Neuropathology in Canada: Overview of Development and Current Status

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ABSTRACT: Background: The expansion of neurosurgery and neurology in Montreal and Toronto in the early 20th century was the stimulus for the development of neuropathology in Canada. Rooted in the disciplines of the neurosciences and laboratory medicine, neuropathology evolved into an independent discipline with the founding of the Canadian Association of Neuropathologists in 1960, and the recognition as a specialty by the Royal College of Physicians and Surgeons in Canada in 1965, fostering the development of several successful training programs. Nonetheless, a paucity of data remains concerning the background of training, scopes of practice, and career paths. Method: We conducted a survey of all physicians in Canada who have either practiced neuropathology or undergone relevant training. Results: In 2009, 53 physicians were engaged in the practice of neuropathology, either exclusively or a substantial proportion of their time. Most work in tertiary hospitals, but a few service non-academic medical centers. Three routes of training were identified: direct from medical school (often with relevant research training), indirect from another clinical neuroscience specialty, and following or in conjunction with certification in one of the other pathology specialties. Practice profiles differ slightly, and some of the neuropathologists entering from pathology have mixed anatomical pathology/neuropathology responsibilities. Many of those with prior exposure in the neurosciences are more productive with regard to research and publications. Conclusions: Existing multiple options for neuropathology training have facilitated recruitment and allowed development of a mosaic of specialists able to fulfill the diversity of needs in Canadian medical and scientific communities.

Neuropathology became recognized in Canada as a distinct discipline in a series of disjointed but interrelated stages. Each stage was contingent upon the development of the allied disciplines of neurosurgery and neurology throughout the country and paralleled the emergence of the laboratory medicine specialties and tools available\(^1\). This evolution over the past century was similar to that in the United States and Europe\(^2-6\). Although there remains a commonality in the issues referable to the contemporary furthering of the discipline, in relation to the laboratory medicine and clinical neuroscience disciplines, neuropathology in Canada has become different with regard to professional status, the format of training, and the mosaic background of practitioners contributing to the whole. This article addresses the historical underpinnings of the organization of neuropathology in Canada. Biographical details of the early practitioners will be described in a partner article. Here we also


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report the results of a survey of those currently practicing neuropathology in Canada and discuss the future of Canadian neuropathology with respect to other countries and regions.

The practice of neuropathology began in Canada in the medical centers of Montreal and Toronto, the course of development being in two overlapping stages. The first stage was represented by part-time practice by a few interested physicians, of varied background and training, for individual purposes of clinical study and research. The earliest example is William Osler who, drawing upon his experience from autopsies performed at the Montreal General Hospital (1871-1884), published almost 200 articles concerning neurological diseases. The part-time practice of neuropathology resumed for several decades (1928-1959) at the Montreal Neurological Institute by the neurosurgeons Wilder Penfield and William Cone, both of whom had extensive training in neuropathology.

The second stage, that of full-time practice of neuropathology, was represented by the landmark establishment in 1932 of a Division of Neuropathology, under the directorship of Eric Linell, a neuroanatmist in background, in the Department of Pathology at the University of Toronto. The only laboratory in Canada at that time committed exclusively to the examination of neuropathology specimens, it actively interacted with neurosurgery, neurology, psychiatry and pathology through teaching demonstrations, study projects for trainees, and research on case material.

The development of specialty medicine in Canada burgeoned in the aftermath of the 2nd World War. Consequent to the increase in number of specialty disciplines accredited by the Royal College of Physicians and Surgeons of Canada (RCPSC), new national specialty societies arose, as exemplified by the formation of the Canadian Neurological Society (1948) (predecessor of the Federation of the Canadian Neurological Sciences) and the Canadian Association of Pathologists (1949). Many European medical scientists also immigrated to Canada during this period. Of these, important to the furthering of neuropathology was Jerzy Olszewski, a neurologist and neuroanatomist trained in Poland and Germany. After periods at the Montreal Neurological Institute and the University of Saskatchewan, he succeeded Dr. Linell, as Director of the Division of Neuropathology at the University of Toronto (1959-1964). His seminal contribution, in conjunction with 19 other practitioners of neuropathology was the founding in 1960 of the Canadian Association of Neuropathologists (CANP).

