This issue, and an upcoming issue, of *Psychiatric Annals* address the idea that the “Kraepelinian dichotomy” may be obsolete. This is truly of field-altering effect because the concept that schizophrenia and bipolar disorders are separate and distinct illnesses has been a cornerstone of psychiatric diagnosis for almost a century. This concept has been accepted by academic psychiatry, the mental health professions, physicians in general, the public, and the media and is presented in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition-text revision (DSM-IV-TR), the *International Classification of Diseases* (ICD), and major textbooks in psychiatry. The validity of schizophrenia as separate from psychotic bipolar disorder was established before chronicity and psychosis were recognized as consistent with severe disorders of mood. That schizophrenia and bipolar disorder are more alike than different is no longer a question among some researchers, as represented by several of the authors in these issues of *Psychiatric Annals*. However, the idea of “no dichotomy” remains a minority opinion.

The contributors to these issues of *Psychiatric Annals* were recruited because they are experts in their fields of molecular genetics, neurocognition, neuroimaging, psychopharmacology, and clinical phenomenology, and because, in their areas of expertise, studies have compared patients diagnosed with schizophrenia and bipolar disorders. It has been my privilege to work with these authors and colleagues over the past 2 years.

Although the authors question, if not discount, the dichotomy, the majority support a dimensional approach in which the two disorders are linked across a range of severity of course, symptoms, and endophenotypes. Endophenotypes refer to quantifiable factors linking genotype and phenotype (ie, intermediary measures between genes and aberrant thought and behavior). Examples are cognitive defects, susceptibility loci, and structural changes in the brain based on neuroimaging data.

Several contributors cite data that support the dichotomy and other data that indicate overlap and similarities. A few contributors contend that schizophrenia and schizoaffective disorder are invalid as disorders different from psychotic mood disorders. This is not a new idea. The 1905 theory of Specht that functional psychoses were because of affective disorders, Kraepelin’s reversal in 1920 (see below), and the introduction of schizoaffective disorder in 1933 by Kasanin were early but largely ignored indications of similarities between schizophrenia and bipolar disorder. These were obscured by attention to Kraepelin’s original writings on the dichotomy and the enormous influences of Bleuler from 1911, Schneider in 1949, and others who believed that functional psychosis and chronicity are pathognomonic of schizophrenia.

In his article, Dr. Robert Post draws on his extensive experience from more than 30 years as Chief, Biological Psychiatry Branch, National Institute of Mental Health. He discusses “considerable overlaps” from his own research and the literature between patients diagnosed with schizophrenia and bipolar disorder. These overlaps are across multiple domains and include 1) ventricular enlargement; 2) loss of neuronal gray matter and neuronal numbers; 3) glial dysfunction; 4) hypofrontality based on structural and functional imaging; 5) decreased brain GABA; 6) decrements in brain reelin mRNA; 7) deficits in neuronal and glial markers such as n-acetyl-aspartate and glial acidic fibrillar protein; 8) numerous specific genetic vulnerability factors (see also Craddock and Owen, page 88; and Crow, page 115, in this issue).
Regarding clinical phenomenology, Dr. Post documents that “in some classic cases of bipolar disorder … patients can look indistinguishable from those with [a diagnosis of] schizophrenia.” This can occur in two circumstances: during an acute psychotic manic episode when the presenting symptoms “can include extreme disorganization, hallucinations, delusions, thought insertion/control, and marked regressive behavior such as feces smearing/eating.” Others concur.4-8 The second circumstance is when bipolar patients incur a “progressively deteriorating course of incomplete symptom resolution between episodes and acquire a dysthymic interval between episodes of increasing severity, often accompanied by increasing degrees of cognitive dysfunction.” More inpatient episodes result in an increase in severity and frequency of episodes and dementia. Dr. Post refers to “episode sensitization” and “dementia tardive.” These phenomena occur in both disorders, but Dr. Post states that they are found more frequently in patients diagnosed with schizophrenia. The question is how do we know those patients diagnosed with schizophrenia do not simply have the most severe form of bipolar or unipolar disorder rather than a separate disease? Dr. Post cites multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, each with marked variability in symptom and course severity as “giving pause in attributing the often differential courses and severities of illness in schizophrenia and bipolar disorder to necessarily entirely differential etiological processes.” This seems to suggest that schizophrenia and bipolar disorder are explained by a single disease, in keeping with Ockham’s razor. Dr. Post concludes that, “Thus, while much of our current data are consistent with the continuum hypothesis, I await the details and the new finding that may confirm or disconfirm this notion.”

