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The Pioneer Neuropharmacologist Alfred Fröhlich (1871–1953) and the Origins of Neuroendocrinology: A Sesquicentennial Remembrance

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Short title: Alfred Fröhlich and the Origins of Neuroendocrinology

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Abstract

The birth of neuroendocrinology as a scientific discipline is traced back to 1900–1901, when Joseph Babinski, Alfred Fröhlich, and Harvey Cushing independently identified adiposogenital dystrophy (Fröhlich syndrome), and related gonadal underdevelopment and obesity to a tumor near the pituitary gland. This discovery prompted decades of research into the brain mechanisms responsible for the control of peripheral metabolism and endocrine functions. On the occasion of the 150th anniversary of Fröhlich's birth, this study traces the origins of his intellectual formation and his association with renowned contemporaries in Austria, England, Italy, and finally Cincinnati, Ohio, where he sought refuge after Austria's annexation by Nazi Germany. Fröhlich interacted with seminal figures in biomedicine, including Lothar von Frankl-Hochwart, Hans Horst Meyer, Ernst Peter Pick, Harvey Cushing, John Newport Langley, and the Nobel laureates Charles Scott Sherrington and Otto Loewi. Alfred Fröhlich, one of the 20th century's most emblematic physicians, left his mark on neurophysiology and neuropharmacology with important works, and published authoritative manuals of drug dispensing and clinical therapy. He confronted the calamities of two World Wars with remarkable resilience like many of his Viennese colleagues who, overcoming the constraints of National Socialism, settled overseas to fulfil their calling as physicians, researchers, and teachers.

Keywords

Adiposogenital dystrophy, Babinski–Fröhlich syndrome, Charles S. Sherrington, Harvey Cushing, history of neurology, Otto Loewi

Introduction

The Austrian–American neurologist Alfred Fröhlich (Fig. 1) is eponymously remembered by the syndrome of adiposogenital dystrophy that he presented on October 12, 1901 before the Society for Psychiatry and Neurology of Vienna, while he was a neurology resident. His report (Fröhlich 1901) appeared in print in the November 23, 1901 issue of *Wiener Klinische Rundschau*, a weekly review for general medical practice (Fig. 2).

One hundred and fifty years have elapsed since the birth of Fröhlich, a central figure in European neuropharmacology. On that occasion, I review his academic life and work. He was born on August 15, 1871 in Döbling, Vienna's 19th district, into a Jewish family. Alfred was the middle of the three sons of Siegmund Fröhlich (1832–1904), a native of Prossnitz, Moravia (present-day Prostějov, Czechia) and merchant on the Board of Directors of the Alcohol and Potash Factory and Refinery Company of Kolín in Central Bohemia, and his wife Franziska, née Herrmann (1847–1908), a native of Pless, Silesia (today Pszczyna, Poland) (Brücke 1961; Strauss and others 1983; Posch 2020).

After graduating from the local Gymnasium in 1889, Fröhlich entered the University of Vienna to study medicine, and earned his M.D. degree in 1895. For the following three years he was an intern in the First Clinic of Internal Medicine headed by Hermann Nothnagel (1841–1905). From 1898 to 1900 he worked as an assistant in the Polyclinic of Julius Mannaberg (1860–1941), and from 1899 to 1902 as a neurology resident in the Outpatient Neurology Division (*Ambulatorium für Nervenkranke*) under Lothar von Frankl-Hochwart (1862–1914) (Fischer 1932). Fröhlich and von Frankl-Hochwart (1900, 1902, 1904) conducted experiments relating the innervation of the rectal sphincter and the urinary bladder in dogs.

Concurrently, in 1901, Fröhlich joined the Laboratory of Experimental Pathology, which was headed by Samuel von Basch (1837–1905), as an assistant (Pick and others 1953). The Austrian-Jewish physician von Basch is known for inventing the sphygmomanometer, and for tending to the younger brother of Emperor Franz Joseph I of Austria, archduke Maximilian I, the only Emperor of the Second Mexican Empire (Brücke 1953). In that laboratory, Fröhlich was instructed by Otto Grosser (1873–1951), an assistant in the First Anatomical Institute of Emil Zuckerkandl (1849–1910). Grosser and Fröhlich (1902) completed a study on the dermatomes of the human trunk.

