Neuropsychopharmacology (2005) 30, 1767–1768

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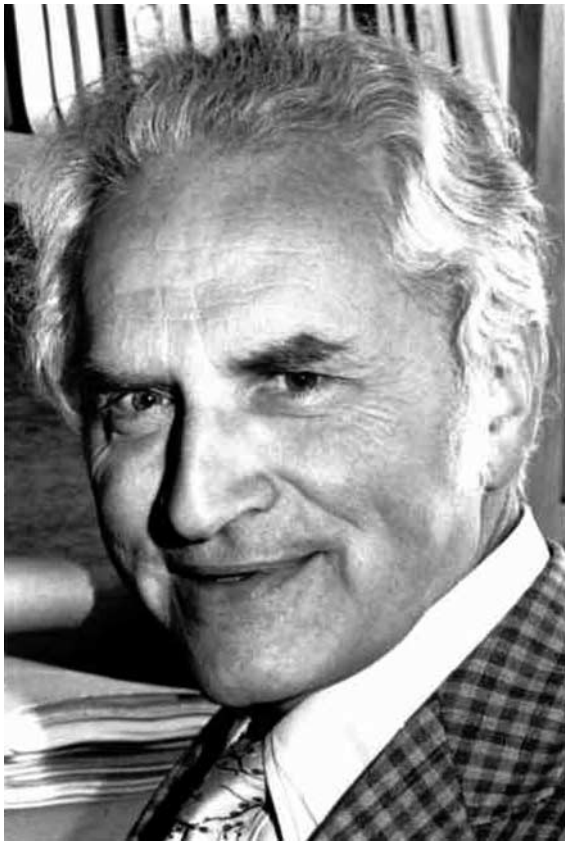
Obituary

Ernest B Sigg, 1924–2004

Neuropsychopharmacology (2005) **30,** 1767–1768. doi:10.1038/sj.npp.1300801



Ernest B Sigg, a Fellow Emeritus of the ACNP, died on October 12, 2004. He had been battling ill health ever since a severe stroke in 1986 that disrupted his creative professional life.

Ernest received his MD degree in 1949 from the University of Basel, Switzerland. After a short period as a Resident physician in surgery in his native country, he relocated to the US for Postdoctoral Training, first at the Illinois Neuropsychiatric Institute, then at Columbia University (Department of Neurology) and the University of Minnesota (Department of Physiology). In 1959, Ernest started his productive career in the pharmaceutical industry, first at the Geigy Research Laboratories (1959–1966), than at the Roche Research Center (1967–1980) and at Wyeth Pharmaceuticals (1980–1986). During his long tenure in the pharmaceutical industry, Ernest Sigg contributed significantly not only to the development of novel psychotherapeutic drugs but also to the elucidation of their mechanism of action. While working at Geigy, Ernest was first to observe that the new antidepressant imipramine enhanced and prolonged physiological responses to exogenous norepinephrine and, importantly, to norepinephrine released by pre- or postganglionic sympathetic nerve stimulation. Moreover, he observed that secondary amines of tricyclics were more potent than their corresponding tertiary amines in enhancing the responses to exogenous norepinephrine. In view of these effects on the peripheral adrenergic system (cat nictitating membrane, blood pressure), Ernest suggested in 1959 that the tricyclic antidepressant may also exert its central effect by sensitization to norepinephrine. Subsequent studies in other laboratories have validated Ernest Sigg's heuristic view. Ernest cherished the central autonomic concepts of WR Hess and entertained the idea that the anticholinergic and adreno-sensitizing actions of tricyclics are synergistic in their end effect, leading to ergotropic predominance and possibly the correction of the autonomic imbalance of depressed patients.

In 1967, Ernest Sigg moved to Roche-Nutley to become Director of the Neurophysiology section of the Department of Pharmacology. There with the assistance of his wife Teddy, a graduate student, and two senior neurophysiologists, he continued his research on the autonomic nervous system and pharmacological influences on autonomic output from the brain. Several of his publications described studies on the influences of centrally acting drugs on hypothalamic catecholamines and sympathetic responses to stress. Ernest's investigations included mechanisms of action of L-DOPA, diazepam, chlorpromazine, haloperidol, desipramine, and pentobarbital.

Aside from his own scientific pursuits, Ernest's presence was a positive influence on many of his colleagues in the pharmacology department. His considerable experience in psychopharmacology and his critical scientific thinking were of immeasurable value to the more junior researchers in the department. Always a willing sounding board for evaluating research proposals and hypotheses, no doubt his wisdom saved many a younger scientist from the embarrassment of a failed project. Better to hear from Ernest that you should 'do something useful, like milk cows' than have to explain to your superiors why you wasted so much time and money on a bad idea. Ernest was unique in that his relationship with his employees and colleagues was more 'professor to student' rather than 'supervisor to employee'.

