HISTORICAL REVIEW

Canadian Pioneers of Amyotrophic Lateral Sclerosis: A Brief History

Andrew Eisen, David Taylor

ABSTRACT: This is an historical account of Canadian pioneers working in amyotrophic lateral sclerosis (ALS) in the 1970s and 1980s. Key contributions included the development of specialized clinics, the ALS Society of Canada, human motor unit estimates *in vivo*, use of transcranial magnetic stimulation (TMS), the dementias of ALS, the importance of neurofilaments and axonal flow, neuroinflammation and immunity related to ALS, use of tissue culture to study pathogenesis, and the story of ALS in Guam. Their work set the stage for future generations of ALS physicians and scientists to bring about meaningful therapies and hopefully a cure for ALS.

RÉSUMÉ : Les pionniers de la recherche sur la sclérose latérale amyotrophique au Canada : bref historique. Plusieurs médecins et chercheurs font figure de pionnier dans la recherche sur la sclérose latérale amyotrophique (SLA) au Canada, par leurs travaux dans les années 1970 et l980 : en voici un bref historique. Sont dignes de mention la mise sur pied de centres médicaux spécialisés dans la prise en charge de la maladie; la fondation de la Société canadienne de la SLA; le recours à l'estimation des unités motrices humaines *in vivo*; l'utilisation de la stimulation magnétique transcrânienne; l'étude de différents types de démence dans le contexte de la SLA; l'importance des neurofilaments et du transport axonal; la neuro-inflammation et l'immunité liées à la SLA; la culture de tissus pour étudier la pathogenèse de la maladie; la présentation des liens entre la SLA et Guam. Grâce à tous ces travaux, les chercheurs ont tracé la voie aux futures générations de médecins et de scientifiques voués à SLA, dans leur quête de traitements efficaces, et surtout curatifs, de la maladie.

Keywords: Amyotrophic lateral sclerosis, History

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Introduction

Amyotrophic lateral sclerosis (ALS) and its syndromic components, primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), and frontotemporal dementia (FTD), are orphan disorders. Comparatively few specialists are attracted to devote lifelong careers to these diseases, especially in the face of a uniformly fatal outcome, and to date, a lack of meaningful therapy. Despite this, the Canadian contribution to the ALS spectrum of diseases is impressive. On a per-capita basis, Canada ranks high in the uniformity of its quality of care offered to ALS patients, and Canada's ALS researchers are recognized worldwide. Those pioneering ALS care and research in Canada were few. One of us, AE, was privileged to have participated in the beginnings of ALS work in Canada, which in the early 1970s was in its infancy, compared with the United Kingdom, but comparable to the USA. On a worldwide basis, there have been approximately 30,000 publications related to ALS. Of these, less than 1300, about 5%, appear in PubMed between 1970 and 1984, years that Canadian ALS work was beginning. Exponential advances in ALS molecular and genetic biology has occurred in the last two decades, and early contributions are readily overlooked or ignored. When critically analyzed, the early work of Canadian ALS physicians is more than just of historical interest as within it resided the seeds of future advances.

This paper describes the contributions made by Canadian neurologists and basic scientists pioneering ALS, during the 1970s, and 1980s, and the foundation they built for modern-day advances in care and research (see Table 1 and Figures 1 and 2). Prior to these two decades, ALS was not on the radar of neurological disorders in Canada. From the 1990s onwards, there has been exponential growth in the number of Canadian ALS physicians and basic researchers, particularly coinciding with the discovery of genetic linkages to a subset of ALS cases, permitting an era of studying the disease with molecular biology. This second and now third wave of experts have contributed immensely to the disease, both clinically and through innovative research. They represent a new generation associated with an exciting future for ALS that must surely result in significant slowing of the disease and one hopes a cure.

Multidisciplinary ALS Clinics and the ALS Society of Canada

Arthur Hudson is widely considered the "Father of Canadian ALS". His major contributions have withstood the test of time and those that he has mentored, and others have advanced his concepts. Arthur Hudson made four important contributions to ALS, and each is described in relevant sections of this review.

