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Assen Jablensky

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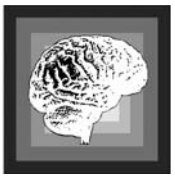

Living in a Kraepelinian world: Kraepelin's impact on modern psychiatry

ASSEN JABLENSKY*
The University of Western Australia

Kraepelin's works are made more accessible in English by the publication in 2002 of a 5-volume book of reprints of original translations. Together with his Memoirs *(Kraepelin, 1987) and the translations of several of his papers published in* History of Psychiatry*, they present a fair, though still incomplete picture of Kraepelin's lifetime work. This paper draws on those publications to assess Kraepelin's legacy and his influence on contemporary psychiatric theory and practice..*

Keywords*: DSM; Emil Kraepelin; neo-Kraepelinian; psychiatric nosology; psychiatry*

It is hard to imagine a debate taking place today among practising physicians on the evidence base for Virchow's description of leukemia, or on the prognostic implications of the diagnosis of Osler-Vaquez disease. Yet Emil Kraepelin's views on the typology of mental disorders – often quoted, occasionally misquoted and at times hotly debated – continue to frame much of the present-day psychiatric discourse. It looks indeed as if 'psychiatry still lives in a Kraepelinian world' (Berrios and Hauser, 1988), but the exact contours of its map are still disputed and often get blurred. While European psychiatry rarely departed in a significant way from the nosological concepts formulated by Kraepelin and his followers, decades of psychodynamic psychiatry in North America were followed by a 'neo-Kraepelinian revolution' (Compton and Guze, 1995; Klerman, 1978) and the development of operational diagnostic criteria (APA, 1980, 1987, 1994; Feighner et al., 1972; Spitzer, Endicott and Robins, 1978), which were presumed to incorporate

* *Address for correspondence:* School of Psychiatry & Clinical Neuroscience, University of Western Australia, MRF Building, 50 Murray St, Mail Bag Delivery Point M571, Perth WA 6000, Australia. Email: assen@cyllene.uwa.edu.au

Kraepelinian diagnostic conventions. Among other things, the American rediscovery of Kraepelin in the 1970s has raised the question, what exactly were Kraepelin's views on the defining features and boundaries of the major psychiatric disorders? What did Kraepelin actually say?

English language readers will now find it easier to search for answers to these recurring questions thanks to the exquisitely produced five-volume edition of reprints from the original translations of Kraepelin's seminal texts, *Lifetime Editions of Kraepelin in English* (2002). Together with his *Memoirs* (Kraepelin, 1987) and the translations of several of his papers published in this journal, they present a fair, though still incomplete picture of Kraepelin's lifetime work.

Although Kraepelin's legacy is best known for the set of ideas about the nature and classification of psychiatric disorders, an exclusive focus on the disease entity concept and the nosology of psychoses may detract from a proper appreciation of the extraordinary breadth and depth of his achievement. Kraepelin's many and varied research pursuits were often well ahead of his time, laying some of the enduring cornerstones for scientific psychiatry as a medical discipline. In one of the early papers, based on his 1886 inaugural lecture at the University of Dorpat (now Tartu, Estonia), Kraepelin, then only 30 years of age, outlined the 'research programme' that was to become a driving preoccupation for the rest of his life (Kraepelin, 2005). Five key themes, articulated with great clarity, illustrate his critical insights into the actual state and future prospects of the discipline, as well as what many would consider a strong pro-'medical model' bias: (i) psychiatry needs a 'profound and deep union with general medicine'; it is 'above all the medical, somatic side of our science' that provides the 'point of departure for psychiatric research'; (ii) the task of psychiatry is the clinical study of mental disorders, i.e. 'the empirical determination of individual forms' of illness according to their cause, course and outcome by applying 'impartial observation and tireless pursuit of individual psychiatric cases', rather than 'medico-speculative' theory which 'strives to be more than it really is'; (iii) the existing nomenclature subsumes 'all those small variations and intermediate forms … under excessively large and therefore meaningless and blurred categories'; (iv) 'as long as it is impossible to relate a simple and unequivocal patho-anatomic observation to an equally simple and unequivocal psychopathological observation', scientific psychiatry will not have reached the goal it should be capable of reaching; (v) among psychiatry's auxiliary sciences, the 'strictly empirical research methods' of experimental psychology 'hold out the most promise' of 'validity and scientific utility'. Which of the goals of his 'research programme' did Kraepelin achieve and where did he fail?

