

Collated

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Thomas A. Ban: Psychiatry for Neuropsychopharmacologists

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This collated document includes Thomas A. Ban's Introduction, his essay From Kraepelin's manic-depressive psychosis to Leonhard's cycloid and phasic psychoses and the exchange that followed.

Three participants exchanged a total of eight postings with four postings by Thomas A. Ban, two by Peter Martin and two by Carlos Morra. The last entry in this exchange was made on September 22, 2016.

This project was introduced as a "course" that was terminated. after the exchange that followed the first lecture.

This collated document is now open to all INHN members for final comment.

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Psychiatry for Neuropsychopharmacologists

1. Thomas A. Ban: Introduction

Neuropsychopharmacology is dedicated to the study and treatment of mental disorders with the use of centrally acting drugs. Its birth in the mid-1950's was triggered by the introduction of effective pharmacological treatments for mental disorders; recognition of the importance of chemical mediation at the site of the neuronal synapse; detection of the presence of several neurotransmitters in the brain; and the construction of the spectrophotofluorometer, an instrument with sufficient resolution power to measure drug-induced changes in the concentration of monoamine neurotransmitters involved in neuronal transmission at the synaptic cleft in the brain. Spectrophotofluorometry provided direct access to detect biochemical changes which might be responsible for a psychotropic drug's therapeutic effect (Ban 2004).

The new discipline has grown on the premise that neuropharmacological research on the mode of action of psychotropic drugs with well-defined therapeutic indications will generate the necessary knowledge about the pathophysiology and biochemistry of the mental disorder that will guide research to develop more effective and selective pharmacological treatments (Ban 2006). An essential prerequisite of neuropsychopharmacological research is a well-defined treatment responsive population to a psychotropic drug, i.e., the sub-population within a diagnostic group to which the drug's efficacy can be attributed. Yet, when the introduction of lithium, chlorpromazine and imipramine, the first psychotropic drugs with demonstrable therapeutic efficacy in manic-depressive psychosis, schizophrenia and endogenous depression, respectively, focused attention on the pharmacological heterogeneity within these diagnoses in responsiveness to treatment, no attempt was made to examine whether employment of diagnoses in Karl Leonhard's (1957) classification could identify the treatment responsive subpopulations to these drugs.

Leonhard's classification was published in 1957, just about the time of Roland Kuhn's (1957) discovery of imipramine's therapeutic effect in some patients with endogenous depression. It is the final product of a tradition in psychiatry which began with Carl Wernicke and passed to Leonhard via Karl Kleist (Kleist 1947; Wernicke 1900). In Leonhard's

classification, Kraepelin's (1896, 1899, 1903-4, 1908-15) diagnostic concepts of manic-depressive psychosis and dementia praecox (schizophrenia) were deconstructed into four classes of disease with a total of 35 diagnoses.

As the treatment responsive subpopulations to lithium, chlorpromazine and imipramine have still not been identified, INHN is launching an educational program in preparation for research to examine whether using clinical end-points based on the Wernicke-Kleist-Leonhard tradition, and especially on Leonhard's classification, could identify pharmacologically more homogeneous populations to these prototype drugs than with Kraepelinian diagnoses.

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December 24, 2015

2. Thomas A. Ban: From Kraepelin's manic-depressive psychosis to Leonhard's phasic and cycloid psychoses

Background

The “insanity” that was to become Kraepelin’s (1899) “manic depressive psychosis” (MDP) was first described by Aretaeus, “The Incomparable”, of Capadox toward the end of the 1st century (Menninger, Mayman and Pruyser 1968). It was separated from other “insanity” in the mid-19th century in France independently by Julius Baillarger (1854) and Jean-Pierre Falret (1854). To characterize the “insanity”, Baillarger (1845) coined the term “*la folie a double forme*” (“insanity in double form”), and Falret (1854), “*la folie circulaire*” (“circular insanity”). A somewhat similar diagnostic concept to Falret’s (1854), “*cyklisches Irresein*” (“cyclothymia”) was introduced, in 1882, in Germany by Karl Kahlbaum. The signal difference between Falret’s (1854) diagnostic concept and Kahlbaum’s (1882) was that “circular insanity” affected the whole mental apparatus, whereas “cyclothymia” was restricted to emotional life and left drive and intellect unaffected (Healy 2008; Shorter 2005).

Until Kraepelin’s introduction of his diagnostic concept of MDP, in 1899, “mania” and “melancholia” were perceived as distinct forms of illness from “cyclothymia” and “circular insanity” (Kahlbaum 1863; Meynert 1884; Ziehen 1894). The Zeitgeist in psychiatry during the second part of the 19th century was dominated by two major discoveries: the linking of “motor aphasia” to a lesion of the posterior part of the frontal lobe by Paul Broca, in 1861 in France, and the linking of “sensory aphasia” to the posterior part of the temporal lobe by Carl Wernicke, in 1874, in Germany. These breakthrough discoveries about the structures involved in speech, a unique human function, stimulated interest in research to study the relationship between mental and brain pathology, and cross-sectional syndromes such as the “manic syndrome” and the “melancholic syndrome” seemed to provide more suitable clinical end-points for studying such relationships than “circular psychosis” and “cyclothymia”.

Carl Wernicke

One of the leading proponents of studying the relationship between mental and cerebral pathology, in the last quarter of the 19th century was Wernicke (2000), himself. To facilitate the use and amplify the utility of syndromes for this research, he developed, in the 1890s, his “elementary symptom” approach for identifying (diagnosing) and classifying psychoses (Ban 2015; Krahl 2000; Wernicke 1893). It was with the use of “elementary symptoms”, i.e., symptoms from which assumedly all other symptoms of a syndrome were derived, that Wernicke

(1895) separated “anxiety psychosis”, “psychic motility psychosis”, and some other “psychoses”, which by the end of the 19th century were engulfed by Kraepelin’s (1899, 1913) diagnostic concept of MDP. By identifying these psychoses and recognizing their independence from each other, and from “circular psychosis” and “cyclothymia”, Wernicke (1893) set the stage for a development that led to the deconstruction of the diagnostic concept of MDP before the diagnostic concept was born (Leonhard 1957).