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Table 1: Those pioneering ALS in Canada

Name (Affiliation)	PubMed year	Main contributions
Stirling Carpenter (McGill)	1968	Axonal swellings
Andre Barbeau* (University Montreal)	1970	National ALS registry
Alan McComas (Hamilton)	1971	Motor unit estimates
Andrew Eisen (McGill/UBC)	1971	ALS Clinic, C-M hypothesis, TMS
George Karpati* (McGill)	1971	Dendritic attrition, neurofilaments
Morrison Finlayson* (McGill)	1973	Dementia and ALS
William Brown (Western)	1973	Motor unit estimates, TMS
John (Jock) Murray (Halifax)	1974	Epidemiology of ALS
Joel Oger (Chicago/UBC)	1974	Immunology of ALS
Jack Antel (Chicago/McGill)	1976	Immunology of ALS
Seung Kim* (UBC)	1979	Neuronal tissue cultures
Arthur Hudson* (Western)	1981	ALS Clinic, ALS Canada, Dementia,
Jean-Pierre Julien (Laval)	1981	Neurofilaments, axonal flow, tissue culture
Charles Krieger (Simon Fraser/UBC)	1982	Protein kinases, rodent models, stem cells
Heather Durham (McGill)	1983	Tissue culture, neuronal survival
Patrick and Edie McGeer (UBC)	1983	Excitotoxicity, inflammation, aging
Neil Cashman (Toronto/UBC)	1985	Immunology, prion disease, misfolding
John Steele (Toronto/Guam)	1987	Guamanian ALS-PD (Lytico-Bodig)
Michael Strong (Western)	1988	ALS dementias, International workshops
Guy Rouleau (McGill)	1991	Molecular genetics/biology of ALS
Denise Figlewicz (Wayne State/Western)	1991	Molecular genetics/biology of ALS

C-M = corticomotoneuronal; TMS = transcranial magnetic stimulation.
*Deceased.
Year refers to the first ALS-specific paper published as searched through PubMed (many of those listed published work prior to the date given, but not specifically ALS-related).

Figure 1: *The first Canadians who pioneered amyotrophic lateral sclerosis (ALS).*
Top (left to right): Thomas (Jock) Murray, Andrew Eisen, Arthur Hudson, Stirling Carpenter, George Karpati, Andre Barbeau.
Middle (left to right): John Steele, Seung Kim, Alan McComas, William Brown, Morrison Finlayson.
Bottom: Pat and Edie McGeer.

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Figure 2: *Those that followed shortly after.*
Top row (left to right) Charles Krieger, Jack Antel, Heather Durham, Michael Strong.
Bottom Row (left to right) Guy Rouleau, Jean-Pierre Julien, Neil Cashman, Denise Figlewicz, Joel Oger.

The first major contribution was the formation of a multidisciplinary ALS clinic, the first of its kind in Canada and one of the first in the world. To our knowledge, the only dedicated ALS clinics in North America to predate the one started by Hudson were those developed by Forbes Norris in San Francisco, and Theodore (Ted) Munsat at the Tufts University, Boston. Hudson's clinic at the University of Western Ontario, London, opened in 1977 serving much of the surrounding community in Ontario.[1] It demonstrated that patients with ALS could be managed almost entirely as an outpatient with an expert multidisciplinary care team. Over a 7-year period after the clinic became operational, there was a decline in the annual mortality rates of those attending it. This occurred in the absence of a significant change in the incidence of ALS. Other Canadian clinics dedicated to ALS were started by Andrew Eisen, soon after arriving in Vancouver in 1980, and by Timothy Benstead in Nova Scotia shortly thereafter. The benefit that specialized clinics confer on ALS patients has been substantiated.[2] Thomas (Jock) Murray, working at the Dalhousie University, Nova Scotia, did not have a formalized multidisciplinary ALS clinic, but as early as 1974, he was centralizing care and observation of a significant number of ALS patients.[3]

Arthur Hudson's second significant contribution was the establishment of the ALS Society of Canada as a not-for-profit charity registered on October 1, 1977. This predated the Motor Neurone Disease Association of Great Britain, which was registered in October 1979. Arthur Hudson was the founding Chairperson of the Medical Advisory Committee of ALS Canada and Patrick McGeer was a member of the committee. An initial proposal of the fledgling society was to establish a Nationwide Registry of ALS patients. This occurred in conjunction with the ALS Society of America (ALSA) through its liaison member to Canada, Barry Arnason, working in Chicago. Reciprocally Arthur Hudson was Canada's liaison to ALSA. Andre Barbeau, Professor of Neurology at the University of Montreal, was chosen to oversee the project. Although his work was almost entirely devoted to Parkinson's disease and dopamine and its pharmacology, he recognized that some ALS patients may have Parkinson's dementia as a component of their disease.[4] Two decades later, positron emission studies in ALS confirmed there was indeed reduced dopamine activity in sporadic ALS.[5] Three years after ALS Canada was established, a provincial society, ALSBC, was organized in British Columbia and subsequently other provincial partners were organized throughout Canada, ultimately resulting in a unique collaborative Federation of Societies to provide provincial care locally and share obligations for research and advocacy nationally.