Another contributor, Dr. Conrad Swartz, who recently published a major book on psychotic depression, finds psychotic depression often indistinguishable from schizophrenia.9 Dr. Swartz opens his contribution by stating, “The standard of clinical practice makes it too easy to diagnose schizophrenia when psychotic depression should apply. One reason is that DSM criteria for both conditions are met by subjective impression, and one diagnostician’s psychotic depression is another’s schizophrenia.” Dr. Swartz notes that all of the DSM diagnostic criteria for schizophrenia are entirely compatible with psychotic depression. He cites case reports from his long experience with psychotically depressed patients, noting that in such psychotic presentations, symptoms of depression are easily overlooked: “The drama of psychosis can hide depression.” He discusses the influence of the interviewing psychiatrist’s “subjective judgment” upon diagnosis. Diagnosis can be influenced by “the psychiatrist’s own personal issues (eg, avoidance of criticism, need to conform, drive to dominate, inadequate training [as about psychotic depression], financial sensitivity.”) He further notes that, “overdiagnosing schizophrenia is a defensive ploy.” He discusses tardive psychosis when “antipsychotics produce negative symptoms indistinguishable from those of traditional concepts of schizophrenia.” He further questions the validity of schizophrenia and schizoaffective disorder, saying, “In a practical sense, because 50 years and billions of dollars spent on modern science have not identified the specifics of schizophrenia, it has none and is not a distinct disease.”

Heritability and molecular genetic findings may reveal the endophenotypes most destructive to the dichotomy because of similarities and overlap between patients diagnosed with schizophrenia and bipolar disorder. For decades, schizophrenia and bipolar disorder were reported to “breed true,” but more recent large family studies have reversed this idea.10 Another widely published pair of authors, from Cardiff, Wales, Dr. Nick Craddock and Dr. Michael Owen, predicted the “end of the Kraepelinian dichotomy” in 2005, based on their data and that of others documenting family, twin, and molecular genetic overlap and similarities.11 Although Drs. Craddock and Owen discount a dichotomy, they also argue against a single disorder based upon results that have “provided clear evidence for the existence of genetic risk factors that are specific to one or the other of the two clinical categories.” For reasons discussed below, psychotic mood-disordered patients can be misdiagnosed as having schizo-

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**Guest Editorial**

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Dr. Tim Crow begins his paper with Kraepelin’s only recently famous dichotomy-busting statements from his 1920 publication: “No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis” and “Nevertheless it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect.” Although this statement by Kraepelin is “crystal clear,” Kraepelin’s dichotomy has been embraced for a century, withstanding his own reversal. Dr. Crow, recipient of the 65th Maudsley Lecture Award for his work, develops the history of his perspectives of the genetic contribution to psychosis across all three disorders, linking them in a continuum. His current conclusions encompass the origins of language and the speciation process that occurred nearly 6 million years ago, to account for the diverse but continuous phenomena of psychosis. As I interpret Dr. Crow’s hypothesis, a continuum of psychosis from none to blatant is accounted for by an ancient genetic occurrence so the single disease process, a mood disorder, can account for patients diagnosed with schizophrenia and schizoaffective disorder.

Drs. Craddock and Owen also report a very interesting genetic overlap among schizophrenia, autism, and mental retardation. It is possible that an organic neurodevelopmental defect explains some patients misdiagnosed with schizophrenia without any hint of a mood disturbance. Their conclusion is very solid that the data “suggest the need to embrace the complexity of brain function and move toward approaches to diagnosis and classification in which the clinical variables measured (be they symptoms or ‘laboratory tests’) map onto the underlying biological brain mechanisms that give rise to abnormal experiences and impairments.”
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guest editorial

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Dr. Lake graduated from Tulane University in 1965. He received an MS in Insect Physiology, also from Tulane, in 1966. He graduated from Duke University, School of Medicine and Duke Graduate School (Department of Physiology and Pharmacology), in 1971 and 1972. He studied at Oxford University and at St. Bartholomew’s Hospital, London. His residency in psychiatry was completed at Duke and at the National Institute of Mental Health (NIMH). He remained at the NIMH, Laboratory of Clinical Sciences, as a research associate and staff psychiatrist until 1979 when he took a professorship of psychiatry and pharmacology at the new Uniformed Services University of the Health Sciences (USUHS) School of Medicine. He secured two Research Project Grants (RO1s) and continued his research on the regulation of the sympathetic nervous system in health and in patients with neuropsychiatric and/or cardiovascular disorders.

In 1993, he accepted the chairmanship of psychiatry at the University of Kansas School of Medicine for 3 years, after which he continued on the full-time faculty until his recent partial retirement. As Professor Emeritus, he continues to publish and teach students and residents about mood disorders, and follow his long-term patients. He has more than 250 publications and has achieved life-fellowship status in the American Psychiatric Association (APA) and the American College of Neuropsychopharmacology (ACNP). He is under contract for a book regarding the misdiagnosis of schizophrenia.

His wife has a PhD in psychology and was a member of the clinical psychology faculty at the University of Kansas for 10 years. She is currently in her third year of study at Georgetown Law Center in Washington, D.C. They have three wonderful children. Dr. Lake is competitive in tennis.