Of immediate concern to the members of the CANP was the establishment of a formal program of training and certification in neuropathology under the aegis of the RCPSC, the last stage in consolidating the development of the discipline. The CANP began in 1962 a series of discussions with the RCPSC that eventually culminated in 1965 with approval for a specialty level program. Concurrent initiatives in other branches of laboratory medicine begot similar status for anatomical pathology, hematological pathology, and medical biochemistry. In 1976 the RCPSC Specialty Committee in Neuropathology was established to oversee all aspects of training. The outcomes have been that training in neuropathology has evolved from an apprenticeship into an accredited academic program, and that all university-based medical centers in Canada have neuropathologists on faculty. There are active sites of training located at the Université de Montréal, University of Toronto, University of Western Ontario, University of Calgary, and University of British Columbia. With a shift in emphasis toward centers with large diverse volumes of case material and commensurate numbers of faculty, the previously vibrant programs at McGill University and Queen’s University have ceased in the past decade.

Notwithstanding the successes of the neuropathology program and other laboratory medicine specialty programs, the RCPSC began in the mid-1980s to consider the concept of a core curriculum for training in the laboratory medicine specialties. Further impetus came as a consequence of changes introduced in undergraduate and post-graduate medical education at Canadian medical schools, and pivotal task forces of the RCPSC. Among the recommendations of these task forces were a reduction of the number of entry points into programs, an increase in flexibility in changing career paths, and a shift toward generalism with emphasis on a foundational core of knowledge upon which specialization would develop. Therefore, the feasibility of introducing a core competency model for the laboratory medicine specialties was explored, beginning in 1998 and concluding with two sessions of the Working Group in Laboratory Medicine. Nonetheless, a consensus for a core curriculum could not be achieved and, with the Final Report of the Core Competency Project failing to endorse this model for post-graduate medical education, this issue is unlikely to be revisited.

An additional outcome of the aforementioned RCPSC task forces was the assignment to the Committee on Specialties (COS) to revise the definitions of a specialty versus subspecialty and establish a mechanism for periodic review of each discipline in this context. Thus, in 1999, neuropathology became one of seven specialties, with fewer than 15 candidates per year in the certification examinations, selected for the review by the COS. The result of this process was a recommendation by the COS, approved in Council 2004, that neuropathology become a subspecialty with entry from either anatomical pathology or general pathology. Contentious debate ensued and grave concerns over the proper adherence to due process of this review were expressed by the Specialty Committee in Neuropathology, the CANP, and the Canadian Association of Pathologists. In response, the Office of Education in the RCPSC formed a Neuropathology Review Panel that, following examination of the process, recommended suspension of the previous decision on specialty status because of procedural deficiencies. This recommendation was accepted by Council and the specialty status of neuropathology was restored in 2007.

A salient awareness in all parties engaged in the debates over a core curriculum and specialty status was the dearth of demographic information on the practice of neuropathology in Canada. Fundamental are questions pertaining to current status of practice, future workforce needs, routes of entry and training background of practitioners, and the influence of background on scopes of practice and academic activities. In an attempt to address these questions, a demographic survey was undertaken for the CANP by one of the co-authors (MRD) of all practicing neuropathologists in Canada, the results of which are reported. The imminent 50th anniversary of the CANP in 2010 makes this survey even timelier.
method
Canada neuropathology survey
A structured questionnaire was devised to ascertain route of training into neuropathology, certifications and qualifications, practice location and environment, current practice spectrum, associated research, associated non-neuropathology professional practice, and intent to retire in the foreseeable future. We defined the practice of neuropathology (NP) as the medical specialty involved in the diagnosis of disorders of the central and peripheral nervous systems and skeletal muscle using microscopic and ancillary techniques. We were interested in determining whether neuropathologists were more closely aligned with the neurosciences or with laboratory specialties and the extent to which individuals practiced in both disciplines. We identified three entry routes into neuropathology. Physicians who entered a NP training program immediately following medical school with or without a period of research training in neurosciences were classified as “direct to NP”. Individuals who trained in anatomical (AP), general (GP), or clinical pathology (CP) first were classified as “pathology to NP”. The survey included a question that attempted to determine whether individuals planned to do NP primarily but for reasons related to counseling, location, or misinformation did pathology training first, or if they decided on NP later during this training. The third category was “clinical neuroscience to NP”. This included individuals who during or upon completion of a residency in neurology or neurosurgery switched to NP. The survey was sent initially by email December 2007. Non-responders were contacted by telephone call (MRD). Recipients included members of the Canadian Association of Neuropathologists currently practicing in Canada, individuals known to be certified in neuropathology in Canada (publicly listed on the website of the RCPCS), other individuals known by residency directors to have trained in Canada but who are neither CANP members nor RSCPC fellows, CANP members and RCPCS fellows who were now practicing elsewhere, and individuals known by regional reputation to be practicing neuropathology in Canada. The last category included individuals in smaller centers who practice a limited spectrum of neuropathology with only minimal training. The resulting database was updated May 2009. The PubMed database was searched to assess the individuals’ publication records, acknowledging that this overlooks important academic contributions such as books and book chapters. The average number of post-training publications per year was calculated.

