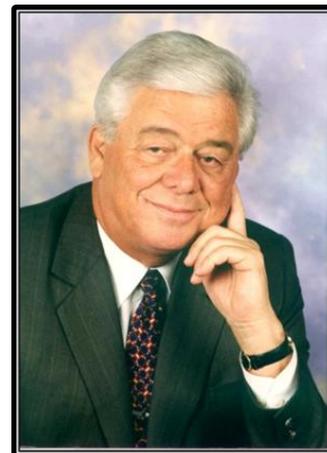


In Memoriam

Joseph Knoll (1925 – 2018)

Ildiko Miklya



Joseph Knoll passed away on April 17, 2018.

He lived a long, struggling but meaningful, marvelous life. He was one of the internationally best known Hungarian pharmacologists and a prominent talent of modern neuropharmacology, full of vitality and with a very strong, independent personality. He was not only a hard and efficiently working, productive scientist, but also an unusually cultured person. The scientific world lost one of the pioneers of the field of neuropsychopharmacology.

Early life and Education

He was born in May 30, 1925, in Kassa, Hungary (now Kosice, Slovakia), to Blanka Deutscher and Jakab Knoll. In the second World-War he lost his family, his parents and his brother. He was one of the 1,300 survivors of the Death Train that reached Dachau on April 27, 1945 (Dann 1998). Returning to his native city of Budapest and recovering from the man's trying condition, he wanted to be physician and he matriculated in the Pázmány Péter University, Faculty of Medicine, Budapest (from 1951 University of Medicine, Budapest; from 1969 Semmelweis University of Medicine; from 1999 Semmelweis University). After medical studies he earned MD degree in 1951.

Career and research

From 1949-1951 he was Teaching Assistant in the Department of Pharmacology of the University of Medicine, Budapest (now Department of Pharmacology and Pharmacotherapy Semmelweis University, Faculty of General Medicine), invited by Bela Issekutz, the Head of the Department. In his memories of 45 years in research he remembered: "In 1949 the laboratory was poorly equipped but compensated by enthusiastic day and night research activity. The spirit of the department was exciting. Dipping into experimental work made me unbelievably happy." After getting his Medical Diploma, he decided to stay on in the

department and he never left (Knoll 1994). In the next seven years (1951-1958) he worked as an Assistant Professor and later as a Docent (1958-1962). In 1963 he became Chairman of the Department of Pharmacology. Knoll started researching the brain from an original new angle. Unexpected findings soon convinced him that with the evolution of brains capable of acquiring drives species appeared whose members could manipulate each other's behavior and act in concert. He worked for 16 years to better understand his results and described in 1969 his theory in his first monograph: *The Theory of Active Reflexes* (six editions were published in English and held by 208 libraries worldwide) (Knoll 1969). From 1993 until 2004, he worked as a Scientific Adviser of the Department and for the last 14 years he was Professor Emeritus at the University.

After 35 years of further experimental analysis, he summarized his lifework in his second monograph: *The Brain and Its Self* (Knoll 2005) (16 editions were published in English and held by 399 libraries worldwide). This monograph concluded that the appearance of the mammalian brain with the ability to acquire drives ensured the development of social life and eventually led to the evolution of the human society. This most sophisticated form of organized life on earth is still in the trial and error phase of its development. It seeks to outgrow the myth-directed era of its history and come to its final state, the ration-directed human society (Knoll 2005).

He described the details of his work published with his pupils in 894 papers (citations: 10,055) and was the originator of 55 patents. Many of his co-workers and pupils became well-known doctors and scientists.

His work gave birth to the recognition of previously unknown brain mechanisms some of which resulted in the development of new drugs. The best known of his discoveries of practical importance is Deprenyl (Selegiline) which he developed in the early 1960s (Knoll et al. 1965). This drug is described in thousands of research papers and is registered in more than 60 countries, including Japan, where the Fujimoto Pharmaceutical Company placed it on the market. Since 1990 Knoll has worked in close collaboration with the Fujimoto Research Laboratory. He has developed with them R-(-)-1-(benzofuran-2-yl)-2-propylaminopentane (BPAP) the presently known most potent and selective enhancer substance (Knoll et al. 1999).

Deprenyl became available worldwide as the first selective irreversible inhibitor of B-type monoamine oxidase (MAO) (Knoll and Magyar 1972). Knoll realized later that phenylethylamine (PEA), the physiologically highly important trace amine in the brain known as a releaser of catecholamines, is in low concentration a peculiar catecholaminergic activity enhancer (CAE) substance, and this is the physiological effect of this trace amine. This effect

remained undetected because the releasing effect concealed it. Deprenyl, the first PEA-derivative devoid of the catecholamine releasing property allowed discovering the enhancer regulation in the brain (Knoll et al. 1996). The development of BPAP, a hundred times more potent enhancer substance than deprenyl, is now the best experimental tool to detect hitherto unknown enhancer-sensitive regulations in the mammalian brain (Knoll et al. 1999).

