

FOREWORD

The original version of this book, published in 1990, was a unique contribution to the literature on manic-depressive illness. For a long time, certainly since Bleuler and Schneider developed broad criteria for schizophrenia, manic-depressive illness had been neglected both as a clinical diagnosis and as a topic for research. The influence of psychoanalysis and Meyer's psychobiology exacerbated this neglect. Meaningful attention to the illness began to increase with the discovery of lithium as a surprisingly effective treatment for mania (this book is very appropriately dedicated to John Cade and Mogens Schou). But it was Goodwin and Jamison's work, coming at a time when manic-depressive illness remained curiously marginalized in the scientific literature, that gave the subject the treatment it deserved. Remarkably, their text was lengthy enough to allow detailed accounts and comprehensive summaries of all the available literature while at the same time being accessible in style and presentation, with an authentic continuity in the voice of its two authors.

Kay Jamison and Fred Goodwin are, of course, giants in this field, and their contribution seemed even then a remarkable one: Jamison for her profound clinical and psychological understanding, and Goodwin for his immense pharmacological and biological knowledge. To attempt a repeat of their efforts in a new edition was an enormous challenge, especially since the rapid expansion of scientific and clinical information that has occurred in the last 20 years has made the single- or dual-author textbook an increasingly endangered species. The authors' solution for this new edition of *Manic-Depressive Illness* is an innovative one that works exceedingly well: by enlisting the help of close colleagues with various specialized interests and producing an interpretive synthesis of those views through the filter of their own unparalleled expertise, they have avoided creating a compilation of chapters written by individual authors and preserved the unity and structure of the original work.

The book is divided into five parts covering the diagnosis, clinical characteristics, psychology, pathophysiology, and treatment of manic-depressive illness. It is an exceptional record of the current state of the art, and we are confident

that it will satisfy the most discriminating readers, from those who simply want to acquaint themselves with a single aspect of the illness and its many manifestations to those who wish to use this text as the basis for a comprehensive understanding of the subject.

A number of key differences between this and the first edition of the book deserve to be highlighted. The discussion of the spectrum diagnoses has been greatly expanded and informed by an increase in empirical work on the topic: diagnoses such as bipolar-II were not as commonly accepted prior to the publication of the *Diagnostic and Statistical Manual*, 4th edition (DSM-IV) in 1994, and the previously underappreciated topic of mixed states, especially depressive mixed states, is now properly included. Phenomenological studies of manic-depressive illness in children, women, and the elderly are now examined. The chapter on course of illness incorporates some major new outcome studies that began in the 1990s and have since expanded. The treatment chapters are, inevitably, greatly expanded to review the literature on benchmark therapies such as electroconvulsive therapy and lithium, as well as to accommodate the new literature on atypical antipsychotics, novel anticonvulsants, antidepressants, and structured psychosocial interventions. These chapters are also preceded by a discussion of the research methods now needed to evaluate increasingly complex clinical trials. Studies of molecular genetics, second messenger and intracellular mechanisms, and functional imaging were just starting two decades ago, but are quite central now. Even the historical assessment of how the illness was understood in previous eras is being revised on the basis of new evidence discussed in this edition.

The title of the second edition remains *Manic-Depressive Illness*, with the addition of a subtitle, *Bipolar Disorders and Recurrent Depression*. As in the first edition, the main emphasis is on the inclusive Kraepelinian concept of manic-depressive illness, a perspective too easily lost within the post-DSM-III nosology of mood disorders. This second edition underlines how Kraepelin's "central insight—that all of the recurrent major mood disorders (in today's terms) belonged together under the rubric of *manic-depressive*

illness—still provides the best model for what we know to date, as well as for understanding emerging clinical, pharmacological, and genetic data.”

We have no doubt that this second edition of *Manic-Depressive Illness*, like the first, will have an immense impact on the field; it will be a great resource for research, and it will help improve diagnosis and treatment of those who suffer from the illness. While the volume of new work it describes is encouraging, however, manic-depressive illness remains a much lower public health priority than schizophrenia and depression, not to mention many physical conditions, as evidenced by the relative paucity of research funds devoted to its study. Hence this second edition

can help us all in an important additional task: to promote awareness and investment of both time and money in this major illness by the best and brightest around the world. As Kraepelin said, “What goal could be more sacred than that of caring for a brother in distress, especially when the affliction stems from his very humanity . . . and when it cannot be halted by reason, rank or riches?”¹

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¹Emil Kraepelin, quoting Anton Mueller, in *Hundert Jahre Psychiatrie* (Berlin: Verlag von Julius Springer, 1918), p. 112.

