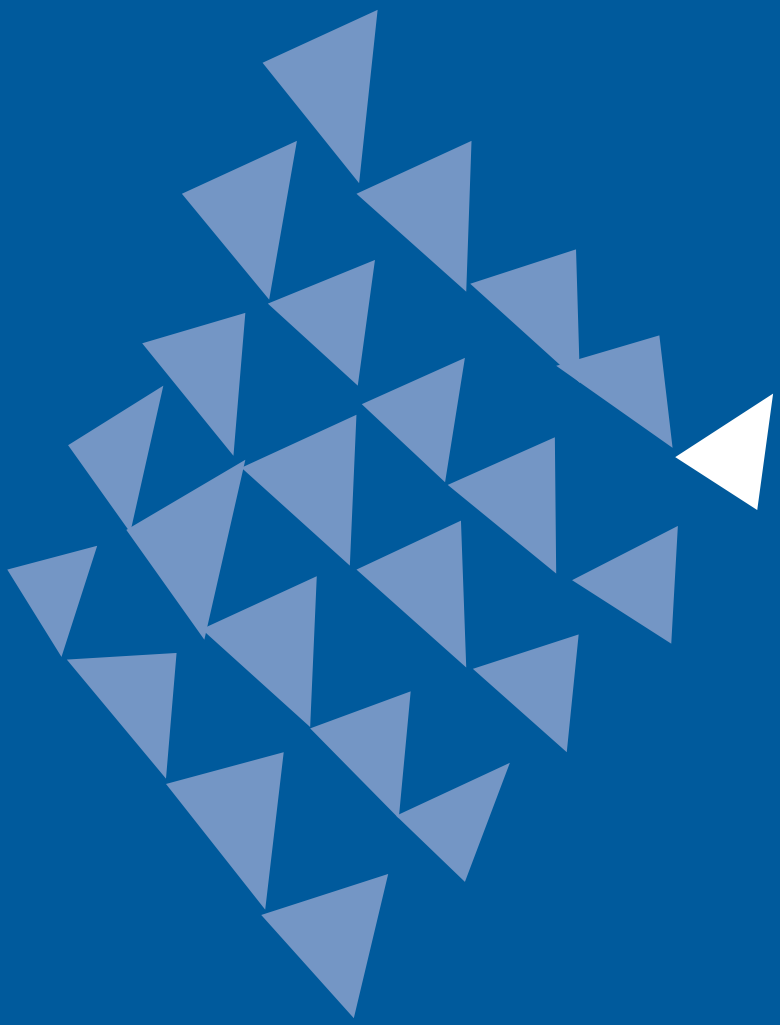

Breaking Ground, Breaking Through:
The Strategic Plan
for Mood Disorders Research

of the National Institute of Mental Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • NATIONAL INSTITUTES OF HEALTH

NIMH
National Institute of Mental Health

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Preface

Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research marks the advent of a new era in the long quest to understand, treat, and prevent mental disorders. Prepared by staff of the National Institute of Mental Health (NIMH) working in close collaboration with members of the National Advisory Mental Health Council, scientists, health care providers, advocates, and persons who themselves live with mood disorders, the plan builds on the remarkable progress of the past half century. Thanks to research, an array of treatments exist today that are highly effective in the acute treatment and long-term management of major depression and bipolar disorder—illnesses that we now know tend to be recurrent and cyclical for a majority of persons who have the conditions. Research has demonstrated a strong genetic component to mood disorders, particularly bipolar disorder, and is beginning to elucidate the nature of brain-gene-environmental interactions that often appear to trigger a latent vulnerability or susceptibility to mood disorders. We now recognize the frequency with which depression tends to co-occur with diverse general medical illnesses—including, for example, cancer, coronary heart disease, diabetes, many neurological illnesses, and HIV/AIDS—and the importance of appropriate treatment of depression to overall health outcomes.

For all our knowledge and clinical capabilities, it nonetheless is humbling to consider how much we do not know about the basic neurobiological mechanisms involved in the regulation and dysregulation of mood, the ways in which yet unknown genes are triggered by the environment or behavior, or how our treatments exert their positive effects—or too frequently fail to achieve lasting benefits.

What we do not yet know figures centrally in a public health reality that, only 6 years ago, was surprising to many policymakers and citizens: the finding by the World Health Organization, in its landmark Global Burden of Disease study, that major depression and bipolar disorder are, respectively, the first- and sixth-ranked causes of years lived with disability for people in the developed world. To the extent that mood disorders hobble workers' productivity while demanding massive expenditure of societal resources, these disorders are not only a clinical and public health challenge but also a threat to the economic well-being of the global community.

Breaking Ground, Breaking Through reflects the best collective thinking of some 200 experts about how we can fill in the gaps in our knowledge and reduce the individual,

family, community, and worldwide burden of these illnesses. In issuing a research strategic plan, NIMH remains committed to the hallmark of the U.S. biomedical research enterprise, that is, the support of independent investigator-initiated research. The Institute also recognizes the need to take stock of where we stand today and help establish a road map for future research. Accordingly, this plan has identified scientific needs and opportunities in ten domains, extending from basic molecular and neurobiological research to studies of service delivery systems and barriers to care. Given its breadth, the plan clearly envisions a scientific assault that will benefit from the participation of diverse disciplines and approaches: molecular genetics and basic behavioral science; cognitive and affective neuroscience and epidemiology; developmental psychology and translational research; clinical investigation, including novel approaches to clinical trials; and health services/systems research.

It is our privilege to express, on behalf of NIMH, deep appreciation to all those who participated in the development of this strategic plan. We would especially like to thank Dr. Dennis Charney, Scientific Director, and Dr. Karen Babich, Project Director of this strategic plan. Without their expert guidance, this complex project would not have succeeded. We fully intend that this plan will serve the Nation and the world as a tool not only to break new scientific ground, but also, by assigning highly visible priority to scientific excellence in the conquest of mental disorders, to break through the hurtful and damaging stigma that should never again be unjustly borne by those who live with mood disorders.

Thomas R. Insel, M.D
Director

Richard K. Nakamura, Ph.D.
Deputy Director

Executive Summary

Mood disorders, the foci of this strategic plan for research, are serious medical illnesses that affect more than 20 million Americans of every race and ethnic group and at every stage of life, from childhood through old age. Mood disorders are "brain disorders," meaning they are mediated through the brain, yet they disrupt every facet of a person's life: emotions, thought processes, behavior, and physical health. Left untreated, or inappropriately treated, mood disorders are potentially fatal; nearly one in six persons with severe, untreated depression will die by suicide. Short of this tragic outcome, mood disorders are immensely disabling. A landmark study sponsored by the World Health Organization and the World Bank reports that in the United States and other nations with developed economies, major depression is the *leading* cause of disability. The same study projects that by the year 2020, depression will be the second leading cause of disability worldwide. The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. Clearly, improved understanding, recognition, treatment, and prevention of mood disorders are critical scientific and public health priorities.

The Nature and Impact of Mood Disorders

Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research of the National Institute of Mental Health addresses two types of mood disorder—major depression and bipolar disorder, also known as manic-depressive illness. The term depression, of course, refers not only to an illness, but also to moods and behaviors that occur in the normal course of life. Unlike the normal shifts in mood that most people experience, however, the symptoms of *depression* are more extreme and frequently incapacitating. These symptoms include a persistent sad mood; loss of interest or pleasure in activities that were once enjoyed; significant change in appetite or body weight; difficulty sleeping or oversleeping; physical slowing or agitation; loss of energy; feelings of worthlessness or inappropriate guilt; difficulty thinking or concentrating; and recurrent thoughts of death or suicide. A diagnosis of depression is made if an individual has five or more of these symptoms every day during a 2-week period. In *bipolar disorder*, episodes of depression alternate with episodes of mania, a condition marked by periods of abnormally and persistently elevated mood or irritability accompanied by at least three of the following

symptoms: overly inflated self-esteem; decreased need for sleep; increased talkativeness; racing thoughts; distractibility; increased goal-directed activity or physical agitation; and excessive involvement with pleasurable activities that have a high potential for risky consequences.

By far the more common of the two, major depression affects approximately 19 million American adults at any given time and an estimated 6 percent of children ages 9 to 17. For reasons that are not clearly understood, depression occurs twice as often among women as men. Five to 14 percent of women will have an episode of depression at some point in their lives in contrast to 2 to 4 percent of men. Bipolar disorder affects some 2.3 million American adults, or approximately 1 percent of the population, and distributes roughly equally between men and women. Although firm data are lacking on the extent to which bipolar disorder affects children and adolescents, clinical experience suggests that some proportion of children and adolescents who have major depression eventually will be found to have bipolar disorder; this likelihood increases if the depressed young person has a family member with bipolar disorder.

Today, the intense and disabling symptoms of depression and bipolar disorder often can be relieved through treatment involving combinations of medications and psychotherapy. Yet even with appropriate treatment, both depression and bipolar disorder tend to be episodic and recurrent; that is, after a person has been depressed once and recovers, he or she is likely to have in the future one or more episodes of depression, and/or mania in the case of bipolar disorder. Single episodes are the exception. This pattern of illness implies high, and sustained, personal, family, and societal costs—costs that can and will be reduced substantially through an accelerated program of research and discovery.

The Scope of the Problem

As described below, and in greater detail in the Introduction, the strategic planning process began in late 2000 when NIMH established nine workgroups, each with expertise in an area of research relevant to some facet of mood disorders, to develop comprehensive reviews of the state-of-the-science in a given area. That such a large number of workgroups were judged necessary to assess research needs and opportunities associated with mood disorders should not be surprising. Mood disorders occur across the life span, affecting children, adults, and the elderly. They affect people of all races and ethnicities, across cultures. Although the brain is the organ most directly implicated in mood disorders, these illnesses often are described as “systemic illnesses,” meaning that they affect the body in its entirety; that is, mood disorders can affect—and be affected by—one’s general health, behavior, and environment. While responsibility for treating mood disorders commonly is assigned to psychiatrists, psychologists, psychiatric nurses, social workers, and counselors, in fact, the preponderance of treatment of mood disorders occurs

in the general health care sector. Accordingly, the reader of this strategic plan who pores through each of its major sections will find all of the following topics addressed.

- **Brain Science**—Neuroscientists are gaining the ability to determine just how brain cells and circuits function to enable cognition, emotion, and behavior. Advances in brain imaging technologies are enhancing the practicality of approaches that will image brain function in real time and over periods of development. The challenge is to apply this fundamental knowledge, along with information about how the brain changes as it develops and ages, to reveal the exact brain regions that function incorrectly in depression and bipolar disorder.

- **Genetics**—The completion of the draft sequence of the human genome provides enormous impetus to ongoing efforts to identify the genes responsible for vulnerability and resilience to depression and bipolar disorder. When combined with growing knowledge of how these disorders are inherited within families and with information about the environmental triggers needed to activate vulnerability, the genetics revolution permits us to anticipate one day using the word "cure" in the context of the mood disorders.

- **Behavior**—The explosion in new knowledge about genetics, structure, and function of the brain has challenged behavioral scientists to radically expand the traditional boundaries and methods of their discipline to determine how specific behaviors are directed and modified by genes, how behavior can modify the brain, how behavioral therapies for mental disorders can be strengthened, and how behavioral strategies for preventing the onset or recurrence of depression and bipolar disorder can be refined.

- **Treatment**—With greater understanding about the brain mechanisms involved in memory, decision making, and emotional responses to traumatic events, researchers are revisiting and redesigning many of the treatments currently in use for mental disorders. Translation of basic science findings into innovative behavioral and pharmacological treatments that can either correct or compensate for brain dysfunctions will yield more effective treatments.

- **Prevention**—Though genetic factors may play some role in predisposing individuals to developing depression, it is clear that the triggers for depression are largely environmental. As a result, studies aimed at identifying and understanding the environmental risk factors for depression should provide insights for developing novel behavioral, educational, and pharmacological methods for preventing depressive symptoms from occurring or reducing their duration and severity when they do recur.

- **Service Systems and the Delivery of Treatment**—Understanding and correcting disparities in access to and quality of mental health treatment not only will benefit individuals who have mood disorders, but also will help to raise the overall quality and effectiveness of health care services.

In addition, during the development of the strategic plan, the need for research focused on the particular needs of special segments of the population—women, children, elderly persons, members of racial and ethnic minority groups, and persons who simultaneously have a mood disorder and another general medical illness—became glaringly apparent. Accordingly, these issues come up repeatedly in both the scientific reviews and the listing of research priorities and objectives, and warrant special mention.

- **Women and Depression**—There is evidence that women are at least twice as likely as men to experience a depressive episode within a lifetime, a fact that would not only suggest the need for the development of gender-specific therapies and prevention strategies, but also may provide important biological insights into the causes of depression. For example, women are more likely than men to experience the symptoms of depression on a seasonal basis. They are also more likely than men to have a prior history of anxiety disorder and to experience physical symptoms along with depressive symptoms. Childhood-onset depression appears to confer similar risk of subsequent depression for girls and boys. However, earlier onset in boys is associated with comorbidity and suggests a "purer" form of depressive disorder. Depressed girls report higher levels of mood disturbance, while boys report more irritability. Since gender differences in rates of depression emerge in early adolescence, there are obvious questions about the role of biological factors, specifically sex hormones, as well as social and cultural influences in the development of depression. For women, the age of onset of depression also often coincides with the age period of childbearing, and there is evidence that pregnancy and the postpartum state are associated with heightened risk for bipolar depression.

