Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 30

Profiles of clinicians and researchers who were instrumental for the birth and/or contributed to the development of neuropsychopharmacology

Alfred Pletscher, Juri Saarma, Sydney Spector, Leo Sternbach, Edward Trautner and Joseph Wortis

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Alfred Pletscher by Fridolin Sulser

Alfred Pletscher was born, in 1917, in Altstaetten/SG, Switzerland. He received his M.D. degree in 1942 and his Ph.D. in chemistry in 1948 from the University of Zurich, Switzerland. After a year as Visiting Scientist with Bernard B. Brodie at the National Heart Institute of the National Institutes of Health (NIH), he returned, in 1955, to Switzerland to assume the position of Director of Corporate Research at Hoffmann-La Roche, Basel. "My time in Brodie's laboratory was one of the highlights of my scientific career," he said. In an interview with Tom Ban, Pletscher reflected on his position in industry: "My primary motivation in industry was not profit but helping people." This statement is an expression of Pletscher's humanistic philosophy. In 1978 he left industry and became Chairman of the Department of Research at the University of Basel.

Alfred Pletscher's scientific contributions had an enormous impact on the development of Biochemical Neuropsychopharmacology, worldwide. In 1955, together with Parkhurst Shore and Bernard B. Brodie, Alfred Pletscher demonstrated, using spectrofluorimetric methodology, that reserpine's tranquilizing action is associated with a dose-dependent depletion of brain serotonin (5HT). This finding opened up world-wide research on the neurobiology of monoamines (Pletscher 2005). Pletscher was first to demonstrate that pretreatment with iproniazid, a monoamine oxidase (MAO) inhibitor, not only attenuated the reserpine-induced decrease of brain 5HT but was associated with behavioral stimulation by reserpine instead of tranquilization. Since the reserpine-like syndrome was viewed as a "model depression," the discovery provided the scientific rationale for the introduction of MAO inhibitors for the treatment of depression (Pletcher 1957). It also stimulated research for mechanisms of action of tricyclic antidepressants which, like iproniazid, also antagonized the "reserpine-like syndrome," but without blocking MAO, culminating in the discovery by Axelrod and Herting of the reuptake mechanism for the non-enzymatic termination of the action of biogenic amines.

When Pletscher returned to Switzerland, he developed the synthetic benzoquinolizines — tetrabenazine and Ro-41284 — which displayed a short-lived reserpine-like syndrome associated with a short-lived depletion of brain 5HT and were widely used as tools to discover "antidepressant" activity in laboratory animals (Pletscher 1957).

Pletscher was also instrumental in introducing the benzodiazepines, discovered by Leo Sternbach at Roche, in Nutley, NJ — chlordiazepoxide (Librium), first, followed by diazepam

(Valium) — for the treatment of anxiety disorders.

Another pivotal contribution to the monoamine field was the development of decarboxylase inhibitors and their combination with levodopa for the treatment of Parkinson disease (Pletscher, Gey and Burkard 1965). Pletscher's rationale for the combination was based on the discovery that these decarboxylase inhibitors enhanced the levodopa-induced rise in brain dopamine, while they decreased the concentration of peripheral dopamine. This combination of levodopa with a peripheral decarboxylase inhibitor is still a standard treatment of Parkinson's disease.

In meticulously designed studies, Alfred Pletscher utilized blood platelets as models for brain neurons to study uptake, storage, release and metabolism of biogenic amines and receptors for monoamines and peptides.

Collectively, Alfred Pletscher's scientific contributions have provided the conceptual framework for much of what we are doing today, e.g., studies on amine transporters, amine receptor-mediated second messenger formation and activation of protein kinases. His pioneering research endeavors and his scientific astuteness did not go unnoticed by the political authorities in Switzerland. Thus, in 1981, he was elected President of the research council of the Swiss National Science Foundation, and in 1988, President of the Swiss Academy of Medical Sciences. Alfred Pletscher catalyzed the creation of the Biocenter of the University of Basel, the Roche Institute of Molecular Biology, in Nutley, and the prestigious Basel Institute of Immunology.