Elaborating on ideas first enunciated by Griesinger and Kahlbaum, Kraepelin reinforced greatly the primacy of the clinical method as the *firma terra* of psychiatry but went beyond its confines by actively seeking and building alliances with the 'auxiliary sciences' of psychology (Kraepelin, 1896),

neuropathology, pharmacology and genetics. By attracting as co-workers a number of brilliant clinicians and researchers, including Nissl, Spielmeyer, Alzheimer, Brodmann, Plaut, Aschaffenburg and Gaupp, among others, Kraepelin created an ethos of scientific innovation and discovery, which earned for psychiatry a respectable place among the medical disciplines. The German Research Institute of Psychiatry (Deutsche Forschungsanstalt für Psychiatrie, now Max-Planck Institute of Psychiatry in Munich), established in 1917 after a decade of Kraepelin's tireless campaigning, was the world's first centre specifically planned and designed for multidisciplinary studies of the mental disorders. Kraepelin's team pioneered the staining and microphotography of neurons and glia; produced contiguous microphotographic maps of the cortex; developed a technique for determining the specific weight of particular brain structures; formulated the principles of pedigree analysis in psychiatric genetics; and were the first to use cinematography as a documentation tool in psychiatry. Kraepelin himself carried out original work in experimental psychology and pharmacology (the performance curve; manipulation of time perception; measurement of the effects of alcohol and caffeine on cognition) and much of his characterization of dementia praecox has definite neuropsychological underpinnings. Although not directly involved in population studies, Kraepelin stimulated others to conduct community surveys. Following a trip to south-east Asia, he outlined in 1904 the rationale for cross-cultural clinical and population research in his programmatic paper on comparative psychiatry (Kraepelin, 1974*a*). Last but not least, Kraepelin's advocacy of a population-based reduction in alcohol consumption and of a screening programme for the early treatment of syphilis, revealed his sound judgement on targeting the state's public health priorities towards the top two preventable causes of mental morbidity at the time.

Two components of Kraepelin's legacy continue to influence profoundly the theory and practice of psychiatry: the idea of the disease entity in psychiatry and the conceptual map of the psychiatric disorders with the distinction between dementia praecox (re-named schizophrenia in 1911 by Bleuler; see Bleuler, 1950) and manic-depressive insanity. As pointed out by Janzarik (1978), Kraepelin's principal merit was the articulation of the 'multitude of pathogenetically unclarified psychoses' into those leading to a 'state of weakness' (*Schwächezustand*) and those spared such outcome. The ultimate validation of the proposed disease entities, Kraepelin believed, would come from neuropathology, physiology and biological chemistry of the brain, whereas the specific contribution of clinical research to their delineation consisted in identifying replicable patterns of intercorrelations between symptoms, course and outcome.

Kraepelin's approach to the problem of definition and classification of psychiatric disorders was, essentially, a nosographic one, i.e., based on comprehensive clinical observations and naturalistic descriptions of a large number of individual cases. However, in contrast to earlier nosographers, Kraepelin was the first to apply explicitly and systematically a longitudinal,

lifetime approach to the description of individual illness, which resulted in 'a concrete living picture … with the help of ordinary language and no conceptual elaboration' (Jaspers, 1963). Kraepelin never issued a definitive list of diagnostic criteria for dementia praecox and manic-depressive insanity, and was particularly careful to avoid claims about any 'pathognomonic' symptoms. Considering the whole of the clinical picture, as well as the characteristics of the individual personality invaded by the illness, was the rule he taught his students (see the 'Lectures on Clinical Psychiatry' in Kraepelin, 2002, Vol. 1).