- **Children**—One of the most fundamental advances in mood disorders research has been to demonstrate that depression and bipolar disorder are as much illnesses of childhood and adolescence as they are of adulthood. Now, researchers need to better understand the childhood precursor forms of depression and bipolar disorder and how and when to intervene preventively in children who are most at risk of developing these illnesses. Designing the most effective mental health care services for children and adolescents is also a critical task for the future.

- **Elderly Persons**—Although depression is strikingly prevalent among older people, its assessment and diagnosis can be especially challenging. The clinical presentation of depression in older adults may differ from that seen in young adulthood and midlife. For example, many

older people tend to report to their health care provider somatic complaints rather than psychological problems, and often do not present with the full range of symptoms that constitute the threshold for diagnosis of clinical depression. In addition to the complications associated with social isolation and loss, detection of depression in late life can be obscured by other co-occurring general medical disorders.

- **Comorbidity**—The occurrence of depression and other mood disorders in the context of other illnesses is particularly common among elderly people, yet it is increasingly clear that depression may play a role in both the cause and progression of many other ailments across the life span. Research has shown that treatment of co-occurring, or comorbid, depression can often improve health outcomes for many people with a wide variety of diseases. Not only may relief from depression help a person adhere to complex treatment plans and improve his or her quality of life, but also researchers are tracing the biological aspects of depression at the physiological and cellular levels that could affect these other illnesses.

- **Race, Ethnicity, and Culture**—America draws its strength from its cultural diversity, but the full potential of our diverse, multicultural society cannot be realized until all Americans gain access to quality health care that meets their needs, particularly when those needs include treatment for depression or bipolar disorder. Unfortunately, there exists a striking disparity in the quality of mental health services and the underlying knowledge base as it pertains to Americans who are members of a racial or ethnic minority group. The U.S. Surgeon General recently found that racial and ethnic minority groups bear a greater burden from unmet mental health needs and thus suffer a greater loss to their overall health and productivity (http://www.mentalhealth.org/cre/default.asp). Addressing this disparity will take equal action in two areas: training a scientific workforce for research on mood disorders that reflects the full racial and ethnic diversity of the Nation, and requiring researchers to conduct investigations using study groups that reflect the full racial and ethnic diversity of the Nation. Both steps are vital because culture influences so many aspects of mood disorders, including how individuals from a given culture communicate and manifest their symptoms, their style of coping, their family and community supports, and their willingness to seek treatment. Likewise, the cultures of researchers, clinicians, and the service system influence diagnosis, treatment, and service delivery. Cultural and social influences are not the only determinants of mood disorders and patterns of service use, but they do play critically important roles.

Scientific Opportunities for Research on Mood Disorders

Advances in the capability to investigate brain function at multiple levels have been among the signal achievements of health science over the past decade. NIMH collaborates

with multiple, diverse scientific disciplines to utilize the tools of molecular and cellular biology, genetics, epidemiology, and cognitive and behavioral science to gain a more thorough and comprehensive understanding of the factors that influence brain function and behavior in normal as well as abnormal states, including mental illness. Evidence from neuroscience, genetics, and clinical investigation has demonstrated unequivocally that the brain is the primary organ affected in depression and bipolar disorder. Modern brain imaging technologies are revealing that in both disorders, neural circuits responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly and that critical neurotransmitters—chemicals used by nerve cells to communicate—are out of balance. Genetics research indicates that vulnerability to depression and bipolar disorder results from the interaction of multiple genes and environmental factors. Ongoing research examining brain chemistry and the mechanisms of action of antidepressant medications and mood stabilizers, as well as psychosocial interventions, continues to inform efforts to develop new and better treatments. As this work progresses, NIMH is placing greater emphasis on mental health services and service systems research with the aim of improving the field's capability to deliver existing evidence-based treatments with a high degree of fidelity to standards developed and evaluated in research settings.

Looking to the future, scientists agree that advances in multiple arenas will continue to frame, at an increasingly rapid pace, remarkable opportunities for mood disorders research.

Developing the NIMH Strategic Plan for Mood Disorders Research

To ensure an investment of resources that will take maximal advantage of proliferating opportunities, NIMH last year convened nine workgroups to examine the status of key areas of research relevant to mood disorders. Workgroup foci included genetics, neural and behavioral substrates of mood regulation, preclinical models, pharmacologic and somatic treatment development, psychosocial intervention development, development and natural history, aging and medical comorbidity, clinical trials and translation, and overcoming barriers to care/reducing public burden. Leading researchers in the field, a broad cross section of consumer and advocacy group members, NIMH staff, and members of the National Advisory Mental Health Council (NAMHC) were invited to participate in the workgroups. Nearly 200 people were engaged in an iterative process that resulted in a series of in-depth reviews to be used by NIMH staff to help guide the Institute's research on mood disorders (Appendices A-C).

Drawing on the workgroup reports and other sources, NIMH professional staff aggregated the assessments of current knowledge and conclusions regarding scientific needs and opportunities into three major sections, described and summarized below.

In a final phase of the strategic planning process, NIMH staff used the consolidated scientific reviews that were endorsed by the NAMHC as the foundation, along with other resources, for developing specific research priorities and objectives for the Institute. In its entirety, the NIMH Strategic Plan for Mood Disorders Research lists 52 research objectives buttressed by specific implementation steps; these objectives form the core of the plan. This executive summary of the strategic plan presents selected short- and long-term research priorities that represent the scope of the plan.

Basic and Clinical Neuroscience: Foundation for Discovery

Advances in basic neuroscience over the past two decades have provided a rich and increasingly mature knowledge base for understanding pathophysiology and developing rational therapies—pharmacologic and psychosocial—for treating brain diseases. Progress in the Human Genome Project actually has been faster than predicted and is expected to contribute exponentially to the identification of genes that produce vulnerability and resilience to mood disorders, information that will lend itself in rapid order to greater diagnostic precision and to the identification of novel drug targets.

Neuroimaging technologies such as positron emission tomography, or PET scanning, and magnetic resonance imaging (MRI) have emerged as invaluable tools for research that seek to identify specific brain regions that are involved in and affected by mood disorders. The ability to observe regional blood flow in the brain and patterns of brain metabolism during specific tasks and events is enabling investigators to recognize alterations in particular brain regions that are associated with illness. Some of these persist regardless of a subject's immediate mood state; others can be seen to reverse when a subject is responding positively to antidepressant medications or other forms of treatment. Piecing together such glimpses of brain activity with what is known of the neural circuits and neurochemical pathways associated with specific brain structures and regions implicated in mood disorders affords researchers a more comprehensive understanding of how existing medications exert therapeutic effect and, in turn, to consider novel targets for treatment development studies.

As neuroscientists delineate with both precision and cross-laboratory consistency the brain regions involved in modulating mood, they are achieving a much finer appreciation of the role of various neurotransmitter systems, including those using glutamate, gamma-aminobutyric acid, serotonin, norepinephrine, and dopamine, that are involved in depression and mania. Recent work has identified other neurochemical systems that also may be involved in mood disorders, including cell membrane-bound signal transduction elements and intracellular signaling systems that modulate gene transcription and protein synthesis. Such insights are providing important clues that point to neurochemical targets for novel selective pharmacologic manipulation. By encouraging investigators to think differently about drug targets, this concentration of new knowledge will contribute progressively to new therapeutics.

Approaching the question of mood from another perspective, research conducted over recent decades has yielded an increasingly coherent picture of the critical roles that behavioral and learning processes assume in the development, maintenance, and treatment of depression. Findings that certain cognitive styles—for example, a person's tendency to make negative global attributions when confronted with discrete, stressful life events—have been associated with vulnerability to relapse in depression and bipolar disorder, and offer leads for refining and developing new psychosocial therapies.

Advances in genetics and molecular biological technologies have ushered in a new era in the use of animal models for research on mood disorders. Over the years, much informative research has drawn inferences about clinical depression on the basis of animal models of "depression." As an alternative approach, investigators today are finding it useful to identify intermediate components—for example, sleep disruption in depression—that occur somewhere between genes and clinical syndromes. Called "endophenotypes," such components offer a means of parsing out with considerable precision a particular feature of a disorder that can be measured in animal behavior—another example might be a physiological response to a stressful stimulus. Such strategies simplify the task of identifying the genetic basis for the feature in question, and they facilitate the translation of findings among various animal models and from animals to humans.

What makes this a particularly promising time is the manner in which information is converging from genetics, neurobiology, animal models of mood disorders, basic behavioral research, and cognitive neuroscience. Seemingly unrelated advances in each of these areas collectively are pushing the field toward the discovery of biological markers for mood disorders, which in turn will yield improved diagnostic measures and point to the ultimate biological causes and environmental triggers for mood disorder symptoms. This information, scientists anticipate, will culminate in the development of new behavioral and pharmacological treatments.

Selected Research Priorities and Objectives: Basic and Clinical Neuroscience

Opportunities to Discover a Genetic Basis of Mood Disorders

- Enhance the broad availability and coordination of core research resources in extramural and intramural genetics research programs for use in future genetic studies of mental disorders.

Opportunities to Understand the Neural Basis of Mood and Emotion

- Identify measures of core symptoms of depression and mania that can be modeled in animals (e.g., indices of cognitive processes, sleep disturbances, or reward mechanisms) as an essential first step in model development.
- Establish how experiential and genetic factors interact to modulate neural and behavioral indicators of mood disorders.

- Expand resources in support of greater quality, availability, and use of postmortem brain tissues for studies of brain structure and circuitry related to mood disorders.

Opportunities to Discover New Drug and Physiologic Treatments

- Establish quantitative outcome measures and biological markers for the diagnosis and assessment of disease progression and treatment of mood disorders.
- Establish long-term partnerships between government, academia, and industry to accelerate innovative drug discovery and the development of behavioral assays for evaluating novel therapeutics.

Dimensions of Age and Disease

A central consideration in developing the strategic plan was that the prevalence of mood disorders is not constant throughout the human life span. Not only do rates of depression vary, but also the types of depression that occur early in life are likely to be different than those that occur late in life, when comorbid illnesses often play a significant role in psychological well-being. Prior to the 1980s, most clinical research and virtually all epidemiologic research on depression was confined to adult samples. Only as research involving children and adolescents has been undertaken in recent decades have clinical investigators begun to appreciate that many—perhaps most—individuals with a depressive disorder began to experience serious symptoms early in adolescence and that their vulnerability to develop these conditions may have been established even earlier.

An equally important and researchable insight has been that depression is not a normal feature of aging and that late-life depression principally affects individuals with other medical and psychosocial problems, including cognitive dysfunction, disability, medical illnesses, and social isolation. The prospect of a rapidly expanding "old-old" population in the United States over the next decades portends significantly increased rates of comorbid depression and cognitive impairment, a malign duo that will drive up health care costs while diminishing substantially the quality of life for affected individuals. These clinical associations are guiding the development of hypotheses regarding mechanisms that predispose, initiate, and perpetuate specific mood syndromes in late life.

Yet another arena of robust research activity in recent years has examined gender disparities in depression. Issues under study include the question of a marked gender-by-age change during adolescence; prepubertally, boys and girls have comparable rates of depression, but beginning in early adolescence, the rate in girls rapidly increases to the point where women's lifetime rates of depression are twice those experienced by men. Some early evidence suggests that genes play a larger role in the development of depression in women than they do in men. Also, investigators are attentive to the possibility of subtle interactions among neurotransmitters such as serotonin that are known to be involved in depression and neuroendocrine rhythmicity associated with the menstrual cycle or reproduction; such interaction, scientists believe, may be associated with the

possibility of greater sensitivity on the part of some women to environmental, psychosocial, and psychological risk factors for depression.

Awareness is growing, too, throughout the medical and health care fields, of the frequent co-occurrence of depression with a broad array of illnesses—coronary heart disease, diabetes, stroke, cancer, and HIV/AIDS, to name but a few. In the course of developing the strategic plan, it became evident that a major obstacle to research is the lack of attention that existing diagnostic systems give to the recognition and diagnosis of depression in the context of medical illness. Depression, investigators now know, should not be viewed as—or, worse, somehow dismissed as—an understandable consequence of one's having a life-threatening or chronic illness; rather, depression should be recognized as a discrete condition usually amenable to appropriate treatment. A nascent body of research, moreover, points to clinical depression as a factor that, left untreated, can have an active and negative impact on the course and outcome of general medical illness.

Selected Research Priorities and Objectives: Dimensions of Age and Disease

Opportunities to Identify Depression and Bipolar Disorder During Development

- Determine the developmental pathophysiology of mood disorders.
- Improve the diagnostic validity of mood disorders in children and adolescents.
- Develop effective treatments for children and adolescents with mood disorders.
- Understand the effects of sex and gender on etiology, diagnosis, treatment, and prevention of depression and bipolar disorder in women.