INTRODUCTION

Melancholia is the beginning and a part of mania . . . The development of a mania is really a worsening of the disease (melancholia) rather than a change into another disease.

—Aretaeus of Cappadocia, ca. 100 AD¹

It has been 17 years since the publication of the first edition of this text; they have been the most explosively productive years in the history of medical science. In every field relevant to our understanding of manic-depressive illness—genetics, neurobiology, psychology and neuropsychology, neuroanatomy, diagnosis, and treatment—we have gained a staggering amount of knowledge. Scientists and clinicians have gone an impressive distance toward fulfilling the hopes articulated by Emil Kraepelin in the introduction to his 1899 textbook on psychiatry. Those who treat and study mental illness, he wrote, must first, from bedside observation, delineate the clinical forms of illness; they must define and predict its course, determine its causes, and discover how best to treat and then ultimately prevent insanity. Psychiatry, he argued, was a “young, still developing science,” and it 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 the 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.”² Kraepelin was right, as usual. And he was remarkably astute in his observations and predictions about the immensely complex group of disorders collectively known as manic-depressive illness.

Manic-depressive illness magnifies common human experiences to larger-than-life proportions. Among its symptoms are exaggerations of normal sadness and joy, profoundly altered thinking, irritability and rage, psychosis and violence, and deeply disrupted patterns of energy and sleep. In its diverse forms, manic-depressive illness afflicts a large number of people—the exact number depending on how the illness is defined and how accurately it is ascertained. First described thousands of years ago, found in widely diverse cultures, manic-depressive illness always has fascinated medical observers, even as it has baffled and frightened

most others. To those afflicted, it can be so painful that suicide seems the only means of escape; indeed, manic-depressive illness is the most common cause of suicide.

We view manic-depressive illness as a medical condition, an illness to be diagnosed, treated, studied, and understood within a medical context. This position is the prevailing one now, as it has been throughout history. Less universal is our diagnostic conception of manic-depressive illness, which evolved as we were writing both editions of this book. Derived from the work of Kraepelin, the “great classifier,” our conception encompasses roughly the same group of disorders as the term *manic-depressive illness* in European usage. It differs, however, from contemporary concepts of bipolar disorder. Kraepelin built his observations on the work of a small group of nineteenth-century European psychiatrists who, in their passion for ever finer distinctions, had cataloged abnormal human behavior into hundreds of classes of disorder. More than any other single individual, Kraepelin brought order and sense to this categorical profusion. He constructed a nosology based on careful description, reducing the categories of psychoses to two: manic-depressive illness and dementia praecox, later renamed *schizophrenia*.

It is to Kraepelin, born in the same year as Freud, that we owe much of our conceptualization of manic-depressive illness. It is to him that we owe our emphasis on documenting the longitudinal course of the illness and the careful delineation of mixed states and the stages of mania, as well as the observations that cycle length shortens with succeeding episodes; that poor clinical outcome is associated with rapid cycles, mixed states, and coexisting substance abuse; that genetics is central to the pathophysiology of the disease; and that manic-depressive illness is a spectrum of conditions and related temperaments.

Kraepelin’s model consolidated most of the major affective disorders into one category because of their similarity

in core symptoms; presence of a family history of illness; and, especially, the pattern of recurrence over the course of the patient's lifetime, with periods of remission and exacerbation and a comparatively benign outcome without significant deterioration. Kraepelin viewed mania as one manifestation of the illness, not as the distinguishing sign of a separate bipolar disorder as it is regarded in today's American (and increasingly worldwide) diagnostic practice.