results of survey
Ninety-six physicians are known to have trained in or practiced neuropathology (full-time or part-time for at least one year) in Canada during the period 1988-2009. In May 2009, 53 were active in Canada, 11 were practicing in the US, 1 was practicing in Ireland, 26 were retired or deceased, 3 had switched specialty following training without ever practicing NP (one to psychiatry, one to neuroradiology, one to general practice), one switched to AP only following several years of mixed NP/AP practice, and two had switched to general medical practice in mid-career. Seventy survey responses were received, including all 53 individuals active in Canada in May 2009 (none requested anonymity). Partial data for 19 other individuals could be ascertained from published information, records from work sites, and personal knowledge of coworkers; because some of the data are incomplete, the sums in this section are not necessarily equal. Fifty-five individuals did their neuropathology training in Canada (17 Western Ontario, 18 Toronto, 8 Queens, 5 Vancouver, 4 McGill, 2 Montreal, 2 Calgary), 10 in the United States of America (US), 8 combined Canada and US, and 6 in European countries including the United Kingdom. Among this broad group, 33 were pathology to NP, 24 were direct to NP, 14 had prior training in neurology (some with certification), and 3 had prior training in neurosurgery. For those individuals whose year of NP certification or beginning practice was known, we tallied the route of entry 1970-1993 and 1994-2009; this split was the median year. There was no statistically significant shift in the entry route, although direct entry tended to increase at the expense of the clinical neuroscience entry route (pre-1993: pathology 9, direct 9, neurology 9; 1993 to present: pathology 9, direct 14, neurology/neurosurgery 4) (p=0.22; contingency table and Chi square analysis).

Among the 53 individuals practicing neuropathology in Canada in 2009 (full time or significant part time), 25 (47%) were pathology to NP, 17 (32%) were direct entry, and 11 (21%) were neuroscience to NP. Thirty-five (66%) trained exclusively in Canada, 8 (15%) in the US, 7 (13%) combined Canada / US, and 3 (6%) in Europe. Those directly entering neuropathology training reported 4.0±0.2 years of neuropathology training, clinical neuroscience to NP reported 3.0±0.2 years, and pathology to NP reported 2.3±0.2 years (p<0.0001; Kruskal-Wallis test). In the last group, the majority indicated that they had intended to train in neuropathology at the beginning of their pathology training. Twenty-one individuals practiced neuropathology in Ontario, nine in Alberta, nine in Quebec, seven in British Columbia, four in the Maritime provinces, and three in Manitoba/Saskatchewan region. Seven individuals reported a desire to retire within five years and an additional 11 plan to retire within ten years. Forty (75%) were NP certified by the RCPCS and / or American boards, while 27 (51%) were AP/GP certified (15 had dual certification). Thirty-nine (74%) did diagnostic reporting on NP specimens only, 1 did exclusively ophthalmic pathology, 1 combined NP with a clinical practice in pediatric neurology, and 12 (21%) had a mixed AP/NP practice. Not surprisingly, AP certification was a predictor of mixed AP/NP practice (p<0.0001; Chi square analyzed by route of entry). Among the 12 individuals with mixed AP/NP practice (NP ranging from estimated 20 to 50% of time), the AP focus of 5 was pediatric/fetal pathology. The majority of neuropathologists (50/53) practiced in a tertiary hospital / medical school setting. Several individuals had mixed practices in a non-university community laboratory setting (Vancouver and Toronto region). All individuals reported their practice profile semiquantitatively with respect to the breakdown of various subspecialty areas in neuropathology including pediatric, neoplastic, neuro-degenerative, forensic, and nerve / muscle (See Table). Chi square analysis did not demonstrate a statistically significant influence of training route on the practice of any of the subspecialty areas, although pathology to NP trained individuals accounted for all of those doing none / minimal nerve and muscle diagnostic work (Chi square P value 0.075). It should
also be noted that relatively high proportions of individuals from all entry routes minimized their involvement in the pediatric and forensic neuropathology subspecialty areas.

