Herbert Wertheim College of Medicine, Florida International University, Department of Cellular Biology & Pharmacology, Miami, FL, USA

Neuropathic organophosphates: from Scrugham, Heim and Lorot to Jake leg paralysis

G. A. Petroianu

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Prof. Dr. med. Georg A Petroianu, Herbert Wertheim College of Medicine, Florida International University, Department of Cellular Biology & Pharmacology, University Park (11200 SW 8th Street), Miami, 33199 FL, USA
georg.petroianu@fiu.edu

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Henry Scrugham (1811–1898), the father of triphenyl-phosphate, was a student of Alexander Williamson (1824–1904), Professor of analytical and practical chemistry at the University College London. Williamson using the approach perfected by Scurgham reacted phosphorus pentachloride with cresol (a mixture of ortho, para and meta isomers) thus obtaining tricresyl phosphate (TCP). The triesters of phenol, cresol and naphtol were prepared with a higher yield by Rudolf Heim (1861–1919) by their respective reaction with phosphorus oxychloride ($POCl_3$). Heim is also the first one to obtain pure tri-o-cresyl phosphate (TOCP). In the meantime French pharmacist Jules Brissonnet (1859–1915) synthesized creosote phosphate (containing i.a. TOCP) and popularized its use in the treatment of pulmonary phthisis (tuberculosis). Camille Lorot (1872–1951) and others in France and Germany recognized the ability of creosote phosphate to induce polyneuropathies but this knowledge did not prevent the Ginger Jake epidemic (Jake leg) of the 1930*s* in the US. The Jake induced neuropathy was first recognized and described in Oklahoma City by a General Practitioner, Ephraim Goldfain (1894–1983). Soon thereafter Maurice Isadore Smith (1887–1951), a pharmacologist, and chemist Elias Elvove (1883–1962) identified TOCP in Jamaican ginger extract as the causative agent. We attempt to shed some light on the life and family of the less known chemists, pharmacists and physicians associated with the synthesis of neuropathic organophosphates and with the recognition of their toxicity.

1. Introduction

The first neutral ester of phosphoric acid, triethyl phosphate was synthesized 1848 in the laboratory of Gustav Magnus (1802–1870) in Berlin by the Swiss chemist Franz Anton Voegeli (1825–1874) using the tedious method of directly reacting "spirit of wine" (ethanol) and phosphoric acid (Petroianu 2009). The synthesis 1854 of the first organophosphate cholinesterase inhibitor (tetraethyl pyrophosphate) was achieved by the French organic chemist Philippe de Clermont (1831–1921) and Russian chemist Wladimir P. Moshnin from Moscow, both working in the laboratories of Adolphe Wurtz in Paris (Petroianu 2008). The synthetic approach used by de Clermont and Moschnin was made possible by the work of Alexander Williamson (1824–1904), an English chemist trained in Germany (in Heidelberg and Gießen) who became Professor at the University College in London: Williamson serendipitously discovered a new way to produce *ethers* using ethyl iodide and potassium salts of the acid to be esterified. It was seventy-eight years later, in 1932, that Willy Lange (1900–1976) and his graduate student Gerda von Krueger realized the acute toxicity of organophosphates (Petroianu 2010).

A mixture of tricresyl phosphates was obtained by Williamson in 1854, while the neuropathic isomer tri-ortho cresyl phosphate (TOCP) was isolated by Rudolf Heim (1861–1919) in 1883. Within sixteen years the first warning concerning the neuropathic potential of phenol based phosphor esters was issued by the French physician Camille Lorot (1872–1951).

With this short contribution we attempt to shed some light on the life and family of the less known chemists, pharmacists and physicians associated with the synthesis of neuropathic organophosphates and with the recognition of their toxicity.

2. Excise and inland revenue laboratories

An excise tax is an inland tax on the sale or production of specific goods and as such an important source of revenue for the government; in order to impose appropriate taxes analytical chemistry abilities are needed. The Excise Laboratory was founded in Great Britain in 1842. The issue of manning the laboratory with competent chemists was solved in an original un-bureaucratic way: excise officers were sent to the University College in London for studies, all expenses paid. The Board of Excise was merged with the existing Board of Taxes and Board of Stamps to create the new Board of Inland Revenue in 1849. The practice of sending civil servants to University College continued under the new board into the late 1850*s* and a number of highly qualified Excise Chemists and later Inland Revenue Chemists were the result (Hammond and Egan 1992). Henry Scrugham (1811–1898) was one of them.

Scrugham became an *Excise man* in 1838. He attended University College, possibly with some interruptions, between 1851 and 1854. He is first mentioned November 1851, when he took classes in mathematics, analytical chemistry and chemistry. November 1852 he is listed as paying for classes in mathematics, natural philosophy, analytical chemistry and chemistry. October 1853 he is given as studying chemistry. His last entry in the registers is from November 1853. He is noted as studying French, geology & mineralogy, botany and analytical chemistry (personal communication, Robert Winckworth, UCL Records). During his University College time he worked, as most Excise men did, in the analytical laboratory (Birkbeck Laboratory, Fig. 1) under the guidance of Alexander Williamson (1824–1904). Williamson was since 1849 Professor of analytical and practical chemistry. His role as father of the modern ether chemistry cannot be underestimated (Priesner 1986): his early synthetic approach using ethyl iodide and salts of the acid to be esterified made possible the work of many others, such as Wladimir Petrovich Moshnin († 1899 or 1900) and Philippe de Clermont (1831–1921), the creators of the first cholinesterase inhibiting phosphorous ester, tetraethyl pyrophosphate (TEPP) (Wiliamson 1851; Petroianu 2015).