Kraepelin's main research tool was the database provided by the 'counting cards' (*Zählkarten*) – annual collections of case summaries in a semi-standardized format (Weber and Engstrom, 1997), which he used in a kind of 'pattern recognition' process involving iterative permutation-recombination to detect differences and similarities among cases. Thus, hierarchically ordered groups and subgroups emerged for a refined description of prototypes of disorders that included only rudimentary statistics. These prototypes, presented as *categories* of mental disorder, were not cast in stone and underwent numerous modifications. For example, the initial formulation of dementia praecox was fairly narrow, heavily weighted for features characterizing Hecker's hebephrenia (Kraepelin, 2002, Vol. 2, based on the seventh German edition of *Psychiatrie*). The later version (Kraepelin, 2002, Vol. 5), translated into English from the eighth edition and published in 1919 under the title *Dementia Praecox and Paraphrenia*, is considerably richer in descriptive detail and wider in scope, comprising nine quite different 'clinical forms', including several that today might be classified as schizoaffective or acute transient schizophrenia-like disorder. Therefore, the widely held notion that Kraepelin's dementia praecox was a narrowly constrained, severe psychotic illness of an invariably poor outcome in a 'defect state' is only partially correct – insofar as it applies to the early version of the concept.

It is arguable by what kind of mental operation Kraepelin arrived at the primordial idea about the two major categories of schizophrenic and affective psychoses, but one thing is certain: they were not 'atheoretical' products of a mechanical accumulation of empirical facts (Weber and Engstrom, 1997). As Kraepelin himself wrote in his *Memoirs*, the idea of dementia praecox gradually 'dawned' on him when observing that many patients, who initially present with mania melancholia or amentia, develop progressive dementia and, in spite of individual differences, begin to resemble one another. This led him to the insight that: (a) *one* uniform disease process must be affecting them all; and (b) the process might be slow or quick, *sometimes* accompanied by delusions, hallucinations and excitement, but always leading to a loss of 'intellectual' capacity.

Kraepelin's goal of developing a consistent 'natural' classification of the major mental disorders was never attained, and the system he created contained internal contradictions that necessitated frequent revisions and

adjustments. The initial hope that neuropathology would reveal brain abnormalities unique to dementia praecox had to be dashed; the use of the long-term outcome criterion as a validity check on the diagnosis was unreliable and impractical, requiring prolonged monitoring of the patients; and varying proportions of the cases initially classified as dementia praecox actually recovered. As regards the differentiation between schizophrenia and manic-depressive psychoses, there were too many cases where a clear distinction was impossible to make on purely clinical grounds. Kraepelin was fully aware of these difficulties and, in a seminal paper from his late period (published in 1920; see Kraepelin, 1974*b*), he not only acknowledged 'the suspicion that our formulation of the problem may be incorrect', but went as far as to propose that 'the affective and schizophrenic forms of mental disorder do not represent the expression of particular pathological processes, but rather indicate the areas of our personality in which these processes unfold'.

Notwithstanding such difficulties and doubts, as well as many attempts at alternative formulations of the diagnostic classification of the psychoses, the categorical nosology constructed by Kraepelin gained more or less general acceptance and its essential features are still clearly present in *ICD-10* (WHO, 1992) and *DSM-IV* (APA, 1994). This occurred in spite of criticisms and challenges that have accompanied the Kraepelinian nosology since its inception to the present day. The various objections raised by its critics fall into several groups:

(i) Searching for disease entities in psychiatry on the basis of clinical data on subjective symptoms is like the 'chasing of a phantom' (Hoche, 1912); it is impossible to infer anything about the aetiology and cerebral localization from the symptoms and course of the illness.
(ii) Similarity in outcomes does not necessarily imply that the same disease is present; the same illness may result in deterioration in some cases and in recovery in other cases.
(iii) A categorical distinction within the group of major psychoses is impossible to sustain as there are many inter-forms and transitions in symptomatology, as well as in the individual course of illness over time.
(iv) The diagnostic categories of schizophrenia and manic-depressive disorder do not define genetically distinct biological entities.
(v) Kraepelin's nosology is not based on a scientific methodology, has no empirical support and represents an arbitrary grouping of heterogeneous cases.

