

## OLEH HORNYKIEWICZ (1926-2020): SIXTY YEARS SINCE THE PIONEERING L-DOPA APPLICATION - ONE YEAR SINCE THE DEATH OF THE PIONEER

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### SUMMARY

Oleh Hornykiewicz was born on November 17, 1926 in Lamberg, Ukraine. After completing his studies in July 1951, he moved to the "Pharmacological Institute of the University of Vienna". In 1958, he started his research on centrally acting drugs at the same institute and came up with the idea of linking laboratory observations with animals with the basal ganglia of the human brain. Soon, Hornykiewicz initiated a new question: L-DOPA as a therapy for Parkinson's disease? Fortunately, after administration of this new drug, patients were able to perform motor activities which could not be prompted to any comparable degree by any known drug. In the following decades, initial fiction became an unavoidable fact. Dopamine, adapted and combined with carbidopa or benzerazide, has evolved into a drug that no longer recognizes the borders of countries and continents. Distinguished emeritus prof. Oleh Hornykiewicz died on May 26, 2020 at the age of 93 in Vienna, Austria. Unfortunately, despite everything he has done and deserved, the Nobel Prize was not received.

**Key words:** basal ganglia - Parkinson disease – dopamine - L-DOPA

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### THE FIRST STEPS

In the book "The History of Neuroscience in Autobiography" (Squire 2004) Hornykiewicz describes his life as simple and uncomplicated. He was born on November 17, 1926 and spent his early childhood in rural surroundings in the Sychiw district – one of six districts in the western Ukrainian city of Lamberg. In 1933 he moved to Lviv and began his training there. His carefree and happy childhood ended on September 1, 1939. Thanks to his mother's Austrian ancestors, he fled to Austria with his whole family at the age of thirteen. After successfully completing the language test, Hornykiewicz continued his education in Austria. His language skills gave him access to a new world of written knowledge, literature and poetry. In October 1945, Oleh Hornykiewicz had the opportunity to begin studying medicine. After completing his studies in July 1951, he moved to the "Pharmacological Institute of the University of Vienna" under the direction of Franz von Brücke (Squire 2004).

Three teachers contributed most to Hornykiewicz's research career: Friedrich Wessely (Professor of Chemistry for Medical Students), Friedrich Ehmman (Professor of Neuroanatomy and Brain Development), and Franz von Brücke (Professor of Pharmacology and Toxicology). Thanks to a British scholarship, Hornykiewicz spent the period from September 1956 to February 1958 in the Department of Pharmacology at Oxford University. This department was at that time the most productive pharmacological institute in

England, where new research programs and ideas were implemented. Hornykiewicz gained access to important research and laboratories in the UK. He spent most of his time in Hugh Blaschko's laboratory, with whom he worked intensively (Squire 2004).

### PIONEER'S WORK

During Blaschko's absence, Hornykiewicz studied the absorption of adrenaline and noradrenaline in the isolated platelets. Hornykiewicz caught the attention of Blaschko with his theory about dopamine. The substance dopamine had only been known for four years at the time and was discovered by Sir Henry Dale through the modification of 3,4-dihydroxyphenylethylamine or 3-hydroxytyramine. Until then, dopamine was considered a metabolic precursor in the synthesis of norepinephrine in the body. Hermann Blaschko was the first in Oxford to question the functional importance of dopamine. He expressed his idea in a lecture entitled "Metabolism and the supply of biogenic amines". Hornykiewicz earned Blaschko's trust and was also able to provide him with experimental evidence (Squire 2004).

