Received: 11 March 2024 | Accepted: 7 May 2024

DOI: 10.1097/CLD.0000000000000238

REVIEW

The history of Wilson disease

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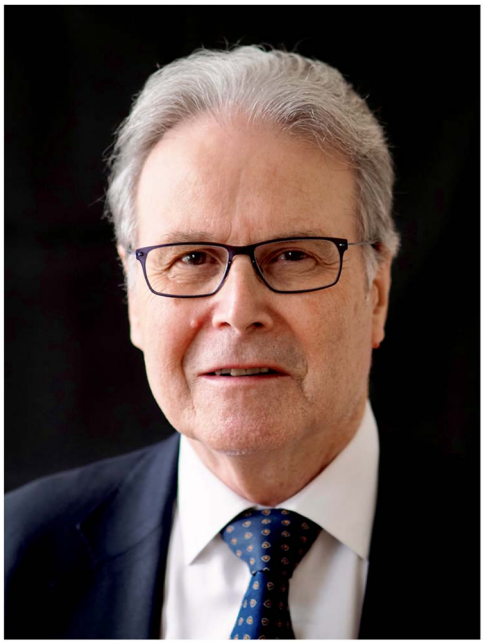

INTRODUCTION

In 1912, Samuel Alexander Kinnier Wilson (SAKW) (Figure 1A), a remarkable physician and neurologist, published his seminal article entitled "Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver ".[2] Although there had previously been scattered reports of neurological disease in patients also found to have cirrhosis, until SAKW's work for his 1911 Doctor of Medicine (MD) thesis at Edinburgh University Medical School (Figure 1B),[1] this particular association with liver disease had not been recognized formally. And so began the story of what became known as Wilson's disease or increasingly more commonly known by the non-possessive eponym,[3] Wilson disease (WD), since SAKW neither had the disorder nor owned it.

In this essay, we shall look at what came before and the journey after 1912 (Figure 2) through clinical associations, recognition of the role of copper, the disease genetics, therapeutic developments, and eventually, the cloning of the gene harboring mutations, which led to mutation analysis and an increased understanding of the cellular mechanisms involved in copper metabolism. Much remains to be understood and studied, but the strands that have led to our present knowledge are fascinating and highlight "translational medicine" as the product of serendipity and an alert mind (or as Pasteur would have it "a prepared mind"), [… in 1854 during a lecture at the University of Lille, Pasteur declared "In the field of observation, chance favors only the prepared mind "], with insights into chemical and cellular detail and the application of advances in molecular genetics.

Now read on…

SAKW'S EARLY YEARS, THE DRAW TO NEUROLOGY, AND HIS CAREER AS A NEUROLOGIST

SAKW was born in Cedarville, New Jersey in the USA in 1878, the son of an Irish Presbyterian clergyman, the Reverend James Kinnier Wilson, and a Scottish mother, Agnes Legerwood. After his father died of yellow fever in SAKW's infancy, young Samuel Alexander returned with his mother and sister Edina to Edinburgh,[4] where he was educated at George Watson's College [established as a hospital school in 1741, which then became a day school in 1871 — later to merge with George

Abbreviation: BAL, British Anti-Lewisite; EMI, Electric Music Industries; KF, Kayser-Fleischer; MD, Doctor of Medicine; RFH, Royal Free Hospital; RFHSM, Royal Free Hospital School of Medicine; WD, Wilson disease.

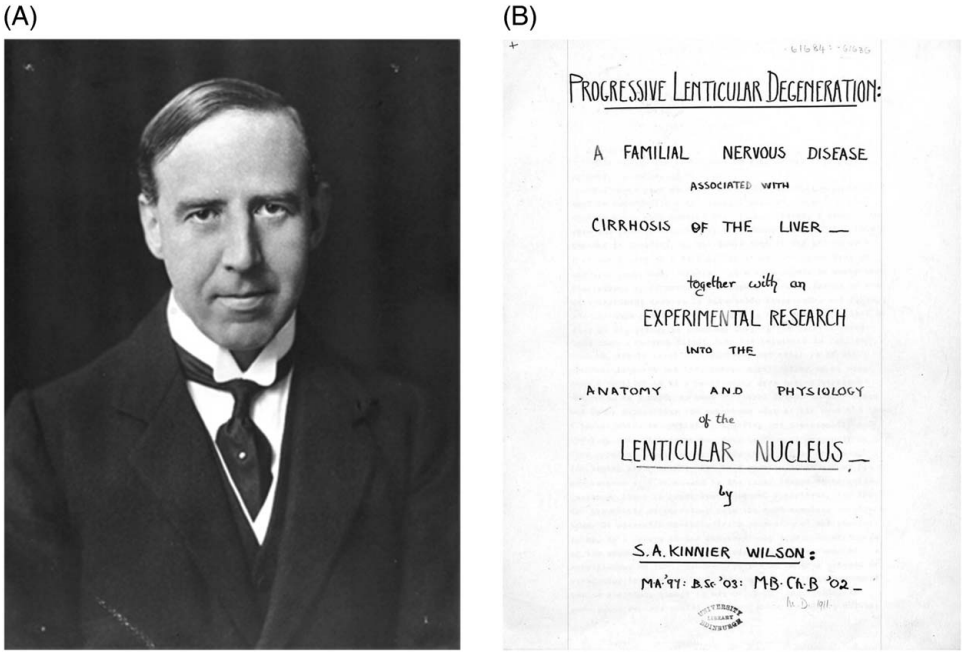

FIGURE 1 (A) Samuel Alexander Kinnier Wilson (1878–1937): A photograph from the early 1920s. Included with the kind permission of his grandson, James B Kinnier Wilson. (B) Title page from SAKW's 1911 MD Thesis, which is unusual as is it handwritten; awarded by Edinburgh University Medical School. Courtesy of the University of Edinburgh[1].

Watson's Ladies College in 1974] after which he studied at Edinburgh University. He was an exceptional student graduating MA in 1897 aged 19, with prizes in Latin, Greek, History, Fine Art, and Archaeology.[5] He then paid his way through Medical School by supervising students studying Latin and Greek,[4] and he graduated