Using a new synthetic approach Scrugham reacted phosphorus pentachloride (PCl_5; *Fuenffach-Chlorphosphor*) with phenol (C_6H_5-

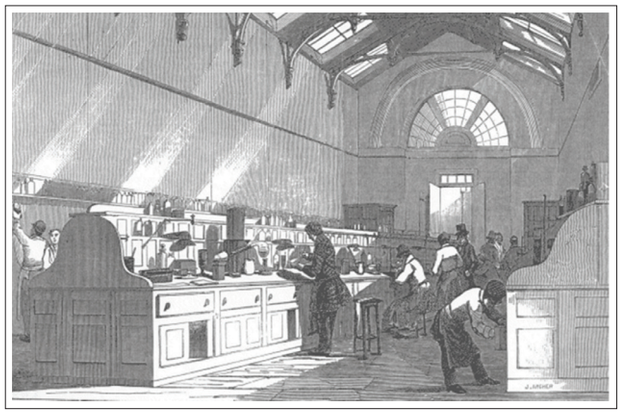
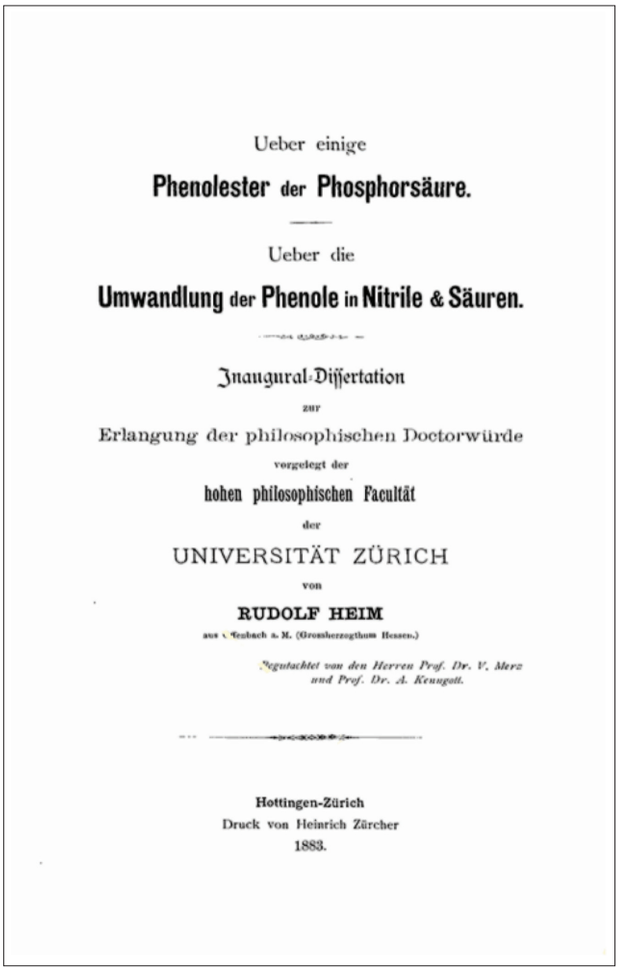


Fig. 1: The Analytical Laboratory (Birkbeck Laboratory) at the University College in 1846; the persons seen wearing hats are demonstrators. George Birkbeck MD (1776–1841) after whom the Laboratory was named was a major benefactor. Original in Illustrated London News, 1846 reproduced in "Weighed in the Balance" by Hammond and Egan, 1992; reproduced with kind permission of the National Archives and HMSO.



Ueber einige

Phenolester der Phosphorsäure.

Ueber die

Umwandlung der Phenole in Nitrile & Säuren.

Inaugural-Dissertation

zur

Erlangung der philosophischen Doctorwürde

vorgelegt der

hohen philosophischen Facultät

der

UNIVERSITÄT ZÜRICH

von

RUDOLF HEIM

aus Neubach a. M. (Grossherzogthum Hessen.)

Begutachtet von den Herren Prof. Dr. V. Merz und Prof. Dr. A. Kenngott.

Hottingen-Zürich
Druck von Heinrich Zürcher
1883.

Fig. 2: The triesters of phenol, cresol and naphtol were prepared with a much higher yield by Rudolf Heim (1861–1919) by their respective reaction with phosphorus oxychloride ($POCl_3$); the synthesis is described in his Doctoral thesis prepared under the supervision of Professor Victor Merz (1839–1904) submitted 1883 in Zurich.

OH) and obtained phosphorus oxychloride ($POCl_3$) and triphenyl phosphate (Scrugham 1855). Phenol was available since 1834 when Friedlieb Ferdinand Runge (1795–1867) extracted the substance from coal tar and called it carbolic acid (*Karbolsäure*). Phosphorus pentachloride was obtained earlier by Sir Humphry Davy (1778 –1829).

