

Review

L-DOPA

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Oleh Hornykiewicz was born in 1926 in Sykhiw, Poland (now Ukraine). In 1951, he received his M.D. degree from the University of Vienna and joined the faculty of his alma mater the same year and has worked there ever since. He also served for twenty years as chairman of the Institute of Biochemical Pharmacology. In 1967, he began a long association with the University of Toronto in Canada and, in 1992, he was named professor emeritus at that institution. One of his seminal accomplishments was the discovery that Parkinson's Disease was due to dopamine deficiency in the brain. He also played a key role in the development of L-dopa as a therapy for the disorder.

PUTTING (NEARLY) EVERYTHING IN A NUTSHELL: IN LIEU OF AN “ABSTRACT”

Today we would find it difficult to place ourselves in the position of the physician or the patient prior to the L-DOPA era of Parkinson's Disease (PD). David Marsden, the eminent British neurologist, neuroscientist and PD researcher of the second half of the last century and an eyewitness to that historical turning point, paints with few brush strokes, as it were, a vivid, telling picture of that period: “... Before the 1960s the clinical features and basic neuropathology of the disorder had been established, anticholinergic drugs and stereotaxic surgery were popular, but the illness progressed relentlessly and was the cause of miserable disability... The discovery of selective striatal dopamine deficiency in the parkinsonian brain in the early 1960s changed everything” [1].

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HOW THEN DID “... THE DISCOVERY ... [THAT] ... CHANGED EVERYTHING” COME ABOUT?

The timespan between January 1957 and December 1960 decided everything. In those four years dopamine (DA) made a splendid career for itself. At first relegated to the minor role of a mere metabolic intermediate in the biosynthesis of the highly respected noradrenaline (NA) in the body, DA rose to the position of a substance of physiological importance in its own right, first in the peripheral tissues and soon afterwards in the brain; to reach ultimately the top status of a neurotransmitter in the brain's basal ganglia (caudate nucleus and putamen), whose deficiency in patients with PD “... was the cause of miserable disability”. How did DA accomplish that feat?

WHAT WAS KNOWN IN THE LATE 1950S AND THE EARLY 1960S ABOUT DA AND ITS PHYSIOLOGICAL SIGNIFICANCE?

In the late 1950s sensitive chemical assays began to show that in addition to the long-known NA

and adrenaline, a third catecholamine occurred in many peripheral organs of laboratory animals and humans – this was DA. Initially, these observations were not seen as being especially sensational. At that time it was already firmly established that DA – formed in the body from L-DOPA (=L-3,4-dihydroxy-phenylalanine) through the enzymatic action of L-DOPA decarboxylase – was a metabolic intermediate, and immediate precursor, in the biosynthesis of NA in chromaffin tissue and adrenergic nerves [2]. The striking observation was, however, that in some peripheral tissues DA was found in amounts equal to those of NA. This was unexpected behavior of a true metabolic intermediate – and raised doubts about DA being merely a NA precursor substance in the body. Hermann (Hugh) Blaschko in Oxford was the first to ask, in January 1957, the question: “... What is the functional significance of dopamine? ... In chromaffin tissue, only very small quantities of dopamine occur; this suggests that in this tissue, like a true metabolic intermediate, it is not stored ... In adrenergic nerves this appears to be different. Here the amounts of dopamine found are comparable with those of noradrenaline. This suggests the possibility that dopamine has some regulating functions of its own which are not yet known” [3].

WHAT “... REGULATING FUNCTIONS OF ITS OWN...” MIGHT DA HAVE IN THE BODY?

Under the standard experimental conditions DA produced physiological effects identical with, although considerably weaker than, those of NA – though with one notable exception. In the guinea pig DA consistently lowered the blood pressure, whereas NA raised it [4]. Since DA is metabolized in the body by the enzyme monoamine oxidase (MAO) to the corresponding aldehyde, Peter Holtz, who had discovered this divergent cardiovascular effect in the guinea pig, hypothesized that it was not caused by DA itself but rather by its aldehyde metabolite.

When in the Fall of 1956 I joined Blaschko's Oxford laboratory with a British Council Scholarship, he was just then ruminating upon his idea of DA having “... some regulating functions of its own”. He soon referred me to the DA/guinea pig blood pressure work of Holtz and asked me to do something about it.