Opportunities to Improve Mental Health for the Elderly

- Expand the knowledge base of safe and effective treatments for late-life depression and associated suicide risk.

Opportunities to Understand Mood Disorders as Diseases of the Brain and Body

- Identify the mechanisms and processes that have a relatively large influence on the development of comorbid disorders (i.e., explain a relatively large amount of variance in the outcomes) and can also be modified through intervention.

Treatment, Prevention, and Services: Improving Outcomes

The scientists and consumer advocates alike who participated in the workgroups acknowledged that although refinements in pharmacological, behavioral, and psychosocial interventions are of immense benefit to many persons with mood disorders, all too many people with depression or bipolar disorder go untreated or receive less than optimal

treatment. Even when persons with these illnesses receive treatment, only slightly more than half of all of them respond well to therapy, which typically is defined as experiencing a 50 percent or greater reduction from baseline symptom severity. If complete symptom remission or restoration of function is the outcome criterion, then the proportion is even lower.

Most of what is known about the efficacy of pharmacological and behavioral treatments is derived from research conducted in academic settings involving relatively homogeneous populations of almost exclusively Caucasian people without co-occurring general medical or mental illnesses. Thus, in addition to translating information newly acquired from basic research into clinical applications, urgent need exists for research to assess the effectiveness of existing treatments in actual urban and rural community settings. This is a challenge that calls, in turn, for studies that will identify and validate markers of treatment outcome—physiological, cognitive, functional, and behavioral—that extend well beyond acute symptom remission. Research also is needed that will focus on innovative strategies for improving the delivery of care to diverse populations, particularly racial and ethnic minority groups. A related challenge common to all mood disorders, but particularly nettlesome in the management of bipolar disorder, is the need for new approaches to encouraging adherence to treatment regimens.

The high risk for suicidality in the context of mood disorders makes imperative the need for innovative research despite such formidable obstacles as the ethical concerns that surround the inclusion of actively or potentially suicidal subjects in controlled clinical trials.

In today's world of constantly shifting health care organizations and a rapidly expanding array of treatments, a central challenge for intervention research in mood disorders is to select research priorities and design trials that will have high public health significance while promising to yield information relevant to continuously evolving service delivery and reimbursement systems. In clinical trials and prevention studies, researchers must actively strive to reach out to diverse communities and populations to ensure that persons representative of all Americans will participate in research, so that the findings will reflect the best outcomes for all groups.

Selected Research Priorities and Objectives: Treatment, Prevention, and Services

Opportunities to Expand and Improve Clinical Trials

- Assess the long-term effects of treatment interventions on physiological and functional status.

Opportunities to Develop New Psychosocial and Behavioral Therapies

- Determine the basic mechanisms by which psychosocial interventions operate to produce therapeutic change to increase opportunities for innovative developments.

Opportunities for the Prevention of Mood Disorders

- Determine what interventions are needed during various phases of an illness to help prevent the recurrence and relapse of mood disorders.

Opportunities to Improve Delivery of Services

- Understand the processes by which theoretically based research information on mood disorders is effectively disseminated and implemented or utilized by clinicians or delivery systems.
- Increase the development of practice-level interventions that are based on research tested theoretical models.
- Identify the individual, social, and cultural determinants of stigma and develop interventions to change these determinants.

Expanding and Strengthening the Research Foundation

The utility of the scientific agenda that holds center stage throughout the pages of this mood disorders research strategic plan ultimately will be measured by the extent to which it improves the lives of individuals who themselves have a mood disorder or who deal with the impact of mood disorders in the context of family, work, or other social groupings. The centrality of the human element in planning, conduct, and application of research was recognized by every workgroup that contributed to the strategic plan. Clearly, the needs of individuals with mood disorders are a driving force behind development of the plan. But many other persons are equally critical: educators who play a vital role in training young scientists in the techniques and nuances of research relevant to mood disorders; researchers and communicators whose primary responsibility is to disseminate the knowledge generated through research; and clinicians and other health and social service professionals who apply the products of research in diverse settings.

Challenges in two particular arenas—training tomorrow's researchers and putting the fruits of research in the hands of public health practitioners, clinicians, and members of the general public—crosscut the entire strategic planning process. Absent a solid foundation in these areas, even the most innovative scientific agenda becomes a sterile exercise. In compiling this final document, NIMH staff culled from the workgroup reports an array of implicit and explicit recommendations for research training that encompass disciplinary as well as demographic gaps in the contemporary research community and, importantly, that anticipate the impact of future scientific advances and shifts in the Nation's age and racial/cultural composition in the years ahead. A second category of needs and opportunities involves educating front-line clinicians and the public at large about mood disorders, using a mix of media and language and formats that will be broadly accessible. An example of a more specific educational challenge is that of informing

interested individuals—clinicians as well as patients—how to learn about and participate in clinical services and prevention trials.

Selected Research Priorities and Objectives: Expanding and Strengthening the Research Foundation

Opportunities to Expand and Strengthen the Research Foundation in Training

- Address the shortage of new and established investigators in various disciplines to conduct mood disorders research, particularly racial and ethnic minority investigators, and those focusing on child and elderly populations.

Opportunities to Expand and Strengthen the Research Foundation in Public Education

- Expand the dissemination and translation of mood disorders risk factors, diagnosis, and treatment knowledge to the community.

Suicide: A Spouse's Story

I will never forget July 6, 2001. It was a Friday and we started the day full of hope and the promise of recovery. Heinz, my husband of 24 years, felt better this morning than he had in months. He had struggled with his third bout of manic depression in over three decades. The shroud of hopelessness that had immobilized him for what seemed an eternity had lifted at last. For the first time in months, he rose early and full of energy to work out. I was relieved, elated. At 8:00 a.m., the phone rang twice. I picked it up, but the line was dead. A sudden rush of fear overcame me, and I ran across the driveway to the guesthouse where Heinz used to work out. It was there I found his lifeless body. In the act of ultimate despair, he hung himself. Heinz left without a word. There were no goodbyes for our twins, Paul and Stephanie. There was no goodbye for me. He was 59 years old, a world-class entrepreneur, a business leader, a man who gave back to the community, a man loved by his family and those around him. A man who created opportunities for thousands but in the end, saw no opportunity for himself. That is the mark of this disease.

The accompanying photograph to each vignette in the strategic plan is not of the actual patient/consumer or family member described.

Introduction

Mood disorders, the foci of this strategic plan for research, are serious medical illnesses that affect more than 20 million Americans of every race and ethnic group and at every stage of life, from childhood through old age. Mood disorders are "brain disorders," meaning they are mediated through the brain, yet they disrupt every facet of a person's life: emotions, thought processes, behavior, and physical health. Left untreated, or inappropriately treated, mood disorders are potentially fatal; nearly one in six persons with severe, untreated depression will die by suicide. Short of this tragic outcome, mood disorders are immensely disabling. A landmark study sponsored by the World Health Organization and the World Bank reports that in the United States and other nations with developed economies, major depression is the *leading* cause of disability. The same study projects that by the year 2020, depression will be the second leading cause of disability worldwide. The mission of NIMH is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. Clearly, improved understanding, recognition, treatment, and prevention of mood disorders are critical scientific and public health priorities.

The Nature and Impact of Mood Disorders

Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research of the National Institute of Mental Health addresses two types of mood disorder—major depression and bipolar disorder, also known as manic-depressive illness. The term depression, of course, refers not only to an illness, but also to moods and behaviors that occur in the normal course of life. Unlike the normal shifts in mood that most people experience, however, the symptoms of *depression* are more extreme and frequently incapacitating. These symptoms include a persistent sad mood; loss of interest or pleasure in activities that were once enjoyed; significant change in appetite or body weight; difficulty sleeping or oversleeping; physical slowing or agitation; loss of energy; feelings of worthlessness or inappropriate guilt; difficulty thinking or concentrating; and recurrent thoughts of death or suicide. A diagnosis of depression is made if an individual has five or more of these symptoms every day during a 2-week period.

In *bipolar disorder*, episodes of depression alternate with episodes of mania, a condition marked by periods of abnormally and persistently elevated mood or irritability accompanied by at least three of the following symptoms: overly inflated self-esteem; decreased need for sleep; increased talkativeness; racing thoughts; distractibility; increased goal-directed activity or physical agitation; and excessive involvement with pleasurable activities that have a high potential for risky consequences. The symptoms of depression and mania can occur at the same time. The cycles of depression, mania, or mixed mania and depressive symptoms usually recur and may become more frequent, often interfering with work, school, family, and social life.

Severe mania or depression can be accompanied by periods of psychosis. Psychotic symptoms include hallucinations (hearing, seeing, or otherwise sensing the presence of stimuli that are not actually there) and delusions (false, fixed beliefs that are not subject to reason or contradictory evidence and are not explained by a person's usual cultural concepts). Psychotic symptoms associated with bipolar disorder typically reflect the extreme mood state at the time, such as the grandiosity during mania or worthlessness during depression. Bipolar disorder with rapid cycling is defined as four or more episodes of illness within a 12-month period. This form of the illness tends to be more resistant to treatment than non-rapid-cycling bipolar disorder.

Far more common than bipolar disorder, major depression affects approximately 19 million American adults at any given time and an estimated 6 percent of children ages 9 to 17. For reasons that are not clearly understood, depression occurs twice as often among women as men. Five to 14 percent of women will have an episode of depression at some point in their lives in contrast to 2 to 4 percent of men. Bipolar disorder affects some 2.3 million American adults, or approximately 1 percent of the population, and distributes roughly equally between men and women. Although firm data are lacking on the extent to which bipolar disorder affects children and adolescents, clinical experience suggests that some proportion of children and adolescents who have major depression eventually will be found to have bipolar disorder; this likelihood increases if the depressed young person has a family member with bipolar disorder.

Today, the intense and disabling symptoms of depression and bipolar disorder often can be relieved through treatment involving combinations of medications and psychotherapy. Yet, as noted, even with appropriate treatment, both depression and bipolar disorder tend to be episodic and recurrent; that is, after a person has been depressed once and recovers, he or she is likely to have in the future one or more episodes of depression, and/or mania in the case of bipolar disorder. Single episodes are the exception. This pattern of illness implies high, and sustained, personal, family, and societal costs—costs that can and will be reduced substantially through an accelerated program of research and discovery.

Mood Disorders Research at NIMH: A 50-Year Perspective

Because of their high prevalence, morbidity, and mortality, mood disorders, along with serious illnesses including schizophrenia, autism, and severe anxiety, historically have been important research priorities for NIMH. Nearly half a century ago, shortly after NIMH was established, two classes of effective antidepressant medications—the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs)—were introduced concurrently with the first antipsychotic medications. These new compounds signaled the start of what would be termed the "psychopharmacology revolution." That these compounds were discovered serendipitously did not diminish their utility in research any less than in clinical practice. In their clinical effects, the new medications lent themselves to early efforts to enhance classification and diagnosis in psychiatry; they invigorated clinical research; and they were invaluable tools to pioneering neuroscientists engaged in studies of the brain and mental illnesses. By 1970, NIMH investigators were among those who had participated in research that influenced the Food and Drug Administration's approval of another compound new to this country—the mood stabilizer lithium carbonate, used to manage the mood swings associated with bipolar disorder.

Psychotropic medications and the burgeoning discipline of neuroscience accurately heralded a new era focused on the role of the brain in mood disorders, but diverse other areas of research also were thriving. Throughout the 1960s and 1970s, following a long period of Freudian-inspired attention to "insight" in both the treatment and explanation of mental disorders, many psychologists and others became increasingly interested in the behavior of a depressed individual and the role of the environment in reinforcing and negating that behavior, lines of research that led to new theories about the origins of the illness. Other research was focusing on cognitive aspects of mood disorders, with investigators speculating that persons might experience sadness, loss of motivation, and suicidal wishes because their thinking was disturbed rather than vice versa. In fairly short order, these hypotheses and subsequent research led to fundamentally new forms of psychotherapeutic interventions.

At this time too, preclinical investigators were striving to identify circumstances in which depression-like symptoms might be generated in animal models. Approaches ranged from separating infant monkeys from their mothers, to psychopharmacologic manipulations to deplete brain catecholamines, to "learned helplessness" models which suggested that early experience with persistent and uncontrollable trauma could lead to the development of a passive, helpless approach to dealing with frustration in later life.