The same reaction as used by Scrugham (phosphorus pentachloride with phenol) was studied earlier by Charles Frédéric Gerhardt (1816–1856) and Auguste Laurent (1807–1853) in their attempt to synthesize chlorobenzene (C_6H_5Cl), but they failed to identify the presence of the triester (Gerhardt and Laurent 1850).

Scrugham's innovative work was recognized and he received an honorable mention 1854 at the Williamson Prize for chemical research. The other recipient of a mention was George Kay (1815–1867) while the first prize of 50 pounds sterling went to Robert Railton (1822-1875). All three laureates were Excise men. During his London stay Scrugham rented in a boarding house in St. Pancras (18 Somers Place), quite close to the laboratory, together with John Brown and John Farguharson, all of them Excise (Inland Revenue) men from Cumbria (1851 Census).

3. Henry Schrugham (1811–1898)

The Scrughams were a large family of hard-working people residing mainly in Cumbrian cities; our Henry hailed from Workington, as did his father and his grandfather; 1838 he joined the Excise. Towards the end of his London period (1853) he married the daughter of the *ironmonger* (hardware store owner) from Workington. Henry Scrugham retired from service as a *Superanuated Internal Revenue Supervisor*.

Scrugham describes triphenyl phosphate as a *clear oily substance, having a yellow tinge, like that of uranium glass. It is inodorous, soluble in alcohol and ether but insoluble in potash, except by boiling. It also possesses the peculiar property of epipolic diffusion; by ordinary day-light the epipolic rays, which have a fine violet tint, are visible at some distance below the surface*.

Epipolic diffusion is a term coined by Sir John Herschel (1792–1871) when describing the luminous appearance of some solutions of quinine (Scrugham 1855; Herschel 1845).

Williamson using the approach perfected by Scurgham reacted phosphorus pentachloride with cresol (a mixture of ortho, para and meta isomers of methyl-phenol) thus obtaining tricresyl phosphate (TCP) (Williamson 1854).

The triesters of phenol, cresol and naphtol were prepared with a much higher yield by Rudolf Heim (1861–1919) by their respective reaction with phosphorus oxychloride ($POCl_3$) (Heim 1883, Fig. 2). While Heim acknowledges that tri-naphtyl phosphate was previously obtained in the laboratory of Hermann von Wichelhaus (1842–1927) by Louis Schaeffer (1840–1906) and that tri-p-cresyl phosphate (TPCP) was previously prepared by Anna Wolkow (1837–1876) (Anna Feodorovna Volkova; Анна Федоровна Волкова), both using the Scrugham approach, he points out that he is the first one to obtain pure tri-o-cresyl phosphate (TOCP) (Schaeffer 1869; Heim 1883; Fischer 1906; Creese 1998).

4. Rudolf Christof Heim (1861–1919)

Rudolf Heim hailed from a wealthy industrialist family from Offenbach (Hesse), the youngest child among seven boys and two girls. His father and his uncle had established in Offenbach the *Gebrüder Heim Maschinenfabriken*; their products were state-of-the-art and recognized worldwide. In 1880 he matriculates in Zurich and studies Chemistry; his doctoral thesis prepared there under the supervision of Professor Victor Merz (1839–1904) dates from 1883.

5. The French contribution

In the meantime in France, pharmacist Jules Brissonnet (1859–1915), Professor *suppleant* at the Medical School in Tours, reacted phosphorus oxychloride with *creosote* obtaining *phosphate de creosote.* Creosote, described in 1832 by Carl von Reichenbach (1788–1869), is a mixture of numerous substances containing about 1/5 cresol isomers, 1/3 guaiacol, 1/3 creosol, the rest consisting of various phenol related compounds (Reichenbach 1833). Brissonnet copyrighted the name *Phosote®* for the product, which he strongly recommended for the treatment of tuberculosis (Fig. 3). Dr. René

