GUEST EDITORIAL: MEDICAL HISTORY

Emil Starkenstein – one of the most important personalities of European continental pharmacology in the period between the two world wars

Jaroslav Jezdinský

Institute of Pharmacology, Faculty of Medicine, Palacký University in Olomouc, Czech Republic

Correspondence to: Prof. MUDr. Jaroslav Jezdinský, CSc.
Medical Faculty of Palacký University in Olomouc
Institute of Pharmacology, Hněvotínská 3
775 15 Olomouc, CZECH REPUBLIC
PHONE: 00420 585 426 811; FAX: 00420 585 632 517
EMAIL: lang@tunw.upol.cz

Submitted: May 21, 2006 *Accepted: May 29, 2006*

Key words: **Emil Starkenstein; biography; bibliography; clinical pharmacology; reprints collection**

Neuroendocrinol Lett 2006; **27**(5):557–561 **PMID:** 16892002 NEL270406X01 **www.nel.edu**

Abstract

Emil Starkenstein (1884–1942), professor of pharmacology at the German Medical Faculty of Charles University in Prague, was not only an exprimental pharmacologist, but also the pioneer of clinical pharmacology. During the World War I (1914–1918) he took advantage of his knowledge of experimental pharmacology for the new approaches to the treatment of bacillary dysentery, cholera and of epidemic typhus fever. In 1918 he published the article "Clinical Pharmacology – Theory and Praxis at the Patient's Bedside", in which he defined the main task of clinical pharmacology as the implementation and verification of experimental pharmacology achievements in clinical therapy. During the period 1921–1933, his scientific interests involved namely analgesic combinations, seasickness therapy and pharmacology of iron. He published more than 240 scientific articles and three textbooks. Emil Starkenstein died on November 6, 1942 as a victim of Holocaust. Starkenstein's collection of more than 20 000 reprints of scientific studies, which has been deposited recently in the Archives of Charles University in Prague is very valuable.

Introduction

Emil Starkenstein (1884–1942), professor of pharmacology and director of the Institute of Pharmacology at the German Medical Faculty of Charles University in Prague (1929–1938) was not only an experimental pharmacologist and the author of a number of original and review articles and of three textbooks. He was also a pioneer in the field of clinical pharmacology. As far back as the First World War, he enunciated and applied the concepts of clinical pharmacology, which he published in 1917 and 1918 [9, 10, 11].

However, Starkenstein's scientific and academic activities are much larger and all the more admirable, as he died at the age of 57 as a Holocaust victim. Relatively little attention has been paid to Starkenstein's personality in the world pharmacological literature in the years following the Second World War. K. Junkmann, professor of pharmacol-

ogy in Berlin published Starkenstein's obituary in 1946 [3]. Later on, three articles dealing with the personality of Emil Starkenstein were published by M. Matoušek [4, 5, 6], professor of the history of medicine in Olomouc (Czech Republic). In 1984, on the occasion of the 100th anniversary of Starkenstein's birth, a Finnish pharmacologist, Kari Senius, compiled an almost complete bibliography of Emil Starkenstein – a list of 243 articles, monographs, and textbooks published in the years 1907–1942 [7]. Starkenstein's tragic fate also inspired Senius to a rendering in the form of a radio play *Guarantee* broadcast in Czech on May 31, 1989 by Prague Vltava station. The importance of Starkenstein in the history of clinical pharmacology was the topic of a short communication of J. Jezdinský and J. Jančíková in 1994 [2]. Another article dedicated to the 120th aniversary of Starkenstein's birth was published in Czech by J. Jezdinský in a local Czech medical journal Klinická farmakologie a farmacie [1]. In the opinion of the author the Starkenstein's personality deserves a more detailed international commemoration. This represents the purpose of this article.

1884–1909 (Undergraduate Studies)

Emil Starkenstein was born on December 18, 1884 in Poběžovice (Ronsperg) near Domažlice (Taus) in southwestern Bohemia. He came from a German-Jewish family with a two-century tradition in the medical profession. After graduating from the German secondary school in Pilsen, he studied medicine at the German Medical Faculty of Charles University in Prague (1903–1909). During his studies, he volunteered at the Institute of Pharmacology of this medical faculty. His teacher there was the then head of the Institute Professor Julius Pohl M.D. In his student years, Starkenstein published at least ten experimental studies [7] dealing with the pharmacology of methylxanthins, metabolism of inositol, and with electrocardiographically documented arrhythmias induced in animals by glyoxalic acid. Starkenstein's lecture, published in a periodical focused on natural sciences *Lotos* (1909) entitled "Vivisection and its opponents" is quite interesting. The readers are informed here that societies calling for a ban on animal experiments at universities operated in Germany, Austria, and Switzerland as early as the 1850s.