As work in all of these various areas progressed, NIMH sponsored several large multisite research programs on depression. These included, for example, the NIMH Collaborative Depression Study, a longitudinal naturalistic follow-up study that began recruitment in 1978 and today is the longest-running depression study in the world. At the

start of the project, the major aim was to further the knowledge on the genetics and comparative nosology of depression and related mood disorders. As the research developed, the aims broadened to include investigations of risk factors in the onset of first episodes of depressive illness, course of illness in subjects and relatives, reliability and validity of diagnosis, and investigations of the effect of comorbidity, as well as many more. Among other NIMH projects begun in the 1970s were the Collaborative Study of the Psychobiology of Depressive Disorders, which was designed to explore how biological, psychological, and environmental forces combine to create depressive states, and the Treatment of Depression Collaborative Research Program, the first multisite, coordinated study initiated by NIMH in the field of psychotherapy research. The mid-1980s saw release of initial findings from the Epidemiologic Catchment Area (ECA) study; while not specific to depression, its quantification of mental disorders in the United States was critical to all NIMH research on mental disorders. In the late 1980s, NIMH launched its Genetics Initiative, a centralized resource needed to achieve large sample sizes of complex genetic disorders. The initiative creates cell lines from blood samples and saves detailed behavioral and clinical information on subjects with a variety of disorders, including bipolar disorder, and makes these samples broadly available to qualified investigators.

Although the field of mood disorders research remained active, in the absence of any fundamentally new insights into pathophysiology or etiology, refinements in treatments were hard won, at best. In fact, as is noted later in this document, the introduction and apparent effectiveness of lithium in treating bipolar disorder, which some observers predicted would become as significant a development as the use of insulin for diabetes, tended to foster a sense of complacency about the need for new types of medications and contributed to a worrisome decline in treatment research and clinical trials focused on the disorder. By the late 1980s, sustained progress in neurobiological research that was capitalized on and augmented by the pharmaceutical industry had contributed to the introduction of fluoxetine, a novel antidepressant that selectively increased availability of serotonin at synapses. While the compound proved to be safer and easier to use than the TCAs and MAOIs, it and successive compounds like it called selective serotonin reuptake inhibitors, again failed to yield fundamentally novel insights into the mechanisms of mood disorders.

Paralleling and, in some instances, outpacing scientific and clinical advances were the increased understanding of depression by the public and an increasing receptivity to acknowledging mood disorders as a treatable condition. This shift was attributable both to the vastly increased access to safe and effective pharmacologic treatment through the primary care sector, and to a handful of acclaimed and widely read accounts of depression, including William Styron's *Darkness Visible: A Memoir of Madness*, Patty Duke's *A Brilliant Madness*, and Kathy Cronkite's *On the Edge of Darkness*. Also, the importance of research to improved treatment of mental disorders was benefiting from both public and private educational efforts. In 1986, NIMH launched its Depression Awareness, Recognition and Treatment (D/ART) program, and the energetic efforts of consumer-driven advocacy groups

including the National Alliance for the Mentally Ill, the National Depressive and Manic-Depressive Association, the Anxiety Disorders Association of America, and others were highly supportive of research needs.

The 1990s, designated by presidential proclamation as the "decade of the brain," was indeed enormously fruitful in basic science. Cognitive neuroscience was maturing rapidly. Increasingly sophisticated studies of learning and memory contributed to elucidating the mechanisms of brain plasticity, enriching understanding of functional and structural brain changes in mood disorders and other serious mental illnesses. A new appreciation of neural circuitry, including circuitry putatively involved in mood regulation, had grown out of steady progress in tract tracing, physiology, research involving lesions in animal models, and neuroimaging in humans. The completion of the draft sequence of the human genome was imminent, and as the looming relevance of molecular biology and genetics to research on genetically complex mental disorders became indisputably evident, the realization added urgency to the need for innovative cognitive and behavioral science research that would, ultimately, provide a framework for molecular-cellular and systems-level neurobiological discoveries.

Even as NIMH continued to invest heavily in all of these areas, the pressure for increasing scientific attention to the more effective use of existing treatments prompted NIMH to launch an unprecedented series of clinical trials designed to move beyond traditional randomized, controlled efficacy trials conducted in academic medical settings, and to evaluate treatments as they are routinely used in community settings, with demographically and diagnostically diverse subjects. Three of these new effectiveness trials focus on mood disorders—the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Sequenced Treatment Alternatives to Relieve Depression (STAR*D), and Treatment for Adolescents with Depression Study (TADS). Also, in 2000, NIMH undertook a major revitalization of its intramural, or in-house, Mood and Anxiety Disorders Research Program, recruiting a distinguished roster of senior investigators from academia.

Viewed collectively, the stunningly broad array of scientific activities and opportunities, combined with the well-documented public health significance of depression and bipolar disorder, impressed the NIMH leadership with the need for a systematic analysis of the broadest possible arena of mood disorder-relevant research and the timeliness of a major strategic planning effort focused on mood disorders.

About Strategic Planning at NIMH

Strategic planning offers a means of strengthening the traditional formula of investigator-initiated research that is a central feature of NIH-funded research. Today, an abundance of scientific capabilities and opportunities exists in the areas of brain and behavioral research. We are increasingly able to perceive how particular research emphases will achieve desired goals or outcomes, whether this is new knowledge about basic

processes, the design and development of clinical interventions, or other objectives. As we refine scientific tools and capabilities for treating and preventing mental illness, we also are gaining unprecedented knowledge about the distribution, determinants, and costs of mental disorders, information that underscores the urgency of research.

Development of this strategic plan for mood disorders research has involved nearly 200 individuals, including members of the National Advisory Mental Health Council (NAMHC) and representatives of scientific and advocacy organizations, working in collaboration with NIMH. The participation of knowledgeable advocates, including consumers and families who can offer valuable information and insights about issues that warrant research, has been a particularly useful source of input to the planning process.

The strategic planning process began in late 2000 when NIMH established small workgroups of scientific leaders and public stakeholders, each focused on a key area of research. These areas included genetics, neural and behavioral substrates of mood regulation, preclinical models, pharmacologic and somatic treatment development, psychosocial intervention development, aging and medical comorbidity, development and natural history, clinical trials and translation, and overcoming barriers to care and reducing public burden. The Institute invited leading researchers in the field, NIMH staff, members of the NAMHC, and a broad cross section of consumer and advocacy group members to participate in the process. Participants were assigned to one of the nine workgroups with the following charges:

1. **Genetics and Epidemiology of Mood Disorders:** Discover risk genes for mood disorders.
2. **Neural and Behavioral Substrates of Mood Regulation:** Apply cognitive neuroscience, and molecular-cellular and systems-level neurobiology to understand representation and regulation of mood states in human and animal models.
3. **Preclinical Models:** Develop novel animal models to advance understanding of mood disorders.
4. **Development and Natural History:** Understand risk factors, course, and expression of mood disorders during childhood development through adulthood.
5. **Aging and Medical Comorbidity:** Focus on etiology, morbidity, treatment, and outcomes of mood disorders associated with aging and other medical conditions.
6. **Pharmacologic and Somatic Treatment Development:** Advance the development and testing of fundamentally new, rationally designed medications and treatments for mood disorders.
7. **Psychosocial Intervention Development:** Explore opportunities to advance the development of innovative treatments for mood disorders and understand the mechanisms underlying change.
8. **Clinical Trials and Translation:** Improve methods, speed, and cost of research that addresses clinical questions, and translates preclinical to clinical models and clinical to service models.

9. **Overcoming Barriers to Care and Reducing Public Burden:** Determine means to eliminate personal, social, professional, financial, and cultural barriers to treatment for mood disorders.

Each workgroup was asked to answer a series of questions about the state of current research findings, gaps in the research, and important scientific opportunities. The workgroup chairs determined the delegation of work, timing, and frequency of conference calls, and the need for meetings prior to the convening of all workgroup members at a major conference held on March 24-25, 2001, in Pittsburgh, Pennsylvania. Through a round of well over 60 conference calls, the preparation and circulation of draft papers, and the 2-day meeting in Pittsburgh, the nine workgroups produced in-depth reviews of the current status, needs, and opportunities in each topic area. In the 12 months following the Pittsburgh meeting, which was essentially the launch of the strategic planning process, NIMH staff have carefully analyzed the findings and conclusions contained in the workgroup reports and other source materials, and evaluated these in the context of the current NIMH mood disorders research portfolio, including planned activities and initiatives. Staff, with the assistance of a science writer, drafted multiple versions of a research strategic plan, with each iteration moving closer toward consensus on a set of broad priorities and specific research objectives ultimately endorsed by the NAMHC.

NIMH intends that this strategic plan for mood disorders research not only will guide the Institute's funding initiatives in the years ahead, but also will serve as a resource for all who take an interest in seeing the burden of depression and bipolar disorder become a thing of the past.

Almost from the day Jeff was born, I knew that he was unlike other children. He was constantly irritable, slept very little, and became extremely agitated when I was not holding him. When Jeff was 3 years old, my second son was born. Although Roger was relaxed and easygoing compared to Jeff, I felt guilty for having to spend so much time with Jeff, at the expense of attention to the baby. By Jeff's 5th birthday, he had the whole family on edge, and we sought psychiatric help. Although we told the doctor that my mother had been diagnosed with bipolar disorder, Jeff was diagnosed as having ADHD and prescribed Ritalin. The medication helped him concentrate, but did nothing for his mood swings or for the bouts of destructive behavior, including fire setting, that he was having at age 10. Again, we found a psychiatrist for Jeff to see, but when there were no apparent results after 2 months, the doctor recommended inpatient treatment. After only 3 days in treatment, Jeff was given a diagnosis of bipolar disorder, and put on an anticonvulsant used in treating the illness. Within 3 weeks he was a different boy, at peace with his brother and playing nicely with other neighborhood kids. I hold my breath, thinking this is all too good to be true. While I mourn over how my son has suffered, I rejoice that we finally know why and can do something about it. I'm worried about what effect all this has had on my youngest son, but right now we're picking up the pieces and moving forward.

Basic and Clinical Neuroscience: Foundation for Discovery

Significant advances in basic neuroscience over the past two decades have provided a rich and increasingly mature knowledge base for understanding patho-physiology and developing rational pharmacotherapy in treating brain diseases. New discoveries based on novel experimental techniques have repeatedly provided human brain researchers with emerging models of neural mechanisms that will potentially contribute to disease understanding, as well as a more comprehensive understanding of current drug action. Progress in the Human Genome Project has actually been faster than predicted and is expected to contribute exponentially to the identification of genes producing vulnerability and resilience to mood disorders, and to the identification of novel drug targets.

With considerable precision and cross-laboratory consistency, neuroscientists are delineating the brain regions involved in modulating mood. Research has uncovered several neurotransmitter systems, including those using glutamate, gamma-aminobutyric acid (GABA), serotonin, norepinephrine, and dopamine, that are involved in depression and mania. Recent work has also identified other neurochemical systems that may be involved in mood disorders, including membrane-bound signal transduction elements and intracellular signaling systems that modulate gene transcription and protein synthesis. Such insights have provided important clues that point to neurochemical targets for novel selective pharmacologic manipulation. This concentration of new knowledge will progressively contribute to new therapeutics and allow scientists interested in mood disorders to think differently about drug targets.

What makes this a particularly promising time is the convergence of information from genetics, animal models of mood disorders, basic behavioral research, and neuroscience. Together, research from each of these areas is pushing the field toward the discovery of biological markers for mood disorders, which in turn will yield improved diagnostic measures and the discovery of the ultimate biological causes and environmental triggers

for mood disorder symptoms. Such knowledge will culminate in the development of new pharmacological and behavioral treatments.

Current Status of the Field

Triggering the Mood Changes in Depression and Bipolar Illness

A critical area of research in the field of mental illness aims to gain a better understanding of the factors that influence mood. These factors may reflect changes in brain chemistry or even in brain structure, genetic effects, or behavioral characteristics, such as a particular style of coping with stress or change. Whatever the underlying cause of the mood disorders may prove to be, there is little doubt that multiple factors contribute to the development of depression and bipolar illness.

The Connection Between Neurochemistry and Mood Disorders

One of the most consistent findings from depression and bipolar disorder research is that individuals with mood disorders display a variety of changes in brain chemistry and even in brain structure. What is still unclear is whether these abnormalities cause the vulnerability to abnormal mood episodes or whether they represent the ways in which the brain compensates for other, as yet undiscovered, disease processes. Another possibility is that these observed changes are consequences of recurrent brain illness. Whatever their origin, none of these abnormalities are specific or sensitive enough to be useful as either diagnostic measures or prognostic indicators of treatment outcome in routine clinical care.

The brain systems that have received the greatest attention in mood disorders research have been those that use the neurotransmitters dopamine, serotonin, and norepinephrine to transmit nerve signals between neighboring nerve cells. These monoamine neurotransmitter systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders.

The evidence showing that monoamine neurotransmitter systems play an important role in mood disorders comes from two types of studies. One avenue of research shows that effective antidepressant drugs exert their *primary* biochemical effects by regulating the action of these neurotransmitters. Along similar lines, drugs used to treat high blood pressure that reduce brain levels of these monoamines can trigger major depressive episodes.

There is also evidence suggesting that at least some of the biochemical events involved in the normal function of monoamine neurotransmission—the ability of a neurotransmitter to bind to its receptor on the ends of nerve cells, for example—differ in individuals with mood disorders. Neuroimaging, postmortem, and pharmacological challenge studies have all shown, for instance, that abnormalities of serotonin$_{1A}$ receptor

function and binding and serotonin transporter binding are associated with mood disorders.

