Carlos Morra and Mateo Kreiker: Psychopatholog**y**

Thomas A. Ban: Towards structural psychopathology*

Forgetting the language of psychiatry

The dream of Moreau de Tours' (1845) in the mid-19th century to use drugs in the study of insanity has become a realistic goal in the mid-1950s with the introduction of effective pharmacological treatments, such as chlorpromazine, reserpine, imipramine and iproniazid in psychiatry; the demonstration of the presence of monoamine neurotransmitters in the brain, such as norepinephrine and serotonin; the recognition of chemical mediation at the site of the synapse; and the construction of the spectrophotofluorimeter (Ban 1969; Bowman, Caulfield and Udenfriend 1955; Delay and Deniker 1952; Kline 1958; Kuhn 1957; Twarog and Page 1953; Vogt 1954). The capability to measure changes in the concentration of neurotransmitter monoamines and their metabolites in the brain led to the development of neuropharmacology, a branch of pharmacology that deals with the detection of the mode of action of centrally acting drugs. It has also opened the path for the development of neuropsychopharmacology, a new discipline that studies the relationship between neuronal and mental events with the employment of centrally acting drugs (Ban and Ucha Udabe 2006). By the end of 1955, the year the new technology (spectrophotofluorimetry) became available, Pletscher, Shore and Brodie (1955) at the National Heart Institute in the United States, reported a decrease in brain serotonin levels after the administration of reserpine, a substance that was seen to induce depression in some patients when used in the treatment to hypertension (Freis 1954; Mueller, Pryor, Gibbons and Orgain 1955). And in 1956, one year later, Pletscher (1956) first, and then Besendorf and Pletscher (1956), reported increase in brain serotonin levels after the administration of iproniazid, a monoamine oxidase inhibitor that was reported to induce euphoria in some tubercular patients in the course of treatment (Flaherty 1952; Selikoff, Robitzek and Orenstein 1952).

One of the first to recognize that neuropsychopharmacology opened a new perspective in the understanding and treatment of psychiatric illness was Abraham Wikler (1957), an American psychiatrist and pharmacologist. In his monograph, *The Relation of Psychiatry to Pharmacology*, published in 1957, he entertained the possibility that studying the mode of action of psychotropic drugs with known therapeutic effects might lead to the neurochemical underpinning of mental disorders, a pre-requisite for the development of rational treatments.

In the 1960s a paradigm shift in psychiatry from psychopathology/psychodynamics to psychopharmacology followed and by the 1970s with hopes that using drugs would get directly to the biological substrate of mental pathology, interest from psychopathology and psychiatric nosology turned to research in the biochemistry of psychiatric disease.

Neuropsychopharmacology received wings in the 1960s from Arvid Carlsson's (1961) report on selective changes on brain monoamines with psychotropic drugs. His findings set the stage for a development that led to the formulation of the catecholamine hypothesis of affective disorders by Joseph Schildkraut in 1965, and Bunney and Davis (1965) independently, and the dopamine hypothesis of schizophrenia by Jacques Van Rossum in 1967.

Yet, they were warning signals already in the early years that something was wrong. It was apparent to all those working with patients from the beginning that one of the essential prerequisites of neuropsychopharmacological research, a clearly identified treatment responsive population, was not fulfilled. The heterogeneity in pharmacological responsiveness to the new drugs was so great within the diagnostic groups that it took eight years (1952-60) to demonstrate the therapeutic efficacy of chlorpromazine in schizophrenia and seven years (from 1957 to 1965) to demonstrate the therapeutic efficacy of imipramine in depression (Casey, Lasky, Klett and Hollister 1960; Delay and Deniker 1962; Klerman and Cole 1965; Kuhn 1957).

