NEUROPSYCHOPHARMACOLOGY AND THE FORGOTTEN LANGUAGE OF PSYCHIATRY

Madness: From Psychiatry to Neuronology

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Neuropsychopharmacology and the Forgotten Language of Psychiatry[1]

From Psychiatry to Neuronology via Neuropscyhopharmacology[2]

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FROM NEUROSIS TO PSYCHOSIS

Madness may be as old as mankind (Porter 2002). Yet, development that led to the birth of psychiatry, the discipline that deals with "madness," began only in the late 18th century. It was triggered by: (1) William Cullen's (1777) introduction of the term "neurosis", in his First Lines of Physic, for a class of disease he believed were diseases of

[1] This mini E-Book is an expansion of my presentation on Grand Rounds in the Department of Psychiatry, Vanderbilt University (Nashville, Tennessee, USA) on March 5, 2009.
[2] Title of the slide show prepared for the Grand Rounds presentation on March 5, 2013. It was posted in INHN's "Electronic Archives" on October 10, 2013

the “nerves”, and (2) his classifying the “vesanias”, that included the various forms of madness, as one of the four “orders” of the “neuroses”[3] (Littre 1877).

Cullen was an influential professor of medicine and physics at the University of Edinburgh, Scotland and his classification attracted attention in Continental Europe and the United States. Hence, his classifying “madness” as diseases of the “nerves” could not be dismissed by the “mentalists” (referred to by some as “German Romanticists”), powerful group of physicians at the time that believed that “insanity” was an affliction of the “mind” (Pichot 1983; Shorter 2005).

To shift emphasis from the nerves (brain) back to the mind (psyche) in the understanding of “madness”, the term “Psychiaterie” was introduced in 1808 by Johann Christian Reil, the professor of medicine in Halle (Germany). It was adopted and modified to “Psychiatrie” by Johann Christian Heinroth, the professor of medicine in Leipzig (Germany).

It was through Heinroth’s influential *Textbook on the Disturbances of Psychic Life*, published in 1818 that the term “psychiatry” spread around the world (Pichot 1983).

The “mentalists” profoundly affected the language and thinking- of “psychiatry” with a long lasting effect.

In 1845 Ernst Feuchtersleben, the dean of medicine at the University of Vienna (Austria), not a mentalist himself, had adopted the “mentalist” term, “psychosis” in his *Textbook of Medical Psychology* for patients with “madness”, who qualified for the “vesanias“ in Cullen’s classification. His separation of patients with “madness”, i.e., patients with “psychosis” from the other patients with “neurosis”, marks the separation of “psychiatry” from “neurology”. Within Feuchersleben’s frame of reference, ”Every mental disorder implies a disease of the nervous system, but not every defect of the nervous system is accompanied by mental disorder (Pichot 1983).

[3] In his First Lines of the Practice of Physic, Cullen characterized the “class” of ”neuroses” by “injury of sense and motion without an idiopathic pyrexia or any local affliction”, and divided the “neuroses” into four “orders” of diseases: “comata” (“diminution of voluntary motion with sleep or deprivation of senses”), “adinamiae”(diminution of involuntary motions whether vital or natural”), “spasmi” (“irregular motions of the muscles or muscle fibres”), and “vesaniae” (disorders of judgment without pyrexia or coma”) (Menninger, Mayman and Pruyser 1968).

Introduction of terms that set the stage for the development of psychiatry

William Cullen
Edinburgh (Scotland)
Neurosis
1777

Johann Christian Reil
Halle
Psychaterie
1808

Johann Christian Heinroth
Leipzig
Psychiatrie
1818

Ernst Feuchtersleben
Vienna (Austria)
Psychosis
1845

INTRODUCTION OF CONDITIONED REFLEX

In the same year, 1845 that Feuchtersleben's textbook appeared, Wilhelm Griesinger published his treatise, *The Pathology and Therapy of Psychic Illnesses*. For Griesinger, psychiatry was part of the natural sciences; mental activity was nervous activity, and mental pathology was a symptom of brain disease.

Stimulated by Sir Charles Bell's (1811) discovery and François Magendie's (1822) recognition of the importance of the "reflex arc" that links sensory input with motor output in the functioning of the nervous system (spinal cord), Griesinger (1843) was first to perceive mental activity as "reflex" activity. He was also the first to describe in 1843 "psychic reflex actions" (psychische Reflexactionen).

