

## Making Progress in Schizophrenia Research

Stephan Heckers<sup>1,2</sup>

<sup>2</sup>Department of Psychiatry, Vanderbilt University, Vanderbilt Psychiatric Hospital, 1601 23rd Avenue South, Room 3060, Nashville, TN 37212

*Psychiatry is a young, still developing science, that must, against sharp opposition, gradually achieve the position it deserves according to its scientific and practical importance. There is no doubt that it will achieve this position—for it has at its disposal the same weapons which have served the other branches of medicine so well: clinical observation, the microscope and experimentation. Emil Kraepelin (p. 8)<sup>1</sup>*

Emil Kraepelin wanted to make progress in psychiatry. He pioneered psychiatric research to improve the status of psychiatry within the field of medicine. His optimism continues to shape psychiatry today.<sup>2–4</sup> There is increasing concern, however, that Kraepelin did not lead us in the right direction. Most authors have focused on Kraepelin's dichotomy of schizophrenia and bipolar disorder as the Achilles heel of his diagnostic system.<sup>5,6</sup> Some have argued that there is no clear point of rarity between these 2 diagnoses.<sup>7</sup> Others have proposed that there are several additional, clearly distinguishable psychotic disorders in the borderland between schizophrenia and bipolar disorder.<sup>8</sup> The discontent with Kraepelin's concepts is fueled by new scientific evidence and by the opportunity to overhaul the current diagnostic concept of psychotic disorders in the next edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM).<sup>5,9</sup>

But we should not concern ourselves too much with disproving Kraepelin's definitions of schizophrenia and bipolar disorder. Rather, we need to revise our current model of psychiatric research. It appears that progress in schizophrenia research will require not simply an adjustment of the classification of psychotic disorders, but a new set of studies that can challenge the Kraepelinian model of psychiatric research.

### Kraepelin's Research

For Kraepelin, scientific progress in psychiatry was a struggle (*against sharp opposition*, see above). His choice

of *weapons* for this struggle—clinical observation, microscope, and experimentation—was not a coincidence. They were the leading scientific tools at the end of the 19th century, and he was committed to all 3 of them.<sup>10</sup>

As a young physician, Kraepelin worked with Bernhard von Gudden, a prominent neuroanatomist and psychiatrist. While Kraepelin himself did not enjoy work in the morgue and laboratory (and made some disparaging statements about the value of postmortem research in psychiatry),<sup>11</sup> he ultimately embraced neuroanatomy. In the later editions of his textbook of psychiatry, he prominently displayed Alois Alzheimer's studies of dementia praecox with several microphotographs, convinced that microscopic abnormalities are a diagnostic feature of schizophrenia.<sup>12</sup>

After his time with von Gudden, Kraepelin became interested in laboratory studies of human behavior. He moved to Leipzig and worked with Wilhelm Wundt, the father of experimental psychology. Kraepelin was seriously considering leaving clinical psychiatry and joining Wundt's laboratory, but his mentor advised him to remain focused on clinical psychiatry.<sup>13</sup>

While Kraepelin's contribution to experimental psychology has received little attention, his clinical observations have shaped many current concepts of psychiatric disorders. Kraepelin provided detailed description of mental states and abnormal human behavior in the 7 editions of his textbook of psychiatry, published between 1883 and 1915. Most importantly, he collected longitudinal clinical data and defined the course and outcome of several psychiatric disorders. The 2 most influential psychiatric diagnoses that can be traced back to his textbook are dementia praecox (renamed schizophrenia by Eugen Bleuler in 1911)<sup>14</sup> and manic-depressive illness (which was separated from unipolar depression and renamed bipolar disorder by Karl Leonhard in 1957).<sup>15</sup>

### The Evolution of Kraepelin's Dementia Praecox Concept

Kraepelin constantly reevaluated his diagnostic constructs, changing some aspects while holding on to others. Initially, Kraepelin grouped 3 distinct clinical presentations—catatonia, dementia paranoides, and hebephrenia—together and called the syndrome dementia praecox. In the last edition of his textbook, he expanded these 3 subtypes of dementia praecox into 10.<sup>12</sup> He defined

<sup>1</sup>To whom correspondence should be addressed; tel: 615-322-2665, fax: 615-343-8400, e-mail: stephan.heckers@vanderbilt.edu.

them based on clinical observation, but did not suggest different mechanisms or etiologies.

Poor outcome was central to the original formulation of dementia praecox (hence the name). But Kraepelin questioned his original assertion that dementia praecox always leads to poor outcome<sup>16</sup> and suggested new diagnostic labels, including schizophrenia.<sup>12</sup>

He acknowledged a lack of scientific data and radically changed his views on disease mechanisms and etiology. In the initial formulation of dementia praecox as a psychiatric disorder, he classified it as an endocrine disorder. In subsequent editions, he hypothesized a process of auto-intoxication, leading to cortical neuron loss.

