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The history of cholinesterase reactivation: hydroxylamine and pyridinium aldoximes

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Received January 18, 2012, accepted February 3, 2012

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Pharmazie 67: 874–879 (2012) *doi: 10.1691/ph.2012.2519*

Hydroxylamine (NH_2OH) the substance which will turn out to be of importance to those interested in the treatment of organophosporus cholinesterase inhibitor exposure, was synthesized by Wilhem Clemens Lossen in 1865 while working in Halle as an assistant in the laboratory of Wilhelm Heinrich Heintz. The Lossen synthesis generated hydroxylamine in aqueous solution. Anhydrous hydroxylamine was prepared almost simultaneously by Lobry de Bruyn and Crismer (1891). Using hydroxylamine as a starting point Meyer synthesized aldoximes and ketoximes (1897). Lange, a PhD student of Ladenburg, isolated 2-methyl-pyridine (α-picoline). Some fifty years later Wilson, working in the laboratory of Nachmansohn, demonstrated the ability of hydroxylamine to reactivate cholinesterase inhibited by organophosphates. Finally Wilson and Ginsburg using 2-methyl-pyridine as a starting point synthesized the first pyridinium aldoxime reactivator of clinical relevance, pralidoxime (1955).

1. Introduction

Organophosphorus esters (organophosphates and organophosphonates) are serine esterase and protease inhibitors widely used in agriculture as insecticides and acaricides, in industry and technology as softening agents and additives to lubricants, and some of them are classified as chemical warfare agents. The acute toxicity of these compounds is due to inhibition of the enzyme acetylcholinesterase (AChE), which metabolizes the neurotransmitter acetylcholine (ACh). Sarin (GB) and VX were used in terrorist attacks in Japan, illustrating the terrorist threat these compounds represent. The inhibition of esterases (butyrylcholine: 3.1.1.8 and acetylcholine: 3.1.1.7) results from reacting covalently with the active centre serine (by phosphylation, i.e. either phosphorylation or phosphonylation) and translates into an "endogenous acetylcholine poisoning".

The inhibition of cholinesterases causes accumulation of acetylcholine which drives an initial sympathomimetic response due to stimulation of nicotinergic receptors in the adrenal medulla followed by a longer-lasting parasympathomimetic response due to stimulation of muscarinic receptors. Both responses can and must be controlled by appropriate medications. In addition, organophosphates and organophosphonates cause an acetylcholine overflow at neuromuscular synapses with ensuing depolarizing block, requiring artificial ventilation. Furthermore activation of central cholinergic receptors results clinically in seizure activity.

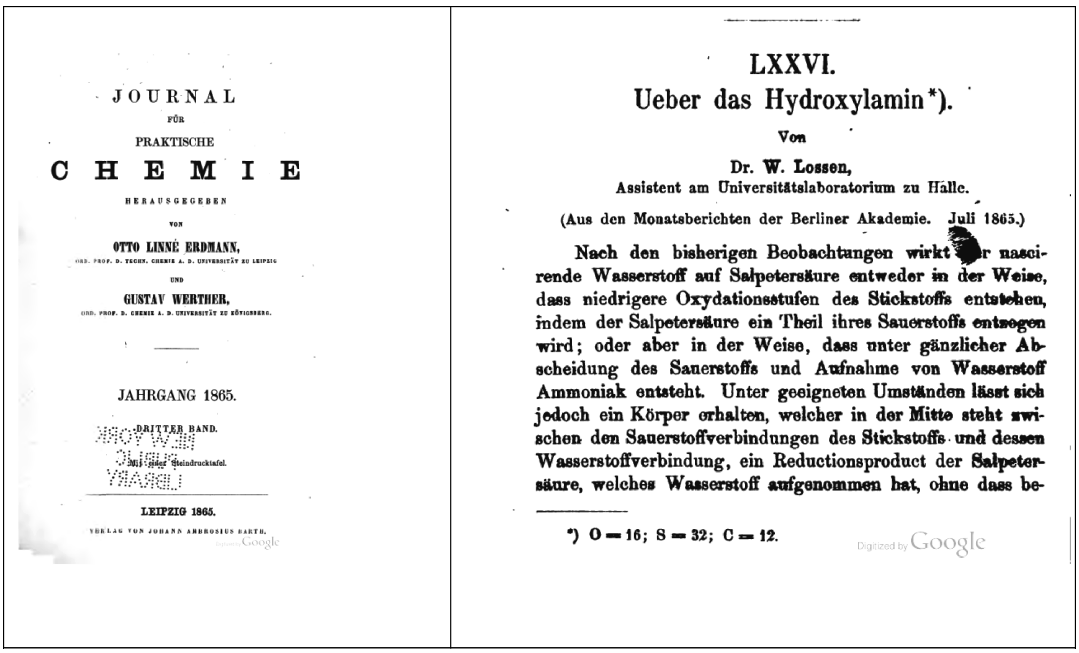
The therapy of organophosphorus inhibitors of cholinesterase poisoning is known by the catchy acronym ***A FLOP*** = ***A***tropine, ***FL***uids, ***O***xygen, ***P***ralidoxime (Petroianu 2005). The mnemonic is an oversimplification in as much as it does not include the GABA-A receptor agonists (benzodiazepines) used to control convulsions. A more comprehensive version would be ***A FLOOD*** = ***A***tropine, ***FL***uids, ***O***xygen, ***O***xime, ***D***iazepam. The latter version of the mnemonic has the added advantage as to remind of the clinical symptoms of organophosphorus inhibitors of cholinesterase exposure: the "flood" of secretions generated by cholinergic excitations.

