Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Education in the Field in the Post-Neuropsychopharmacology Era

Collated 7

Thomas A. Ban: The Wernicke – Kleist – Leonhard Tradition with Special Reference to Mania, Melancholia and Manic – Depressive Psychosis

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Thomas A. Ban: The Wernicke – Kleist – Leonhard Tradition with Special Reference to Mania, Melancholia and Manic – Depressive Psychosis

Fundamentals of the Wernicke-Kleist-Leonhard Tradition

In 1956, Fritz Freyhan, a German born American pioneer of neuropsychopharmacology focused attention on the heterogeneity in responsiveness to neuroleptics in patients with the diagnosis of schizophrenia and called for a pharmacological re-evaluation of Kraepelin's diagnostic concepts (Bleuler 1911; Freyhan 1956; Kraepelin 1899). One year later, in 1957, Karl Leonhard, a German professor of psychiatry, presented his "classification of endogenous psychoses", in which Kraepelin's diagnoses, "dementia praecox" and "manic-depressive insanity" were split into several forms and sub-forms of diseases (Leonhard 1957).

In 1959, Christian Astrup, a Norwegian professor of psychiatry was first to report that patients with "slight paranoid defect" and "periodic catatonia", i.e., those with a diagnosis within the class of "unsystematic schizophrenias" in Leonhard's classification, responded more favorably to "neuroleptics" than patients with "severe paranoid defects", "hebephrenic defect", and "systematic catatonia", i.e., those with a diagnosis within the class of "systematic schizophrenias" (Astrup 1957; Ban 1990; Leonhard 1957). Astrup's observations were further substantiated in the mid-1960s by Frank Fish, a British professor of psychiatry, who found significant differences in responsiveness to neuroleptics in the different forms and sub-forms of schizophrenia (Fish 1964; see also Part 4).

In spite of Astrup's observations and Fish's findings, Leonhard's classification remained unrecognised during the "neurotransmitter era", the first epoch in the history of neuropsychopharmacology. Moreover, by the dawn of the 21st century, a whole tradition of psychiatry, the Wernicke-Kleist-Leonhard (WKL) tradition (of which Leonhard was the last prominent representative), has become a "forgotten language of psychiatry" (Ban 2013).

Outline of Development: From Griesinger to Wernicke

The roots of the WKL tradition are in the mid-19th century, in Wilhem Griesinger's contributions (Griesinger 1845). Stimulated by Sir Charles Bell's discovery and François

Magendie's recognition of the importance of the "reflex arc" that links sensory input with motor output in the functioning nervous system (spinal cord), Griesinger was first to perceive mental activity as "reflex" activity (Bell 1811; Magendie 1822). He was also first to describe, in 1843, "psychic reflex actions" (*psychische Reflexactionen*) (Griesinger 1823).

The role of the "reflex" in mental activity was further elaborated about 20 year later, in the 1860s, by Ivan Mihailovich Sechenov, a Russian physiologist, while studying "nervous inhibition" in the central nervous system of the frog, in Claude Bernard's laboratory in Paris. In his monograph, *Reflexes of the Brain*, Sechenov concludes that all activity in the brain, including the "psychological", is reflex (activity) and as such follows fixed laws determinable by investigation (Sechenov 1863, 1935; Wells 1956).

The structural underpinning of "reflex" was established between the 1870s and the early years of the 20th century by: Camillo Golgi (1874), an Italian histologist, who described with the employment of silver staining multi-polar (Golgi) cells in the "olfactory bulb"; Santiago Ramon y Cajal (1894), a Spanish histologist, who established that the "neuron" is the morphological and functional unit of the nervous system and Sir Charles Sherrington (1906), an English physiologist, who demonstrated that the "synapse" is the functional site of transmission from one neuron to another (Cajal 1894; Golgi 1874; Sherrington 1906).

