

In Honour of Dr John Walshe on the Occasion of his 100th Birthday

In 1957, doctors from the United Birmingham Hospitals, UK, published a study of twelve patients with Wilson's disease, a rare genetic condition characterised by the deposition of copper in the brain, liver, cornea and other organs. What is noticeable about this paper is the limited treatments on offer in the early 1950s for treating Wilson's disease and, sadly, the premature deaths of the patients (many in their teens). Each July, the Wilson's Disease Support Group – UK, a support group for patients with Wilson's disease, their friends and families, holds its annual meeting in Cambridge. Many of the patients who attend these meetings are now well into their late middle-ages, and enjoy successful careers and family lives. It is no exaggeration to say that the lifetime's work of the English physician Dr John Michael Walshe of Hemingford Grey, Cambridgeshire, has transformed the outcomes of the majority of patients with Wilson's disease both in the UK and worldwide. Wilson's disease has become a treatable (but not curable) disorder, and the link between Wilson's disease and copper has stimulated research into copper biochemistry and other copper-related diseases.

By the early 1950s, it was recognised that by removing copper in patients with Wilson's disease, damage caused by this metal to vital organs could be reduced. One way of removing a metal *in vivo* is to use a chelating agent. Until 1956, the only way of reducing copper levels in Wilson's disease was by the intramuscular administration of British Anti-Lewisite (BAL). In 1956, John Walshe introduced the first oral chelating agent for treating Wilson's disease, **D-penicillamine**. Later, in the 1960s, Dr Walshe introduced a second oral chelating agent, **trientine dihydrochloride**, and finally, in the 1980s, he began studying the use of **ammonium tetrathiomolybdate** in a limited number of patients with the neurological symptoms of Wilson's disease. Zinc salts were discovered by Dutch physicians in the 1950s-1960s to be another effective (but non-chelating) way of treating Wilson's disease. To this day, the accepted options for treating Wilson's disease are the two oral drugs discovered by Dr Walshe, D-penicillamine and trientine dihydrochloride, or zinc ion maintenance therapy.

Dr Walshe's discovery of these drugs is no accident. It has resulted from a perseverance and dedication to improve the lives of Wilson's disease patients, and an immersion in the techniques of clinical and analytical chemistry. His early training in paper chromatography resulted in the observation of D-penicillamine in the urine of (non-Wilson's disease) patients receiving penicillin and led just a few years later to the hypothesis that the arrangement of atoms in D-penicillamine meant that the molecule would bind with copper ions, and hence act as a chelating agent. With the therapeutic acceptance of D-penicillamine, Dr Walshe began pioneering work on copper metabolism using radioactive copper, and he has also published on the mechanism of action of D-penicillamine and of trientine.

Experimental investigations were combined with clinical work on the diagnosis and treatment of Wilson's disease. In 1957, John Walshe was appointed to a post in the Department of Experimental Medicine, University of Cambridge with an honorary consultant appointment at Addenbrooke's Hospital, Cambridge, where he specialised in the treatment of Wilson's disease until 1987 (and thereafter at The Middlesex Hospital, London until 2000). In this century, he has continued to be involved with his former patients from his home in Cambridgeshire, and, happily, is able to attend the annual meeting of the Wilson's Disease Support Group – UK.

On the occasion of his 100th birthday in April 2020, appreciation of Dr Walshe's outstanding legacy to medicine was celebrated in a booklet containing tributes and birthday greetings from his former patients both in the UK and worldwide. The booklet was presented to Dr Walshe by his friend, former patient and Secretary of the Wilson's Disease Support Group – UK, Mrs Valerie Wheeler.

Rupert Purchase, April 2020