By adopting the "reflex" as he elementary unit of "mental activity" in 1843, Griesinger set the stage for the development of psychiatry as a medical discipline. Twenty years later, in 1863, Ivan Mihailovich Sechenov, a Russian physiologist, who studied "nervous inhibition" in the central nervous system of the frog in Claude Bernard's laboratory in Paris, elaborated on Griesinger's descriptions. In his monograph, *Reflexes of the Brain*, he concluded that all activity, including the "psychological" in the brain, is reflex and as such follows fixed laws determinable by investigation (Sechenov 1935; Wells 1956).

The structural underpinning of the "psychic reflex" was established in the late 19th century by Camillo Golgi (1874), an Italian histologist, who described multi-polar (Golgi) cells in the "olfactory bulb" with the employment of silver staining; Santiago Ramon y Cajal (1894), a Spanish histologist, who established that the "neuron" is the morphological and functional unit of the nervous system; and Sir Charles Sherrington (1906), an English physiologist, who demonstrated that the "synapse" is the functional site of transmission from one neuron to another..

Discoveries that provided the structural foundation of brain functioning

Camillo Golgi
Italy
1874
multipolar cells in olfactory bulb

Ramon y Cajal
Spain
1883
multipolar cells
in olfactory bulb

Charles Sherrington
England
1906
synapse
functional site of transmission

Carl Wernicke (1881-1883), the professor of neurology and psychiatry in Breslau (Germany at the time), in the late 19th century, adopted Griesinger's view that mental activity is "reflex" activity, and classified "psychoses," i.e., psychiatric diseases, on the basis of "hyper-functioning," "hypo-functioning, or "para-functioning" in the "psycho-sensory", "intra-psychic" (trans-cortical) and/or "psychomotor" components (paths, phases) of the "psychic reflex" (Franzek 1990).

The "psychic reflex", became central in the research of Ivan Petrovich Pavlov, a Russian physiologist, recipient of the Nobel Prize in 1904 for the discovery of the nervous regulation of the heart. His interest in the "psychic reflex" was triggered by his (and others) observation that "sham feeding" produced gastric secretion in a dog (Pavlov 1906). To study this phenomenon he developed a behavioural method for the detection and measurement of salivary secretion in chronic experiments in dogs with a surgical fistula in their parotid glands. With the employment of this method Pavlov discovered that any sensory stimulus (ringing of a bell in the original experiments) by repeated (preceding) coincidence with a specific stimulus for a particular reflex (food in the mouth for salivary secretion in the original experiments) became a signal for the specific stimulus, i.e., ringing of a bell became a signal for eliciting salivary secretion for which food in the mouth was the only signal before.

Pavlov could explain his findings only by assuming the opening of a new, formerly non-operating path in the brain with each newly formed CR. Hence, he postulated that "psychic activity", as salivating to the ringing of a bell, translates into changes in the processing of sensory signals in the cerebral cortex. He also rendered the "psychic reflex," i.e., the changes in the processing of sensory signals in the brain, accessible to study with a behavioural method he developed in his laboratory. To distinguish the behaviourally indistinguishable acquired reflex from the innate reflex, he coined the term conditioned reflex (CR) for the former, and the term unconditioned reflex (UR) for the latter.

In the first two decades of the 20th century Pavlov with his associates established that the brain of some mammals has built-in potential to form, i.e., acquire, CRs (CR acquisition); extinguish-inhibit, acquired CRs (CR extinction); and "disinhibit" extinguished CRs (CR disinhibition). They also revealed that before the CR becomes

restricted to a particular CS by differentiating the CS from other stimuli (CR differentiation), it becomes "generalized" in a manner that transiently, any qualitatively similar stimulus to the CS can elicit the CR (CR generalization). Based on two assumed ongoing "elementary basic processes" in the brain, "excitation" and "inhibition", which become manifest behaviourally in CR acquisition and CR extinction, the brain has the potential for differentiation (CR differentiation), by reinforcing one stimulus (positive stimulus) and not-reinforcing another (negative stimulus), and CR reversal, by shifting reinforcement from the positive to the negative stimulus. Furthermore, the brain also has the potential to delay the onset of the CR (CR delay or retardation) and to form secondary CRs or chains of CRs built on established CRs[4] (Ban 1964; Gantt 1948; Pavlov 1927).

Ivan Petrovich Pavlov's contributions:

DISCOVERED that any sensory stimulus can become a signal for a specific sensory stimulus if repeatedly coincides (preceding coincidence) with the specific stimulus;
EXPLAINED his finding by assuming opening of new, formerly non-operating path in the brain;
HYPOTHESIZED that "psychic activity" is based on changes in the processing of sensory signals in the brain;
REPLACED the term "psychic reflex" with the term "conditioned reflex" (CR);
RENDERED the built-in potential of the brain for processing signals accessible to study via CR functions:

acquisition
extinction
disinhibition
generalization
differentiation
reversal
retardation
secondary CR formation
CR chain formation

[4] Within Pavlov's frame of reference, CR disinhibition is a function of "external inhibition, whereas CR extinction, CR differentiation and CR delay (retardation) are functions of "internal inhibition.

