OBITUARY

Oleh Hornykiewicz: A Giant who Transformed Neuroscience over a 70-Year Career

Oleh Hornykiewicz was born on November 17, 1926 in Sichw (now Sylkiv) a small town that was then in Poland and is now part of Ukraine, and he died in Vienna on May 26, 2020, at the age of 93. His impact on neuroscience is almost beyond measure.

When he was about 13, the family moved to the Polish city of Lviv. Then, in 1939, the German army entered Poland, the Hitler-Stalin non-aggression pact was signed, and the Russians occupied Lviv. A few months later, and only because his mother had Austrian ancestry, Oleh and his family were allowed to leave for Vienna, although without virtually any of their possessions. His youth in Vienna presented challenges of course but it also brought with it exposure to literature, poetry, and music – lifelong loves that may help account for the outstanding quality of his prose in English, which eventually became his third language.

Oleh’s paternal family had served in the Catholic church for several generations. However, Oleh took a different tack and entered the University of Vienna to study medicine, receiving his medical degree at there in 1951. Upon his graduation, Oleh briefly joined the laboratory of Herman Blaschko a pharmacologist at the University of Oxford who had made major contributions to the understanding of the biosynthesis and degradation of catecholamines. This was the first of many interactions that Oleh had with the great personages in neuropharmacology and neuroscience of the time including Julius Axelrod, Henry Dale, Ulf von Euler, Sidney Udenfriend, and many others. Blaschko encouraged the young researcher to consider the possibility that dopamine (DA) was a neurotransmitter in its own right, basing his recommendation on a much older finding by Peter Holtz that DA lowered arterial blood pressure (Holtz et al., 1942). Oleh not only replicated the Holtz finding but also showed that the effect of DA could be mimicked by the precursor to DA, L-dopa.

Almost simultaneously with Oleh, Weil-Malherbe (1958) and Arvid Carlsson (1957) published separate papers on the action of reserpine, a drug isolated in 1952 as the active principle of the plant Rauwolfia serpentine (Sarpagandha) that had been long used in Ayurvedic medicine to treat a number of conditions, including insanity. Carlsson had injected reserpine into the brains of rabbits and found that it not only dramatically reduced their motor activity, but it also depleted the brain of DA, and that both effects could be reversed by injecting L-dopa. And Carlsson went several steps further, suggesting that the reduction in movement seen in reserpinized rabbits might be analogous to human Parkinsonism and that, if so, L-dopa could be used as a treatment for Parkinson’s disease (PD), a hypothesis he first presented in 1958 at the First International Catecholamine Symposium (see Carlsson, 1959).

The suggestion that DA be taken seriously as a chemical transmitter was a revolutionary idea. Although these findings and the interpretation are now taken for granted, in order to appreciate their full impact, one needs to remember that at the time most investigators – especially in the United States – thought that DA was simply a precursor to norepinephrine. I still remember when Guy Everett visited our laboratory at the University of Chicago from the nearby Abbott Labs while I was still a graduate student and told me that I should be measuring DA as well as norepinephrine. Though he did not explain his reasoning, I accepted his advice and continued to measure DA for the next 55 years! I remember the day several years later when, while a junior faculty member at the University of Pittsburgh, we gave 6-hydroxydopamine to a rat in such a way as to block its uptake in noradrenergic neurons and produced akinetias and an almost complete loss of DA. It was to us a startling finding.

Another suggestion that Oleh made – that there was a nigrostriatal dopaminergic pathway whose degeneration was responsible for PD – was also not quickly accepted. Damage to the substantia nigra had been observed as early as 1894 (Blocq and Marinesco, 1894), but the suggestion that a pathway connected this structure to telencephalon was extremely controversial. No projection of any kind had previously been described that connected the midbrain to the forebrain and the general assumption seems to have been that all rostralward input to the telencephalon had to come from the diencephalon. Indeed, the definitive detection of the pathway had to await the development of more sensitive methods of detecting neurodegeneration (see reviews by Moore, 1970; Fuxe et al, 2006). And, although we now know that nigrostriatal degeneration is only part of the etiology of PD (see Braak and Del Tredici, 2008), it is also clearly explains a significant motor component of the disease.