The monoamine neurotransmitters are not the only neurochemical system affected in individuals with mood disorders. For example, elevated activity of the hypothalamic-pituitary-adrenal (HPA) axis, which plays a critical role in the body's response to stress, is one of the most replicated biological findings in major depression. Relative to healthy control subjects, individuals with depression have elevated levels of the stress hormone cortisol in 24-hour collections of plasma and urine, enlarged adrenal and pituitary glands, and exaggerated cortisol response to stimulation by the hormone adrenocorticotropin (ACTH).

While dysfunction within these neurotransmitter and neuroendocrine systems is likely to play a role in the disease process, researchers now believe that these abnormalities may represent downstream effects of other, more primary neurobiological problems. It may be, for example, that the disruption of signaling networks that integrate multiple chemical signals and regulate the functional balance between interacting neuronal circuits constitute a common downstream abnormality. Such an abnormality could account for the abnormalities observed in so many neurotransmitter, neuroendocrine, and physiologic systems in mood disorders.

Specific Brain Regions Are Affected in Mood Disorders

Neuroimaging studies in people with mood disorders have revealed multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism—two proxies of neuronal activity—in various limbic and prefrontal cortical brain structures. Some of the changes observed in specific brain regions persist independent of mood state, that is, whether or not a person is experiencing depressive or manic symptoms. In addition, some of these abnormalities reverse during antidepressant drug therapy in individuals who respond positively to the treatment, while others of these neurobiological changes do not vary during treatment.

Data from unmedicated individuals with depression have shown that CBF and metabolism are above normal in brain regions such as the amygdala—a brain region involved in acquiring and recalling emotional or arousing memories—and parts of the orbital cortex, while those same measures are below normal in parts of the prefrontal cortex and anterior cingulate cortex. The overall pattern of these metabolic changes during an episode of major depression suggests that structures implicated by other types of evidence in mediating emotional and stress responses, such as the amygdala, are abnormally activated. These patterns also suggest that areas such as the posterior orbital cortex that are thought to modulate or inhibit emotional expression are also activated. At the same time, brain regions implicated in attention and sensory processing, including parts of the anterior cingulate cortex, are deactivated.

Elevated metabolism in the amygdala seen during depression, taken with these other observations, suggests that the amygdala may be excessively stimulating cortical structures

involved in forming certain types of memory and that this chain of events may account for the tendency of depressed subjects to ruminate on memories of emotionally aversive or guilt-provoking life events. Similarly, abnormal activity in the amygdala related to depression may conceivably alter the initial evaluation and memory consolidation related to sensory or social stimuli in such a way as to magnify their emotional significance, an idea supported by other data. For example, norepinephrine release in the amygdala plays a critical role in at least some types of emotional learning, and activation of the HPA axis stimulates norepinephrine release. At least some depressed subjects have abnormally elevated secretion of both norepinephrine and cortisol, which in the presence of amygdala activation might increase the likelihood that ordinary social or sensory stimuli are perceived or remembered as being aversive or emotionally arousing.

The hippocampus is another brain region that may play a central role in depression. The hippocampus is known to play an important role in context-specific emotional responses, and individuals with depression often display normal emotional responses but in inappropriate contexts. In individuals with long-term depression, magnetic resonance imaging (MRI) studies indicate the hippocampus is reduced in size. This reduction may result from hyperactivity of corticotropin releasing hormone (CRH) or of other components of the HPA axis. Future studies will examine if therapeutic treatments can reverse changes in hippocampal structure or function.

Thought Processes Affect Mood Disorders

Over the past 30 years, it has become clear that behavioral and learning processes play critical roles in the development, maintenance, and treatment of depression. For example, individuals who exhibit negative cognitive styles, such as a tendency to make stable, global attributions, are more vulnerable to depression and suicide when they experience stressful life events than are individuals with more positive cognitive styles. These same cognitive vulnerabilities also may increase risk for symptoms or episodes of bipolar disorder in combination with stressful life events.

Rumination, the tendency for a person to focus repetitively on the symptoms of depression and the causes and consequences of those symptoms, can increase the severity and duration of a depressive episode. Rumination also mediates the effects of negative cognitive styles and other vulnerability factors for depression, including past history of depression and personality vulnerabilities, in predicting onsets of major depressive episodes. Rumination may worsen depression by enhancing negative thoughts about the past, present, and future; by interfering with effective interpersonal problem solving; and by impairing social relationships. In fact, rumination may be an early predictor of depression.

Though it is clear that life events play a role in triggering episodes of depression and mania or hypomania, various kinds of life events may not be equivalent in their propensity to trigger depression or mania. For example, major negative events that remove a person from his or her normal social network appear to be potent triggers of depression. Events

that disrupt circadian rhythms, particularly the sleep/wake cycle, or that involve goal attainment or "challenge," are likely triggers of mania or hypomania. Furthermore, events that match specific content areas of vulnerability for individuals (e.g., rejection for an individual who is highly dependent) may be particularly likely to prompt depressive and manic or hypomanic episodes.

Each of these life event triggers can be seen as a form of stress, but the precise manner in which vulnerability and stress combine to lead to depression, mania, or hypomania is unknown. It may be that only high-risk individuals with negative cognitive styles who experience high stress develop depression, or that high "doses" of stress can precipitate depression in individuals with low cognitive vulnerability and low "doses" of stress are sufficient to trigger depression in highly vulnerable individuals. Another possibility is that high-risk individuals may be drawn to lifestyles that increase their exposure to greater life stress and this greater stress, in turn, precipitates depressive or manic symptoms.

Cognitive research has also shown that hopelessness—the expectation that highly desired outcomes will not occur or that highly aversive outcomes will occur and that one cannot change this situation—may be an important cause of depression. Certainly, hopelessness is the best single psychological predictor of suicidal thoughts, attempts, and suicide deaths, but whether hopelessness should be best regarded as an early symptom of some other factors that trigger depression requires further study.

While a lack of social support appears to be one factor involved in triggering depression, the presence of a strong social support network appears to protect against depression when people experience stressful events. Similarly, social support may protect individuals with bipolar disorder from mood swing episodes. Strong social support, particularly when it can counter negative events, may in fact make a person more resilient by preventing the development of hopelessness.

Using Computers to Model Mood Disorders

Computational modeling—using computer programs to mimic brain function and behavior—is an important tool that can provide valuable insights into cognitive and other behavioral functions, their links to neuronal activity, the nature of disorders of these functions, and the interdependency between disorders at the neural and functional levels. The behavioral and cognitive sciences use many different kinds of models, but at present the most widely used and broadly applicable models treat thinking, or cognition, as information processing.

One valuable aspect of computational models is that they frequently enable the design of new solutions to practical problems by virtue of their link to mechanism. As with models in other sciences, computational models in the behavioral sciences both reduce the complexity of behavioral phenomena and provide testable mechanistic accounts of the underlying mental processes causing the behavior. Though there are as yet no

computational models capable of representing the complex changes that occur in mood disorders, models have been developed that focus on some of the learning and behavioral aspects of these brain illnesses. In addition, some recent modeling work involving so-called executive function—brain processes that integrate basic behavioral activities—has shown promise in explaining how deficits in dopamine function may be responsible for the most severe cognitive problems experienced by people with schizophrenia.

There are several models available that explore certain aspects of learning, a brain function thought to malfunction to at least some degree in mood disorders. Some of these models are able to capture the function of various brain circuits involved in learning. Others provide insights into how neural circuits in the brain might adapt and change with learning, and how slight changes in those processes could lead to maladaptive behaviors, including some of the precursors of mood change. These modeling efforts could lead to new methods for "retraining" the brain for changing behavior itself.

Finding the Genes Involved in Mood Disorders

Family, twin, and adoption studies of mood disorders have demonstrated conclusively that genetic factors are involved in the susceptibility to mood disorders, particularly bipolar disorder. The weighted average risk ratio (comparing the prevalence of mood disorders among relatives of patients compared to those of controls) for bipolar disorder among relatives of individuals with bipolar disorder is 9.2, whereas the average risk ratio of major depression among relatives of individuals with bipolar disorder compared to those of controls is 1.9. This indicates a very high magnitude of familial aggregation of bipolar disorder, similar to that found for many of the major diseases for which the genetic basis has been identified. In contrast, the average risk ratio for major depression among relatives of individuals with major depression compared to those of controls is 2.0, indicating only a moderate influence of familial aggregation on non-bipolar mood disorders.

The initial enthusiasm generated by early claims of linkage between bipolar disorder and various DNA markers faded when these results were not replicated in subsequent studies. In fact, numerous linkage studies of bipolar disorder have "identified" putative genes on nearly all chromosomes. Investigators have reported weak associations of bipolar disorder to several genes involved in the GABA, serotonin, and dopamine systems. Recent studies have also identified genes mediating signal transduction and other loci relevant for further genetic analysis. However, none of these results have been confirmed upon further study. To date, genomic scans have not been conducted in studies of depression, and association studies for specific genes have been inconclusive.

There is, however, good reason to be optimistic about identifying genes that increase the vulnerability to mood disorders. Advances in gene identification technologies, combined with the completion of the Human Genome Project, have provided a new foundation of understanding and the tools to undertake a more meticulous analysis of the

genetics of mood disorders. Recent successes in detecting susceptibility genes for other common but genetically complex disorders, including non-insulin dependent, or type II, diabetes and inflammatory bowel syndrome, that also had experienced the same type of conflicting analysis raise the real possibility that a concerted research effort using the same types of tools will yield similar breakthroughs in the genetics of mood disorders.

Gene-Environment Interactions

While mood disorders are highly heritable, non-genetic factors are also important and, for many depressive syndromes, may be just as significant as genetic factors. To date, the most studied non-genetic factor that is believed to contribute to depression or bipolar disorder is stress. Many cases of mood disorders seem to be preceded by periods of stress, but stress per se is not sufficient to induce depression or bipolar disorder in the vast majority of individuals. Accordingly, there has been considerable interest in preclinical research in studying the ways in which stress (including early life stress) might interact with genetic vulnerabilities to modify behavioral phenotypes.

Conversely, several forms of psychotherapy, including interpersonal psychotherapy (IPT) and cognitive-behavioral therapy (CBT), have been shown to be effective treatments for mild to moderate depression and effective additions to medications for more severe cases. As a result, there has been interest in understanding the neural and molecular mechanisms by which positive environmental experiences (e.g., enriched environment, optimized early life) modulate complex behavior.

Based on studies of different rodent inbred strains or mutants, it is clear that genetic factors can dramatically alter an animal's responses to stress, antidepressant treatments, and related perturbations. Conversely, environmental factors can compensate for genetic-based abnormalities. These interactions are not surprising, given the fact that experience changes the brain, that such changes are mediated by the same signal transduction pathways implicated in the long-term actions of psychotropic drugs on the brain, and that the functioning of these pathways is heavily dependent on an individual's genetic constitution. One goal of current research, then, is to better understand the precise mechanisms of interaction and use a combination of genetic and non-genetic perturbations to create improved animal models of mood disorders as well as of the effects of positive experiences on stress-related abnormalities.

Animal Models

Many studies of inbred strains of laboratory animals have shown that genetic factors are important in determining an animal's responses to stress as well as to antidepressant treatments. An understanding of these genetic factors could facilitate human genetic studies by suggesting individual genes, and even families of genes, that might contribute to mood disorders in humans. Such an understanding might also assist in the development of better animal models of mood disorders, discussed later in this chapter. However, as

with human studies, no specific gene to date has been related to naturally occurring differences in mood-related characteristics, or phenotypes, seen in animals.

One approach to improve the likelihood of identifying such genetic factors is to use a more carefully selected phenotype or perhaps intermediate biological traits on the pathways from genes to complex observable behavioral outcomes (so-called "endophenotypes") as an endpoint. For example, where depression might be considered a complex phenotype, increased physiological responses to a stressful stimulus would be considered endophenotypes. A given endophenotype may be a more precisely measured biological characteristic with a simpler genetic basis, and as such, identifying an endophenotype may make it easier to translate results between different species, including humans. As a result, as endophenotypes are identified in humans, it should be possible to model these in laboratory animals and attempt to identify any genetic determinants. In the case of bipolar disorder, for instance, disturbances in the sleep/wake or rest/activity cycle, as well as changes in the level of behavioral arousal during these cycles, could be conceptualized as possible endophenotypes that would be easily studied in rodents. Many individuals with bipolar disorder show abnormalities in rest/activity patterns and sleep/wake cycles that precede the onset of changes in mood, and mood stabilizing medications significantly alter the cycling of affective episodes over the longitudinal course of these disorders.

In some cases, endophenotypic traits can be observed in lower organisms, such as nematodes, flies, or zebrafish. Studies of such organisms are clearly not going to teach us about the detailed neural circuitry underlying complex emotions, but they do have the power to reveal new biochemical pathways that modulate basic neural and cellular functions that are abnormal in mood disorders. As an example, analyzing the pathways underlying carefully selected endophenotypes in model organisms could facilitate gene discovery and analysis of gene function in mammalian systems.