Note that the detailed survey data excludes additional pathologists practicing in eight small Canadian centers who spend <20% of their time with neuropathology specimens. At these community hospitals the pathologists typically had three to four months neuropathology training during an AP residency. In 7/8 of the centers, one or two pathologists within the group did all of the neuropathology casework, with the bulk of diagnostic work comprised of neoplasms (estimated at 30 to 60 cases per year) and including a few neurodegenerative autopsies. All reported well-developed consultation relationships with the larger centers in the vicinity.

Among the 53 individuals practicing neuropathology in Canada, 14 (26%) have a neuroscience-oriented PhD degree and 21 (40%) of the others report an MSc degree or postdoctoral research training in the neurosciences. This observation would be noted that relatively high proportions of individuals from all entry routes discounted their involvement in the pediatric and forensic neuropathology subspecialty areas.

Table: Practice profiles of individuals providing diagnostic neuropathology services in Canada

<table>
<thead>
<tr>
<th>Subspecialty area</th>
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<th>Moderate volume</th>
<th>High volume</th>
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<tr>
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<tr>
<td>Nerve / muscle</td>
<td>6</td>
<td>38</td>
<td>8</td>
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Note: Data from 53 neuropathologists active in Canada May 2009; one individual who practices only ophthalmic pathology is not included in the table.

DISCUSSION

One observation to be made from this survey is that the workforce engaged in the practice of neuropathology in Canada is small, fractionated in commitments, and might not meet future needs. In 2009, 39 physicians commit the bulk of their professional time to the pathological diagnosis of neurological lesions (including skeletal muscle) from surgical or autopsy specimens, and another 12 work as neuropathologists for 20 to 50% of their time. Eight centers have pathologists minimally trained in neuropathology who spend <20% of their time in neuropathology service predominantly related to brain tumors. The Canadian Association of Pathologists annual survey indicates that 33 people identified themselves as neuropathologists in 2007; this is reflected in our identification of 39 full-time individuals who practice exclusively neuro-pathology. Inclusion of the part-time practitioners is, however, a more accurate reflection of the scope of neuropathology workload across the country. The information concerning intent to retire suggests that at least two new neuropathologists will be needed per year to replace these retirees over the next ten years to maintain the Canadian workforce at its current status. Nonetheless, this rate might not be sufficient for the anticipated need for growth in the workforce as service volumes and clinical expectations for greater diagnostic refinement. In this context the current Canadian workforce in neuropathology represents approximately 1.5 neuropathologists per million population. In the United Kingdom there are <1 per million, and this is considered a critical level of understaffing.

The present study reveals a composite of practitioners that fulfill needs for neuropathology in various settings. That a preponderance of formally trained neuropathologists are in academic institutions and tertiary medical centers is not to be unexpected in that it parallels the historical development and patient referral pattern for the clinical neurosciences. These centers, moreover, are able to provide the resources and facilities required for neuropathology practice. In tandem is the observation that an extraordinarily high proportion (67%) of practitioners possess graduate degrees and/or postdoctoral research training in the neurosciences. This observation would seem to suggest that not only is there a need for this level of background training but, as an extension, that neuropathology attracts research-oriented and academically focused physicians. Entry via a pathology specialty (anatomical or general) was recorded in 47% of respondents, of whom half (12/25) have a mixed AP/NP practice. However, five of these pathologists combine neuropathology with pediatric/fetal pathology, a discipline that relies strongly on knowledge of neuropathology to understand malformations and neoplasms of the nervous system. The remaining pathology entry neuropathologists are engaged in full time neuropathology practice, mirroring the trend in larger medical centers and affiliated medical laboratories towards specialization. Hence, these observations suggest that complete training or certification in anatomical or general pathology is of variable relevance to the practice of neuropathology, depending upon the setting. In support, several pathology-trained neuropathologists indicated in their responses a preference to have had their training streamlined by decreasing the time spent in anatomical pathology. Of note, it was identified long ago in the United States...
and United Kingdom that mandated lengthy years of training in general and/or surgical pathology serve as potential impediments for recruitment into neuropathology. Nevertheless, a small proportion of AP/NP trained individuals do practice neuropathology in non-tertiary or community care settings where there is a need due to expansion of neurosurgery services. Moreover, in a significant number of smaller centers with active neurosurgical units, one or more anatomical pathologists practice a limited spectrum of neuropathology.