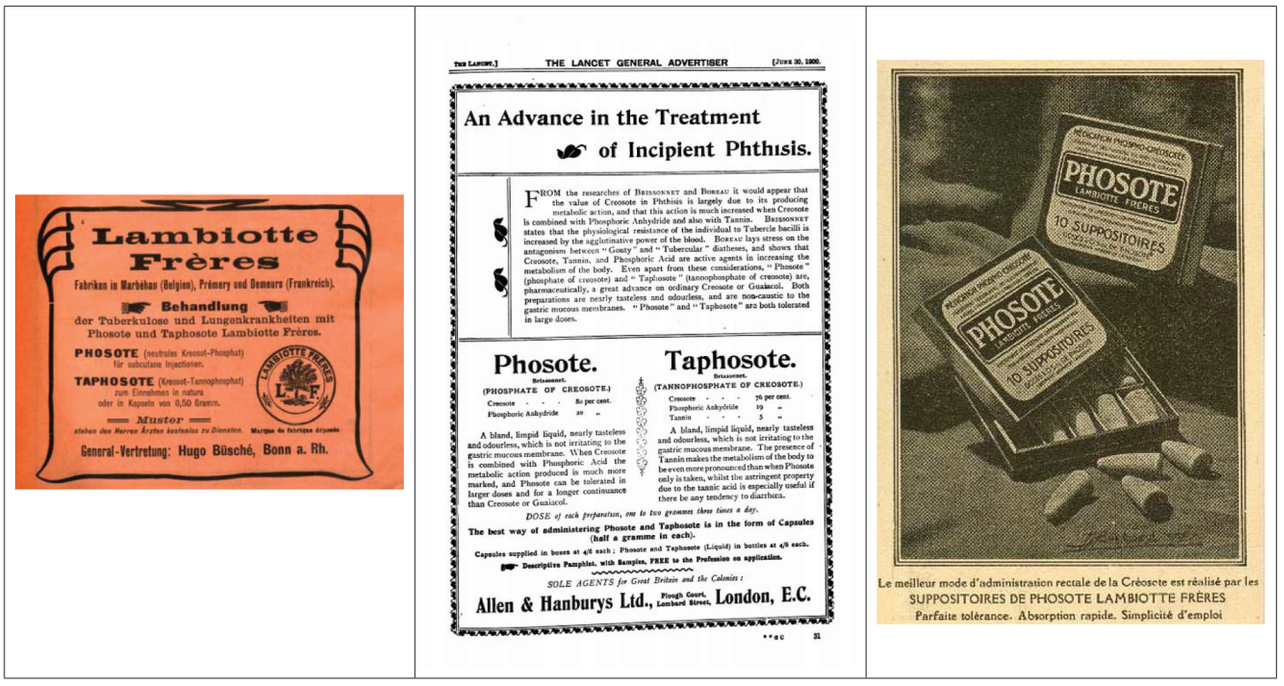


Fig. 3: Jules Brissonnet (1859–1915), Professor suppleant at the Medical School in Tours, reacted phosphorus oxychloride with creosote obtaining phosphate de creosote. He copyrighted the name *Phosote*® for the product, which he strongly recommended for the treatment of *Incipient Phtisis*. The product was manufactured by the chemical company of the brothers Lambiotte and marketed in many countries. The ad states *Phosote: A bland, limpid liquid, nearly tasteless and odourless, which is not irritating to the gastric mucous membranes. When creosote is combined with phosphoric acid the metabolic action produced is much more marked, and Phosote can be tolerated in larger doses and for a longer continuance than Creosote or Guaiacol. Dose of the preparation, one to two grammes three times a day.*

Boureau (1854-1936), a clinician from the same city of Tours, treated a good number of patients with *Phosote*® (Allais 2009).

In his doctoral thesis from 1899 Camille Lorot (1872–1951) gives a detailed description of the clinical use of various *creosote* derivatives, including a detailed description of the adverse drug reactions encountered while working at St-Joseph's Hospital in Paris under the guidance of Dr Edouard Tison (*1842) (Lorot 1899). In Chapter V titled *La polynevrite phospho-creosotee* (creosote-phosphate induced polyneuropathy) one can find a detailed description of treatment induced polyneuropathy: "*Meanwhile the gait becomes difficult, the sick woman trots, she puts her knees forward not to lock her joints, and the rhythm of the gait is characteristic. Her legs are so weak that they can hardly hold her up. If you have her sit on the side of the bed, and try to elicit patella reflexes, you notice her knee reflexes are almost gone.*" In chapter IX: *Phosphate et Tannophosphate de Creosote (Syn.: Phosote & Taphosote)* a stern warning is issued: "*While these ethers are neither caustic nor toxic, one cannot conclude that high dosages are harmless….If such dosage is continued one can observe after a while brutal occurrences of polyneuropathy, more rapidly and commonly with the phosphate….*" Lorot was therefore most likely the first one to recognize the ability of phosphoric acid esters to induce polyneuropathy. This is however disputed by Dr Edmond Chaumier (1853-1931) in a publication titled *De la paralysie produite par le phosphore* (Chaumier 1904). Chaumier writes: *"I believe to have been the first to observe the paralysis due to phosphorylated creosote ethers. In fact, Mr. Brissonnet Adjunct Professor at the Medical school in Tours, who had discovered the creosote phosphate gave me some samples of this product the 4th of April 1898 and on May 14th, less than a month and a half later, I already wrote him that his drug caused paralysis. …..I did not immediately publish the observation that I made on my little patient that I was looking after, because I wanted a more complete observation and not a preliminary study, and also because I was held back by other work."*

Chaumier might have been indeed very busy those days as he had just purchased a castle, Plessis-les-Tours (formerly Château of King Louis XI) and was establishing there his *Institute vaccinal* and the industrial production line for vaccines (Fig. 4). As to the veracity of his *post hoc* adjudication of the paternity of the observation of *Phosote* toxicity this is an entirelely different issue which we will not be able to solve.

Lorot's father was a public school teacher in Arthonnay (Yonne, France); he served there for forty years and had three children: Auguste-Armand (*1870), Charles-Camille (*1872) and Marie Eugenie (*1875). Auguste became a pharmacist while Camille pursued a medical career, graduating in Paris 1899. Camille had various interests publishing before entering medical school on aerodynamics and the construction of an *Aeroptere*. In 1901 Camille married Palmyre Juliette Mestivier.