Alfred Pletscher received many honors, among them four Honorary Doctor degrees from the Universities of` Paris (France), Genève, Lausanne and Fribourg (Switzerland); the prestigious Marcel Benoist Prize, the Science Prize of the city of Basel and the CINP Pioneer in Psychopharmacology Award.

Alfred Pletscher, a true Pioneer of Psychopharmacology, passed away, age 90, on December 12, 2006.

References:

Pletscher A, Shore PA, Brodie BB. Serotonin release as a possible mechanism of action of reserpine. Science; 1955; 122:374-5.

Pletscher A. The dawn of the neurotransmitter era in neuropsychopharmacology. In: Ban TA, Ucha Udabe R, editors. The Neurotransmitter Era in Neuropsychopharmacology, Buenos Aires: Polemos; 2005, pp. 27-37.

Pletscher A, Gey KF, Zeller P. Monoamineoxydase – Hemmer. Biochemie, Chemie, Pharmakologie, Klinik. In: Jucker E, editor. Progress in Drug Research, volume 2. Basel/Stuttgart: Birkhäuser Verlag; 1960, pp. 419-590.

Pletscher A. Release of 5-hydroxytryptamine by benzoquinolizine derivatives with sedating action. Science 1957; 126:507.

Pletscher A, Gey KF, Burkard WP. Inhibitors of monoamineoxidase and decarboxylase of aromatic acids. In: Eichler O, Farah A, editors. Handbook of Experimental Pharmacology, volume 19. Berlin: Springer; 1965, pp. 593-735.

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Jüri Saarma by Jaanus Harro

Jüri Saarma was born on October 24, 1921, in Viljandi, Estonia. He received his medical degree from the University of Tartu in 1945. He joined the University's Department of Psychiatry as a volunteer assistant in 1943, as a doctor and lecturer in 1945 and was appointed as professor in 1965. Jüri Saarma served as head of the department during 1975-1983 and also held other influential administrative positions throughout his career (Saarma 2000).

In 1952, Jüri Saarma founded a laboratory for research on higher nervous activity at the department. This and the subsequent formation of the laboratory of experimental and clinical psychopharmacology in 1967 were pivotal to the development of one of the most prolific medical research schools in the region, as this endeavor seamlessly complemented the psychopharmacological investigations of Lembit Allikmets and his disciples in the Department of Pharmacology of the University of Tartu.

In 1973, Saarma was a visiting professor at McGill University, in Montreal. He also lectured at the universities of Helsinki, Oulu, Toronto and Turku.

Jüri Saarma’s early research was devoted to the effects of insulin therapy on autonomic nervous system (Saarma 1966). The laboratory he led contributed to characterization of the actions

of a large variety of antipsychotic and antidepressant drugs (Saarma 1963, 1970, 1974). Saarma was an excellent teacher and superb clinician, who published a series of textbooks in Estonian and Russian. He advanced his own variant of a nosological system of psychiatric syndromes. He aimed at personalized psychiatry by developing the highly complex Tartu Psychometric Test Battery to delineate the diagnostic profile of schizophrenias, affective and anxiety disorders and to differentiate therapeutic profiles of prototype psychotropic drugs (Saarma 1976).

Jüri Saarma died on February 7, 2001, in Tartu.

References:

Saarma J. Trial to specify indications for treating schizophrenics on the basis of higher nervous activity data. (In Russian). Korsakoff Journal 1963; 3:431-5.

Saarma J. Prognosis of insulin therapy in schizophrenia based on higher nervous activity data. International Journal of Psychiatry 1966; 2:431-45.

Saarma J. The practical use of higher nervous activity data in pharmacotherapy of psychoses. International Journal of Psychobiology 1970; 1:35-8.

Saarma J. Autonomic component of the orienting reflex in schizophrenics. Biological Psychiatry 1974; 9:55-60.

Saarma J. The Tartu Psychometric Test Battery. In: Guy W., editor. ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville: DHEW Pub No (ADM) USPGO; 1976, pp.583-603.

Saarma J. Initial period of psychopharmacotherapy in Estonia. In: Ban TA, Healy D, Shorter E, editors. The Triumph of Psychopharmacology and The Story of CINP, pp. 146-148. Animula, Budapest 2000.