One approach to searching for genes involved in endophenotypes associated with depression is to start with an animal that has a genetic alteration—a mutation—associated with a particular abnormal behavior that is relevant to the mood disorders; disturbances in sleep would be one example. Such phenotype-based mutagenesis offers a powerful means of genetically dissecting complex behavior. Though these efforts will be difficult, several such phenotype-based mutagenesis programs focused on behavioral endpoints have been initiated recently. These programs will soon provide researchers with a large collection of mutant mice that have specific behavioral abnormalities relevant to the study of mood disorders. The power of this approach is its ability to generate a series of mice with subtle variants of phenotypes, something that will be critical for identifying a specific gene. The availability of the mouse genome sequence and rapid development of genomic technologies that enable mapping and positional cloning of mutations, combined with development of suitable phenotypic screens, should facilitate the search for the genes underlying behavioral traits in mice.

Many traits of biomedical interest exhibit continuous, quantitative variation and are therefore believed to be under the control of many genes. Simple examples of quantitative traits include height and weight; more complex examples would be mood, thought processes, and cognitive capacity. Genes controlling such traits can in theory be detected using an approach referred to as quantitative trait locus (QTL) analysis. Most QTL studies to date have been conducted on inbred mouse or rat strains that differ dramatically in a particular phenotype. The parental inbred strains are then mated, and the phenotype of individual animals resulting from these crosses are associated with a marker in a specific chromosomal region. Recent advances in both statistical methodology and molecular genetics have increased the possibility of identifying QTLs involved in several complex behavioral traits, such as fear and emotionality, learning and memory, response to mood-affecting drugs, and circadian behavior. However, despite these methodological advances, there have been no reports to date identifying the specific genes underlying QTLs related to behavioral abnormalities. It remains to be seen whether sequencing the mouse genome will facilitate successful identification of these genes or whether the traits identified involve too many different genes to isolate any individual genetic variation using a classical QTL mapping approach. In these circumstances, random mutagenesis approaches as described above may prove to be fruitful.

Several experimental strategies are currently being employed to generate single gene mutations in mice, and there are now many instances of such "transgenic" and "knockout" mice contributing to our understanding of mood disorders. For example, transgenic mice that overproduce the brain peptide CRH show several characteristics consistent with enhanced stress responsiveness and anxiety-like behavior. In contrast, mice lacking CRH or one of its receptors show the opposite phenotypes. Transgenic mice are also playing a critical role in efforts to understand the role that each of the fourteen subtypes of serotonin receptors plays in brain function and behavior. Mice lacking the 5HT1A receptor, for example, show increased anxiety-like behavior, whereas those lacking the 5HT1B receptor are more aggressive and more sensitive to mood-stimulating drugs.

The major limitation with these types of genetic models is that the mutations affect all stages of development and often many tissues and brain regions. As a result, it is difficult to ascribe a particular phenotype to a brain region of interest or to determine whether a phenotype reflects a developmental abnormality caused by the mutation or, rather, reflects loss of the adult function of the mutated protein. However, molecular biologists have now devised several "inducible" technologies that allow investigators to alter gene expression in specific tissues or at specific times during development. Though these techniques have only recently been developed, they hold particular promise for studying genetic factors involved in behavior and mood.

Behavioral Models of Mood Disorders

The best model of a disease is theory-driven. In the case of depression, for example,

researchers could replicate in a laboratory animal the various factors that cause depression in humans and, consequently, many of the symptoms as well. A related approach is to model a disease mechanism in a laboratory animal and recreate particular features of the disorder. Both of these approaches have been used with considerable success in recent years in creating animal models for several neurological conditions, such as Huntington's disease and certain forms of familial Alzheimer's and Parkinson's diseases, for which the underlying genetic abnormalities are known. These models are now being used to explore possible medications that can oppose or even reverse the fundamental mechanisms of the diseases. However, as stated earlier, we are still in the early stages in understanding the etiology and pathophysiology of depression, let alone the genetics, and so such approaches are not yet feasible for studying mood disorders. Also, many of the core symptoms of depression and mania involve higher brain functions that cannot readily be modeled completely in animals.

An alternative approach, then, is to reproduce in laboratory animals particular symptoms of depression. These models, which include most of those available today, can then be used to study the biological mechanisms underlying those symptoms and to develop new treatments that alleviate the symptoms. The main limitation of these models is that they may poorly reflect mechanisms involved in the human situation and as a result, the biological basis of the animal symptoms may differ from the biological basis of human symptoms. Drugs that treat the former may not treat the latter.

Studying Depression in Rodents

The most widely used animal models of depression involve subjecting rodents to a repeated stress and measuring the effects on behavior. For example, the forced swim test is the most widely used animal model in depression research, more specifically as a screen for antidepressant treatments. The test involves a rat's response to being forced to swim for some period of time. Short-term treatment with most antidepressants increases the time a rat will swim. Although this test is used empirically as a proxy for depression, one interpretation is that antidepressants may increase active coping responses to swim stress.

The test also provides a useful model in which to study the neurobiological and genetic mechanisms underlying stress and antidepressant responses. The test is not perfect, however. For example, antidepressants decrease immobility in the test after even single doses, despite the fact that the clinical effects of these agents require administration for several weeks or longer. Thus, the test is sensitive to the immediate effects of these agents and may not be picking up the true "mood-elevating" changes per se that these medications produce in the brain. A critical question in the field is whether any antidepressant, regardless of its mechanism, would be active in the forced swim test or whether the test can only detect drugs with monoamine-based actions. Ultimately, the answer to this question must await the development of clinically effective antidepressant drugs with novel mechanisms.

Learned helplessness is another one of a relatively large number of tests that helps us understand the stress response and its role in depression. Animals that develop learned helplessness show several changes that are reminiscent of depression, such as REM sleep alterations, reduced body weight, diminished sexual behavior, and elevated CRH and corticosterone levels. Repeated dosing with antidepressants, as well as repeated ECT, decreases the number of animals that show learned helplessness. Such treatment is also reported to reduce the various neurological changes seen in these animals.

The attractiveness of learned helplessness as a behavioral model of depression is that it is based on a plausible theory that links cognitive function to visceral results. Experience of exposure to uncontrollable stress leads the animal to learn that voluntary actions are no longer effective. Controversy has centered on whether the effects of learned helplessness are truly cognitive or simply products of stress-induced inactivity. However, it seems likely that both the cognitive and other behavioral outcomes may well be linked, thus helping to provide a reasonably integrated and broad picture of depressive symptomatology that is seen in humans.

Chronic mild stress and social defeat may serve as more naturalistic stress models, and thus may represent more accurately the relationship between stress and human depression. Stressed animals are reported to exhibit a general loss of pleasure as inferred from a reduction in sucrose drinking, as well as a variety of cardiovascular and neurochemical changes that may be reversed by longer-term antidepressant treatment. The major disadvantage of the chronic stress models is their poor reproducibility. Both the behavioral abnormalities produced by chronic stress and the palliative effects of antidepressants in these paradigms have been difficult to replicate across laboratories, which has reduced their general application.

Several models involving manipulation of early life environment have been used, including prenatal stress, early postnatal handling, and maternal separation, with environmental enrichment used as the opposite stimulus. The early life stress models produce neuroendocrine and behavioral changes in rats and mice that persist into adulthood. For example, animals subjected to early stress show a hyperactive HPA axis in response to stress. They also exhibit increased locomotor responses to novelty and, in some studies, greater vulnerability for learned helplessness and drug self-administration. The models are generally good in terms of their replicability, and have been successfully used with a variety of species, from rodent to non-human primate. In addition, many of the resulting abnormalities can be reversed by antidepressant treatment. On the other hand, abnormalities in cognitive performance that persist into adulthood have been less reliable, perhaps in part because such tests require a more sophisticated level of analysis. Studies aimed at understanding the neurobiological mechanisms of the various abnormalities seen are just now getting underway.

Non-Human Primate Models of Depression

While rodent models of depression have the obvious advantage of providing inexpensive

and readily accessible subjects for high throughput studies, there are limitations to studying exclusively rodents in animal models of human diseases, particularly those that involve a cognitive and emotional component. For this reason, it would be particularly useful to have a well-defined primate animal model.

There is a body of literature, albeit still relatively small, that has explored models of depression in primates. The focus of much of this research has been on the effects of early life stress in the form of maternal separation. In general, animals reared under these conditions show some signs that are similar to those of depressed humans. More recently, less extreme forms of early life stress have been explored in non-human primates. For example, mothers exposed to unpredictable stress are more likely to raise offspring with altered HPA activity and depression-like behavior as adults. These results are largely consistent with the rodent literature and are encouraging as potential primate models.

However, the majority of primate studies has been carried out on macaques, which are large animals that take 3 to 5 years to reach sexual maturity, making these studies difficult and expensive to carry out. Primate species that are smaller with shorter life spans may be more amenable to these studies. Any new primate model of depression should take into consideration special behaviors and environmental requirements of the particular species used and examine animals living in more naturalistic settings.

Animal Models of Mania

Bipolar disorder is unique among mental illnesses in that it is characterized by spontaneously alternating episodes of depression and mania, which often become more severe and cycle more rapidly as the syndrome persists. This oscillating pattern of the illness introduces a special difficulty in the development of an appropriate animal model for the overall syndrome. Traditional animal models for bipolar disorder have concentrated on modeling a single manic episode. Several such models have focused on the hyperactivity aspect of the disorder, while others are based on measures of motivation and reward or the effects of sleep deprivation. Nevertheless, there is as yet no bona fide rodent model of mania. There have also been attempts to develop animal models that target the progressive and cycling nature of bipolar disorder, including psychostimulant-induced sensitization. These paradigms, too, have failed to provide adequate models of the human syndrome; they also lack predictive validity of the efficacy of mood stabilizing medications. The lack of an appropriate, reliable model of mania and of bipolar disorder continues to greatly hinder attempts to understand the neurobiology of the syndrome as well as to develop improved therapeutics.

Psychostimulants, such as amphetamines, produce a range of behaviors in animals that appear similar to mania, including hyperactivity, heightened sensory awareness and alertness, and changes in sleep patterns. Furthermore, psychostimulant-induced hyperactivity is reportedly sensitive to lithium. Psychostimulant-induced hyperactivity is mediated by increased dopaminergic transmission in striatal regions of the brain, and

antipsychotic drugs, used in the management of acute mania, are dopamine receptor antagonists. Some studies have demonstrated that this model is also sensitive to anticonvulsant drugs that are effective against mania. Based on these findings, psychostimulant-induced hyperactivity in rodents has become a standard model for the screening of drugs to treat mania. However, the relevance of psychostimulant-induced hyperactivity to the mechanisms underlying mania remains unproven.

Sleep deprivation has a rapid antidepressant effect in approximately one-third of individuals, and is also capable of inducing manic episodes in susceptible individuals. Similarly, sleep deprivation in rats appears to trigger behaviors reminiscent of those characteristic of manic episodes. After 72 hours of sleep deprivation, rats demonstrate a period of insomnia lasting about 30 minutes. During this period, they are hyperactive, irritable, aggressive, and hypersexual; the insomnia and hyperactivity are reduced by lithium treatment. Sleep deprivation appears to enhance dopaminergic function in the brain, important for motivation, reward, and incentive drive. Overall, sleep deprivation in rats, despite the difficulties in controlling for non-specific stress effects and lack of reproducibility, is a potential model of mania that deserves further study.

The models described so far are designed to model a single manic episode. These models, while they may be valid to an extent, inherently fail to represent the full scope of bipolar disorder because they do not model the progressive and cycling nature of the syndrome. Such models require that animals display progressive responses that alternate between states that are similar, at least in part, to depression and mania.

One progressive phenomenon proposed to model aspects of mania is behavioral sensitization. The repeated administration of many psychostimulants leads to a gradual increase in drug-induced behavioral responses, most typically locomotor activity. The development and expression of sensitized behavior may resemble the progression of manic episodes in bipolar disorder, with gradual enhancement in severity and onset. However, attempts to "treat" behavioral sensitization with antimanic agents have been largely unsuccessful: lithium, valproate, and carbamazepine do not reliably inhibit this phenomenon. These findings have cast doubt on the usefulness of behavioral sensitization as an animal model for bipolar disorder.

Neurobiology and Drug Action

There is little doubt that over the next several years researchers will capitalize on data from the Human Genome Project and ongoing proteomics efforts to identify a host of new targets for drug development efforts. In the meantime, medicinal chemists and their colleagues are not at a loss for novel targets. For example, recent work has shown that monoamines and other neurotransmitters initiate a cascade of events within the post-synaptic neuron. This cascade can include effects on a variety of so-called second messenger systems, including those involving the regulatory molecule known as cyclic-adenosine monophosphate (cAMP), that in turn can trigger a wide range of biochemical events within the stimulated cell.

Evidence suggests that, in general, stimulation of some of these pathways is necessary for the action of currently available antidepressants. Consequently, medications that act directly on second messenger systems may be effective antidepressants.