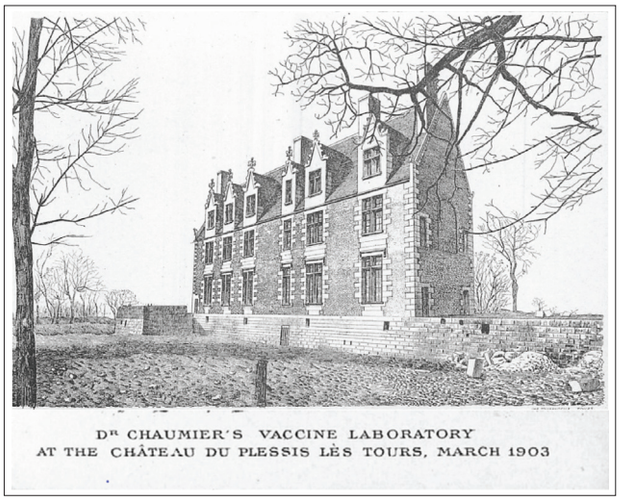


Fig. 4: Dr Edmond Chaumier (1853–1931) purchased Plessis-les-Tours (former Château of King Louis XI) and established there his *Institute vaccinal.* [Postcard from the private collection of the author; 1903, Imprimerie Tourangelle – Tours]. While Chaumier's contributions are unquestioned his assertion *Je crois avoir été le premier à observer la paralysie due aux éthers phosphorés de créosote* is questionnable.

Few details are available (to the author) about his later life except that he treated patients with unlicensed preparations (*toxyline*) for which he was charged but acquitted (1911).

6. *Kreosotum phosphoricum* in Germany and the Netherlands

While in Germany the enthusiasm for *Phosote* was less pronounced than in France, the product was used nevertheless. The first warning about neuropathy came early when Hofrat Dr. Leopold Loewenfeld (1847–1924) reported on a number of cases: "*The unpleasant experiences we had here with the Phosphot treated cases are not isolated ones. As the manufacturer, the chemical factory von Heyden (Radebeul at Dresden), informed me in a letter 'it turns out that creosote phosphate possesses undesirable side effects and therefore after a short initial phase its use ceased almost entirely"* (Loewenfeld 1903).

Johannes Karel August Wertheim Salomonson (1864-1922) in the Netherlands publishes on the same topic and recognizes that while both creosote and phosphorous taken separately are nontoxic, their (unidentified) combination is not (Wertheim Salomonson 1906, Fig. 5). He writes: "*A later analysis should show whether the constituents of phosphoric creosote were regrouped in such a way that either the creosote or the phosphoric acid acquired toxicity. In recent chemistry there are ample and numerous examples how through transformation of one constituent such toxicity seems possible.*"

Dr Willem Gerard Huët (1869–1911, Fig. 6) of Haarlem in the Netherlands reports in the Centralblatt (Huet 1907): "*In the fall of 1905, a small epidemics of neuritis was observed in Haarlem. A physician who was not licensed to practice in Holland prescribed creosote to multiple patients, some of which showed signs of paralysis. After seeing my note warning of the dangers of creosote he published a warning in local newspapers asking patients to discontinue the treatment.*" (Fig. 7).

Fig. 6: Dr Willem Gerard Huët (1869-1911) warned the population of Haarlem against using creosote phosphate; reproduced with kind permission of Alexander de Bruin, the Noord-Hollands Archief, Haarlem, inventory number 54-045522.

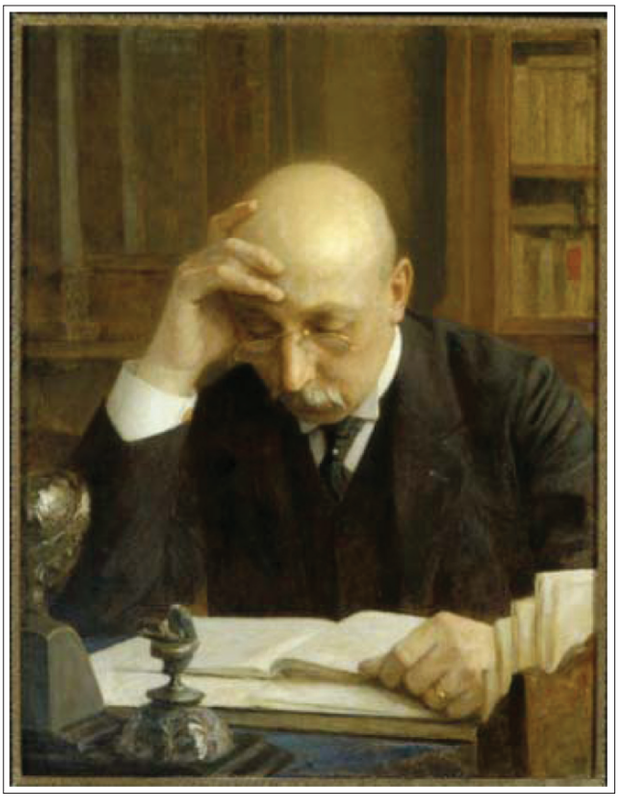


Fig. 5: Johannes Karel August Wertheim Salomonson (1864–1922) recognizes that while both creosote and phosphorous taken separately are nontoxic, their combination is not. Portrait by Jan Veth (1864–1925) from Museum of the University of Amsterdam. Reproduced with kind permission.