1910–1914 (Postgradual Studies)

After his graduation in 1909, Emil Starkenstein continued to work at the Institute of Pharmacology as an assistant lecturer. During his years as an assistant, Starkenstein completed his knowledge of botany and of physical chemistry by external studies at the German Faculty of Philosophy (1911–1912), and spent his two summer vacations (1911 and 1913) as a substitute physician aboard of steamers of the Austrian Lloyd Shipping Company. On this occasion, he was introduced to seasickness, which later became one of his major research topics.

In 1911, Professor Wilhelm Wiechowski was appointed the head of the German Institute of Pharmacology in Prague. In 1909, as a professor of pharmacology in Vienna, Wiechowski became famous thanks to his discovery of adsorption effectivity of animal charcoal. Starkenstein cooperated with Wiechowski in research on possible adsorption therapy of intoxications by various drugs and bacterial toxins. Together, they also demonstrated the strong antiinflammatory effect of a then novel uricosuric agent phenylcinchonic acid (Atophan) in experimental inflammation [8]. By 1913, Starkenstein published at least 44 scientific articles [5,7]. Thoroughly original – and among the very first enzymologic studies – were his articles on the role of diastase in the digestion of polysaccharides, dated 1910–1912 [7]. In 1913, Professor Wiechowski supported Starkenstein's habilitation in pharmacology and pharmacognosy. The habilitation thesis of Emil Starkenstein dealt with the pharmacology of adrenaline and the theme of his habilitation lecture was the upcoming problem of rational drug combinations.

1914–1918 – The First World War (Clinical Pharmacology)

Since the autumn of 1914, Emil Starkenstein, a thirty-year old assistant professor of pharmacology, spent more than four years in the First World War as a physician and commanding officer of the Austrian field infection hospital in Radom (Poland). There, he was presented with an opportunity to make use of his knowledge of experimental pharmacology in the treatment of epidemic typhus fever, bacillary dysentery, and cholera.

When dealing with epidemic typhus fever, Starkenstein's attention turned to autopsy findings, evidencing inflammatory changes in brain and heart arteries resembling periarteritis nodosa. He supposed that the arterial permeability, increased by inflammation, would enable the penetration of hypothetical toxic substances from blood into the myocardial and cerebral tissue, resulting in secondary damage to the organs and in the patient's death. To prevent the increase of blood vessel permeability, he administered high doses of Atophan p.o. and of soluble calcium salts i.v. to patients in early stage of the disease. Thus, he managed to decrease the mortality rate of epidemic typhus patients from 16 percent to 2.5 percent [9].

In the treatment of initial stages of bacillary dysentery and cholera, Starkenstein managed to decrease substantially the period of severe diarrhea by administering high doses of animal charcoal (50–100 g per day), thereby preventing dehydration and resorption of bacterial toxins resulting in circulatory failure. Patients undergoing this therapy tended to recover quickly. The effect of this adsorption therapy could not be induced in the already full-blown stage of the disease [10].

Unfavorable war conditions did not prevent Starkenstein from continuous publishing his findings. Altogether, thirteen Starkenstein's publications dated 1915–1919 are

registered [7]. In 1917, he published an article on the implementation of experimental pharmacology findings in the clinical practice [10]. His most important study written during the war was published in 1918 and entitled "Klinische Pharmakologie. Theorie und Praxis am Krankenbette" (Clinical Pharmacology – Theory and Practice at the patients bedside) [11]. Originally, it was a lecture with the same title, delivered at a meeting of Austrian field physicians in Lublin (Poland) on March 16, 1918. Starkenstein considered clinical pharmacology a perspective branch of medicine, contributing to the development of new rational ways of medical treatment, based on scientific findings of experimental pharmacology. He defined the main role of clinical pharmacology as the transfer and verification of experimental pharmacological research results in clinical practice.

1919–1934 (Collaboration with the Pharmaceutical Industry)

Upon returning from the war, Emil Starkenstein resumed his work at the Institute of Pharmacology in Prague. In 1920, he was appointed associate professor, and in 1929, after the death of Professor Wiechowski, he took charge of the institute as full professor of pharmacology and pharmacognosy.