A multifaceted personality and an accomplished physician already by the age of 30 years, Fröhlich switched to basic science, where he left a major impact with around 200 publications in comparative physiology, pharmacology, and autonomic neuroscience (Freissmuth and Sitte 2018). He also co-authored a handbook on the economic and efficiency factors related to the preparation and dispensing of medicines in Austria and Germany (Fröhlich and Wasicky 1921), and compiled the eleventh edition of Ernst Landesmann's authoritative manual of therapy (Fröhlich 1930) (Fig. 3).

Adiposogenital Dystrophy or Babinski–Fröhlich Syndrome

Fröhlich's fame rests with his 1901 description of "a case of tumor of the hypophysis cerebri without acromegaly" (Fröhlich 1901). It concerned a 14-year-old boy (patient "Richard D.") who was first examined by Fröhlich in November 1899 for cephalalgia and vomiting, and again in August 1901 with severer symptoms, including loss of vision in the left eye, abnormal weight gain, and exhaustion. As the patient showed a stigma of myxedema, he was treated with thyroid tablets.

Using the literature and studying the case, Fröhlich (1901) described the clinical manifestations of adiposogenital dystrophy (Fig. 2). He was able to scrutinize an adequate number of cases from the earlier bibliography to justify the assumption of a new clinical entity (Cushing 1912), and emphasized for the first time that disturbances such as obesity and infantilism may be associated with pituitary tumors, an observation that became an important stimulus to neuroendocrine research. Actually, Fröhlich (1901) attributed the syndrome to a new growth of the pituitary gland, "or to be more exact in the region of the hypophysis." English translations of Fröhlich's paper can be found in Bruch (1939) and Major (1945).

It is to the clinical merit of Fröhlich that he recognized the diagnostic importance of adiposity and other trophic disturbances, such as genital underdevelopment, in relation to a cerebral localization of the pathological process. His assumption of the "region of the hypophysis" was apposite (Bruch 1939).

The syndrome was subsequently referred to as Fröhlich's dystrophia adiposogenitalis or Babinski–Fröhlich syndrome (Poirier and Philippon 2011), as Joseph Babinski (1857–1932) had described a similar condition in 1900. Babinski (1900) communicated his case of a "tumor of the pituitary body without acromegaly and with developmental arrest of the genital organs" before the Society of Neurology of Paris in the session of June 7, 1900 (Babinski 1900). The case concerned a 17-year-old girl, who had suffered for years from headaches and seizures. Upon examining her, Babinski noted bilateral papilledema, obesity, an infantile aspect of the genitals, and amenorrhea; there was neither acromegaly nor gigantism. At autopsy, a tumor lying in the sella turcica was detected (Fig. 2).

Around the same time, in 1901, Harvey Cushing (1869–1939) in Baltimore had actually missed the diagnosis of a cyst of Rathke's pouch in a 16-year-old girl (patient "Mary D.") who had presented in December 1901 with headaches, vision loss, obesity, and sexual immaturity; he operated three times, twice to decompress the brain bilaterally, and a third time to expose the cerebellum, after which the patient died (Fulton 1946; Pascual and others 2016). Cushing presented that case five years later, together with a similar case characterized by obesity and sexual infantilism and caused by a tumor located in the base of the brain, at the 32nd annual meeting of the American Neurological Association in Boston on June 4–5, 1906 (Cushing 1906, 1912, p. 43–5).

As Cushing (1912) and Hurxthal (1948) attest, the term dystrophia adiposogenitalis was introduced by the ophthalmologist Martin Bartels (1875–1947), at the time a lecturer (*Privatdocent*) in the Institute

of Pathological Anatomy of the University of Marburg headed by Karl Aschoff (1866–1942). Bartels presented his case before the Society for Natural and Medical Science of Strassburg on December 6, 1907 (Bartels 1908).

Fröhlich's discovery was crucial because it also made a deep impression on Cushing. The cases of Babinski, Fröhlich and Cushing were instrumental in developing the concept of the hypothalamic control of body homeostasis and mental stability (Pascual and others 2016), and their identification of the adiposogenital syndrome led to the rise of neuroendocrinology as a new medical discipline (Pascual and others 2018).