The thematic crux of the COS review of neuropathology and the RCPSC discussions over a core competency model for the laboratory medicine specialties has been the need to resolve a key aspect in the working definition of a specialty: “a specialty encompasses a broad base of foundational knowledge upon which additional competencies develop”. Not sufficiently explored, however, has been the related question of whether the appropriate prerequisite background for training in neuropathology is anatomical pathology or neuroscience. The COS, in its recommendation of subspecialty status under AP/GP, focused on the overlap of the tools used by specialists in the disciplines. It failed to grasp the scope of divergences in theoretical background, seemingly to conclude that AP provided sufficient foundational competencies. However, this survey has clearly demonstrated that physicians currently practicing neuropathology in Canada entered the discipline via different routes. From the standpoint of delivery of clinical service, the survey has not shown that one route is better that another. As previously discussed, in secondary medical centers and small community hospitals, prior training in AP/GP would likely be appropriate. This is reflected in the comment of one survey respondent who opined that additional AP training would improve employment opportunities. However, the majority of neuropathologists work in tertiary medical centers and allied academic institutions where there is the expectation to fulfill a diversity of roles including service with the incorporation of new diagnostic techniques and development of subspecialty fields of expertise, teaching at undergraduate and post graduate levels in medicine and the neurosciences, and research be it collaborative or independent. Although no one format of preparatory training may be adequate for all these roles, entry into a neuropathology program direct from medical school with prior training in basic neuroscience or from the clinical neurosciences may offer an advantage, as reflected by the publication output. In this regard, surveys in past decades in the United States and the United Kingdom have identified lack of knowledge in clinical neuroscience as a problem in training. This type of knowledge is required for provision of clinically meaningful diagnoses in several areas of neuropathology, in particular with respect to autopsy material. Under the RCPSC Requirements of Training for neuropathology, entry after certification in AP/GP requires only two core years of neuropathology training, whereas direct entry, as stipulated, entails three years following the introductory Post Graduate Year (PGY) 1 and 2 years. This longer training, combined with a background in neuroscience concepts and techniques, would afford broader exposure and consolidation of knowledge that predispose to engagement in research and scholarly activities as reflected in this survey. These activities are as important as diagnostic service. By advancing the science and practice of neuro-pathology, the competencies that define it as a distinct discipline are also advanced.

The status of a separate specialty discipline, in conjunction with the multiple routes of entry, is a distinctive attribute of the neuropathology training program in Canada. As documented in the survey, length of training does vary with entry route but, at minimum, one year training in anatomical pathology is required in addition to a two year core of neuropathology. This approach is comparable, if not more flexible, than many countries in the European Union. In Germany, where neuropathology historically arose from psychiatry and neurology and is considered one of the clinical neurosciences, neuropathology is likewise considered an independent specialty. Training includes two years pathology, three years neuropathology, and one year clinical neurosciences. In other European countries where neuropathology is a specialty following training in anatomical pathology (i.e., Austria, Hungary, Ireland, Poland, and United Kingdom), training typically consists of one to two years of histopathology, zero to two years of clinical neurosciences, and two to four years of neuropathology. In seven other European countries neuropathology is a subspecialty of anatomical pathology. To homogenize training requirements the European Confederation of Neuropathological Societies was established. Eligibility to write the European Examination in Neuropathology includes minimum training experience of three years full time neuropathology, one year full time in anatomic pathology, and one year “preferentially spent in clinical neurology or neurosurgery”. This course of training is essentially the same as that done in Canada since 1976. It should be noted that in the UK, where neurology and neurosurgery are recognized as having critical influences on the development of neuropathology, there are activities directed to making it an independent specialty (personal communications, Dr. Seth Love and Dr. James Ironside, June 2009). In the United States, neuropathology is regarded as a subspecialty of anatomical pathology. The origin of the pathology link dates from the 1950s, and appears to have been meant as a tactic to ensure a commitment of trainees to laboratory medicine, rather than a schism from the clinical neurosciences. Nevertheless, some leaders at the time expressed intense opposition to the effective separation from neurology and psychiatry and the association with the American Board in Pathology. In following years the divergent affiliations of neuropathology were discussed with the conclusion that the affiliation with neurology should be stronger that with pathology. Currently a combined four-year AP/NP program is available with examination in both fields. Entry from clinical pathology, neurology or neurosurgery is feasible, but supplemental training of one year in anatomical pathology is required. In other countries training routes are less well established. Despite a large membership in the Japanese Society of Neuropathology, the profession is not recognized as an independent specialty in Japan (personal communication Dr. Hitoshi Takahashi, September 2008). Similarly, neuropathology training in China remains somewhat informal. Notwithstanding an argument cited in the RCPSC COS review of neuropathology that neuropathology has not been accorded specialty status in many countries, this summary suggests that there is a groundswell of opinion that “neuropathology needs to be recognized as a separate specialty in as many countries as possible”. The motive for this sentiment is not only to satisfy future needs for diagnostic service, but, as echoed in the above
discussion, the hope that “attracting trainees with a background in basic neuroscience into neuropathology will help to strengthen research and academic activities”.