Wernicke (1900), in keeping with Wilhelm Wundt’s (1874, 1896) teachings, perceived the brain as an associative organ and saw mental pathology as the result of “sejunction”, i.e., “loosening of or detachment from the rigid structure of associations” (Franzek 1990). Yet, as his conceptual framework was based on Griesinger’s (1843) “psychic reflex”, he used the components of the reflex path as reference points for classifying “psychoses”. Accordingly, Wernicke (1900) recognized three classes of “psychoses”: one displayed by “anesthesia”, “hyperesthesia” or “paresthesia”, that he perceived as the result of malfunctioning of the “psychosensory path” and corresponding brain areas; another, displayed by “dysfunction”, “hyperfunction” or “parafunction”, the result of malfunctioning of the “intrapsychic path” and corresponding “trans-cortical” brain areas; and a third, displayed by “akinesia”, “hyperkinesia” or “parakinesia”, the result of malfunctioning of the “psychomotor path” and corresponding brain areas (Ban 2013; Franzek 1990; Wernicke 1896, 1899, 1900).

To refine further clinically the site of malfunctioning, Wernicke (1900) divided consciousness (awareness) into consciousness (awareness) of the outside world (“allopsyche”), consciousness (awareness) of one’s body (“somatopsyche”) and consciousness (awareness) of one’s self-individuality (“autopsyche”) and distinguished among “allopsychoses”, characterized by disorientation in the representation of the outside world, “somatopsychoses”, characterized by disorientation in the representation of one’s own body and “autopsychoses”, characterized by disorientation in the representation of one’s own self and individuality. In his clinically oriented alternative classification, he classified “delirium tremens”, “Korsakoff psychosis” and “presbyophrenia” as “allopsychoses”; “anxiety psychosis” and “hypochondriacal psychoses” as “somatopsychoses”; and “mania” and “melancholia” as “autopsychoses”. In describing “mania”, Wernicke (1900) emphasized the presence of “ideas of grandeur”, and in describing “melancholia”, the presence of “ideas of indignity”. He saw “manic” and “melancholic” psychoses as independent from each other, but recognized that they frequently occur in the same patient (Angst and Grobler 2015; Menninger, Mayman and Pruyser 1968; Wernicke 1896).

It was against this background that Kraepelin (1899) developed his diagnostic concept of MDP.

Emil Kraepelin

Instrumental to the development of Kraepelin's (1896, 1899) diagnostics concept of MDP was Thomas Sydenham's conceptualization of disease, in the late 17th century, as a "process" with a "natural history of its own" that "runs a regular and predictable course" (Ban 2000). The disease concept was dormant in psychiatry until Jean-Pierre Falret (1854), in the mid-19th century identified "la folie circulaire", on the basis of its "temporal characteristics" and stipulated 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" (Falret 1864; Pichot 1983). A similar notion to Falret's was expressed in 1874 by Kahlbaum. Nevertheless, it was Kraepelin (1896, 1913) first who fully adopted Sydenham's concept of disease in psychiatry and by shifting emphasis from "cross-sectional" clinical manifestations to their "origin", "course of evolution" and "outcome" ("termination"), replaced syndromic classifications by a clinically (disease) oriented classification. His shift of emphasis resulted a radical change, as in his clinically oriented classification all the different syndromes of "endogenous psychoses" were engulfed by two broad diagnostic concepts: "dementia praecox" and MDP (Kraepelin 1896, 1899, 2013).

Tracing the development of the diagnostic concept of MDP in subsequent editions of Kraepelin's textbooks one finds that in the first five editions, published in 1883, 1887, 1889, 1891 and 1896, he perceived "mania", "melancholia" and "circular psychosis" as independent diagnoses. It was in the sixth's edition, published, in 1899, that he first introduced his diagnostic concept of MDP. The diagnostic concept was finalized only 15 years later, in 1913, in the third volume of the 8th edition of Kraepelin's textbook with the engulfment of "involuntional melancholia" on the basis of G.E. Dreyfus' (1905) findings (Kraepelin 1909-1915). In the same edition, he defined MDP in terms of "etiology", an "endogenous psychosis whose appearance is generally unrelated to external circumstances"; he characterized it, in terms of "symptomatology", as an illness that becomes manifest in one of three states/forms: (1) "manic states" manifested by heightened mood, flight of ideas and increased drive, (2) "depressive states" manifested by sad or anxious mood, thought retardation and decreased drive, and (3)

“mixed states”, in which “signs of mania and depression appear simultaneously, so that pictures ensue whose traits correspond to those of both illnesses and yet they cannot be classified to either one”; and described it, in terms of “course”, an episodic, remitting and relapsing disease, which “as a rule consists of separate attacks more or less sharply delimited from each other and from the normal state of health” (Berner et al 1983).

Kraepelin’s (1913) final diagnostic concept of MDP united the “entire realm of periodic and circular insanity, uncomplicated mania, the majority of illness entities taken from ‘melancholia’, and also a non-negligible quantity of amentia cases, including certain mild and moderate mood modifications, which on the one hand were considered as preliminary stages of more severe disorders, on the other were blending into the realm of individual nature”. He argued for bringing all these varied conditions together under the diagnosis of MDP by pointing out that despite the differences in the clinical pictures, “some basic traits in all these illnesses recur, that the various illness forms merge into each other without recognizable boundaries, supersede each other in the same patient, have a uniform prognosis and can replace one another in genetic ascendancy” (Berner et al 1983).

