In memory of three pioneers

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Abstract
During the past 6 months three major figures in the history of psychopharmacology passed away: Leo Sternbach, Mogens Schou and Roland Kuhn. The historical contributions of these pioneers opened the path for the development that has led to the current state of the art in pharmacological treatment in psychiatry.

Received 14 March 2006; Accepted 17 April 2006; First published online 31 May 2006

Leo Sternbach (1907–2005)
Leo Sternbach, the son of a Polish pharmacist, was born in Abbazia, Croatia, in 1907. He studied pharmacy and chemistry at Jagellonian University in Cracow, Poland, and as a postgraduate student, synthesized several heptoxdiazine compounds.

After a short academic career at the Swiss Federal Institute of Technology in Zurich, Sternbach joined Hoffmann–La Roche, one of the major Swiss pharmaceutical companies. Prior to the outbreak of World War II, he moved to the United States and some years later became Director of Medicinal Chemistry at Roche’s research facility in Nutley, New Jersey.

In 1954 Sternbach resumed his research with heptoxdiazines with the hope of finding new compounds possessing psychopharmacological activity. This effort was inspired by the phenomenal success of chlorpromazine and early reports on meprobamate (Cohen, 1970). In the course of this research he discovered that the drugs he perceived as heptoxdiazines were benzoxadiazepines, and synthesized 40 benzoxadiazepine compounds that turned out to be pharmacologically inert. He stabilized one of his benzoxadiazepines, chlormethyl-quinazoline N-oxide, with methylamine (Ban, 1969), labelled the white water soluble crystalline powder as Ro 5-0690, and placed it on the shelf. In 1957, Ro 5-0690 was found, literally during a laboratory clean-up, and submitted for pharmacological evaluation, which showed that it had similar activities to meprobamate. Prompted by these findings the structure of Ro 5-0690 was correctly identified as 1,4-benzodiazepine.

Ro 5-0690, the first anxiolytic benzodiazepine, was introduced in 1960 with the generic name of methamindiazepoxide (chlordiazepoxide), and the brand name of Librium. It was followed by the introduction of diazepam (Valium), another anxiolytic benzodiazepine in 1963, and several other benzodiazepines, e.g. the hypnotic, nitrazepam (Mogadon), the anti-convulsant, clonazepam (Klonopin). Sternbach’s productivity is reflected in the 241 patents on drugs ascribed to his name. For some time diazepam topped all other drugs in the United States, and Sternbach drugs generated one-quarter of all revenues for Roche.

In recognition of his contributions to psychotropic drug development, Sternbach was the recipient in 1970 of the Chemical Pioneers Award of the American Institutes of Chemistry.

Leo Sternbach died on 28 September 2005, aged 97.
Mogens Schou (1918–2005)

Mogens Schou, the son of a psychiatrist, was born in Copenhagen, Denmark, in 1918. He graduated in medicine from the University of Copenhagen in 1944 and was trained in psychiatry at St Hans Hospital in Roskilde and at Dikemark Hospital in Norway.

After a post-doctoral fellowship in neurochemistry with Heinrich Waelsch in New York, Schou returned to Denmark and became a research associate of Erik Strømgren at the Psychiatric Hospital in Risskov. Later he was chief of the research laboratories and head of the psychopharmacology unit at the hospital. In 1971 he was appointed to the first Chair in Biological Psychiatry in Denmark at the University of Aarhus.

Schou’s lifetime dedication to lithium research began in 1951. In the course of his research, in 1954, he verified preliminary findings on the therapeutic effect of lithium in mania in a double-blind controlled clinical study, and, in 1966, demonstrated the prophylactic effect of lithium in manic-depressive illness. Subsequently he also showed the prophylactic effect of lithium in unipolar depression, and its efficacy in treatment-refractory depression. He studied and carefully documented the adverse effects of lithium, including lithium intoxication, and the possible teratogenic consequences of lithium treatment. During 50 years of research Schou, virtually single-handedly, generated all the necessary clinical information for the discriminate and safe use of lithium.

