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Bernhard Witkop (1917–2010)

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On November 22, 2010, Dr. Bernhard Witkop died in his home in Chevy Chase, MD, USA. He was 93 years old. He is survived by his wife Marlene, married to him for 65 years, and by his daughters Cornelia and Phyllis, his son Thomas, and six grandchildren. Witkop worked for 37 years at the National Institutes of Health (NIH) and was one of the most well-versed and successful organic chemists of his generation.

The admiration of our common academic mentor, in this case Heinrich Wieland at the Ludwig-Maximilans-Universität Munich, was the foundation of our friendship. Bernhard Witkop, three years my senior, already commanded respect at a time when I was still doing my Gattermann preparations. Witkop's gripping intelligence in combination with his universal education, equanimity, and sense of irony, including his ironic view of himself, were impressive in my encounters with him—both early on and later.

Bernhard Witkop was born in May 1917 as the son of Philipp Witkop, a well-known specialist in German studies at the University of Freiburg, and his wife Hedwig Hirschhorn. At the suggestion of Richard Willstätter, he studied chemistry in Munich and completed his doctoral studies in 1940 at age 23 under the tutelage of Heinrich Wieland with a thesis on the isolation and crystallization of the death cap toxin phalloidin, a cyclopeptide. Wieland was able to protect the (in Nazi jargon) half-Jewish scientist. After the destruction of the Munich institute during air raids, Witkop continued his studies of indole alkaloids in Weihenstephan and completed his habilitation in 1946 at the Ludwig-Maximilians-Universität Munich.

Witkop did not believe that the German universities would recover quickly from wartime destruction and emigrated to the USA in 1947. When I asked my friend Bernd if the foreign language was causing him problems, he replied that his English was so much better than most Americans' that he was afraid he might stick out as a European immigrant.

A fellowship enabled Witkop to conduct research and teach at Harvard University. He became friends with Robert B. Woodward, who was already a rising star in natural-products synthesis. Witkop also felt the influence of the clarity with which Paul D. Bartlett developed reaction mechanisms.

The NIH in Bethesda, MD, initiated basic bioorganic research in 1950 and recruited Witkop along with other high-ranking scientists. The "Laboratory of Chemistry", which Witkop led from 1957 to 1987, offered working conditions and a degree of independence comparable to those of top-class universities. The NIH enacted a program for visiting professors and postdoctoral fellows from abroad, many of whom came from Japan. The results of Witkop's rich research activities led to ca. 370 publications.

Rather than simply listing projects, let me mention some of the insights gained from them. The "NIH shift" was discovered in 1967 by Witkop and his colleagues during studies on the hydroxylation of aromatics with O_2 and monooxidases.[1] When the 4-H atom in the oxidation of phenylalanine to tyrosine was replaced by D or T, the marker was not removed by hydroxylation but instead shifted to the 3-position. Arene oxides are intermediates formed by O_2 and P450 oxidases.[2]

Proteases hydrolyze the peptide chain at defined positions. Gross and Witkop observed that cyanogen bromide selectively cleaves peptide bonds next to methionine.[3] The new method made it possible to correct an error in the ribonuclease structure (1962). With *N*-bromosuccinimide, it was possible to selectively hydrolyze the chain adjacent to the tryptophan residue.[4,5] Witkop referred to a review article from 1968 as his "star paper", since he received more than 1000 reprint requests for it.[6]

Witkop collected contributions on the oxidation and degradation of tryptophan, including pathways to indole alkaloids and the photooxidation to the metabolite kynurenine, in a review, "Forty Years of Trypto-fun",[7] which also discussed the formation of the neurotransmitter serotonin from 5-hydroxytryptophan.

Witkop's interest in natural toxins led in 1963 to the isolation of batrachotoxin from a frog of the genus *Phyllobates*, which Columbian Indians use to prepare arrow poison.[8] A new type of steroid alkaloid was resolved by X-ray structure analysis in cooperation with Jerome and Isabella Karle.[9]

For two decades, Bernhard Witkop was a member of the board of the Paul Ehrlich Foundation in Frankfurt. The selection of the candidate for the annually awarded Paul Ehrlich Prize gave him occasion for regular visits to Germany. With words and pictures (bank note), Witkop cultivated the memory of the great scholar who founded the field of chemotherapy.

In later decades, Witkop became interested in the history and philosophy of natural sciences. His reminiscences were dedicated to Emil Fischer, Heinrich Wieland, Theodor Wieland, Percy Julian, and Munio Kotake. In May 1987, the Israel Academy of Sciences and Humanities honored Bernhard Witkop on the occasion of his 70th birthday with a symposium "Mind Over Matter". The body–soul dualism dates back to Aristotle and was particularly important in the teachings of Descartes. In his speech in Jerusalem, Witkop endeavored to mitigate the dualism in discussion with a line of arguments including philosophical

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doctrines, the Bible, poetry, and insights from natural sciences.[10]

More than 50 Japanese scientists worked in Witkop's lab over the years. Regular trips to Japan familiarized him with the Japanese culture—and language. The polyglot Witkop learned Japanese and held his first lecture in Tokyo in 1961.

The National Academy of Sciences accepted Bernhard Witkop as a member in 1969, and the University of Zurich awarded him the Paul Karrer Medal (1971). The Emperor of Japan honored Witkop with the "Order of the Sacred Treasure" (1975). The NIH appointed him "Institute Scholar" (1987) when he reached emeritus status. In 1990, the Faculty of Chemistry and Pharmacy of the University of Munich renewed Bernhard Witkop's doctoral diploma after 50 years. Witkop was especially pleased by his election as a member of the American Philosophical Society, Class of Biological Sciences (1999).

As an organic chemist, Witkop acted as a sort of liaison between disciplines, with intensive contact to biochemical, medical, pharmacological, and natural-products research. This interdisciplinarity was the key to his success.

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