Kinnier Wilson's puzzling features of amyotrophic lateral sclerosis

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MRT conceived the manuscript, and drafted the abstract, introduction and text concerning the first of Kinnier Wilson's puzzling features.

MS, AE, JR and MCK drafted one section for each of the four remaining puzzling features in that order.

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Abstract

Pre-eminent neurologist S.A. Kinnier Wilson's posthumously published 1940 textbook 'Neurology' included a detailed clinicopathological account of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS). In providing a comprehensive discussion of the breadth of the clinical heterogeneity, he highlighted five "puzzling features" that appear prescient of the modern recognition of ALS as a complex multisystem syndrome. The issues he raises span the areas of ongoing debate and active research in ALS, including clinical and pathological discordance, upper versus lower motor neuron loss, and the apparent non-random onset and spread of clinical symptoms. We discuss each of his observations in light of the great advances in histopathology, molecular biology, neurophysiology and neuroimaging over the subsequent 75 years.

Introduction

It is more than 150 years since Jean-Martin Charcot (1825-1893) published the first descriptions of the adult neurodegenerative disorder amyotrophic lateral sclerosis (ALS) (1). Though an unmistakable clinical syndrome in its classical form, ALS has been increasingly understood as representing a complex clinical and molecular syndrome that overlaps with frontotemporal dementia (FTD) (2). Samuel Alexander Kinnier Wilson (1878-1937) (**Figure 1**) is perhaps best known for his eponymous hepatolenticular degenerative syndrome linked to copper dysregulation (3). He is also distinguished as the founding editor, in 1920, of the *Journal of Neurology & Psychopathology* which then became the *Journal of Neurology, Neurosurgery and Psychiatry* (4). It is, however, his two-volume textbook *Neurology* published posthumously in 1940, that stands as the greatest testament to the breadth of his clinical and scientific insight. Chapter 64 demonstrates his extraordinary understanding of the clinical heterogeneity of ALS, in which he highlights five "puzzling features":

1. Implication of certain afferent tracts, and of ventro-lateral columns in the cord;
2. Irregular degree of morbid change as between spinal nerve-cell, nerve-fibre, and muscle respectively;
3. Similar disparity as regards Betz-cell and pyramidal fibre lesions;
4. The acuteness of many cases, suggesting a toxic and diffuse process, yet the lesions appear to be systematized;
5. Occasional discord between clinical and pathological findings.

Intrigued by the issues raised by each of his five comments, we here discuss them in light of developments in understanding of the syndrome of ALS during the subsequent 75 years (5).

Implication of afferent tracts and ventro-lateral columns in the cord

Kinnier Wilson set out his thoughts on ALS nearly half a century after Charcot's description. The latter recognized ALS as what he considered to be a uniquely "deuteropathic" condition, one characterised by combined lower (LMN) and upper motor neuron (UMN) loss. Kinnier Wilson recognised that François-Amilcar Aran (1817-1861) (6) and others had earlier described forms of progressive muscular atrophy, for which syphilis and lead were both plausible differential aetiological agents at that time. Furthermore, Wilhelm Erb (1840-1921) had identified a syndrome confined to the UMNs, now termed primary lateral sclerosis (7). Kinnier Wilson was bold enough to point out inconsistencies in Charcot's combined model, and was prescient in emphasising that ALS might reach well beyond the traditional boundaries of the motor system:

> Though sanctioned by long usage, the title given the affection by Charcot is now known to be inadequate. On the clinical side the syndrome ranges from severe spasticity with little wasting to profound atrophy with trifling stiffness, or none that is apparent…The underlying lesions…include something beyond degeneration of the corticospino-muscular systems, and with transcortical and intraspinous connexions…

The concept of ALS as a profoundly cerebral neurodegeneration may seem modern, since it was reinforced by the 2006 discovery that cerebral ubiquitinated cytoplasmic inclusions of TDP-43 are present in nearly all cases of ALS, plus 50% of those with FTD (8). However, involvement of the corpus callosum in ALS had been observed as early as

the turn of the 19th Century (9) and, indeed, Kinnier Wilson noted involvement of fibres in the body of the corpus callosum, a finding that has recently been revisited by *in vivo* studies utilizing modern developments in non-invasive neuroimaging (10, 11).

A spectrum of UMN and LMN involvement has long been recognized in ALS, with recognition that the predominance of one or other is linked to slower progression (12, 13), a feature captured in Swank & Putnam's article published contemporaneously to Kinnier Wilson's textbook (**Figure 2**). These ideas were prefigured by Gowers, as set out in his Manual of Diseases of the Nervous System, and led to Russell Brain's usage of the term 'motor neuron disease' to include all these related and overlapping clinical syndromes.