The pathologist Jakob Erdheim (1874–1937) described neoplasms originating in, or near, the infundibulum without involvement of the pituitary; he identified and defined the tumors known as craniopharyngiomas, and named them "hypophyseal duct tumors" (*Hypophysenganggeschwülste*), a term that denoted their presumed origin in cellular remnants of the primordial hypophyseal duct (Pascual and others 2015). Erdheim (1904) was the first to point out that, although immaturity and hypogonadism were probably the result of a pituitary lesion, adiposity was related to the upward pressure of the tumor on the base of the brain. This distinction derived from the careful study of autopsy material in patients with craniopharyngiomas. Thus, Erdheim postulated the hypothalamic origin of adiposity (Carmel 1985). Today, craniopharyngioma (a term introduced by Cushing in 1930 to replace the old category of interpeduncular or suprasellar cyst) is considered an epithelial tumor, presumably derived from cell remnants of Rathke's pouch, the embryonic anlage of the pituitary (Pascual and others 2016, 2018).

The cystic tumor of Fröhlich's patient was successfully operated upon and drained by Anton von Eiselsberg (1860–1939), chairman of surgery in Vienna (Eiselsberg and Frankl-Hochwart 1907, 1908; von Eiselsberg 1910a, 1910b). He approached the pituitary space through a transnasal–transsphenoidal route (subsequently also adopted by Cushing), and exposed the cyst that had replaced most of the pituitary gland. During convalescence, the headache slowly subsided, but vision returned only partially. Thereafter, further improvement ceased, and, at the last report 12 years postoperatively, the infantile habitus persisted (Bruch 1939; Editorial 1969).

Regarding the relative consequence of Fröhlich or Babinski in the description of adiposogenital dystrophy, it is true that Babinski reported his case one year earlier than Fröhlich (although the pathological study of that tumor was made eight years earlier, in 1892 by Onanoff), but his report only documented succinctly the symptoms of this condition, without adding any etiological or physiopathological insight. On the contrary, Fröhlich's report provided a comprehensive review of the existing medical literature up to that time (dozens of cases), and included, besides obesity, the description of numerous signs derived from hypothalamic dysfunction (somnolence, body temperature disturbances, mental disturbances). Regrettably, the exact site of injury along the hypothalamic–hypophyseal axis

caused by the tumor in each case was not easily discernible at the time (excepting in some of the pituitary tumor specimens examined by Erdheim), and Fröhlich could only assume a gross pituitary dysfunction as the major cause of the symptomatology. Consequently, on the basis of priority it is fair to use the combined eponym Babinski–Fröhlich syndrome, but considering the thoroughness and degree of insight into the pathology, Fröhlich syndrome should undoubtedly be the chosen term to employ. Curiously, the eponym Fröhlich syndrome has sort of fallen into oblivion since the introduction of modern hormonal replacement therapies and is now very rarely employed in the medical literature. This term, however, should not be forgotten given the current active research on obesity and hyperphagia of hypothalamic origin, particularly when associated with pituitary tumors and craniopharyngiomas.

Nevertheless, in 1901, very little was known about the physiological role of the pituitary, and almost nothing about the functions of the hypothalamus. The "grey matter lining the third ventricle" was undiscovered country. Thirteen years elapsed before Fröhlich's description as an example of "hypophyseal tumor without acromegaly," which shows how confused the ideas of pituitary function were in those days of the widely discussed syndrome of adiposogenital dystrophy (Cushing 1932, p. 19). Four decades later, when invited to open a discussion at the 20th annual meeting of the Association for Research in Nervous and Mental Disease in New York City on December 20–21, 1939, Fröhlich acknowledged that he was wrong in 1901: "It was not the hypophysis, but the hypothalamus—but in 1901 all we knew of the hypothalamus was its position below the thalamus" (Fröhlich 1940; Marshall and Magoun 1998, p. 231).

