FROM CONDITIONING AND PSYCHIATRY TO PSYCHOPHARMACOLOGY

Thomas A. Ban

I arrived in Canada from Hungary, my native country, in early 1957. After a fellowship in neuroanatomy at the Montreal Neurological Institute, and a rotating internship, I enrolled in McGill University's training program in psychiatry. I already had two years of psychiatry in Hungary and – thanks to George Sandor, my service chief at the National Institute of Psychiatry and Neurology – some familiarity with the use of new psychotropics, such as chlorpromazine, reserpine, lithium and isocarboxazid.

During the 1950s, psychiatric residents at McGill were required to write a "thesis," and I was fortunate to have Dr. Heinz Lehmann of chlorpromazine's fame as my advisor.

My thesis dealt with Pavlov's original experiments and brain model in a modern (1950s) neurophysiological framework. It was based on the notion that conditional reflex variables are functional patterns of the brain; and focused on the need – created by the rise of psychopharmacology – to replace conventional psychopathologies with a functional psychopathology, in which mental illness is described in terms of conditional reflex variables instead of psychopathological symptoms.

As a follow-up to my thesis, we developed a diagnostic test procedure based on the conditional reflex method (1) and a conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects (2). Since the action of psychotropics could be characterized in terms of conditional reflex variables, with the battery in place, by the end of the 1960s the stage was set to develop a methodology for the matching of the pharmacological (conditional reflex) profile of drugs with the clinical (conditional reflex) profile of psychiatric patients.

In 1960 I received my diploma in psychiatry with distinction at McGill. *Conditioning and Psychiatry* was published in the mid-1960s (1964 in the US and 1966 in the UK) with a

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Ban was elected fellow of CINP in 1962 and served as secretary of the 8th and 9th executives, as vice-president of the 10th, and as treasurer of the 12th, 13th, 14th and 15th. He presented papers on "Comments on the use of Sernyl", on "The effects of phenothiazines on the human electrocardiogram" (Ban, St. Jean and Desautels), on "Predictors of therapeutic responsivity to thiothixene in schizophrenia" (Ban, Lehmann, Sterlin and Saxena), and on "Methodological problems in the clinical evaluation of anxiolytic drugs" at the 4th (2x), 6th and 7th congresses respectively. Ban was formal discussant of G.V. Morozov's paper (Role of different structures of the brain stem in the genesis of catatonic stupor) at the 4th congress.

foreword by the late W. Horsley Gantt, at the time one of the last living pupils of Pavlov. For the "battery," we received in 1969 the annual McNeil Award of the Canadian Psychiatric Association.

From left: Carlo L. Cazzullo, Thomas A. Ban and W. Horsley Gantt

In the early 1960s I joined Heinz Lehmann as his co-principal investigator in our Early Clinical Drug Evaluation Unit (ECDEU) supported by the US Public Health Service. Ours was one of the first units of the network, which met with some regularity to exchange observations and findings on new psychotropics. The first meetings were chaired by Bertrum Schiele, the most senior member of the group, and the key players of those meetings were Art Sugerman, George Simpson (at the time still an associate of Nate Kline), and Don Gallant (at the time an associate of Bob Heath). Doug Goldman, Max Fink, and Sid Merlis were present too, if my recollection is correct; so were Dave Engelhardt, Leo Hollister, and Gerald Klerman. Others, like Turan Itil, Barbara Fish, Don Klein and David Wheatley became ECDEU investigators later in the 1960s.

Although the nature of the research to be conducted in the units was not clearly defined, the overall objective of the program was the development of an acceptable methodology – acceptable to both the drug companies and the drug regulatory agencies – for establishing the therapeutic efficacy of psychotropic drugs. To achieve this objective testimonials were replaced by the idiosyncratic methodologies employed in the different units (e.g., we used the Verdun Target Symptom and Depression Scales, the Psychopathological Symptom Profile, and the Verdun Psychometric and Conditioning Test Batteries) during the leadership of Jon Cole (the first half of the 1960s); and during Jerry Levine's administration (the second half of the 1960s), these idiosyncratic methodologies were replaced by uniform, standardized data collection, processing and analytic procedures. By the end of the 1960s the Early Clinical Drug Evaluation Units, Biometric Laboratory Information Processing Sysytem (ECDEU-BLIPS) was in place (5) to dominate the field during the 1970s.