Investigating the Lower Motor Neurone in ALS

Prior to the end of the 1980s, investigative work in living ALS patients was uniformly limited to the lower motor neuron. As a result, ALS was classified as a neuromuscular disease. This erroneous nomenclature reflected the fact that only function and dysfunction of the lower motor neurone was readily accessible for study *in vivo*, primarily using electromyography.[6,7] Now, that it is accepted that ALS is a multisystem disorder, with prominent cortical involvement, it is untenable in the twenty-first century to continue to classify ALS as a neuromuscular disorder.[8] It is should be classified as a neurodegenerative disease, as was suggested several decades ago by Eisen and Calne.[9]

In 1971, Eisen and Karpati[10] described what at the time was a little recognized spontaneous activity in ALS, referred to as complex repetitive discharges. These are commonly recorded in this disease, but not unique to it. Most reflect ongoing motor axonal reinnervation.[11]

Shortly before Alan McComas moved to Hamilton, Ontario, from Newcastle, England, he described a methodology for measuring the number of motor units in human muscles.[12] This marked the birth of decades of using motor unit estimates in ALS to measure disease progression and response to therapeutic agents

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in human and animal trials.[13–15] William (Bill) Brown with Nicholas (Nick) Jaatoul, at the University of Western Ontario, in London were among the first to apply the McComas method to investigate ALS.[16,17]

Corticomotoneuronal Studies in ALS

The third major contribution made by Hudson appeared in a rarely appreciated letter to the Lancet, written in 1988,[18] entitled "Preservation of certain voluntary muscles in motorneurone disease". It was proposed that cortical neurons may normally provide trophic support for neurons with which they make contact in the anterior horn and motor nuclei of the cranial nerves and, therefore, the primary pathology of motoneurons disease might be sought in the cortex rather than the spinal cord. The Lancet letter, essentially reiterated Charcot's concept of ALS postulated over 100 years ago,[19] and concurred with Andrew Eisen, who had been conceiving the primacy of the brain in ALS for some time.[20] He proposed "the primary cell involved in amyotrophic lateral sclerosis (ALS) is the corticomotoneuron," a term coined by Porter and Lemon.[21] The spinal motoneuron becomes affected as a result of antegrade degenerative effects.

It only became feasible to study the upper motor neuron in ALS and related diseases, *in vivo* in the 1990s. Even in the late 1980s, MRI studies of ALS were sparse, limited to very few patients, and the results were mostly nonspecific.[22,23] In the late 1980s, transcranial magnetic stimulation (TMS) of the brain started to be used to investigate the upper motor neurone in ALS in the United Kingdom.[24] Andrew Eisen, in Vancouver, was the first in Canada to use the methodology to explore ALS.[25,26] This was quickly followed by Bill Brown, who applied TMS to the study of PLS.[27] This legacy of pioneering in ALS has evolved in the present day to a national platform that uses these techniques to search for biomarkers and to approach heterogeneity of the disease alongside deep phenotyping and biofluid capture.[28]

Dementias and ALS

The fourth of Hudson's major contributions was to bring to the fore the importance of dementia in ALS. Following the identification of the C9orf72 gene, shared by ALS and FTD, acceptance of dementia as a part of ALS spectrum of diseases, has become commonplace.[29,30] However, 30 years prior to this, in a seminal paper published in Brain in 1981,[31] Hudson proposed that dementia and Parkinsonism are associated with sporadic and familial ALS reflecting variants of classical ALS. Hudson's interest in dementia and its association with ALS continued throughout his career. This ground-breaking work has continued through his student, and later colleague and close friend, Michael Strong, who has been recognized worldwide for his contributions as an ALS physician -scientist. In 2005, he initiated biannual workshops with international attendees, devoted to better understanding ALS-related dementias. This, alongside Hudson's seminal and visionary work in ALS dementia, resulted in the ALS journal changing its name in 2013 to Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration.