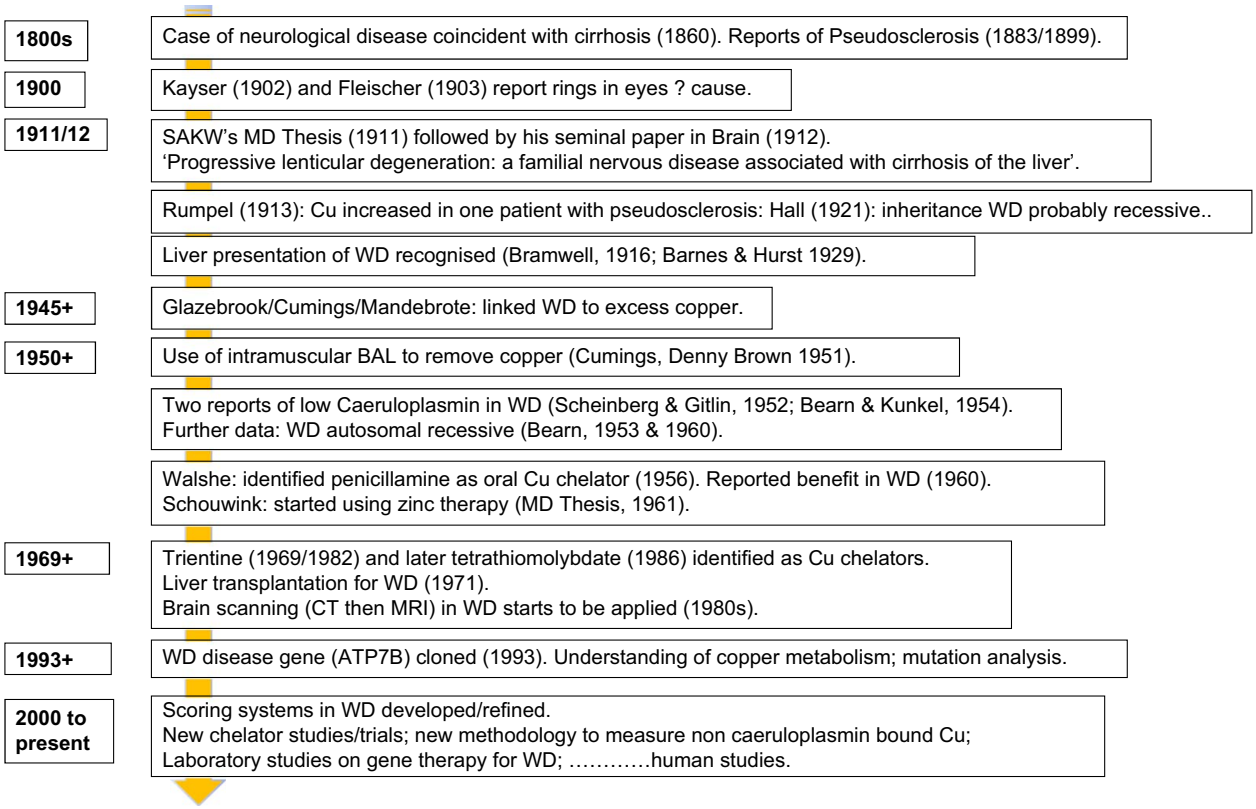

FIGURE 2 Wilson disease: timeline (devised by the author)

MB BCh, in 1902. [Medicinæ Baccalaureus et Baccalaurens Chirurgiæ (MB BCh) — also designated alternatively as MB BS, MB BChir, and BM BCh — is a primary (bachelor) medical degree awarded by medical schools in countries that follow the tradition of the United Kingdom. The historical degree nomenclature indicates that there are 2 degrees, but they are usually combined and considered together as 1. In the United Kingdom, an MD is awarded on subsequent successful completion of a research thesis.]

SAKW was awarded first-class honors in Anatomy, Physiology, Medicine, Surgery, Midwifery, and Pathology.[5] In 1903, he was appointed Junior House Physician (ie, Intern) to Dr Byrom Bramwell (1847–1931, later President of the Royal College of Physicians of Edinburgh, who was knighted by King George V in 1924) at the Royal Infirmary in Edinburgh. SAKW also worked for a Bachelor of Science degree in Physiology, for which he received a distinction (honors). Unusual for that stage in his career, he then took up a placement in Paris for 1 year (1903–1904), as a Carnegie research fellow working both clinically and in pathology with the famous neurologist Professor Pierre Marie (1853–1940), renowned for the neurological hereditary motor and sensory neuropathy "Charcot-Marie-Tooth" disorders, and the first description of acromegaly, at the Bicêtre Hospital in the southern suburbs of Paris; there he was befriended by many other famous neurologists in Paris, including Joseph Jules François Félix Babinski (1857–1932) and Georges Charles Guillain (1876–1961).[6,7] While abroad, SAKW also visited Paul Emil Flechsig (1847–1929), a neuroanatomist, neuropathologist and psychiatrist, in Leipzig. These links also underscored his linguistic abilities, particularly in French and German. SAKW's interest in neurology had been piqued by Dr Bramwell, but the opportunity in Paris was pivotal for his future choice of career, and his lifelong appreciation of French mores, and neurology and philosophy.[7] In 1904, 5 papers with SAKW as author or co-author were published in French journals,[6] including 4 in Revue Neurologique, which is the journal of the Société de Neurologie de Paris — co-founded by Babinski.

The secondment in Paris gave him experience that likely enhanced his successful application in 1904 for a House Physician post at the National Hospital for the (Relief and Cure) of the Paralyzed and Epileptic [later the National Hospital for Nervous Diseases, and since 1990, the National Hospital for Neurology and Neurosurgery[8]], in Queen Square, Bloomsbury, London (Figure 3)[9] — which Robert Louis Stevenson romanticized as "…a little inclusion of tall trees and comely brick houses … It seems to have been set apart for the humanities of life and the alleviation of all hard destinies. As you go round it, you read upon every second door plate, some offer of help to the afflicted".[8,9]

FIGURE 3 The National Hospital for Nervous Diseases, Queen Square. Reproduced from Hamilton.[9]

SAKW's 6 glowing references for his application for the Queen Square post came from many sources, including Bramwell and Marie.[5,6] Dr George Alexander Gibson MD, DSc, FRSE, FRCPE (1854–1913), a prestigious Scottish physician, wrote: "I know of no one whom I could more confidently recommend for the vacancy at the National Hospital. Dr Wilson is admirably equipped for the prosecution of neurological work, an expert pathologist, conversant with the most modern methods of histological and bacteriological investigation, a skillful photographer (for clinical and pathological work), and a man of great clinical insight and of ready resource in treatment".[5] Clearly, here was a young physician (aged only 26) with exceptional skills and talents, and these are exemplified by his subsequent work. He was a house physician at Queen Square between 1904 and 1908 and then a Registrar[10] (British equivalent to a Senior or Chief Resident) between 1908 and 1912. In addition to his enduring career-long appointment at Queen Square, he was the first physician in Britain to be given a purely neurological appointment at a general hospital, that is, junior neurologist (later Senior Neurologist) at King's College Hospital, after resigning his assistant physician appointment at Westminster Hospital in 1919.[10]

He was the founding editor in 1920 of the *Journal of Neurology and Psychopathology,* now known as the *Journal of Neurology, Neurosurgery and Psychiatry*, and he wrote a renowned 2-volume textbook of neurology, which was published posthumously in 1940,[11] edited by Dr Alexander Ninian Bruce, a neurologist in Edinburgh, and SAKW's brother-in-law.[6] Dr Bruce wrote in his foreword,[11] "Dr Wilson possessed an encyclopedic mind; he read everything he could find about any subject which attracted his interest at the time, and he seemed to have the special gift of remembering anything he ever read." SAKW also succeeded in private practice in Harley Street where he lived in Central London, and where fashionable private

specialists in medicine and surgery have practiced since the 19th century.

If it were not for SAKW's untimely death in 1937, at age 58 from cancer, he might have enjoyed the rare distinction and possibly unique honor of being elected a Fellow of the Royal Society, having been proposed by the 1932 Nobel Laureates, Sir Charles Sherrington and Lord Edgar Adrian.[12]

Critchley has written how remarkable SAKW was as a man and as a neurologist[13]; that he was the Marco-Polo (1254–1324, famed Venetian 13th-century merchant, explorer, and writer) of the extrapyramidal nervous system, and that in the 1920s and 1930s, he and the Anglo-Irish Gordon Morgan Holmes (1876–1965) were the 2 supreme figures among the world's neurologists. SAKW published on disorders of mobility and motor tone, epilepsies, aphasia, ataxia and tics, and pathological laughing and crying.[6] When seeing patients, he was always probing, questioning, and speculating — not just interested in describing the signs or the problems but questioning — Why? Why?[13] He was an investigator of startling originality. When colleagues discussed a case with him, he would shed a "penetrating ray of light" on the problem that was there, typically from an unexpected angle. "What was unique in SAKW was that element of wonder that he detected in every facet of neurology and which he transmitted to others."[13]

He was a legendary teacher, quick-witted and with excellent judgment, stimulating to students and junior colleagues alike. In his personal life, his son James KW recorded how he could be very funny and loved writing funny poems.[4] Additionally, there was his puckishness. He was a remarkable man whose life was cut short long before his time.