In the early 1930s Pavlov with his associates extended their research from animal to man and revealed that the human brain has the potential to use a corresponding verbal signal of a sensory stimulus as a signal to elicit the CR. Since verbal signals are built on sensory signals, Pavlov referred to CR activity with the use of words as second signal system activity, and CR activity with the use of sensory signals as first signal system activity. Furthermore, since CR activity in both, the first and the second signal systems are built on UR activity, he distinguished between lower, UR based nervous activity, and higher, CR based nervous activity.

In Pavlov's frame of reference mental functioning is higher nervous activity, and mental pathology is an expression of abnormal functioning in the second signal system. The findings that CRs to verbal signals suppress CRs to sensory stimuli, and CRs to sensory stimuli, suppress URs indicate that human behaviour is dominated by verbal signals (Ban 1966; Bykov 1957; Ivanov-Smolensky 1954; Wells 1956). Since CRs in the first and the second signal systems are based on the same built in potential of the brain for CR functions, CR parameters, such as CR acquisition, CR extinction, generalization, differentiation, secondary CR formation, etc., provide an indirect means for the study of normal and abnormal mental functioning. Hence, if abnormal CR functions could be linked to psychopathology and its underlying abnormality, CR parameters would provide a bridge between the "language" of mental pathology and the "language" of pathological brain functioning.

Potentials of the Human Brain that provides the basis for mental activity

1. **to use corresponding word of a sensory CS as a signal to elicit CR;**
2. **CRs to sensory signals suppress URs and CRs to verbal signals suppress CRs to sensory signals;**
3. **CRs in the first (sensory) and CRs in the second (verbal) signal systems are based on the same built in potential of the brain for CR functions;**
4. **operates prevailingly with CRs, dominated by CRs to verbal signals;**

5. **mental pathology is an expression of an abnormality in second signal system functioning;**
6. **CR parameters such as CR acquisition, CR extinction, etc., provide a means for the study of normal and abnormal functioning in both the first and the second signal systems;**
7. **if abnormal CR functions could be linked to psychopathology and its underlying pathophysiology, CR parameters could serve as a bridge between the language of psychiatry and the language of brain functioning.**

DEVELOPMENT OF THE LANGUAGE OF PSYCHIATRY

INTRODUCTION OF PSYCHOPATHOLOGY

It was Galen (131-201) first to recognize that "symptoms" follow disease as shadow its substance (Garrison 1929). Yet, development of "psychopathology", the "language of psychiatry", began only in the mid-19th century in the course of early attempts to differentiate sub-populations within "insanity".

The term, psychopathology first appeared in the psychiatric literature in 1845, in Feuchtersleben's textbook, the same book in which the term "psychosis" was adopted, and throughout the second half of the 19th century the term was used as a synonym for psychiatry.

During the 19th century the vocabulary of psychopathology steadily grew. Esquirol's (1838) divided false perceptions into "illusions" (distortion or misinterpretation of real perception) and hallucinations (perceptual experiences without corresponding stimuli in the environment); Griesinger's (1845) distinguished between "pale (pseudo) hallucinations" (that appear in the inner subjective space and can be controlled voluntarily) and "true (real) hallucinations" (usually referred to hallucinations" simply), and Wernicke's (1881) separated "dysmnesia" (memory impairment) from "dementia" (personality deterioration).

Psychopathology became a discipline to provide a foundation for psychiatry in the early years of the 20th century. Instrumental to this development was Karl Jaspers (1910, 1913) observation that in different psychiatric disease patients' process (in their brain)

and consequently perceive the same "content" (information) in different "forms". His recognition of the relationship between the "forms" in which information ("content") is perceived by patients and their illness, led to the birth of "phenomenological psychopathology" (phenomenology), the branch of psychopathology that deals with "abnormal subjective experiences of individual psychic life". It also led to his separation of "psychiatric disease process", displayed by "abnormal forms of experiences", from "abnormal personality development", displayed by behaviour that deviates from the statistical norm.