The European and American concepts of manic-depressive illness began to diverge almost immediately after Kraepelin's ideas became widespread in the early years of the twentieth century. Europeans, adhering to a traditional medical disease model, emphasized the longitudinal course of the illness in both research and clinical work. Ever pragmatic, Americans wanted to treat the illness with the techniques at hand, which at that time were derived from the "moral treatment" movement in mental hospitals and the emerging dynamic therapies based on psychoanalytic theory. Research and clinical efforts in the United States thus slighted clinical description and genetics and turned instead to the psychological and social contexts in which the symptoms of the illness occurred.

Exploration of the linkages between clinical typology and family history led to the formulation of the bipolar–unipolar distinction, by which manic-depressive patients were grouped according to the presence or absence of a prior history of mania or hypomania. First proposed by a German, Karl Leonhard, the distinction was elaborated by other Europeans, such as Jules Angst and Carlo Perris, and by the Washington University group in St. Louis, Missouri, the neo-Kraepelinians who gave impetus to the new concern for an etiology-free, description-based diagnostic system in the United States.

The bipolar–unipolar distinction represented a logical refinement of the already well-defined Kraepelinian model, with its emphasis on recurrence and endogeneity. As useful as the distinction is in both research and clinical contexts, it proved to be problematic when applied to the much broader American conception of affective disorders. The bipolar subgroup was clearly defined, but the other component of Kraepelinian manic-depressive illness—endogenous, recurrent unipolar depression—was obscured by its confusion with other affective disorders. In American usage, *unipolar* disorder came to mean any mood disorder that was not bipolar, regardless of its severity or course. Although the third edition of the *Diagnostic and Statistical Manual* (DSM-III) clarified the situation somewhat by requiring that criteria for major affective disorder be met before the bipolar–unipolar distinction is drawn, a diagnosis of unipolar disorder was still broader than the Kraepelinian concept since it did not require a prior course of illness. Even the DSM-III/IV category of

recurrent depression is overly broad, requiring only two episodes in a lifetime.

Our own struggle to confine and limit the focus of the first edition of this text followed a course similar to the larger historical one. We started with a framework of Kraepelinian manic-depressive illness, that is, recurrent major affective illness with and without mania. Later, we focused more exclusively on bipolar disorder as a way of imposing workable boundaries on the scope of our efforts. Once thoroughly immersed in the subject, however, we became increasingly convinced that isolating bipolar disorder from other major depressive disorders and unduly emphasizing polarity over cyclicity (as do DSM-III and DSM-IV) prejudices the relationships between bipolar and unipolar illness and diminishes appreciation of the fundamental importance of recurrence. By the end, we had returned to a position close to where we began, convinced of the value of the original unified concept of manic-depressive illness, albeit with a special emphasis on the bipolar form. Scientific and clinical advances of the past two decades have only added to the strength of our belief that, as important as polarity is, cyclicity or recurrence is fundamental to understanding manic-depressive illness. This conviction is made clear in the second edition's new title: *Manic Depressive Illness: Bipolar Disorders and Recurrent Depression*. Genetic findings will have the ultimate etiologic and diagnostic say, of course, but in the interim we think a broader rather than narrower concept of the illness is warranted by the data; we also think it is heuristically most valuable.

DIMENSIONS OF THE ILLNESS

It bears repeating that the presence or absence of mania in addition to depression is but one critical aspect of manic-depressive illness. The other is cyclicity, which may ultimately prove to be as useful as polarity in differentiating forms of affective illness. The classic European focus on longitudinal studies has provided an ample database for redirecting the emphasis of pathophysiology to mechanisms of cyclicity—that is, the biology of recurrence. To conduct such research, an investigator must analyze each patient's biological functioning over time and relate it to the natural course of illness. The priority that American clinicians are beginning to assign to recurrence is a tribute to the persuasiveness of our European colleagues' meticulous longitudinal clinical observations. Kraepelin's descriptions have been enduring: again and again during our study of the contemporary literature, we returned to his original writings to rediscover modern ideas. To a remarkable degree, his work anticipated, explicitly and implicitly, contemporary theoretical developments. One example is the spectrum concept—the continuity of manic-depressive symptoms with normal fluctuations in mood, energy

patterns, and behavior—a concept whose database has greatly expanded since the publication of the first edition.