Griesinger's notion that mental activity is reflex activity was adopted in the late 19th century by Carl Wernicke, the professor of neurology and psychiatry in Breslau (Germany at the time) (Wernicke 1899b). He classified "psychoses," i.e., psychiatric diseases, on the basis of "hyper-functioning," "hypo-functioning or "para-functioning" in the "psycho-sensory," "intra-psychic" and/or "psychomotor" components of the "reflex arc" and postulated that the substrate of mental pathology was in the "transcortical area" between the motor and sensory "projection fields" in the cerebral cortex (Franzek 1990; Wernicke 1881-3, 1889, 1900, 1906). Wernicke divided consciousness into consciousness of the body (*somoatopsyche*), consciousness of the self (*autopsyche*) and consciousness of the external word (*allopsyche*) and argued, in the 1890s, that mental pathology should be identified by "elementary symptom" (*elementarsymptom*) from which all other symptoms of the pathology were derived. Pursuing his approach, Wernicke identified clinical entities, such as "anxiety psychosis" and "hallucinosis" (Krahl 2000; Wernicke 1893, 1895).

Outline of Development: From Kraepelin through Kleist to Leonhard

Emil Kraepelin's division ("dichotomy") of the "endogenous psychoses towards the end of the 19th century, in the 6th edition of his textbook," on the basis of "temporal characteristics," i.e., "course" and "outcome, into "manic depressive insanity," a disease that follows an episodic course with full remission between episodes, and "dementia praecox," a disease that follows a continuous deteriorating course, distracted attention from Wernicke's contributions (Kraepelin 1899). Thereafter, in the 1920s, Kraepelin's dichotomy of "endogenous psychoses" was re-evaluated by Karl Kleist (1921, 1923, 1928), a disciple of Wernicke, and subsequently by Karl Leonhard, a disciple of Kleist. (Kleist 1921, 1923, 1928; Leonhard 1936, 1957).

In his re-evaluation, Leonhard employed Edna Neele's concept of "polarity" and Wernicke's concept of "mental structure" in classifying patients (Neele 1948; Wernicke 1881, 1899). With the employment of "polarity," he divided the population, already separated by "course" and "outcome," into "bipolar" and "unipolar diseases" and separated within both, several subpopulations on the basis of the site of the dominant psychopathology, i.e., the afferent-cognitive ("psychosensory"), central-affective ("intrapsychic") or efferent-motor ("psychomotor") component, in Wernicke's "mental structure" (Leonhard 1936, 1957,1979 1986).

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

On the basis of "polarity", Leonhard splits Kraepelin's "dementia praecox" and Bleuler's "schizophrenias," into two classes of disease: "(bipolar) unsystematic (non-systematic) schizophrenias" and "(unipolar) systematic schizophrenias"; and on the basis of Wernicke's "mental structure" he divides "unsystematic schizophrenias" into three diseases, i.e., "cataphasia," "affect-laden paraphrenia" and "periodic catatonia" (Bleuler 1911). Similarly, on the basis of Wernicke's "mental structure" he divides the "systematic schizophrenias" into three groups of diseases, i.e., "paraphrenias" (with six psychopathology-based sub-forms: hypochondriacal, phonemic, incoherent, fantastic, confabulatory and expansive), "hebephrenias" (with four psychopathology-based sub-forms: silly, eccentric, insipid or shallow and autistic), and

"catatonias" (with six psychopathology-based sub-forms: parakinetic, affected or manneristic, proskinetic, negativistic, voluble or speech prompt and sluggish or speech inactive).

On the basis of "polarity", Leonhard also splits Kraepelin's "manic depressive insanity" into "(bipolar) manic depressive disease" and "(unipolar) phasic psychoses," and with consideration of Wernicke's "mental structure" he separates from "manic depressive disease" the "cycloid psychoses" and divides the "cycloid psychoses" into "excited-inhibited confusion psychosis," "anxiety-happiness psychosis" and "hyperkinetic-akinetic motility psychosis." Furthermore, on the basis of "totality," the organizing principle introduced by William Cullen, he separates "pure mania" and "pure melancholia" from the "pure euphorias" (unproductive, hypochondriacal, enthusiastic, confabulatory and non-participatory) and "pure depressions" (harried, hypochondriacal, self-torturing, suspicious and non-participatory), each displayed in five distinct psychopathology-based forms (Cullen 1769, 1772, 1776).