MD THESIS: PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER

After 5 years working clinically, SAKW passed his Membership of the Royal College of Physicians of London (MRCP Lond) examination (1907) and then, with a research scholarship from the British Medical Association (1909), he started his work on this "new" neurological entity, which comprised his MD thesis (Edinburgh University Gold Medal, 1911 (Figure 1B), now available electronically[1]), and his historic paper published in Brain in March 1912.[2]

His link to Paris gave him the opportunity to present his findings at the Société de Neurologie de Paris on January 25, 1912. This was followed by a 6-page article in Revue Neurologique in February 1912.[14] After his 214-page paper was published in Brain,[2] there was also a 5-page "brief communication" on this "new nervous disease" in the Lancet in April 1912.[15] These short communications focused on the nub of Progressive Lenticular Degeneration. They drew attention to the neurological features, the association with cirrhosis, and the cause possibly being a toxin coming from the liver — remarkable since the cause turned out to be due to copper accumulation. As in his Brain paper, SAKW concluded that the condition was not congenital.[15]

Thus, he documented in detail the clinical and, where available, pathological findings in 12 patients with a constellation of neurological features, in particular involuntary movements (eg, tremor), spasticity of the limbs, and the smile (Figure 4), dysphagia and dysarthria, and occasionally some mental symptoms (usually transitory). It later came to light through a collaboration (Figure 5) between SAKW's son, a Cambridge University Assyriologist, James Vincent Kinnier Wilson[16] (who died in December 2022), the eminent British neurologist, Edward H Reynolds, and James Vincent Kinnier Wilson's nephew (SAKW's grandson), another James KW, that a remarkable film had been made in the 1920s by SAKW of patients with various movement disorders.[10] It has been conjectured that SAKW had been stimulated and facilitated to make this film through his personal contact with Charlie Chaplin, with whom he stayed at the latter's California estate.[4] James Vincent Kinnier Wilson wrote that what SAKW most admired in Charlie Chaplin was that the latter considered it "the supreme achievement of the art of comedy to create laughter by action alone and without the support of words".[4] He added that SAKW himself both "created and enjoyed laughter."

The neurological condition that SAKW described was progressive and invariably eventually fatal. Of importance, he recorded that in these patients, there was cirrhosis, but he thought that this was rarely manifested clinically.[2] In his paper, these and other features were recorded from a group of 12 patients, 4 of whom he had seen personally and studied clinically (with a post-mortem in 3), 2 cases from case records at the National Hospital, Queen Square, and 6 cases from the literature (see Table 1 in Broussolle et al[6]). Fundamental to his thesis was the finding of degeneration of the lenticular nucleus in 7 of the 9 patients in whom brain pathology along with liver histopathology was examined microscopically (Figure 6A and B) — the lenticular nucleus being comprised of the putamen and globus pallidus.

Such was his dedication to recording the clinical features of WD and elucidating the pathological basis of the disease that he specifically travelled to the Chexbres municipality in the Canton of Vaud, Switzerland, twice in 1910; first in June to clinically evaluate a patient whom he had not physically seen for some

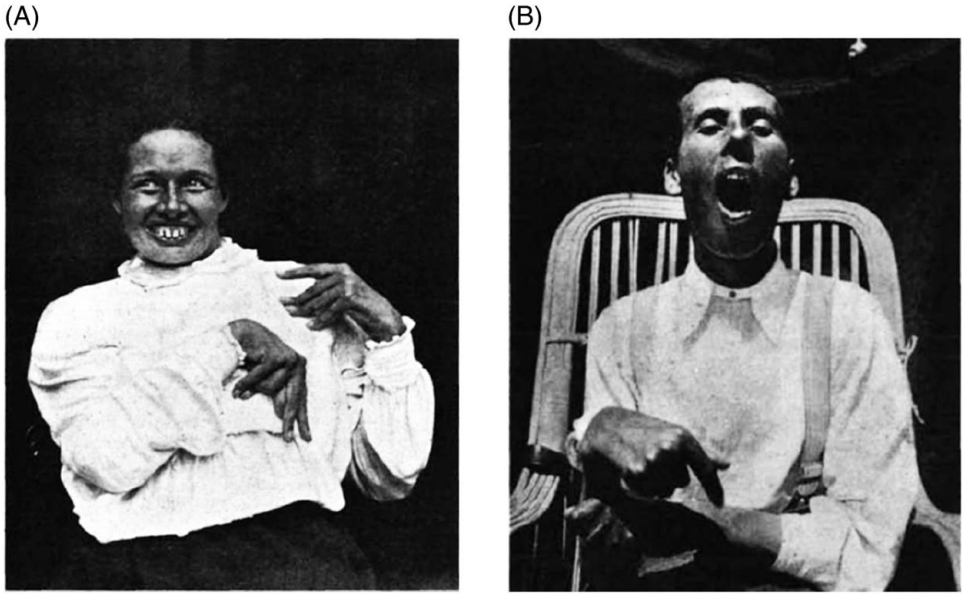

FIGURE 4 Wilson disease patients with neurological features. (A) Photograph of ST, taken at Virginia Water, in the County of Surrey, UK, which SAKW received from Dr GW Smith. Note the characteristic appearance of her face and upper limbs. (B) Photograph of EP in June 1910. Note the vacant expression, open mouth, sialorrhea, and contractures. Exposure of 1/250s, to counteract the effect of the constant tremor. (A and B) Reprinted from Kinnier Wilson.[2]

years, and then in September, immediately after the patient had died, to perform an autopsy.[2] This commitment to the patient and his own research is amazing, considering how difficult it must have been in 1910 to arrange a journey to Switzerland, presumably by train and at short notice. What is also a measure of SAKW's extraordinary focus on WD are the 10 pages of his Brain publication devoted to this patient's clinical features, and then 34 pages describing the pathological features, containing over 30 pictures of tissue both macroscopic and microscopic (Figure 6A Liver, and 6B are from this patient). The detail is remarkable.

FIGURE 5 Photograph of James Vincent Kinnier Wilson (on the left), son of SAKW, and Edward H Reynolds (on the right), who collaborated on Babylonian texts describing neurological and psychiatric disorders.[16] Edward H Reynolds reported that the Babylonians described epilepsy, stroke, psychoses, depression, and anxiety. Photograph courtesy of Edward H. Reynolds.