Kinnier Wilson did not address the concept of a primacy of UMN versus LMN loss in the pathogenesis of ALS. This issue remains controversial, with many still favouring a 'dying back' spread of pathology from LMN origins (14), or perhaps simultaneous involvement of LMN and UMN structures with variable dynamics. Nonetheless there is currently increasing interest in a primary 'corticofugal' process (15, 16). Anterior horn cell loss appears maximal in the region of the cord corresponding to the first symptoms in limb-onset cases, with contiguous spread to neighbouring motor structures (17). However, parallel studies in the brain have not been carried out to date, and the sensitivity and specificity of methods used to detect UMN abnormality (neuroimaging and cortical neurophysiological techniques to assess cortical excitability) and LMN abnormality (EMG) are not congruent. Nonetheless, there is clearly imprecision between clinically apparent UMN signs and corticospinal tract pathology (18). For example, in apparently pure LMN cases brain and cord motor pathway involvement is demonstrable

both histopathologically (19, 20) and with neuroimaging (21). Kinnier Wilson noted that while ALS is:

> …generally considered a motor affection *par excellence,* implicating the cortico-spinal system from the Rolandic field to the periphery, the involvement is seldom complete topographically and incidence on invaded sections often far from equal; some afferent tracts and paths for 'involuntary' mechanisms may degenerate as well.

As well as highlighting autonomic system involvement in ALS (reviewed in (22)), Kinnier Wilson was particularly interested in the involvement of the lateral region of the spinal cord, beyond the corticospinal tracts. In his neuropathological studies, he noted degeneration of the whole of the ventrolateral columns, sometimes including the spinocerebellar paths. This observation was specifically revisited may decades later (23), These tracts convey impulses derived from muscle spindles and from tendon organs. The spindle sensory innervation appears normal histologically, but gamma motor neurons and the gamma motor innervation of muscle spindles is lost (24), together with loss of segmental interneurons in the cord (25). Contemporary physiological studies also suggest a subtle impairment of cutaneous sensory function in some patients (26).

Spinocerebellar involvement may perhaps have relevance for the prodromal symptom of dysequilibrium reported by some patients with ALS, particularly those with clinically prominent UMN presentations (MRT: personal observation). Although overt ataxia is not a feature of ALS, sub-clinical cerebellar pathology has emerged from neuroimaging studies (27, 28), and appears common to neurodegenerative disorders more broadly (29). Significant ocular fixation errors have also been noted in eye-tracking experiments in ALS (30, 31).

Kinnier Wilson concluded that ALS could not be considered a pure motor disorder, but he could not be sure if the process "attacked" cells first, or fibres, or both at once, rendering any sense of a single directionality to the degenerative process untenable. As well as noting the involvement of ventrolateral columns in addition to the pyramidal pathways, he observed sparing of the dorsal columns. Secondly, he observed that atrophic anterior horn cells of the spinal cord were often found co-existing with preservation of their roots beyond the edge of the cord, so that at times only the intra-spinal portion of the root was affected. He concluded that this was distinct from Wallerian-type degeneration, and he referred to it as "funicular" with "some diffuse noxa radiating amid ventral columns" only affecting the root fibres as they traverse them. He deduced that a separate lymphatic supply to the dorsal columns might be the reason for this local involvement in ALS, containing a toxic element attacking motor neurones from within:

> "Once this occurs, it might diffuse itself through them (peri-axonally or otherwise) causing cellular degeneration at one end and interfering with the trophicity at the other e.g. in muscles…Pyramidal fibres are doubly affected, by being caught in the lateral funiculi along with others, and by being invaded from within."

The lymphatic system of the spinal cord had been studied previously by Scottish neurologist Alexander Bruce (1854-1911), who concluded that "there is no doubt that it permits of a current inwards or of an invasion by cellular elements, micro-organisms and toxic substances" (32). A more sophisticated contemporary framework has emerged to account for central nervous system waste processing, the so-called glymphatic system (33). Dysfunction has been linked to neurodegenerative disorders, and there has been a

specific renewed interest in the CSF as a potential mediator of pathological spread in ALS (34), so that Kinnier Wilson's observations may yet prove prescient.

Irregular degree of morbid change in cord, nerve fibre and muscle

The thoughtful discussion on ALS in Kinnier Wilson's textbook touches on a number of issues of nosology and causation concerning the pathological changes found in cord, peripheral nerves and muscles that are still contentious today. He clearly stated his opinion that familial cases, which were rare in his experience, were nosologically different from the much more frequent sporadic cases of ALS encountered in clinical practice, a view that is of uncertain provenance in an era in which various genetic causations or risk factors have been elucidated (35) and which, in some populations may be relevant in approaching 50% of cases.