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

Leonhard's classification of "endogenous psychoses" was first published in 1957, just about the time when neuropsychopharmacology was born (Ban 2013).

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August 6, 2015

Carl Wernicke's classification of psychoses with special reference to mania and melancholia

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

Carl Wernicke (1848-1905), the professor of neurology and psychiatry in Breslau, Germany (1890-1904), adopted Griesinger's view that mental activity is "reflex" activity, and perceived "psychoses," as "hypo (deficit)-functioning," "hyper (excess)-functioning" or "para (distorted)-functioning" of one or more components (paths, phases) of the "psychic reflex" (Ban 2013; Franzek 1990; Wernicke 2000). Accordingly, he attributed "psychoses" displayed by "anaesthesia," "hyperaesthesia" or "paraesthesia" to malfunctioning of "psychosensory" brain areas; "psychoses" displayed by "afunction," "hyperfunction" or "parafunction" to malfunctioning of "intrapsychic"(trans-cortical) brain areas and "psychoses" displayed by "akinesia," "hyperkinesia" or "parakinesia" to malfunctioning of "psychomotor" brain areas (Wernicke 1899).

Wernicke was operating within the frame of reference of contemporary "associationism." He conceptualized the brain as an associative organ, consciousness as a product of associative activity and the "soul" as the sum of all possible associations (Menninger, Mayman and Pruyser 1968). He divided consciousness into consciousness of the outside world (*allopsyche*), consciousness of one's body (*somatopsyche*) and consciousness of one's self-individuality (*autopsyhe*) and classified psychoses into *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-individuality. In diagnosing and classifying, Wernicke employed his "elementary symptom" approach (Ban 2015; Krahl 1910; Wernicke 1893)) and, in 1900, in his *Fundamentals (Grundriss) of Psychiatry*, he classified "delirium tremens," "Korsakoff psychosis" and "presbyophrenia" as *allopsychoses*; "anxiety psychoses" and "hypohondriacal psychoses" as *somatopsychoses*; and "mania" and "melancholia" as *autopsychoses*.

In describing "mania," Wernicke emphasized the presence of "ideas of grandeur" and in describing "melancholia" he emphasized" ideas of indignity." He saw "manic" and "melancholic" psychoses as independent from each other but recognized that they frequently occur in the same

patient. He also noted that “mania” was “more recurrent” with “shortening intervals between episodes” than “melancholia” and that the prognosis of ”mania” was worse than of “melancholia” (Angst and Grobler 2015; Menninger, Mayman and Pruyser 1968; Wernicke1896).

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October 22, 2015

Karl Kleist and the deconstruction of Kraepelin's diagnostic concept of manic-depressive psychosis

Deconstruction of Kraepelin's (1899, 1913) diagnostic concept of "manic depressive psychosis" began in 1911 by Karl Kleist, a former assistant to Wernicke during his short tenure, from 1904 to 1905, as professor of Neurology and Psychiatry in Halle, Germany.

In a paper published, in 1911, in the *Zeitschrift fur die Gesamte Neurologie and Psychiatrie*, Kleist, challenged Kraepelin's (1899) diagnostic concept of "manic-depressive insanity" and argued for the independence of the "manic syndrome" from the "melancholic syndrome." By using the terms *einpolig* mania that translates into English as "unipolar" mania and the term, *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 "mood disorders" (Angst and Grobler 2015; Kleist 1943; Leonhard 1948). Subsequently, in the next three decades, Kleist referred to "unipolar mania" and "unipolar melancholia" as "pure mania" and "pure melancholia," respectively, and to "bipolar (*zweipolig*) mania" and "bipolar (*zweipolig*) melancholia" as "polymorphous mania" and "polymorphous melancholia."

It was also in his 1911 paper that Kleist (1911) 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 (Kleist1925).

The term "cycloid psychoses" was introduced by Kleist in 1925 for a group of recurrent psychoses with full remission between episodes, which circled between two "poles." as "manic-depressive psychosis" but in which the dominant psychopathology was not "elated" and "melancholic" mood, as in "manic-depressive insanity," 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 are bordering on "manic-depressive insanity" (Kleist 1928; Teichmann 1990). By the time of the mid-1930s, he recognized three "cycloid psychoses": "anxiety-ecstatic delusional psychosis," "excited-inhibited confusion psychosis" and "hyperkinetic-akinetic motility psychosis" (Funfgeld 1935).