There is also evidence that antidepressants stimulate a host of other intracellular events that affect gene regulation and expression. Each of these elements is a potential target for antidepressant drug development. Already, researchers believe that phosphorylation inhibitors active in the central nervous system (CNS) may possess antidepressant activity.

There is evidence, too, that depression and stress may interfere with natural nerve cell growth, or neurogenesis, perhaps in part by inhibiting the activity of neurogenic factors, such as brain-derived neurotrophic factor (BDNF), or of genes that prevent programmed celled death, also known as apoptosis. So far, all somatic treatments known to be effective in treating depression, including ECT, have in common the property of stimulating the expression of BDNF, and those tested also appear to enhance neurogenesis. Thus far, there is evidence that neurogenesis occurs in the hippocampus of the mammalian brain. At least one validated animal model of depression, maternal depression, is associated with reduced nerve cell growth in the hippocampus. Hence, molecules that enhance nerve cell growth could function as antidepressants.

There is limited and controversial evidence that changes in the expression of the signaling molecules known as cytokines, which are usually associated with immune function, may be involved in the disease processes that cause depression. Cytokines are expressed in the brain, and during development they play important roles in normal brain growth during fetal development. A recent study revealed that induction of increased cytokine activity was associated with depressed mood in normal volunteers. Should further work confirm a relationship between cytokines and depression, medications directed at cytokines might represent novel antidepressants.

Communication Between Cells

CRH is a major neuropeptide mediator of stress responses in the CNS. It is produced in the hypothalamus and causes the pituitary gland to release ACTH. CRH is also present in the limbic and cortical areas of the brain. Preclinical studies indicate that it plays an important role in a variety of behaviors relevant to anxiety and depression. Levels of CRH are increased in the cerebral spinal fluid of individuals with depression. Neuroendocrine studies are suggestive of increased CRH drive in the hypothalamus, and postmortem investigations have reported an increase in CRH neurons and a likely compensatory down-regulation in CRH receptors. This evidence suggests that a CRH antagonist might be useful for the treatment of depression or anxiety. CRH antagonists capable of reaching the brain have been developed, thereby allowing in the near future for an adequate investigation of their clinical utility in the treatment of depression and anxiety.

A class of compounds known as neurokinins, which includes substance P, was initially characterized for its potential role in pain control. Preclinical studies have found stress

increases the release of substance P. Some recent clinical studies have demonstrated that an antagonist of the neurokinin-1 (NK_1) receptor may be effective for the treatment of depression. NK_1 receptor activators may dampen serotonin neurotransmission, with the antagonist exerting the opposite effect. It is still unclear if this is the primary mechanism of action of NK_1 antagonists and, indeed, whether NK_1 antagonists truly possess antidepressant activity in humans. Large-scale clinical trials are currently underway to test this hypothesis.

There has also been interest in the possibility that the serotonin receptor known as 5-HT_7 may be a target for treatment of depression and possibly jet lag, the symptoms of which are caused by a disruption of circadian rhythms. The 5-HT_7 receptor is expressed in limbic brain structures, including the cerebral cortex and hippocampus, and it is also expressed in a part of the brain known as the suprachiasmatic nucleus, where it controls circadian rhythm. The 5-HT_7 receptor is coupled to the cAMP signal transduction cascade—antidepressant treatment up-regulates the cAMP signal transduction cascade in the hippocampus.

Another receptor that may be a good target for antidepressant drug development is known as the N-methyl-D-aspartate (NMDA) receptor, one of several that binds to the neurotransmitter glutamate. At least one research team has reported that chronic antidepressant administration has the effect of reducing this receptor's activity. In addition, NMDA receptor antagonists have antidepressant efficacy in certain animal models of depression. This is consistent with a preliminary report demonstrating that the anesthetic ketamine, an NMDA receptor antagonist, produces a rapid, but transient improvement in individuals with depression. NMDA receptor antagonists are also reported to block the atrophy of neurons in the hippocampus as well as the drop-off in neuronal growth that occurs in hippocampus response to stress. Further studies are needed to determine whether the NMDA receptor is a valid target for antidepressant medication. Excessive release of glutamate may be related to the pathophysiology of mood disorders. Several drugs that decrease the glutamate release by different mechanisms are currently being evaluated as antidepressants.

Receptors for the neurotransmitter GABA are of interest because of the discovery that levels of this neurotransmitter are decreased in the brains of individuals with depression and are increased by antidepressant treatment. This would suggest that molecules that interact with GABA receptors could have antidepressant efficacy. Since there are many different types of GABA receptors in the brain, it may be possible to find those that are most important in depression and target them for drug development efforts.

Communication Within a Cell

Intracellular signaling pathways, such as those involving cAMP, have many components and interact at many levels, forming complex signaling networks that allow the cell to receive, process, and respond to information. These networks are involved in integrating

nerve impulses across different time scales. They also generate distinct nerve-signal outputs depending on input strength and duration, and they regulate intricate regulatory loops. Given their widespread and crucial role in integrating and fine-tuning physiological processes, it is not surprising that abnormalities in signaling pathways have now been identified in numerous human diseases.

Such post-receptor signaling pathways represent the physiological targets for the nuclear receptor superfamily of hormones, which include glucocorticoids, thyroid hormones, gonadal steroids, and retinoids, that act within the cell nucleus. These actions presumably mediate the clinical manifestations of altered hormonal levels in many individuals with mood disorders. For example, they may be related to the frequent onset of bipolar disorder in puberty, triggering of episodes in the postpartum period, association of depression and possibly rapid cycling bipolar disorder with hypothyroidism, and triggering of depression in response to prescribed or illicit steroids. In addition, post-receptor signaling pathways have been implicated in regulating such complex and diverse behaviors such as mood, appetite, wakefulness, reward, learning, and memory consolidation. It is possible, then, that these signaling pathways are involved directly or indirectly in the treatment of mood disorders.

Chronic antidepressant treatment increases the activity of the cAMP cascade in the hippocampus and cerebral cortex, suggesting that agents that activate this pathway could be useful for the treatment of depression. One enzyme—cAMP-specific phosphodiesterase (PDE4)—degrades cAMP in the brain, raising the possibility that inhibitors of this enzyme might have antidepressant efficacy. Indeed, one relatively selective inhibitor of PDE4 appears to have antidepressant activity in both humans and animal models of depression, but this compound also produces intolerable nausea. Further work may be able to build off this discovery, however, since there are four distinct PDE4 genes in humans, three of which are expressed in the brain. It appears that two of these—PDE4A and PDE4B—may be good targets for further drug development efforts that could yield effective antidepressants that do not produce nausea.

Another important intracellular signaling pathway that may be involved in depression is the MAP (mitogen activated protein) kinase cascade. Antidepressants appear to interact with BDNF, an important molecule in the brain that activates MAP kinase and other intracellular cascades. Stress reduces BDNF expression in the hippocampus, whereas chronic antidepressant treatments cause neurons to increase their expression of BDNF genes. Antidepressant therapy also appears to prevent the stress-induced reductions of BDNF in nerve cells. In addition, BDNF has antidepressant efficacy in certain behavioral models of depression, suggesting that the BDNF-MAP kinase pathway may play an important role in some of the deleterious effects of stress on the hippocampus and that one mechanism by which antidepressants work may include increasing the activity of this pathway. Although speculative, this hypothesis forms the framework of preclinical

antidepressant discovery efforts aimed at identifying small molecules that might promote the activity of BDNF and the MAP kinase pathway.

The mood stabilizer valproate, used to treat bipolar illness, has also been shown to activate the MAP kinase cascade, though it is still unclear if this activity has anything to do with the mood stabilizing effects of the drug. However, it is clear that valproate and lithium both target another signaling pathway involving protein kinase C (PKC). PKC is highly enriched in the brain, and plays a major role in regulating neuronal excitability, neurotransmitter release, synaptic plasticity (how nerve cell connections change in response to a variety of stimuli), and long-term alterations in gene expression. Lithium and valproate, despite their completely different chemical structures, exert significant effects on PKC in a number of cell systems, including the brain, at therapeutically relevant concentrations. In particular, chronic, but not acute, administration of lithium or valproate causes selective reductions in the levels of PKC.

In view of the pivotal role of the PKC signaling pathway in the regulation of neuronal excitability, neurotransmitter release, and long-term synaptic events, it may be that decreasing the activity of the PKC pathway may contribute to the treatment of acute mania. To test this hypothesis clinically, a recent study investigated the potential antimanic effects of the breast-cancer therapy tamoxifen, which is a PKC inhibitor in addition to an estrogen receptor antagonist. Preliminary results suggest that tamoxifen does, indeed, possess antimanic efficacy. Larger double-blind, placebo-controlled studies of tamoxifen are currently under way, and it is anticipated that the availability of more selective PKC inhibitors will allow for a more direct test of this hypothesis in the future.

Glycogen synthase kinase-3β (GSK-3β) may be another target for lithium. GSK-3β not only controls developmental patterns in diverse organisms, including mammals, but also plays an important role in the mature CNS through its involvement in several intracellular signaling pathways. GSK-3β has also been implicated in regulating the phosphorylation of a protein known as tau, which is implicated in neurodegenerative processes such as those characteristic of Alzheimer's disease. Thus, inhibition of GSK-3β by lithium may afford protection against cell death that is induced by certain stimuli. Researchers have developed several selective GSK-3β inhibitors recently, and are currently testing them in rodent models of mood and neurodegenerative disorders.

Postmortem analyses have shown that recurrent mood disorders and other stress-related illnesses may be associated with significant reductions in the volume of specific regions of the brain, as well as in the numbers or sizes of neurons and glia in those regions. A new area to explore in this regard is the effect of lithium on neuronal plasticity.

Opportunities for Progress

The past 15 years have seen an unprecedented advance in our knowledge about the biochemical, neural, genetic, and behavioral foundations of depression and mania. There is no doubt today that depression and bipolar illness are brain disorders resulting from

complex interactions among many biochemical, genetic, cognitive, behavioral, and environmental factors. Although the task of identifying those factors and how they interact to produce the ultimate symptoms of depression and mania is undoubtedly one of the more difficult facing biomedical researchers, it is apparent that the past decade and a half of research has laid the groundwork for dramatic progress in the near future.

Opportunities to Discover a Genetic Basis of Mood Disorders

The tremendous progress in molecular biology, neuroscience, and related fields is likely to lead to new approaches to the genetics of mental disorders in general and mood disorders in particular. Identification of all of the genes in the human genome and their functional variation will provide opportunities for studying the impact of those variants on phenotypic outcomes of interest. New research tools, such as microarray techniques that can detect tissue-specific expression, transgenic mice, expression arrays, and proteomics, are allowing researchers to identify gene function. Parallel research across numerous species is providing important sources of information regarding gene expression, phenotypic models, and gene-environment interaction.

However, as geneticists move from studying single gene disorders to complex disorders, they will require still other tools to dissect the multiple interacting factors. The major focus on genetic studies has now shifted from a search for the gene to which genes in which contexts lead to the development of mood disorders. The highly restricted sampling of the earlier generation of studies is likely to move into the general population where the concept of attributable risk will become important. Finally, enhanced knowledge regarding genetics will be critical for health care professionals and the public alike to ultimately apply genetics findings to human diseases.

There is widespread agreement among researchers in the field regarding the limitations in applying the current nomenclature for mental disorders to biologic studies. Mood disorder phenotypes based solely on clinical manifestations without biological markers lack conclusive evidence for the validity of classification and reliability of measurement. The lack of specificity of biologic and psychosocial risk factors and correlates, as well as the lack of longitudinal stability, still suggests etiologic and phenotypic heterogeneity.

It will be critically important to establish population-based samples of mental disorders, including members of all the racial and ethnic groups that make up our society. Having such populations available for study will be increasingly valuable in validating the numerous genetic tests that will emerge from advances in human genetic research and the Human Genome Project. It will be necessary to identify more homogenous subtypes of mood disorders through family and high-risk research investigating both biologic and contextual factors, as well as familial patterns among affected and unaffected individuals to estimate strength and mode of genetic transmission. Quantification of risk at the levels of the individual and population will also be an important area of study, as will the

development of a richer conceptualization of environmental factors that may be important mediators of expression of genetic risk for mood disorders.

The lack of public understanding of the concepts of genetics and ethical standards employed in mental health/mental illness genetics studies has led to substantial concern regarding the possible risks of participating in genetic studies. Accurate information, based on solid empirical testing, is the cornerstone of genetic counseling. Even though there is still a lack of specific genetic or biologic markers for mood disorders that can be employed for pre-diagnostic testing or genetic counseling, familial recurrence risks, adjusted for the effects of familial loading, clinical severity, age at onset, mood disorder subtype and comorbid disorders, can provide estimates of the probability of mood disorders in unaffected relatives.

Since the majority of studies to date involve families of people in treatment for mood disorders, there is generally ample opportunity for explaining the goals, benefits and possible risks of participation in genetics studies. As the sampling base expands to the community, more attention should be devoted to the development of education programs regarding the role of genes in disease in general as well as their current and predicted future role in informing our understanding of both individual and population-based risk. Recruitment, consent procedures, testing, and interpretation remain important future areas that must be addressed.