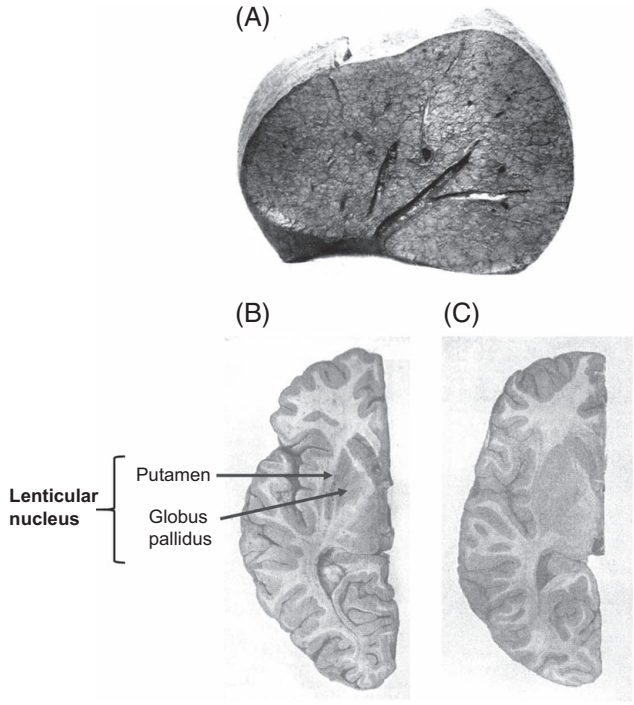

FIGURE 6 (A) Liver from EP, case 3 in SAKW's publication.[2] Subtle nodular appearance due to cirrhosis. (B) Coupe d'élection, left hemisphere from the same patient, as in (A) Atrophic degeneration of lenticular nucleus. (Arrows indicate the lenticular nucleus). (C) Coupe d'élection. Normal brain of a youth who died of cirrhosis of the liver without nervous symptoms. Note full full-rounded contour of lenticular nucleus, for comparison with 6B. (A–C) Reprinted from Kinnier Wilson.[2]

EARLIER REPORTS CONSISTENT WITH WD; DESCRIPTIONS OF "PSEUDOSCLEROSIS"

It is important to note that other reports had previously drawn attention to patients with cirrhosis and coincidental neurological disease. In his treatise in 1860, Friedrich Theodor von Frerichs described such a patient who has now been thought to have actually had WD.[17] It is possible that in 1761, Morgagni also described a case consistent with this diagnosis, which was suggested by one of the giants in WD research[18]—as will soon become apparent—Dr John Walshe (Figure 7), who died aged 102, in October 2022.[19,20] Moreover, through the later years of the 1800s, several neurologists had described a syndrome with clinical features similar to Multiple Sclerosis but without its recognized characteristic neuropathological features, and described by them as "Pseudosclerosis"; subsequently, this syndrome became known as Westphal-Strümpell Pseudosclerosis.[21–23] Cirrhosis was an attribute in some of these patients.

SAKW, in an addendum to his paper in Brain, drew attention to a paper by Völsch[24] published in 1911 describing another patient with possible pseudosclerosis and cirrhosis, but noted (on page 508) that "this unsatisfactory and makeshift expression … coined for certain cases which were said to resemble disseminated sclerosis clinically, but not pathologically, should be abandoned, and that re-examination of the subject should be undertaken".[2] Yet the term Pseudosclerosis persisted for some time after SAKW published his paper in *Brain* describing the neurological aspects and other associations of what became known eponymously as his disease, namely WD.[2,25] However, Spielmeyer in 1920[26] and Hall in 1921,[27] in their analyses, concluded that pseudosclerosis and Wilson disease were the same entity. Thus, Spielmeyer from Munich reported the neuropathology of pseudosclerosis and WD. Hall, from Copenhagen, analyzed (in a book of over 350 pages, with a Preface by Pierre Marie, entitled "La Dégénérescence Hépato-lenticulaire") the features in 4 of his own cases and 64 cases from the literature. Apart from his conclusion regarding WD and pseudosclerosis, he also opined that it was an inherited condition.

Thus, pseudosclerosis and progressive hepatolenticular degeneration became recognized in the 1920s as one and the same condition. The experience that WD patients could have a range of neurological features, explained the separation of terms initially. So, while the "classic," that is, a typical SAKW WD, patient had a predominance of rigidity, the pseudosclerotic form showed more tremor—both with a wide range of other neurological features. This is reviewed in the paper by Dusek et al,[28] wherein a table shows the change in neurological classification in publications through the years. The most recent classification from 1996 showed 4 forms: dystonic, tremor, rigidity/tremor, and rigidity forms.

FIGURE 7 Dr John Walshe. Courtesy of Clare Armstrong.

WILSON DISEASE—OTHER CHARACTERISTICS

Since SAKW's seminal paper, the wide spectrum of clinical features of WD has been recognized and described—but as Dr John Walshe has said, "no two patients are ever the same, even in a kinship."[29] Kayser-Fleischer (KF) rings, if present and recognized, constitute an important clinical sign of WD although ironically, SAKW did not report them in his initial paper. These eye signs had, in fact, been reported earlier by German ophthalmologists, Bernhard Kayser (1902)[30] and Bruno Fleischer (1903),[31] respectively, a decade before SAKW's paper appeared, but the cause of KF rings and their association with WD took some years to establish.

KF rings were thought at one time to be due to an accumulation of silver,[32] but they are golden-brown, dark greenish-brown, or variations thereof, and in fact are due to the deposition of copper granules at the periphery of Descemet's membrane (where the cornea meets the sclera), first as a crescent superiorly, then at 6 o'clock and eventually encircling the iris (Figure 8).[33] Clinically, a slit-lamp examination by an experienced ophthalmologist should be done (Figure 8A and B), because KF rings may not always be seen by naked eye inspection. New techniques are now being suggested to help with their identification, for example, anterior segment optical coherence tomography (AS-OCT), as described in Chevalier et al.[33]

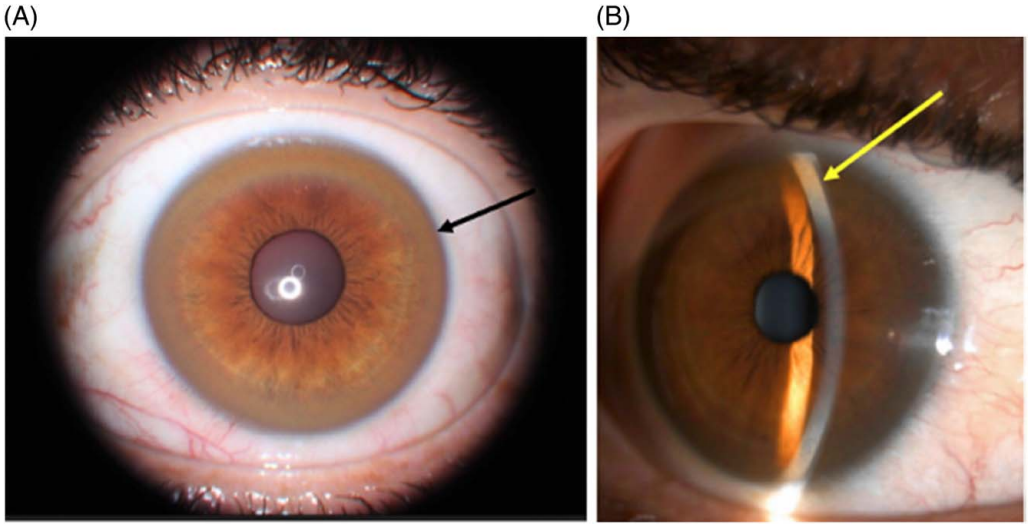

FIGURE 8 Kayser–Fleischer Rings. (A) Slit-lamp examination showing a diffuse circumferential Kayser-Fleischer ring in the left eye (black arrow), (B) Slit-lamp examination visualization of the copper deposit at the posterior part of the cornea in fine slit (yellow arrow), (A and B) Reprinted from Chevalier et al.[33] https://creativecommons.org/licenses/by/4.0/.