In spite of Schou’s efforts, the introduction of lithium was delayed because of the absence of commercial interest in the substance (Schou, 1996). Another contributory factor to the delay was the objection of a group of British psychiatrists to Schou’s findings (Schou, 1998). But Schou prevailed and by the 1970s lithium was the primary form of treatment of manic-depressive illness. Furthermore, unlike other drugs, such as chlorpromazine and imipramine that were replaced by ever newer drugs in the treatment of schizophrenia and depression, respectively, lithium has remained the primary form of treatment in bipolar disorder to date.

In recognition of his research Schou received numerous distinctions, including the prestigious Kittay Prize, the Lasker Award of the American Public Health Association, and the CINP-Pfizer Pioneers in Neuropsychopharmacology Award.

Mogens Schou died on 29 September 2005, aged 87.

Roland Kuhn (1912–2005)

Roland Kuhn was born in Biel, Switzerland, in 1912. He graduated in medicine from the University of Bern in 1937 and was trained in psychiatry at the University Psychiatric Clinic in Waldau/Bern with Professor Jakob Klaesi.

In 1939 Kuhn was appointed senior physician at the cantonal mental hospital of Münsterlingen in the Swiss Thurgau county. He continued at the hospital throughout his professional life, pursuing his interest in psychotherapy and pharmacological treatment.

Kuhn became involved in the clinical testing of new drugs for Geigy, one of the major Swiss pharmaceutical companies, in the mid-1950s. The company was looking for a chlorpromazine-like substance for the treatment of schizophrenia and Kuhn suggested the testing of one of the antihistamines of the company, G 22,355, the substance that showed the
closest structural resemblance to chlorpromazine. But contrary to his expectations, the substance was ineffective in schizophrenia. Nonetheless, before returning his supply of the drug he decided to try it in one of his female patients with severe endogenous depression. This led to the recognition on 18 January 1956 that G 22,355 may have antidepressant effects. Encouraged by his findings he administered the drug to two more female patients with severe endogenous depression and in both patients the drug had favourable effects. Furthermore, in all three patients discontinuation of treatment resulted in relapse that was reversed by resumption of the medication. Subsequently he treated 40 depressed patients with G 22,355 at the clinic and on the basis of his observations he reported on the therapeutic effect of the substance in depression with particular effectiveness in endogenous depression in which vital disturbance is in the foreground (Kuhn, 1996). Kuhn’s first paper on the treatment of depressive states with an iminobenzyl derivative, G 22,355 was published in the 31 August issue of the Swiss Medical Journal in 1957 (Kuhn, 1957).

On 2 September, he also presented his findings at the 2nd World Congress of Psychiatry in Zurich. By the end of the year, G 22,355, the first tricyclic antidepressant, was released for clinical use in Switzerland with the generic name of imipramine, and the brand name of Tofranil. Kuhn described the antidepressant effect of imipramine so carefully and thoroughly that later research has added nothing of radical importance to the findings published in his first account (Angst, 1970).

There was a strong opposition by academic psychiatry against drug treatment of depression in the late 1950s but Kuhn prevailed and the introduction of imipramine opened the path for the development of other antidepressants. Yet, Kuhn remained an outsider of the psychopharmacology establishment. This was primarily due to his strong opposition to the statistical methodology in clinical drug trials. Nevertheless, he was one of the key speakers at the 2nd Taylor Manor Hospital Scientific Symposium, in April 1970, the first meeting which honoured the pioneers of biological treatment of mental illness by gathering personal accounts of their original discoveries.

For his contributions to the pharmacotherapy of depression Kuhn was made an honorary doctor of medicine at the University of Louvain and at the University of Basle. For his contributions to existential analysis, a form of psychotherapy, he was made an honorary doctor of philosophy at Sorbonne.

Roland Kuhn died on 10 October 2005, aged 93.

Acknowledgements
None.

Statement of Interest
None.

References