain barrier than penicillamine or trientine. It is particularly indicated for patients with advanced neurological lesions which have failed to respond to other forms of therapy.

A major, but perhaps unexpected problem when initiating treatment is giving a reasonably accurate prognosis. No two patients with Wilson's disease are, clinically, ever quite the same\textsuperscript{26} and whilst most patients improve or recover completely, some do not. Some get worse before they get better (approximately 25%), some get worse and do not get better, remaining permanently disabled; some die, fortunately very few.\textsuperscript{16} In view of the fact that there are more than 25 mutations of the gene responsible for Wilson's disease, the number of possible compound heterozygotes is in excess of 300\textsuperscript{27} a fact that may well account for the varying clinical spectrum and differing responses to treatment. The role of free radicals also needs exploring, and it may be that the initial deterioration seen in some patients after starting treatment is due to free radical release in excess of the body's ability to remove them. The simultaneous administration of a free radical scavanger, such as \textit{$\alpha$}-tocopherol, might help to eliminate the problem. However, in view of the rarity of Wilson's disease, it may be necessary to establish a cooperative international study to answer this question.

In summary, the majority of patients with Wilson's disease will respond well to one of the established regimes. Penicillamine is the drug of which there is most experience and it has an excellent track record, despite the fact that some 10% of patients have unfavourable reactions. Trientine is clinically as effective and has fewer side-effects. There is less experience with zinc and molybdate, although both clearly have a place. BAL can be used as a fallback when all else fails, and transplantation is available for patients with irreversible liver damage.
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References

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