The realization that dopamine has an independent physiological function motivated the pharmacologist Hornykiewicz. After returning from Oxford in 1958, he started research on centrally acting drugs at the "Pharmacological Institute of the University of Vienna" in order to find out how these dopamine levels affected the brain of rats (Hornykiewicz 2017). For

nearly half a century and a multitude of studies on dopamine and L-DOPA, especially research on the animals treated with reserpine, Hornykiewicz tried to reach a conclusion. Shortly after the drug reserpine was used as an antipsychotic, he conducted an experiment on mice and canaries with the drug, which caused a decrease in the levels of dopamine and other amines. However, this led to the continued occurrence of side effects similar to the symptoms of Parkinson's disease. Reserpine-induced akinesia and catalepsy could be reduced and resolved by intravenously (i.v.) administration of L-DOPA (Riederer & Umek 1985).

Hornykiewicz's determination to resolve the role of dopamine in the brain was supported by various publications immediately after his return to Vienna in February 1958 (Carlsson et al. 1958, Weil-Malherbe & Bone 1958). These publications again confirmed the existence of dopamine in the animal brain and demonstrated that the active ingredient reserpine reduces the amount of dopamine in the brain and L-DOPA increases it again (Squire 2004). After reading a report on experiments in 1959 (Bertler & Rosengren 1959), Hornykiewicz came up with the idea of linking laboratory observations with animals with the basal ganglia of the human brain, especially the brains of patients with Parkinson's disease. Studies on the human brain began in 1959 and ended in 1960 (Squire 2004).

## DOPAMIN / L-DOPA

Discoveries in the characteristics of the regional distribution of dopamine in experimental animals (Holzer & Hornykiewicz 1959, Bertler & Rosengren 1959, Carlsson 1959) were a very interesting basis and impetus for the continuation of similar ones. At the end of 1960, Ehringer & Hornykiewicz published in the journal "Klinische Wochenschrift" the results of research on the distribution of noradrenaline and dopamine and their effect on diseases of the extrapyramidal system in humans. The experimental group consisted of patients with postencephalitic parkinsonism and Parkinson's syndrome. The first group had a history of encephalitis, the existence of oculomotor crises, extrapyramidal and autonomic signs, and demelanization of the nigra substance at autopsies. The second group had a clinical picture characteristic of Parkinson's syndrome, with a late manifestation of signs and the absence of a history of encephalitis and oculomotor crises (Ehringer & Hornykiewicz 1960).

New knowledge broadened the horizons and created reasons for optimism. Encouragingly, a decrease in intracerebral dopamine and norepinephrine levels was observed in 4 patients with postencephalitic parkinsonism. Particularly noticeable was the reduction in the amount of dopamine in the corpus striatum (nucleus caudatus and putamen), even up to 1/10 of the normal

value. In 2 patients with Parkinson's syndrome, the amount of dopamine in the corpus striatum (nucleus caudatus and putamen) was also reduced, but not as much as in patients with postencephalitic parkinsonism. Furthermore, the amount of norepinephrine in the hypothalamus of patients with postencephalitic parkinsonism and Parkinson's syndrome was not sufficient. On the contrary, in several patients with extrapyramidal manifestations of Huntington's disease, the amount of dopamine was in the reference values. This research will prove to be fundamental in the future because it sheds light on the physiological role of dopamine in the human brain (Ehringer & Hornykiewicz 1960).

This new study included the brains of six Parkinson's disease patients, two Huntington's disease brains, five brains of patients with extrapyramidal symptoms of unknown etiology, one infant / one neonate brain and seventeen control brains. The reduced amounts of dopamine in the caudate nucleus and putamen were only found in the six brains of patients with Parkinson's disease. The results of this study were published on December 15, 1960 in the "Klinische Wochenschrift", official Journal of Vienna's Medical Society (Ehringer & Hornykiewicz 1960). From then on, this discovery provided a rational basis for further exploration of the mechanism, causes, and treatment of Parkinson's disease (Squire 2004).