For the "phenomenologist," it is not the subject matter, the information, ("content") the patient talks about, but how ("form") the patient talks, and it is not the "somatic (hypochondriacal) complaints" ("contents), but the form, how these complaints are experienced, as "bodily hallucinations" (somatic experiences without corresponding stimuli in the environment), "obsessive ideas" (ideas that persist against one's will), "hypochondriacal delusions" (false beliefs based on a priori evidence) that is relevant to diagnosis (Fish 1967; Taylor 1981). Even in case of "delusions", a "content disorder of thinking" that signals the presence of an ongoing psychiatric disease ("psychosis"), it is not the "content" of the "delusions", such as "delusions of reference", "delusions of love", "delusions of persecution", etc., but the "form" in which the "delusion" appears, i.e., a "sudden delusional idea" (a delusional idea that appears to be fully formed), a "delusional perception" (a delusional meaning attributed to a normally perceived object), that is relevant to the characteristic abnormality of the processing of signals by the brain that differentiates one psychiatric disease (process) from another (Guy and Ban 1982; Hamilton 1985).

It was on the basis of "phenomenological analyses" that Kurt Schneider (1920, 1950), distinguished between "vital depression," a disease, from the "other depressions", and separated "personality disorders", displayed in "abnormal variations of psychic life", the subject matter of "abnormal psychology", from "psychoses" (mental disorders), displayed in "abnormal forms of experiences", the subject matter of "psychiatry."

During the years from 1918 to 1933 a group of psychiatrists that included Hans Gruhle and Wilhelm Mayer-Gross, in Kurt Wilmanns' department of psychiatry at Heidelberg University in Germany, spearheaded "phenomenological analyses" in

psychiatric patients (Shorter 2005). Their effort has yielded a vocabulary that includes distinct words (symptoms) from pathologies of "symbolization", such as "condensation" (combining diverse ideas into one concept) and "onematopoesis" (building new phrases in which the usual language conventions are not observed), to pathologies of "psychomotility", such as "ambitendency" (the presence of opposite tendencies to action) and "parakinesis" (qualitatively abnormal movements). In "phenomenology", "dysphoria", the negative pole of "vital emotions", is distinguished from "dysthymia", the negative pole of mood, "psychomotor retardation", the experience of a spontaneous slowing down of motor activity, is distinguished from "psychomotor inhibition", the experience of slowed down motor activity, etc.

Furthermore, by linking the terms that identify the different abnormalities to psychiatric diagnoses in use at the time, e.g., "tangential thinking", characterized by talking past and around the point, with the "schizophrenias", "circumstantial thinking", characterized by overbearing elaboration on insignificant details without losing track, with the "dementias", and "rumination", characterized by endless repetition of unpleasant thoughts, with "depressions", the Heidelberg group set the foundation of a language for psychiatry.

Heidelberg School of Psychiatry
(1918-1933)

Phenomenological Analysis

VOCABULARY
for
language of psychiatry

WORDS
from pathologies of "symbolization" ("condensation", "onematopoesis")
to
pathologies of "psychomotility" ("ambitendency", parakinesis")

DISTINCTIONS
between

"dysphoria" vs "dysthymia,"
"psychomotor retardation" vs "psychomotor inhibition"

SYMPTOMS & DIAGNOSES
tangential thinking - schizophrenias
circumstantial thinking – dementias
rumination - depressions

INTRODUCTION OF NOSOLOGY

The vocabulary of "psychopathology" that deals with cross - sectional features of disease, was extended to include the vocabulary of "psychiatric nosology" for describing psychiatric disease in its "dynamic totality" from "onset" through "course" to "outcome" (Ban 1987).

The two disciplines, "psychopathology", and "psychiatric nosology" are intrinsically connected; psychopathology deals with symptoms, i.e., abnormal subjective experiences ("phenomenology") and signs, i.e., "objective performance changes" ("performance psychology"), whereas "nosology" deals with the synthesis of "disease entities" from symptoms and signs, and classification of the diseases synthesized (Jaspers 1963). While classifications provide names (denominations) and descriptions of disease (qualifications), nosology provides the methodology "how" diseases and classification of diseases are derived (Ban 2000).

The term "nosology", first appeared in 1743 in Robert James' Medical Dictionary. Twenty-five years later in 1768, it reappeared in the title of Francois Boissier de Sauvages' *Nosologia Methodica*.

In his treatise, Sauvages stipulates that a disease should be defined by the enumeration of symptoms that suffice to recognize it and distinguish it from others (diseases), and a classification should be devised in a manner that it should allow the attribution of each patient to one and only one class. Thus, the emphasis in disease is that each patient with the same disease displays the same symptoms and thereby is different in terms of symptoms from patients with any other disease, whereas the emphasis in a class

is on shared characteristics of diseases in terms of "course" and "outcome" regardless of differences in symptomatic expressions.