The history of the development of organophosphorus inhibitors of cholinesterase has been described already (Petroianu 2008, 2009). The present contribution attempts to identify the people who made the development of cholinesterase reactivators, the pyridinium aldoximes (oximes) possible, as exemplified by the first reactivator of clinical relevance, pralidoxime.

2. The very early days

Some of the readers interested in the history of organophosphate ester synthesis might remember Professor Lossen as being the one who donated trimethyl phosphate to his assistant Weger (Petroianu 2010a).

Wilhem Clemens Lossen (1838–1906), was since 1877 Chair of Chemistry at the Albertus University in Koenigsberg. He was the first born son of Dr. med. Valentin Lossen (1803–1884), practicing physician in Kreuznach. Wilhelm studied first in Gießen (winter 1857 to summer 1859), than in Göttingen with Friedrich Wöhler (1800–1882) where he received his Ph.D. in 1862 with a Dissertation titled "*Ueber das Cocain*". After working as an Assistant to Karl Weltzien (1813–1870) in Karlsruhe he went on to become an assistant to Wilhelm Heinrich Heintz (1817–1880) in Halle only to move on to Heidelberg where he received his habilitation 1877. After being appointed extraordinary Professor in Heidelberg 1877 he became the same year "*Ordinarius*" (chair) in Koenigsberg, succeeding Professor Carl Graebe. He chaired the Department until 1903 when he retired, being suc-



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DRITTER BAND.
Mit einer Steindrucktafel.
LEIPZIG 1865.
VERLAG VON JOHANN AMBROSIUS BARTH.

LXXVI.
Ueber das Hydroxylamin*).
Von
Dr. W. Lossen,
Assistent am Universitätslaboratorium zu Halle.
(Aus den Monatsberichten der Berliner Akademie. Juli 1865.)
Nach den bisherigen Beobachtungen wirkt der nascirende Wasserstoff auf Salpetersäure entweder in der Weise, dass niedrigere Oxydationsstufen des Stickstoffs entstehen, indem der Salpetersäure ein Theil ihres Sauerstoffs entzogen wird; oder aber in der Weise, dass unter gänzlicher Abscheidung des Sauerstoffs und Aufnahme von Wasserstoff Ammoniak entsteht. Unter geeigneten Umständen lässt sich jedoch ein Körper erhalten, welcher in der Mitte steht zwischen den Sauerstoffverbindungen des Stickstoffs und dessen Wasserstoffverbindung, ein Reductionsproduct der Salpetersäure, welches Wasserstoff aufgenommen hat, ohne dass be-
*) O = 16; S = 32; C = 12.

Fig. 1: Lossen is best remembered for elucidating the exact molecular formula of cocaine (work performed under Professor Woehler in Goettingen) and the synthesis of hydroxylamine (work performed under Professor Heintz in Halle). Hydroxylamine (NH_2OH) will turn out to be of great importance for those interested in the treatment of organophosphate cholinesterase inhibitor exposure

ceeded by Heinrich Klinger. Professor Lossen was a privy government council (*Geheimer Regierungs-Rath*) and a member of the Imperial Leopoldine Carolinian German Academy of Nature Researchers (*Kaiserlich Leopoldinisch-Carolinischen deutschen Akademie der Naturforscher*).