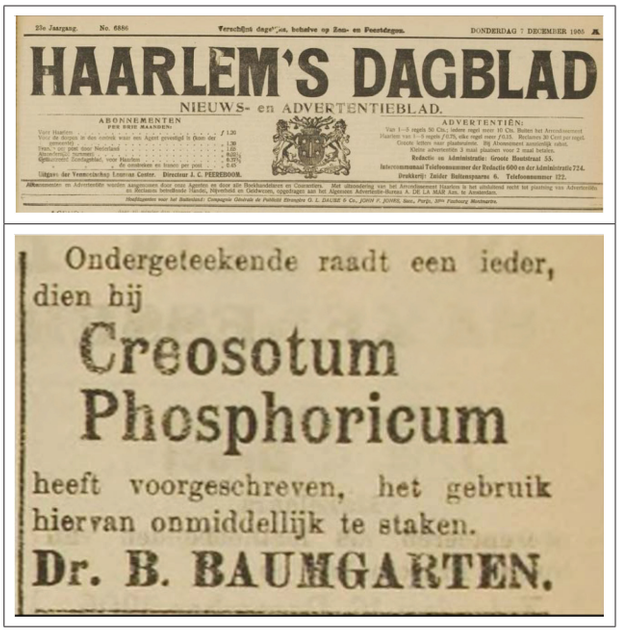


Fig. 7: On Thursday December 7th, 1905 an ad was placed by Dr. Baumgarten in the Haarlem's newspaper warning his patients of the use of the very creosote phoshate he had previously prescribed to them. The action was the result of Dr. Huet's campaign to make the dangers of the medication known; Baumgarten (*De Indische Wonderdokter*) ended by leaving 1910 the Netherlands.

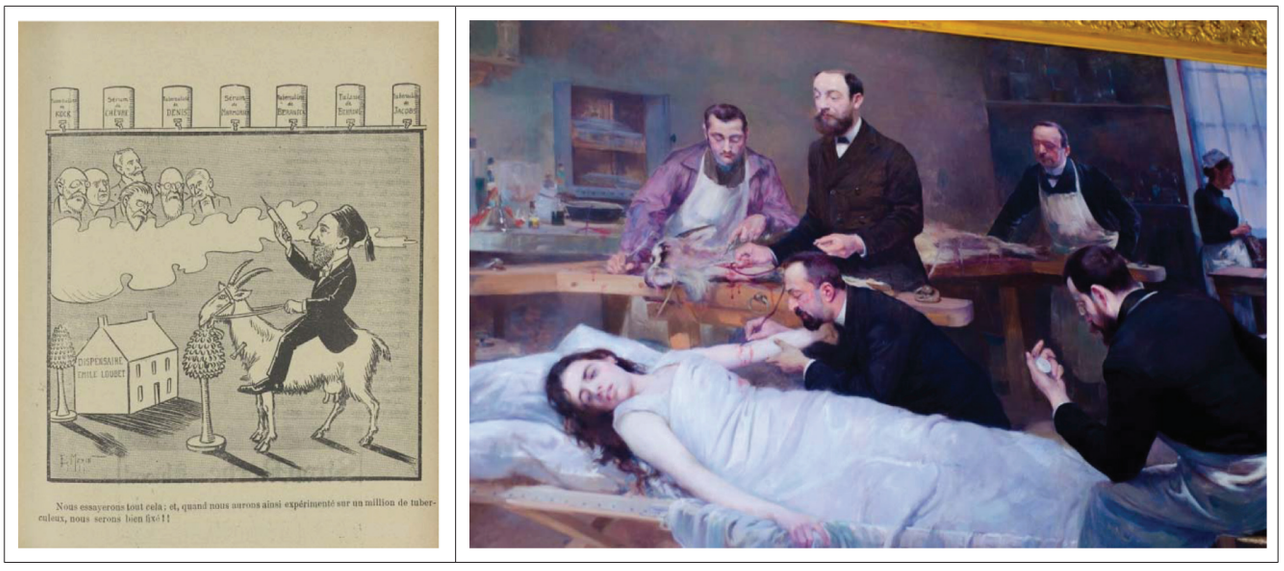


Fig. 8: Dr Samuel Bernheim (1855-1915), *Président de l'Œuvre de la Tuberculose Humaine, Médecin en chef des Dispensaires antituberculeux français, et Président de la Société internationale de la Tuberculose* gained notoriety for his experiments transfusing goat blood to tuberculous patients, the ratioanle being that goats never develop tuberculosis.
Left: caricature of Dr Bernheim, reproduced with kind permission of Bibliothèque interuniversitaire santé. L'Album du Rictus, journal humoristique mensuel: deuxième série, Edition Paris, s. n., 1907-1908 (ref. med24432x02x0091)
Right: Painting by Jules Adler (1865-1952; insert) titled *Transfusion of a Goat's Blood* comissioned by Dr. Bernheim in 1892. Reproduced with kind permission of Musée d'histoire de la médecine, Université Paris-Descartes.