One year after the publication of Sauvages' treatise, the term, "nosology" was adopted also by William Cullen (1869, 1872) in the title of his *Synopsis Nosologiae Methodicae*.

Cullen divided "madness" into four classes of disease: "amentia" ("imbecility of judgment, by which people do not perceive, or do not remember the relation of things"), "melancholia" ("partial madness' without dyspepsia, varying according to the different subjects concerning which the person raves"), "mania" ("universal madness"), and "oneroidynia" (violent and troublesome imagination in time of sleep") (Mennninger, Mayman and Pruyser 1968). His separation of "universal" (total) from "partial" madness, on the basis of "totality" of mental pathology was to dominate classifications of insanity in the 19th century from Philippe Pinel's (1798) and Jean-Étienne Dominique Esquirol's (1838) in France, who distinguished between "mania" (universal insanity) and the "monomanias" (partial insanities), to Karl Kahlbaum's (1863) in Germany, who distinguished between the "vesanias" (total-universal insanities) and the "vecordias" (partial isanities).

The separation of "universal" from "partial" madness during the second half of the 19th century was based on pervasiveness of pathology manifested by "deterioration of personality" and/or "absence of insight." Thus, Ernest-Charles Lasègue's (1852) diagnostic concept of "persecutory delusional psychosis", the predecessor of Kahlbaum's (1974) diagnostic concept of "paranoia", was referred to as "partial insanity", because lack of "personality deterioration", and Carl Friedrich Otto Westphal's (1878) diagnostic concept of "obsessive states" (Zwangsvorstellungen), the predecessor of the diagnostic concept of "obsessive-compulsive neurosis", was referred to as "abortive insanity", a form of "partial insanity", because patients had "insight" about the pathological nature of their condition.

The distinction between "universal" and "partial" madness was lingering on during the first six decades of the 20th century. In 1913, in the 8th edition of his textbook, Emil Kraepelin used the distinction between "universal" and "partial madness" for the separation of "paranoia" and the "paraphrenias" (partial insanities) from "dementia

praecox" (total insanity); and in 1957 in his *Classification of Endogenous Psychoses*, Karl Leonhard used the distinction for the separation of "pure mania" and "pure melancholia (total insanities) from the "pure euphorias" and "pure depressions".

Prior to Boissier de Sauvages and Cullen, in the late 17th century, Thomas Sydenham's conceptualized disease as a "process" with a "natural history of its own" that "runs a regular and predictable course" (Ban 2000). Yet, in psychiatry, it was only about 200 years later that Jean-Pierre Falret (1854) in the 1850s, identified a disease, "fôlie circulaire", the predecessor of "manic-depressive insanity", on the basis of its "temporal characteristics". It was also Falret first in the mid-1860s to stipulate that "a natural form of psychiatric illness implies a well defined predictable course", and vice versa, "a well defined predictable course presupposes the existence of a natural species of disease with a specified pattern of development" (Pichot 1983). A similar notion to Falret's was expressed in 1874 by Karl Ludwig Kahlbaum in his "nosological postulate". It was also Sydenham's concept of disease that led Emil Kraepelin to replace his syndromic classification in the 4th edition of his textbook, published in 1894 with a disease oriented classification in the 5th edition (1896).

Kraepelin's (1899) division ("dichotomy") of the "endogenous psychoses" on the basis of "temporal characteristics", i.e., "course" and "outcome," in the 6th edition of his textbook into "manic depressive insanity", a disease that follows an episodic course with full remission between episodes, and "dementia praecox", a disease that follows a continuous deteriorating course, led to a re-evaluation of psychiatric diagnoses and classifications, and especially (but not only) of the classification of diseases that Paul Julius Möbius' (1893, 1900) referred to as "endogenous psychoses". In the course of this re-evaluation both, diseases with and episodic course and diseases with a continuous course were divided into several forms. Within the diseases with an episodic course with full remission between episodes, diseases which manifest in "attacks" (that last from minutes to hours), as Lasegue's (1877) "mental vertigo", or in "phases" (that last from days to years), as Edna Neele's (1949) "phasic psychose", were distinguished from diseases characterized by an episodic course without full remission between episodes which manifest in "thrusts" ("shifts"), as Bleuler's schizophrenias (1911). And within the diseases with "continuous course", diseases which lead to highly differentiated "end-

states", as Leonhard's (1936) "defect (referred to later as 'systematic') schizophrenias" in the "endogenous psychoses", were distinguished from diseases which lead to a dedifferentiated "terminal state", as Alzheimers' (1907) disease (Ban 2000).