The distinctiveness of the "cycloid psychoses," "mania" and "melancholia" from each other and from "manic-depressive insanity" received support 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 "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 in Neele's monograph, in which the "phasic psychoses" were separated for the first time into "pure (unipolar) phasic psychoses," that included "melancholia," "anxious melancholia," "anxious reference psychosis," "hypochondriacal depression," "depressive stupor," mania," "ecstatic inspiration psychosis" and "hypochondriacal excitement," and "polymorphous (bipolar) 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).

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November 19, 2015

Karl Leonhard and the re-evaluation of Emil Kraepelin's diagnostic concept of manic-depressive psychosis

The re-evaluation of Kraepelin's diagnostic concept of "manic-depressive psychosis" 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.

Leonhard began with his research in the late 1920s, after graduating from medical school, in 1928. By 1936, the year he joined Karl Kleist's Department of Psychiatry at Goethe University in Frankfurt, he had already published some findings in "episodic psychoses," "atypical psychoses" and "defect schizophrenias" which were in line with Karl Kleist's reports (Kleist 1911, 1923, 1925, 1928; Leonhard 1931, 1934, 1936).

During the Frankfurt years, Leonhard collaborated with Kleist and Edna Neele in studying "phasic psychoses," i.e., "episodic psychoses" with full remissions between episodes, and was instrumental in the conceptualization of findings in this project. It was in the course of this research that Kleist's (1928) introduced his original concept of "bipolarity," a combination of two "unipolar" syndromes ("manic psychosis," "melancholic psychosis") and "polymorphous-bipolar psychoses" ("manic-depressive psychosis") (Kleist 1943; Leonhard 1943). It was also in the course of this research that it was recognized that "polymorphous-bipolar psychosis" was not restricted to "manic-depressive illness of affect" but also included other "psychoses" which were based on other "pairs of syndromes" like "manic-depressive psychosis" in which the "elementary symptom" was not in mood, but in other areas of psychopathology (Teichmann 1990). By the time of the

1940s, several such ”psychoses” were described and referred to as “cycloid psychoses” by Kleist (Fünfgeld 1936; Kleist 1911, 1925, 1928, 1953; Leonhard 1939).

The currently used, Latin-derived terms, “unipolar” and “bipolar” were coined, in 1948, by Leonhard and the distinction between “unipolar depression” and “bipolar depression” in reference to “mood disorders” was supported by Neele’s “epidemiological genetic” findings reported in her monograph on “Phasic Psychoses” in 1949 (Angst and Grobler 2015). It was also in Neele’s report in which Kraepelin’s (1913) all embracing diagnostic concept of “manic-depressive psychosis” was deconstructed into various forms of “phasic psychoses”: “simple-unipolar” and “polymorphous-bipolar” (Teichmann 1990).

The concept of “polarity” became central, but not an exclusive organizing principle in Leonhard’s (1957) re-evaluation of Kraepelin’s (1913) “manic-depressive psychosis.” On the basis of “polarity” he split it into “bipolar manic depressive disease” and “unipolar phasic psychoses” and with consideration of Wernicke’s (1899, 1900) “mental structure” 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.” Then, on the basis of “totality,” the organizing principle introduced by William Cullen (1769, 1772, 1776), 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 (unproductive, hypochondriacal, enthusiastic, confabulatory and non-participatory) of “pure mania” and five distinct forms (harried, hypochondriacal, self-torturing, suspicious and non-participatory) of “pure depression.”

In 1957, at the time it was first published, Leonhard’s classification had already some support, from epidemiological genetic findings, as indicated before (Neele 1949). Yet, it was only in 1964, one year before the publication of the third edition of the text, in 1965, that Leonhard succeeded to demonstrate 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 “separable.” The signal difference between the two populations was that patients with “bipolar depression” had a significantly higher rate of “psychoses” among their relatives than patients with “unipolar depression.” The

(epidemiological) genetic distinctiveness of “unipolar depression” and “bipolar depression” was further substantiated in 1969 by Winokur, Clayton and Reich.