The clinical features of the manic syndrome and the melancholic syndrome were based originally on information that Kraepelin (1899, 1913) collected on his “counting cards” (Zählenkarten), a symptom check list that included only ten items: nervousness, restlessness, irritability, depression, psychomotor retardation, aggression, grandiosity, negativistic behavior, hallucinations and paranoid ideas (Bech 2012; Kraepelin 1909-15; Weber and Engstrom 1997). But, as time passed the symptoms of the core syndromes of MDP, “mania” and “depression”, were conceptualized in terms Jaspersian psychopathology and by the 1960s, MDP was perceived as a group of “affective disorders” (“affective psychoses”) with a primary disturbance of mood from which all other symptoms were derived (Jaspers 1923; Mayer-Goss, Slater and Roth 1960; Woodruff, Goodwin and Guze 1974). “Affective psychoses” are manifest by episodic recurrence of the “manic syndrome”, characterized by “hyperthymia” (elated mood) with “acceleration of mental (including psychomotor) activity” and “sleep disturbance”, or the “depressive (melancholic) syndrome”, characterized by “dysthymia” (depressed mood) with “deceleration (slowing) of mental (including psychomotor) activity”, and “sleep disturbance”, or both, the “manic” and the “depressive” syndrome in the same patient, and in all variations of “affective

psychoses”, there is full remission between episodes. In recognition of the variations in clinical (psychopathological) manifestations in the basic syndromes, several “manic syndromes” and several “depressive syndromes” were described. Included among them are: “anxious”, “delirious”, “dysphoric”, “furious”, “hypochondriacal”, “querulous”, “simple”, “stuporous”, “transitory” and “unproductive mania”; and “anxious”, “agitated”, “hypochondriacal”, “simple” and “stuporous depression” (Nyiro 1962). Kraepelin’s (1913) broad “unitary concept” of MDP was lingering on and as late, as in 1977, in the 9th edition of the International Classification of Diseases, the five “affective psychoses” recognized, were: “MDP manic type”, “MDP depressed type”, “MDP circular type, currently manic”, “MDP circular type, currently depressed” and “MDP circular type, mixed” (World Health Organization 1977).

Karl Kleist

While Kraepelin’s (1899) dichotomy of the “endogenous psychoses” into “dementia praecox” and MDP was becoming main stream psychiatry, Wernicke’s tradition continued by Karl Kleist, one of his assistants during his short tenure (1904 to 1905), as professor of Neurology and Psychiatry in Halle, Germany.

By the time Kleist (1911) embarked on his research, the structural underpinning of the “reflex” was established and the emphasis in brain research shifted from pathological anatomy to neurohistology. Instrumental to this development were the contributions of 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’s (1894), a Spanish histologist, who established the “neuron” as the morphological and functional unit of the nervous system; and Sir Charles Sherrington’s (1906), an English physiologist, who demonstrated that the “synapse” was the functional site of transmission from one neuron to another. Recognizing the potential that the neuronal network provides for studying the relationship between mental and neuronal processing in the brain, Kleist (1925, 1934), in Wernicke’s (1900) tradition, attributed different clinical pictures in psychiatry to abnormalities at different sites in the functioning of this network (Teichmann 1990).

While Wernicke’s contributions set the stage for the deconstruction of Kraepelin’s (1899, 1913) diagnostic concept of MDP, Kleist (1911), on the basis of findings in his early research challenged Kraepelin’s (1899) diagnostic concept of MDP and argued for the independence of

“manic psychosis” from “melancholic psychosis.” By using the terms “*einpolig mania*” that translates into English as “unipolar mania”, and “*einpolig melancholia*”, in reference to these distinct syndromes, Kleist (1911) set the stage for a development that led, in the 1940’s to the “unipolar-bipolar dichotomy” of “phasic psychoses” (Angst and Grobler 2015; Kleist 1943; Leonhard 1948). For Kleist (1928), “polarity” was a psychopathological concept. He perceived “bipolar psychosis” as a combination of two “unipolar psychoses”, i.e., “manic psychosis” and “melancholic psychosis”, that becomes manifest in a “polymorphous (multiform) psychosis”. He continued all through his life to refer to “unipolar mania” and “unipolar melancholia” as “pure (monomorphous) mania” and “pure (monomorphous) melancholia”, respectively, and to “bipolar (*zweipolig*) mania” and “bipolar (*zweipolig*) melancholia” as “polymorphous mania” and “polymorphous melancholia” (Kleist 1928, 1943; Leonhard 1943).

Similar to Wernicke (1900) Kleist (1911) also described several syndromes, in which changes in “motility” were central (Shorter 2005). Included among them was the syndrome that was to become the diagnostic concept of “akinetic motility psychosis” and the syndrome that was to become the diagnostic concept of “hyperkinetic motility psychosis”. Recognition of the affinity of this pair of “motility syndromes” to each other, opened the path for the development of the diagnostic concept of “cycloid psychoses”, in the mid-1920’s (Kleist 1925). Kleist defined “cycloid psychoses” as a group of recurrent psychoses with full remission between episodes, which circle between two “poles”, as MDP but in which the dominant psychopathology is not “elated” or “melancholic” mood, as in MDP but in another area of mental pathology. He also referred to the same group of psychoses as “marginal psychoses” (Randpsychosen) or “marginal degeneration (constitutional) psychoses” as he perceived them as psychoses which were bordering on “manic-depressive psychosis” (Kleist 1928; Teichmann 1990). By the time of the mid-1930’s Kleist recognized three “cycloid psychoses”: “anxiety-ecstatic delusional psychosis”, “excited-inhibited confusion psychosis” and “hyperkinetic-akinetic motility psychosis” (Fünfgeld 1935).

The distinctiveness of several “episodic psychoses” with full remission between episodes was supported by the findings of Edda Neele, a student of Kleist. She evaluated all “phasic sicknesses” diagnosed at Kleist’s University Clinic in Frankfurt between 1938 and 1942 and presented the results of her “epidemiological genetic study”, in 1949, in a monograph with the

title *Die phasischen Psychosen nach ihrem Erscheinungsbild und Erbbild* (The Phasic Psychoses According to Presentation and Family History). It was in Neele's monograph first, in which the "phasic psychoses" were separated into "pure phasic psychoses", that included "melancholia", "anxious melancholia", "anxious reference psychosis", "hypochondriacal depression", "depressive stupor", mania, "ecstatic inspiration psychosis" and "hypochondriacal excitement", and "polymorphous phasic psychoses" that included "manic-depressive illness of affect", "hyperkinetic-akinetic motility psychosis", "excited-stuporous confusion psychosis" and "anxious-ecstatic delusional psychosis" (Angst and Grober 2015; Shorter 2005; Teichmann 1990). Her classification of "phasic psychoses" was endorsed by Kleist (1953).

Karl Leonhard

The clinical tradition of Wernicke (1900) and Kleist (1953) continued by Karl Leonhard (1957), a member of Kleist's faculty from 1937 to 1954 at Goethe University, in Frankfurt.