DA'S FIRST SIGNS OF LIFE AS A PHYSIOLOGICALLY ACTIVE SUBSTANCE OF ITS OWN

To me, this task appeared a rather simple matter. First, I confirmed the observations published by Holtz; and second, I repeated them in guinea pigs pretreated with iproniazid, a just at that time newly introduced long-acting inhibitor of MAO – the enzyme Holtz blamed for the deviant blood pressure effect of DA in the guinea pig. The use of this MAO inhibitor was the decisive step. Contrary to Holtz's hypothesis, I found that inhibition of MAO actually potentiated DA's blood pressure lowering effect in the guinea pig [5]. The action of DA was dose-dependent and evidently due to the amine's own biological activity. I also found that the blood pressure lowering action of L-DOPA, DA's immediate precursor, was also potentiated by inhibition of MAO.

These observations demonstrated, for the first time experimentally, that in principle DA had an own physiological activity independent of, and different from the other two catecholamines NA and adrenaline.

While I was preparing the results of my DA/guinea pig study for publication, brain DA appeared on the scene.

AT THE BEGINNING OF THE “BRAIN DA STORY” WAS THE WHOLE BRAIN HOMOGENATE

With the brain DA it all happened as Hermann (Hugh) Blaschko had prophesied. On August 5, 1957, Kathleen Montagu of the Research Laboratory at Runwell Hospital in Wickford, near London, reported something bordering, for me, on the sensational. She had homogenized whole brains of rabbits, guinea pigs, rats, chicks and, in addition, a whole human brain. Montagu found in all brain homogenates a new catechol compound. She identified it with 3,4-dihydroxyphenyl-ethylamine, i.e. DA. The amounts of this DA were in all species roughly equal to those of NA [6]. According to Blaschko's reasoning, this pointed to DA having an own physiological role in brain function.

The discovery that DA – the substance whose “own regulating function” in the body I was just then trying to test experimentally in Blaschko's laboratory – occurred in substantial amounts in the brain, excited me enormously.

After returning, in February 1958, from Oxford to Vienna's Pharmacological Institute, I immediately

started studying the actions of several centrally acting drugs, among them the parkinsonism-inducing chlorpromazine, on the whole brain levels of DA in the rat [7]. To do this study, I found myself forced to set up from scratch (using pieces from published information) the whole biochemical/analytical methodology; this included purification of the brain tissue extracts and separation of DA from NA and adrenaline by means of ion-exchange chromatography on Dowex 50-X 8 columns [8] as well as establishing a specific chemical DA assay procedure. Although this was a labourious and tricky “exercise”, it proved crucial for my later work with human brain tissue, including brains of patients with PD.

THE “WHOLE BRAIN DA” OFFERS ITSELF TO SOME SOUND NEUROPHARMACOLOGY

Kathleen Montagu’s discovery triggered immediately hectic experimental activity about some basic pharmacology of DA in the animal brain. Among the most important studies were (in chronological order):

- Sep/Oct 1957: L-DOPA produces “. . . due to DA formed from it” central excitation and abolishes the (anesthesia-enhancing) action of reserpine [9];
- Nov 1957: Intracellular DA distribution in brain-stem demonstrated [10]
- Nov 1957: D,L-DOPA abolishes reserpine “tranquillization” due to “an amine formed from it” [11];
- Dec 1957: L-DOPA increases brain “catecholamine levels” [12];
- Feb/May 1958: Reserpine depletes the brain of DA and L-DOPA restores the DA levels to normal [13, 14].

It can be easily seen that, taken together, the above studies suggested an important role for brain DA as a target of several centrally acting drugs. However, at that stage of brain DA research nobody knew or wrote anything about a physiological role of DA in brain function. This early period of experimental brain DA research can thus be characterized as representing ‘research on pharmacology of brain DA without knowledge of DA’s neuro(brain)physiology’. This situation may sound odd, but it is not for the first time in the history of medical research that ‘pharmacology paved the way for physiology’.

Leafing, after more than a half-century, through those brain DA and L-DOPA studies, especially the studies specifically involving reserpine-treated animals, I am puzzled by their evident lack of an explicit reference to reserpine’s major neurological side effect, i.e. the “reserpine parkinsonism”, at that time already well-known as a serious side effect of reserpine in human subjects. Perhaps it was the above mentioned lack of knowledge of the functional aspects of brain DA, together with the stereotype thinking of reserpine being chiefly a “tranquilizer” drug (see “reserpine sedation”) that led the thinking of many astray and blinded all of us to the plainly visible physical brain dysfunctional aspects of the reserpine-induced loss of brain DA.