Kinnier Wilson commented on neuronal cell shrinkage, a phenomenon illustrated by Charcot in his published Tuesday lectures (36, 37), as occurring in neurons in the anterior horns (**Figure 3**) and also in the fifth and third layers of cerebral cortex and in basal ganglia, thus involving "motor association connexions". He noted loss of Nissl granules in the shrunken neurons, a finding equivalent to loss of staining of rough endoplasmic reticulum and ribosomes, and further commented on disparity between degeneration of the cortico-spinal tract and histological cellular change in cortical neurons.

In the spinal cord itself Kinnier Wilson recognised that neuronal cellular changes vary among different groups of neurons and among different cells in the same group, a finding confirmed in contemporary quantitative studies (38, 39). He also recognised

degenerative change in vestibulospinal, tectospinal and rubrospinal tracts, pathways, acknowledging the work of Probst in 1903, from Vienna. Since the epochal work of Lawrence and Kuypers (40) these tracts are considered components of the ventromedial brainstem propriospinal motor system, concerned with postural and programmed movements, whether learned or innate, such as walking and reaching, and involving integration of limb and body movements. Lawrence and Kuypers (41) found that the classical lateral brainstem and corticospinal pathways are concerned with the capacity for independent use of the extremities and fractionation of distal movements, for example finger movements (42). Since these pathways are all subject to degeneration in ALS a profound abnormality in motor control involving proximal and distal motor systems would be expected – a component of the clinical phenomenology of the disease that has been conspicuously neglected. He also recognised degeneration of ascending spinal pathways, especially the spinocerebellar tracts, as previously described. Kinnier Wilson thus recognised that in ALS there are abnormalities in both ascending and descending spinal pathways and in anterior horn cell neurons, as well as more widely in the brain itself.

He noted histological evidence consistent with the progressive course of the disease, including varying abnormality among groups of anterior horn cells, more marked in cervical cord regions than in lumbar or thoracic regions, and with loss of myelinated fibre networks within affected cord segments. He commented that degeneration in descending spinal pathways was more marked distally than proximally, a feature consistent with length-dependent axonal degeneration. He concluded that motor fibre degeneration was not purely Wallerian, but that it involved "axonal change". In a ruminative paragraph Kinnier Wilson posited that "the disease tends to follow physiological paths rather than anatomical paths". In support of this notion, perhaps

based on the Jacksonian concept of the organization of motor function in the brain, which can be summarized as 'movements are represented in the brain and muscles in anterior cord segments', but which remains unexplained in his text in detailed terms, he stated that he had observed that:

1. the upper face was usually more involved than the lower face,
2. the abductors of the larynx are more affected than the adductors
3. prevertebral muscles innervated by the ansa hypoglossi, derived from C1-3, are more affected than the posterior rotators of the neck at the same level
4. the tongue may be immobile when the accessory muscles of respiration still function

To a modern reader these statements do not necessarily seem congruent with the hypothesis as set out, although the observations remain true today. Curiously he does not make much of the striking sparing of external ocular movements so often observed even in the late stages of ALS, or of the sparing of the anal and urinary sphincter muscles – admittedly functionally a combination of smooth and striated muscles. His observation of relative sparing of posterior rotators of the neck is consonant with differential involvement often noted in muscles innervated by the same spinal segment.

Kinnier Wilson was intrigued by the irregularity and focal nature of pathology in the brain and in the spinal ventral horns, as confirmed in more recent studies of anterior horn cell loss in ALS (38). He felt that distal axonal degeneration was the major pathological process, although he recognised slow degeneration of neurons with shrinkage and loss of their cytoplasmic Nissl granules. The work of Wohlfart (43), 50 years later, established that more than 30% of degeneration of anterior horn cells was necessary in ALS before muscular atrophy and weakness was detectable clinically; and that in poliomyelitis more than 50% of anterior horn cells and motor axons could be lost

before weakness and atrophy become evident. The latter finding indicates that compensatory reinnervation in ALS is not as robust as in more stable, non-progressive denervating disorders. However, such considerations were not available to Kinnier Wilson, since muscle pathology was then crude and uninformative, based on paraffin–embedded sections. Nonetheless, he might have been interested to learn that axoplasmic flow and transport are compromised in ALS (44), a concept that has led to much recent work and is consistent with the disparity he observed between nerve fibre and cellular pathology. The description of the pathology of ALS in Greenfield's influential 1958 textbook owes much to Wilson's description.