In addition Huët asks a distinguished Haarlem pharmacist and chemist, Nicolaas van der Sleen (1853-1923), to examine the composition of the drug and notes that contamination by arsenical can be excluded.
Despite many voices warning of the dangers associated with creosote phosphate, not everybody was convinced. One of the strongest reasons for doubting the causal role of creosote phosphate and of the associated tricresyl phosphate was the inability to reproduce the symptoms in the animal models used.
In France Dr Samuel Bernheim (1855-1915) (Fig. 8), *Président de l'Œuvre de la Tuberculose Humaine, Médecin en chef des Dispensaires antituberculeux français, et Président de la Société internationale de la Tuberculose* enthusiastic supporter of *Phosote* and author of a comprehensive study titled *La tuberculose et la médication créosotée* writes: "*.....experimentaly one can never induce these attacks of polyneuritis in animals, even when exposed to massive doses, not even toxic ones. In dogs, guinea pigs and rabbits, when we injected them with high doses of creosote phosphate, we never observed any nervous system symptoms such as paraesthesias, paralysis, or coordination problems or limb paralysis.*"

7. Ginger Jake paralysis

Fast forward to prohibition era America: alcohol not being easily available, people used - despite the horrible taste - as a surrogate alcohol containing medicines that were legal and cheap. In order to qualify as medicine such alcoholic potions had to fulfill certain criteria such as containing a proportion of non-volatile/solid constituents. Brothers-in-law Harry Gross (President) and Max Reisman (part-owner) of Hub Products in Boston, identified (with a little help from some friends) tri-o-cresyl phosphate (TOCP) as the ideal adulterant: TOCP was already quite popular as a plasticizer, having found as diverse uses as improving the quality of the celluloid films for motion pictures or that of celluloid billiard balls (Toy and Walsh 1987). The man behind the commercial success of the tri-aryl phosphate was a very talented chemist William G. Lindsay (1879–1925), chemical director of the Celluloid Company of Newark, New Jersey; he replaced both castor oil and camphor in the celluloid synthesis with TOCP, in the process not only obtaining a better celluloid but also significantly improving the company's bottom line. As a sign of recognition and token of appreciation Celluloid's TOCP received the trade name of *Lindol*.
Gross added *Lindol* to Jamaican ginger extract, a popular patent medicine known on the street as *Jake*. TOCP was used to partially replace the ill tasting and much more expensive original ginger resin contained in the genuine preparation. The improved product was shipped around the country in big barrels, sufficient to fill over half-a-million medicine bottles (Parascandola 1994; Canorel 2010). They acted on the assumption that TOCP was nontoxic, as they apparently were assured by the chemist advising them (Albert Benjamin Werby, 1888–1953) and by the Lindol manufacturer (Satin 2007). In fact, TOCP does not cause any toxicity in the rodent models used for routine toxicological evaluation and therefore TOCP toxicity when ingested by humans was unknown then.
The consequences were devastating, thousands of people developed *Jake leg* a mostly irreversible condition (later to be named OPIDN - *Organo Phosphate Induced Delayed Neurotoxicity*) characterized by degeneration of axons with subsequent secondary degeneration of myelin in the peripheral and central nervous systems (Abou-Donia 1981).
Organophosphates able to cause OPIDN are called neuropathic, TOCP being the first neuropathic OP to be synthesized (1883 by Heim) and to be identified as such (1930 by Smith and Elvove). Neuropathic OP*s* have in general a low acute toxicity i.e. limited or no ability to inhibit the acetyl choline esterase (AChE) which assures survival on exposure and provides the timeframe necessary to develop the delayed neuropathy. TOCP has no AChE inhibitory ability and needs to be hydroxylated by the cytochrome P450 system to an intermediate that spontaneously cyclizes to the neurotoxic saligenin cresyl phosphate (Fig. 9). This cyclic phosphate compound is able to inhibit the enzyme neuropathy target esterase (NTE; neurotoxic esterase) and thus clinically to cause OPIDN. The other two isomers, TMCP or TPCP are not neuropathic (cannot induce OPIDN) because they are unable to form stable cyclic saligenin phosphate esters (Aldrige 1953; Eto et al. 1962; Johnson 1973).
The clinical picture of Jake induced neuropathy (Jake leg; OPIDN) was first noticed and reported in Oklahoma City in February 1930 by Dr. Ephraim Goldfain [Goldfain, 1930]. Soon thereafter Maurice Isadore Smith, a pharmacologist and Elias Elvove, a chemist, both working for the government identified TOCP in