It was only 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, 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 maia from depression that “unipolar mania” and “bipolar mania” are distinct diseases (Angst and Grobler 2015; Hicki 2014).

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November 26, 2015

Psychopathology, Leonhard's classification and the deconstruction of Kraepelin's manic-depressive psychosis

In the 8th and last edition of his *Textbook*, in which the chapter on manic-depressive psychosis was written by himself, Kraepelin (1913) defined manic-depressive psychosis (MDP) in terms of "etiology" as an endogenous psychosis "whose appearance is generally unrelated to external circumstances." He described it in terms of "symptomatology" as an illness that becomes manifest in one of three states/forms: (1) "manic states" characterized by heightened mood, flight of ideas and increased drive; (2) "depressive states" characterized by sad or anxious mood, thought retardation and decreased drive; and (3) "mixed forms" 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 he characterized it in terms of "course" as an episodic, remitting and relapsing illness, which "as a rule consists of separate attacks more or less sharply delimited from each other or from the normal state of health" (Berner, Gabriel, Katschnig et al. 1983).

By stipulating these criteria, Kraepelin (1913) 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 are to be considered as preliminary stages of more severe disorders, on the other as 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 picture, "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).

In contrast to Kraepelin (1913), Leonhard (1957, 1986) offers only minimal guidance for diagnosing the 16 forms (including 10 sub-forms) of illnesses that resulted from his deconstruction of Kraepelin's MDP. His monograph on The Classification of Endogenous Psychoses has remained from the 1st to the 6th and last edition published in his life time a collection of case reports with little introductory and summarizing texts characterizing the different forms and sub-forms of these illnesses. 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 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 is not based on the presence or absence of a specific psychopathological symptom or a set of psychopathological symptoms in a point of time, but on the entire ("holistic") clinical picture in permanent flux, arguably it would be more proper to refer to "monomorphous" and "polymorphous" phasic psychoses then to "unipolar" and "bipolar" phasic psychoses (Petho 1990).

Within Leonhard's frame of reference, pure mania/pure melancholia can be differentiated from the pure euphorias/pure depressions on the basis of their psychopathology, as pure euphorias/pure depressions are exclusively affective diseases, whereas in pure mania/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 obligatorily 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 exclusively on the dominant "elementary" symptom pair, i.e., depressed or elated mood, in case of manic-depressive illness; anxious mood or ecstasy in case of anxiety-happiness psychosis; excited or inhibited confusion in case of excited-inhibited confusion psychosis; and hyperkinesia or akinesia in case of hyperkinetic-akinetic motility psychosis.

The first diagnostic algorithm that provided diagnoses in Leonhard's classification, relevant to Kraepelin's MDP 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 algorithm was its English adaptation, the DCR Budapest-Nashville, developed in the mid-1980s by Petho and Ban in collaboration with Kelemen, Ungvari, Karczag, Bitter, Tolna (Budapest), Jarema, Ferrero, Aguglia, Zuria and Fjetland (Nashville); and the third, the Schedule for Operationalized Diagnosis for the Leonhard Classification (SODLC), developed in the late 1980s by Fritze and Lanzig. Both, the DCR and the SODLC were published in Psychopathology, in 1997 and 1990, respectively.

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December 3, 2015

Ernst Franzek's comment

Congratulations for the article about "Karl Leonhard's re-evaluation of Kraepelin's diagnostic concept of manic-depressive psychosis."