Wilhelm's younger brother Karl August (1841–1893) was not less renowned; he was professor and state geologist (*Landesgeologe*) at the Royal Geological State Institution and Mining Academy (*Königliche Geologische Landesanstalt und Bergakademie*) in Berlin.

The chemist Lossen is best remembered for elucidating the exact molecular formula of cocaine (1863) and the synthesis of hydroxylamine NH_2OH (1865), a substance which will turn out to be of great importance to those interested in the treatment of organophosphate cholinesterase inhibitor exposure (Lossen 1865) (Fig. 1).

Anhydrous hydroxylamine was prepared almost simultaneously 1891 by the Dutchmen Lobry de Bruyn[1] (1857–1904) and the Belgian Leon Crismer[2] (1858–1944) (Bruyn 1891; Crismer 1891) (Fig. 2).

Reacting hydroxylamine with aldehydes and ketones Victor Meyer (1848–1897) (Fig. 3) and his students in his Zurich laboratory synthesized 1882 aldoximes (Joseph Petraczek)[3] and ketoximes (Alois Janny)[4] (Thorpe 1900; Petraczek 1882; Meyer and Janny 1882).

Hydroxylamine turns out to be one of the first substances shown to be able to reactivate cholinesterases affected by organophosphorus inhibitors. Irwin B Wilson (*1921) working at Columbia in the laboratory of David Nachmansohn (1899–1983), using hydroxylamine delivered the proof of concept that cholinesterases inhibited by organophosphates can be reactivated (Wilson 1951).

While hydroxylamine as a reactivator is far superior to water, the kinetics of the reaction are still far from useful. Using the 2-methyl-pyridine (Lange 1886) as a starting point, Sara Ginsburg (1908–1997) synthesized a number of pyridine oximes. Among those was also the first aldoxime cholinesterase reactivator of clinical relevance, pralidoxime or 2-PAM (2-pyridinium aldoxime) (Wilson and Ginsburg 1955) (Fig. 4).

2-methylpyridine was isolated by Otto **Lange** (1863–1941) (Lange 1886): Born in Varel (Oldenburg) in a well-off merchant family, Otto was a cousin of Helene Lange (1848–1930), the turn of the century German feminist who significantly advanced the cause of women emancipation and right to education (Otto's father Wilhelm (1824–1891) was a brother of Carl Theodor (1819–1864), Helene's father).

Otto studied chemistry in Hannover, Tubingen and finally Kiel where he became a PhD student of Albert Ladenburg (1842–1911). His doctoral dissertation titled "On Methyl-Derivatives of Pyridine" where he described alpha-methyl pyridine [alpha-picoline] was submitted 1886. Subsequently (1886–1889) he worked as an assistant at the agricultural-chemical experimental station "*Landwirtschaftlich Chemische Versuchsstation*" in Kiel. From there he moved on to join the Fleitmann & Witte nickel foundry in Iserlohn and subsequently to become technical director (≈ 1906) of the Phoenix foundry in Dortmund-Hoerde. He died in Dortmund 1941.

He is not to be confused with the homonymous contemporary chemist Otto **Lange** (1875–1936) originating from Prague, who

[1] Lobry **de Bruyn:** Cornelis Adriaan Lobry van Troostenburg de Bruyn obtained a PhD in chemistry in 1883 from the University of Leyden. He supervised the Dutch navy's chemical laboratory for explosives. In 1896 he was appointed professor of organic chemistry and pharmacy at the University of Amsterdam. 1897 he was invited to be a member of the Dutch National Academy of Sciences.

[2] Leon **Crismer:** Pharmacy graduate of the University of Liege (Luettich) class of 1879. Appointed 1893 Professor of Chemistry at the Military Academy Brussels (Thorburn-Burns and Deelstra 2008). Member of the Belgian Royal Academy of Sciences.

[3] Joseph **Petraczek:** PhD student of Meyer in Zurich; moves to Great Britain where he works for Read Holliday & Sons at Huddersfield. Within the organization he is known as the "German Emperor" (Whittaker 1956). Leaves Read Holliday to set up a chemical consulting company in Bradford (together with Christopher Rawson (1860–1940), first Secretary of the Society of Dyers & Colourists and for some time Editor of the Journal of the Society).

[4] Alois **Janny:** PhD student of Meyer in Zurich; works in Germany, France and Britain before moving to New York City where he works as a consulting chemist.