The longitudinal view provided by Kraepelin and many others both before and since persuaded us to survey the literature on recurrent unipolar illness along with that on bipolar illness, our primary focus. If we had confined ourselves to the bipolar literature, we would have excluded many potentially relevant data and insights. This recognition of the essential unity of major recurrent affective illness is evident throughout the book. When discussing lithium prophylaxis in Chapter 20, for example, we point out that similarities between recurrent unipolar and bipolar illness constitute firm ground for speculating about common neurobiological substrates.

The issue of cyclicity opens up many new areas of inquiry. Manic and depressive episodes can be predicted to revert to normal at some finite time, either spontaneously or in response to effective treatment. The opportunity to compare biological measures during the illness with the same measures in the recovered state is essential in psychobiological research, since it permits longitudinal studies that can circumvent the problem of variability among individuals. The recurrent pattern of the illness—that of recovery to normal or change to an opposite state—makes it an unsurpassed paradigm for separating state and trait variables in mental illness. The regularity of recurrence in some patients permits the clinical investigator to anticipate the onset of an episode and thus to schedule data collection at critical points. The frequent rapidity of the switch from one state to another, especially the switch into mania, allows for intensive efforts to understand the relationships between stress and biological changes in the onset of illness by looking at the temporal sequence of events—one approach to the ultimate question of causality.

The bipolar form of the illness also is an interesting study in the coexistence of opposites or, more precisely, deviations from normal in opposite directions. Even lay observers may recognize that bipolar disorder is at times accompanied by periods of euphoric mood, productivity, and high energy, but at other times by despair and profound lassitude. Clinicians see a more subtle manifestation of this Janus-like illness in lithium's effects in preventing its apparently opposite expressions. Lithium's dual action, perhaps diminishing some of the silver lining along with the cloud, challenges the clinician's psychotherapeutic skills in managing the issue of treatment acceptance, especially medication adherence.

THE SCIENCE OF THE ILLNESS

Over the past six decades, research has yielded effective treatments that have radically altered clinical work in manic-

depressive illness. Principally, it was the discovery of lithium that galvanized the treatment community, instilling new hope among clinicians, their patients, and the public. Also important, the emergence of lithium, the antidepressants, the antipsychotics, and the anticonvulsants gave birth to whole new fields of scientific investigation. Studies of the illness have dominated biological psychiatry, which itself has begun to lead the profession. Manic-depressive illness has been an increasingly important focus of work in other disciplines as well. Insights gained from the study of an illness that is biological in origin yet psychological in expression have underscored the urgency and inevitability of paradigms of mental illness that give balanced attention to biology, psychology, and the environment. Methodologies developed expressly for studies of manic-depressive illness have been incorporated as standard tools of clinical investigation in other areas of biomedical and behavioral research in psychopathology. Because symptoms of the illness shade over into normal human experience, it provides a model for the study of normal states as well.

Nearly 60 years have passed since the initial clinical observation of lithium's effectiveness in treating manic-depressive illness and 50 years since early clinical trials—most important, those completed by Mogens Schou, Poul Christian Baastrup, G. P. Hartigan, and Alec Coppen—were conducted so that lithium could be approved for general clinical use throughout the world. More recently, research on manic-depressive illness has played a central role in efforts to apply new and emerging techniques, such as molecular genetics, to the study of psychiatric conditions. The application of these techniques depends on the use of sensitive and reliable epidemiological and diagnostic case-finding methodologies to identify family pedigrees with a high incidence of the illness. Preliminary results suggest that several genotypes underlie different forms of manic-depressive illness. It is also possible that, as with the multiple genetic forms of diabetes, several genotypes are expressed in clinical phenomena commonly associated with the illness.

Research on manic-depressive illness also has contributed new, empirically based theories about the pathophysiology of psychiatric disorders, including the influence of the physical environment—light and temperature in particular—on their course and expression. Of equal interest are efforts to describe mechanisms by which the psychosocial environment interacts with the individual's biology to produce symptoms. One of the most promising lines of inquiry grew out of longitudinal observations: external stress appeared to activate or precipitate some initial episodes of illness, but eventually the illness seemed to take on a life of its own, since later episodes began without obvious precipitating stress.

