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Ildiko Miklya: The History of Selegiline (-) Deprenyl the First Selective Inhibitor of B-Type Monoamine Oxidase and the First Synthetic Catecholaminergic Enhancer Substance

Collated by Olaf Fjetland

This collated document includes Ildiko Miklya's essay, "The History of Selegiline/(-)-Deprenyl the First Selective Inhibitor of B-Type Monoamine Oxidase and The First Synthetic Catecholaminergic Activity Enhancer Substance," posted on March 13, 2014, and the exchange that followed the posting of this essay.

Three participants exchanged a total of seven postings, including three postings by Ildiko Mikya and two postings each by Samuel Gershon and Ervin Varga. The last entry in this exchange was made on February 19, 2015.

This collated document is now open for a final comment to all INHN members.

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Collated by Olaf Fjetland (July 27, 2017)

Ildiko Miklya: The History of Selegiline/(-)-Deprenyl the First Selective Inhibitor of B-Type Monoamine Oxidase and The First Synthetic Catecholaminergic Activity Enhancer Substance

(-)-Deprenyl (D) was developed in the early 1960s by Joseph Knoll, professor and head of the Pharmacological Department of the Semmelweis University in Budapest (Hungary). Knoll, a survivor of Auschwitz and the Dachau death train (Dunn, 1988), started in the early 1950s his behavioral studies on rats: (*i*) aiming to understand the mechanism of the manipulability of the behavior of the most developed, domesticable mammals; (*ii*) to find reasonable explanation why humans possess the most manipulable brain among all living beings on earth; and (*iii*) to throw light upon the role of the manipulability of human behavior in the birth and development of the human society. He summarized his findings and conclusions in three monographs (Knoll, 1969, 2005, 2012).

The early resounding success of his work was the discovery that manipulability of behavior appeared with the development of species capable to fix acquired drives. The rat for example possesses this ability; the mouse is devoid of it.

He realized from the very beginning the extraordinary importance of the catecholaminergic brain machinery (he called it: *the engine of the brain*) in the fixation of acquired drives. To stimulate the brain engine he used amphetamines as experimental tools. His problem with the amphetamines was that as soon as the dose surpassed the 1-2 mg/kg level they blocked purposeful behavior, because the drug-induced continuous, irresistible release of catecholamines from the intra-neuronal stores in the brain stem neurons resulted in aimless hypermotility. He decided to start a structure-activity-relationship (SAR) study in an attempt to develop an amphetamine-derivative devoid of this unwanted effect. Amphetamine and methamphetamine are long-acting synthetic analogues of β-phenylethylamine (PEA). In order to change substantially their pharmacological profile, Knoll decided to combine in the same molecule the structural features of methamphetamine and pargyline, the newly developed monoamine oxidase inhibitor (MAOI). It was the propargyl group in pargyline which by making a covalent binding with the flavin in the enzyme inhibited monamine oxidase (MAO) activity irreversibly. He designed a series of new structures and asked Mészáros, his close friend, the research director of Chinoin, the Hungarian pharmaceutical company, to contact him with a chemist experienced in the synthesis of phenylethylamines and pargyline. Zoltán Ecsery synthesized about 30 of the compounds designed by Knoll, who selected for the detailed studies E-250, as the one fitting best with his expectations. E-250 was later named deprenyl, to emphasize that the compound was planned for treating depression.

The first publication on E-250 appeared in 1964 in Hungarian, followed by a paper in English in 1965. For further pharmaceutical development Knoll chose the (-)-enantiomer. (R)-N-methyl-N-(1-phenylpropan-2-yl)prop-1-yn-3-amine [Selegiline, (-)-Deprenyl, Eldepryl, Jumex, Zelepar, Emsam, Anipryl, and about 100 further trade names]. Selegiline is the presently world-wide available drug, registered in 63 countries to treat Parkinson's disease (PD), Alzheimer's disease (AD), major depressive disorder (MDD) and also used as a prophylactic anti-aging compound to slow the age-related-decline of the catecholaminergic brain engine (Knoll, 2012).