Percival Bailey (1892–1973) and Frédéric Bremer (1892–1982) were the first to prove that an experimental lesion of the basal hypothalamus alone, and not of the pituitary, results in adiposogenitalism (Bailey and Bremer 1921; Pascual and others 2015; Prieto and Pascual 2019). One should add here the pioneering contribution by the French physicians Jean Camus (1872–1924) and Gustave Roussy (1874–1948) who, in 1913, published their model of thermal injury to the tuberal region of the hypothalamus in hypophysectomized dogs, identifying the origin of diabetes insipidus in the lesions of this hypothalamic area and the associated sexual dystrophy and obesity owing to the dysfunction of separated hypothalamic centers (Camus and Roussy 1913a, 1913b, 1913c; for a critical review of these experiments see Castro–Dufourny and others 2017). These works were known by Bremer and were the inspiration for the more systematic studies of Bailey and Bremer. On the other hand, Cushing did not accept the theory of a hypothalamic dysfunction for the origin of diabetes insipidus or Fröhlich syndrome, and tried to obstacle Bailey's report, a major source of conflict between the two scientists. However, Cushing took advantage of his friendship with Fröhlich and could get news from the latter about his paper, which represented a primary source of evidence for developing the theory of hypopituitarism or pituitary deficiency states versus hyperpituitarism (acromegaly).

From the 1920s to the 1940s, substantial experimental evidence was obtained that pointed to the role of the hypothalamus and the pituitary in growth, sexual development, certain aspects of metabolism, and obesity (Kunstadter 1941). The disturbances of hypothalamic function were the primary cause of Fröhlich syndrome, with the pituitary often being intact. Besides obesity and delayed sexual development, somnolence, diabetes insipidus, disturbances in temperature regulation, and mental changes were commonly seen (Morgan 1959).

Adiposity associated with genital hypoplasia may result from a variety of pathological conditions, including internal hydrocephalus or remote tumors (e.g. cerebellar) that distend the floor of the third ventricle and compress the sella turcica, infectious and inflammatory conditions such as granulomatous or syphilitic meningitis and, especially, encephalitis lethargica (Walton 1977). In the latter pathological state, cases of adiposogenital dystrophy were repeatedly observed as sequelae, probably caused by the predilective localization of inflammatory lesions in the hypothalamic area and the loss of cells in the tuber cinereum (von Economo 1931). Adiposogenital dystrophy frequently began during acute encephalitis lethargica and further evolved into the chronic phase (Foley 2018). It was frequently encountered in younger patients (Marañón 1920; Kreuser and Weidner 1927).

Today, we know that the hypothalamus regulates and coordinates central autonomic activity. The clinical significance of adiposogenital dystrophy has undergone considerable modification since Fröhlich's description. It is currently recognized that the lesion primarily affects the hypothalamus and is usually associated with craniopharyngioma in the infundibulo-tuberal region in the floor of the third ventricle. Impaired vision may result from impingement of the tumor on the optic nerves. The destruction of hypothalamic nuclei results in hormonal dysfunction, with obesity, growth retardation, and hypogonadism. In some cases, patients may exhibit intellectual disability and diabetes insipidus (Bissonnette and others 2019).

Liverpool and Cambridge: Sherrington and Langley

Between 1901 and 1904, Fröhlich, accompanied by his first wife Johanna "Jenny" Fröhlich (1879–1939), traveled to England to work in the Physiological Laboratory of Sir Charles S. Sherrington (1857–1952) at University College Liverpool, where he became increasingly interested in neurophysiology and neuropharmacology (Pick and others 1953, Editorial 1969).

Fröhlich and Sherrington (1902) examined decerebrate rigidity in the cat, dog, and macaque, and observed that inhibitory effects were evoked by electrical stimulation of a limited area of the spinal cord. Such effects were more pronounced on the side ipsilateral to the stimulation. Overall, the predominant effect from the hindlimb seemed to be a relaxation of the contralateral triceps. The authors concluded that the path of inhibition in the ventrolateral column might be connected with afferent nerves of the

contralateral hindfoot.

In Sherrington's laboratory, the 30-year-old Fröhlich met the 32-year-old Cushing; the two physicians established a lifelong friendship, and subsequently shared their publications. It was in the summer of 1901 that the scientific interaction between Sherrington and Cushing, two seminal figures in the brain sciences, began, leading to an intermingling of basic neurophysiology and clinical neurosurgery with regard to cerebral cortical localization (Louis 2020).