Kraepelin's classification of the "endogenous psychoses" was first re-evaluated in the 1920s by Karl Kleist (1921, 1923, 1928); then by Karl Leonhard (1957) in the 1950s with the incorporation of some of Kleist's contributions, e.g., the diagnostic concept of "cycloid psychoses".

In his re-evaluation, Leonhard employed Neele's (1948) "polarity", and Wernicke's (1881, 1899) "mental structure" in classifying patients. With the employment of "polarity" he divided the population already separated by "course" and "outcome" into "bipolar" and "unipolar diseases", and separated within both, several subpopulations on the basis of the site of the dominant psychopathology, i.e., the afferent-cognitive ("psychosensory"), central-affective ("intrapsychic"), or efferent-motor ("psychomotor") component, in Wernicke's "mental structure".

In Leonhard's (1957) classification, "bipolar diseases" are characterized by a continuously changing "polymorph" (multiform) disease picture with a potential to display both extremes in mood, thinking, emotions and/or motility, whereas "unipolar (monopolar) diseases" are characterized by a consistent, unchanging, "monomorph" (simple, also referred to as pure) disease picture with no variation of mood, thinking, emotions and/or motility.

On the basis of "polarity, Leonhard splits Kraepelin's "dementia praecox", [Bleuler's (1911) "schizophrenias"], into two classes of disease: "(bipolar) unsystematic (non-systematic) schizophrenias", and "(unipolar) systematic schizophrenias", and on the basis of Wernicke's "mental structure", he divides "unsystematic schizophrenias" into three diseases, i.e., "cataphasia", "affect-laden paraphrenia" and "periodic catatonia". Similarly he divides the "systematic schizophrenias" into three groups of diseases, i.e., paraphrenias" (with six psychopathology-based sub-forms), "hebephrenias" (with four psychopathology-based sub-forms), and "catatonias" (with six psychopathology-based sub-forms).

He also splits, on the basis of "polarity", "manic depressive insanity" into "(bipolar) manic depressive disease" and "(unipolar) phasic psychoses", and with

consideration of Wernicke's "mental structure", he separates from "manic depressive disease" the "cycloid psychoses", and divides the "cycloid psychoses", into "excited-inhibited confusion psychosis", "anxiety-happiness psychosis", and "hyperkinetic-akinetic motility psychosis".

Furthermore, on the basis "totality", the organizing principle introduced by Cullen (1769), he separates "pure mania" and "pure melancholia" from the "pure euphorias" and "pure depressions", each displayed in five distinct psychopathology-based forms.

Within the "bipolar-polymorph" diseases the signal difference between "manic depressive disease" and the "cycloid psychoses" is that in "manic depressive disease" the "polarity" is prevailingly in mood, whereas in the "cycloid psychoses" the "polarity" is prevailingly in thinking ("excited-inhibited confusion psychosis"), emotions ("anxiety-happiness psychosis"), or psychomotility ("hyperkinetic-akinetic motility psychosis"); and within the "unipolar-monomorph" diseases the signal difference between "pure mania/melancholia" and the "pure euphorias/depressions" is, that in "pure mania" and in "pure melancholia" the entire "mental structure" is affected, whereas in the "pure euphorias" and :"pure depressions" only parts of the mental structure is involved.

Leonhard's classification of "endogenous psychoses" was published in 1957 just about the time when neuropsychopharmacology was born.

Karl Leonhard
1957

Classification of Endogenous Psychoses

UNIPOLAR
Pure Mania
Pure Melancholia
Pure Euphorias
unproductive, hypochondriacal, enthusastic, confabulatory, non-participatory
Pure Depressions
harried, hypochondriacal, self-torturing, suspicious, non-participatory

Systematic Schizophrenias
paraphrenias (hypochondriacal, phonemic, incoherent, fantastic, confabulatory, expansive), hebephrenias (silly, eccentric, insipid, autistic) catatonias (parakinetic, affected, proskinetic, negativistic, voluble, sluggish)

BIPOLAR
Manic Depressive Psychosis

Cycloid Psychoses
excited/inhibited confusion psychosis; anxiety/happiness psychosis
hyperkinetic/akinetic motility psychosis

Unsystematic Schizophrenias
cataphasia, affect-laden paraphrenia, periodic catatonia

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; Muelleret al. 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 monamine oxidase inhibitor that was

reported to induce euphoria in some tubercular patients in the course of treatment (Flaherty 1952; Selikoff et al 1952).

One of the first to recognize that neuropsychopharmacology opened a new perspective in the understanding and treatment of psychiatric illness was Abraham Wikler (1952), an American psychiatrist and pharmacologist. In his monograph on *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 et al 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 end-points, 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 will 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[5] (Ban 1987).