I would like to reference an important family study of Phuhlmann, Jabs, Althaus et al. (2004) to the discussion. Based on modern and highly sophisticated methodology, the authors investigated the relations of cycloid psychosis to bipolar affective disorders. The authors personally examined all living and traceable adult first-degree relatives of 45 cycloid psychotic, 32 manic-depressive and 27 control probands blind to the diagnosis of the index proband. A catamnestic diagnosis was established for each of 431 relatives blind to family data. Age-corrected morbidity risks were calculated using the life-table method. The results were striking. Relatives of cycloid psychotic patients showed a significantly lower morbidity risk for endogenous psychoses in general and manic-depressive illness compared to relatives of patients with manic-depressive illness. The familial morbidity risk for cycloid psychoses was low and did not differ significantly in both proband groups. Further, relatives of cycloid psychotic patients did not differ from relatives of controls regarding familial morbidity. This study indicates that cycloid psychoses can hardly be integrated in the highly genetically loaded bipolar affective spectrum. The obvious fact that cycloid psychoses in almost all cases are triggered by endogenous or exogenous stress factors like giving birth to a child, by psychosocial stress during work or in relationships, by cocaine or other stimulant drug use (Franzek and Musalek 2011) seems to justify the term "stress induced psychoses." It is suggested that a genetically vulnerable stress (related) system may be a major

etiologically factor in cycloid psychosis that is different form the genetically based bipolar affective disorders.

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February 18, 2016

Thomas A. Ban's reply to Ernst Franzek's comment

Thank you for reminding us about Phuhlmann and his associates' findings, published in 2004 in the Journal of Affective Disorders. I hope it will help to clarify the frequently held misconception that the cycloid psychoses are an integral part of an alleged "bipolar affective spectrum." The concept of "spectrum disorder" is contrary to the thinking of the Wernicke-Kleist-Leonhard tradition. In his Classification of Endogenous Psychoses, Leonhard (1957, 1979) referred to "cycloid psychoses" as the "evil relatives" of "unsystematic schizophrenias."

Clinical experience indicates that the cycloid psychoses are pharmacologically different from both bipolar manic-depressive psychosis and the unsystematic schizophrenias. I am looking forward with interest whether the findings which indicate that the "cycloid psychoses" are "stress-induced psychoses," could be replicated.

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March 24, 2016

William E. Bunney Jr.: final comment

In my view Tom Ban has written an amazing, comprehensive, historical review on the "Fundamentals of the WKL Tradition" and the impact of a number of scholars on these concepts concerning mood disorders. I believe these individuals have made highly significant contributions to our clinical understanding of these disorders.

I also think that in the future we will continue to have sophisticated refinement of phenotypes and identification through hundreds of thousands of patients and controls, risk loci, genes and alleles associated with these illnesses. Recently a paper was published in *Nature Medicine* identifying 15 risk loci using 130,620 patients and 347,620 controls. It may be possible to use three new gene editing tools (CRISPRcas9 [Clustered Regularly Interspaced Short Palindromic Repeats], RNA Repair, and Base Editing) to correct genetic defects which allow one to delete or modify genes in the human genome. However, editing multiple genes as identified in these disorders currently presents a challenge. Also, in the future there will be a continued focus on identifying and treating vulnerable patients, some with newly discovered risk genes shared by schizophrenia and bipolar disorder, prior to the emergence of clinical symptoms. Finally, the development over the last decade of extremely rapid-acting (within 24 hours) medications such as low-dose ketamine for treatment resistant mood disorders have significant potential along with the intense study of their relevant mechanisms of action could identify drug targets for even more effective treatments.

June 14, 2018

Donald F. Klein's final comment

What bothers me is the basis for these numerous nosological distinctions. Much sounds symmetrical *a priori*. The detection of supposed descriptive classes, after poring over a mass of such data, is weak, too easy to do and too easy to contradict. But even such efforts are not described, instead there are even weaker confirmatory anecdotes. The pattern of validating studies is that two of the very many nosological distinctions show different patterns of familial disorders. It is not at all clear how these hypothesized familial distinctions (assuming there were hypotheses) follow from the nosological distinctions.

But even worse — let's say every nosological distinction is proved correct by the most exacting genetic analyses, how does that help the clinician, since none have been related to simple prognosis, not to speak of differential treatment effects, and prognosis covariates?

Kraepelin became enormously popular because his data-based system was clinically useful. In an era that lacked beneficial treatments, he made prognosis possible, enabling, right there, prediction of different courses for two apparently similar raving maniacs. This was an enormous benefit to the families as it enabled rational planning. Further, the families were all in despair, but now some had grounds for hope — a wonderful clinical accomplishment.

There are many scientific reasons why Kraepelin outshines the Wernicke-Kleist-Leonhard tradition that seems dominated by an *a priori* symmetrical approach divorced from validity criteria — but clinical utility is the crushing distinction.