At first, Starkenstein pursued the search of an optimal analgesic combination of two drugs that would join decreased toxicity with increased final analgesic effect. His experiments resulted in proposing of an additive compound of two molecules of aminophenazone with one molecule of diethylbarbituric acid [12]. Commercial production of this compound as a novel analgesic agent with the brand name *VERAMON* launched in 1922 by a German pharmaceutical company Schering-Kahlbaum A.G. Berlin [13]. At that time, Veramon came to be one of the most preferred analgesic drugs in Central Europe. And it started a prolific and mutually advantageous collaboration between Starkenstein and Schering-Kahlbaum, which lasted for almost twelve years.

Another medication manufactured under the name *VASANO* (va sano = travel sound) and intended for the prevention and treatment of seasickness, was devised by E. Starkenstein in 1927 [14, 15]. It was a combination of camphoric acid salts of anticholinergic agents l-hyoscyamine and l-scopolamine in the ratio of 4:1. Vasano was produced in the form of tablets, suppositories, and injections containing 0.5 mg, 1 mg or 0.25 mg of camphoric acid salts of the above given alkaloids. When developing Vasano, Starkenstein exploited the findings of Příbram and Fischer published simultaneusly in the year 1913. They both evidenced of a certain but unstable therapeutical effectiveness of atropine injections in the treatment of seasickness. Starkenstein speculated about the inability of atropine to prevent vomiting in seasickness effectively due to the presumption that its peripheral vagolytic effect was suppressed by its central stimulation of the emetic center. He supposed that the central suppressing effect of scopolamine would antagonize the unwanted central stimulating effect of atropine or of l-hyoscyamine. Atropine is a racemate representing a mixture of l-hyoscyamine and d-hyoscyamine, in which only the l-form is effective. Therefore, he used pure l-hyoscyamine only. A marked antiemetic effect of Vasano was evidenced experimentally in dogs with apomorphine-induced vomiting. The effectiveness of Vasano in seasickness prevention and treatment was verified by Starkenstein himself for the first time in 1926 in a group of European physiologists and pharmacologists on board of a steamer during the journey to Stockholm where the Twelfth World Congress of Physiology was held. The criterion for effectiveness of the medication in that pilot study was the number of participants taking breakfast in the canteen [15]. Vasano was later proved to be very effective also in the treatment and prevention of other kinetoses. At least two priorities can be attributed to Starkenstein in relation with Vasano: (1) introduction of scopolamine in the treatment of seasickness, and (2) probably the very first therapeutical use of an active enantiomer (l-hyoscyamine) replacing a racemate (atropine). Moreover, the camphoric acid salts of l-hyoscyamine and of scopolamine were not used before and even later at any other occasion. Starkenstein finished this chapter of his research activities in 1932 by publishing an extensive review on seasickness [16].

At that time, Starkenstein was already concerned with the pharmacology of iron. The aim of his research was to evaluate iron compounds useful in the treatment of sideropenic anemia. He discovered that only inorganic compounds of bivalent iron are appropriate; and considered as optimal iron dichloride in stabilized form of tablets. The company Schering-Kahlbaum started to manufacture the drug under the brand name of FERROSTABIL in 1933 [17]. At least 22 articles covering the topic of iron pharmacology were published by E. Starkenstein in the period between 1926 and 1934 [7]. The last one was a voluminous review „Eisen", dated 1934 [18].

FERROSTABIL was the last result of twelve-year cooperation between Starkenstein and the company Schering-Kahlbaum A.G. Berlin, that ended in 1933 [17]. It was the year of Hitler's ascent to power in Germany, followed by the promulgation of the Nuremberg laws shortly thereafter.

1930–1938 (Academic Activities)

Early in the 1930s, professor Starkenstein was a highly respected personality. He was elected dean of the German Medical Faculty of Charles University in the academic year 1931–1932 and vice-dean in the following year. As vice-dean, he wrote an open letter to the Czechoslovak president, T. G. Masaryk, entitled "Hochschulen und Sparsystem" (Universities and the Austerity Measures). In it, he called attention to the critical condition of Czechoslovak universities, caused by government auster-

ity measures. Starkenstein dealt also with the reform of studies of pharmacy in Czechoslovakia, at that time lasting two years only. This was the topic of a number of his lectures and of several articles in periodicals published by the associations of German and of Czech pharmacists in Czechoslovakia in the years 1930–1934. Almost all Starkensten's articles were published in German. He published in Czech only exceptionally, a text translated from German.