Kraepelin deserves credit for his ability to change several core features of the original dementia praecox concept. But despite such flexibility, Kraepelin did not change his belief that schizophrenia is a “natural disease unit” (*natuerliche Krankheitseinheit*)—ie, it is *one* disorder that can be studied at *several* level, including etiology, disease mechanism, and clinical presentation.<sup>17</sup>

### The Kraepelinian Model of Psychiatric Research

In the first 4 editions of his textbook, Kraepelin did not propose that psychiatric disorders could be studied in the clinic as well as the laboratory. He introduced dementia praecox simply as a syndrome, which allowed him to group together patients, with different clinical profiles but, as he believed, similar outcomes. This was an extension of Kahlbaum’s syndromal approach in psychiatry.<sup>18</sup> The Kraepelinian syndromes deemphasized the unique clinical presentation of each patient (which remained the focus of various schools of psychopathology) and stressed common features. For Kraepelin, the most important clinical feature was outcome. He strongly believed that prediction of outcome should be the guiding principle of a psychiatric classification system.

The 5th edition of his textbook was his Copernican turn. He went beyond the clinical syndrome and introduced the concept of the natural disease unit. Kraepelin proposed that psychiatric research should not revolve around the patient’s clinical presentation. Instead, psychiatric research should begin with the definition of an illness at the level of clinical features, disease mechanism, and etiology—and data collection should then follow.

Kraepelin saw diagnostic constructs as means toward a full scientific exploration of mental illness. He built the first major psychiatric research institute in Germany, attracting an outstanding cadre of researchers.<sup>19</sup> Their research (clinical studies, pathology, genetics, experimental psychology) relied on psychiatric diagnoses, and dementia praecox became the paradigmatic natural disease unit. The diagnosis did not appear in the first 3 editions of his textbook, occupied only 46 pages in the 5th edition, but reached 356 pages in the 8th edition, including many figures and graphs. Kraepelin felt that all 3 lines of inves-

tigation were coming together and that research was solving the puzzle of dementia praecox. While his diagnostic concepts have been criticized, his concept of the natural disease unit has remained the prevailing view in schizophrenia research.<sup>17</sup>

### Influence of the Kraepelinian Model on Current Research

Most current schizophrenia research starts out with a categorical classification of patients (typically according to DSM-IV) and then tests for differences between a group of schizophrenia patients and a control group (either healthy volunteers or another disease group of interest, eg, bipolar disorder). By doing so, we limit ourselves to exploring disease mechanisms and etiologies of diagnostic constructs. It is more likely that dimensions of behaviors, some of which traverse diagnostic categories, are more relevant for the study of the genetic and neural mechanisms of mental illness. It is this procrustean bed that has held psychiatric research back.

But it is important to acknowledge the value of Kraepelin’s natural disease units. While not perfect, they have predictive power. They simplify complex human behavior and provide a framework for communication among affected individuals, relatives, caregivers, and the society at large. They also justify research efforts that pledge to uncover the basis of mental illness (eg, the gene or brain region for schizophrenia). Kraepelin’s vision of progress in psychiatric research gives hope to those who struggle to make sense of mental illness. Any research agenda that challenges the Kraepelinian model will have to provide the same kind of inspiration.

### A New Research Agenda for Psychiatry?

Psychopathologists and neuroscientists have always been skeptical of the Kraepelinian model of research.<sup>20</sup> Geneticists are now joining their chorus.<sup>5</sup>

Psychopathologists are interested in the details of abnormal mental states and the better understanding of the nonunderstandable, particularly in psychosis.<sup>21</sup> They have argued that the relevant scientific unit for psychiatric research is not the diagnostic group but the individual mental state. This approach does not lend itself to simple classification schemes and requires significant training in patient interviewing and knowledge of a challenging vocabulary. This has limited the practical value of psychopathology in clinical practice or research. However, there is no doubt that we need to rediscover a more detailed documentation of the mental state in both clinical practice and research.<sup>22,23</sup>

Neuroscientists have argued for a more refined mapping of the clinical features of schizophrenia to the brain. Such efforts have been successful when circumscribed

lesions give rise to distinct behavioral deficits. It is no surprise that one of the pioneers of such clinicopathological correlations, Carl Wernicke, strongly disagreed with Kraepelin's neural models of schizophrenia. He proposed a model that conceptualized psychiatric disorders as a failure of distributed neural networks.<sup>24,25</sup> His ideas resonate with cognitive neuroscientists and neuroimaging researchers.

Rather than studying human mental states and brains, genetic research has the power to bypass the laborious process of working from the top down, by identifying genetic factors (eg, allelic variation giving rise to risk genes, epigenetic factors, gene transcription abnormalities) that can explain substantial components in the variation of human behavior. It is very likely that such mechanisms will be able to explain significant aspects of mental illness.

More recently, all 3 lines of research reviewed above have been called upon to develop a new research agenda, from the phenome to the genome.<sup>26</sup> Some have proposed that endophenotypes could become bridges between the bottom and the top of the scientific hierarchy.<sup>27,28</sup> But it is not clear how such efforts will surpass the Kraepelinian research model if they do not develop a dimensional approach that goes beyond our current focus on diagnostic categories.