November 30, 2017

Ernst Josef Franzek's comment on Donald F. Klein's final comment

The analysis of the development of the currently used classification systems of mental disorders indicates that sticking to established terms and methodologies more and more impedes progress of research. Modern research requires homogenous clinical syndromes or homogenous disease spectra to examine them with improved and advanced available methodologies and technologies.

Is the concept of a dichotomy of mental disorders, which is attributed to Kraepelin, really incompatible with a concept of several different disease spectra including a sophisticated description of clinical and nosological pictures according to Leonhard, or is there a not yet known link between them?

The prerequisite for answering above question is going back to clinical and empirical realities. Kraepelin postulated that only the cause decides on the special course and peculiarity of the mental illnesses. According to Kraepelin, it is insignificant which research methods were used because the psychoses will independently converge on identically diseases. This paradigm is the basis of Kraepelin´s prognostic dichotomy of the endogenous psychoses into a spectrum of prognostic favorable manic-depressive illnesses and a spectrum of prognostic unfavorable endogenous insanities with severe residual psychic defects. In the 8th edition of his textbook, Kraepelin divided the spectrum of prognostic unfavorable insanities into two major groups: the "paranoid insanities" (German: *paranoide Verblödungen*) and the "Group of Dementia Praecox." As another special type of disease, he described the "Paranoia," a disorder characterized with delusions of reference, delusions of grandeur, erotic delusions, delusions of persecution and other delusions. Affectivity, activity and also the logical thought processes, however, were almost undisturbed in this type of mental disease (Kraepelin 1913, 1915). The characteristic symptoms of dementia praecox according to Kraepelin were weakening of judgment, mental initiative and creative abilities, deadening of affectivity and sympathy, loss of energy and drive, and, in particular, a loosening of the integration and unity of inner life. These processes result in a peculiar and odd destruction of the personality with prominent damages of affectivity and will functions (Kraepelin1915). There are clear similarities of the Dementia Praecox concept to the concept of Hebephrenia according to Hecker (1871) and Kahlbaum (1874, 1890).

Kraepelin has tried to adjust his classification system again and again until his death. He was dissatisfied because a great deal of psychoses, appearing in the daily clinical praxis, did not meet its criteria. In 1920, six years before he died, Kraepelin suggested that the scientific community should look for new strategies to classify the mental diseases (van Tilburg 1990).

Kleist was the first to describe remitting atypical psychoses which he originally called "autochthon degeneration psychoses." Because of their good prognosis without remaining psychic defects after remission of the acute psychotic episodes and other similarities to Kraepelin's manic-

depressive diseases, he later proposed to call them "Cycloid Psychoses." On the other hand, he regarded the different clinical pictures of schizophrenia as genetically based degenerations of psychic systems and dimensions. He compared them with, at that time already well-known, systematic neurological diseases (Kleist 1925, 1926, 1928).

Leonhard´s classification of the endogenous psychoses has its roots in the work of Kahlbaum, Hecker, Kraepelin, Wernicke and Kleist. The main result of Leonhard´s lifelong studies was the differentiation of the endogenous psychoses into five distinct groups or spectra of diseases which are independent of each other with respect to symptom clusters, course, long-term outcome and genetic loading: Unipolar affective psychoses, bipolar affective psychoses, cycloid psychoses, unsystematic schizophrenias and systematic schizophrenias (Leonhard 1995, 1999). Cycloid psychoses, unsystematic and systematic schizophrenias exhibit first rank symptoms according to Kurt Schneider (1992).

The cycloid psychoses often show bipolar clinical pictures and have a favorable long-term prognosis with respect to lacking residual psychopathology. This mainly differentiates them from the whole group of schizophrenias which have an unfavorable long-term course and outcome and have to be divided nosologically into unsystematic und systematic forms. The residual states of the schizophrenias can vary from slight forms to very serious and disabling ones. In accordance with Kleist, Leonhard (1999) regarded the systematic forms of schizophrenia as genetically determined degenerations of high and highest psychic systems in the brain. There is some resemblance with the "catastrophic schizophrenias" as described by Bleuler (1911). Most of the schizophrenias as described by Leonhard fit into Kraepelin´s dementia praecox concept. The cycloid psychoses according to Leonhard, however, have to be allocated to the spectrum of manic-depressive illnesses in Kraepelin´s system because of their prognostic favorable long-term outcome.