Apparently, Cushing took a great fancy to Fröhlich. He gave an entertaining account of the formation of the "Manx Club" and of a combined *Wissenschaft und Vergnügen* (science and pleasure) excursion to the Isle of Man in July 1901 made with a view to studying problems of inheritance in tailless cats (Fulton 1946, p. 239).

Besides Cushing, Fröhlich also developed a strong friendship with Sir Ronald Ross (1857–1932), the recipient of the Nobel Prize in 1902 for his discovery that the malaria parasite is transmitted by mosquitos. The two men corresponded from 1901 to 1912 (Gibson 2003).

Next, Fröhlich spent the summer months of 1904 at the University of Cambridge, working in the Physiological Laboratory of John Newport Langley (1852–1925) on the autonomic nervous system. Furthermore, Fröhlich (1905) carried out a study on the toxic properties and cardiac and muscle effects of an arrow poison—used by the Munchi tribe on the Ome River of northern Nigeria—in frogs, rabbits, and dogs. He concluded that the water-insoluble poison most likely belonged to the family of resin acids.

Naples and Invertebrate Biology

Fröhlich visited the Physiological Laboratory of the Zoological Station of Naples, where, in collaboration with the zoologist Salvatore Lo Bianco (1860–1910), he worked on the physiology and behavior of invertebrates. Lo Bianco was known for his method of fixation of marine invertebrates. Fröhlich was also advised in these experiments by the naturalist Giuseppe Jatta (1860–1903), who taught him the operation methods, and the biologist Jakob von Uexküll (1864–1944), whose name is linked to the academic field of semiotics.

During November and December 1902, Fröhlich studied the central ganglion of *Ciona intestinalis* (Fröhlich 1903), an ascidian (sea squirt) commonly known as the vase tunicate. He concluded that even an elementary nervous system can underpin behaviors that are mediated by a complex brain in more evolved animal classes.

He returned to Naples in January and March of 1903, with grant support from the Imperial Ministry of Culture and Education, to study the invertebrate statocyst (the balance sensory receptor) of cephalopods (Fröhlich 1904a) and crabs (Fröhlich 1904b), and the implications for disturbances of the inner ear in human pathology. In April 1903, he investigated the effects of the destruction of the labyrinth

on swimming behavior in the seahorse (Fröhlich 1904c).

Cultural Endeavors: Bruckner and Kipling

Fröhlich had diverse cultural and literary interests. Not to be confused with the German court music director (*Oberkapellmeister*) Alfred Fröhlich (1875–1942), founder of the Collegium Musicum in Düsseldorf, the Viennese Alfred Fröhlich was also a musician and an accomplished pianist, having studied harmony with the composer Anton Bruckner (1824–1896). Listening to Fröhlich's piano playing was admittedly a joy, and, when he began to gradually lose his vision in his later years, music remained his gentle consolation (Brücke 1953).

Fröhlich met Rudyard Kipling (1865–1936) at the Engelberg Ice Rink, Switzerland, on December 28, 1908—the day of the Messina–Reggio Calabria earthquake, the most destructive earthquake ever to strike Europe with an estimated death toll of 80,000 lives. Fröhlich helped Kipling to take his very first steps on the ice, and the two families met winter after winter (Fröhlich 1936). A young pharmacologist of considerable perception, but with little experience in the treatment of human ailments, Fröhlich became the "winter holiday family physician" of the Kiplings. He mused: "To me, as to all pharmacologists, the prospect of experimenting on two-legged rabbits was uncommonly alluring" (Fröhlich 1937, p. 44).

Kipling repeatedly invited Fröhlich and his wife to visit Sussex. The last invitation, dated spring 1914, closed with the statement: "Remember, you are pledged to tell us when you come to England. Keep your promise or I'll make an international affair of it. I'll send the British fleet up the Danube and destroy the Austrian Empire." Kipling's last letter to Fröhlich, sent from Vernet-les-Bains, Northern Catalonia, is dated March 14, 1914. The First World War put an end to the further exchange of correspondence (Fröhlich 1936, 1937). It also caused Fröhlich to lose all his fortune (Brücke 1953).