Ernest left Roche in 1980 and joined Wyeth Pharmaceuticals as the Director of Experimental Therapeutics. He often told us that it was of great value and advantage to change jobs every 5–10 years to avoid stagnation and to keep zest and interest in one's profession and this move was consistent with that philosophy. Wyeth was at this time a mid-sized pharmaceutical company under the umbrella of American Home Products Corporation and corporate management was faced with the mounting challenges of transitioning from classical animal model-based drug

discovery and development to a more target-based approach. With his strong leadership skills and extensive background in drug discovery and development, Ernest was the right person to lead this transition.

Ernest assumed his new responsibilities with his characteristic enthusiasm, charm, and sharp wit. He was responsible for and led a research team consisting of multiple therapeutic disciplines including Endocrinology, Cardiovascular, Gastrointestinal, Immunopharmacology, Metabolic Disorders, and CNS. Ernest quickly assessed the strengths and weakness of these research programs and set upon a strategic plan to re-engineer and develop the Wyeth drug discovery and development pipeline. He always told us that he was hired to 'create a sense of urgency' and he certainly revitalized drug discovery research. Ernest was a master at merging the value of classical pharmacology with the new target-based approach. He was a true mentor to all of his staff and played a critical role in reshaping the strategic scientific course and careers of many research scientists at Wyeth. Out of his team effort emerged a H2 blocker, proton pump inhibitor, leukotriene antagonist, lipoxygenase inhibitor, and an ACE inhibitor that went into development.

Although Ernest was committed to all areas in Experimental Therapeutics, his first love was the CNS. The CNS research team Ernest assembled was relatively small by the industry standards of the time and certainly of today. However, he strongly believed in the power of small teams when addressing challenging scientific questions. He had focused the research efforts of the CNS group in discovering a new antidepressant with combined norepinephrine and serotonin reuptake inhibition. The rationale at the time was that a drug with this profile would be more effective and perhaps a more rapidly acting antidepressant in comparison to drugs that only affected the serotonergic system. One remarkable day in 1981 while meeting with his research team, we were reviewing an extensive series of novel chemical structures. Ernest became excited by a particular compound that struck him as being a promising antidepressant. He could not predict how unique this compound would be, but he challenged us with the task of characterizing its properties and differentiating it from other antidepressants. Ernest's excitement for this compound grew stronger each time he reviewed new experimental results. Indeed, WY-45030 was found to be a combined norepinephrine and serotonin reuptake inhibitor. He recommended this compound for development and his confidence in its potential was instrumental in addressing many hurdles and issues along the way. He often had to defend WY-45030 in the face of issues of competing resources and priorities. He persevered and today this antidepressant is known as Effexor (venlafaxine). One could say Ernest is truly the 'Father of Effexor'!

Sadly, Ernest witnessed only the early days of the development of Effexor since he suffered a severe stroke while working in his office in 1986. The stroke left him disabled with some motor deficit and an impaired ability to speak English. Interestingly, his ability to speak Swiss German was retained. There is some irony to this since some of us experienced situations where Ernest would become excited, animated, or quite angry and lapse into Swiss German. Ernest never returned to work following his stroke and it is quite unfortunate his productive career was prematurely ended.

Ernest Sigg will best be remembered for his passion for science, leadership, strength as a mentor, and true nature as a 'drug hunter'. The embodiment of a 'renaissance man', Ernest Sigg not only excelled as a man of science and philosophy but continually pursued interests in music—he was an excellent cellist—and art. He and Teddy enjoyed traveling to some of the more exotic places of the world and each journey resulted in additions to their collection of primitive or tribal art. Near the end of his time with Roche, Ernest was assigned to help establish a pharmaceutical evaluation unit in Australia. On their way home, the Sigg's paid a visit to New Guinea. Soon after their return to New Jersey, large crates began to arrive and their home was quickly filled with substantial pieces of tribal sculpture. A visit to the Sigg home was always a special treat for the mind and the senses. There were evenings with Teddy and Ernest in their house perched on a hillside in West Chester, PA (reminiscent of those seen in Switzerland) with dinner accompanied by good wine and followed by 'Ouzo' or 'Kirschwasser'. There was very little discussion of business at these pleasurable events, instead we were all intrigued by stories of Ernest's days in the Swiss Cavalry and how he built his own EEG machine as a young man. He was also proud of his musical instrument collection from around the world. Perhaps somewhere in the mountains of Switzerland, his music still can be heard.

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