Several years prior to Hudson's paper in Brain, Morrison Finlayson,[32] a neuropathologist working at the Montreal General Hospital, together with Joseph Martin who later became the fourth Director of the Montreal Neurological Institute, before moving to the USA, described two cases of familial ALS associated with dementia. Some of the pathological features were common to those seen in Guamanian ALS. This intrigued John Steele, who at the time was also working at the Montreal General Hospital.

John Steele is probably best associated with the Steele–Richardson–Olszewski syndrome (progressive supranuclear palsy),[33] which he described in 1964, while a neurology resident in Toronto. However, he has devoted much of his career to Guamanian ALS/PD also known as Lytico-Bodig disease.[34] His initial publication on the condition was with Anthony (Tony) Guzman in 1987. After working at the Montreal General Hospital, Steele moved to reside in Guam, devoting his work to Lytico-Bodig disease.[35] In 1990, Andrew Eisen, performed field studies on Guamanian ALS, using TMS. On return to Vancouver, employing positron emission tomography, it was shown that there were nigrostriatal lesions in Guamanian subjects with ALS, even in the absence of clinical Parkinsonism, exemplifying subclinical neuronal damage.[36] It was not until many years later that ALS was more commonly recognized as having a long presymptomatic period.[37] An ALS symposium held in Vancouver in 1987, organized by Hudson and Eisen, emphasized the Guam story,[38] and was the basis of a book edited by Arthur Hudson in 1990.[39] Other Canadians who contributed to the Vancouver meeting included Seung Kim, Jack Antel, John Steele, and Donald Calne.

Work with Tissue Culture

Seung Kim started working with cultured spinal cord neurones as early as 1972.[40] In 1979, he started working on human tissue cultured spinal neurons,[41,42] and the effect of aging.[43] At the Vancouver meeting he described work relating to the possible cytotoxic activity of ALS sera using human fetal spinal cord neuron cultures.[44] No deleterious effect was found, contradicting an earlier study in which a high proportion of diluted serums of patients with ALS were toxic to the anterior horn cells of the mouse in tissue culture.[45] In recent years, ALS sera have been shown to have variable effects on cultured cells.[46] Heather Durham commenced using tissue culture in connection with neurofilaments in 1986,[47] she subsequently used primary cultured neurones and transgenic animals expressing mutant genes linked to familial forms of neurodegenerative diseases. This enabled her to examine the interaction between expression of a predisposing gene and exposure to neurotoxic chemicals.[48] In 1987, while working with Tom Sears in London, UK, Charles Krieger performed whole-cell patch-clamp recordings on embryonic cultured spinal cord neurones.[49]

Neurofilaments and ALS

Neurofilaments are proteins selectively expressed in the cytoskeleton of neurones. Their potential utility has recently increased as advances have made it possible to measure levels in both the cerebrospinal fluid and blood. Increased levels are a marker of ongoing disease activity and decreased levels occur in response to therapy.[50,51] Pioneers of ALS in Canada have explored different aspects of neurofilaments. In 1968, Stirling Carpenter, working at the Montreal Neurological Institute, described frequent focal enlargement of axons in motor neurone

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disease.[52] Their absence was associated with severe neuronal loss in the spinal cord.[53] Twenty years later, George Karpati, Stirling Carpenter, and Heather Durham suggested that the earliest abnormality in ALS was a progressive depletion of dendritic neurofilaments with consequent dendritic atrophy leading to shrinkage and eventual death of the perikaryon.[54] George Karpati should be recognized for mentoring Heather Durham and Guy Rouleau, and later Angela Genge. These ALS physicians have all made major contributions and have become internationally recognized as leaders in the field.

Jean-Pierre Julien devoted his early years of work to neurofilament abnormalities.[55] One of the co-authors of Julien's first paper was Ian Duncan, one of the world's best exemplars of veterinary research providing the basis for significant new insights into the understanding and treatment of human disease. In the early 1990s, both Denise Figlewicz and Guy Rouleau, collaborated with Julien working on neurofilamentous abnormalities in ALS.[56,57] Subsequently, working with transgenic ALS mouse models, Julien, proposed that neurofilament accumulation causes neurodegeneration by disrupting axonal transport, a mechanism that may account for the pathogenesis of ALS.[58]