There are several limitations to this survey. First, the data are self-reported perceptions of relative work and are not based on actual specimen quantities or hourly documentation. Second, absolute distinction of training paths is not possible; for example, in many countries prior training in AP is mandated rather than chosen prior to neuropathology, and in Quebec AP, but not NP, certification is mandatory for licensure with the consequence that not all individuals pursue NP certification. Therefore, training route does not necessarily distinguish the desires of an individual early in his or her training. Third, the average annual number of publications is an incomplete marker of academic output because it does not account for variations in productivity, it does not include other forms of scholarly work such as chapter or textbook writing, a consistent and comparable starting point for publishing career is not clearly definable, and it does not reflect teaching.

CONCLUSIONS

This brief historical review and demographic survey offers some insight into the training and practice of neuropathology in Canada. Whereas in the first part of the 20th century there were a few part time autodidacts in the discipline, most of the contemporary practitioners have received part or all of their formal training in this country and are certified in the specialty. The physicians who practice neuropathology range in their relative alliance to other fields of laboratory medicine and the clinical neurosciences. As noted, entry into neuropathology from AP/GP has historically been, and will continue to remain, a constant source of recruitment. Practitioners from this route tend to liaise with anatomical pathology and have a range of commitments in diagnostic service and teaching. Nonetheless, this source is insufficient to meet future recruitment needs. Direct entry from medical school into training programs appears to represent the emerging mainstay of recruitment, supplemented by transfers from the clinical neurosciences. As reported in this survey, a large proportion of these physicians have academic backgrounds in neuroscience that facilitate the melding of the functions of diagnostic service with involvement in research. Thus, this founding in neuroscience more likely predisposes these practitioners along the career path of scholarly activities. Having multiple entry points into the training program offers a broader catchment for recruitment, promotes a diversity of practitioners to fill a variety of practice profiles, and creates a mosaic of neuropathology practice that encompasses the needs of medical, academic, and scientific communities, the hallmark of a vital specialty. As suggested by the survey, adequacy of the workforce in neuropathology is a crucial problem, in common with many other specialties in Canada. Because the discipline tends to attract undergraduate medical students with an interest or background in neuroscience, these individuals may be amenable to recruitment initiatives. In addition, examination of the availability of positions in training programs and employment opportunities is necessary to identify and remove barriers to further recruitment. An amalgam of concepts, knowledge base and skills from anatomical pathology and neuroscience, neuropathology has fused these elements in the crucible of its evolution into an independent discipline with a distinct foundational knowledge and sets of competencies. In Canada, neuropathology is recognized as a specialty, as in leading centers in the European Union. In this capacity as a specialty with a training program that allows different routes of entry, it has developed a cadre of practitioners capable of meeting the medical, academic, and scientific needs of Canadian society.

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COMPETING INTERESTS

Dr. Johnson is the President of the Canadian Association of Neuropathologists. Dr. Del Bigio is the Chair of the Specialty Committee on Neuropathology for the RCPSC.

REFERENCES