Most of these objections are essentially valid, but the last one appears to be simply ill-informed. The extensive documentation that Kraepelin left on his clinical research allows original material to be re-examined or re-analysed using modern statistical methods. Having been granted access to the entire

set of 721 *Zählkarten* from the year 1908, we (Jablensky, Hugler, von Cranach and Kalinov, 1993) extracted and coded the symptoms and other recorded clinical features of all the 53 cases of dementia praecox and 134 cases of manic-depressive insanity admitted to the Munich clinic during that year, using the syndrome checklist and glossary definitions of the Present State Examination (PSE; Wing, Cooper and Sartorius, 1973). After processing the data with the CATEGO computer classification algorithm, we found an overall concordance of 80.2% between Kraepelin's original diagnoses and the computer-assigned *ICD-9* diagnoses. At a next step (Jablensky and Woodbury 1995), we applied grade of membership analysis (a form of latent structure analysis) to obtain a statistical grouping of Kraepelin's patients based solely on their symptom profiles, disregarding the original diagnoses. This independent taxonomic analysis reconstituted three 'pure types' of disorder, clearly corresponding to bipolar affective disorder, recurrent unipolar depression, and dementia praecox, thus suggesting high content validity for Kraepelin's typology and a consistent 'goodness of fit' between the categories and the actual clinical data on which the typology was based.

The relevance of the Kraepelinian classification to genetic research is more difficult to evaluate. Long before the advent of molecular genetics, Robert Gaupp, a close collaborator of Kraepelin, wrote: 'We are, of course, clearly aware of the fact, which we don't deny even for a second, that the greatest part of all genetic work in psychiatry would immediately collapse like a house of cards if Kraepelin's theory was shown to be altogether mistaken' (Gaupp, 1939). The lack of spectacular advances in unravelling the genetic causes of schizophrenia and the major mood disorders during the last 15 years leads researchers to question whether the current diagnostic criteria of *DSM-IV* (or *ICD-10*), incorporating Kraepelinian concepts, define phenotypes suitable for genetic research (Jablensky, 2006). Recent genetic linkage and association findings, pointing to shared genetic risks and the existence of sets of genes with overlapping effects on both schizophrenia and bipolar disorder, e.g., dysbindin, neuregulin, DISC1, BDNF (Craddock and Owen, 2005), suggest that the nosological boundaries, on which a whole generation of molecular genetic studies was predicated, do not 'carve nature at its joints'. It is, however, premature to draw radical conclusions about the overall validity and utility of the distinction between schizophrenia and mood disorders, as there is still an 'explanatory gap' between the findings of a statistical association and the demonstration of causality with regard to specific illness phenomena. This gap might be easier to bridge by employing intermediate (or endo-) phenotypes in the domains of cognitive function, neurophysiology or neuroanatomy. As objectively measurable quantitative traits, endophenotypes are better anchored in brain biology than clinical symptoms and can help delineate subtypes of disorder with likely distinct genetic basis (Hallmayer *et al.*, 2005). Parsing the major clinical syndromes into 'modular' endophenotypes with specific neurocognitive or

neurophysiological underpinnings is likely to cut across the conventional diagnostic boundaries and may prove a promising approach in the genetics of psychotic disorders. The current evidence is neither final nor static, and will need to be re-examined as new concepts and technologies coming from molecular genetics and genomics, cognitive science or brain imaging bring forth new perspectives on disease causation and brain function. With the rapid advances in molecular neuroscience, genetics and genomics, the role of clinicians in defining and evaluating refined, reliable and valid phenotypes will be critical to the success of the discovery enterprise – and will be entirely along the lines of Kraepelin's envisaged 'research programme'.

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