Immunology and Inflammation in ALS

Neuroinflammation is a common pathological characteristic of neurodegeneration, including ALS. Features include activated CNS microglia and astroglia, proinflammatory peripheral lymphocytes, and macrophages. Genetic mutations linked to ALS (e.g. mutations in SOD1, TARDBP, and C9orf72) amplify neuroinflammation providing compelling evidence for immune dysregulation in the pathogenesis of ALS.[59,60] A large proportion of clinical trials in 2020 aim at targeting some aspect of the immune/inflammatory response. During the late 1960s and early 1970s, Patrick (Pat) and Edith (Edie) McGeer, working in the Kinsman Laboratory of Neurological Research, University of British Columbia, worked on varied aspects of neurochemical changes in aging, and diseases of the nervous system.[61–64] Subsequently the McGeers's research turned to inflammation and its role in neurodegenerations. They demonstrated a cell-mediated immune response identified immunohistochemically in ALS spinal cord and Alzheimer's disease (AD) hippocampus.[65]

Several years prior to the McGeer's immunology-related work in neurodegeneration, Jack Antel while working with Barry Arnason, a Canadian, in Chicago, developed a keen interest in the immunity and ALS.[66–68] Jack, a Canadian, later moved to the Montreal Neurological Institute as Neurologist-in-Chief, where his main interest changed to multiple sclerosis. Joel Oger, another member of the Arnason group also had an early interest in ALS immunology.[69] He moved to Vancouver, in the early 1980s, where his interest also changed to multiple sclerosis and then myasthenia gravis. Neil Cashman's interest in ALS also commenced while he worked with Arnason and Antel in Chicago.[70] The collaboration led him to Montreal and Toronto before finally settling in Vancouver, where he continues to contribute as an ALS clinician-scientist.

Excitotoxicity

Excitotoxicity is not the newest and most spectacular hypothesis in the ALS field, but it is undoubtedly one of the most robust pathogenic mechanisms supported by an impressive amount of evidence. Moreover, the therapeutic efficacy of riluzole, which until recently was the only approved drug proven to slow disease progression in ALS, is most likely related to its anti-excitotoxic properties.[71] The excitotoxic hypothesis of neurodegeneration came to the fore in the early 1980s, and Pat and Edie McGeer turned their interest to this.[72] Somewhat later, Charles Krieger also worked on excitotoxicity.[73–75] Charles Krieger and Andrew Eisen collaborated on many publications, highlighted by a monograph on ALS.[76] When at the Montreal Neurological Institute, he got to know George Karpati, Heather Durham, and Guy Rouleau. It was there that he published his first ALS-related papers.[77,78]

Summary

The pathogenesis of the selective neuronal degeneration in ALS and its related disorders, in particular, FTD remains unsolved. Over the years, many pathogenic mechanisms have been proposed. Among others, these include oxidative stress, excitotoxicity, aggregate formation, inflammation, growth factor deficiency, abnormal RNA biology, protein disposal mechanisms, particularly autophagy, and neurofilament disorganization. Those pioneering work in ALS in Canada as described in this paper, contributed to many of the postulated causative hypotheses often leading the field at the time. In the 70s and 80s, a strong connection between research and the clinic drove much of this foundational work but, the current Canadian landscape does not support the development of the physician-scientist in the same way. Many of the ALS leaders in other countries are able to balance their clinical work with protected research time, providing a critical view of the discovery to treatment spectrum and there is a danger of these individuals being in short supply in Canada, particularly those dedicated to ALS. We write this in the sincere hope of encouraging some Canadians training in neurology to turn their enthusiasm and devotion to the ALS spectrum of disorders and remember the early days that paved the way for current discoveries through collaboration, intellectual curiosity, and dedication to a brighter day for the disease.

Disclosures

The authors have no conflicts of interest to declare.

Statement of Authorship

Andrew Eisen – conception and writing.
David Taylor – conception and writing.

References

1. Hudson AJ, Jr. Outpatient management of amyotrophic lateral sclerosis. Semin Neurol. 1987;7:344–51.
2. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. J Neurol Neurosurg Psychiatry. 2003;74:1258–61.
3. Murray TJ, Pride S, Haley G. Motor neuron disease in Nova Scotia. Can Med Assoc J. 1974;110:814–7.
4. Barbeau A. Dopamine and disease. Can Med Assoc J. 1970; 103:824–32.

https://doi.org/10.1017/cjn.2020.269 Published online by Cambridge University Press