Knoll designed originally to use D as a new antidepressant and asked his close friend, the psychiatrist Ervin Varga, who worked that time in the Semmelweis University, later in the USA, to perform a clinical study with E-250. Already in 1965 a preliminary note on the promising clinical trial with racemic E-250 in depressed patients was published in German (Varga, 1965). The first paper showing that racemic E-250 is an efficient prompt acting antidepressant was published in English in 1967 (Varga and Tringer, 1967). The first clinical trial with (-)-E-250 (later named Selegiline) in depressed patients showing its significant antidepressant effect was published in 1971 (Tringer et. al., 1971). The finding was later confirmed in a couple of papers; nevertheless, Selegiline was first registered as an antidepressant only in 2006 in the USA. Emsam is the first transdermally applied antidepressant (Bodkin and Amsterdam, 2002).

Knoll discovered in 1967 that D is a unique MAO inhibitor which, in contrast to the known ones, does not potentiate the catecholamine releasing effect of tyramine. Thus he realized that his compound must be free of the "cheese effect". The hypertensive crisis associated with the ingestion of high amounts of tyramine in cheese, the metabolism of which is inhibited by MAO inhibition, restricted in the early 1960s the clinical use of the MAO inhibitors. An exact analysis of this nature of E-250 was published in 1968 (Knoll et al., 1968). Knoll asked Varga to perform a rapid test investigating the safeness of E-250. Varga found that, as expected, even provocative cheese consumption failed to produce headache or hypertensive crisis. This finding was cited as a personal communication in the Knoll et al. paper (1968), but since Varga left Hungary, the work was not brought to fullness and was never published. The first two publications which exactly proved that D is free of the cheese effect in humans were published in 1978 in England (Elsworth et. al., 1978; Sandler et. al., 1978).

Knoll realized in 1970 that D is a highly selective inhibitor of B-type MAO and presented his finding at the First International MAO Symposium, held in Cagliari (Sardinia, Italy) in 1971. The first paper which described this novel property (Knoll and Magyar, 1972)

has become ten years later a citation classic. D became first famous as a key important experimental tool in MAO research.

The finding that D protects the nigrostriatal dopaminergic neurons from the toxic effect of 6-hydroxy-dopamine (6-OHDA) (Knoll, 1978) was the first proof of the neuroprotective effect of the drug. The finding that D protects the striatum from the toxic effect of 6-OHDA *via* the blockade of B-type MAO, the inhibition of the uptake of 6-OHDA into the neuron, the facilitation of scavenger function, and the improvement of the removal of the neurotoxic free radicals (Knoll, 1987) catalyzed the discovery that D is significantly enhancing scavenger function in the striatum. Knoll's discovery that D-treatment significantly enhances in the striatum of both male and female rats the activity of superoxide dismutase (SOD) (Knoll, 1988), was soon confirmed (Carillo et. al., 1991), and D-induced enhancing of scavenger function was analyzed later in detail in series of papers. It was later described in dozens of papers that D protects neurons against a variety of neurotoxic agents:1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), DSP-4, 5,6-dihyroxyserotonine, AF-64A (Ebadi et al. 2002), and enhances the production of neurotrophins which are natural protective agents of neurons (Shimazu et. al., 2003).

The first clinical trial with D, published in Lancet, proved that, in contrast to the known MAO inhibitors, D can be safely combined with levodopa and with this combination the levodopa sparing effect was achieved in patients without signs of significant hypertensive reactions (Birkmayer et. al., 1977). This paper and the following Lancet Editorial (1982) initiated the world-wide use of D in PD.