From the point of view of the liver, SAKW had remarked that cirrhosis did not appear to be clinically relevant. However, Bramwell in 1916[34] and then Barnes and Hurst between 1925 and 1929[35] reported that liver involvement could give features of clinical liver disease that in some patients could be severe.

Thus, the predominant manifestations of WD are hepatic, neurologic, and psychiatric[36] (often in combination[37]), with or without K-F rings. However, other clinical features may occur, including several renal abnormalities, osteoarthritis and other arthropathies (as reported by Bearn from the Rockefeller Institute of Medical Research in New York in 1957[38]), and nonimmune (Coombs-negative) hemolysis. The latter severe complication of WD was first described in detail in 1967 by McIntyre et al.[39] from Sheila Sherlock's unit at the Royal Free Hospital (RFH) and School of Medicine (RFHSM) in London. Neil McIntyre (1934–2020, Figure 9)[40,41] was an energetic Welshman who had a rigorous approach to research and clinical medicine. As a medical student he had achieved the considerable kudos of having his research published in *Nature* and the *British Journal of Experimental Pathology.* Neil also enjoyed a passionate interest in medical training, philosophy, and history, especially of medical statues about which he often published[42] and the training of women in medicine,[43] in which capacity the RFHSM was the renamed London School of Medicine for Women (founded in 1874)—the first teaching Hospital in England to admit women. Neil was later appointed to the Chair of the RFHSM Academic Department of Medicine and Head of the RFH Liver Unit, succeeding Professor Dame Sheila Sherlock, who in 1959 had been appointed to the Chair of the Department of Medicine at the RFHSM.[44] She was then the first Professor of Medicine at the Royal Free and the first woman to be appointed to the Chair of Medicine in a British Medical School. She was belatedly elected a Fellow of the Royal Society in England in 2001.[44]

FIGURE 9 Professor Neil McIntyre (1934–2020), Professor of Medicine at RFHSM and later Chair of the RFH Academic Department of Medicine and Head of the RFH Liver Unit. Reprinted with permission from Warren.[40]

WD PATHOPHYSIOLOGY

WD pathophysiology remained obscure until the late 1940s and early 1950s. SAKW had written that the condition was perhaps due to a toxin but not due to alcohol or syphilis and that it was "familial but not inherited." This conflict of terms was probably due to the fact that understanding of the inherited disease, although recognized then with dominant inheritance, was in its infancy, and that SAKW meant that it might be inherited but not dominant.

The relationship to copper excess had been raised as a possibility previously by Rumpel in 1913[45] (in a patient with pseudosclerosis), and others later, including Glazebrook.[46] A clear recognition of this copper association eventually came from Cumings at Queen Square in 1948,[47] who reported increased copper levels in the brain and liver of patients with WD. In the same year, in a study by Mandlebrote et al that focused on urinary copper in multiple sclerosis, British Anti-Lewisite (BAL) was given to assess the copper status, and one of the "control" patients, who it transpired had WD, was found to have high urinary copper levels.[48] This link to increased urine copper excretion raised the question whether liver damage per se could occur from copper toxicity. The answer lay in a report by Mallory's group in 1921, at the Boston City Hospital, of experiments in which rabbits that were given copper (in a study of the cause of hemochromatosis) developed liver damage.[49] But whether copper accumulation in WD was the primary defect as opposed to being secondary to an abnormality of peptide metabolism, as suggested by Uzman et al in 1956,[50] took some years to resolve.[51] The primary role of copper in WD was shown by Scheinberg and Sternlieb in the 1960s when treatment of asymptomatic patients with WD with penicillamine (by then used as a copper chelator) prevented the development of symptomatic disease.[52]

Meanwhile, the 1950s saw fundamental advances in the biochemistry, genetics, and drug treatment of WD. Holmberg and Laurel first isolated and characterized ceruloplasmin in 1948.[53] They were misled, however, by their finding of a normal serum level in a patient with presumed WD, who it subsequently turned out did not have this disorder. Deficiency of ceruloplasmin in WD was, however, reported soon after this, in 1952, by Scheinberg and Gitlin[54] using an immunological assay, and in 1954 by Bearn and Kunkel[55] employing an enzymatic assay, since ceruloplasmin is a ferroxidase enzyme.

SAKW's comments on inheritance, that is, familial versus acquired, have been mentioned above. However, Hall in 1921 published data from his large group of patients and concluded that inheritance was probably recessive.[27] Bearn, in 1953, studied 26 cases in 16 families and concluded indeed that this was an autosomal recessive condition,[56] which he reinforced in a further report in 1960.[57] The gene involved (ATP7B) was not identified until 1993 — more on that later.

The answer to how and why patients with WD retain copper had to await the findings of studies with radioactive copper and the later analysis of copper in bile. Walshe reported a series of studies using injected ^{67}Cu and ^{64}Cu showing the distribution of copper on follow-up isotope scans.[18,58] The uptake of copper by the liver varied according to the stage of disease — greatest in early disease and after removal of excess copper by chelators, and less in advanced disease when the liver was loaded with copper — but in neither situation was there a peak of activity in the lower abdomen (representing excretion of copper in bile and thence into the intestine) as seen in normal individuals. The low biliary copper excretion in WD was subsequently confirmed by Frommer in 1974,[59] and Gibbs and Walshe in 1980,[60] using direct measurement. However, the lack of these pathophysiological data did not hold back progress in treatment.

THE PATH TO D-PENICILLAMINE

That copper was involved in WD was supported by the findings of the study mentioned above in Multiple Sclerosis using BAL[48] — an antidote developed in the Second World War for arsenic poisoning. BAL is a heavy metal chelating agent, not only of copper but other metals including mercury, lead, and gold. Cumings suggested that BAL might be used to treat WD, and in 1951, he in the UK,[61] and Denny Brown in the USA,[62] independently reported the use of BAL in WD. However, BAL had to be given by repeated intramuscular injection, and this made its use difficult. An effective oral copper chelator was needed.

And this is how Dr John Walshe (Figure 7) entered the WD scene. His contribution is an extraordinary example of "translational research" — serendipity that brought together a clinical challenge linked to WD, and the chemical structure of a compound studied for a completely different reason in his earlier research. This conflation of ideas identified a possible oral agent to treat excess copper. So, in the early 1950s, Walshe was working in the Metabolic Unit at University College London with Dr (later Professor) Charles Dent, studying amino acids in the urine of patients with liver disease, using paper chromatography. In one patient's urinary chromatogram, there was a novel band, which initially it was thought might be a new amino acid. However, the patient was receiving penicillin, and it transpired that this novel band was, in point of fact, penicillamine – a metabolic breakdown product of penicillin. Walshe published this laboratory work in 1953,[63] and not long after this, he travelled to Boston in 1954 on a Fulbright Scholarship to work in the Liver Unit at Boston City Hospital with Dr Charles Davidson. On a ward round

there, the neurological team asked for advice on the treatment of a patient with Wilson disease who was not doing well on BAL.[64] Remembering his work on penicillamine, Walshe predicted that, based on its chemical structure, it would bind copper. He therefore suggested that this oral agent might chelate copper and increase its urinary excretion. To cut a long story short, a small supply was obtained, and its short-term safety was ascertained by Dr Walshe taking some himself after considerable thought about the pros and cons.[64] Then the patient received some and this led to a sharp rise in urinary copper excretion. This seminal intellectual link and short study led Walshe in Boston and, on his return to England, to study more patients with WD who were given penicillamine. The data confirmed its effectiveness as a cupuretic agent, reported in 1956 in the Lancet (his US data)[65] and the *American Journal of Medicine* (his US and British data).[66] Subsequent studies by John Walshe,[67] and Herbert Scheinberg and Irmin Sternlieb[52] at the Albert Einstein College of Medicine in New York — two other towering experts in WD[68] — showed the clinical effectiveness of D-penicillamine. The latter innovation transformed the treatment of WD and has had a fundamental impact on the lives and survival of innumerable patients over the subsequent 60+ years.