The age-related decay in the brain's PEA supply, due to the progressive increase of MAO-B activity in the aging brain, and dopamine, due to the better than average decline of the dopaminergic neuronal activity during the post-developmental phase of life, are irresistible biochemical lesions of aging. The deterioration in behavioral performances with the passing of time and longevity depends significantly on the pace of the worsening of these lesions. Deprenyl increasing the supply of the brain with PEA and dopamine counteracts this aging process. Maintenance of male rats from sexual maturity until death on deprenyl slows the age-related decline of learning ability and prolongs life (Knoll and Miklya 2016).

Contribution to society

The development of efficient new spectrum drugs is a true contribution to society. Knoll, as chairman of one of the biggest pharmacological university departments, initiated structure activity relationship studies in collaboration with chemists aiming to develop patentable new spectrum drugs and the search for unknown endogenous substances. Of Note:

- In the early 1950s he developed a battery of tests for the pharmacological analysis and rapid screening of tranquillizers, psychostimulants and psychotomimetics (Knoll and Knoll 1959).
- Developed the pyrido-(1,2a)-pyrimidine family of anagelsic-antiinflammatory compounds; Rimazolium (Probon) was registered in 1976 (Knoll et al. 1971 a,b,c).
- Developed the azidomorphins, a new family of opioid analgesics with peculiar pharmacological spectrum (Knoll 1973).
- Discovered satietins, an endogenous family of anorectic substances, thought to play the role of a rate limiting satiety signal (Knoll 1978, Knoll 1979).
- He was invited in 1981 to introduce the discovery of the satietins in one of the plenary lectures in the 8th International Congress of Pharmacology in Tokyo (the media gave detailed information about this lecture).

- He discovered angiohypotensin, an endogenous substance selectively inhibiting the release of noradrenaline from the intramural sympathetic nerves of the resistance vessels (Knoll 1979).

Up to the present his most efficient contribution to therapy was the development of Deprenyl/Selegiline. At present, more than 100 preparations containing selegiline circulate in the global market under different brand names. Eldepryl, Jumex, Movergan, Anipryl, Zelapar, Emsam are the best-known ones. They are widely used in the treatment of Parkinson's disease, Alzheimer's disease, major depression and as a geroprotective/anti-aging drug. Deprenyl could be combined with levodopa in Parkinson's disease without signs of hypertensive reactions. The "Deprenyl and tocopherol antioxidative therapy of parkinsonism"(DATATOP) Study in the USA revealed that (-)-deprenyl delayed the onset of disability associated with early, otherwise untreated Parkinson's disease (Parkinson Study Group 1996). This unique decrease-modifying effect is due to its CAE effect. Prof. Knoll recently summarized in his monograph, "How Selegiline ((-)-Deprenyl) Slows Brain Aging"(Bentham Science Publishers, 2012), all the experimental and clinical data which support his proposal. In humans, maintenance from sexual maturity on (-)-deprenyl (1 mg daily) is, for the time being, the most promising prophylactic treatment to fight against the age-related decay of behavioral performances, prolonging life and preventing or delaying the onset of age-related neurodegenerative diseases such as Parkinson's and Alzheimer's (Knoll 2012).

A retrospective analysis of the survival of patients treated with madopar(used for the treatment of Parkinson's disease)alone (N=377) and with madopar plus deprenyl (N=564) showed that the supplementation of madopar with deprenyl significantly prolonged the survival of patients. Since the decay of the catecholaminergic machinery with the passing of time plays an obviously important role in brain aging, and there is unequivocal evidence that deprenyl slows the aging of the catecholaminergic system, prophylactic deprenyl-treatment will not only improve the quality of life in senescence but it seems to be a pharmacologically well-founded expectation that the prevalence of Parkinson's disease and Alzheimer's disease might be significantly lower in the deprenyl-treated group than in the placebo-treated one. Over 60 years of age, the occurrence of the most common age-related neurodegenerative diseases, Parkinson's and Alzheimer's, starts to increase because in a sensitive part of the population the decay of some functionally key important neuronal systems surpass a critical level (like the dopaminergic machinery in case of Parkinson's disease), thus the maintenance

of the enhancer regulation on a higher activity level may slow this process. Considering the rapid increase of the population over 65, Knoll's work is a great promise for the future (Knoll 2016).