Leonhard´s classification is complex and asks for a thoroughly clinical training. It can be clearly stated that Leonhard's approach is a sophisticated further development of Kraepelin' s dichotomic system. In this context, a serious scientific discussion over apparently conflictive positions seems to be necessary. Probably the combination and integration of both diagnostic approaches, which so far appear mutually exclusive, will drive the research forward again. Classification systems have to be free of any dogmatic ideation and irreversible paradigms. This

could bring a new dynamic in research and clinical praxis and new insights in the puzzle of mental disorders.

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December 7, 2017

Carlos Morra´s comment on Donald F. Klein's final comment

I see the point that Donald Klein raised in his final comment and I may say that it maintains the point of view of many of the psychiatrist and psychologists of the Western world, shared by many, but possibly contradicted by many, too. The basic objective of nosology is to identify the natural categories of diseases; we have not completed this task, specially in the field of psychosis.

Natural categories are still a mystery to us. Although we have for many years followed the psychopathology of Kraepelin and Bleuler, doing so has led to a divorce between clinical practice and research; continuing to do so will condemn us to failure and/or isolation.

Regarding genetics, there are several reports of families studied based on Leonhard´s classification which showed better correlation than Kraepelin´s subtypes of schizophrenia (Ungvári 1985; Franzek, Schmidtke, Beckmann and Stöber 1995; Beckmann, Franzek and Stöber 1996; Franzek and Beckmann 1996, 1998; Ban 2004; Schanze, Ekici, Pfuhlmann et al. 2012; Peralta, Goldberg, Ribeiro et al. 2016), but still the findings are not sufficiently strong to change the modern paradigm of several genes that are not directly responsible for the disease, but for the predisposition to generate the disease (DiLalla, McCrary and Diaz 2017).

There have been certain groups that adopted Leonhard´s Classifications and found a significant difference in electrophysiological and brain perfusion studies between the three main groups of schizophrenic patients: Hebephrenic, Catatonic, and Paraphrenic. In a conference at the World Psychiatric Association (WPA) meeting in Buenos Aires, Strik (2008) presented the analysis of his data separated in three groups: patients who had predominant affective Symptoms/signs, patients who had predominant thought symptoms/signs and patients who had predominant motor symptoms/signs. This year the WPA published a study with similar results on cerebral perfusion patterns in schizophrenic patients (Stegmayer 2017). The three groups where significantly discriminated.

Despite of the complexity of the clinical subtypes within each category, the main groups are still there to be studied and validated. We cannot say that the categories are not valid because there isn´t enough evidence to eliminate this hypothesis.

The power of prediction is pretty much the same between the different categories. Unsystematic schizophrenias have a better prognosis than systematic schizophrenias and they both have a worse prognosis than cycloid psychosis. Within the group of systematic schizophrenias, hebephrenia has the worst prognosis while catatonia has a better prognosis than hebephrenia, but still worse than paraphrenia (Leonhard 1995).

In my everyday practice, I use Leonhard´s classification to stablish a prognosis, an evaluation of possible dangers and also a better selection of the treatment because there wasn´t a

valid prognosis and treatment use for the DSM-IV, and we have introduced some of Leonhard´s categories camouflaged in RDoC´s dominions (i.e., affect, delusions/hallucinations, etc.).

I also may say that we know that the brain´s complexity is likely to have several different manifestations of each single nosological entity. We have only a few types of cells in the pancreas, yet we can have several diseases (cancer, pancreatitis, diabetes, etc.). Having several types of cells, circuits and structures, we shouldn´t wait to have only a few diseases in the brain. Leonhard´s classification is difficult to teach and also difficult to learn, but the difficult road, which often leads to the right finding, is the one less used. Everyone choses the simple road that, in the best of the cases, leads to partially true, but incomplete findings.

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December 14, 2017