Knoll presented first in his lecture at the Second Strategy in Drug Research IUPAC-IUPHAR Symposium held in Noordwijkerthout (The Netherlands) in 1981 his concept that preventive D medication which facilitates dopaminergic and trace-aminergic activity in the brain is a reasonable strategy to improve the quality of life in the latter decades (Knoll 1982). He presented first in his lecture at the 7th European Symposium on Basic Research in Gerontology held in Budapest in 1983 experimental evidence proving that this effect of D is unrelated to the inhibition of MAO-B (Knoll 1985). To support his concept, Knoll proposed Birkmayer, that time the only clinician who treated long-lastingly hundreds of patients with D, to analyze in retrospect the survival of his patients treated with D. In an open, uncontrolled study the long term (9 years) effect of treatment with Madopar alone (n=377) or in combination with D (n=564) have been compared in parkinsonian patients. The survival analysis revealed a significant increase of life expectancy in Madopar+D group regardless of the fact whether or not the significant demographic differences between the two groups were taken into account (Birkmayer et. al. 1985). The first longevity study with D on the long

living, robust Wistar-Logan rats, starting with two-year old males, was performed between 1985 and 1988. The study furnished unequivocal experimental evidence that prophylactic D-treatment prolongs the life of rats significantly (Knoll. 1988; Knoll et. al., 1989). The finding was soon confirmed on the short living Fischer F-344 strain of rats (Milgram et. al., 1990). D-induced prolongation of lifespan was later further confirmed on rats and demonstrated also on mice, Syrian hamsters, dogs and even on Drosophila melanogaster. Knoll performed with his coworkers a second longevity study with 28-week old Wistar-Logan rats between 1990 and 1994. The aim of this study was to learn how low-dose, lifelong D treatment is influencing the lifespan of low and high performing rats. Out of 1600 sexually experienced male rats the 94 sexually inactive (low performing, LP) and the 99 most sexually active (high performing, HP) rats were selected. The LP rats died significantly earlier than their HP peers and D-treatment eliminated this difference (Knoll et. al., 1994).

In the DATATOP multicenter clinical trial (USA, Canada) in 23 University Institutions, the ability of D and α-tocopherol, antioxidant agents that act through complementary mechanisms were studied, expecting to delay the onset of disability necessitating levodopa therapy (the primary end point) in patients with early, untreated PD. Eight hundred subjects were randomly assigned in a two-by-two factorial design to receive D, α-tocopherol, a combination of both drugs, or placebo, and were followed up to determine the frequency of development to the end point. The study proved that the treatment of *de novo* parkinsonians with D has a unique beneficial influence on the natural history of PD. D-treatment delayed significantly the need for levodopa therapy. The study also revealed that in contrast to the expectation of the authors α-tocopherol was ineffective. The first papers of this study were published in Science and New England Journal of Medicine in 1989 (Tetrud and Langston, 1989; Parkinson Study Group, 1989). The ineffectiveness of α-tocopherol in this study was explained later. D is enhancing the impulse propagation mediated release of dopamine (catecholaminergic activity enhancer - CAE effect), α-tocopherol is devoid of this property (Miklya et. al., 2003).

In the early 1990s Knoll developed (-)-1-phenyl-2-propylaminopentane [(-)-PPAP], the D-analogue equally active with its parent compound but being devoid of the MAO inhibitory property. Zoltán Török performed the chemical work in Chinoin. This study furnished direct evidence that the main effect of D, the specific stimulation of the catecholaminergic brain engine, is unrelated to the inhibition of MAO (Knoll et. al., 1992).

It was analyzed in detail between 1994 and 1996 that PEA acts, in a dose-range below the one which is continuously releasing catecholamines from the intra-neuronal stores, as a

selective enhancer of the impulse propagation mediated release of catecholamines. Amphetamine and methamphetamine the long acting PEA-derivatives act similarly (Knoll et al. 1996a). Since the catecholamine-releasing property of PEA and the amphetamines concealed their CAE effect (Knoll, 2012), this property remained undetected. D, the only PEA derivative free of the catecholamine releasing property which exerts its CAE effect in concentrations below the dose which inhibits MAO-B activity, enabled the discovery of the enhancer regulation in the catecholaminergic neurons (Knoll and Miklya 1994; Knoll et. al., 1996b; Knoll, 1998).