Disparity as regards Betz-cell and pyramidal fibre (tract) lesions

> "Lesions of upper motor neurones (giant cells of Betz) are usually pronounced, but, a disconcerting feature is the disparity between the respective amounts of pyramidal cell and fibre disease…Whether the process attacks cell first, or fibres, or both at once, is so undecided as to put an exclusively central origin out of the question."

The corticospinal tract (CST) has multiple functions sharing one characteristic, namely cortical control of bulbar and spinal cord activity, through monosynaptic corticomotoneurons and other pyramidal, indirectly synapsing neurons. Most CST axons originate in cortical layer V of the primary motor and sensory cortex (M1 and S1). A smaller proportion arise from the premotor cortex, supplementary motor cortex, and secondary somatosensory cortices. Corticomotoneuronal connections from fast conducting CST fibers arise exclusively from the caudal primary motor cortex (new M1) and its border with 3a. But the more rostral primary motor cortex (old M1), also has corticomotoneuronal connections through more slowly conducting CST axons, and

through di-synaptic connections with motoneurons via interposed interneurons (45). At the spinal level the CST terminates in the ventral horns, but also sends connexions into the dorsal spinal cord, traditionally viewed as the "sensory" horn. These and other key characteristics of the CST and corticomotoneuronal system, were unknown in Kinnier Wilson's era.

In humans, fast conducting corticomotoneurons comprise 5-8% of pyramidal tract neurons, and synapse with all motor neuron pools, except those to the external ocular muscles and sphincter muscles (both relatively spared in ALS) (46). These long-range axonal corticomotoneuronal synapses distinguish primates from other mammalian species and their number is a particular characteristic of humans (47). Different muscle functions are generated by separate populations of corticomotoneurons, which are widely separated within the neocortex. Corticomotoneuronal synapses in humans are widely distributed onto many functionally-related anterior horn cells For example, they may make up a 'decisive' proportion of the synaptic input in relation to thumb opposition and finger/hand function, with different corticomotoneuronal populations subserving precision versus power grip. Such synaptic arrangements also determine gait functions requiring finesse to explore uneven terrains, and possibly in the complex functions of vocalization, breathing and other multi-neuronal bulbar properties (48). These functions, seem to be uniquely vulnerable in ALS, as the split-hand syndrome (49, 50), the split leg syndrome (51) and possibly specific combinations of ALS and bulbar manifestations (52).

The numeric relationship between corticomotoneurons, their axons, and anterior horn cells is not one-to-one. Each anterior horn cell receives input from many corticomotoneurons (convergence) and a single corticomotoneuron innervates many

different anterior horn cells of the same motor neuron pools, subserving both agonist and antagonist functions (divergence) (42, 53). This functional arrangement precludes meaningful autopsy correlation of corticomotoneurons and fibre tracts. An additional factor is the *de novo*, age-dependent macrostructural white matter changes that have been shown to induce loss of descending fibres, disrupting cortical connections independent of corticomotneuronal loss *per se* (54).

Although Kinnier Wilson avoided this issue, debate continues as to the primacy of the UMN in ALS pathogenesis, as originally postulated by Charcot (55). The issue particularly concerned Gowers (56). This 'dying forward' hypothesis proposes that ALS is primarily a disorder of corticomotoneurons, many of which are Betz cells (15, 57, 58). An unknown number of smaller diameter, slower conducting, pyramidal neurons are also monosynaptic. Although ALS is an adult-onset disease, often with an apparently abrupt onset, there is a lengthy pre-symptomatic period during which excitotoxicity may be particularly important inducing anterior horn cell degeneration (58, 59).

Corticomotoneuronal complexity has been driven by evolutionary demands, which among other characteristics, parallel hand dexterity. The *C9orf72* hexanucleotide repeat is only found in humans, chimpanzees and gorillas, species having high prehensility, with a relationship between the *C9orf72* hexanucleotide bit score, a measure of genomic conservation of the aligned region across different species, and thumb opposition (60). Selective vulnerability of corticomotoneurons in relation to the thumb is manifest most obviously in the 'split hand' syndrome in ALS (49) (**Figure 4**).