ZINC

Before describing the later discovery of other oral chelators, it is now necessary to cross to another therapeutic path — the use of oral zinc salts, which, put simply, increase intestinal mucosal levels of metallothionein (which binds copper), resulting in reduced copper absorption. In the late 1940s and early 1950s, there had been a string of papers on copper metabolism in sheep, in which both low levels and toxicity were known to produce disease. In this literature, the Australian scientist Alexander Thomas Dick (1911–1982), who published a large number of papers on the subject, had shown in 1954 that zinc sulphate reduced liver copper levels in sheep.[69] Gerritt Schouwink, in the Netherlands, aware of these data, started using zinc to treat WD patients, in the late 1950s. He published this work in his Thesis in 1961[70] and reviewed his experience with this approach at an Orphan Disease and Orphan Drug meeting at Leeds Castle in Kent in the UK in 1986.[71] Tjaard Hoogenraad, also from the Netherlands, extended the report on the benefit of zinc therapy at this meeting and in later publications.[72]

Another chance observation, however, led to the use of zinc in the United States, when Drs Prasad and Brewer et al, in Michigan, reported that patients with sickle cell anemia being treated with zinc acetate developed copper deficiency.[73] This serendipitous event led distinguished Michigan geneticist, George J Brewer, to publish a large series of original articles on zinc and copper dynamics, and outcomes in patients with WD when treated with zinc.[74,75] Thus, the use of zinc in WD was derived from observations of the effect of zinc salts in animals and humans.

OTHER CHELATORS

Meanwhile, in the 1960s, Walshe was looking after a patient who could not continue on D-penicillamine because of side effects and who needed an alternative treatment. He discussed this dilemma with his colleague Dr HBF (Hal) Dixon, a biochemist and Fellow of King's College, Cambridge University in England, who was an expert on chelators. When Dr Dixon suggested that triethylenetetramine might be effective (an encounter Walshe relates in his highly personal scientific autobiography[64]), Walshe developed and produced the agent now simply called trientine dihydrochloride and indeed showed it to increase copper excretion and to be an effective treatment for WD.[76,77]

We have already seen how observations in animals influenced drug discovery for WD; another group of chelators used today were also derived by such happenstance. Veterinarians knew that molybdate induced copper deficiency in sheep and cattle and that this was potentiated by sulphate dietary supplements.[78,79] The explanation was that the formation of thiomolybdates bound copper in the gut and systemically. Through this path of discovery, ammonium tetrathiomolybdate was used in WD, first by Walshe[80] (which he also reported at the Leeds Castle meeting) and then in a series of studies (and 1 randomized trial in which tetrathiomolybdate and trientine were compared in a double-blind design) by George Brewer and colleagues.[81] More recently, bis-choline tetrathiomolybdate, a more stable form, appeared to have beneficial effects,[82] but further development of this compound has been discontinued.[83] Its mode of action has been studied in detail.[84] Meanwhile, results of a study of trientine tetrahydrochloride have recently been reported, assessing its effectiveness in relation to D-penicillamine.[85] Other new chelators, for example Methanobactin, are in preclinical studies in rats.[86]

And so, while more potential agents have been and are being developed, which of the chelators currently available is most appropriate and for which clinical phenotype remains an area of discussion and investigation. These and other new aspects of WD are discussed in a recent comprehensive review.[83] Much work is being focussed on end points — in particular, new methods for measuring non-ceruloplasmin–bound copper[87] — and evaluating the relationship of these end points to clinical progress and treatment. This indicates that although treatment is

usually effective and successful, outcomes may be unpredictable. As noted above, Walshe wrote that no two patients are the same,[29] and despite all his work and experience, he was not able to predict which patients would or would not respond to treatment or deteriorate on what was thought to be the best available treatment.[64]

Meanwhile, for a subgroup of patients, liver transplantation is performed after appropriate review. This approach was first reported for WD by a team led by Professors Tom Starzl, Herbert Scheinberg, and Irmin Sternlieb in 1971.[88] And now, liver transplantation is a potentially life-saving approach for patients with WD with fulminant liver failure and for those with decompensated chronic liver disease who are unresponsive to medical treatment.[89] Replacement of the liver cures the metabolic defect. Outcomes are generally similar to those with other etiologies of fulminant liver failure and decompensated chronic disease undergoing liver transplantation. On the other hand, neurological WD as the primary indication for transplantation remains controversial.[83,90]

CLONING OF THE WD GENE

For the future, gene therapy is an exciting prospect as an approach to correcting the genetic and thence the metabolic defect of WD. This approach has been studied in animal models, but reaching this stage has taken years of work toward the identification of the chromosomal location of the defect and then cloning of the WD gene and study of its cellular function.

In 1985, the chromosomal location of the locus linked to WD was reported[91] as being on chromosome 13 close to the locus for esterase D. In 1990, using restriction fragment length polymorphisms, the location was refined to between D13S31 and D13S55 of the q14-q21 band.[92] The next major advance (see Chelly et al[93] for review) was the cloning of the Menkes "Kinky hair" disease gene (ATP7A) early in 1993—this being a condition in which copper absorption is defective, leading to copper deficiency and a range of serious consequences.[94] Later in 1993, 3 groups independently reported the cloning of the WD gene (ATP7B), 2 of whom used information from the Menkes disease gene,[95,96] whereas the third used a heavy metal binding motif from the amyloid β-protein precursor.[97] The WD gene product is a transporter of copper between cytoplasm and Golgi and, in the presence of high copper levels, between the cytoplasm and vesicles that carry copper to the bile canaliculus[98] (Figure 10). Thus, dysfunctional ATP7B leads to (i) a lack of transport of copper to apoceruloplasmin in the Golgi, and therefore reduced secretion into the circulation of copper bound to ceruloplasmin, and (ii) defective secretion of copper into the bile, as described above in WD. Results of other studies have shown that ATP7B mutations can have a range of other metabolic effects.[99]