OVERVIEW OF THIS TEXT

In a text of this size and scope, a certain amount of redundancy is inevitable. Issues pertaining to the dimensional aspects of manic-depressive illness, such as severity, polarity, and cyclicity, are introduced in the first two chapters and then discussed further throughout the book. Where an issue could logically be discussed in more than one chapter, our decisions on placement occasionally were somewhat arbitrary.

Clinical Description and Diagnosis

The text is divided into five parts, the first of which focuses on clinical phenomenology and diagnosis. Chapter 1 traces the evolution of the concept of the illness, which has remained remarkably consistent since the time of Hippocrates, and describes the spectrum of the illness in detail. We highlight the fact that diagnostic and subgroup boundaries represent somewhat arbitrary distinctions, with individual patients often falling in a gray area. Also emphasized is the spectrum of manic states, which, unlike the well-described depressive spectrum, is often overlooked. We stress that while the spectrum concept has validity and utility, there are risks in subclassifying the bipolar forms of the illness to such an extent that they are confusing, on occasion to the detriment of both clinical and research purposes.

We begin the chapter on clinical description (Chapter 2) with classic descriptions of the illness by early clinical observers who worked in the era before effective medications altered the natural expression of the illness; these are followed by patients' descriptions of their experiences of the illness. We also review data-based studies of mania, mixed states, and bipolar depression, with a particular emphasis on new research findings pertaining to mixed states and bipolar depression.

Chapter 3 guides the clinician through the problems of diagnosis. Most important is the differential diagnosis of bipolar disorder and unipolar depression, schizophrenia, organic brain disorders, substance abuse, and borderline personality disorders. The shortcomings of our current diagnostic systems, including their emphasis on polarity rather than cyclicity, the absence of a category for highly recurrent depression, the underrecognition of bipolar-II disorder, and the inadequacy of the diagnostic criteria for mixed states, are discussed in detail.

Clinical Studies

The second part covers various clinical aspects of manic-depressive illness. Appropriately, we begin in Chapter 4 with a discussion of course and outcome, fundamental characteristics of the illness that provide the basis for differentiating it from schizophrenia. In addition to its obvi-

ous importance for clinicians who are assessing prognosis and planning treatment, natural course is important to scientists since it offers many useful clues as to pathological processes. We consider historical observations on course and outcome together with data gathered from the large-scale studies conducted since the first edition of this text.

Chapter 5, on epidemiology, argues that manic-depressive illness, especially its bipolar form, is more common than is usually thought. Among the most important recent observations are the early age at onset documented in careful community surveys; determinations of the rates of bipolar-II and bipolar spectrum disorders; and the results of several important international studies, including those of death and disability, that document the high toll exacted by manic-depressive illness worldwide.

The next three chapters highlight special clinical aspects of manic-depressive illness. Chapter 6 addresses aspects of the illness in children and adolescents. Because there are essentially no data on highly recurrent depression in these populations, the chapter focuses exclusively on bipolar disorder, which all too often goes unrecognized in youth. Although relatively rare in prepubertal children, classic bipolar disorder often begins in adolescence; indeed, well over one-third of all cases begin before the age of 20. Were the kindling hypothesis substantiated, early recognition and immediate, vigorous treatment would be expected to reduce subsequent pathology. Early treatment would reduce the psychological scarring caused by untreated illness, as well as the high mortality rate from suicide, which is disproportionately likely to occur early in the course of bipolar disorder. All too typical is the individual, initially treated in his or her mid- to late twenties, who has already lived with the disorder for more than a decade, a period critical for life's major beginnings in relationships, education, and career. The research findings on childhood bipolar disorder published since the first edition of this text have been prodigious, but continue to be marked by confusion and controversy. Even so, many more young children with severe mood lability and behavioral dyscontrol are now being identified and treated with mood stabilizers, antipsychotics, and antidepressants.

A focus on the young highlights the frequent coexistence of drug and alcohol abuse among young manic-depressive patients. Growing recognition of the frequent coexistence of the illness with substance abuse prompted us to devote an entire chapter (Chapter 7) to describing these problems and another (Chapter 24) to reviewing their treatment. In these two chapters, we also discuss other important comorbid conditions, such as anxiety disorders, eating disorders, cardiovascular disease, thyroid dysfunction, overweight and obesity, and migraine, as well as their treatment. The presence of a depressive or anxiety disorder can double the

chances of subsequent substance abuse. Conversely, illicit drugs and alcohol can adversely affect the course and treatment of manic-depressive illness by altering the same brain mechanisms that regulate mood, including the potential for kindling.