Much remains to be learnt about the molecular biology of the corticomotoneuronal system, but findings in humans and animal models of ALS pose the intriguing question

as to whether or not TDP-43 mutations may contribute to altered neuronal synaptic activity and structure, particularly at disease stages preceding neuronal loss. Pathologically altered TDP-43 in Betz cells reacts differently from bulbar and spinal motoneurons (61). In motoneurons, there is formation of phosphorylated TDP-43 aggregates within the cytoplasm, whereas in Betz cells, the loss of normal nuclear TDP-43 expression remains mostly unaccompanied by the development of cytoplasmic aggregations. It has been postulated that abnormal but soluble (and, thus, probably toxic) cytoplasmic TDP-43 could enter the axoplasm of Betz cells, with anterograde transmission to the bulbar and spinal neurons (61). However, this requires specificity in the corticomotoneuronal connexions to vulnerable anterior horn cells, yet the synaptic connexions of corticomotoneurons to anterior horn cells appear to be rather diffuse. Additional molecular biological abnormalities characterizing the corticomotoneuronal-motoneuron relationship will prove important.

Topography is a key feature of the somatosensory-motor system (62), but the existence of a defined anatomo-functional organization within different segments of the same cortical region is controversial. Multiple motor representations in the primary motor area and in the parietal lobe interconnected by parieto-frontal circuits, widely overlapped, form a complex motor organization. Brain regional activity elicited by observed movement of specific body parts overlaps with that elicited by actual movement, but there are differences in physical versus observed movement which, at least in part, is dependent on mirror neuron activity (63). Compared with actual movement execution, M1 pyramidal tract neurons (PTNs) show greatly attenuated activity during action observation. It remains to be confirmed that such suppression mirror neurons are present in humans (64), but there are daily occasions when one wants to covertly imitate an observed action, allowing the observer to watch the actor, while using their own

motor system to identify and categorize the observed movement, without the activation overflowing into self-movement (65).

The acuteness of many cases, yet the lesions appear systematized

Kinnier Wilson offers an insightful consideration of the apparently acute aetiology of ALS, and aspects of selective vulnerability which now seem prescient. He recognized patients' frequent unshakeable belief in a clear preceding, triggering life-event such as trauma or an emotional shock, although it seems clearer now that the emergence of symptoms in ALS reflects a long pre-clinical period reaching the limits of redundancy (66). In noting that both lead toxicity and syphilis might produce similar symptoms, he highlighted the lack of "systematization" of the lesions as the fundamental difference as compared to ALS. One of the prime mysteries enumerated by Kinnier Wilson is that despite the generalized nature of the problem, there is highly selective affliction of the motor system, what is today often referred to as selective vulnerability.

The phenotypes and clinical classification of ALS are largely determined by the site of clinical onset of motor deficits in limb or bulbar regions, and accompanying clinical features of UMN or LMN dysfunction (typically a combination of both). Regional spread of muscle weakness is not random and typically contiguous to the limb of initial onset (17). *Post mortem* analysis of the spatial distribution of spinal cord pathology in ALS patients support the striking focality of symptom onset (67) (**Figure 5A**), and neuroimaging studies have provided some support for a parallel somatotopic cortical correlate (68). As ALS progresses the clinical disorder generalizes, converging on a phenotype characterized by, sometimes, near total paralysis, with respiratory failure as the main cause of death. This phenomenology indicates that while there is diffuse

generalized involvement of the entire central nervous system, both cerebral and spinal, the most significant affliction involves motor neurons. The realization that there is overlap with frontotemporal dementia (FTD) implies a related vulnerability of cortical neurons in the frontal and temporal lobes. At a simple level frontal and temporal cortex can be regarded as motor in the sense of executive function, thought before action, and expressive language function (69), so that one comes to realize that ALS is very much an anterior brain disease, that appears to spare posterior sensory, visual, and association cortex. Similarly, corpus callosal (70) and basal ganglia (71) involvement can be seen as related to motor function. The spinocerebellar tract and Clarke's nucleus degeneration are themselves functionally integral to the motor system and seem to be similarly vulnerable.

In discussing mechanisms of selective motor neuron vulnerability and degeneration, pathogenesis can be considered in two parts—mechanisms of cell death, and mechanisms of neuroanatomical progression. One of the key insights over the last fifteen years has been the recognition that motor neuron degeneration occurs in conjunction with complex interactions between surrounding cells, that is, motor neuron degeneration is non-cell autonomous (**Figure 5B**). This has been most clearly shown with *SOD1* mutations (72, 73). Experimental data shows that mutant-expressing SOD1 abnormalities within motor neurons determine the timing of disease onset, and abnormalities within astrocytes and microglia drive disease progression. Loss of function of glutamate handling through decreased expression and function of glutamate transporters in astrocytes seems to contribute to CNS hyperexcitability (74, 75). Soluble toxic gain-of-function factors that are protein in nature, thermo-labile, and negatively charged are one hypothesis. Microglia, the resident innate immune cells of the CNS, related to macrophages, can be either neuroprotective or cytotoxic, probably through the

release of neurotrophic factors and cytokines (76-78). Oligodendroglia in the grey matter have recently been found to have a significant role in ALS in addition to their role in axon myelination, where they provide trophic and possibly metabolic support to neurons and proliferate both in mouse models and human disease (79). The exact mechanisms of the contributions of the different cell types are largely unknown, but the astrocyte failure to turn over glutamate may be an important abnormality, at least in driving progression of the disease.