In a final exchange, Fröhlich mailed two photos to Kipling on December 30, 1935 on the occasion of the latter's 70th birthday, and received a thank you card a week later. Within a fortnight, on January 18, 1936, the great poet of the British Empire passed away. A watercolor by Kipling hung on the wall of Fröhlich's working room, depicting an enormous bacillus with the designation, "Bacillus Tussis Engelbergensis, var. Frölich. Enlargement 1:1,200,000. Pictor Ignotus [unknown painter]" (Fröhlich 1936, p. 289).

Vienna University Faculty

In 1905, Fröhlich was solicited by Hans Horst Meyer (1853–1939), chairman of the Pharmacological Institute of the University of Vienna, to work there as an unsalaried assistant (Brücke 1953). Fröhlich received his habilitation and established himself as *Privatdocent* in experimental pathology in 1906 and in pharmacology in 1908. He was appointed associate professor (*Extraordinarius*) of pharmacology and

toxicology in 1912, promoted to full professor (*Titular Ordinarius*) in 1921 (Fig. 4), and retired in 1936 (Gibson 2003).

Harvey Cushing credited the discovery of the concept of the physiological antagonism or balance between the sympathetic and the parasympathetic nervous system to Fröhlich and Loewi (1908). The idea was subsequently elaborated by Meyer, and became popularized by other researchers of the Vienna School (Cushing 1932).

With Otto Loewi (1873–1961), Fröhlich demonstrated that small doses of cocaine potentiated the responses of sympathetically innervated organs to epinephrine (Browne 1970). They tested the interaction of cocaine with epinephrine on blood vessels, the urinary bladder, the iris (mydriasis), and the submaxillary salivary gland. Doses of cocaine, which were completely ineffective when given alone, greatly increased the effect of epinephrine, in both intensity and duration (Fröhlich and Loewi 1910). The argument has been made that this work ultimately led to a better understanding of how neurotransmitters are inactivated by their reuptake into the presynaptic nerve terminal (Freissmuth and Sitte 2018).

In 1910 Fröhlich was hosted by Yves Delage (1854–1920) at the Biological Station of Roscoff, Brittany, where he examined chromatophore expansion and color change in the prawns, *Palaemon serratus* and *Palaemon adspersus* (Fröhlich 1910). In these studies, he was advised by the zoologist Hans Leo Przibram (1874–1944), founder of the Biological Research Institute of the Austrian Academy of Sciences. Fröhlich also visited the marine laboratories of Helgoland, Germany, where he made valuable contributions to invertebrate and vertebrate physiology (Editorial 1969). In Vienna, he founded the Biological Society, in which he served for many years as secretary-general (Pick and others 1953).

The neuroendocrinological experiments of von Frankl-Hochwart and Fröhlich (1910) in rabbits led to the practical use of posterior lobe pituitary extract in childbirth. They explored the effects of hypophysin (or pituitrin, a proprietary preparation of the neurohypophysis) on the autonomic nervous system, and its application to stimulate uterine contraction. Thus, they extended the work of Sir Henry Dale (1875–1968) on the sensitivity of the rabbit uterus to posterior pituitary extract. Pituitary extract stimulated the non-pregnant uterus, and produced powerful contractions on the uterus of pregnant animals:

> In the majority of experiments, especially in lactating or gravid rabbits, the uterus is stimulated by small doses of pituitrin into strong, sometimes persistent contractions with pallor of the organ. Immediately the sympathetic nerves to the uterus, the hypogastric nerves, are easily stimulated by a faradic current and react with a stronger response. According to our studies, pituitrin can be regarded as essentially non-toxic and should be considered by obstetricians and urologists in pertinent cases who might profit from the increased excitability which we have demonstrated in the animal experiments on the bladder and the uterus and use it therapeutically in such instances (von Frankl-Hochwart and Fröhlich 1910; English translation in Editorial 1969, p. 2276).

Furthermore, Fröhlich studied the effects of radon on the heart of the frog and the rat (Fröhlich 1923), and the increased ability of many tissues in marine mammals to take up various dyes after theophylline administration (Fröhlich 1932). Other topics that he investigated dealt with changes to the excitability of the autonomic nervous system by calcium deprivation, nicotine intoxication, the physiology and pharmacology of muscle contraction, the pharmacological effects of purines, and the pathways of visceral pain (Pick and others 1953; Editorial 1969).