As with substance abuse and other comorbid conditions, the importance of suicide in manic-depressive illness is reflected in our devoting two chapters to the subject—one describing rates, putative causes, and clinical correlates (Chapter 8), and another detailing preventive measures (Chapter 25). The high mortality associated with this illness cannot be overemphasized. Fortunately, considerable progress has been made in understanding the causes of suicide in manic-depressive patients, in addition to the accumulating evidence that lithium exerts a strong protective influence.

The reader may note that there is no chapter on gender differences in manic-depressive illness, reflecting the relative scarcity of literature on this subject. However, reports of male–female differences are noted throughout the book; here we summarize those for which there is general agreement: the first episode is more likely to be mania in males and depression in females, while women have more mixed episodes (consistent with a predominance of depression) and are overrepresented among rapid cyclers; consistent with the general population, men are more likely to have comorbid substance abuse and histories of pathological gambling and conduct disorder, while women are more likely to have comorbid eating disorders as well as changes in appetite and weight during depressive episodes; and, in contrast to the general population, the completed suicide rate for bipolar women is higher than that for bipolar men. It may be that the risk of suicide associated with manic-depressive illness is so powerful that it overrides the usual male–female patterns. Bipolar women generally are more likely than their male counterparts to seek treatment, but there is as yet no consensus regarding gender differences in response to mood stabilizers.³

Psychological Studies

Manic-depressive illness has been a rich source of theory and data for investigators interested in psychological mechanisms. The third part of the book considers these developments. Manic-depressive illness has contributed to the general study of psychology by serving as a paradigm for explorations of state and trait differences. It also has been a model for the general psychological assessment of cognition and for the more specific differentiation of cognition in manic and depressive states from that in schizophrenia. We begin with a survey of what is known about neuropsychological deficits in mood disorders, including recent research documenting significant impairments in intellec-

tual functioning, attention, learning and memory, and executive functioning (Chapter 9).

The psychological manifestations of manic-depressive illness, observable in personality and behavior as well as cognitive patterns, can result in profound discord in family life and other social relationships; this is especially true for those with the bipolar form of the illness. In Chapter 10 we review studies of personality functioning in manic and depressed states and how it compares with that in normal states in patients themselves and in the general population. We also discuss personality disorders that commonly coexist with manic-depressive illness, as well as the effects of medication on personality. The chapter then addresses interpersonal aspects of the illness, with emphasis on the bipolar subgroup.

Chapter 11 is devoted to the wide array of methods that now exists for assessing manic, mixed, and depressive states; these assessment measures add the perspective of formal psychological evaluation to the discussion of differential diagnosis in Chapter 3.

Widespread interest in creativity, the subject of Chapter 12, has lent visibility to this aspect of the study of manic-depressive illness. The age-old link between “madness” and creativity has been studied with increasingly sophisticated methods in recent years. Research has demonstrated that it is not schizophrenia but manic-depressive illness, especially its bipolar forms, that is more often associated with creative accomplishment. Among the most interesting developments in this field is the hypothesis that the genetic predisposition for manic-depressive illness also confers a creative edge on affected individuals and their close relatives. Explorations of the characteristics that help make some individuals more creative than others should have implications for the general population. Among the positive features of the bipolar form of the illness being examined in relation to creativity are the heightened energy level and speed of cognition of hypomania, linked to a global, inclusive associative process, and certain temperamental factors; positive (and painful) experiences derived from having affective illness are salient as well. In addition to raising important psychological, social, and ethical issues, these and related positive features of the bipolar form of the illness can play a key role in reducing the burden of stigma borne by patients. Understanding these features is, of course, necessary in dealing with one of the most sensitive and difficult issues in treatment—medication adherence.

Pathophysiology

The size of the fourth part of the book, the largest, testifies to the wealth of biological knowledge that has accrued through research on manic-depressive illness. The illness has come to represent an extraordinarily rich

source of information about the interrelationships between behavioral and biological phenomena; certainly it has stimulated fascinating and productive theories about brain–behavior relationships.