In October 1960, two months after the published report on the discovery of dopamine, Hornykiewicz increasingly pursued the idea that motor deficits in Parkinson's disease could be eliminated by replacing the missing dopamine. At that time Hornykiewicz was on a study visit to Blaschko's laboratory in Oxford. Encouraged by the working atmosphere that prevailed in this laboratory and the previous work on dopamine / L-DOPA that he had carried out there, Hornykiewicz initiated a new question: L-DOPA as a therapy for Parkinson's disease? (Squire 2004). He presented his idea to Birkmayer. At that time Birkmayer was one of the main neurologists in a nursing home in Vienna and had access to numerous Parkinson's patients (Squire 2004). These very useful and interesting findings greatly influenced the future pioneering neurological-pharmacological feat of Hornykiewicz. Namely, from previous findings, it became clear that the penetration of administered dopamine through the blood-brain barrier was not adequate. Therefore, in the presence of Professor Brücke, Hornykiewicz suggested to his colleague Birkmayer that he tried to help patients with the dopamine precursor, L-DOPA. He hypothesized that this precursor would be exposed to the decarboxylation process only within the brain, thus raising its level in patients. The group which received L-DOPA consisted of patients with moderate to severe postencephalitic parkinsonism, but also those with Parkinson's syndrome. L-DOPA, left behind in the laboratory as a gift

from the pharmaceutical company “Hoffmann-LaRoche”, was prepared in the way that Degkwitz and co-workers did during 1960 (Degkwitz et al. 1960).

In July 1961, Birkmayer injected 150 mg L-DOPA intravenously (i.v.) into one of his patients. This kind of L-DOPA administration was chosen for economic reasons, as only a very small dose, about 2 g of L-DOPA, was required. Another reason for choosing the intravenous method was the fact that L-DOPA was tested and classified as a safe method back in early 1940's (Squire 2004). The effect of L-DOPA on the first patients showed spectacular results. Akinesia, one of the most severe motor deficits, was reduced almost immediately after injection of L-DOPA. Hornykiewicz with Birkmayer started their first clinical study with L-DOPA in July 1961. In August of the same year, they made a famous documentary film about five patients treated with L-DOPA, which they wrote eight weeks later in their first written report entitled “L-DOPA Effect in Parkinson's Akinesis” (November 1961) to the “Wiener Klinische Wochenschrift” sent for publication (Birkmayer & Hornykiewicz 1961).

The original description of the “L-DOPA effect” reads as follows: “The effect of a single i.v. administration of L-DOPA, was, in short, a complete abolition or substantial relief of akinesia. Bedridden patients who were unable to sit up; patients who could not stand up when seated; and patients who, when standing could not start walking, performed after L-DOPA all these activities with ease. They walked around with normal associated movements and they even could run and jump. The voiceless, aphonic speech, blurred by palilalia and unclear articulation, became forceful and clear as in a normal person. For short periods of time the patients were able to perform motor activities which could not be prompted to any comparable degree by any known drug” (Birkmayer & Hornykiewicz 1961).

The results were such that they required new experiments. Soon, Bernheimer and Hornykiewicz published the results of a study which showed that the amount of dopamine was reduced not only in the corpus striatum but also in the substance nigra (Bernheimer & Hornykiewicz 1962). Of course, such encouraging results created fertile ground for the influx of new ideas. Hornykiewicz did not stop, and research to test the practicality of using L-DOPA continued with relentless ferocity. On July 21, 1962, he published (with Birkmayer) the new results of the continuation of his pioneering neurological-pharmacological endeavor (Birkmayer & Hornykiewicz 1962).