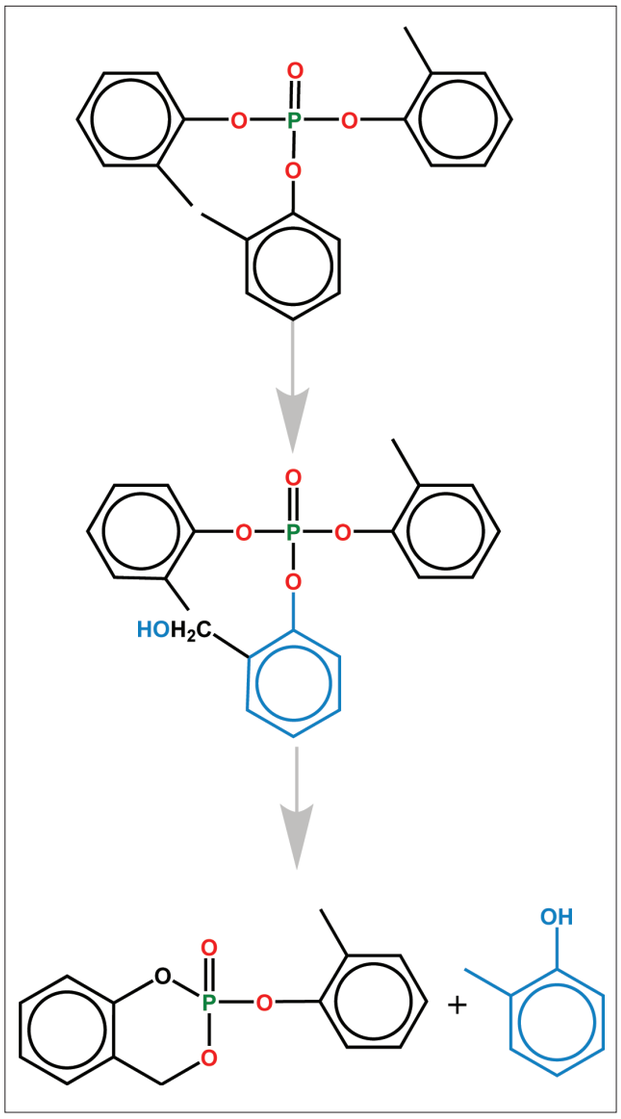


Fig. 9: TOCP (top) has no AChE (EC 3.1.1.7) inhibitory ability and is hydroxylated by the hepatic cytochrome P450 system to an intermediate (middle) that spontaneously cyclizes to the neurotoxic ester saligenin cresyl phosphate (bottom). This compound is able to inhibit the enzyme **N**europathy **T**arget **E**sterase (EC 3.1.1.5; NTE; Neurotoxic Esterase) thus clinically causing OPIDN. The other two isomers, TMCP or TPCP are not neuropathic (cannot induce OPIDN) most likely because they are unable to form stable cyclic esters. Modified from Eto et al, 1962.

Jamaican ginger extract as the causative agent (Smith et al. 1930; Kirk and Jacobson 2014).

8. Goldfain, Smith and Elvove

Ephraim Goldfain (1894–1983): The parents moved to America from Bucharest, Romania with their four children at the turn of the century (landed 1900) and settled in Colorado. Ephraim, the second oldest son studied medicine at the University of Colorado at Denver, class of 1921. Dr. Ephraim Goldfain practiced medicine in Oklahoma City (Fig. 10). **Elias Elvove** (1883–1962) was a chemist of Ukrainian origin who moved to America at age 14; he worked for over forty years at the NIH (Kirk and Jacobson 2014, Fig. 11). Maurice Isadore Smith (1887–1951) was a pharmacologist of Russian origin (Fig. 12). He arrived in the United States as a child. His medical degree was granted by Cornell University Medical School in 1913. He then taught pharmacology at the University of Michigan and at the University of Nebraska. In 1920 he joined the staff of the pharmacology division of the Hygienic Laboratory.

Fig. 10: The Goldfain family at the turn of the century in Denver. The parents, Joseph (*1858) and his wife Nettie (*1868) moved to America from Bucharest, Romania with their four children George (*1892), Ephraim (*1895), Rose (*1896) and Samuel (*1899). Ephraim Goldfain (1894-1983), the second oldest son, is standing next to his mother. Reproduced with kind permission from Dr. Jeanne Abrams, Professor & Curator, Beck Archives of Rocky Mountain Jewish History CJS and Special Collections, University Libraries University of Denver.


N.I.H. record

FEDERAL SECURITY AGENCY Vol. III, No. 26 - 26 December 1951 PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

87 AT NIH CITED IN AWARDS CEREMONIES

Dr. Elvove, recipient of FSA's Second Highest Honor.

Shown here with Dr. Sebrell (center) are four NIH employees who received 40-Year Length of Service Awards. From left, Dr. Elvove, Miss Louden, Dr. Bender, and Mr. Feeser.

Fig. 11: Cover page of the *NIH record* from December 26th, 1951 showing Dr Elias Elvove (1883-1962) twice: Left, as a recipient of the Award for Superior Service from the Federal Security Agency; Right, in the group photo as a recipient of Forty-Years of Service Award from the National Institute of Health. Reproduced with kind permission from Kenneth A. Jacobson, PhD, National Institutes of Health.

He devoted his entire professional career to Government service (McCoy 1952; Barry 1960).

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Fig. 12: Maurice Isadore Smith (1887-1951), the pharmacologist working for the government identified (with Elias Elvove, a chemist) TOCP in Jamaican ginger extract as the causative agent of the neuropathy. Reproduced with kind permission from Dr. Stephen Greenberg, History of Medicine Division, National Library of Medicine.

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