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

[5] 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 pschopharmacology uring the second part of he 20th century was developed without the possible benefit of those contributions.

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 FOR 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, Tenesssee, USA); and two years later, in 1984, a Hungarian team, lead by Bertalan Pethö published research diagnostic criteria with the title, KDK Budapest for use in diagnosing functional psychoses (in Hungarian) 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 DCR 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, and Marek Jarema (from Poland), Francois 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. [6]

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).

[6] From the 10 members of the team 4 were to become professors and heads of university departments of psychiatry: Eugenio Aguglia in Trieste (Italy), Istvan Bitter in Budapest (Hungary), Francois Ferrero in Geneva (Switzerland) and Marek Jarema in Warsaw (Poland). .

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).

COMPOSITE DIAGNOSTIC EVALUATION

While the DCR was still in development the DSM-III of the American Psychiatric Association (1980), introduced in 1980, has become an unprecedented success. By combining both major traditions of medicine, the tradition of Galen (131 -201 AD), focussed on disease (Axis 1 and Axis III), and the tradition of Hippocrates (460 -370 BC), focused on patient (Axis IV and Axis V), the DSM-III with its multi-axial diagnoses was received with open arms by practicing psychiatrists (Ban 2000). Yet, the adoption of DSM-III was counterproductive for neuropsychopharmacological research. Progress in neuropsychopharmacology is dependent on pharmacologically homogeneous populations, as indicated before, and the DSM-III reified pharmacologically heterogeneous diagnostic concepts which, for psychopathologists were only "ideas" and not carved-in-stone realities. It also blocked nosological research in psychiatry that "guided by the idea of disease entity" gave preference to certain, particular elements of the clinical picture to "isolate for diagnostic purposes relative disease-entities" that best fit the needs of a particular research (Jaspers 1913).

To provide a methodology for uncovering diagnostic concepts that might fit better the needs of neuropsychopharmacological research than consensus-based diagnoses, a Composite Diagnostic Evaluation (CODE) System was developed in the late 1980s and early 1990s (Ban 1989).

The CODE System is a set of instruments that can assign to a patient simultaneously a diagnosis from several diagnostic systems. Each instrument (CODE) can provide for a poly-diagnostic evaluation in a distinct category of mental illness by the employment of an integrated criteria list and standardized data collection; and each instrument consists of a set of symptoms ("codes") that yield diagnoses in all its component diagnostic systems, a semi-structured interview, suitable for the elicitation of

all the symptoms ("codes") encountered in the system, and diagnostic decision trees that organize symptoms into distinct psychiatric disorders (Ban 1991).

The prototype of the CODE System is CODE-DD, the CODE for depressive disorders that provides a depressive diagnosis in 25 different classifications (from Kraepelin's to the DSM-III-R) of depressive disorders on the basis of the "presence" or "absence" of 90 symptoms ("codes"), determined in 30 to 40 minutes with the use of a semi-structured interview that can be administered with or without computer prompting (Ban, Fjetland, Kutcher and Morey 1993).

CODE-DD is a reliable and valid instrument. In the first reliability study, there was an 87.8% inter-rater agreement on the presence or absence of the 90-items of the vocabulary; in the second, inter-rater agreement increased to 100%; and in two validation studies, the correspondence between the clinical DSM-III-R diagnosis of "major depression," and the CODE-DD diagnosis of "major depression," was 99.6% and 97.2%, respectively (Ban et al, 1993; Morey 1991).

CODE-DD was translated and adopted from the English original into several languages, including Estonian by Mehilane, (1992), French by Ferrero, Crocq, and Dreyfus, (1992), Italian by Aguglia and Forti (1989), Polish by Puzynski, Jarema and Wdowiak (1989), and Portuguese by Nardi and Versiani (1990). Early development of the instrument was linked to clinical studies with reboxetine. It was used in a series of clinical trials that led to the demonstration of the therapeutic efficacy of reboxetine, a selective norepinephrine re-uptake blocker, in "major depression" (Ban et al. 1998).

Findings with CODE-DD correspond with the commonly held view that the DSM-III-R diagnosis of major depression is a broad diagnostic category. If depressive illness were characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes, as in the latest version of CODE-DD, from the 322 patients with the clinical diagnosis of major depression, included in the second validation study of CODE-DD, only 119 patients, i.e., 37% would have qualified for depression. Findings with CODE-DD are also in keeping with the notion that depression consists of more than one form of illness; from the 322 patients only 95 patents, i.e., 29.5%, fulfilled definite criteria of Kraepelin's (1896, 1913) depressive states, characterized by motor retardation, retardation of thought and difficulties of concentration, and even less, 45

patients, i.e., 14%, fulfilled criteria of Schneider's (1920) vital depression. The overlap between the two forms of depressive illness was negligible (Ban, 2001, 2007).

