

# Erich Harnack (1852–1915) and a Short History of Apomorphine

Pille Taba<sup>a</sup> Andrew Lees<sup>b</sup> Gerald Stern<sup>c</sup>

<sup>a</sup>Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia; <sup>b</sup>University College London, Reta Lila Weston Institute of Neurological Studies, and <sup>c</sup>Department of Clinical Neurology, University College Hospitals, London, UK

## Key Words

Apomorphine · Erich Harnack · History

## Abstract

Apomorphine, now established as an efficacious therapy for refractory motor fluctuations in levodopa-treated Parkinson's disease, has a long and chequered history in medical and veterinary therapeutics. The preclinical *in vivo* pharmacological effects of apomorphine were first studied about 150 years ago following which the drug was introduced for the treatment of behavioural vices in domesticated animals. Erich Harnack's early pharmacological studies in Dorpat (now Tartu, Estonia), where he belonged to the pharmacological dynasty of Buchheim and Schmiedeberg, are of particular historical significance as he emphasised that while apomorphine had potent emetic effects, the drug also had complex effects on the central nervous system.

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Apomorphine, the prototype dopamine agonist that stimulates D1, D2 and D3 receptors, has a long and intriguing history. This will be briefly recapitulated, drawing particular attention to the little known contributions of Erich Harnack and the Tartu School of Clinical Pharmacology in Estonia.

Awareness of the effects of apomorphine on the brain probably extends back to ancient civilisations. The bulbs and roots of the water lily species (*Nymphaea caerulea*, the blue lotus and *Nymphaea ampla*, which has a white flower) are now known to contain a wide range of aporphines including apomorphine. Ethno-botanical scholars have suggested that the *Nymphaea* species were employed for their narcotic, aphrodisiac and hallucinogenic properties in magical-religious rites by the Maya civilisation of Central America (2000 BC–250 AD). Their ritual use has also been depicted within Ancient Egyptian tomb frescoes and in early papyrus scrolls. The famous ancient Egyptian Tutankhamun tomb contained a golden shrine decorated with a pharaoh holding a large water lily, and frescoes within the tomb of Nebaum (XVIII Dynasty, 1370–1318 BC) in the British Museum, illustrate a funeral dance with two women garlanded with water lily petals [1].

Apomorphine was first synthesised by Arppe in 1845, from morphine and sulphuric acid (*Ueber eine merkwürdige Veränderung des Morphius durch Schwefelsäure*. Liebig's Annalen der Chemie und Pharmacie 1945;LV: 96), and later by Matthiesen and Wright who introduced the synthesis of apomorphine from morphine and hydrochloric acid (Proceedings of the Royal Society 1869; XVII:455) [2]. Not long after its discovery, the drug was investigated by veterinary scientists and recommended as a treatment for stereotypies in farmyard animals [3].

For the first comprehensive pharmacological study of the effects of apomorphine, we turn to Erich Harnack (fig. 1). He was born in 1852 in Dorpat, now Tartu, Estonia, into a gifted academic family. His father, born in St. Petersburg, was a professor of theology, and his four sons including Erich all grew up to become professors in pharmacology, theology, physics and history, at different European universities [4, 5]. In 1873, Erich Harnack graduated from the University of Dorpat one of the oldest universities in the Northern Europe having been established in 1632, which has justifiably been dubbed the 'cradle of modern pharmacology'. He soon joined a dynasty founded by Rudolf Buchheim who was the Head of the Department of *Materia Medica* (Pharmacology) between 1847 and 1867, and who had been influential in the early promotion of analytical and experimental work in pharmacology from its purely descriptive foundations: his experimental pharmacological laboratory remained unique in the world for almost 20 years. This was further developed by his student, Oswald Schmiedeberg, who once he had assumed the Chair created a school of pharmacology that through its inspirational training programme provided the heads of many academic institutes of pharmacology throughout the world. It was in this intellectually stimulating setting in the Old Anatomical Theatre in Dorpat that Harnack began his research into animal pharmacology (fig. 2) [6, 7].

Harnack worked in Dorpat/Tartu as an Assistant Professor until 1877, later moved to Strasbourg and finally to Halle University as Professor of Pharmacology and Physiological Chemistry, where he founded a new Institute of Pharmacology in 1890 [5]. He was soon recognised as a distinguished and innovative scientist and a popular teacher. However, his eccentricities and liberalism were not always appreciated by the inflexible academic hierarchy. Sometimes he lectured outside the university in a café where students were allowed to smoke and drink beer [6, 7]. He encouraged and relished criticism, especially when it was coloured with gentle satire. Writing in *The New York Times* of 1909, he ridiculed 'alcohol-free beer' and 'caffeine-free coffee' as 'emasculated stimulants' and 'self-deceptors'. He had an engaging whimsical sense of humour and regarded life with its attendant risks, dangers and temptations to be preferable to living in an artificial 'ideal' safe community [8].