The first two papers demonstrating the beneficial effect of D in AD were published in 1987 (Martini et. al., 1987; Tariot et. al., 1987). Series of clinical studies with small sample sizes confirmed thereafter the usefulness of D in this disease. In 1997 the first controlled trial of D in the treatment of AD was published in New England Journal of Medicine (Sano et. al., 1997).

Based on his finding that tryptamine is like PEA a natural enhancer of the impulse propagation mediated release of transmitters from the catecholaminergic and serotonergic neurons Knoll developed R-(-)-1-(benzofuran-2-yl)-2-propylaminopentane [(-)-BPAP], a tryptamine-derived selective enhancer substance which exerts this effect in femto-picomolar concentrations. The chemical part of the SAR study was performed with a group of chemists in the research laboratory of the Fujimoto Pharmaceutical Corporation (Osaka) led by Fumio Yoneda (Knoll et. al., 1999). (-)-BPAP is an about 100 times more potent CAE substance than D and acts even more potently on the serotonergic neurons. D is an almost selective CAE substance. With the development of (-)-BPAP the proper experimental tool is now available to search hitherto unknown enhancer-sensitive regulations in the brain.

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March 13, 2014

Ervin Varga's comment

When I try to relate my memories about the birth of deprenyl, I have to remind myself that I worked as Associate Professor in Budapest at the Semmelweis University Psychiatric Clinic. I was trained and conditioned to be a clinician with a narrow focus on my patients. I was both a neurologist and a psychiatrist, but I was neither biochemist nor pharmacologist. My exclusive interest was diagnostic evaluation and treatment of patients under my care.

In the 1960s, Hungary was a communist country. We had limited access to literature or exchange with western colleagues. But since the discoveries of the phenothiazines and tricyclic antidepressants in the 1950s, we became involved in drug trials. They were

unsophisticated clinical trials, especially Phase 1 studies with unknown substances, reviewed only by pharmacologists without clinical experience.

At the same time, we had complete freedom with little involvement with drug companies or ethics committees. We were not restrained by cost issues, because there were no grants. Healthcare in Hungary in those days was free. Doing research, we were on our own. +++Depression was the target of our research. Tricyclic antidepressants were fine for many patients, but it took time until they improved and the severity of their depression simply did not permit us to wait. So, we went for ECT. The chairman of my Department was Professor Gyula Nyirö, who with Meduna introduced convulsive treatment in the 1930s. It was still the treatment of choice in severe delusional cases or when we were concerned about suicide. There was need for a faster acting antidepressant, since ECT was not applicable to frail patients with involutional depression. We still did not use muscle relaxants with anesthesia.

I remember my discussion with Joseph Knoll, my old friend and classmate, about the available choices. That was the time when endorphin became the vogue and opiates promised the route to developing the ultimate antidepressant. Knoll did not believe this, and went on the catecholamine path.

He wanted me to examine a group of new substances, phenylethylamines, which he combined with pargyline (all I knew was that this was a sedative antihypertensive drug).
The combination of a stimulant with a sedative reminded me of the once famous Brom Caffeine tablets.

Sometime in 1964, Knoll started to send me experimental samples. First, I took such tablets myself for 1-2 days, and since it seemed harmless, I gave it to patients. If I remember, I gave 5 mg tablets and when no change was noticed, I increased the dose to 15 mg/day, but for no longer than another 5-6 days. When still no improvement was noticeable, I stopped the experimental drug and continued either with Tofranil or ECT. This went on with 5 different patients, one after the other, without any result until the 6th patient showed marked improvement after only 4 days. It was as dramatic as an ECT treatment. I called Knoll, told him the last sample was an antidepressant.

The rest is well described by Dr. Miklya.