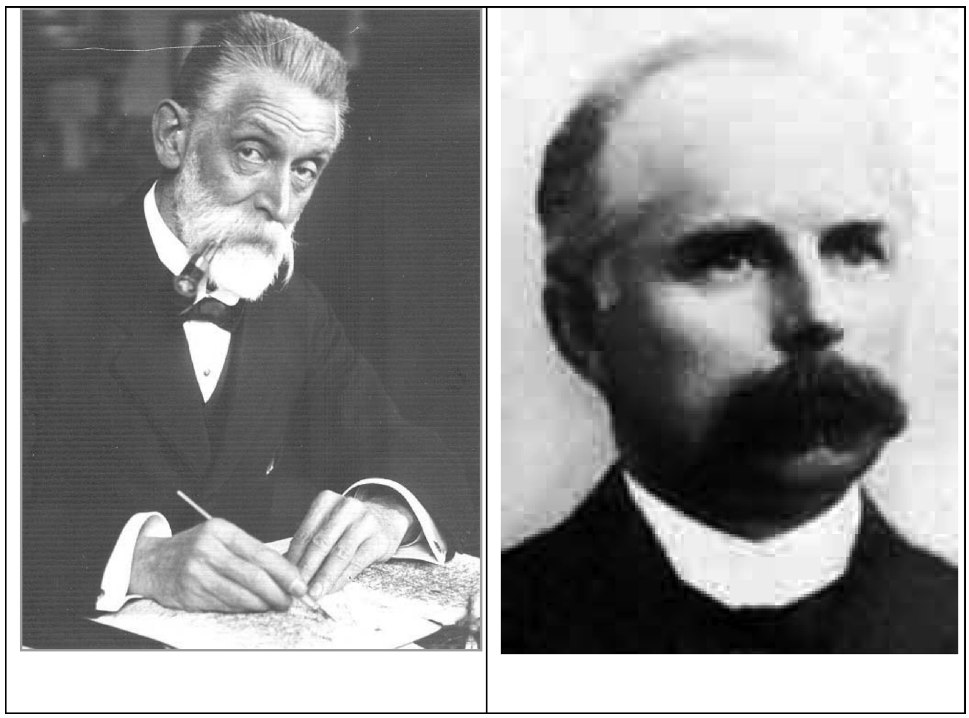
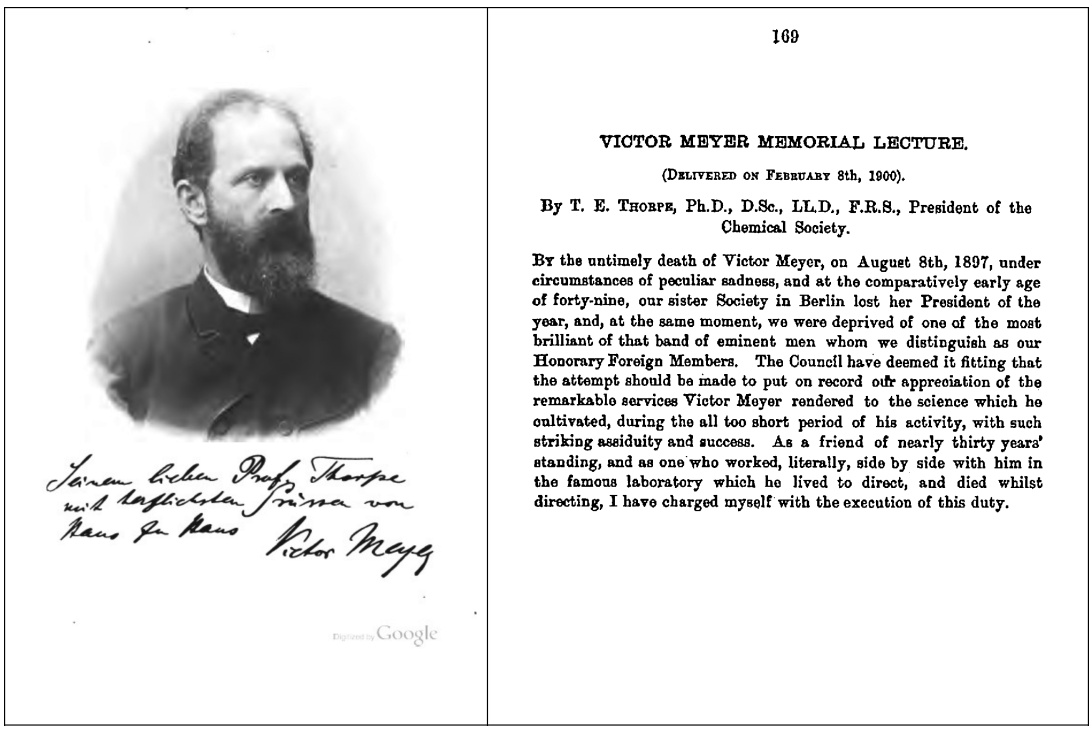