Harnack published widely in the field of pharmacology including papers on the action of alcohol and the symptoms of potato poisoning, and he also became interested in the medical uses of electricity and magnetism. He wrote textbooks of medicine and his doctoral dissertation



**Fig. 1.** Professor Erich Harnack (1852–1915).

concerned the pathogenesis and treatment of diabetes mellitus [9].

In 1874, at the age of 22 years and when working in Dorpat, Erich Harnack published a 50-page account '*Ueber die Wirkungen des Apomorphins am Saugerthier und am Frosch*' (The effects of apomorphine in mammals and frogs) in the '*Archiv für experimentelle Pathologie und Pharmakologie*', the journal that was founded in 1873, and is now known as *Naunyn-Schmiedeberg's Archives of Pharmacology* [10]. By then his colleague Vincent Siebert, also at the University of Dorpat (Tartu), had already studied the emetic effects of apomorphine and established that its associated circulatory changes were restricted to certain species, including humans, dogs and cats but not frogs or rabbits; but in his dissertation of 1871, Siebert who had been supervised by Oswald Schmiedeberg, concluded that knowledge of the possible effects of apomorphine on the central nervous system 'remained shrouded in darkness' [2].

In his introduction, Harnack emphasised that while drugs may have obvious effects such as emesis, there may be other less evident but important actions equally worthy of attention, and it was this tenet that became his main experimental strategy in relation to apomorphine. In addition to a detailed review of the literature, Harnack went on to describe his own extensive animal experiments. These included studies on the effects of apomor-



**Fig. 2.** Old anatomical theatre of the University of Dorpat (now the University of Tartu, Estonia), by Louis Höflinger (1860).

phine at different dosages on dogs, cats, rabbits and frogs. He drew particular attention to the fact that emetic doses of apomorphine in children could concomitantly induce circulatory collapse but that in adults, doses of 5–10 mg only provoked vomiting. Higher doses were already known to provoke motor effects in cats and dogs and to elucidate these differential actions, Harnack studied rabbits that did not exhibit an emetic response. Following parenteral administration of 2 mg of apomorphine, agitated locomotor behaviour was provoked which increased after repeated doses. With higher doses the animals licked and gnawed continuously on their litter and at the walls of their cages. He noted that cumulative doses of 10 mg caused muscle paralysis, respiratory failure and terminal convulsions. Further studies indicated that the convulsions were not due to hypoxia from respiratory failure, but to central nervous stimulation. Chloroform anaesthesia suppressed apomorphine-induced vomiting but not the effects on respiration indicating separate central centres for respiration and emesis. In his studies on frogs, Harnack observed that motor stimulation was followed by muscle paralysis. He concluded that low doses stimulated the vomiting centre but large doses inhibited it; in rabbits without an emetic response, the respiratory centre was stimulated in lower doses, and in-

hibited by larger doses; in dogs, only stimulatory effects were observed. He also observed differences of these effects when comparing apomorphine and morphine: central stimulatory effects were more prominent in apomorphine, but after morphine, the inhibitory stage started faster and was more pronounced than after apomorphine [10].

His experiments led him to conclude that apomorphine acted at several different centres in the brain including those involved in wilful behaviour, cardiovascular and respiratory control and sensation. This work occurred almost a century earlier than the studies of Andén et al. (1967) and Ernst (1967) which demonstrated for the first time that apomorphine directly activated specific dopamine receptors and that neuroleptics blocked dopamine receptors and acted as antagonists to apomorphine [11, 12].

Around the same time as Harnack was carrying out his pharmacological studies, Samuel Gee in London was studying the emetic effects of apomorphine in low dosage in humans demonstrating its considerable potential as an emetic [13]. The earliest reference to the potential use of apomorphine in the treatment of Parkinson's disease was made by Weil in 1884 although it had by this time been proposed as a treatment for Saint Vitus' dance [14].

During the 20th century there were many detailed studies of the numerous motor and behavioural effects including yawning and penile erection, leading to the identification of different types of dopamine receptors to account for the diverse clinical and experimental consequences of apomorphine administration. The introduction of blockers of dopamine receptors greatly facilitated understanding of the differential effects of apomorphine as well as its use in clinical practice [15, 16]. The effects of apomorphine were further exploited, often controversially, for a wide variety of disorders, from the treatment of homosexuality, alcohol, tobacco and morphine addiction to erectile dysfunction but it was the Boston neurologist Robert Schwab (1951) and the clinical scientist George Cotzias (1970) who finally confirmed Weil's suggestion that apomorphine might have anti-parkinsonian effects [17, 18]. It is beyond the scope of this account to evaluate present uses of apomorphine in the assessment, diagnosis and management of motor complications of Parkinson's disease [19].

Erich Harnack's crucial contribution was to demonstrate that apomorphine had potent effects on the central nervous system. It would have amused him if not surprised him that following the demonstration of its efficacy in Parkinson's disease, a number of drug-regulatory authorities delayed the re-introduction of apomorphine into modern therapy because of unjustified apprehension arising from its chemical similarity to morphine.

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### Disclosure Statement

The authors have no conflicts of interest to disclose.

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