With Ernst Peter Pick (1872–1960), Meyer's successor in the Pharmacological Institute, they studied poison resistance of the conduction system in the isolated frog heart. They observed that the "Stannius ligation" at the atrial-ventricular border caused ventricular automatism despite 1% morphine, which spoke against a direct effect on heart muscle (Fröhlich and Pick 1918a, 1918b). The effects of cardiac toxins were reversed through physostigmine (Fröhlich and Pick 1920). With the physiologist Alois Kreidl (1864–1928), Fröhlich carried out pharmacological studies on heat narcosis (or thermal anesthesia) in marine crabs (Fröhlich and Kreidl 1921).

Fröhlich and Zak (1927) studied the tissue effects of theophylline. The effect of acid sulfonated dyes was increased by a prior injection of theophylline. Theophylline allowed ferrocyanide to penetrate the guinea pig brain, a phenomenon that did not occur in untreated animals. In frogs, theophylline decreased the latent period observed before the onset of seizures induced by the injection of acid fuchsin. By increasing the permeability of blood vessels, theophylline increased in a similar manner the effect of subliminal doses of morphine in frogs, cats and rabbits.

On February 25, 1921 Fröhlich lectured before the Society of Physicians of Vienna on new directions in the treatment of syphilis, and reported on pharmacological studies with mirion, a novel iodine compound (Fröhlich 1921). In the same year, he published the "Handbook on the economic and efficiency factors related to the preparation and dispensing of medicines, with special consideration for Austrian and German conditions" (Fröhlich and Wasicky 1921). The book went through two revised editions, in 1923 and in 1936. It was co-authored with fellow pharmacology professor Richard Wasicky (1884–1970), chairman of the Pharmacognostical Institute. In 1938, Wasicky was dismissed from his academic position because of his non-Aryan wife, and in 1940 he emigrated to Brasil, where he was appointed on the faculties of the University of São Paulo and the Federal University of Santa Maria (Freissmuth and Sitte 2018).

Fröhlich authored the chapters on the pharmacology of the central and the autonomic nervous system and the general paralyzing and excitability-inducing poisons for "Bethe's Handbook of normal and pathological physiology" (Fröhlich 1927a, 1927b, 1929). In 1907, the neurologist Otto Marburg (1874–1948) acknowledged Fröhlich (1907) for contributing a newly revised chapter on the management of

acute and chronic poisoning to "Landesmann's Therapy of the clinics of Vienna" by summarizing toxicology from both a clinical and a therapeutic perspective. In 1930, Fröhlich fully revised and edited "Landesmann's Therapy," a vade mecum for the practitioner that comprised "the most modern and accepted methods of treatment, operative and non-operative, set forth systematically and comprehensively" (Fröhlich 1930).

Emigration to America

After the annexation of Austria by Nazi Germany in 1938, even though he had retired as professor emeritus, Fröhlich was dismissed from the University by the National Socialists on racial grounds (Posch 2020). With his second wife (since 1916), baroness Adelheid Ida "Ilse" Charlotte, née von Tiesenhausen (1883–1985), a native of Riga, Fröhlich left Vienna. The couple sailed to New York on September 7, 1939. Harvey Cushing had asked the father-in-law of his daughter Betsy, President Franklin D. Roosevelt, to intervene, so that the Fröhlichs could find shelter in the United States (Zárate and Saucedo 2007).

Fröhlich joined the May Institute for Medical Research of the Jewish Hospital of Cincinnati, Ohio. Founded in 1850, it was the first Jewish hospital in the United States. Today, it forms part of the University of Cincinnati Medical system (Krome 2015). Here, he collaborated with I. Arthur Mirsky (1907–1974), founding director of the Institute in 1935, and his successor, Sol Sherry (1916–1993) (Pick and others 1953; Editorial 1969). Mirsky is known for his contributions to diabetes, gastric ulcer, and psychosomatic medicine, and Sherry for his contributions to thrombosis research.