To overcome the difficulties created by the heterogeneity within the diagnostic groups for the demonstration of therapeutic efficacy of a rapidly growing number of new psychotropic dugs, a regulatory requirement for introducing a drug for clinical use in some countries by the early 1950s, a statistical methodology, the randomized clinical trial

(RCT) was adopted. It was hoped that the data collected in RCTs would help to resolve the heterogeneity within the diagnoses by identifying treatment responsive populations with the use of linear regression equations or other statistical methods. But this was not to be the case (Roth and Barnes 1981). To meet the needs of RCTs for reliable diagnostic endpoints, consensus-based diagnoses, such as the DSM-III, and for the detection and documentation of changes, sensitized rating scales were adopted (American Psychiatric Association 1980, 1987, 1994; Guy 1976). Since consensus-based diagnoses cover up their component diagnoses and rating scales are sensitized by retaining only the most sensitive symptoms and signs to treatment, their use has precluded the possibility of studying "psychopathology" and indices relevant to "psychiatric nosology," in the collected data in the numerous clinical studies, to find relevant information about the treatment responsive subpopulations within the diagnostic groups (Ban 2006).

During the 1960s and '70s there was still hope that the pharmacological heterogeneity within the diagnostic group would be resolved by the replacement of old psychopathology-based diagnoses with diagnoses built from new buildings blocks based on biological measures, such as neuroendocrine tests, biochemical changes, neurophysiological indicators and/or brain images (Buchsbaum and Haier 1978; Carroll 1985; Dreger 1968). It was only in the 1980s, after the introduction of DSM-III, that it became evident that this was not to be the case.

By 1987, the time of the postulation of a "clinical prerequisite" for rendering findings in neuropsychopharmacological and biological research in psychiatry interpretable, psychopathology and psychiatric nosology became forgotten languages in psychiatry (Ban 1987). Major European developments in psychopathology and psychiatric nosology during the first half of the 20th century were translated only many years after the introduction of psychotropic drugs. Karl Jaspers' *General Psychopathology* published in 1913 was first translated into English in 1962, and Karl Leonhard's *Classification of Endogenous Psychoses* published in 1957 was first translated in 1979.The psychometric methodology that dominated psychopharmacology during the second part of the 20th century was developed without the possible benefit of those contributions.

It was also forgotten that in the late 1950s Christian Astrup (1959), a Norwegian professor of psychiatry, and in the mid-1960s Frank Fish (1964), a British professor of psychiatry had shown that pharmacological heterogeneity in schizophrenia could be considerably reduced by adopting Karl Leonhard's (1957, 1979) classification of endogenous psychoses.

The findings of Fish were especially convincing. By re-classifying 474 schizophrenic patents with the employment of Leonhard's diagnostic criteria, he found moderate to marked response to neuroleptics in as many as 79% of his 123 patients with the diagnosis of "non-systematic (unsystematic) schizophrenia" and only in 23% of his 351 patients with the diagnosis of "systematic schizophrenia." In addition to the more than three-fold difference in responsiveness to neuroleptics between the two groups, Fish also revealed that from his 51 patients with "affect-laden paraphrenia," a form of "non-systematic (unsystematic) schizophrenia," characterized by delusions with intense emotional participation (delusional dynamics), more than 4 in 5 patients (43 or 84.4%) had a moderate to marked response to treatment, whereas from his 100 patients "with systematic hebephrenia," less than 1 in 4 (23 or 23%) had a similar response.

Frank Fish (1964)

Schizophrenia

(474 patients)

Marked to Moderate Response to Phenothiazine Tranquilizers

UNSYSTEMATIC SCHIZOPHRENIAS	SYSTEMATIC SCHIZOPHRENIAS
79% of 123	**23% of 351**
Affect-laden Paraphrenia	**Systematic Hebephrenias**
84.4% from 51	**23% of 100**
More than 4 in 5	**Less than 1 in 4**

Rediscovering the Language of Psychiatry

Revival of Nosology

Diagnostic Criteria of Research

In spite of Fish's (1964) report, Leonhard's (1957) classification was dormant for almost 20 years. Then in 1982, a guide to Leonhard's classification of chronic schizophrenias (GUIDE) was introduced at the Tennessee Neuropsychiatric Institute (TNI) of Vanderbilt University (Nashville); and two years later, in 1984, a Hungarian team led by Bertalan Pethö published (in Hungarian) research diagnostic criteria with the title "KDK Budapest" for use in diagnosing functional psychoses that was based primarily on Leonhard's work (Ban 1982; Pethö, Ban, Kelemen, et al. 1984).

