Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 38

Thomas A. Ban

Lithium in psychiatry in Historical Perspective

7. Diagnosis

Thomas A. Ban

Content

Thomas A. Ban: Development of the diagnostic concept of Manic-Depressive Psychosis in

Thomas A. Ban: Emil Kraepelin's classifications
From Emil Kraepelin's Manic-Depressive Psychosis to Karl Leonhard's Phasic and Cycloid Psychoses

Thomas A. Ban: Development of the diagnosis of Manic-Depressive Psychosis in Emil Kraepelin's classifications

In 44 years, from 1883 to 1927, Emil Kraepelin's *Compendium of Psychiatry* grew from about 400 pages into a 1,425-page *Textbook of Psychiatry* in which his syndromic classifications in the first three editions (1883, 1886 and 1889) were replaced by his disease-oriented classifications. The shift from syndromic to disease-oriented classification was completed by 1899

with the introduction of the diagnostic concept of manic-depressive psychosis (insanity) in the 6th edition (Pichot 1983).

Tracking the development that led to the diagnostic concept of manic-depressive psychosis, an episodic disease with full remission between episodes, one finds the following chain of events (Menninger, Mayman and Pruyser 1968):

- 1st edition, 1883: Depression (simple melancholia and melancholia with delirium); excitement (melancholia active and mania); and *periodic psychoses (periodic mania, periodic melancholia and circular states).*
- 2nd edition, 1886: Melancholia (activa, simplex, attonita); mania; *periodical insanity (mania, melancholia*) and *circular insanity*.
- 3rd edition, 1889: Mania; melancholia; *periodical mental disease (delirious form, manic form, circular form and depressive form).*
- 4th edition, 1893: Mania; melancholia; *periodical mental disease (delirious form, manic form, circular form and depressive form).*
- 5th edition, 1896: Involutional melancholia; *periodic psychosis (mania, circular psychosis and depression).*
- 6th edition, 1899: Involutional melancholia; *manic-depressive psychosis (manic states, depressive sates and mixed states).*
- 7th edition, 1903-4: Involutional melancholia*; manic-depressive psychosis.*
- 8th edition, 1909 -15: *Manic-depressive psychosis.*
- 9th edition, 1927: *Manic-depressive psychosis.*

Kraepelin's all-embracing diagnostic concept of "manic-depressive psychosis" was first fully presented in 1913 in the third volume of the 8th edition of his textbook in which, on the basis of his own comprehensive observations with consideration of earlier German and French research, he united in this diagnosis "the entire realm of periodic and circular insanity, uncomplicated mania, the majority of illness entities taken for 'melancholia,' and a non-negligible quantity of 'amentia' cases," as well as "certain mild, partly periodic, partly chronic morbid mood modifications, which, on the one hand are to be considered as preliminary stages of more severe

disorders, on the other as blending into the realm of individual nature" (Berner, Gabriel, Katschnig et al. 1983).

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

The "insanity" that was to become Kraepelin's (1899) "manic-depressive psychosis" (MDP) was first described by Aretaeus, "The Incomparable," of Cappadocia 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 fôlie a duble forme* ("insanity in double form") while Falret (1854) used *la fôlie circulaire* ("circular insanity"). A somewhat similar diagnostic concept to Falret's (1954) *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; 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 the19th century was Wernicke (1900), 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 lead

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" (Franzek1990). 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 "afunction," "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 clinically refine further 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; Wernicke1896).

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) diagnostic 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 fôlie 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 classification by clinically- (disease) oriented classification. His shift of emphasis resulted in 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, 1913).

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 6th 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 "involutional 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," as 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, Gabriel, Katschnig 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 ascendency" (Berner, Gabriel, Katschnig 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 10 items: nervousness, restlessness, irritability, depression, psychomotor retardation, aggression, grandiosity, negativistic behavior, hallucinations and paranoid ideas (Bech 2012; Kraepelin 1909-15; Weber and Engstrom1997). But, as time passed the symptoms of the core syndromes of MDP, "mania" and "depression," were conceptualized in terms of Jasperian 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. 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 lingered 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 mainstream psychiatry, Wernicke's tradition was 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 (1894), a Spanish histologist, who established the "neuron" as the morphological and functional unit of the nervous system; and Sir Charles Sherrington (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 1940s, 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-1920s (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 mid-1930s 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 titled *Die*

phasischen Psychosen nach ihrem Erscheinungs und Erbbild (The Phasic Psychoses According to Presentation and Family History). It was first in Neele's monograph that the "phasic psychoses" were separated into "pure phasic psychoses" which 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 with Karl Leonhard (1957), a member of Kleist's faculty from 1937 to 1954 at Goethe University in Frankfurt.

Leonhard (1931, 1934, 1936) began his research in the late 1920s 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; Teichman1990). It was also in the course of this research that Leonhard (1948) introduced his concept of "polarity," a nosological organizing principle, and made 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 the 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 in demonstrating that his diagnoses of "cycloid psychoses" were "catamnestically 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 "familiality": 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 lifetime, 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, Cui, Kattan 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 in1990, 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, "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 extremes (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:

1. *Manic-depressive psychosis:* At least three of the following five functional areas must be disordered: mood, drive, sex drive, sleep and psychomotility.
2. *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.
3. *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.
4. *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:

1. *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.
2. *Pure melancholi*a: At least three of the following five symptoms must be present: dysthymic mood, psychomotor retardation, retarded thinking, indecisiveness and feelings of inadequacy.
3. *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.
4. *Hypochondriacal depression*: At least three of the following five symptoms must be present: monomorphous clinical picture, hypochondriasis, homonome bodily hallucinations, hopeless complaintiveness and corporization.
5. *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.
6. *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.
7. *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.
8. *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.

9. *Hypochondriacal euphoria*: At last three of the following four symptoms must be present: monomorphous clinical picture, hypochondriasis, homonome bodily hallucinations and cheerful complaintveness.
10. *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.
11. *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.
12. *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; Twaog 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 the1950s, 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 10 "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 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 Trautner in a study that included several 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, Strömgren 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 would guarantee a smooth entry for lithium in the treatment of mania," but this was not the case. Attention to lithium and to 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; Vojtechowsky 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 of 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 Bunney1969; Goodwin, Murphy, Dunner et al. 1972; Johnson 1974; Mendels 1975; Noyes, Dempsey, Blum and Cavanaugh 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, Juel-Nielsen, Strömgren and Voldby 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 the1960s 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, 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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