JUST AS IN LIFE, SO ALSO IN RESEARCH, THERE IS NOTHING MORE USEFUL THAN FOLLOWING GOOD EXAMPLES – THE DISCOVERY OF STRIATAL DA

Such good example for brain DA was Marthe Vogt’s demonstration of NA’s regional distribution in the dog brain [15]. Although the presence of NA (and adrenaline) in extracts of the whole mammalian brain was first observed by von Euler [16] and Holtz [17] in 1946, the amounts found were so modest that the amine was thought to be contained mainly in the noradrenergic nerves innervating the walls of the cerebral blood vessels. This changed dramatically when Marthe Vogt showed in her 1954 study that brain NA had a highly uneven distribution pattern, with highest levels in the hypothalamus. This landmark study very convincingly demonstrated the vital importance of studying the regional distribution of neurotransmitter-like substances in the brain, in order to understand their physiological role in brain function. In this very specific way, this study can rightly be looked upon as a model for all subsequent studies in the field of brain neurotransmitter research.

Following the example of Marthe Vogt’s 1954 brain NA study, at the beginning of 1959 both Bertler and Rosengren [18] and Sano et al. [19] published practically at the same time (January/February) observations on the regional distribution of DA in the dog and human brain, respectively. They found that about 80% of the total brain DA was concentrated in the striatal nuclei caudate and putamen.

Both research groups mentioned, for the first time in printed literature, the possible relevance

of their observations to extrapyramidal/parkinsonian dysfunctions. This suggestion also Carlsson made at a symposium in December 1958, at which he presented the still unpublished results of Bertler and Rosengren; his presentation appeared in print about six months later, in June 1959 [20].

(As an aside, it is somewhat surprising to note that neither of the three research groups found it necessary to quote or refer to Kathleen Montagu's fundamental discovery of DA's occurrence in the brain [6], which clearly implied the amine's own physiological role in brain function. [Montagu's study had been published in "Nature" one and a half years earlier!])

IT WAS AS IF SOMETHING LIKE SCALES HAD FALLEN FROM MY EYES – TURNING FROM THE ANIMAL MODEL TO THE HUMAN BRAIN

I did not have to read the Bertler and Rosengren report twice. In a flash, I saw in my mind the brain DA riddle solved: The clear connection between "the brain DA" – now mainly the "DA in the striatum" – and the central excitation caused by DA's precursor L-DOPA; "the brain DA depletion" – now "the depletion of striatal DA" – and the parkinsonism induced by reserpine; and, as a glimpse of the things to come, the human PD as a "depletion of striatal DA".

It was a matter of one or two weeks to conclude my whole brain DA study in the rat and, turning from working with animal models, go directly to the human brain and see whether there was in PD a striatal DA deficit or not.

I started the human brain project with the collaboration of Herbert Ehringer who had just recently finished his medical studies and wanted to gain some experience in basic research. I made Ehringer responsible for collecting the postmortem brains in the respective pathology departments which involved dissecting the brains (under the supervision of the chief prosectors of the autopsy rooms) and transferring the tissue samples quickly to my laboratory in Vienna's Pharmacological Institute. Myself, I managed the whole analytical work, which included adapting for the human brain tissue the chemical-analytical methodology (Dowex 50-X 8 ion exchange columns) that I had set up for my rat brain study done a year earlier with Georg Holzer [7]. Since Ehringer had some previous experience (in our Institute) with the fluorimetric NA assay procedure, he did the NA assays, whereas I myself performed all the DA

measurements using the adapted von Euler and Hamberg colorimetric procedure [21] that I had learnt one year earlier in Blaschko's laboratory in Oxford. All patient information, all methodology, and all individual DA results I recorded by my own hand, as was the rule in our Institute, in a separate "experimental protocol note-book".