August 7, 2014

Ildiko Miklya's reply to Ervin Varga's comment

Thank you very much Dr. Varga for your comment. The relatively slow international acceptance of deprenyl (selegiline) in the treatment of depression is difficult to understand considering the world wide use of selegiline in increasing amounts supported by thousands of publications. Professor Knoll is working now on his new book ("*The enhancer regulation in*

the mammalian brain") from which two paragraphs presented with his permission below should provide a better understanding of the story of selegiline in psychiatry.

"Unfortunately, Hungary was in 1960s cut from the western world, we worked isolated from the mainstream of science and our results remained almost unnoticed. Since our studies confirmed that E-250, now known as selegiline, is antagonizing the effect of tyramine, I asked my good friend and classmate, Ervin Varga, who worked as a psychiatrist in our University Clinic, to test in a preliminary trial the antidepressive effect of E-250 and also the lack of the 'cheese effect'. Varga published in 1965 a preliminary note (in German) on the promising results of a clinical trial with racemic E-250 in depressed patients (Varga, 1965). He wrote with his coworker the first paper, in English, showing that racemic E-250 is an efficient, prompt acting antidepressant (Varga and Tringer, 1967). They wrote in 1971 the first paper demonstrating that E-250, is a potent antidepressant (Tringer and Varga, 1971). In retrospect it is almost incredible that selegiline was first registered as an antidepressant only in 2006 (luckily in the USA: Emsam), though our first paper which proposed this indication appeared in the Hungarian version in 1964 and in the English version in 1965 (Knoll et. al., 1964; 1965).

Varga also found that in harmony with our findings in animal experiments, E-250 was free of the cheese effect in humans. This finding was cited in the discussion of our paper published in 1968 as follows: 'Even provocative cheese consumption failed to produce headache or hypertensive crisis' (Knoll et. al., 1968). Since Varga left Hungary for the USA, where he still lives, he never continued his clinical studies with selegiline. His convincing preliminary study which confirmed that E-250 is devoid of the 'cheese effect' was never completed and remained unpublished. It marks the era in Hungary in the 1960s that in the discussion of the Knoll et al.1968 paper also two other Hungarian studies are mentioned which confirmed that E-250 was devoid of the 'cheese effect' (Kardos and Füredi, 1966). None of them were completed, but later performed studies confirmed the correctness of their observation. The validity of my proposal that deprenyl must be free of the 'cheese effect' was tested with perfection in volunteers by Sandler and his co-workers and published in 1978. They confirmed that in harmony with our findings in animal experiments, (-)-deprenyl is in humans an MAO inhibitor free of the cheese effect. After pretreatment with deprenyl, parkinsonian volunteers who received levodopa or levodopa+carbidopa suffered no adverse pressor reaction after challenged with oral tyramine in considerably greater amounts than the dose likely to be encountered in a normal diet" (Elsworth et. al., 1978; Sandler et. al., 1978).

Let me again thank you for sharing with us the story of the first experiences with deprenyl in humans.

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November 27, 2014

Samuel Gershon's comment on Ildiko Mikya's reply to Ervin Varga's comment

I agree with Dr. Miklya that early clinical research with selegiline in psychiatry was done at a difficult time in Hungary. However I don't think that the difficulties encountered in the introduction of deprenyl in the treatment of depression can be attributed entirely to those difficulties. In my Psychopharmacology Research Unit at New York University we also did open studies, like the Hungarian investigators with selegiline in the 1970s and we found that it had only a minimal effect in inpatient depression. Probably an even more important contributing factor was that the Hungarian investigators were not able to provide findings from double-blind controlled studies. This alone would explain the little interest in the drug outside of Hungary. Finally, I think the most important contributing factor to the delay in the introduction of selegiline in the treatment of depression was the *publicity* of other antidepressants in the West, The intensity and the funding for advertising a new claimed therapeutic agent in the USA is colossal. Direct advertising of drugs in some countries still prohibited whereas in the USA it is perfected to the extent that a patient with a particular set of depressive symptoms could ask their doctor to prescribe one or another antidepressant.