Over the last 25 years, a number of molecular mechanisms have emerged as significant contributors to motor neuron degeneration. The most profound of these is the identification of the role of RNA processing proteins. This was spearheaded by the recognition of the importance of the RNA/DNA-binding protein called TDP-43, which is widely expressed, predominantly nuclear, and involved in critical functions of RNA biology including transcription, RNA splicing, RNA transport, translation and microRNA processing. In nearly 95% of ALS nervous systems TDP-43 is found to be mis-localized to the cytoplasm and aggregated predominantly but not exclusively in motor neurons. A similar protein, FUS/TLS has also been identified as an inclusion in ALS motor neurones, reinforcing a mechanistic role for disturbed RNA biology. These emerging TDP-43 and FUS stories have led to the proposal that defects in RNA processing play a central role in neurodegeneration (80). It is unresolved as to whether neurodegeneration is due to a loss of nuclear function, a gain of toxicity or a combination of the two. The nuclear clearance of TDP-43, and to less extent FUS in neurons containing cytoplasmic aggregates, is consistent with pathogenesis driven, at least in part, by a loss of TDP-43 or FUS nuclear function. An alternative, and not mutually exclusive hypothesis, is that the accumulated proteins acquire a toxic function in the cytoplasm of affected neurons.

The importance of RNA biology is widened by the recent discovery of repeat expansions in *C9orf72* as the most common genetic mechanism in ALS and the related frontotemporal dementia (FTD) (81, 82) (**Figure 5C**). This finding has three immediate implications. First, the same genetic defect can cause either ALS or FTD phenotype or, in many patients, both disorders. Second, this form of ALS and FTD is an expanded nucleotide repeat disorder, a group of >22 inherited neurodegenerative diseases characterized by abnormal nucleotide sequences (sometimes referred to as microsatellites) in the genome. Third, new mechanisms are postulated such as gain-of-function due to production of toxic RNA (83-85), or a toxic, unconventionally transcribed, aggregation-prone protein comprising dipeptide repeat disorder, or loss of gene function. However, the normal functions of the C9orf72 protein are currently unknown, apart from the notion of a significant role for impaired nuclear-cytoplasmic transfer in the pathogenesis of C9orf72-related ALS.

Disruption of protein homeostasis is likely to be an important mechanism of selective motor neuronal degeneration. The identification of mutations in *SOD1* paved the way for such a hypothesis. Mutant SOD1 misfolds and then cannot be appropriately degraded through the ubiquitin pathway. This disrupts two important components of the cells degradation machinery, the proteosomal pathway and autophagy (86). Further evidence for impaired protein degradation in ALS comes from the recent identification of a number of mutations in genes such as *UBQLN2* (87), and *VCP* (88), both of which have functions in these pathways. UBQLN2 delivers ubiquitinylated proteins to the proteasome for degradation. VCP is a multifunctional ubiquitin sensitive chaperone that unfolds and disassembles protein complexes and also has a role in autophagy. In

addition, abnormalities of OPTN, TBK1 and p62 are all recognized in ALS and are proteins involved in both the proteosomal pathways and in autophagy.

Disruption of axonal dynamics is another mechanism that leads to motor neuron degeneration. Several genes linked with axonal dynamics have been found associated with ALS. Mutations in the neurofilament heavy chain and in peripherin have been found in a small number of ALS patients (89). Most recently mutations in profilin 1 (*PFN1*) have been linked to ALS (90). PFN1 is essential for the polymerization of actin. Mutations in this gene lead to inhibition of axonal outgrowth through decreasing actin polymerization in embryonic motor neurons in vitro. This inhibitory affect may enhance retraction and denervation in the adult neuromuscular system. EPHA4 has also recently been identified as having a potential role in axonal dynamics. EPHA4 is a receptor of the ephrin axonal repellent system that induces cytoskeletal rearrangements. Studies in zebra fish and rodents demonstrated that genetic or pharmacological inhibition of EPHA4 improved axonal outgrowth (91) and mutations in EPHA4 were found in two ALS patients with an unusually long survival. NOGO-A, an axonal outgrowth inhibitor, is upregulated in muscle of patients with ALS and other denervating disorders (92). Finally, a genome-wide association study identified kinesin-associated protein 3 (KIFAP3), a protein that forms a complex with motor proteins KIF3A and KIF3B, associated with increased survival (93).