THE DISCOVERY OF STRIATAL DA DEFICIENCY IN PD – SEEN WITH MY OWN NAKED EYE

We started the human brain study in Spring 1959 and finished it in early July 1960. It was comparatively slow work, leaving us sufficient time for some other projects done in parallel. When by the end of 1959 we had analyzed three PD brains and wanted to write up the results for publication, Professor Franz Brücke, the head of our institute, wanted us to analyze another three PD brains "just to make sure that your results are not due to some artefact". This requirement cost us another six months of work. For the final study we analyzed 6 PD brains, 17 control brains, 2 Huntington's disease brains, 5 brains of patients with extrapyramidal symptoms of unknown etiology, 1 infant and 1 neonate brain. We measured, thanks to Ehringer's perseverance in dissecting the brains, the two monoamines (DA and NA) in 19 subcortical regions in control brains; and in caudate, putamen and pallidum in the six PD brains. Only the six PD cases had severely reduced DA levels in caudate and putamen. In the hypothalamus, the NA levels measured by Ehringer, were also subnormal, but not as much as the striatal DA. Since for the detection of DA in the brain samples, always done by myself, I used the von Euler and Hamberg iodine color reaction [21], the presence of DA gave a very distinct pink color. Therefore, I could see by the lack of the pink color in the samples of PD patients, the striatal DA deficiency in PD – for the first time ever – with my own naked eye!

AN UNFORESEEN INCIDENT ROBS PD OF AN HISTORICAL DOCUMENT

We finished our study in mid-summer 1960. At that time, Ehringer was already making preparations to leave our institute and move permanently to the Pharmacological Institute of the University of Innsbruck. I asked him to quickly write up the results in a first draft of the paper. For that purpose,

I handed over to him my “experimental protocol note-book”.

In the beginning of September 1960, the first draft of the paper was on my desk – but to my great alarm, my “experimental protocol note-book” was not there. “It somehow got lost” was the reply to my urgent requests. To make things worse, it soon turned out that the postmortem brain material, including PD brains, was to be redirected from us in Vienna to the Pharmacological Institute in Innsbruck. The Head of our institute, Professor Brücke – who had been personally involved in procuring for us the postmortem material – was angered by this incident to such a degree that he wrote a firm “explanatory” letter to his counterpart in Innsbruck, Professor Heribert Konzett, with the result that both the brains and the “Human Brain DA/PD project” – being my intellectual property – remained in Vienna’s Pharmacological Institute.

And that is how it came to pass that our joined 1960 paper resulting from my brain DA/PD project, was the first and, sadly, the last on this subject bearing also Ehringer’s name. Alas, my “experimental protocol note-book” – the evidence – has not turned up to this day. What a loss for the history of PD!

Be that as it may, at the time when these strange incidents were happening, I did not waste much of my time brooding about “the enigma of the human nature”, as the idea of replacing the missing DA with L-DOPA in patients with PD was already crystallizing in my mind.

BETWEEN THE STRIATAL DA DEFICIENCY AND THE PATIENT – A VERY SHORT RESPITE ONLY

After Ehringer’s departure from Vienna, I was left with the first draft of our paper in my hands that now needed to be carefully revised before I could submit a manuscript suitable for publication. This was not so simple considering that I was left without my “experimental protocol note-book” that had “somehow got lost”. After eventually converting the draft into a publishable manuscript I sent it off, at the end of September 1960 to the German “Klinische Wochenschrift” in Berlin. The paper was immediately accepted and appeared in print three months later in record time, in the December 15, 1960 issue of the journal [22].

The results of our, for its completeness remarkable study, were immediately accepted by the research community and never put in doubt. They have become

common textbook knowledge. For the first time ever, a specific chemical abnormality was found in a specific region of the human brain, in a specific neurodegenerative brain disorder. This discovery has become a model for all subsequent research into the causes and treatments of neurodegenerative disorders in general.

Even before our paper came out in print, I convinced myself in November 1960, that now was not the moment for wasting time and to relax; rather it was high time to take the practical step “from (striatal) homogenate to the patient”.

“THE L-DOPA MIRACLE”

If the adage that “the most incredible thing about miracles is that they happen” [23] needed proof, the “L-DOPA effect” in the PD patient would convince even the most recalcitrant unbeliever.

The idea of using L-DOPA, the biologic precursor of DA, in the patient came quite natural to me. Besides all the available evidence from the laboratory studies, at that time my thinking was still very much influenced by the special emphasis that had been placed on patient-oriented research during my medical studies at the University of Vienna in the late 1940s. As Professor Brücke, my teacher in pharmacology, used to put it in a nutshell: “Pharmacology is about helping people, not just about rats”.