5. Takahashi H, Snow BJ, Bhatt MH, Peppard R, Eisen A, Calne DB. Evidence for a dopaminergic deficit in sporadic amyotrophic lateral sclerosis on positron emission scanning. Lancet. 1993;342: 1016–8.
6. Marinacci AA, VonHagen KO. Electromyography in amyotrophic lateral sclerosis. A review. Bull Los Angeles Neurol Soc. 1974; 39:17–29.
7. Daube JR. Electrophysiologic studies in the diagnosis and prognosis of motor neuron diseases. Neurol Clin. 1985;3:473–93.
8. van Es MA, Goedee HS, Westeneng HJ, Nijboer TCW, van den Berg LH. Is it accurate to classify ALS as a neuromuscular disorder? Expert Rev Neurother. 2020;20:895–906.
9. Eisen A, Calne D. Amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease: phylogenetic disorders of the human neocortex sharing many characteristics. Can J Neurol Sci. 1992;19:117–23.
10. Eisen AA, Karpati G. Spontaneous electrical activity in muscle. Description of two patients with motor neurone disease. J Neurol Sci. 1971;12:121–35.
11. Posa A, Niskiewicz I, Emmer A, Hanisch F, Kornhuber ME. Complex repetitive discharges: a sign of motor axonal reinnervation? Brain Sci. 2020;10:349–52.
12. McComas AJ, Fawcett PR, Campbell MJ, Sica RE. Electrophysiological estimation of the number of motor units within a human muscle. J Neurol Neurosurg Psychiatry. 1971;34:121–31.
13. Shefner JM, Cudkowicz ME, Zhang H, Schoenfeld D, Jillapalli D. The use of statistical MUNE in a multicenter clinical trial. Muscle Nerve. 2004;30:463–9.
14. Shefner JM, Cudkowicz M, Brown RH, Jr. Motor unit number estimation predicts disease onset and survival in a transgenic mouse model of amyotrophic lateral sclerosis. Muscle Nerve. 2006;34:603–7.
15. Shefner JM. Recent MUNE studies in animal models of motor neuron disease. Suppl Clin Neurophysiol. 2009;60:203–8.
16. Brown WF, Jaatoul N. An electrophysiological estimation of the number of motor units and rate of decay of motor units in amyotrophic lateral sclerosis. Trans Am Neurol Assoc. 1973;98: 183–6.
17. Brown WF, Jaatoul N. Amyotrophic lateral sclerosis. Electrophysiologic study (number of motor units and rate of decay of motor units). Arch Neurol. 1974;30:242–8.
18. Hudson AJ, Kiernan JN. Preservation of certain voluntary muscles in motoneurone disease. Lancet. 1988;1:652–3.
19. Charcot J. Sclerose laterale amytrophique. Oeuvres Compltes. Bureaux du Proges Medical. 1874;2:249–66.
20. Eisen A, Kim S, Pant B. Amyotrophic lateral sclerosis (ALS): a phylogenetic disease of the corticomotoneuron? Muscle Nerve. 1992;15:219–24.
21. Porter R, Lemon R. Corticospinal function and voluntary movement. Physiological Society Monograph. Oxford: Clarendon Press; 1993.
22. Goodin DS, Rowley HA, Olney RK. Magnetic resonance imaging in amyotrophic lateral sclerosis. Ann Neurol. 1988;23:418–20.
23. Iwasaki Y, Kinoshita M, Ikeda K, Takamiya K. Central nervous system magnetic resonance imaging findings in amyotrophic lateral sclerosis. Eur Arch Psychiatry Neurol Sci. 1989;239: 125–6.
24. Mills KR, Murray NM, Hess CW. Magnetic and electrical transcranial brain stimulation: physiological mechanisms and clinical applications. Neurosurgery. 1987;20:164–8.
25. Eisen AA, Shtybel W. AAEM minimonograph #35: clinical experience with transcranial magnetic stimulation. Muscle Nerve. 1990;13:995–1011.
26. Eisen A, Shytbel W, Murphy K, Hoirch M. Cortical magnetic stimulation in amyotrophic lateral sclerosis. Muscle Nerve. 1990; 13:146–51.
27. Brown WF, Ebers GC, Hudson AJ, Pringle CE, Veitch J. Motor-Evoked responses in primary lateral sclerosis. Muscle Nerve. 1992;15:626–9.