Fig. 2: Anhydrous hydroxylamine was prepared almost simultaneously 1891 by Leon **Crismer** (1858–1944) (left) and Lobry **de Bruyn** (1857–1904) (right)

received his PhD 1900 in Rostock for a doctoral dissertation titled "*On the structure of Chinophtalon and Chinophtalin*" on which a prize is bestowed. He goes on to work in Frankfurt/Main with Arthur von Weinberg (1860–1943) at the Leopold Cassella Company, Frankfurt, where the two share a number of patents. This younger and more flamboyant Otto Lange published with Professor Alexander Eibner and went on to teach (*Dozent*) in Munich at the Royal Technical University. He authored quite a number of chemical technical books. His involvement 1921 with the Metallytwerke AG, where he sat on the Advisory Board was less successfull; the shares of the Company become 1924 worthless. He died in Berlin 1936.

None of the Langes mentioned above was related to Willy **Lange** (1900–1976) who recognized the toxicity of phosphor ester (Petroianu 2010b); as indicated in the cv attached to his doctoral dissertation Willy's parents were Adolf Lange, a civil servant from Berlin (*Beamte beim Staatstheater)* and his wife Marie nee Rehberg (Peter Meiers 2011 personal communication).

Wilson, Nachmansohn and Ginsburg are holders of the US Patent # 2.816.113 (1957) describing the synthesis of prali-



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VICTOR MEYER MEMORIAL LECTURE.

(Delivered on February 8th, 1900).

By T. E. Thorpe, Ph.D., D.Sc., LL.D., F.R.S., President of the Chemical Society.

By the untimely death of Victor Meyer, on August 8th, 1897, under circumstances of peculiar sadness, and at the comparatively early age of forty-nine, our sister Society in Berlin lost her President of the year, and, at the same moment, we were deprived of one of the most brilliant of that band of eminent men whom we distinguish as our Honorary Foreign Members. The Council have deemed it fitting that the attempt should be made to put on record our appreciation of the remarkable services Victor Meyer rendered to the science which he cultivated, during the all too short period of his activity, with such striking assiduity and success. As a friend of nearly thirty years' standing, and as one who worked, literally, side by side with him in the famous laboratory which he lived to direct, and died whilst directing, I have charged myself with the execution of this duty.

Fig. 3: Victor Meyer (1848–1897), Chair & Professor of organic chemistry in Zuerich, Goettingen and Heidelberg, died of his own hand at the early age of forty-nine. Reacting hydroxylamine with aldehydes and ketones Meyer and his students in his Zurich laboratory synthesized 1882 aldoximes (Joseph Petraczek) and ketoximes (Alois Janny)