Leonhard (1931, 1934, 1936) began with his research in the late 1920's, and by 1936, the year he joined Kleist's Department of Psychiatry, he had already published some findings on "episodic psychoses", "atypical psychoses" and "defect schizophrenias" which were in line with Kleist's (1911, 1923, 1925, 1928).

During the Frankfurt years (1936-1954), Leonhard (1943) collaborated with Kleist (1943) and Neele (1949) in studying "phasic psychoses" and was instrumental in the conceptualization of findings in this project (Kleist 1943; Leonhard 1943). It was in the course of this research that it was recognized that "polymorphous psychosis" was not restricted to "manic-depressive illness of affect" but included also the "psychoses", Kleist (1911, 1925, 1928, 1952) referred to as "cycloid psychoses" (Fünfgeld 1936; Leonhard 1939; Teichman 1990). It was also in the course of this research that Leonhard (1948) introduced his concept of "polarity", a nosological organizing principle, and his distinction between "unipolar depression" and "bipolar depression", based on this principle (Angst and Grobler 2015).

Deconstruction of Kraepelin's (1913) diagnostic concept of MDP culminated in 1957 with the publication of Karl Leonhard's monograph, *The Classification of Endogenous Psychoses*. In his classification, Leonhard integrated the contributions of Wernicke, Kleist and his collaborators with his own findings and conceptualizations.

The concept of “polarity” became central, but not the exclusive organizing principle in Leonhard’s (1957) nosological re-evaluation of Kraepelin’s (1913) MDP. While it was on the basis of “polarity” that he split MDP into “bipolar manic depressive disease” and “unipolar phasic psychoses”, it was with consideration of Wernicke’s (1899, 1900) “mental structure” that he separated the “cycloid psychoses” from “manic depressive disease” and divided the “cycloid psychoses” into “excited-inhibited confusion psychosis”, “anxiety-happiness psychosis”, and “hyperkinetic-akinetic motility psychosis”. Furthermore, it was on the basis of “totality”, the organizing principle introduced by William Cullen (1769, 1772, 1776) that he separated “pure mania” and “pure melancholia”, both “universal” diseases, from the “pure euphorias” and “pure depressions”, in which the “mental structure” was only “partially” affected. Finally, on the basis of Wernicke’s (1893) “elementary symptoms”, he distinguished five distinct forms of “pure mania”: “unproductive”, “hypochondriacal”, “enthusiastic”, “confabulatory” and “non-participatory”; and five distinct forms of “pure depression”: “harried”, “hypochondriacal”, “self-torturing”, “suspicious” and “non-participatory”.

In 1957, at the time it was first published, Leonhard’s classification had already some support, from epidemiological genetic findings (Neele 1949). Yet, it was only in 1964, one year before the publication of the third edition of his text, in 1965, that Leonhard succeeded to demonstrate that his diagnoses of “cycloid psychoses” were “catamnistically” correct” (Leonhard and Trostorff 1964); and it was only, in 1966, two years before the publication of the fourth edition, in 1968, that Jules Angst (1966) and Carlo Perris (1966) independently demonstrated that “bipolar depression” and “unipolar depression” were distinct. The signal difference between the two populations was in “familiarity”: patients with “bipolar depression” had a significantly higher rate of “psychoses” among their relatives than patients with “unipolar depression”. The distinctiveness of “unipolar depression” and “bipolar depression” in epidemiological genetic research was further substantiated, in 1969, by Winokur, Clayton and Reich.

It was well after the publication of the 6th edition of Leonhard’s monograph, in 1986, the last edition published during his life time, that findings relevant to the distinctiveness of “unipolar mania” and “bipolar mania” emerged. First, in three independent clinical epidemiological studies, it was found that “unipolar mania” had an earlier onset and was characterized by fewer episodes and lower comorbidity with anxiety disorders than “bipolar

mania” (Merikangas et al 2012; Pacheco Palha and Arrojo 2009; Young, Marek and Patterson 2009). Then, Yazici and Cakir (2012) noted that patients with “unipolar mania” were less responsive to lithium therapy than patients with “bipolar mania”, and Grobler, Roos and Bekker (2014) reported that patients with “unipolar mania” were prescribed more “neuroleptics” than patient with “bipolar mania”. Finally, in an epidemiological genetic study, Merikangas and associates (2014) found the familial aggregation of depression in relatives of “depressed probands” much lower than the familial aggregation of mania in the relatives of “manic probands”, indicating the genetic independence of “mania” from “depression” (Angst and Grobler 2015; Hicki 2014).

With the exception of a “catalogue” of symptoms presented in 1990, Leonhard (1957, 1986, 1990) offers little direct guidance for diagnosing the 16 forms (including 10 sub-forms) of illnesses that resulted from the deconstruction of Kraepelin’s (1913) MDP. His monograph on “The Classification of Endogenous Psychoses” has remained through six editions a collection of case reports. Yet, Leonhard argues (1957) that within the “phasic psychoses” already in the first phase (episode) of the illness “bipolar manic-depressive disease” can be separated from “unipolar pure mania” and “unipolar pure melancholia”, as well as from the “unipolar pure depressions” and “unipolar pure euphorias”. He contends that the signal difference between “bipolar manic depressive disease” and the “unipolar forms of phasic psychoses” is that the “bipolar” form displays a more colorful appearance by varying not only between two poles, but by displaying in each phase, and even during a phase, different clinical pictures to the extent that no clear syndrome can be described. In contrast, the “unipolar” forms return in a periodic course with the same symptomatology, with every individual “unipolar” form characterized by a syndrome associated with no other form and not even related transitionally to any other forms. As the differentiation between “unipolar depression” and “bipolar depression” or “unipolar mania” and “bipolar mania” is not based on the presence or absence of a specific psychopathological symptom or syndrome in a point of time, but on the entire (“holistic”) clinical picture in a permanently moving time (Petho 1990), arguably it would provide a better guide for their recognition if they would be referred to as “polymorphous-” or “monomorphous depression” and “polymorphous-” or “monomorphous mania”, as Kleist (1828, 1943) did, than “bipolar-” or “unipolar depression” and “bipolar-” or “unipolar mania”. By doing so one could restrict the use of “bipolar diagnosis” to those patients who already displayed both “poles” in

their episodes, and use the term “polymorphous” for those who display a “multiform” clinical picture in their episode but so far, all their episodes were in the same direction.