When he returned to the University of Vienna as an assistant professor, Oleh set about to measure DA in postmortem human brains. He focused on the corpus striatum based on the reports made the previous year that the concentration of DA was particularly high in this region, (Bertler and Rosengren, 1959; Sano et al., 1959). He quickly discovered that the DA concentration in
the striatum from brains of parkinsonian patients was reduced by about 90% when compared to that in control brains. He decided that the logical conclusion from his work was that L-dopa would be an effective treatment for the motor disorders associated with PD as it was for reversing the akinesia of reserpinized rabbits in the hands of Carlsson. He managed to collaborate with a skeptical Walther Birkmayer to test his idea by carrying out clinical trials on the impact of L-dopa on patients with PD and observed remarkable improvement in the patients' motor function (Birkmayer and Hornykiewicz, 1961) and, years later, a marked increase in striatal DA levels (Lloyd et al., 1975). A fictionalized portrayal of these startling effects of L-dopa on parkinsonian patients was provided in Dr. Oliver Sachs’s book “Awakenings” and in the movie of the same name. Perhaps it is fitting to note that in the 1976 edition of his book, Sacks quotes the poet W.H. Auden who wrote “Healing, papa would tell me, is not a science, but the intuitive art of wooing Nature.” Oleh may have felt the same way. In any event, the use of L-dopa for PD continues to save millions of patients around the world, yet another of Oleh's major contributions to neuroscience. Nature.” Oleh may have felt the same way. In any event, the use of L-dopa for PD continues to save millions of patients around the world, yet another of Oleh’s major contributions to neuroscience. Moreover, it has led to the more generalized concept of treating brain disorders with a transmitter-related drug.

In analyzing the corpus striatum of brains from parkinsonian patients Oleh also noticed that the reduction in the DA metabolite homovanillic acid (HVA) was less than was the loss of DA itself, a finding he published in 1965 in a German language paper (Bernheimer and Hornykiewicz, 1965). This was followed up in 2006 with the observation of a comparable rise in the ratio of tyrosine hydroxylase activity to DA (Pif and Hornykiewicz, 2006). Oleh’s conclusion was that the extended preclinical phase of PD in which clear motor signs were not detectable until after an extensive loss of striatal DA had occurred was a result of a compensatory increase in the synthesis and release of DA from the remaining neurons. Years later, my colleagues and I drew the same conclusion when we observed a similar discrepancy in HVA levels and tyrosine hydroxylase activity in rats given the DA neurotoxin, 6-hydroxydopamine (Acheson et al., 1980). However, not being familiar with the German literature, we initially failed to give Oleh the proper credit for his findings, though they had appeared many years earlier, a matter we soon corrected (Zigmond et al., 1984). Later reflecting on his groundbreaking work, Oleh noted that his observations were made by a simple and relatively insensitive assay and “did not require any complicated machinery or out-of-the-way chemistry” (Hornykiewicz, 2004) – an observation that might be taken to heart by reviewers who criticize manuscripts and grant proposals (including some of my own) because they do not use "the most modern methods"!

Using assays of human brain tissue to understand the etiology of human disease had never been attempted before and opened up an avenue of research that is now common practice. Indeed, as of this writing more than 250,000 papers have been published in which assays of human brain have been used to explore everything from traumatic brain injury to brain cancers, yet another contribution that can largely be attributed to Oleh.

In 1967 Oleh accepted a post at the University of Toronto, a position he held alongside his position at the University of Vienna, eventually becoming Professors Emeritus at both institutions. Among his many contributions while at the University of Toronto was the demonstration with Kenneth Lloyd and Ted Sourkes that L-dopa could be decarboxylated to form DA in brain, a direct prediction from his clinical study.

Although Carlsson was rightly awarded the Nobel Prize for his work in 2000, Oleh was not, much to the disappointment of many, including myself, and a letter of complaint to the Nobel committee signed by some 250 people did not alter this oversight (Helmuth, 2001). The basis of this slight has always been a mystery to me and may have been what Oleh had in mind when he wrote years later about the “disregard of intellectual property...[which] has always been deeply saddening to me” (Hornykiewicz, 2004). Nonetheless, Oleh received a large number of awards during his 70-year scientific career including the Gold Medal of the Parkinson’s Disease Association (1970), the Wolf Prize (1979), and the Wiigenstein Prize (1993).

Later in life, Oleh commented that as he progressed in his profession, he spent less time on his own research and more on providing guidance to those for whom he served as an advisor and mentor. However, rather than express disappointment at this shift in emphasis, he noted that: “I think it is right to pass on what one has received” (Hornykiewicz, 2004). That process will endure even after the death of this great man as his career will continue to provide guidance to those who will follow him.

I was privileged to meet Oleh a only a couple times, once soon after I discovered his much earlier observation of neurochemical compensation in patients with PD, when he honored me by accepting an invitation to visit the University of Pittsburgh as a speaker. But through those few meetings and my familiarity with his work, he will always remain a cherished figure in my memory, and I am sure that this is also true for his large family of professional and familial children, grandchildren, and great grandchildren.

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