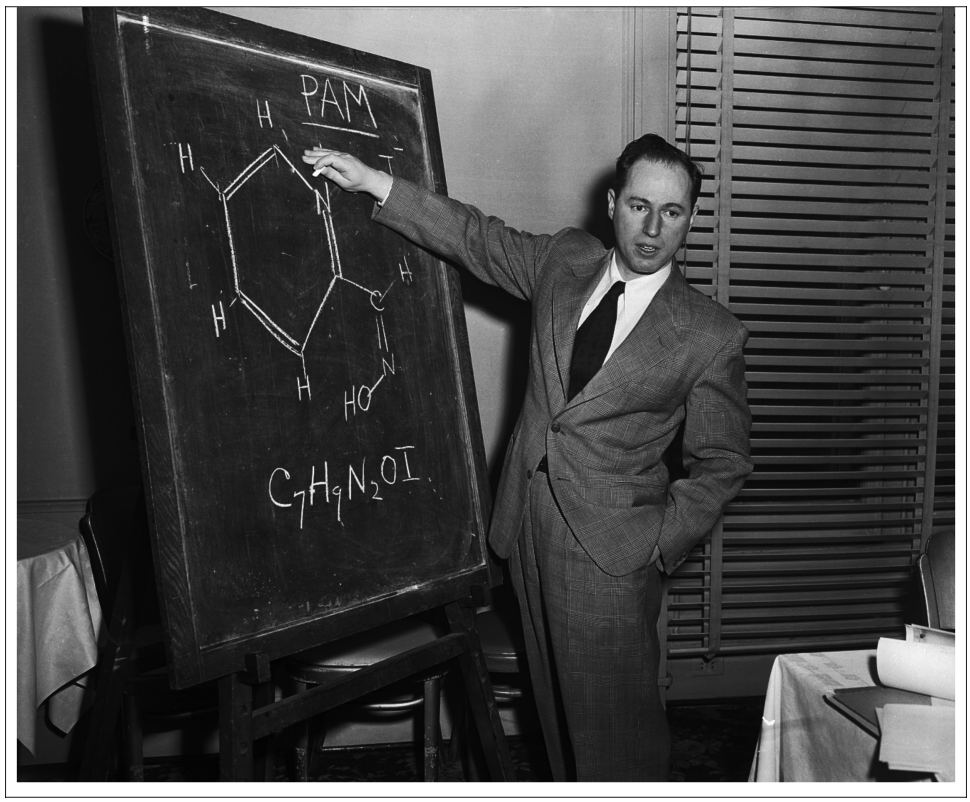


Fig. 4: **Irwin B Wilson**, the father of pralidoxime. According to Theodor Alston "*Wilson did not sketch the pralidoxime molecule as an analog of some serendipitously discovered existing drug. Instead, he applied his theory of enzyme action to design a peerless pharmaceutical. As Wilson predicted, organophosphorus-poisoned cholinesterase is not completely "dead." Instead, the poisoned enzyme retains catalytic ability to transfer its blocking organophosphorus group away from its enzyme active site and onto pralidoxime*". Reproduction with permission of the copyright holder: Corbis

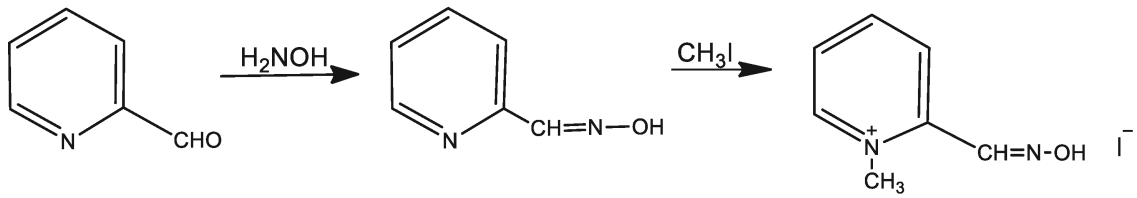


Fig. 5: Wilson, Nachmansohn and Ginsburg are holders of the US Patent # 2.816.113 (1957) describing the synthesis of pralidoxime by reacting pyridine-2-aldehyd (picoline-aldehyde) with hydroxylamine to yield pyridine-2-aldoxime (picoline-aldoxime) and then with methyl iodide to obtain the desired pralidoxime

doxime by reacting pyridine-2-aldehyd (picoline-aldehyde) with hydroxylamine to yield pyridine-2-aldoxime (picoline-aldoxime) and then with methyl iodide to obtain the desired pralidoxime (Wilson et al. 1957) (Fig. 5).

Such research was also been conducted in Britain (and elsewhere); Davies and Green report on the reactivating properties of pyridinium aldoxime in 1955 at a Meeting of the Farraday Society (Davies and Green 1955). Due to the non-transparent situation of research with military relevance in the transition period between the end of the Second World War and the beginning of the Cold War, especially considering the restrictions related to the publication of results, it is impossible to unequivocally determine who synthesized first 2-PAM.