Prescient as ever, Kinnier Wilson theorized on the propagation of ALS pathology, acknowledging the possibility of a "toxi-degenerative" cause, but "*sui generis"* in terms of known viruses and the prolonged course of some cases. ALS is a disease that progresses topographically and temporally, suggesting that pathogenic factors are propagating pathologically from cell to cell creating a complex temporal-spatial summation. This

theme has also emerged in other neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and FTD, related to proteins such as alpha-synuclein, beta-amyloid and tau. SOD1 and TDP-43 are ALS proteins that have been shown to spread from cell to cell (94-97). While the molecular basis of propagation is not well understood, the propagation of pathological conformation of disease-related proteins (pathological templating) could underlie this phenomenon. Transmission or propagation is not the same as infectivity and the terms that should be used for these properties are "prion-like" or "prionoids" (98), to distinguish them from *bona fide* prions, which are infectious. Indeed, misfolded SOD1 and TDP-43 were recently shown to induce a pathologic conformation on their natively folded counterparts when introduced to cells in culture (reviewed in (99)). Kinnier Wilson even touches on modern issues of transmissibility, recording pioneering work by the French neurologist Théophile Alajouanine (1890-1980):

> By suitable methods Alajouanine was able to transmit to one animal (out of many trials) the affection diagnosed by him as 'subacute anterior poliomyelitis' or subacute nuclear amyotrophy; the incubation period was no less than six months. Similar attempts with an emulsion of bulbar tissues from patients dead of Charcot's disease were unsuccessful.

A similar attempt at prion-like transmissibility of ALS was attempted in a monkey (100). While it has not been replicated in the context of ALS, successful prion-like transmission of pathology has been observed in a transgenic mouse model of multiple system atrophy (101). Interestingly, TDP-43, FUS and other heterogeneous ribonucleoproteins (hnRNPs) such as hnRNPA1 have low complexity, prion-like domains that harbour most ALS mutations. These proteins are not only involved in multiple levels of RNA metabolism, but also have unique biophysical properties that create phase change from

soluble, gel or liquid droplets and insoluble aggregates and these critical phase-states may play an important role in ALS pathogenesis and propagation (102). Another important frontier of ALS propagation is the identification of intergenic areas of the human genome that have evolutionarily-inserted retrotransposons and endogenous retroviruses that may have unique regulatory functions and actions that contribute to pathogenesis (103).

Occasional discord between clinical and pathological findings

Consistent with Kinnier Wilson's treatise, ALS remains to this day a clinical diagnosis, with evidence of muscle wasting (signifying involvement of the LMN) combined with a brisk tendon reflex for the same clinically affected muscle (evidence of UMN dysfunction) (104). There has been further refinement over the years, with different levels of diagnostic certainty as proposed through consensus criteria (possible, probable and definite) (105), and the integration of supportive investigations, particularly clinical neurophysiology (93) and, more recently, neuroimaging (106). There has been a recent shift towards establishing the diagnosis in a active, positive fashion, as opposed to the defensive approach of ruling out other possibilities, playing for time, and so driving a diagnostic delay that is harmful for patient well-being (107). Indeed, some have argued that even waiting for test results should be discouraged, and neurologists should be guided mainly by their clinical acumen or, at least, involve the patient in the physician's diagnostic uncertainty (108).

One of the key issues that have impeded adoption of a more active clinical approach has related to the identification of signs of UMN dysfunction. The concepts of discord, as espoused by Kinnier Wilson, ring true when considering that degeneration of the

corticospinal tract has been identified in 50% of PMA patients, in other words, those patients without clinical evidence of corticospinal involvement during the course of their disease (20). Conversely, an up-going toe seems only to be present in half of ALS patient cohorts, despite clear features of UMN dysfunction, with spasticity and brisk reflexes elsewhere (109). As noted as a "peculiarity" by Kinnier Wilson, the disease appears to "follow physiological rather than anatomical lines".

From the pathological perspective, degeneration of the corticospinal tracts and of anterior horn neurones remains the hallmark of ALS, although degeneration may also be evident across other descending pathways, especially involving the propriospinal motor system in the brainstem and spinal cord (18). The difficulty in eliciting UMN signs, apparently a source of discrepancy between clinical and pathological findings relates to the co-existent destruction of LMN, interneuronal and gamma neurons in the anterior horns so that not only is there muscle wasting but the local interconnexions required for the development of UMN signs, including spasticity, increased tendon reflexes, and extensor plantar responses, and for the typical "corticospinal pattern" of weakness cannot develop (110) (**Figure 6**). The Babinski response requires coordinated multi-synaptic reflex action across several spinal segments (111).