As a university lecturer, Starkenstein wrote three textbooks. As early as 1914, he published a textbook for physicians, in cooperation with Dr. Skutetzky "Novel drugs and pharmacological principles of their use in medical practice". In 1929, he wrote, together with J. Pohl and E. Rost, a textbook of toxicology for physicians, health care officials and medical students [7]. The information of Starkenstein's authorship of a textbook of clinical pharmacology, allegedly written in 1928 in cooperation with Hugo Příbram, a professor of internal medicine in Prague, is erroneous. This information was published by Professor Matoušek [5] and was based on the list of Starkenstein's publications dated 1928 and stored in Archives of Charles University in Prague. Apparently, the list was written by Starkenstein himself for his professorial appointment. The list reads: "Klinische Pharmakologie – mit Hugo Přibram – in Vorbereitung", i.e. under preparation. It relates to an intention, which, unfortunately, was never realized. In 1938, Starkenstein published his educational life work – Lehrbuch der Pharmakologie, Toxikologie und Arzneimittelverordnung (Textbook of Pharmacology, Toxicology and Drug Prescription). The Leipzig publisher F. Deuticke published this German textbook. At the time of its origin, it was highly appreciated by both German and Czech medical students who used it even in the post-war years.

1938–1942 (Persecution, Emigration and Imprisonment)

In 1938, the drift to unfortunate events in Starkenstein's life accelerated rapidly. In autumn, the Nazi activities at the German university in Prague intensified and German students started to boycott and disturb Starkenstein's lectures. Starkenstein was forced to apply for a discharge from lecturing, and to resign his post as director of the institute. After the occupation of Czechoslovakia in March 1939, he was denied access to the German university in full. At the age of 54, he had to retire and attempted to leave the country. At that time, his son Walter was already missing. It is assumed that he illegally crossed the border to Poland and his fate has never been fully ascertained. In the spring of 1939, Starkenstein, with his wife and daughter, Magda, obtained a permit to emigrate to Holland. In Amsterdam, he promptly began to work as a pharmacologist in a research laboratory of the pharmaceutical company Amsterdamsche Chininenfabriek, and he stayed there for almost two years. Even then he published at least eleven articles, above all dealing with the pharmacology of quinine and quinine-related alkaloids [6,7]. In 1940, Holland was occupied by German troops and in the autumn of 1941, Starkenstein was arrested by German secret police. After imprisonment in Prague and in Terezín (Theresienstadt) he was transported to the concentration camp Mauthausen in October 1942, where he died on 6 November, 1942.

Starkenstein's Reprint Collection

Professor Starkenstein moved to Holland his extensive collection of reprints of scientific studies covering various branches of medicine, biochemistry and natural sciences, compiled continuously since his undergraduate years. The collection, consisting of more than 20,000 items, his own works included, served him as the primary source of information. Shortly after the end of the World War II, his wife who lived in Holland, donated the collection to the Czechoslovak state. It was left in trust with Palacký University in Olomouc and deposited at the Institute of Pharmacology of Medical Faculty until 2002.

Original articles from Starkenstein's collection were studied by Professor Matoušek, and they also served as the major source of information for the author of the present article. In 2002, this precious legacy of Emil Starkenstein was deposited at the place most appropriate to its origin – the Archives of Charles University in Prague. At present, the collection is being catalogued in order to enable access to precious sources of information to researchers and other interested individuals .

Conclusion

In 1961, in his lecture on the history of pharmacology, a British professor of pharmacology, J. H. Gaddum, described Emil Starkenstein as "the most important personality of the European continental pharmacology between the two World Wars" [7]. My article aims to support the accuracy of Gaddum's claim.

Acknowledgements:

The author would like to thank to Professor Helena Rašková M.D., D.Sc. for her continuous interest and support during preparation of this publication and to PhDr. Francis Raska, Ph.D. for his careful revision of the English manuscript.

The Study was supported in part by the Grant MSM 6198959216.