In November 1960, I proposed to the neurologist Walther Birkmayer an acute clinical trial with iv injections of up to 150 mg L-DOPA. Birkmayer was the head of the neurology ward of the largest (at the time) “Home-for-the-Aged Wien-Lainz”. Consequently, he had a sizeable population of permanently housed PD patients and rich clinical experience with this disorder. Because of earlier disagreements, Birkmayer actively delayed (“sabotaged”) my proposal for something like eight months. At the beginning of July, 1961, he finally injected the first patients with L-DOPA. The effect was so stunning that Birkmayer immediately called me up and asked to come and see for myself. I came – and saw the “L-DOPA miracle” happen right before my own eyes.

After testing the action of iv L-DOPA in 20 patients, we wrote up the results and submitted the short report to “Wiener Klinische Wochenschrift”, the (at the time) official Journal of Vienna’s Medical Society. We also made a film in order to document what we called the “L-DOPA-Effekt bei der Parkinson-Akinese” [24].

Our report came out in print in November 1961. The original description of the “L-DOPA effect” reads as follows:

“The effect of a single iv administration of L-DOPA, was, in short, a complete abolition or substantial relief of akinesia. Bed-ridden 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 pallialia 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” [24].

Both this 1961 report and the preceding 1960 study demonstrating the striatal DA deficiency in the PD brain were written in German. They were twice republished in English translations: in 1974 in a book [25], and in 1998 in a neurological journal [22, 24].

Coincident with our L-DOPA study in Vienna, Ted Sourkes, an eminent catecholamine expert of the by-gone era, and his assistant Gerald Murphy in Montreal suggested to the neurologist André Barbeau a clinical trial with L-DOPA given orally (100–200 mg). They published their report in 1962 in which they state that “...In all cases with Parkinson’s disease L-dopa ameliorated the rigidity, especially when combined with an inhibitor of monoamine oxidase” [26]. Within the same time-span, a third encouraging report on iv L-DOPA by Franz Gerstenbrand and Kurt Patejsky came out from Vienna’s University Department of Neurology and Psychiatry [27].

TOO EARLY FOR L-DOPA COMMERCIALIZATION?

We explicitly called the action of iv L-DOPA an “effect”, because we were well aware of the fact that the short-lived action of the iv injected L-DOPA was unsuited as a continuous mode of long-term drug application in the treatment of a chronic condition such as PD. But we never for a moment doubted the actual existence and reality of the “L-DOPA miracle” nor L-DOPA’s future as an antiparkinson drug.

Very soon, our firm belief in L-DOPA appeared to be rewarded when in the Fall of 1961, the “Regional Scientific Director” (Europe) of the Squibb Insti-

tute for Medical Research, Brunswick, NJ, USA, Rudolph Weissgerber passed through Vienna and, as was his routine, visited our Pharmacology Institute. I showed him our film on the “L-DOPA-Effekt” in PD patients. Dr. Weissgerber was immediately highly impressed and greatly interested. A few weeks later, we exchanged several letters in which I expressed my ideas on how I thought to improve the clinical use of the iv L-DOPA, whereupon a “Confidentiality Agreement” between the Squibb Institute and me was signed. In fact, immediately prior to this, Dr. Alfred Pletscher, the Director of Research at Hoffman-LaRoche, Basel, from whom I had been receiving the L-DOPA for our iv injections, invited us to Basel for a confidential conference with the company’s experts. We came, October 26, 1961, and were met by a group of leading members of the brain monoamine research and the marketing departments. I gave a lecture explaining the crucial significance of the striatal DA loss for PD and the importance of L-DOPA as a pharmacological agent. We showed our film on the “L-DOPA-Effekt”, and Birkmayer very convincingly pointed out the therapeutic aspect of the L-DOPA as a completely new approach to drug treatment of the disease. The company’s researcher listened to us attentively and looked thoughtful – yet the marketing experts plainly said that the PD market was far too small to justify the risks of going into the business of commercializing a non-patentable substance such as L-DOPA. So, we left Basel exactly as we had come, with the generous assurance of additional free of charge samples of iv L-DOPA injections “for further studies”.

FOR L-DOPA THE ASCENT TO THE TOP WAS NOT AS SMOOTH AS IT MIGHT APPEAR TODAY

Despite the striking results of the three earliest L-DOPA studies – two from Vienna, one from Montreal – it was not until George Cotzias, in New York, well aware of, and explicitly referring to the Vienna and Montreal studies, introduced in 1967 L-DOPA into clinical routine practice by giving the drug orally in high gradually increasing daily doses [28]. This “Cotzias regimen” [29], which is basically still used today, converted our dramatic short-lasting iv L-DOPA antiparkinson effect into a sustained dramatic improvement by oral L-DOPA.