The number of patients in the experimental group increased successively to 53. They were administered dopamine-based preparations (D-DOPA, Dopamine, O-methyl-DOPA, DOPS, 5-HTP, L-DOPA), monoamine oxidase inhibitors (isocarboxazid-MARPLAN,

Ro-4/2637, Ro-4/2308, Ro-3/1620), amphetamine, pervitin, caffeine, ephyllin, regitin as well as vitamin B6. They are administered individually or in different combinations, in different doses and in different ways of ingesting the drug. L-DOPA was administered i.v. or rectally in doses of 50-100 mg to 21 patients. Those who were not able to get up (from a lying position) or those who could not walk managed to do so with the positive effects of L-DOPA. Mimicry, numerous other movements, and speech in the patient improved after application. The effect of L-DOPA was clearly visible as early as half an hour after application, would peak after 2-3 hours and then decline within 24 hours. Patients in the earlier stages of the disease showed a significantly better therapeutic response. However, orally or rectally administered L-DOPA showed almost the same effect on akinesia as i.v. injections of L-DOPA. Side effects (vomiting, sweating, bradycardia) were more pronounced in patients administered by injection. The active component was dopamine ( $\beta$ -3,4 dihydroxyphenylethylamine or 3-hydroxytyramine), a brain amine generated in the central nervous system after L-DOPA administration. The effect on akinesia and rigidity was five times better in patients already receiving monoamine oxidase inhibitor (isocarboxazide) therapy. Other preparations from the so-called DOPA group did not show an effect on improving the patient's condition (Birkmayer & Hornykiewicz 1962).

Monoamine oxidase inhibitors were administered to 15 patients orally, with 25-50 mg of L-DOPA i.v. Their effect was expected to be more pronounced and longer. Long-acting monoamine oxidase inhibitors (isocarboxazide-MARPLAN, Ro-4/2637, Ro-4/2308) were administered 10 days before the first injection of L-DOPA. However, when using Ro-3/1620, due to its fast action, the first injection of L-DOPA was administered two days later. The anti-akinetic effect of the combination of monoamine oxidase inhibitors and L-DOPA was a more pronounced and longer effect than their individual action. A dose of 50 mg of L-DOPA for one week was already sufficient for improvement (Birkmayer & Hornykiewicz 1962).

Side effects were similar to those of L-DOPA alone: nausea, vomiting, sweating, and collapse. They could be alleviated by the administration of caffeine (0.2 g), ephyllin (0.24 g) or regitin (0.015 g). The results supported the thinking and assumption that the isomer of L-DOPA in the central nervous system is converted to dopamine and then exhibits a more than noticeable anti-akinetic effect. Furthermore, the increase and prolongation of the anti-akinetic activity of L-DOPA and in the presence of monoamine oxidase inhibitors again indicated a positive effect of dopamine (Birkmayer & Hornykiewicz 1962). Hornykiewicz continued to work with Birkmayer and Bernheimer at full speed, with a multiple increase in the number of respondents in his

research. During 1963, they published a new article on biochemical changes in Parkinson's syndrome (Bernheimer et al. 1963). A year later, *urbi et orbi*, they showed the results of a three-year experimental review of the effects of L-DOPA in Parkinson's syndrome and iatrogenic parkinsonism (caused by the use of reserpine). The 15-page paper was published on September 15, 1964 (Birkmayer & Hornykiewicz 1964).

A group of patients, with a respectable number of over 200, was administered L-DOPA at a dose of 25 mg in 5 ml of saline, i.v. once or twice a week. All subjects had already received some of the so-called antiparkinsonian drugs (Trihexyphenidyl=Artane,  $\beta$ -Dimethyl-aminoethyl-2-methyl-benzhydryl ether hydrochl.=Disipal etc.) and one of the monoamine oxidase inhibitors (isocarboxazid or nialamide) (Birkmayer & Hornykiewicz 1964). The improvement was visible after only 30 minutes – only in rare cases 1-2 days after the administration of L-DOPA. The results showed a reduction of akinesia in about 20% of patients, and the positive effect lasted 1-5 days after drug administration. The positive response was individualized and characteristic for each of the patients, often concentrated on only one side of the body. It was not possible to bring it into a cause-and-effect relationship with any placebo effect. Interestingly, it was not possible to maximize it even when higher or more frequent doses of L-DOPA were administered. On the contrary, in such cases, side effects of nausea, vomiting, or loss of consciousness often occurred. Improvement of the anti-akinetic effect was associated with less side effects. In about 50% of patients, one of the impaired functions improved (eg. Propulsion, aphonia, amimia, anteflexion, etc.). This positive effect of L-DOPA is again placed in close connection with the anatomical structures of the corpus striatum (nucleus caudatus and putamen) and the substance nigra, with an open and conceivable possibility of participation of reticular formation in anti-akinetic action. Unfortunately, in 30% of patients there was no noticeable improvement (Birkmayer & Hornykiewicz 1964).