And so, it seems that neither pathological nor physiological data can lay claim to being the sole driving force of ALS, and we remain confronted with the same problem – that is, not knowing how the disease ALS progresses. Viewed from another more holistic aspect, as Kinnier Wilson expressed, "we do not know the chemical secret of the elixir vitae." Over recent times, concepts underlying the clinical manifestations of ALS and disease spread have developed in relation to the involvement of contiguous regions across compartments of the neuroaxis (39). Support, driven initially through clinical

observation of disease spread, has developed with the advent of neuropathological staging systems based around patterns of deposition of TAR DNA-binding protein 43 (TDP-43, encoded by *TARDBP*), the key protein of ALS, along axonal pathways (112). The pathological sequestration of TDP-43 into cytoplasmic inclusions characterizes the distinct clinical syndromes of ALS and, similarly, behavioural-variant frontotemporal dementia, suggesting that the regional concentration of TDP-43 pathology has most relevance to specific clinical phenotypes (113). These neuropathological classification systems have also incorporated the recent, clearer understanding concerning the extra-classical motor features of ALS, specifically the involvement of frontotemporal, cerebellar, basal ganglia and even sensory systems. Importantly, executive dysfunction appears to be a harbinger of rapid disease progression and reduced survival. The discovery of the hexanucleotide repeat sequence in *C9orf72* makes it easier to comprehend a process of ALS associated with frontotemporal dementia, although the pathological patterns of TDP-43 involvement in ALS patients with significant behavioural involvement, and indeed behavioural variant frontotemporal dementia, may differ, and perhaps microglial activation may be a further contributor to the cellular spread of disease (114). And so, like Kinnier Wilson, we now find ourselves asking questions at the crux of ALS, considering the very core of the disease, where it seems likely that modern technology, with an eye to metabolic and functional neuroimaging approaches, may yet unlock the modern "puzzling features" of the wider cerebral involvement in ALS and how these processes relate to the underlying histopathology.

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Legends

Figure 1

Samuel Alexander Kinnier Wilson (1878-1937) was the founding editor, in 1920, of what became the *Journal of Neurology, Neurosurgery and Psychiatry*

Figure 2

Swank & Putnam's 1943 representation of the spectrum of the clinical features of ALS (13). As well as being prescient of the modern observations of slower speed of progression at the two extremes, it also encapsulates ALS as a heterogeneous syndrome involving an apparently Gaussian distribution of clinical upper and lower motor neuron involvement.

Figure 3

Spinal cord pathology (Wegert-Pal) in ALS is characterised by loss of anterior horn cells, marked pallor (degeneration) of crossed and uncrossed corticospinal tracts, and slight pallor of ventral cord white matter (spinocerebellar pathways) (**A**); Charcot's drawing of shrunken anterior horn cells (a), from his Tuesday lectures, with less-affected cells in (b,c,d) (**B**); Ubiquitinated cytoplasmic inclusion in 'ghost' anterior horn cell in ALS (**C**).

Figure 4

The "split hand" is ALS is the frequent observation of preferential wasting of the lateral hand musculature, involving the thenar muscles (**A**) and first dorsal interosseus (**B**). This

combination of selected muscles is not one easily attributable to peripheral nerve lesions, but more closely recapitulates Penfield's somatotopic representations of the hand (**C**), adding to the wealth of evidence implicating cortically-driven pathophysiology in ALS.

Figure 5

Focality and spread, non-cell-autonomous degeneration and RNA biology disruption in ALS pathogenesis. The highest burden of spinal cord pathology has been noted in the region of the initial limb of symptom onset, with contiguous outward spread (A, adapted from (39)). Motor neuron degeneration may depend just as much on neighbouring astrocyte dysfunction and microglial activity as intrinsic failure of mitochondrial or axonal transport (B, adapted from (104)). RNA biology may be fundamentally disrupted in ALS pathogenesis as a result of TDP-43-centred mechanisms common to nearly all cases of ALS, and processes specific to the 10% of cases associated with *C9orf72* hexanucleotide expansions (adapted from (5)).

Figure 6

The involvement of interneuronal connections and lack of clear sequence to the destruction of local spinal cord circuitry may contribute to apparent discrepancies in clinical findings. We need to understand Wilson's *elixir vitae*, at least as it pertains to motor neurons.