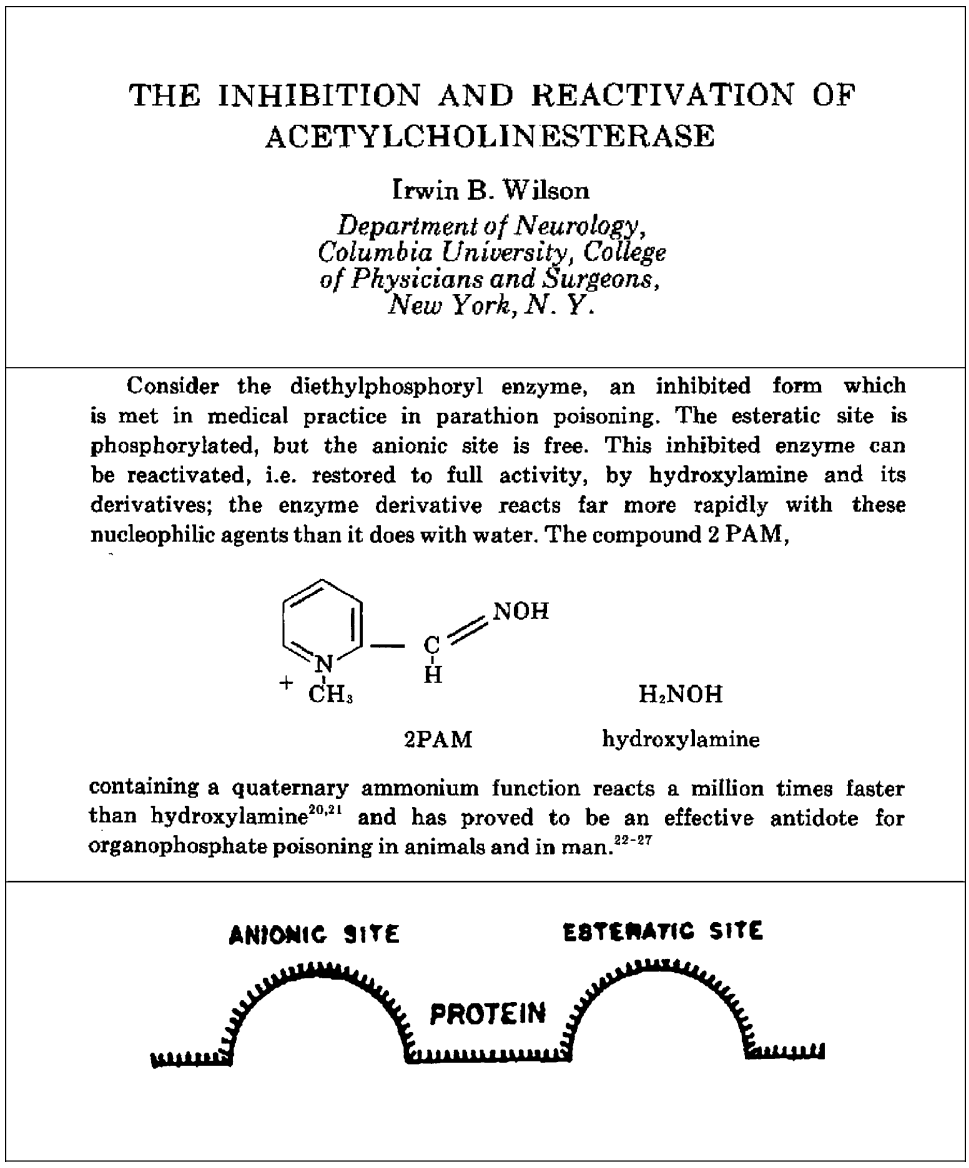
Describing Wilson's search process and achievements Theodor Alston states that "*Wilson did not sketch the pralidoxime molecule as an analog of some serendipitously discovered existing drug. Instead, he applied his theory of enzyme action to design a peerless pharmaceutical. As Wilson predicted, organophosphorus-poisoned cholinesterase is not completely "dead." Instead, the poisoned enzyme retains catalytic ability to transfer its blocking organophosphorus group away from its enzyme active site and onto pralidoxime*" (Alston 2005).

Indeed, Wilson writes, pralidoxime "*containing a quaternary ammonium function reacts a million times faster than hydroxylamine and has proved to be an effective antidote for organophosphate poisoning in animals and in man*". He also draws a representation of the enzyme showing the two sites at which interaction with the substrate occurs. The drawing was lovingly named – for obvious reasons–by Sara Ginsburg the "*Wilson brassiere*" (Wilson 1966; Kitz 2004) (Fig. 6).

Sara Ginsburg [*1908 St. Petersburg, Russia - †1997, NY] was born in a middle class family, her father M(?). being a bank director. She attended the Taganzew[5] School in Petersburg before the family fled the communists first to Riga (Latvia) and then to Germany. In Berlin she attended the Hohenzollern Lyceum, where she graduated 1929. Subsequently she studied Chemistry at the Friedrich-Wilhelms-University in Berlin. Her PhD work was done in Prof. Peter Rona's[6] (1871–1945) Chemistry Division in the Pathology Department at the Charité (the University Hospital). David Nachmansohn (1899–1983), her

[5] **Taganzew** Nikolaj Stepanowitsch (1843–1923), Law Professor at the University in St. Petersburg, politician and statesman. His son Wladimir (1889–1921) and his daughter-in-law were executed (together with other 59 intellectuals) by the Bolsheviks 1921.