28. Bharti K, Khan M, Beaulieu C, et al. Involvement of the dentate nucleus in the pathophysiology of amyotrophic lateral sclerosis: a multi-center and multi-modal neuroimaging study. Neuroimage Clin. 2020;28:102385.
29. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72:257–68.
30. Snowden JS, Rollinson S, Thompson JC, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012;135:693–708.
31. Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: a review. Brain. 1981;104:217–47.
32. Finlayson MH, Martin JB. Cerebral lesions in familial amyotrophic lateral sclerosis and dementia. Acta Neuropathol. 1973;26: 237–46.
33. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving brain stem, basal ganglia andcerebellum with vertical gaze and pseudobulbar palsy, nuchal dystoniaand dementia. Arch Neurol. 1964;10: 333–59.
34. Steele JC, Guzman T. Observations about amyotrophic lateral sclerosis and the parkinsonism-dementia complex of Guam with regard to epidemiology and etiology. Can J Neurol Sci. 1987; 14:358–62.
35. McGeer PL, Steele JC. The ALS/PDC syndrome of Guam: potential biomarkers for an enigmatic disorder. Prog Neurobiol. 2011;95: 663–9.
36. Snow BJ, Peppard RF, Guttman M, et al. Positron emission tomographic scanning demonstrates a presynaptic dopaminergic lesion in Lytico-Bodig. The amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam. Arch Neurol. 1990; 47:870–4.
37. Eisen A, Kiernan M, Mitsumoto H, Swash M. Amyotrophic lateral sclerosis: a long preclinical period? J Neurol Neurosurg Psychiatry. 2014;85:1232–8.
38. Eisen AA, Hudson AJ. Amyotrophic lateral sclerosis: concepts in pathogenesis and etiology. Can J Neurol Sci. 1987;14:649–52.
39. Hudson AJ. Amyotrophic Lateral Sclerosis: Concepts in Pathogenesis and Etiology. Toronto: University of Toronto Press; 1990.
40. Kim SU, O TH, Johnson DD. Developmental changes of acetylcholinesterase and pseudocholinesterase in organotypic cultures of spinal cord. Exp Neurol. 1972;35:274–81.
41. Silberberg DH, Kim SU. Studies of aging in cultured nervous system tissue. Int Rev Cytol Suppl. 1979;117–30.
42. Kim SU, Warren KG, Kalia M. Tissue culture of adult human neurons. Neurosci Lett. 1979;11:137–41.
43. Kim SU. Neuronal aging in tissue and cell cultures: a review. In Vitro. 1983;19:73–82.
44. Kim SU. Human Spinal Cord Neurons in Culture. In: Hudson AJ, editor. Amyotrophic Lateral Sclerosis: Concepts in Pathogenesis and Etiology. Toronto: Univeristy of Toronto Press; 1990, pp. 3–23.
45. Wolfgram F, Myers L. Amyotrophic lateral sclerosis: effect of serum on anterior horn cells in tissue culture. Science. 1973; 179:579–80.
46. Texido L, Hernandez S, Martin-Satue M, et al. Sera from amyotrophic lateral sclerosis patients induce the non-canonical activation of NMDA receptors "in vitro". Neurochem Int. 2011; 59:954–64.
47. Durham HD. The effect of beta,beta'-iminodipropionitrile (IDPN) on cytoskeletal organization in cultured human skin fibroblasts. Cell Biol Int Rep. 1986;10:599–610.
48. Durham HD, O'Brien C, Nalbantoglu J, Figlewicz DA. Use of tissue culture models to study environmental-genetic interactions relevant to neurodegenerative diseases. Clin Exp Pharmacol Physiol. 1995;22:366–7.
49. Fruns M, Krieger C, Sears TA. Identification and electrophysiological investigations of embryonic mammalian motoneurones in culture. Neurosci Lett. 1987;83:82–8.
50. Gafson AR, Barthelemy NR, Bomont P, et al. Neurofilaments: neurobiological foundations for biomarker applications. Brain. 2020;143:1975–98.
51. Gordon BA. Neurofilaments in disease: what do we know? Curr Opin Neurobiol. 2020;61:105–15.
52. Carpenter S. Proximal axonal enlargement in motor neuron disease. Neurology. 1968;18:841–51.