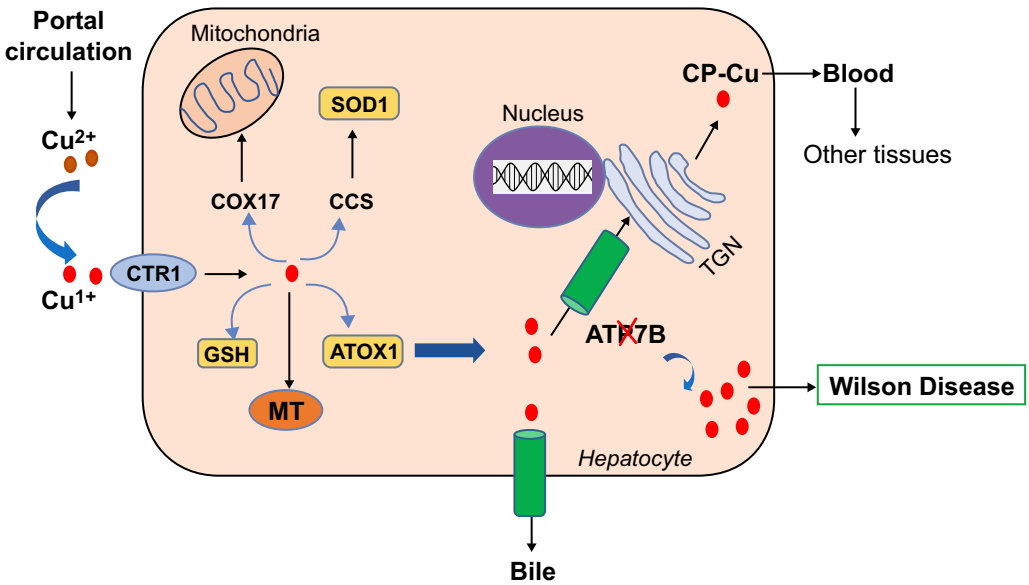

FIGURE 10 Copper Homeostasis in Liver; with Cellular ATP7B activity. Reproduced from Dev et al[98] https://creativecommons.org/licenses/by/4.0/. Copper (Cu) enters the liver through the portal circulation and is transported into liver cells primarily by the high-affinity uptake protein, CTR1. Cytosolic Cu chaperones shuttle Cu to specific intracellular targets; CCS transports Cu to SOD1, ATOX1 to the Cu-transporting ATPase ATP7B. ATP7B transports Cu into the trans-Golgi network (TGN) for incorporation into ceruloplasmin (CP) and to the apical membrane for excretion. Inactivation of ATP7B causes Cu overload, which manifests clinically as WD. Abbreviations: ATP7B, ATPase Cu(I) transporting beta polypeptide; CTR1, high-affinity Cu uptake protein 1; MT, Metallothionein; GSH, Glutathione, ATOX1, antioxidant protein 1; SOD1, Superoxide dismutase; CCS, Cu Chaperone for SOD; COX17, Cytochrome C oxidase.

Identification of ATP7B led to a wide range of studies of intracellular copper metabolism and the recognition that there are more than 600 mutations associated with WD.[100] An amazing database of mutations was collated for many years by Professor Diane Wilson Cox and her team at the University of Alberta and has been of considerable value, but the database has not been updated since around 2010.[101] Techniques are now broadly available for mutation analysis to be done as part of the diagnostic work-up of patients, and much work has also been done to try and identify a genotype/phenotype relationship, but to date, without significant success.[102] Other factors are reported to have a greater influence.[103] Identification of the gene and elucidation of its molecular biology, alongside much work on approaches to gene therapy in other conditions, give the hope of a gene therapy approach for patients with WD. Initial animal work has already been published.[104–106] If this can be successfully applied to humans, as has been accomplished in other conditions, it could be an important potential therapeutic approach for WD patients. Phase 1 and phase 2 studies are underway (ClinicalTrials.gov numbers, NCT04884815 and NCT04537377).[83]

Thus, the goal is to return copper metabolism to as normal a state as feasible, since copper is important for so many cellular and metabolic mechanisms. Our esteemed series editor has reviewed this in his Landmark article in HEPATOLOGY,[107] quoting John Walshe's 1995 publication,[108] "Not too little, not too much, but just right." The emphasis of this history and other articles on the toxicity of copper "should not detract from the fundamental importance of copper to life."

OTHER "RECENT" HISTORY RELEVANT TO WD

Just as the elucidation of the genetics of WD depended on applying developments in molecular biology, other areas of progress in diagnosis, clinical assessment, and management have depended on various other technological advances.

This is highlighted in the review by Trocello et al[109] in which a T2 fluid-attenuated inversion recovery scan is shown (Figure 11). Having read SAKW's historical paper in Brain[2] and included in this article one of the Coupe d'élection (Figure 6B), the point is strongly made that cranial imaging can now define noninvasively pathological changes that previously required histopathology. SAKW's paper was published just over 100 years ago; cranial imaging developed from around 50 years ago onwards, and both are part of the same history.

Assessment of brain structure in WD previously utilized computer-assisted axial tomography (or CT) scanning but now uses sophisticated MRI and advanced image manipulation.

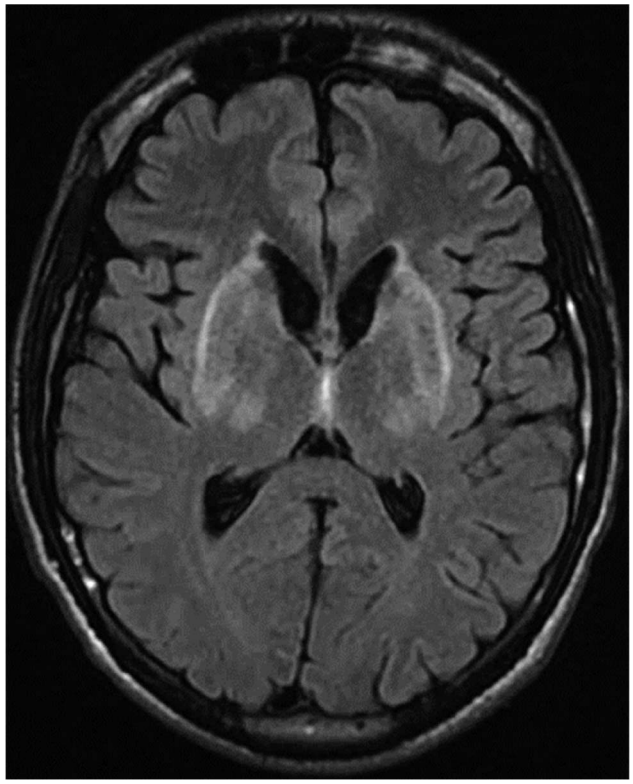

FIGURE 11 Brain MRI, FLAIR: symmetric hypersignal in basal ganglia in a patient with Wilson disease. Reprinted with permission from Trocello et al.[109] © 2013 Elsevier Masson SAS. All rights reserved. Note: Original has been lightened to make features more easily visible. Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Commercially viable human CT scanning began in London UK in 1971, using the EMI-scanner device invented by (later Sir) Godfrey Hounsfield at Electric Music Industries (EMI, hence the original name of the EMI scanner) Central Research Laboratories in Hayes UK.[110] EMI Ltd was better known at the time for publishing the Beatles' records.[110] CT-generated brain imaging was soon reported,[111] and clinical correlation with CT brain imaging in WD was published later,[112] co-authored by Tony Bass, who contributed to this series with a historical essay on hepatic encephalopathy.[113] The first MRI brain scans (developed in principle in the 1970s), became commercially available a decade later, leading to a publication arising from a trans-London UK collaboration between the Royal Postgraduate Medical School/Hammersmith Hospital and the RFH.[114] Progress has been remarkable since then.

Many MRI sequences are available now for detailed brain structural and even functional assessment. On T2 weighted or fluid-attenuated inversion recovery sequences, the characteristic changes in WD are hyperintense signal abnormality in the basal ganglia, thalamus and/or brain stem, seen in 90% or so of patients with a

neurological presentation.[28,115] A hyperintense signal abnormality surrounding the red nucleus and substantia nigra, known as "the sign of the face of a giant panda," is only seen in a minority of patients. The clear message is that noninvasive scanning can show brain changes, previously only accessible on post-mortem histology as described above (Figure 6B). MRI sequences can now be applied to cranial scanning in WD, giving many different analyses of brain tissue and damage and a brain MRI severity scale.[116] Structural and functional changes can be seen, even in neurologically silent patients with WD,[117] and a host of MRI imaging techniques can be correlated with clinical and biochemical data.[118] Ergo, MRI scanning has become an invaluable tool for addressing clinical and research questions in patients with WD, where understanding the neurological features and the risk of progression otherwise remains challenging. Trocello et al,[109] emphasized that the new noninvasive techniques actually confirm what SAKW observed under the microscope, a little over a century ago.