In the mid-1980s the KDK Budapest was adopted with some modifications from Hungarian into English at the TNI with the title " Budapest-Nashville in the Diagnosis and Classification of Functional Psychoses." The DCR was published in 1988 by Pethö and Ban in collaboration with András Kelemen, Gabor Ungvari, István Karczag, István Bittér and Judith Tolna from Budapest; Marek Jarema (from Poland); François Ferrero (from Switzerland); Eugenio Aguglia (from Italy); Giovanni Luca Zurria (from Italy); and Olaf Fjetland (from the United States), at the time working with Thomas Ban at Vanderbilt in Nashville. Of the 10 members of the team four were to become professors and heads of university departments of psychiatry: Eugenio Aguglia in Trieste (Italy), Istvan Bitter in Budapest (Hungary), François Ferrero in Geneva (Switzerland) and Marek Jarema in Warsaw (Poland).

Neither the KDK Budapest nor the DCR Budapest-Nashville is restricted to Leonhard's (1957) diagnostic concepts of "endogenous psychoses." Both include also Wimmer's (1916) diagnostic concept of "psychogenic (reactive) psychoses" and the German diagnostic concept of "delusional development" formulated by Robert Gaupp (1914) and Ernst Kretschmer (1927) at the University of Tübingen (Faergeman 1945; Perris 1974; Retterstol 1978, Strömgren 1974).

At the core of the DCR is a diagnostic decision tree that consists of 524 variables, organized into 179 diagnostic decision clusters that yield 21 tentative, 33 provisional, 45 working and 55 final diagnoses. The variables of the DCR are almost exclusively psychopathological symptoms, as in the course of KDK development it was found that

adding variables of social adjustment lowered predictive validity of the diagnoses (Pethö 1984; Pethö, Tolna and Tusnády 1979; Strauss and Carpenter 1974).

Findings with the GUIDE revealed that the significantly different response to neuroleptics in the two classes of schizophrenias is not restricted to therapeutic effects but extend to adverse reactions. Analyses of data of an international survey conducted with 768 chronic schizophrenic patients showed that tardive dyskinesia (TD) occurred more than three times more frequently in patients diagnosed with "systematic schizophrenia" (13.3%) than in patients diagnosed with "non-systematic (unsystematic) schizophrenia" (4.3%) (Guy, Ban and Wilson 1985). Since in Fish's study moderate to marked response to neuroleptics was more than three times as frequent in the "non-systematic schizophrenias" (79%) than in the "systematic schizophrenias" (23%), the inverse relationship between therapeutic effects and TD (i.e., less TD if the drug works and more TD if it does not) indicates that the functional state of the structures involved in the mode of action of neuroleptics is different in the "systematic schizophrenias" from the "non-systematic schizophrenias."

Guy, Ban and Wilson (1985)
International Survey
768 Chronic Schizophrenic Patients

TARDIVE DYSKINESIA

Present

UNSYSTEMATIC SCHIZOPHRENIAS	SYSTEMATIC SCHIZOPHRENIAS
4.3%	**13.3%**
(Fish: 79% response rate)	**(Fish: 23% response rate)**

The functional state of the structures involved in the mode of action of lithium is also different in the "systematic schizophrenias" from the "non-systematic schizophrenias." In a survey conducted in 24 schizophrenic patients whose neuroleptic medication was supplemented with lithium to potentiate therapeutic effects it was found that 9 of the 10 patients from the population with "non-systematic schizophrenia" responded favourably to the lithium supplementation, whereas 9 of the 14 of patients

diagnosed with “systematic schizophrenia” responded unfavourably. It was also noted that 5 of the 14 patients diagnosed with “systematic schizophrenia” developed neurotoxicity to lithium supplementation whereas in the population with “non-systematic schizophrenia” neurotoxicity was not encountered at all (Prakash, Kelwala and Ban 1982).