We begin with a survey of the salient literature on genetics (Chapter 13). In this chapter we review genetic epidemiology, results of studies using the linkage method, alternative phenotypic definition, association methods, gene expression and pathogenesis, pharmacogenetics, and genetic counseling. We then look at the future of the field, including new technologies and what we can expect to learn from each.

Chapter 14, on neurobiology, provides the conceptual base necessary for an appreciation of the biochemical and pharmacological studies whose review follows. Much of modern neurobiology and neuropharmacology has been driven by efforts to understand the effects of mood-altering drugs. Indeed, attempts to understand why certain drugs affect mood have inspired major hypotheses about the neurobiology of behavior. The chapter also describes animal models designed to simulate affective illness and reviews the formidable literature on the major neurotransmitter, neuroendocrine, and neuropeptide systems involved in manic-depressive illness, along with extensive new findings related to postsynaptic signal transduction networks and gene expression.

With the emergence of highly sophisticated brain-imaging technologies, it has become important to review the anatomical correlates of mania and depression critically, if only to help guide the application of imaging approaches; we do so in Chapter 15. Functional neuroimaging work has advanced rapidly in recent years. We review research findings on cerebral activity in normal, depressed, and manic states, as well as summarize what is known about baseline cerebral activity markers of treatment response.

Chapter 16 covers sleep and biological rhythms, reflecting our judgment that these two fields, which developed independently of one another, have found a natural point of convergence in the pathophysiology of manic-depressive illness. It is increasingly clear that sleep physiology is important to circadian physiology and that sleep disturbances seen in affective illness reflect disturbances in circadian rhythms. This area of study has, in our estimation, yielded some of the most interesting developments in understanding manic-depressive illness. The identification of seasonal affective disorder, for example, represents a systematic, quantitative rediscovery of ancient observations of seasonality in mood disorders and suicide. The speed with which the initial observation of seasonal mood disorder was incorporated into the DSM nosology testifies to the responsiveness of our current diagnostic system. Research

on biological rhythms has spawned the development of three novel physiological but nonpharmacological treatments for mood disorders—sleep deprivation, phase advance, and high-intensity light—that are described in Chapter 19 on the treatment of acute depression, especially in bipolar patients. At a more general level, the contemporary focus on biological rhythms has given rise to environmental psychiatry, and thus the discussion of the subject in Chapter 16 emphasizes the subtle environmental influences on manic-depressive illness and offers relevant clinical suggestions.

Treatment

The final part of the book covers all aspects of the treatment of manic-depressive illness. It is traditional in its organization, separating acute from prophylactic treatment and medical from psychological treatment. Despite this division, we wish to emphasize the profound importance of integrating medical and psychological approaches. Although the structure of this part of the book is traditional, the organization of each chapter is not. Each begins with practical recommendations for clinical management and then reviews the treatment literature, highlighting areas inadequately explored in existing reviews, including the efficacy of lithium in treating depression as well as mania and the quality of the prophylactic response. We discuss treatment controversies such as antidepressant-induced mania, mixed states, and rapid cycling; the use of adjunctive treatments for breakthrough episodes during prophylactic treatment with mood stabilizers; the important but often overlooked distinction between prevention of relapse and prevention of recurrence (new episodes); the relative efficacy and side-effect profiles of the mood stabilizers and the antipsychotics; and the use of alternative or adjunctive approaches for patients who do not respond to initial treatment. It has been of great, often life-saving clinical importance to now have anticonvulsant and antipsychotic medications that provide an alternative for those patients who do not respond to or will not take lithium. We make clear our belief that lithium remains the gold standard of treatment, however, despite an increasing tendency to use less-proven medications.

The two chapters on adherence and psychotherapy (Chapters 21 and 22, respectively) should be read together. Our purpose here is not to provide a general psychotherapy primer but to focus on issues of special importance to the psychotherapy of manic-depressive illness, especially the bipolar form. These issues include fears of recurrence, the psychological scars left by the illness, and concerns about genetic vulnerability. The central issue in the psychological management of bipolar patients is medication adherence. Recent studies suggest that outcomes of medical treatment

are substantially enhanced by adjunctive psychotherapy, no doubt reflecting the contribution of improved adherence. In our discussion of adherence, we return to the core issue of the paradox of drugs that are often very effective, yet can have an impact on some aspects of the illness that may be valued by the patient. Given clinicians' all-too-common tendency to be unaware of subtle adherence problems, we believe this issue warrants a separate chapter.