[6] **Rona**, Peter (1871–1945), studied in Vienna and Heidelberg, habilitated 1905, 1922 Professor (*ausserplanmäβiger*) and Director of the Chemical Division of the Pathology Institute at the Charité in Berlin. After being removed for this position 1933 he returns to his native Hungary 1939 from where he is sent with his wife to a death camp. For a detailed description of his life and achievements please see Ammon (1960).



THE INHIBITION AND REACTIVATION OF ACETYLCHOLINESTERASE

Irwin B. Wilson
Department of Neurology, Columbia University, College of Physicians and Surgeons, New York, N. Y.

Consider the diethylphosphoryl enzyme, an inhibited form which is met in medical practice in parathion poisoning. The esteratic site is phosphorylated, but the anionic site is free. This inhibited enzyme can be reactivated, i.e. restored to full activity, by hydroxylamine and its derivatives; the enzyme derivative reacts far more rapidly with these nucleophilic agents than it does with water. The compound 2 PAM,

2PAM

hydroxylamine

containing a quaternary ammonium function reacts a million times faster than hydroxylamine[20,21] and has proved to be an effective antidote for organophosphate poisoning in animals and in man.[22-27]

Fig. 6: Wilson draws a representation of the cholinesterase showing the two sites at which interaction with the substrate occurs. The drawing was lovingly named–for obvious reasons – by Sara Ginsburg the "*Wilson brassiere*" (Wilson 1966; Kitz 2004)

later boss at Columbia University was also (until 1926) a Rona student (Ochoa 1989).

Her dissertation titled "*On Synthesis of Glycerin-Esters by Fermentation*" was defended in autumn 1933 and the doctoral degree awarded in May 1934. Apparently she was the last student of Jewish origin to be awarded a doctoral title by the Friedrich-Wilhelms-University (Lucien Cote[7], personal communication). Subsequently she did some work in the Willy Lange's laboratory where she met and become friends with Gerda von Krueger; of course Lange and von Krueger were the ones who recognized the toxicity of phosphoric acid esters, the type of toxicity which one would treat i.a. with oximes, the substances Sara will synthesize (Kitz 2004; Petroianu 2010).

The situation in Nazi Germany however prompted her to flee and after some time spent in France and then in Spain she was able to leave for the United States on a ship departing Lisbon [Kitz 2004]. In the US she eventually obtained an Assistant Professor position at Columbia University with Wilson and Nachmansohn: she stayed with the Department of Biochemistry and Neurology at Columbia until her retirement 1985.

While Wilson's contribution is undeniable clinical experience with pralidoxime is however far from satisfactory. Over the years, different groups developed new potential reactivators of cholinesterase inhibited by organophosporus compounds: without exception all compounds are bispyridinium oximes.

Trimedoxime (TMB-4) the first promising bispyridinium AChE reactivator was synthesized by Poziomek († 2001) in 1958 (Poziomek et al. 1958)]. Same year Methoxime (MMC-4) was synthesized and tested by Hobbiger (1920–1994) in Britain (Hobiger et al. 1958).

Obidoxime, developed by Arthur Luettringhaus (1906–1992) and Ilse Hagedorn (1921–2005) in Freiburg, Germany was initially known by the acronym LueH-6. It is the oxime most commonly used in Continental Europe (Luettringhaus and Hagedorn 1964; Eyer 2007).

The latest generation of bispyridinium AChE reactivators comes from the Department of Toxicology at the Faculty of Military Health Sciences (University of Defence, Hradec Kralove, Czech Republic) where the K-series of reactivators were developed by Kuča in the 90ˢ.

[7] **Côté** Lucien, clinician-researcher who specializes in Parkinson's disease. He is since 1964 with the Deptartment of Neurology, Columbia University Medical Center. He published with Sara Ginsburg on centrally active and reversible acetylcholinesterase inhibitors.

Acknowledgments: My gratitude to all those who helped gather the information and/or write the manuscript: Emeritus Professor Lucien J **Cote** [Columbia University], Emeritus Professor Hendrik **Deelstra** [University of Antwerp, Belgium], Professor Wim **Lammers** [United Arab Emirates University, Al Ain], Peter **Meiers** [Saarbruecken, Germany], Gerd **Metelmann** [Stadtarchiv Varel, Germany], Christine **Schummer** [Institut fuer Pharmakologie, Uni Heidelberg-Mannheim], — and to the miracle of Internet connectivity and Google Books, who made these and many other things possible.

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