Leonhard (1957) maintains that the “pure euphorias” and “pure depressions” can be differentiated from “pure mania” and “pure melancholia” on the basis of their psychopathology, as “pure euphorias” and “pure depressions” are exclusively affective diseases, whereas in “pure mania” and “pure melancholia” thought and desire are also disturbed. Thus, in “pure melancholia” and “pure mania” all three cardinal symptoms of the melancholic syndrome i.e., depressed mood, psychomotor retardation and thought retardation, or of the manic syndrome, i.e. elated mood, accelerated thinking and increased psychomotor activity are present, whereas in the “pure depressions” and “pure euphorias” thought and desire are not necessarily affected.

In so far as “bipolar phasic” and “cycloid psychoses” are concerned, Leonhard’s (1957) differentiation is based on the dominant “elementary symptom” pair, i.e., “depressed mood” or “elated mood”, in case of “manic-depressive illness”, “anxious mood” or “ecstasy” in case of “anxiety-happiness psychosis”, “excited confusion” or “inhibited confusion” in case of “excited-inhibited confusion psychosis”, and “hyperkinesia” or “akinesia” in case of “hyperkinetic-akinetic motility psychosis”.

Diagnostic instruments

The first diagnostic instrument that provided diagnoses relevant to Leonhard’s (1957) classification was the KDK Budapest, developed by Petho, Ban, Kelemen, Karczag, Ungvari, Bitter and Tolna. It was published in 1984, in the Hungarian periodical, *Ideggyogyaszati Szemle*. The second diagnostic instrument was its English adaptation, the DCR Budapest-Nashville developed also in the mid-1980s by Petho and Ban in collaboration with Kelemen, Ungvari, Karczag, Bitter, Tolna (Budapest), Jarema, Ferrero, Aguglia, Zuria and Fjetland (Nashville). The third, the Schedule for Operationalized Diagnosis for the Leonhard Classification (SODLC) was developed in the late 1980s by Fritze and Lanzig. Both, the DCR and the SODLC were published in *Psychopathology*, in 1987 and in 1990, respectively.

The DCR is based on diagnostic algorithms and its diagnostic process on a decision-tree model that leads to one diagnosis. The decision whether a diagnosis qualifies for a “unipolar” or a “bipolar” illness, depends on the “presence or “absence” of five variables:

1. Unipolar episodic-course: Course of illness is characterized by recurring shifts in mood and/or tempo of thoughts and/or psychomotor activity which is consistently in the same direction.
2. Bipolar episodic course. Course of disease is characterized by recurrent two-directional positive and negative shifts in mood and/or tempo of thought and/or psychomotor activity.
3. Monomorphous clinical picture: Well defined, pure, distinct disease picture which remains unchanged during the illness or at least within a single episode of the illness.
4. Polymorphous clinical picture: Variable disease picture in which different symptoms and/or syndromes prevail at different times.
5. Polymorphous fluctuating disease picture: Multiform, variable disease picture in which different symptoms and/or syndromes prevail at different times. Behavior is characterized by its rapid and frequent variations alternating between extreme (opposite poles).

To qualify for a phasic or a cycloid “bipolar illness” subjects must qualify for one of the four diagnoses in addition to displaying a “polymorphous” or “polymorphous fluctuating clinical picture”. The four diagnoses with qualifying criteria are:

Manic-depressive psychosis: At least three of the following five functional areas must be disordered: mood, drive, sex drive, sleep and psychomotility.

Anxiety-happiness psychosis: At least three of four from either one or the other sets of symptoms must be present: marked anxiety, marked tension, delusional perceptions and delusions of reference, or feelings of happiness, desire to make others happy, exaggerated self-esteem and misperceptions.

Excited –inhibited confusion psychosis: Incoherence must be present and at least three of four from either one or the other sets of symptoms must be present: decreased talkativeness, decreased activity, reactive stupor and misperceptions, or increased talkativeness, increased activity, misperceptions and fragmentary hallucinations.

Hyperkinetic-akinetic motility psychosis: One of three from the following three symptoms must be present: akinesia, hypokinesia, hyperkinesia , as well as at least three of four from either one

or the other sets of symptoms must be present: confused stupor, absence of purposeful activities, diminished reactive movements and diminished expressive movements, or increased reactive movements, increased expressive movements, agitation and speech characterized by short phrases and long pauses with occasional emotionally charged outbursts.

To qualify for a phasic “unipolar illness” subjects must qualify for one of 12 diagnoses in addition to displaying a “monomorphous” clinical picture. The 12 diagnoses with qualifying criteria are:

Pure mania: At least three of the following five symptoms must be present: hyperthymic mood, psychomotor agitation, flight of ideas, premature decisions and exaggerated self-esteem.

Pure melancholia: At least three of the following five symptoms must be present: dysthymic mood, psychomotor retardation, retarded thinking, indecisiveness and feelings of inadequacy.

Harried depression: At least three of the following five symptoms must be present: monomorphous clinical picture, motor restlessness, marked anxiety, driven complaintiveness and poor thematization.

Hypochondriacal depression: At least three of the following five symptoms must be present: monomorphous clinical picture, hypochondriasis, homonome bodily hallucinations, hopeless complaintiveness and corporization.

Self-torturing depression: At least three of the following five symptoms must be present: monomorphous clinical picture, feelings of guilt, loss of self-esteem, lamentiveness and self-incrimination.

Suspicious depression: At least three of the following five symptoms must be present: monomorphous clinical picture, suspiciousness, ideas of reference, paranoid ideation and lack of hostility.

Non-participatory depression: At least three of the following five symptoms must be present: monomorphous clinical picture, lack of affective participation, abulia, anhedonia and feelings of alienation.

Unproductive euphoria: At least three of the following four symptoms must be present: monomorphous clinical picture, motiveless feeling of happiness, radiant facial expression and poor thematization.