From the beginning, our early clinical drug evaluation unit was very productive. Because of the unique geographic position of Canada, we had been involved with most of the psychotropic drugs marketed in North America during the 1960s and 1970s. I was in regular contact with the late Tom da Silva, the conscientious officer of the Canadian Health Protection Branch (the corresponding organization to the US Food and Drug Administration) responsible for the CNS area, with Peg Milliken of the US Adverse Drug Reaction Reporting Program, and with the pharmaceutical companies involved with the development of psychotropic drugs.

Each drug we worked with has its own story, which will need to be told elsewhere, and our contributions – impressions, observations and findings – were mostly, but not always, further substantiated by subsequent clinical investigations. In case of desipramine, the demethylated metabolite of imipramine, for example, our impression that it had a faster onset of action than

its parent substance – reported in 1962 (6) – was not borne out. On the other hand, our observations that levomepromazine, an aminoalkyl phenothiazine, was somewhat distinct from the typical phenothiazine neuroleptics – reported in 1963 (7) – received further substantiation in recent years. The same as to levomepromazine applies to our finding with trimipramine, reported in 1964 (8).

From left: Gaston Castellanos, Alice Leeds and Nenad Bohacek

We were among the first to conduct series of systematic studies, instead of just an isolated study, with a particular psychotropic, e.g., trimipramine (9), and with a group of psychotropics, e.g., the butyrophenones (10) or the thioxanthenes (11). Since we were just as much interested in exploring therapeutic effects as adverse effects, we were first to demonstrate cardiac conductance changes with thioridazine (12), the phenothiazine promoted for use in geriatrics. We were among the first to describe skin pigmentation and ocular changes with chlorpromazine (13).

With the steadily accumulating preclinical and clinical information in our unit, I became increasingly aware of the heterogeneity of the descriptions provided in the preclinical brochures; of the gap between the preclinical and clinical data; and of the lack of integration of clinical findings in clinical psychopharmacologic research. To overcome the difficulties and to create a common language, I decided to write *Psychopharmacology* (14). It became the first comprehensive text in the field. The writing was greatly facilitated by an invitation to conduct a workshop on "What preclinical information does the clinician expect to be given prior to conducting a clinical trial with a new drug" at the 1966 annual meeting of the American College of Neuropsychopharmacology (ACNP) (15). I also benefitted from the request to write a series of reviews on the different groups of psychotropic drugs for *Applied Therapeutics* (16, 17, 18, 19, 20, 21, 22). There was also my increasing involvement in teaching psychopharmacology to the residents at McGill. The material presented at the ACNP Workshop provided the basis of the first part of the book, General Psychopharmacology; the papers published in *Applied Therapeutics*, for the second part, Systematic Psychopharmacology; and the material used in teaching, for the third part, Applied Psychopharmacology. In my concluding remarks in *Psychopharmacology*, I pointed out that pharmacotherapy with psychotropics focused attention on the biological heterogeneity within the traditional nosologic categories in terms of therapeutic responsiveness; and postulated that progress in pharmacotherapy will depend on how fast this heterogeneity is resolved.

Psychopharmacology was published by Williams and Wilkins in 1969. It shared the 1970 Clarke Institute Annual Research Award with Harvey Stancer's contributions to the role of catecholamines in affective disorders.

Prior to the publication of *Psychopharmacology* I was very much involved in the activities of the Quebec Psychopharmacological Reserach Association (23,) that we founded with Lehmann in the early 1960s and with the coordination of the Canadian Mental Health Association's Collaborative Studies on Nicotinic Acid in the Treatment of Schizophrenia (24). In the late 1960s, after the publication of *Psychopharmacology*, I became increasingly involved with activities of the Mental Health Unit of the World Health Organization, under the direction of the late Boris Lebedev, and with activities of the International Reference Center Network on Psychotropic Drugs, a joint venture between the World Health Organization and the US National Institute of Mental Health, under the direction of the late Alice Leeds, but it's time to stop.

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