Revival of Psychopathology

During the last decade of the 20th century, molecular genetics has entered the psychiatric scene and by the dawn of the 21st century genes encoding the primary targets of psychotropic drugs in the brain, such as G-protein-coupled receptors, nuclear-hormonal receptors, ion channels, enzymes, etc., were identified. It was also recognised that any empirically derived treatment responsive population to a psychotropic drug could serve as a reference point for testable genetic hypotheses about mental illness with the employment of a candidate gene approach. Although patients were still diagnosed with consensus-based diagnoses at the clinic exploration of the molecular genetic basis of the biochemistry of the different diagnostic populations began (Lerer 2002).

To meet the new needs, in 2002 a new methodology for the identification of clinical populations for research was proposed: “nosologic homotyping” with pharmacological validation (Ban 2002).

Nosologic Homotyping

Nosologic homotyping is based on “structural psychopathology,” a term coined by Gyula Nyirö (1958), professor of psychiatry at the Medical University of Budapest (now Semmelweis University) in the 1950s, for a branch of psychopathology in which Wernicke’s (1900, 1906) “mental structure” is combined with 20th century psychopathology (Jasper 1913, 1962).

In structural psychopathology the three components (phases) of Wernicke’s “mental structure” (psychosensory, intrapsychic and psychomotor) are extended into three “psychic structures,” the “afferent-cognitive,” the “central-affective” and the “efferent–adaptive,” in which each hierarchical structure consists of different levels, with

each level functionally connected to each other within and across structures. In defining the functional activity of the different levels in each structure in the processing of signals in the brain, Nyirö (1962) used an ontogenetic model and suggested that the five levels of the afferent-cognitive structure correspond with: (1) diffuse sensation, (2) differentiated perception, (3) image formation, (4) concrete ideation and (5) abstract ideation; the four levels of the central-relational structure correspond with: (1) undifferentiated primitive ("ancient") signal, (2) sensorial and vital emotions, (3) intellectual emotions and (4) ethical, moral and social emotions; and the six levels of the efferent-adaptive structure correspond with (1) autonomic ("vegetative") movements and simple (elementary) reflexes, (2) uncoordinated movements, (3) emotional and instinctual stereotypes, (4) echo phenomena, (5) voluntary goal directed coordinated movements and (6) automatisms.

Gyula Nyirö (1958, 1962)

Structural Psychopathology

STRUCTURES

Ontogenetic Model

afferent-cognitive	central-affective	efferent-adaptive
6.		**automatisms**
5. abstract ideation	**ethical, social emotions**	**voluntary movements**
4. concrete ideation	**intellectual emotions**	**echo phenomena**
3. image formation	**vital emotion**	**emotional stereotypes**
2. differentiated perception	**sensorial emotions**	**uncoordinated movements**
1. diffuse sensation	**undifferentiated signal**	**simple reflexes**

Within the frame of reference of structural psychopathology, psychopathological symptoms arise from abnormalities in processing of signals within and across different levels in these structures and the nature of the abnormality corresponds with the site of the abnormality in processing, e.g., an abnormality of processing from "concrete

ideation" to "abstract ideation" may yield "concretization," or from "abstract ideation" to "ethical, social emotions" to "constricted affect."

Nosologic homotypes are identical in "elementary units" (psychopathological symptoms), i.e., processing of signals in neuronal circuits, but to qualify for a "nosologic homotype," abnormality in the processing of signals does not suffice.

Nosologic homotyping is based on the assumption that even if symptoms follow their disease, as already noted by Galen in the 2nd century, it is the disease that defines its symptoms. Hence, to qualify for a "nosologic homotype" a "psychopathology-based homotype" has to be assigned to the same position in the "nosologic matrix," constructed with consideration of the three classifying principles of psychiatric nosology, i.e., Cullen's (1772) "totality (i.e., "universal" or "partial"); Kraepelin's (1896) "temporality" (i.e., "continuous" or "episodic"); and Leonhard's (1957) "polarity" (i.e., "bipolar" or "unipolar") (Ban, 2000, 2002).

Each pharmacologically valid distinct "nosologic homotype" provides a potential diagnostic concept for a mental disorder in which psychopathologic symptom represent distinct abnormalities in the processing of signals between levels within and across three "mental structures"; the formal characteristics of the "onset" (sudden or insidious), "course" (episodic or continuous) and "outcome (recovery or defect) of the mental syndrome reflect the pathological process in its "dynamic totality" and the "dynamic totality" of the pathological process, as a whole, provides a structure that is determined by the illness (Ban 1987, 1992, 2002, 2007; Pethö1990).