October 30, 2014

Sydney Spector by Fridolin Sulser

Sydney Spector was born in 1923 in New York. He received his PhD in 1956 from the Jefferson Medical College in Philadelphia. After graduation, he joined Bernard B. Brodie's

Laboratory of Chemical Pharmacology at the National Heart Institute of the National Institutes of Health (NIH). Sydney Spector was part of the Laboratory that became the Mecca of Biochemical Pharmacology and gave birth to Biological Psychiatry. His studies on monoamine oxidase (MAO) and MAO inhibitors and on the action of reserpine and biogenic amines in brain contributed significantly to the scientific basis of the heuristic catecholamine hypothesis of affective disorders.

In 1961, he started collaborating with Al Sjoerdsma and Sydney Udenfriend at the NIH. His kinetic studies on catecholamine synthesis demonstrated that the rate-liming step in the biosynthesis of catecholamines is tyrosine hydroxylase (Levitt, Spector, Sjoerdsma and Udenfriend 1965). He then discovered α-methyltyrosine (α-MT) as an inhibitor of tyrosine hydroxylase (Spector, Sjoerdsma and Udenfriend 1965). Because of its specificity, α-MT provided researchers in psychopharmacology with an important tool for the elucidation of the mechanism of action of psychotropic drugs (e.g., the tricyclic antidepressants failed to "reverse" the reserpine-like syndrome in rats whose brain norepinephrine was selectively depleted by αMT, indicating that catecholamines were involved in the antidepressant action). These studies on catecholamines are one of the most frequently quoted papers.

In 1968 Sydney Spector moved to the Roche Institute of Molecular Biology in Nutley, NJ. There, after a sabbatical with Herman Eisen at Washington University, he moved into a new research area: Immunopharmacology. He provided clinicians and basic researchers with tools to measure drug levels in a quantitative way in plasma, brain tissue and cerebrospinal fluid: The "Spector Monoclonal Antibodies" to barbiturates, morphine, reserpine, desmethylimipramine (DMI), naloxone, chlorpromazine, haloperidol, etc. (Spector 1974). Then came the most exciting discovery: the discovery of endogenous morphine in brain. In meticulously designed studies, Sydney Spector demonstrated that brain morphine was endogenous in nature, located in neurons and released by depolarization (Gintzler, Lewy and Spector 1976). The potential of these studies is just beginning to be unraveled.

Sydney Spector received numerous awards for his research accomplishments, including the Paul K. Smith Award of Washington University School of Medicine, the ASPET Award for Experimental Therapeutics and the Julius Axelrod Award. In 1987 he was elected President of the American Society of Pharmacology and Experimental Therapeutics. Sydney Spector excelled in his dedication to nurturing and developing scientific talent. His scientific legacy will live on in the cadre of scientists who trained under his mentorship and subsequently established their own

distinguished career all over the world, occupying leadership positions in government, universities and industry.

Sydney Spector, age 88, passed away October 26, 2012.

References:

Gintzler AR, Lewy A, Spector S. Antibodies as a means of isolating and characterizing biologically active substances: presence of a non-peptide, morphine-like compound in the central nervous system. Proc Natl Acad Sci USA 1976; 73:2132-6.

Levitt M, Spector S, Sjoerdsma A, Udenfriend S. Elucidation of the rate-limiting step in norepinephrine biosynthesis in the perfused guinea pig heart. J Pharmacol Exp Ther 1965; 148:1-8.

Spector S. Development of antibodies to chlorpromazine. In: Forrest IS, Carr CJ, Usdin E, editors. Phenothiazines and Structurally Related Drugs. New York: Raven Press; 1974, pp. 363-4.

Spector S, Sjoerdsma A, Udenfriend S. Blockade of endogenous norepinephrine synthesis by α-methyltyrosine, an inhibitor of tyrosine hydroxylase. J Pharmacol Exp Ther 1965; 147:86-95.

