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IN MEMORIAM

Bo Holmstedt, 1919–2002

Bo Holmstedt, professor emeritus in toxicology at the Karolinska Institute in Stockholm has died after having suffered a cerebral infarction at the age of 83 years. He is survived by his wife, artist Gudrun Åhlberg-Holmstedt. Bo Holmstedt was one of the internationally most well-known Swedish scientists. He had particularly strong relations with his US colleagues, has many US pupils, and much of his work was supported by grants from NIGMS and NIMH. He was a member of 20 learned international societies, and had the distinction of being a Foreign Corresponding Fellow Emeritus of the American College of Neuropsychopharmacology.

Bo Holmstedt was born in the south-eastern part of Sweden but spent all his student years in Stockholm. Here he passed his matriculation examination and completed his studies in medicine at the Karolinska Institute. He received his Ph.D. in pharmacology in 1951, his M.D. in 1952, and was appointed assistant professor of pharmacology that same year. He was promoted to the rank of associate professor in 1960 and became Sweden's first professor in toxicology in 1964. In 1974, he was elected to the Swedish Royal Academy of Sciences.

Bo Holmstedt's research spanned four main areas, each with obvious clinical relevance. Beginning with studies of the nerve gas tabun and other irreversible cholinesterase inhibitors, he was the first to show that atropine and artificial respiration protected against the lethal effects of these substances in experimental animals. His pupils continued this line of research with studies of compounds that reactivated cholinesterase. After a sabbatical in the late 1950s with George Koelle at the University of Pennsylvania School of Medicine in Philadelphia, he refined the histochemical method used to localize the two cholinesterases in the nervous system. Later in life, he developed a novel method to study the metabolism of metrifonate, an old cholinesterase inhibitor used to treat patients with schistosomiasis and Alzheimer's disease. In conjunction with his 80th birthday symposium, speakers from the second and third generation of his students reported on improved treatments of Alzheimer's disease with recently developed cholinesterase inhibitors.

In attempts to find new principles for the treatment of Parkinson's disease, he extended his research on cholinergic mechanisms to include pharmacodynamic and metabolic studies of tremorine and its active metabolite oxotremorine. Many of these studies were performed in collaboration with Donald Jenden at UCLA. It was established that the parkinsonian symptoms evoked by oxotremorine were directly related to changes in the central nervous system turnover of acetylcholine.

Ethnopharmacological studies of active substances in exotic plants constituted a second main topic of Bo Holmstedt's research. In 1967, he participated in the Alpha Helix expedition to the upper Amazon jungle that was sponsored by the US National Science Foundation and Scripps Institution of Oceanography. During this expedition, he and his coworkers identified hallucinogenic substances that were being used by the Indian tribes in the region. This work has been described in the NIMH-sponsored book *Ethnopharmacologic Search for Psychoactive Drugs* (1967) that he coauthored with his friends Daniel Efron and Nathan Kline. This book included chapters describing studies of tryptamine deriv-

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atives in epená, an intoxicating snuff used by South American Indian tribes, and investigations of Natema, the hallucinogenic drink of the Jivaro Indians of Ecuador. The latter was an ethnopharmacological study based on Rafael Karsten's 1917 botanical collection. Bo Holmstedt was a consultant in medical botany at Harvard University and became a member of the Linnean Society of London. Throughout his whole life he maintained a burning interest in the toxicological and pharmacological aspects of active substances derived from the plant and animal kingdom.

In the early 1960s, Bo Holmstedt spent his second sabbatical with Marjorie and Evan Horning at Baylor College of Medicine in Houston. There he gained expertise in biomedical research applications of gas chromatography, mass spectrometry, and other new methods of chemical analysis. Upon returning to Sweden, he collaborated with Ragnar Ryhage, who had just invented a two-stage molecule separator for coupling a gas chromatograph with a mass spectrometer, and Carl-Gustaf Hammar to develop a new ultrasensitive method for specific analysis of drugs, drug metabolites, and endogenous substances in the picogram range. This method, first called mass fragmentography but now more commonly referred to as selected ion monitoring, opened new avenues for research in drug development, drug dependence and clinical psychopharmacology. Initially, this technique was used to identify cholorpromazine and its metabolites in human blood plasma, and to provide the first unequivocal chemical proof of the presence of acetylcholine in rat brain. At the age of 76, Bo Holmstedt reviewed his experience with the mass fragmentography of acetylcholine, which in his earlier years had to be determined with the frog rectus abdominus bioassay.

Subsequent refinement of mass fragmentography led to the development of specific quantitative assays for the main monoamine metabolites 5-HIAA and HVA in cerebrospinal fluid (CSF). This technique made it possible for Bo Holmstedt's collaborators in clinical psychopharmacology to demonstrate an intriguing relationship between low 5-HIAA levels in CSF and the risk of attempted suicide in depressed patients, thereby inspiring further research into the role of serotonin in affective disorders. Mass fragmentographic assays of CSF metabolite levels also made it possible to differentiate between the effects of different kinds of antidepressants on monoamine turnover in the human brain. Equally important was that mass fragmentography could be used to validate and extend the early pharmacokinetic and pharmacogenetic studies of prototype antidepressants (nortriptyline) and neuroleptics (chlorpromazine). The development of this technique also made possible subsequent pharmacokinetically oriented research that included the use of ion-specific detection of internal standards labelled with multiple stable isotopes as well as the conduct of absolute bioavailability and other pharmacokinetic studies in which stable isotope-labelled drugs and metabolites were administered to human subjects.

Bo Holmstedt's fourth main interest was toxicology in which his expertise was recognized both nationally and internationally. He served as a member of a WHO expert advisory panel on insecticides in 1961, as an expert in connection with the occurrence of methyl mercury in fish in 1968, as a chairman of the WHO committee on safe use of pesticides in 1971, and as chairman of the WHO committee for the detection of dependence-producing drugs in body fluids in 1974. He was an honorary member of the Swedish Association for Toxicology, and served as a board member of the European Society of Toxicology and as president of the International Union of Toxicology (IUTOX). There was no toxicological problem that was unknown to him. This included the various mechanisms of action of poisons on the nervous system, risk assessment of chemicals for public health, and expert opinion in murder trials in which the occurrence of poisoning was suspected.

Bo Holmstedt was also interested in the history of pharmacology and together with Professor Göran Liljestrand, long-term secretary of the Medical Nobel Committee, wrote the book *Readings in Pharmacology*, a best seller that was published by Pergamon Press in 1963. This book described the development of modern pharmacology and toxicology with a main focus on the pioneering achievements of the founders of these disciplines, including reprints of their most important contributions.

Bo Holmstedt leaves behind a large number of scientific articles in the fields of pharmacology and toxicology, as well as contributions of historical and cultural interest. But more irreplaceably, he belonged to a passing generation of professors who, in addition to their broad knowledge, had a deep understanding of science as part of humanity. His students received not only a sophisticated training in research methods but also had the opportunity to learn under his tutelage how to write and communicate with ease, perhaps the most important aspect of international research collaboration. He has enriched many by his guidance and by his example, and he will be missed.

For his co-workers and students,

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