Nevertheless the road to this final victory in the L-DOPA drama, whose first act had started in 1961 in

Vienna, with New York being the scene of its last act, was a hard uphill battle. Although our 1961 L-DOPA report was followed by several in principle confirmatory studies, the overall reaction of the clinical neurological community remained from skeptical to openly negative. There were many factors involved in the negative clinical studies, among them diagnostic problems; difficulties with patient selection, or unsuitable trial conditions; a good example of the latter being Isamu Sano's report who – after finding in the summer of 1959 low DA in a single PD brain – injected two patients with 200 mg iv L-DOPA [30], but did not perform a proper evaluation of the clinical effect of L-DOPA – instead he kept the patients supine on the examining table, being "... more interested in ... subjective complaints" [31] and, not surprising, concluding that "... treatment with L-DOPA has no therapeutic value" [30].

Notwithstanding the undeniably superior and sustained antiparkinson efficacy of L-DOPA, as clearly established in the patient studies done between the years 1961 [24] and 1969 [29], some prominent brain scientists and neurologists remained unconvinced, finding the "L-DOPA miracle" simply unbelievable ("How can such a simple chemical ...?") or doubting the striatal DA replacement rationale (for references, cf. [32]). Nonsensical doubts were even raised about the DA formed from L-DOPA being the active agent responsible for the drug's therapeutic and/or side effects [33, 34]; or even doubting that in the human brain any significant amounts of DA could be formed from L-DOPA, claiming that the human brain was practically devoid of any L-DOPA decarboxylase activity [35]; a claim elegantly disproved in my former laboratory in Toronto by Ken Lloyd [36, 37].

In this confusing situation I found myself right in the middle between the diverse factions and opinions. Each of the opposing parties was trying to quote me for their own purposes, in support of their own divergent views – more often than not by misinterpreting or misreading my clear statements on L-DOPA. So, now and then, I was surprised to find myself quoted as if saying that at times even I, "Hornykiewicz, did not believe in L-DOPA".

The many doubts and the confused and critical opinions surrounding L-DOPA were eventually silenced by Donald Calne – an early, never wavering L-DOPA supporter – who demonstrated that the direct acting DA receptor agonist bromocriptine had, in principle, a clinical effect in the patient identical with, though weaker than, that of L-DOPA [38]. The

L-DOPA like clinical effect of direct DA receptor agonists also put to rest the ideas of all those (some of them very prominent DA researchers!) enamoured of the rather strange idea of the DA formed from L-DOPA actually acting as a "false transmitter" (!) on some mysterious non-DAergic (NAergic?) sites in the brain (for lit. see reference [32]).

"ALL'S WELL THAT ENDS WELL"

Although I feel much tempted, I abstain here from a detailed discussion of "Who-said-What" in the "Case of The Many vs. L-DOPA". I very gladly restrain myself because over the many years working together, and suffering the same "ups and downs" we all became very good friends whom I would be unhappy to lose over such trifles – and I sincerely hope that all of them are still with us. Instead, let me call upon my friend Roger Duvoisin, one of the earliest L-DOPA clinicians, to say a few words pertinent to the "L-DOPA case":

"The critical observer of these early therapeutic experiments could only conclude that L-dopa was perhaps deserving a further study. In retrospect, it seems apparent that the uncertain results reflected the small doses used and the lack of adequate controls ... However, the early uncontrolled observations of Birkmayer and Hornykiewicz were clearly correct and consistent with more recent observations on the effect of the intravenous administration of levodopa whereas the conclusions drawn from properly controlled trials proved to be misleading" [39].

A VALEDICTION

Let me now, on taking leave from you, turn the clock two hundred years back and listen to what the leading actor in this PD drama, Doctor James Parkinson – silent up till now – may be murmuring to himself while surveying in his mind the drug treatments popular in 1817, and at last putting down in his "An Essay on the Shaking Palsy" the disheartening final judgement that in this disorder "... the use of medicines [drugs] is scarcely warrantable" [40]. And we can easily imagine how much he would be marveling today, and how highly delighted he would be at hearing the tidings about, and seeing with his own eyes the "miracle" worked again and again by L-DOPA, today's gold standard of drug treatment of PD – as a single drug so far unsurpassed and, in my judgement, unsurpassable.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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