March 27, 2014

Leo H. Sternbach by Thomas A. Ban

Leo Sternbach was born in Abbazia, Croatia, in 1907. He studied pharmacy and organic chemistry at Jagellonian University in Cracow, Poland, and as a postgraduate student, synthesized several heptoxdiazine compounds. After a short academic career, Sternbach joined Hoffmann-La Roche, one of the major Swiss pharmaceutical companies in Basel; moved, in 1941, from Switzerland to the United States; and some years later, became Director of Medicinal Chemistry at Roche's research facility in Nutley, NJ.

In 1954, while searching for drugs with psychotropic

properties, he returned to his early interest as a postgraduate student and synthesized a series of heptoxdiazines, which at the time, he recognized were quinazoline-3-oxides, and treated one of them with methylamine. From the reaction, resulted 2-methylamino-7-chloro-5-phenyl-3H-1,4-benzodiazepine-4-oxide, a substituted 1,4 benzodiazepine that was given the generic name, methaminodiazepoxide first, and chlordiazepoxide subsequently, in 1957. Pharmacologic screening revealed that the substance had similar pharmacologic profile to meprobamate, a widely used drug for relieving anxiety and tension, at the time. In 1960 chlordiazepoxide, the first benzodiazepine compound, was introduced into clinical use as an anxiolytic with the brand name of Librium. From the several other "benzodiazepines" Sternbach synthesized, diazepam was introduced, also primarily, for treatment of anxiety; flurazepam, nitrazepam, and flunitrazepam, for insomnia; and clonazepam, for epilepsy. During the 1960s, chlordiazepoxide, and especially, diazepam became widely used substances around the world; from 1969 to 1982, diazepam was the most prescribed drugs in the United States. They were instrumental in opening up research in the neuropsychopharmacology of anxiety.

Sternbach died, in 2005, at age 98.

References:

Sternbach LH. 1,4-Benzodiazepines: chemistry and some aspects of the structure-activity relationship. Agnew Chem 1971; 10:34-43.

Sternbach LH. The discovery of Librium. Agents and Actions 1972; 2:193-6.

June 13, 2013

Edward Trautner by Samuel Gershon

Edward Trautner was born in 1886 in Germany and received his medical degree in his native country. He left Germany in the 1930s and after a short stay in Spain and England, he arrived in the 1940s, as a refugee, in Australia, where he was invited by Professor Douglas Wright, head of the joint Department of Physiology and Pharmacology at the University of Melbourne, to

join his faculty.

In 1949 John Cade published his report in the Medical Journal of Australia on "Lithium salts in maniacal excitement" that lead to the re-introduction of lithium therapy in psychiatry. Yet, the clinical use of the new treatment entailed difficulties because of lithium's toxicity that was to the extent that Cade himself prohibited the use of the substance in his own hospital. Recognizing the importance of rendering lithium feasible for clinical use, Trautner with his junior associates, including Charles Noack, Douglas Coats and Samuel Gershon, conducted a series of four studies, during the 1950s that set the foundation for lithium therapy.

In the first of these reports, published in 1951, it was established that lithium, if administered in a dose in which plasma lithium levels are kept within 0.6 mEq/l to 1.2 mEq/l, is a safe and effective treatment in manic depressive patients. Plasma level determinations in the study were carried out with the flame photometer, an instrument constructed by Victor Wynn at the University, just a year before. From the other three reports, one published in 1955, showed increase of lithium retention in mania and of lithium excretion, when mania is resolved; another, published in 1956, revealed possible use of lithium in maintaining manic depressive patients in remission; and the third, published in 1957, dealt with the treatment of lithium toxicity. Without Trautner's contributions, implementation of lithium treatment would have been considerably delayed.

Trautner died in Queensland, in 1979, at age 93.

References:

Coats DA, Trautner EM, Gershon S. The treatment of lithium poisoning. Austr Ann Med 1957; 6:11-5.

Gershon S, Trautner EM. The treatment of shock-dependency by pharmacological agents. Med J Austr 1956; 43:783-7.

Noack D, Trautner EM. The lithium treatment of maniacal psychosis. Med J Austr 1951; 2:218-22.

Trautner EM, Morris R, Noack CH, Gershon S. The excretion and retention of ingested lithium and its effect on ionic balance of man. Med J Austr 1955; 2:20-91.