December 11, 2014

Ildiko Miklya's reply to Samuel Gershon's comment on her reply to Ervin Varga's comment

Thank you Professor Gershon for commenting on my reply to Dr. Varga. It was in 1979 when I started working in the Knoll Institute. Deprenyl was already used as an experimental tool in MAO research as the first selective inhibitor of B-type MAO. It was in 1977 when Birkmayer et al. demonstrated in their Lancet paper that deprenyl deserves attention as a unique therapeutic agent. Levodopa treatment in Parkinson's disease had various side effects. Birkmayer and Hornykiewicz tried to achieve a levodopa-sparing effect by the concurrent administration of levodopa with an MAO-inhibitor. They were compelled to terminate this trial because the combination elicited hypertensive attacks. Since selegiline was the unique MAO inhibitor free of the cheese effect, Birkmayer combined selegiline with levodopa, and a levodopa-sparing effect was achieved in patients without side effects (Birkmayer et. al., 1977). The levodopa-sparing effect of selegiline is related to the selective inhibition of B-type MAO. The Lancet Editorial "Deprenyl in Parkinson's Disease" in 1982

catalyzed thereafter the widespread use of deprenyl in Parkinson's disease. The antidepressant effect of deprenyl published first by Dr. Varga in 1965 was first confirmed by you in 1980. Your paper with Mann, published in Life Sciences appeared 15 years after the first Varga paper. Yours was the first study that confirmed the beneficial antidepressant effect of deprenyl in the West. But only in 2006 was deprenyl (Emsam) registered in the USA as an antidepressant. By now it is successfully used in therapy. In my reply to Dr. Varga's comment, I tried to explain that in the early 1960s, when Professor Knoll developed deprenyl and clarified its unique pharmacological spectrum, this important discovery passed almost unnoticed. Only in the mid-1970s when the chances to develop personal contacts with colleagues in the West, did opportunities for Hungarian scientists brightened. I feel honored by and appreciate your informative comment.

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January 22, 2015

Ervin Varga's comment on Samuel Gershon's comment on Ildiko Miklya's reply to Gershon's comment on her reply to Gershon's comment

Last time we had a discussion on deprenyl (D) was in the company of George Simpson and Arthur Sugerman, while Don Gallant introduced his famous crepes. I appreciate your convincing comment concerning the destructive effect of marketing. As far as your negative comment on D's antidepressive effect - the answer is more complicated. I am not aware of any blind comparative study on D. Even if so, an intriguing question in clinical psychopharmacology is how the same drug may produce a different outcome in different blinded studies. An important meta-analysis of efficacy studies comparing new generation antidepressants in Lancet (2009) showed clinically important differences among commonly

prescribed antidepressants. The therapeutic value and the popularity of a drug does not go necessarily hand-in-hand. We clinician are relatively humble, when it comes to administering treatment. It is only occasionally that our first choice of drug lifts severe depression in patients. And I have had patients who did not respond to any antidepressant but to D although that is not always the case. I trust the drug because it has been tested by other psychiatrists as required by the FDA, but the ultimate judgment must be based upon actual clinical response in patients. I remember our discussion and I admired your logic and forthright expression of your opinion. I feel honored to be involved in scientific interaction with you.

January 29, 2015

Samuel Gershon's reply to Ervin Varga's comment on his comment on Ildiko Miklya's reply to Varga's comment

I am sure that your first hand observation of the clinical effects of Deprenyl are very important and possibly the field does not have the data currently to define the really objective efficacy of Deprenyl. The FDA requires at least 2 double-blind randomized clinical trial to establish efficacy and if you have a wealthy company to supporting the studies on a compound they could do 9 clinical trials and if only 2 show significant efficacy they win the game and have a marketable product. This game has been played with many claimed "antidepressants" and that is why we are in a mess.

February 19, 2015