Yet, however broad the DSM-III-R diagnosis of "major depression" is, it covers up diagnostic concepts with possible relevance to treatment. For example, the diagnosis of Schneider's (1920) "vital depression" with the cardinal symptoms of corporization, disturbance of vital balance and feeling of loss of vitality, that provided the key for Roland Kuhn (1957) to recognize imipramine's antidepressant effect, is covered up to the extent that even if the patient is so severely ill that it displays all possible symptoms and signs for the diagnosis of "major depression" in the DSM-IV, one still would not know whether the patient qualifies for vital depression (American Psychiatric Association 1994). The same applies to Kraepelin's (1913) depressive states.

FINDINGS WITH CODE-DD

Number (and percentage) of the 322/233 patients with a *DSM-III-R diagnosis of major depression* fulfilling criteria of depressive illness in a selected number of classifications included in CODE-DD

COMPOSITE DIAGNOSTIC CLASSIFICATION
(Ban 1989)
322 patients
unmotivated depressed mood, depressive evaluations & lack of reactive mood changes
119 (37%)

KURT SCHNEIDER'S VITAL DEPRESSION
(Schneider 1920)
233 patients
corporization, disturbance of vital balance, and feeling of loss of vitality
45 (14%)

EMIL KRAEPELIN'S DEPRESSIVE STATES
(Kraepelin 1913)
233 patients
depressed mood, motor retardation, thought retardation
95 (28.5%)

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 with 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 & 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 neuropsychopharmcological 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 CONDITIONED REFLEX REVISITED

It was also Nyiro 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, Canada) 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 et al 1966; Hattangadi, Lidsky and Ban 1966; Hattangadi et al 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" has become 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). Eric Kandel (2007, 2009), a Nobel Laureate found 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." Kandel with his associates had also shown the neuronal circuits of classical conditioning (withdrawal reflex) in Aplysia Californica (Carew, Walters and Kandel 1981).

Learning and conditioning entered molecular genetic research with Holger Hyden's (1970) recognition in the 1960s that only part of the genome, about 5% to10% is active at birth, and the rest of gene areas activated by external factors. Hyden, another Nobel Laureate, had also shown that external factors, e.g., sensory stimulation, give rise to increased synthesis of messenger ribonucleic acid (mRNA), a prerequisite for the "activation of hitherto silent brain areas" when learning (conditioning) is involved. Furthermore, as early as in the 1980s the possibility was entertained that even if CR formation, the opening up of new, formerly non-operating paths in the brain are under genetic control, activation of these paths are dependent on external factors (Ban and Guy 1985). Nevertheless, in spite of all progress in discovering the biology of learning, the nagging question about the relationship between mental pathology and CR functions, has remained unanswered to-date.

FROM PSYCHIATRY TO NEURONOLOGY

During the past 200 years the language of psychiatry has been continuously changing reflecting the changes in the conceptualization of insanity.

The term "psychic reflex", introduced by Griesinger in 1843 was replaced by the term "conditioned reflex" by Pavlov (1906) in the early years of the 20th century; the term "neurosis", introduced by Cullen in 1777 was dismissed with the publication of DSM-III in 1980; the use of the term, "psychosis," adopted by Feuchtersleben in 1845 was narrowed by Kurt Schneider (1950) in the middle of the 20th century by restricting its use to "psychiatric disease" distinct from personality anomalies; and the term, "psychiatry," coined by Reil in 1908, with its implicit separation of the mind ("psyche") from the "body," became anachronistic with the birth of neuropsychopharmacology in the 1950s.

Considering that within our current frame of reference "psychic activity" is based on processing of signals in neuronal circuits in the brain, with some of the neuronal passes already mapped by Falck-Hillarps' histochemical flurescence method, a term like "neuronology" would correspond more closely with a contemporary concept of "insanity", than "psychiatry" (Dahlström and Fuxe 1964; Falck, Hillarp, Thieme and Torp 1962; Fuxe and Dahlström 1965).

While the search for a language that would help translate insanity into biology continues and the conceptualization of insanity keeps on changing Porter's (2002) contention in the early years of the 21st century, that "Madness may be as old as mankind", has remained just as true today, as Charcot' (1877) contention that "Disease is from of old there has always been and nothing about it changes; it is we who change, as we learn to recognize what was formerly imperceptible," was about 150 years ago.

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