Pharmacologically validated "nosologic homotypes" are more homogeneous populations in terms of psychopathology and psychiatric nosology than populations identified by any other method. Since a treatment responsive population is a prerequisite for neuropsychopharmacological research and for discriminate use of psychotropic drugs, "nosologic homotypes" are today the closest fit for neuropsychopharmacological and molecular genetic research, as well as for research in the pharmacotherapy of psychiatric disorders.

Considering that in "nosologic homotypes" psychopathological symptoms are perceived as abnormalities in the processing of signals in neuronal circuits of the human brain that is dominated by CRs, "nosologic homotypes" might provide the missing link

for using abnormalities of CR parameters for bridging "psychopathology" with "pathophysiology" in the central nervous system (CNS).

The Conditional Reflex Revisited

It was also Nyirö who was first to conceptualize structural psychopathology within the frame of reference of conditioning. In his essay on "The Structural aspect of mental processes on the basis of reflex mechanisms," published in 1957, he suggested that in the formation of mental structures, "differential inhibition" and in the regulation of connections between mental structures "retarded inhibition" plays a prominent role. Both, "differential inhibition" and retarded inhibition," are manifestations of "internal inhibition" in Pavlov's "brain model."

In keeping with Nyirö's conceptualization were Astrup's (1962) findings in the early 1960s which indicated abnormalities of "internal inhibition," as measured by CR differentiation and CR retardation, in chronic schizophrenia.

A great impetus for studying CR variables in clinical research in psychiatry was given by findings in electrophysiological studies in the late 1950s which indicated that in the formation of CRs brain stem and mid-brain reticular nuclei, as well as intra-laminar nuclei of the thalamus, are involved (Ban 1964; Gastaud 1958).

To render CR variables accessible to research a "conditioning test procedure" was developed in the early 1960s in the Department of Psychiatry at McGill University (Montreal) with the employment first only the eyelid closure technique (Ban and Levy 1964). The eight CR parameters studied with the employment of the procedure were: (1) the extinction of the orienting reflex (OR extinction), (2) CR acquisition, (3) CR extinction, (4) CR generalization, (5) CR differentiation, (6) CR delay, (7) secondary CR formation and (8) CR reversal. The procedure was used in studying CR functions in schizophrenia and depression, as well as in clinical investigations with psychotropic drugs. Findings in these studies were published in several reports, including a monograph, *Experimental Approaches to Psychiatric Diagnoses* (Ban and Kerenyi 1951; Ban and Lehmann 1971; Ban, Lehmann and Green 1969, 1970; Choi, Ban, Lehmann and Adamo 1966; Hattangadi, Lidsky and Ban 1966; Hattangadi, Lidsky, Lee and Ban 1968).

In the late 1960s the conditioning-test procedure at McGill was replaced by a conditioning test battery with the employment of seven conditioning techniques for the study of psychopathological mechanisms and psychopharmacological effects (Ban, Lehmann and Saxena 1970). The battery included (1) galvanic skin reflex (GSR), (2) salivary secretion, (3) eyelid closure, (4) defensive finger withdrawal, (5) Ivanov-Smolensky's test for second signal system activity (1954), (6) a modification of Astrup's (1962) word association test and (7) a modification of Lehmann's (1968) active avoidance procedure. Yet, by 1970, the time the "battery" became fully operational, behavioural pharmacology was replaced by neuropharmacology and interest in clinical research with the behavioural conditioning method was lost.

While clinical research in conditioning was abandoned, basic research in conditioning continued and by the down of the 21st century Joseph Knoll (2005), a Hungarian professor of pharmacology recognized that the human cerebral cortex with its 10 billion neurons and its one million billion connections has the capacity to accommodate the steadily growing number of new CR connections throughout life (Edelman 1992). It was also noted that while the architecture of behaviour, the neural circuits of the brain, remain constant, i.e., the same cells invariably hook up with the same cells, the strength of synaptic connections is getting stronger with "learning" and getting weaker with "habituation" (Carew, Walters and Kandel 1981).

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