https://doi.org/10.1017/cjn.2020.269 Published online by Cambridge University Press

53. Delisle MB, Carpenter S. Neurofibrillary axonal swellings and amyotrophic lateral sclerosis. J Neurol Sci. 1984;63:241–50.
54. Karpati G, Carpenter S, Durham H. A hypothesis for the pathogenesis of amyotrophic lateral sclerosis. Rev Neurol. 1988;144: 672–5.
55. Julien JP, Mushynski WE, Duncan ID, Griffiths IR. Giant axonal neuropathy: neurofilaments isolated from diseased dogs have a normal polypeptide composition. Exp Neurol. 1981;72: 619–27.
56. Figlewicz DA, Rouleau GA, Krizus A, Julien JP. Polymorphism in the multi-phosphorylation domain of the human neurofilament heavy-subunit-encoding gene. Gene. 1993;132:297–300.
57. Figlewicz DA, Krizus A, Martinoli MG, et al. Variants of the heavy neurofilament subunit are associated with the development of amyotrophic lateral sclerosis. Hum Mol Genet. 1994;3: 1757–61.
58. Julien JP. A role for neurofilaments in the pathogenesis of amyotrophic lateral sclerosis. Biochem Cell Biol. 1995;73:593–7.
59. Thonhoff JR, Simpson EP, Appel SH. Neuroinflammatory mechanisms in amyotrophic lateral sclerosis pathogenesis. Curr Opin Neurol. 2018;31:635–9.
60. Beers DR, Appel SH. Immune dysregulation in amyotrophic lateral sclerosis: mechanisms and emerging therapies. Lancet Neurol. 2019;18:211–20.
61. McGeer EG, Fibiger HC, McGeer PL, Wickson V. Aging and brain enzymes. Exp Gerontol. 1971;6:391–6.
62. McGeer PL, McGeer EG. Cholinergic enzyme systems in Parkinson's disease. Arch Neurol. 1971;25:265–8.
63. McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. Arch Neurol. 1977;34:33–5.
64. McGeer PL, McGeer EG. Aging and neurotransmitter systems. Adv Exp Med Biol. 1978;113:41–57.
65. McGeer PL, McGeer EG, Kawamata T, Yamada T, Akiyama H. Reactions of the immune system in chronic degenerative neurological diseases. Can J Neurol Sci. 1991;18:376–9.
66. Antel JP, Arnason BG, Fuller TC, Lehrich JR. Histocompatibility typing in amyotrophic lateral sclerosis. Arch Neurol. 1976;33: 423–5.
67. Antel JP, Richman DP, Arnason BG. Immunogenetics and amyotrophic lateral sclerosis. UCLA Forum Med Sci. 1976;151–71.
68. Antel JP, Noronha AB, Oger JJ, Arnason BG. Immunology of amyotrophic lateral sclerosis. Adv Neurol. 1982;36:395–402.
69. Lehrich JR, Oger J, Arnason BG. Neutralizing antibodies to poliovirus and mumps virus in amyotrophic lateral sclerosis. J Neurol Sci. 1974;23:537–40.
70. Cashman NR, Gurney ME, Antel JP. Immunology of amyotrophic lateral sclerosis. Springer Semin Immunopathol. 1985;8:141–52.
71. Van Damme P, Dewil M, Robberecht W, Van Den Bosch L. Excitotoxicity and amyotrophic lateral sclerosis. Neuro-Degener Dis. 2005;2:147–59.
72. McGeer PL, McGeer EG. Excitotoxic amino acids as tools in neurobiology. Rev Pure Appl Pharmacol Sci. 1983;4:213–70.
73. Allaoua H, Chaudieu I, Boksa P, Perry TL, Krieger C, Quirion R. Excitatory amino acid receptors in human spinal cord. Evaluation in amyotrophic lateral sclerosis patients. Ann N Y Acad Sci. 1992;648:260–2.
74. Allaoua H, Chaudieu I, Krieger C, Boksa P, Privat A, Quirion R. Alterations in spinal cord excitatory amino acid receptors in amyotrophic lateral sclerosis patients. Brain Res. 1992;579: 169–72.
75. Krieger C, Perry TL, Hansen S, Mitsumoto H, Honore T. Excitatory amino acid receptor antagonist in murine motoneuron disease (the wobbler mouse). Can J Neurol Sci. 1992;19:462–5.
76. Eisen A, Krieger C. Amyotrophic lateral sclerosis: a synthesis of research and clinical practice. New York: Cambridge University Press; 1998.
77. Krieger C, Melmed C. Amyotrophic lateral sclerosis and paraproteinemia. Neurology. 1982;32:896–8.
78. Melmed C, Krieger C. A cluster of amyotrophic lateral sclerosis. Arch Neurol. 1982;39:595–6.

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