Hypochondriacal euphoria: At least three of the following four symptoms must be present: monomorphous clinical picture, hypochondriasis, homonome bodily hallucinations and cheerful complaintiveness.

Enthusiastic euphoria: At least three of the following four symptoms must be present: monomorphous clinical picture, exaggerated self-esteem, happily enthused when talking about self-related topics and happily enthused when talking about topics related to others.

Confabulatory euphoria: At least three of the four following symptoms must be present: monomorphous clinical picture, confabulations with grandiose ideas, recounting happy experiences and lively talkativeness.

Nonparticipatory euphoria: At least three of the following four symptoms must be present: monomorphous clinical picture, lack of feeling of sympathy (with happiness), impoverishment of emotions (with happiness) and impoverishment of will (with happiness).

Neuropsychopharmacology

By the time of the publication of Leonhard's *Classification of Endogenous Psychoses*, in 1957, the "neuronal network" discovered around the turn of the 20th century was a functional entity and with the discovery of the presence of several neurotransmitters in the brain (serotonin, norepinephrine, dopamine), emphasis shifted in the understanding of the nature of synaptic transmission from a purely electrical to a chemically mediated event (Ban 2006; Montagu 1957; Twarog and Page 1953; Vogt 1954). Furthermore, introduction of the spectrophotofluorometer simultaneously with the first set of effective psychotropic drugs (lithium, chlorpromazine, imipramine) in the treatment of "endogenous psychoses, in the 1950s, provided a capability to measure the corresponding changes in the concentration of neurotransmitter monoamines and their metabolites with their therapeutic effects (Bowman, Caulfield and Udenfriend 1955; Cade 1949; Delay and Deniker 1952; Kuhn 1957.) With these developments, the only tangible obstacle in generating interpretable findings regarding the biochemical underpinning of manifest psychopathology was the pharmacological heterogeneity within the diagnoses derived by

Kraepelin's (1909-15) nosology. In spite of this and the reasonable assumption that diagnoses derived by Leonhard's (1957) differentiated nosology would provide pharmacologically more homogenous populations than Kraepelin's (1913) MDP, Leonhard's (1957) "classification", with the exception of his distinction between unipolar and bipolar depression, remained isolated from main stream of psychiatry to date.

Pharmacotherapy

Developments, relevant to the pharmacotherapy of MDP began, in 1949 with John Cade's report that lithium was effective in controlling excitement in all ten "manic" patients included in his study without any effect on his three depressed patients. Lithium, not even at the time was a newcomer in psychiatry. In the late 19th century the substance was found effective in "periodic depression", but its use was abandoned because of lithium's toxicity (Lange 1886).

Cade's (1949) findings on the therapeutic effect of lithium in mania on 10 patients were further substantiated, in 1951 by Noack and Treutner in a study that included over one hundred patients. It was the historical study that rendered lithium treatment feasible by determining blood levels in which the substance could be safely administered with the employment of the flame-photometer. Still, another three years passed until, in 1954, Schou, Juel-Nielsen, Strömngren and Wolby demonstrated, in a placebo-controlled cross-over study, the therapeutic efficacy of lithium in "mania".

One would have thought that demonstration of lithium's therapeutic efficacy in mania, will guarantee a smooth entry for lithium in the treatment of mania", but this was not the case. Attention from lithium and from Schou and his associates (1954) findings was distracted by Lehmann and Hanrahan's (1954) report on the striking therapeutic effect of chlorpromazine in the treatment of "mania", published in the same year. It took about another 17 years until, in 1971, lithium found its place in the treatment of "mania", supported by findings in four placebo-controlled studies (Goodwin and Jamison 1990; Goodwin, Murphy and Bunney 1969; Maggs 1963; Stoke, Shamoian, Stoll and Patton 1971). Yet, without the identification of the treatment responsive subpopulation to lithium, the primary form of treatment in "mania" remained with neuroleptics.

Instrumental to lithium's further clinical development were the observations that continued treatment with lithium attenuated the severity and duration of subsequent episodes, regardless whether they were "manic" (Noack and Trautner's 1951) or both, "manic" and "depressive" (Schou et al 1954). Lithium's prophylactic effect on both "manic" and depressive" episodes, if they occurred in same patient was supported by the findings of Gershon and Trautner in 1956, Wojtechowsky in 1957, Hartigan, in 1963, Baastrup, in 1964 and Baastrup and Schou, in 1967.

Baastrup and Schou's (1967) report on the "prophylactic effect" of lithium in MDP was challenged by Blackwell and Sheppard, in 1968. It was in response to this challenge that, in 1970 Angst, Weis, Grof, Baastrup and Schou, and independently Baastrup, Poulsen, Schou and Thomsen demonstrated the efficacy of "lithium prophylaxis" in patients diagnosed as "recurrent affective disorder" or MDP. Yet, without the identification of the treatment responsive subpopulation in which lithium could prevent relapse, by the dawn of the 21st century lithium has become one of many competing drugs with the primary indication of depression, psychosis and epilepsy, for prophylactic treatment in bipolar mood disorder.

It was in 1969, in the midst of the lithium controversy (1968 – 1970) about lithium's prophylactic effect that Goodwin, Murphy and Bunney reported their findings in a placebo-controlled study on lithium's "unequivocal" therapeutic efficacy in "bipolar depression", i.e., in "typical "MDP patients, with a history of both, "manic" and "depressive" episodes. Their findings were verified in a pooled analysis of seven placebo-controlled studies, including their own, in which response rate in "bipolar" patients was 79% and in "unipolar" depressed patients 36% (Baron et al 1975; Goodwin and Jamison 1990; Goodwin, Murphy and Bunney 1969; Goodwin et al 1972; Johnson 1974; Mendels 1975; Noyes et al 1974). Without a prior division of the population into "unipolar" and "bipolar depression", lithium's therapeutic potential for some depressed patients would have remained hidden.