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Joseph Wortis by André B.Veras

Joseph Wortis was born in 1906 in Brooklyn and graduated in medicine in 1932 from the University of Vienna, Austria. He was trained in psychiatry at the Bellevue Hospital, in New York, spending 1934-1935 as a Havellock Ellis Fellow in Vienna. It was during this year that he met Manfred Sackel and became familiar with his insulin coma therapy of schizophrenia (Shorter 2011).

After returning to the United States in the mid-1930s and translating Sakel's monograph on insulin coma therapy, Karl Bowman set up an insulin ward for Wortis at Bellevue Hospital. In 1937, with the publication of their experiences on that ward in the American Psychiatric Association Journal, insulin coma therapy was launched in the USA (Wortis and Bowman 1937). In the same year, Wortis was part of Harold Himwich's team that was first to study and report on "brain metabolism during hypoglycemic treatment of schizophrenia" (Himwich, Bowman, Wortis and Fazekas 1937). In the five years that followed, he remained involved in studying "biochemical changes occurring in the cerebral blood" (Himwich, Bowman, Wortis and Fazekas 1939) and exploring the availability of substances, such as lactic acid and sodium pyruvate for brain metabolism during insulin coma treatment (Wortis and Goldfarb 1940). He also developed a simple method for prolonging coma (Wortis and Korr 1942).

In 1935, soon after his return from Europe, Wortis was invited by Clarence Farrar, at the time editor of the *American Psychiatric Association Journal*, to write a review article on insulin coma therapy in the Annual Reviews of Progress of the journal. Instead, Wortis wrote an "Annual Review of Progress in Physiological Treatments," which became a regular feature in the journal for about 20 years, from about 1935 to 1955 (Wortis 2011). It was in his annual review that the first reference to chlorpromazine in the English language appeared (Wortis 1954).

In the late 1950s and early '60s, Wortis explored the effect of chlorpromazine on brain metabolism, using minced rat brains with the employment of a Warburg respirometer. He observed that chlorpromazine had a biphasic effect on brain respiration, in the first phase, lasting about 16 hours, inhibiting, and in the second, lasting for about four days, enhancing it. He also noted that chlorpromazine depressed brain metabolism in the lower and enhanced it in the higher

cortical structures (Wortis and Jackim 1962).

In June 1973, Wortis became the founding editor of *Biological Psychiatry*, the journal of the Society of Biological Psychiatry. He continued in this position until 1992.

Joseph Wortis died in 1995 at age 88 (Gelder 1995).

References:

Gelder LV. Dr. Joseph Wortis, an Editor and Psychiatrist, 88, Dies. The New York Times, February 28th, 1995.

Himwich HE, Bowman KM, Wortis J, Fazekas JF. Brain metabolism during the hypoglycemic treatment of schizophrenia. Science, 1937; 86:271-2.

Hollister LE. Interview of Joseph Wortis. In: Ban TA, editor. An Oral History of Neuropsychopharmacolgy. Volume 1 (Starting Up, Edward Shorter, editor). Brentwood: American College of Neuropsychopharmacology; 2011, pp. 311-26.

Shorter E. Introduction and dramatis personae. In: Ban TA, editor, An Oral History of Neuropsychopharmacology. Volume 1 (Starting Up, Edward Shorter, editor). Brentwood: American College of Neuropsychopharmacology; 2011, pp. XLVI-LXV.

Wortis J. Review of psychiatric progress, 1953, physiological treatment. American Journal of Psychiatry 1954; 110:507-10.

Wortis J, Bowman KM. Further experience at Bellevue Hospital with hypoglycemic insulin treatment of schizophrenia. Am J Psychiatry 1937; 94:135-8.

Wortis J, Goldfarb W. A method of studying the availability of various substrates for human brain metabolism during therapeutic insulin shock. Science, 1940; 91:270-1.

Wortis J, Jackim E. Effects of chlorpromazine on brain tissue respiration. Am J Psychiatry, 1962; 119:363-6.

Wortis J, Korr IM. A simple method for prolonging therapeutic insulin coma. Proceedings of the Society of Experimental Biology 1942; 49:128-30.

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