REFERENCES

1 Jezdinský J. Profesor MUDr. Emil Starkenstein (18.12.1884–6.11.1942). Osobnost a dílo významného pražského německého farmakologa (120. výročí narození). [(Professor Emil Starkenstein, M.D. (18.12.1884–6.11.1942) – The Personality and Work of an Outstanding European Pharmacologist in Prague – The 120th anniversary of his Birth. (In Czech with English abstract)] Klin Farmakol Farm (Solen – Olomouc) 2005; **19** (1): 72–4.

2 Jezdinský J, Jančíková J. Professor Emil Starkenstein and Clinical Pharmacology. Acta Univ Palacki Olomuc, Fac Med 1994; **138**:65–77.

3 Junkmann K. Emil Starkenstein 1884 – 1942. [In German]. Naunyn-Schmiedeberg's Arch Exp Path Pharmakol 1946; **204**:13–19.

4 Matoušek M. Emil Starkenstein. [In Czech with English abstract]. Acta Univ Palacki Olomuc, Fac Med 1958; **14:**237–48.

5 Matoušek M. Zur Bibliographie der Arbeiten des jungen Emil Starkenstein. [(On the Bibliography of the Young Emil Starkenstein.) (In German with English abstract.)] Acta Univ Palacki Olomuc, Fac Med 1965; **38**:35–44.

6 Matoušek M., Kok J. In memoriam Emil Starkenstein (1884–1942). [In German with English abstract]. Arzneim.-Forsch. 1964; **14**: 1367–8.

7 Senius KEO. Emil Starkenstein 1884–1942. The Life and Work of a Pharmacologist. Naunyn - Schmiedeberg's Arch Exp Path Pharmakol 1984; **328**:95–102.

8 Starkenstein E., Wiechowski W. Über die Pharmakologie des Atophans. [(On the Pharmacology of Atophan. (In German)] Wien Klin Wochenschr 1913; **16**: 87–8.

9 Starkenstein E. Beiträge zur Therapie des Fleckfiebers. Untersuchungen der Cerebrospinalflüssigkeit bei Fleckfieberkranken. (Gemeinsame Untersuchungen mit Fähnrich R. Zitterbart). [(Contributions to the Therapy of Epidemic Typhus Fever. The Results of Analysis of Cerebrospinal Fluid from Epidemic Typhus Patients.) (In Cooperation with Sergeant R. Zitterbart.) (In German)] Med Klin 1917; **13**:779–84.

10 Starkenstein E. Symptomatische Therapie auf experimentellpharmakologische Grundlage. [(Symptomatic Therapy based on Experimental Pharmacological Research) (In German)] Ther Monatshefte 1917; **31**:189–200.

11 Starkenstein E. Klinische Pharmakologie – Theorie und Praxis am Krankenbette. [(Clinical Pharmacology – Theory and Praxis at the Patient's Bedside.) (In German)] Therapie der Gegenwart 1918; **59**:289–95.

12 Starkenstein E. Kombinationsversuche in der Analgetikareihe. [(Experiments of Combination within the Group of Analgetics.) (In German)] Ther. Halbmonatshefte 1921; **35**:629–36.

13 Starkenstein E. Synergismus und antagonismus in Veramon. [(Synergism and Antagonism in Veramon) (In German)] Dtsch Med Wochenschr 1926; 2189–90.

14 Starkenstein E. Pharmakotherapie der Seekrankheit. [(Pharmacotherapy of Seasickness.) (In German)] Med Klin 1927; **23:**1489–92.

15 Starkenstein E. Äussere Anlässe zum Studium de Pharmakologie der Seekrankheit. [(External Reasons for Study of Pharmacology of Seasickness.) (In German)] Medicinische Mitteilungen Schering-Kahlbaum A.G. Berlin 1930; **2**(4):87–91.

16 Starkenstein E. Die Seekrankheit. [(Seasickness.) (In German)] In: Klemperer G, Klemperer , editors. Neue Deutsche Klinik 1932; Band IX, Lieferung **45**:636–689.

17 Starkenstein E. Probleme und Untersuchungsergebnisse auf dem Gebiete der Pharmakologie des Eisens. [(Problems and Research Results in the Field of Pharmacology of Iron.) (In German)] Medizinische Mitteilungen Schering-Kahlbaum A.G. Berlin 1933; **5(**2):32–8.

18 Starkenstein E. Eisen. [(Iron.) (In German)] In: Hefter A, Heubner W, editors. Handbuch der experimentellen Pharmakologie 1934; **3**(II): Berlin: Verlag von Julius Springer; p. 682–1286.