### How to Make Progress?

Rather than holding on to the natural disease unit dogma, we need to collect clinical, neuroscientific, and genetic data from large cohorts that are not defined simply by categories such as schizophrenia or bipolar disorder. The data need to be rich, especially at the phenomenological level. The instruments need to have a level of resolution that can detect subtle signs of reality distortion, mood abnormalities, and cognitive impairment in order to map out the continuum from health to disease. Finally, the assessments need to be longitudinal in order to determine the relationship between domains of psychopathology and to assess course and outcome.

It is likely that we will identify several mechanisms and causes for schizophrenia. It is also likely that shared mechanisms and causes will be identified for clinical features that traverse diagnostic categories. Both of these outcomes—multiple disease pathways for one diagnostic category and shared pathways across diagnostic categories—will refute Kraepelin's dogma that separate lines of investigation will uncover natural disease units. That would be progress.

### References

1. Kraepelin E. *Psychiatry. A Textbook for Students and Physicians*. Vol 1: Canton, OH: Science History Publications; 1899.
2. Berrios GE, Hauser R. The early development of Kraepelin's ideas on classification: a conceptual history. *Psychol Med*. 1988;18(4):813–821.
3. Andreasen NC. The American concept of schizophrenia. *Schizophr Bull*. 1989;15(4):519–531.
4. Jablensky A. Living in a Kraepelinian world: Kraepelin's impact on modern psychiatry. *Hist Psychiatry*. 2007;18(71 pt 3):381–388.
5. Craddock N, Owen MJ. Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry*. 2007;6(2):84–91.
6. Greene T. The Kraepelinian dichotomy: the twin pillars crumbling? *Hist Psychiatry*. 2007;18(71 pt 3):361–379.
7. Peralta V, Cuesta MJ. The underlying structure of diagnostic systems of schizophrenia: a comprehensive polydiagnostic approach. *Schizophr Res*. 2005;79(2–3):217–229.
8. Leonhard K. *Aufteilung der endogenen Psychosen und ihre differenzierte Ätiologie*. 7th ed. Stuttgart, Germany: Georg Thieme Verlag; 1995.
9. van Os J, Tamminga C. Deconstructing psychosis. *Schizophr Bull*. 2007;33(4):861–862.
10. Engstrom EJ. *Clinical Psychiatry in Imperial Germany: A History of Psychiatric Practice*. Ithaca, NY: Cornell University Press; 2004.
11. Kraepelin E. *Memoirs*. Berlin, Germany: Springer-Verlag; 1987.
12. Kraepelin E. *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. Achte, vollständig umgearbeitete Auflage. 3 Band. Klinische Psychiatrie. 2 Teil*. Leipzig: Verlag von Johann Ambrosius Barth; 1913.
13. Steinberg H. *Kraepelin in Leipzig*. Bonn, Germany: Edition Das Narrenschiff im Psychiatrie-Verlag; 2001.
14. Bleuler E. *Dementia Praecox oder Gruppen der Schizophrenien*. Leipzig, Germany: Franz Deuticke; 1911.
15. Leonhard K. *Aufteilung der endogenen Psychosen*. Berlin, Germany: Akademie Verlag; 1957.
16. Kraepelin E. Die Erscheinungsformen des Irreseins. *Z Gesamte Neurol Psychiatr*. 1920;62:1–29.
17. Hoff P. Kraepelin. Clinical Section – Part I. In: Berrios G, Porter R, eds. *A history of clinical psychiatry*. New York: New York University Press; 1995:261–279.
18. Kahlbaum K. *Die Gruppierung der psychischen Krankheiten und die Eintheilung der Seelenstörungen. Entwurf einer historisch-kritischen Darstellung der bisherigen Eintheilungen und Versuch zur Anbahnung einer empirisch-wissenschaftlichen Grundlage der Psychiatrie als klinischer Disciplin*. Danzig: Kafemann; 1863.
19. Weber MM. Psychiatric research and science policy in Germany: the history of the Deutsche Forschungsanstalt fuer Psychiatrie (German Institute for Psychiatric Research) in Munich from 1917 to 1945). *Hist Psychiatry*. 2000;11(43 pt 3):235–258.
20. Angst J. Psychiatric diagnoses: the weak component of modern research. *World Psychiatry*. 2007;6:94–95.
21. Jaspers K. *Allgemeine Psychopathologie*. 9th edn, 1973 ed Berlin, Germany,: Springer-Verlag; 1913.
22. Andreasen NC. DSM and the death of phenomenology in America: an example of unintended consequences. *Schizophr Bull*. Jan 2007;33(1):108–112.
23. Cuesta MJ, Peralta V. Current psychopathological issues in psychosis: towards a phenome-wide scanning approach. *Schizophr Bull*. 2008;In press.
24. Wernicke C. *Grundriss der Psychiatrie*. Nijmegen, The Netherlands: Arts & Boeve Verlag; 2000.

25. Lanczik MH, Beckmann H, Wernicke KG. Clinical section. In: Berrios GE, Porter R, eds. *A History of Clinical Psychiatry*. New York: New York University Press; 1995:302–312.
26. Bilder RM. Phenomics: building scaffolds for biological hypotheses in the post-genomic era. *Biol Psychiatry*. 2008;63(5):439–440.
27. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160(4):636–645.
28. Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci*. 2006;7(10):818–827.