Chapter 23 is devoted to the special issues that arise in treating children and adolescents with bipolar illness. Chapter 24 deals with the treatment of comorbid conditions such as anxiety disorders, substance abuse, and medical conditions that frequently accompany manic-depressive illness.

The fact that manic-depressive illness is often lethal bears repeated mention. We have underscored this fact by summarizing what is known about rates and clinical correlates of suicide in Chapter 8; in Chapter 25, we emphasize clinical methods we believe to be most useful in reducing the risk of suicide among acutely ill patients. We emphasize again the fundamental premise that the best approach to the prevention of suicide is the effective and aggressive treatment of the underlying illness.

THE DEVELOPMENT OF THIS BOOK

The overwhelming size of the literature on manic-depressive illness makes it all but impossible for clinicians and researchers to keep pace with the latest findings and to see the broader clinical, human, and scientific picture. The National Library of Medicine's Medline file on bipolar disorder alone has grown from 16 citations in 1950; to approximately 600 citations in 1990, the year the first edition of this book was published; to more than 1,100 citations in 2006. We were aware of the problem before we began writing the first edition of this book. As we struggled through the scientific literature that had grown exponentially since 1990, we once again were concerned that the very magnitude of the new, scattered evidence threatens the ability to form a coherent overall view of the illness. In recent decades, research on manic-depressive illness has contributed to an extraordinary expansion of the knowledge base in increasingly specialized fields. The productivity of the research enterprise has generated diverse points of focus, which are often appreciated only by individuals in a given subfield. An unfortunate outgrowth of such specialization is that the wealth of new information typically has been made available only in the form of individual research reports or reviews of selected areas; at best, these occasionally are published in edited volumes.

Working during this period of extraordinary productivity and ferment in the study of manic-depressive illness, we saw the need for a comprehensive book that would at-

tempt to impose order on a rich but vast and disparate literature. We were convinced that this goal could be accomplished only by seeing the subject through from beginning to end—in other words, by writing a book rather than editing a collection. We were able to accomplish this by jointly authoring the first edition. As indicated in our acknowledgments and in the list of collaborators for this edition, however, we found it imperative to seek the help of colleagues; we could not have completed this book without them. Our intent was to go beyond a review of the literature—to assess the nodal points in knowledge of the illness, to integrate them in a way that would enhance the quality of clinical care available, and to suggest opportunities for future research. In the early twenty-first century, manic-depressive illness continues to present new challenges and questions that extend from the realm of basic neurobiological science to those of clinical practice and social ethics. The skill the field brings to identifying these questions will determine the strategies formulated to answer them, and in turn will bear directly on future advances in treatment and prevention.

Throughout the writing of this edition of the book, as during the first, we have been impressed time and again by the excellent science, imaginative clinical research, and profoundly important treatment advances generated by our colleagues. We are delighted to acknowledge our debt to them, both for their science and for the lives they have saved. As before, our debt to our students and patients is immeasurable.

NOTES

1. Cited in Marneros, A., and Angst, J. *Bipolar disorders: Roots and evolution* (p. 6). Translated from the Greek by A. Marneros. In Marneros, A., and Angst, J. (2000). *Bipolar Disorders: 100 Years After Manic-Depressive Insanity*. Dordrecht, The Netherlands: Kluwer.
2. Kraepelin, E. (1990). *Psychiatry: A Textbook for Students and Physicians*, Sixth Edition. Translated by Helga Metoui. Canton, MA: Science History Publications, p. 8. Originally published as *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte*. Leipzig: Johann Ambrosius Barth, 1899.
3. For reviews of gender differences in bipolar disorder, see Taylor and Abrams, 1981; Leibenluft, 1996; Blehar et al., 1998; Robb et al., 1998; Hendrick et al., 2000; and Kawa et al., 2005.

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