And so, imaging techniques developed 40–50 years ago are part of WD history.

Meanwhile, advances in WD diagnosis and management owe much to WD specialists combining various clinical data to produce clinical scores or scales. To aid in the diagnosis of WD, a scoring system — the Leipzig score — was developed at the International Conference on Wilson Disease and Menkes Disease in Leipzig in 2001 and published later by Ferenci et al.[119] Sad to report, Peter Ferenci, who contributed greatly to so many areas in WD and Hepatology died in April 2023[120]. The Leipzig score, which is recognized as an international standard, is highlighted in the diagnostic decision trees in the AASLD Practice Guidance,[37] and is frequently used to scrutinize subjects for inclusion in WD clinical trials. Additionally, there are several other scores: the revised Nazer King's prognostic score in WD (the New Wilson Index) published by Anil Dhawan et al in 2005 to assist management decisions in patients with acute liver injury,[121] the Unified Wilson's Disease Rating Scale proposed by Anna Czlonkowska et al in 2007[122] (later evaluated[123]), and also a Global Assessment Scale from Aggarwal et al.[124] While these can be used to score the clinical features in patients with WD, other comparisons of various rating scales in WD have also been published.[125] As with other clinically applicable scores and indices, it is mandatory to review such calculations periodically, as experience with other prognostic instruments has shown that their reliability may need to be scrutinized[126] from time to time.

So, the history of WD moves on progressively, with many groups internationally collaborating in research and developing new directions. Guidelines and guidance for WD have appeared from professional associations over the last twenty years,[127,128] some of which are being[127] or have been updated.[37] The strength of the WD community internationally is underlined by the success of international symposia which have been held over the last several decades - the International Conference held in Leipzig in 2001 has already been mentioned. Most recently the *third* Aarhus Wilson symposium, led by Professor Peter Ott, has been held over three days in May 2024.

Of importance additionally, there are WD patient groups that fulfill a very important role in the support of patients and their caregivers and provide a link to specialists. The WD Association in the USA has recently celebrated its 40th year anniversary and the WD Support Group UK is approaching its silver (25-year) anniversary.

IN SUMMARY

The current knowledge, diagnostic approach, and management of the complex disease that is WD, has been built up over the last 100 years by a very dedicated group of physicians — hepatologists, neurologists, psychiatrists, radiologists and transplant surgeons — biochemists, and cellular and molecular biologists. Much research is ongoing worldwide. We owe all those involved a debt of gratitude for their persistence in elucidating what has been and still sometimes remains a very challenging clinical condition. And this all began with Samuel Alexander Kinnier Wilson and his seminal work published over a century ago.

ACKNOWLEDGMENT

The author thanks Professor Adrian Reuben, the editor of this series of historical articles, for all the many contributions that he has made to this article, both to elements of the history of WD but also to the broad history of medical terms used in the text, emphasizing the contribution of other hepatologists in the general history. His knowledge in this area is remarkable, and his drive to excavate terms and information is amazing The author is grateful to have had his guidance in this article.

CONFLICTS OF INTEREST

The author has no conflicts to report.

SERIES EDITOR'S POSTSCRIPT

If my memory serves me well, I first met James Dooley in 1973, when he was an earnest, enthusiastic and knowledgeable newly-minted house officer [equivalent in the US to an intern] on the Professorial Medical Unit at the now demolished Middlesex Hospital in London, where I was just beginning my academic career as a registrar, a middle-ranking hospital doctor undergoing training as a specialist [US equivalent to a very senior resident or a fellow]. The titles of the positions of physicians and university faculty in the UK appear archaic, as indeed they are, but so are old-fangled titles in the US, Europe, and elsewhere, as will be apparent from other essays in

this series. For example, do junior medical doctors (residents) in the US actually reside in their hospitals nowadays, except perhaps for nights on-call? And how often do senior faculty attend? And in German universities, habilitation — derived c.1600 CE, from medieval Latin transitive *habilitatus,* to qualify — serves as evidence of an individual's capability of researching independently and of teaching in a certain subject area. In other words, habilitation serves as a formal qualification equivalent to a second thesis defended before a jury of professors (ie, future peers) needed to become a university professor. Perhaps, the most comical and still entertained in the University of Cambridge UK is the Tripos examination system, likely derived originally from the 19th century mathematics course and examination — the oldest written examination at the university. Before the distinction between honors and ordinary degrees had been formalized, it was the custom at commencement for Bachelor of Arts (BA, the only undergraduate degree awarded at Cambridge) candidates to dispute against a senior BA who was seated on a 3-legged stool (tripod/tripos). In time, the process was simply the provision of an entertaining speech or mock-disputation satirical composition in Latin, or occasionally Greek, verse. The names of the successful, so-called tripos candidates were printed on the back of the verses. By 1894, the name tripos had long since been transferred from the list of successful candidates to the examination itself. In this setting, a student who gains first-class honors in the final year examinations is known as a wrangler, and whoever scores highest is the senior wrangler, and the lowest is the wooden spoon.

Dr James Dooley, rose to the rank of Reader in the University of London, which is roughly equivalent in the United States to a very senior associate professor or professor without a chair.

James hails from the UK County of Surrey, where his parents exchanged careers as university-trained chemists for farmers. After a farming upbringing, James studied Medicine at the Middlesex Hospital Medical School (1967–1973). After various junior clinical positions, he joined Sheila Sherlock's esteemed Liver Unit in 1977 at the RFH. In 1979, he was awarded a Saltwell Research Fellowship by the Royal College of Physicians of London and performed research focussed on the biliary tract. This was the basis for his being awarded his University of London MD Thesis, entitled "*Clinical and Experimental Studies of Percutaneous Bile Drainage in Man*." In 1982, he moved from London to Washington as a guest worker in the Liver Diseases Section (NIADDK) at the National Institutes of Health in Bethesda MD, working with Drs Jay Hoofnagle and E. Anthony Jones, studying α-interferon treatment of Hepatitis B. In 1984, he returned to the RFH. Here he was promoted successively, and while he continued his biliary interest (including the performance of endoscopic retrograde cholangiopancreatography), he began his ongoing ventures in genetic liver diseases, and assumed a major role in postgraduate medical education. Perhaps his major academic accolade was to be invited by Dame Sheila to co-author the next 3 editions (9th, 10th, and 11th) of her renowned and universally acclaimed textbook, "Diseases of the Liver and Biliary System" (1993, 1997, and 2002), and which he has continued to co-edit after her death (latest edition,13th, 2018).

Perhaps less well-known are James's musical vocal accomplishments, particularly in the Italian songs of Francesco Paolo Tosti (b 1846 in the Abruzzo region of Italy, d 1916 in Rome, after a 32-year stay and knighthood in Britain). In my considered opinion, James's recordings, made in Italy with pianist, conductor, and musicologist Antonio Piovano, complement and compete with those made by many current famous tenors and those from the past. Levity aside, these upwards of forty recordings of Romanze by Tosti, comprise a remarkable achievement.

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How to cite this article: Dooley JS. The history of Wilson disease. Clin Liver Dis. 2024;23:e0238. https://doi.org/10.1097/CLD.0000000000000238