The differential responsiveness to lithium between "unipolar" and "bipolar" patients is not restricted to "depression", but applies also to "mania". Already in the first placebo-controlled study it was noted that response rate in "mania", in "typical" patients, i.e., patients with both, "manic" and "depressive" episodes, was considerably higher, 90%, than response rate in atypical patients (62%) (Schou et al 1954). Similar differences in response rates in favor of "typical" over

“atypical” patients were found in other studies by Goodwin and Ebert (1973) in their review of clinical trials and controlled studies with lithium in “mania”. The difference is even more pronounced when response to lithium in “typical manic” patients and “schizoaffective manic” patients is compared. In Goodnick and Meltzer’s (1984) study, “schizoaffective manic” patients required more than twice as long to achieve a full response to lithium than “typical manic” patients.

Re-evaluation

Reintroduction of lithium in psychiatry, in the mid-20th century focused attention on the heterogeneity of responsiveness to the substance within Kraepelin’s (1913) diagnostic concept of MDP. By the 1960s clinical observations and findings indicated that dividing the population on the basis of “polarity” into “unipolar depression”, “bipolar depression”, “unipolar mania” and “bipolar mania” would provide in “bipolar depression” and “bipolar mania” pharmacologically more homogenous populations, in terms of responsiveness to acute, maintenance and prophylactic treatment with lithium than Kraepelin’s (1899) MDP. Yet, it was also recognized that in the subpopulations derived by polarity”, the pharmacological heterogeneity was only reduced but not resolved. A full re-valuation was warranted with the separation within “bipolar psychoses”, “cycloid psychosis” from “manic-depressive psychosis”, and within “unipolar psychoses”, “pure mania” from the “pure euphorias” and “pure melancholia” from the “pure depressions”. This re-evaluation has not taken place to-date.

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April 21, 2016

Carlos Morra's comment

The Diagnostic and Statistical Manuals of the American Psychiatric Association

I noted that in your review, you made no reference to the Diagnostic and Statistical Manuals (DSM) of the American Psychiatric Association (APA). Is there any reason for this?

The first DSM (DSM-I) was published in 1952. In DSM-I, Kraepelin's (1913) "manic-depressive psychosis" (MDP) was referred to as "manic-depressive reaction" (MDR) and classified under "affective reactions". DSM-I recognized three types of MDR, "manic",

“depressive”, and “others”, which included “mixed type”, “circular type”, “manic stupor” and “unproductive mania.”

The second, DSM-II was published in 1968. In DSM-II, Kraepelin’s MDP became “manic-depressive illness” (MDI) and was classified under “affective psychoses”. DSM-II recognized three types of MDI (“manic”, “depressive and “circular”) with three subtypes in the third (“circular, manic,” “circular, depressive,” and “circular, circular”.

The third, DSM- III, was published in 1980. In DSM-III, Kraepelin’s MDP became “bipolar disorder” (BD) and was classified under “affective disorders”. DSM-III recognized four types of BD: “manic”, “depressed”, “mixed” and “atypical”.

In 1987, DSM-III was revised with the introduction of an additional “type”, “non-otherwise specified” (NOS) and a new diagnostic concept, “bipolar II disorder”. While, so far, to qualify for BD, the presence of at least one “manic” and “major depressive” episodes were required, to qualify for “bipolar II disorder”, one “major depressive” and one “hypomanic” episode sufficed.

In DSM-IV, published in 1994, the distinction between “bipolar I disorder” with a requirement of at least one “manic” and one “major depressive” episode and “bipolar II disorder” was consolidated.

In 2000, the text of DSM-IV was revised (DSM-IV-TR) without any change related to BD.

In 2013, DSM- 5, the last DSM so far, was published. In addition to changes to diagnostic criteria, in DSM-5, “mixed episodes” are no longer recognized as a distinct type of BD.

Since the publication of its Third Edition, in 1980, the DSMs of the APA have had a major impact on psychiatric practice, education and research. With their well-defined diagnostic criteria, they facilitated reliable communication about psychiatric disorders. Irrespective of reliability, your review underlines the common clinical experience of the pharmacological heterogeneity within the DSM diagnoses relevant to Kraepelin’s (1913) MDP and it seems your position is that by using diagnoses derived by Leonhard’s (1957) nosology this heterogeneity

could be reduced. Would this mean that in spite of the great impact these classifications have had in the past decades, they have not provided psychiatric populations with greater predictive validity than we could identify 50 years ago with advanced (differentiated) psychiatric nosology?

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April 28, 2016

Thomas A. Ban's reply to Carlos Morra's comment

Thank you for your comment. You are correct. The reason that I did not refer to the classification systems of the American Psychiatric Association (1980, 1994, 2013) in my essay on the history of “manic depressive psychosis” was that they provided less homogenous populations at least in terms of “pharmacological responsiveness” (Fish 1964) and “familiarity” (Peralta et al 2015) than Karl Leonhard's classification presented in 1957. Without separating “bipolar manic depressive psychosis” from the “bipolar cycloid psychoses” and “unipolar pure melancholia” and “unipolar pure mania” from the “pure depressions” and “pure euphorias”,

these new classifications are less suitable for neuropsychopharmacological and genetic research in “manic depressive psychosis” than Leonhard’s (1957) classification.

References:

American Psychiatric Association. Diagnostic and Statistical Manual. Third Edition (DSM-III). Washington: American Psychiatric Association; 1980.

American Psychiatric Association. Diagnostic and Statistical Manual. Fourth Edition (DSM-IV). Washington: American Psychiatric Association; 1994.

American Psychiatric Association. Diagnostic and Statistical Manual. Fifth Edition (DSM 5). Washington: American Psychiatric Association; 2013.

Fish F. The influence of the tranquilizers on the Leonhard schizophrenic syndromes. *Encephale* 1964; 53: 245-9.

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Peralta V, Goldberg X, Ribeiro M, Sanches-Torres AM, Fananas L, Cuesta MJ. Familiarity of psychotic disorders: A polynologic study in multiple families. *Schizophrenia Bulletin Advance Access*, December 26, 2015.