Clear ideas and methodologically clear set research conducted by Hornykiewicz had limits to pioneering work. He could compare the results with only a very small number of similar experiments of that time (Sano et al. 1961, Barbeau et al. 1961, Barbeau 1962, Barbeau et al. 1962). Oleh Hornykiewicz often relied on personal meticulous observations and follow-up of recruited respondents. This approach has led to safer conclusions based on the growing number of patients receiving L-DOPA. By carefully recording the positive and negative effects of treatment, properly looking at the side effects and publishing unique results, Oleh Hornykiewicz (without diminishing the contributions of Birkmayer or Bernheimer, Carlsson or Barbeau etc.) managed to promote the value of the drug to help patients with this extrapyramidal imbalance.

A careful analysis of what has been done points to the undeniable fact of the originality of Oleh Hornykiewicz. He gradually and patiently, in research with various collaborators, changed the paradigm of the impossibility of adequate drug access to patients with Parkinson's disease. Through diligent work, originally initiated by animal experiments, he created the possibility of moving research to a human sample. Elucidation of physiological functions in the human brain was the next step he successfully mastered, alone or with the valuable help of co-workers. At the beginning, he worked on a very small number of patients, statistically almost insignificant, but after 2-3 years the group of respondents grew to several hundred. This was followed by targeted pharmacological action on pathophysiological barriers within the central nervous system, often with a combination of different types of potential drugs, in different doses and with different ways of drug administration.

In the following decades, initial fiction became an unavoidable fact, and the number of researches in which Hornykiewicz participated became respectable and world-renowned. Dopamine, until then only a metabolite of incompletely recognized and even masked action, adapted and then combined with carbidopa or benzerazide, has evolved into a drug that no longer recognizes the borders of countries and continents (Hornykiewicz 1966, 1971, 1973, 1975, 2002, Hornykiewicz & Kish 1986, Lloyd & Hornykiewicz 1970, Lloyd et al. 1975).

## **EMERITUS, BUT NOT A NOBEL'S PRIZE WINER**

In November 1991, Hornykiewicz received the title of Professor Emeritus at the University of Toronto at the age of 65, also in Vienna four years later (Squire 2004). After being nominated for the Nobel Prize in Medicine in 2000, Hornykiewicz received support from over 250 neuroscientists who sent an open letter to the Nobel Prize Committee in Medicine (Rajput 2001). The letter outlines the importance of his work for the study of Parkinson's disease and states, among other things: "Today, 40 years later, L-DOPA is the most effective cure for Parkinson's disease. Because of the direct effects of L-DOPA, the quality of life of more than 31 million Parkinson's patients has improved." (Moskaliuk 2003).

Thanks to his immense effort and steadfastness, 60 years after the first research, we witness that L-DOPA has become and remains the "gold standard" in the treatment of people with Parkinson's disease. Distinguished emeritus prof. Oleh Hornykiewicz died on May 26, 2020 at the age of 93 in Vienna. Unfortunately, despite everything he has done and deserved, the Nobel Prize was not received (Figure 1).



**Figure 1.** Prim. Josip Hudić, MD (Tuzla, Bosnia Herzegovina), Prof. Oleh Hornykiewicz and MSc. Omer Ć. Ibrahimagić (Tuzla, Bosnia and Herzegovina), in Hofburg Imperial Palace, Wien, 2007 (from right to left)

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