At that time, another representative of Viennese neurology also found academic shelter in Cincinnati. The Russian-Jewish neuropathologist Ilya M. Scheinker (1902–1954), of Gerstmann-Sträussler-Scheinker fame, was hired in 1941 by the University of Cincinnati Medical School as an instructor in pathology to head the Neuropathology Service at Cincinnati General Hospital (Zeidman and others 2016). Fröhlich's former chairman of pharmacology in Vienna, Ernst Pick, also emigrated to the United States in 1939; he was appointed clinical professor of pharmacology at Columbia University College of Physicians and Surgeons, and became affiliated with the Mount Sinai Hospital as associate in pharmacology, and with the Merck Institute for Therapeutic Research in Rahway, New Jersey, as a consultant (Antopol 1960).

Fröhlich continued to publish experimental works on neurological topics, including the pharmacology of heat narcosis and the effects of theophylline, methylene blue, and quinine on the absorption of salts from the gastrointestinal tract (Fröhlich 1948), and the prevention of skin lesions and of acid fuchsin- and bile-induced convulsions in young albino rats by vitamin D_2 hypervitaminosis (Fröhlich 1953).

He conducted a series of studies to investigate the effect of age on the susceptibility to seizures in relation to the blood-brain barrier. Part of this work was presented by invitation at the 53rd annual

meeting of the American Physiological Society in Chicago on April 15–19, 1941 (Fröhlich and Mirsky 1941). The influence of acid fuchsin (0.5 mg/g b.w. subcutaneously) was studied in rats aged from 7 to over 100 days. Adult animals did not develop convulsions, even with high doses (3 mg/g b.w.); however, after an injection of theophylline, 60% of the adult animals developed convulsions (Fröhlich and Mirsky 1942). Similar effects were seen after the intraperitoneal injection of a 1% solution of "concentrated bile" (Fröhlich 1952).

In the summers of 1944–1946, Fröhlich spent time at the Marine Biological Laboratory in Woods Hole, Massachusetts. As he aged, he began to progressively lose his vision, until he became blind (Brücke 1953). Fröhlich died in Cincinnati on March 22, 1953 after a brief illness. Thus ended a distinguished biomedical career that had won recognition in the European and American medical worlds (Pick and others 1953). A street, *Alfred Fröhlich Strasse*, has been named to honor his memory in Gerasdorf, on the northern city boundary of Vienna.

Despite the tragic circumstances of two World Wars, Fröhlich had remained serene, resilient, and always willing to help others (Brücke 1953). His admirable dignity against adversity left an indelible lesson to later generations of physicians and scientists. Overcoming the constraints of the Nazi regime, Fröhlich and many of his Viennese colleagues ultimately settled overseas to nurture their ambitions and pursue their interests as physicians, researchers, and teachers. The loss to European scientific and cultural life from the diaspora induced by the National Socialists and their acolytes remains inestimable to this day (Freissmuth and Sitte 2018).

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Figure captions

Figure 1. Alfred Fröhlich in Vienna, circa 1938, left (private collection). Autobiographical data form filled by Fröhlich for Fischer's (1932) biographical lexicon, right (credit: The Waller Manuscript Collection, Uppsala Universitet).

Figure 2. Extracts from the original publications on the syndrome of adiposogenital dystrophy by Babinski (1900) and Fröhlich (1901) (credit: Bibliothèque interuniversitaire de Santé, Paris).

Figure 3. The eleventh edition of Ernst Landesmann's authoritative manual of therapy completely revised by Fröhlich (1930), and the third expanded edition of the pocketbook on economic and efficiency factors of prescriptions in Austria and Germany (Fröhlich and Wasicky 1921) published in 1936 (author's private library).

Figure 4. Faculty and staff members of the Pharmacological Institute, University of Vienna, 1925 (credit: commons.wikimedia.org). Front raw (seated), left to right: Pollak, Rössler, Rössler, Pick, Meyer, Fröhlich, Glaubach, Molitor. Second raw, left to right: Wolpe, La Barre, Nagel, Flaum, Königstein, Donat, Heilig, Sole. Rear raw, left to right: Schneider, Schwitzer, Kwapil, Vartiaynen, Gusenbauer.