May 19, 2016

Peter R. Martin’s comment

It is indeed a pleasure to read such an erudite treatment of the historical developments in conceptualization of “manic depressive psychosis” (MDP). Ban describes, within context of the neuroscientific advances of their day, the contributions of scholars of mental pathology over the last two centuries up to current understanding of MDP. After Wernicke’s “elementary symptom” approach, Kraepelin shifted emphasis from a cross-sectional perspective of mental disorders to one encompassing characteristics of their origin, course and outcome. Notions of etiology and expressed psychopathology subsequently entered the mix, including the idea that MDP was an “endogenous psychosis whose appearance is generally unrelated to external circumstances”. The concepts of polarity and the “polymorphous” or “monomorphous” nature of either depression or mania as attributed to Kleist and Leonhard are then discussed. Finally, Ban describes appropriate diagnostic instruments that presumably are needed for

neuropsychopharmacologic characterization and appropriate selection of the most effective psychopharmacologic treatments.

I believe Ban's historical discussion contains one significant lacuna. (I acknowledge that this opinion is strongly influenced by my own clinical experience focused on addiction psychiatry.) It is difficult to consider the intricacies of MDP without mention of the finding that 60 to 80 percent of those with MDP can also be diagnosed with alcohol or drug use disorders (Rich and Martin 2014). MDP with and without alcohol/drug use disorders seem to be very different expressions of the same disorder. It seems the *typical* course of MDP includes an inexorable intertwining with alcohol/drug use disorders. Therefore, it is difficult to understand why most research on the neurobiology and treatment of MDP is conducted in the minority of MDP patients, namely those in whom alcohol/drug use disorder has been excluded.

Alcohol/drug use disorder patients diagnosed with co-occurring MDP typically have a "polymorphous fluctuating disease picture", described by Ban as one of the criteria for MDP of the DCR Budapest-Nashville; namely, a "multiform, variable disease picture in which different symptoms and/or syndromes prevail at different times. Behavior is characterized by its rapid and frequent variations alternating between extreme (opposite poles)." The essence is mood instability, further accentuated by the alcohol/drug use, initially intended by the affected individual as a means of self-medication. The neurobiology and treatment of MDP associated with alcohol/drug use disorders likely differs from MDP that occurs alone, although this has yet to be extensively studied. I have repeatedly observed that responsiveness to lithium is not as likely in this population and have found better outcomes with anticonvulsants and/or neuroleptics. In part, this might be explained by the efficacy of anticonvulsants in reducing craving and relapse to alcohol and other drugs such as stimulants. Which, of course, leads to the obverse question of how common is alcohol/drug use disorders without mood instability and the etiology of mood instability in alcohol/drug use disorders? Could it be that MDP is characterized by alcohol/drug use disorder and those with MDP but no alcohol/drug use do not represent the natural course of MDP? These questions will never be satisfactorily answered unless academics and the pharmaceutical industry make a serious effort to study alcohol/drug use disorders in MDP. Most important we must recognize the importance of MDP in the etiology of alcohol/drug use disorders and *vice versa*.

References

Rich SJ, Martin PR (2014). Co-occurring psychiatric disorders and alcoholism. In: Sullivan EV, Pfefferbaum A (eds) Handbook of Clinical Neurology Alcohol and the Nervous System. Elsevier, pp 573-588.

July 21, 2016

Thomas A. Ban's reply to Peter R. Martin's comment

Thank you for sharing your finding, reported in 2014 with Rich that 60 to 80 percent of patients with MDP have an alcohol and/or drug use disorder. I also noted your observations that MDP patients with and without alcohol and/or drug use disorder share a common “fluctuating polymorphous disease picture” but respond differentially to pharmacological treatment. It would have important practical and heuristic implications if your notion could be further substantiated that MDP patients with alcohol and/or drug use disorder are more responsive to anticonvulsants or antipsychotics than to lithium, whereas MDP patients without alcohol and/or drug use disorder are more responsive to lithium than to anticonvulsants or antipsychotics.

July 28, 2016

Carlos Morra's comment on Thomas A. Ban's reply to Peter R. Martin's comment

We are ready to start with INHN research and we could launch it with two projects, one designed to verify Rich and Martin's (2014) contention that 60 to 80 percent of patients with MDP have an alcohol and/or drug use disorder and the other designed to test the hypothesis that MDP patients with alcohol and/or drug use disorder are more responsive to anticonvulsants than to lithium whereas MDP patients without alcohol and/or drug use disorder are more responsive to lithium than anticonvulsants. As soon we have developed tentative protocols we will post

them for discussion and as soon as we have the final protocol we will post it again so that all those interested could carry out studies with or without collaboration with INHN research.

INHN research will be conducted in the research department of the Morra Sanatorium, in Cordoba, Argentina.

Reference:

Rich SJ, Martin PR (2014). Co-occurring psychiatric disorders and alcoholism. In: Sullivan EV, Pfefferbaum A (eds) Handbook of Clinical Neurology Alcohol and the Nervous System. Elsevier, pp 573-588.

August 4, 2016

Peter R. Martin's reply to Carlos Morra's comment on Thomas Ban's reply to Peter Martin's comment

I am very pleased that our observations (Rich and Martin, 2014) derived from many years of providing addiction psychiatric care to patients with alcohol and/or drug use disorders resonates with others as reflected by the comments of both Ban and Morra. The idea of heuristic investigations of fundamental questions in nosology and therapeutics by a network of investigators (INHN) provides a unique opportunity, one based on identification and analysis of the clinical experiences of many to seek enhanced understanding. This harkens back to the origins of our field when expert clinicians followed patient populations for long periods (throughout their own lifetimes) and thus developed insights into the important clinical questions (e.g., Kraepelin, Schneider, Leonhard, Schou, Grof and others). I am very enthusiastic about Carlos Morra's proposal to launch INHN research with projects designed to establish the proportion of patients with MDP that have an alcohol and/or drug use disorder and to test the hypothesis that MDP patients with alcohol and/or drug use disorder are more responsive to anticonvulsants than to lithium whereas MDP patients without alcohol and/or drug use disorder are more responsive to lithium than anticonvulsants. I would add the importance also of

clarifying the psychopathological characteristics of the MDP observed in alcohol and/or drug use disorder patients compared to those who do not have alcohol and/or drug use disorders.

Reference:

Rich SJ, Martin PR (2014). Co-occurring psychiatric disorders and alcoholism. In: Sullivan EV, Pfefferbaum A (eds) Handbook of Clinical Neurology Alcohol and the Nervous System. Elsevier; 2014, pp 573-88.

September 22, 2016

Collated by Olaf Fjetland (August 31, 2017)