Awards and honors

Award of Hungarian Academy of Sciences, 1961, 1964

Corresponding member of Hungarian Academy of Sciences 1970

Member of the German Academy of Sciences (earlier Leopoldina Academy of Natural Sciences), 1974

Member of Hungarian Academy of Sciences 1979

Honorary doctor of the Medical Academy of Magdeburg, 1984

National Prize of Hungary, 1985

Honorary doctor of the Bologna University at the occasion of its 900th year anniversary, 1989

Honorary Fellow of the Royal Society of Medicine (London), 1990

Foreign member of the Polish Academy of Art and Sciences, 1995

Award for Distinguished Service in European Pharmacology, 1999

Award for Outstanding Contributions to Anti-Ageing Medicine, 2001

Széchenyi Prize (renamed National Prize of Hungary), 2003

Hungarian Republic's Middlecross Order with the Star, 2010

I had the honor and privilege to work him for 40 years in his lifework. His depth of knowledge and dedication toward his work was exemplary and inimitable.

References:

Dann S, editor. Dachau 29 April 1945, The Rainbow Liberation Memoires. Lubbock: Texas Tech University Press; 1998.

Knoll J. The theory of active reflexes. An analysis of some fundamental mechanisms of higher nervous activity. Budapest: Publishing House of the Hungarian Academy of Sciences, New-York: Hafner Publishing Company; 1969.

Knoll J. Azidomorphine and Rymazolium. An approach to the ideal analgesic. Pharm Res Comm 1973; 5:175-191.

Knoll J. New aspects in the chemoregulation of food intake. Neurosci Lett 1978; Suppl 1: 55.

Knoll J. Satielin: a highly potent anorexogenic substance in human serum. *PhysiolBehav* 1979; 23: 497-502.

Knoll J. Angiohypotensin: a selective endogenous inhibitor of neuromuscular transmission in vascular smooth muscle. In: *Catecholamines: Basic and Clinical Frontiers*. (eds. Usdin E, Kopin IJ, Barchas J), Pergamon Press, New York, Vol. II., pp 1152-1154, 1979

Knoll J. Memories of my 45 Years in Research. *PharmacolToxicol* 1994; 75:65-72.

Knoll J. The brain and its self. A neurochemical concept of the innate and acquired drives, Berlin, Heidelberg, New-York: Springer; 2005.

Knoll J. How Selegiline ((-)-Deprenyl) Slows Brain Aging. Bentham Science Publishers, e-Books, 2012.

Knoll J. Discovery of the enhancer regulation in the mammalian brain and the development of synthetic enhancer substances. A chance to significantly improve the quality and prolong the duration of human life. inhn.org/e-books, 2016.

Knoll J, Ecseri Z, Kelemen K, Nievel J, Knoll B. Phenylisopropylmethyl-propinylamine (E-250) a new psychic energizer. *Arch int PharmacodynThér* 1965; 155: 154-164.

Knoll J, Fürst S, Mészáros Z. The pharmacology of 1,6-dimethyl-3-carbethoxy-4-oxo-6,7,8,9-tetrahydro-homopyrimidazol-methyl-sulphate (MZ-144), a new potent, non-narcotic analgesic. II. Toxicity and analgesic effect of MZ-144 compared to narcotic and non-narcotic analgesics. *Arzneim-Forsch* 1971b; 21: 719-727.

Knoll J, Fürst S, Mészáros Z. The pharmacology of 1,6-dimethyl-3-carbethoxy-4-oxo-6,7,8,9-tetrahydro-homopyrimidazol-methyl-sulphate (MZ-144), a new potent, non-narcotic analgesic. III. Analysis of the central and peripheric effects. *Arzneim-Forsch* 1971c; 21: 727-733.

Knoll J, Knoll B. *MethodezurUntersuchung der spezifischdepressivenWirkung von 'Tranquilizern' auf das Zentralnervensystem*. II. *Arzneimittel-Forschung* 1959; 9: 633.

Knoll J, Magyar K. Some puzzling effects of monoamine oxidase inhibitors. *Adv BiochemPsychopharm* 1972; 5: 393-408. (This week Citation Classic, January 15, 1982)

Knoll J, Miklya I. Longevity study with low doses of selegiline/(-)-deprenyl and (2R)-1-(1-benzofuran-2-yl)-N-propylpentane-2-amine (BPAP). *Life Sci* 2016; 167: 32-8.

Knoll J, Miklya I, Knoll B, Markó R, Rácz D. Phenylethylamine and tyramine are mixed-acting sympathomimetic amines in the brain. *Life Sci* 1996; 58: 2101-2114.

Knoll J, Yoneda F, Knoll B, Ohde H, Miklya I. (-)-1-(Benzofuran-2-yl)-2-propylaminopentane, [(-)BPAP], a selective enhancer of the impulse propagation mediated release of catecholamines and serotonin in the brain. *Brit J Pharmacol* 1999; 128: 1723-1732.

Parkinson Study Group. Impact of deprenyl and tocopherol treatment of Parkinson's disease in DATATOP patients requiring levodopa. *Annals of Neurology* 1996; 39: 37-45.

September 20, 2018