Similar to different distributions in the prevalence of particular diseases in ethnic and racial subgroups, there are now some well-established differences in racial and ethnic groups, particularly with respect to drug response. For example, several recent studies have demonstrated differences among whites, Asians, Black Americans and African Blacks in the frequencies of alleles of CYP2D6, the liver enzyme that metabolizes tricyclic antidepressants. Investigators have shown that such differences usually reflect differences in the distribution of polymorphic traits, rather than a trait that is unique to a particular population subgroup, and that both genetic and environmental factors contribute to racial and ethnic differences in drug response. Such differences may have important implications for the treatment of mood disorders and may ultimately guide selection of pharmacotherapeutic agents. However, the widespread differences within racial and ethnic groups should also minimize characterization of these groups based on race alone, since geographic origins and other shared cultural factors may be equally important in defining diverse population groups.

Despite proportionate representation of racial and ethnic minority groups in many family studies, there is little research on familial aggregation of mood disorders or other mental disorders in samples from the wide variety of ethnic and racial populations that have sufficient statistical power to investigate sources and patterns of familial aggregation. Likewise, despite large ethnic differences in rates of twin births, there has been little research on twins of any given ethnicity, with the exception of a small number of studies involving Caucasian samples. Yet studies of discordant twins are an ideal source of information on cultural and environmental risk factors. Although there is substantial

fear of misuse of genetic data among members of all population groups, the benefits of advances in genetics should be widely available to all individuals, regardless of their gender, ethnicity, or racial origin.

Another issue for future research is the extent to which children should be included in genetic linkage and association studies, since few of the genetic studies of bipolar disorder include youth under age 18. However, researchers have shown similar prevalence rates of bipolar disorder among adolescents and young adults in community samples to those seen in adult samples. Other studies have demonstrated the stability of bipolar disorder from adolescence to young adulthood; nearly one-third of those with bipolar disorder prior to age 18 had additional episodes in early adulthood. Moreover, the expression of bipolar disorder was specific since few adolescents with other disorders, including depression or subthreshold mania, progressed to bipolar disorder in adulthood. This work documents the importance of inclusion of youth in family and genetic studies of mood disorders.

Opportunities to Understand the Neural Basis of Mood and Emotion

Progress in neuroscience, particularly developmental neuroscience that investigates molecular, cellular, and integrative brain functions that are involved in the development of mental disorders, will advance our understanding of the complex biologic processes underlying mood disorders. The tools of neuroimaging, psychophysiology, and preclinical models of emotion are likely to provide information on developmental pathways to mood disorders. Likewise, a better understanding of the impact of environmental exposures in modifying the development of emotion and mood regulation will provide new opportunities to investigate mechanisms underlying changes that occur in the brain both before the development of mood disorders and during the appearance of symptoms.

In the behavioral realm, it is an opportune time for researchers to investigate more fully the cognitive and psychosocial processes involved in depression and bipolar disorder reviewed herein. For example, given the role that negative cognitive styles and information processing play as potential vulnerabilities for depression and possibly for bipolar disorder as well, the opportunity exists to determine the precise biological mechanisms by which cognitive vulnerability is translated into a mood disorder.

Perhaps the biggest challenge—and opportunity—facing researchers in the coming years is to integrate biological and cognitive approaches to depression and bipolar disorder. Indeed, given the major advances that have occurred in understanding both the cognitive and psychosocial antecedents of depression and the biological and neural bases of emotional and motivational systems, respectively, the time is ripe for an integration of the cognitive and biological approaches to depression and bipolar disorder. Work on two fundamental psychobiological systems, the behavioral activation system that regulates approach behavior to attain rewards and goals, and the behavioral inhibition system that regulates withdrawal and/or inhibition of behavior in response to threat and punishment,

may dovetail with the cognitive vulnerability-stress models of depression. For example, when a vulnerable individual experiences a negative life event and makes inferences about that event that lead to hopelessness about achieving important current and future goals, the neurobiological systems involved in these cognitive processes may be those that inhibit the behavioral activation system.

However, the circuitry that supports the behavioral activation system and the behavioral inhibition system is likely to be complicated and distributed across a number of interconnected structures, including the prefrontal cortex, anterior cingulate, amygdala, and hippocampus. It is therefore overly simplistic to describe merely overall changes in the activation of these hypothetical systems. Fortunately, we now have the tools to interrogate the detailed circuitry underlying these systems, and future research will need to harness these methods to better understand the neural substrates of these hypothesized diathesis-stress interactions.

There is also a need for cross-boundary studies that relate specific abnormalities in particular brain regions to objective laboratory tasks that are neurally inspired and designed to capture the particular kinds of processing that are hypothesized to be implemented in those brain regions. Investigators have conducted relatively few studies of this kind, and most studies on people with depression that have tried to relate individual differences in neural activity to behavioral phenomena have used self-report or interview-based indices of symptoms. In the future, it will be important to complement the phenomenological description with laboratory measures that are explicitly designed to highlight the processes implemented in different parts of a particular circuit.

These studies should include measures of both functional and structural connectivity to complement the activation measures. It is clear that interactions among the various components of the circuitry are likely to play a crucial role in determining behavioral output. Moreover, it is possible that connectional abnormalities may exist in the absence of abnormalities in specific structures, underscoring the need to include measures of connectivity in future research.

In addition, there is little argument that depression refers to a heterogeneous group of disorders, suggesting that depression-spectrum disorders can be produced by abnormalities in many different parts of the brain's neural circuitry. As a result, it is likely that some of the heterogeneity that might be produced by deficits in particular brain components will not map precisely onto the diagnostic categories developed from descriptive psychiatry. A major challenge for the future will be to build a more neurobiologically plausible scheme for characterizing the heterogeneity of depression based on the location and nature of the abnormality in particular circuitry. Though undoubtedly ambitious, such an effort will lead to considerably more consistent findings at the biological level and also will enable us to more rigorously characterize different forms of depression.

Brain Structure and Mood Disorders

Opportunities now exist to use the various brain imaging technologies, in conjunction with longitudinal studies, to determine if neurochemical and structural abnormalities precede the onset of the disorder, co-occur with the onset of the disorder, or follow by some time the expression of the disorder. It is likely that the timing of the abnormalities in relation to the clinical course of the disorder varies for different parts of the circuitry.

However, *in vivo* neuroimaging does not permit the direct investigation of diseased brain tissue. Clearly, postmortem human brain studies are limited in certain ways by factors such as confounding variables that cannot be directly controlled. However, direct studies of postmortem human brain tissue provide the only vehicle for exploring, at molecular and cellular levels, the alterations in neural circuitry that give rise to the clinical manifestations of mood and other mental illnesses. In addition, the study of human brain tissue is essential for the harnessing of the recent powerful advances in functional genomics and of the promise of proteomics to our efforts to understand the critical neurobiology of these disorders. Thus, investigations of the postmortem human brain represent a critical component of the programmatic study of mood disorders. However, as in any area of scientific investigation, such studies must be conducted with an astute awareness of their strengths and limitations, and with the inclusion of other types of studies that mitigate these limitations.

In other brain disorders, such as Alzheimer's disease, postmortem studies have proven to be useful by providing the "gold standard" for diagnosis, delineating pathogenesis, producing informative leads for candidate genes, and revealing possible relationships between brain abnormalities and the clinical symptoms of the illness. In the case of mood disorders, as for most mental illnesses, almost no firm data exist in any of these areas. Recent studies from several research groups have produced findings suggesting that depression and bipolar disorder are associated with a reduction in glial cell density in the multiple regions of the prefrontal cortex. However, this abnormality is unlikely to be diagnostic of the disorder, and how it may relate to genetics, pathogenesis, or pathophysiology is unclear at present and certainly represents an important gap in our understanding of this disorder. Effectively utilizing postmortem studies to address these types of questions requires consideration of the following types of resources and research strategies.

Clearly, adequate sample sizes of postmortem human tissue specimens must be available for such studies. But beyond numbers, the success of such investigations rests on the extent to which the samples are well characterized, the studies are well designed and appropriate for the question of interest, and the potential confounds of the studies are well considered. Regarding sample characterization, not only is a full reconstruction of the person's history required for accurate diagnosis, but the outcome of many studies may also be dependent on knowing the state of the illness at the time of death. For example, published studies typically indicate that subjects met diagnostic criteria for depression, but

fail to specify whether the diagnosis was based on a single episode or recurrent illness and whether the subject was actually depressed at the time of death. Similarly, the phase of bipolar illness at time of death is frequently not indicated. Clearly, such information may prove critical for testing hypotheses that episodes of illness are precipitated by changes in nerve growth in certain brain regions or that structural changes in the hippocampus reflect total lifetime duration of depression.

Differentiating between the effects of the illness and the consequences of its treatment on particular brain structures would ideally be assessed in never-medicated subjects. However, since an adequate sample of postmortem brain specimens from never-medicated subjects with depression or bipolar illness is unlikely to ever be available, several less direct approaches must be used to address this question. These approaches include comparing data from subjects who were on or off medications at the time of death, examining subjects with other disorders who also were treated with these medications, and using animal models that mimic the clinical treatment of mood disorders.

Certainly, the first two approaches have obvious, and difficult to control, potential confounds. Long-term exposure to medications, as is typical in the treatment of recurrent major depression and bipolar illness, may have effects on brain morphology, neurochemistry or gene expression that persist for a substantial period of time after the drug is discontinued. In the case of animal models of drug effects, many studies have been conducted in rodents with dosage and time parameters that do not necessarily reflect the human treatment condition. These limitations can be overcome through studies in non-human primates that involve extended periods of treatment with doses that produce serum drug levels shown to be therapeutic in humans. However, that still leaves the problem of potential species differences and the possibility that the medications of interest may have different effects on the brain of an individual with depression or bipolar disorder than on the normal brain. Despite the limitations of each of these three approaches individually, convergent findings across approaches should lead to reasonable, if provisional, conclusions about the influence of medications on the brain measures of interest.

The value of postmortem human studies may be increased when they are conducted within the context of animal investigations that have characterized the neural circuitry of interest. One obvious gap in this regard is the relatively little knowledge that exists about the actual circuitry and functional architecture of the cortical regions in the primate brain that are implicated in mood disorders. Both the design and interpretation of human postmortem studies will be improved by an integration with parallel animal studies of the same systems of interest.

Opportunities to Discover New Drug and Physiologic Treatments

With the wealth of potential drug targets now available, the opportunity exists to accelerate the process of discovery in mood disorder treatments so as to make quantum

leaps toward novel treatment techniques. There are, however, questions concerning the roles that government, consumer advocacy groups, academia, and industry should play in the effort to develop new therapeutics for depression and bipolar disorder. Fortunately, NIMH is able to take advantage of the experience of other NIH institutes that have wrestled with the identical problem of how best to foster the development of novel and better therapeutics.

For example, the National Cancer Institute (NCI) has had a drug development program for over 20 years, started in an era when treatments for cancer were not being aggressively pursued by pharmaceutical companies. NCI has recently articulated the goal of encouraging mechanistically novel drug development for cancer treatments. The institute currently supports a complex set of modular mechanisms including repositories of drugs, natural products, research tools and information, as well as preclinical and clinical drug development services, all available to NCI grantees and small business contractors (http://dtp.nci.nih.gov). The National Institute of Allergy and Infectious Diseases (NIAID) has initiated a program for drug development in AIDS in order to facilitate new therapies and, when necessary, support preclinical and clinical development. NIAID also has a modular, flexible but integrated preclinical/clinical grant program for academia, and a contract program for small business researchers, to facilitate drug development not only for AIDS but also for its accompanying opportunistic infections; they aim to target research to gaps in treatment knowledge (http://www.niaid.nih.gov/aidstherapeutics). In the process of these efforts, NCI and NIAID have both developed a clinical trials network with well-trained clinical scientists who not only conduct scientific trials, but also develop improved rating scales for specified clinical endpoints and focus on identifying biomarkers for drug action.

Biomarkers

New methods from cognitive and affective neuroscience provide an unprecedented opportunity to use non-invasive techniques to examine the function of brain circuitry underlying disturbances of cognitive and affective processing in mood disorders. These methods take the general approach of defining behavioral constructs and developing valid behavioral probes that are incorporated into studies to reveal activity in the relevant brain networks. Reliable methods now exist to examine the brain circuitry associated with attentional and executive functions, and to define the abnormal cerebral activation patterns in unipolar depression and bipolar disorder. Conceivably, a “normalization” of these abnormal cerebral activation patterns could define drug activity, and provide new tools for studying the pharmacology of mood disorders. Similarly, reliable paradigms have been developed to examine activity in subcortical and limbic circuits associated with processing reward, threat and other kinds of emotionally relevant information. Deficits in these functional domains are widely reported to be present in individuals with mood disorders.

Despite the dramatic increase in research into the neural basis of normal cognitive and emotional processes, not enough has been done to apply these methods to the investigation of mood disorders. However, the potential for these tools to provide insights into pathophysiology and mechanisms of action of treatment, as well as to serve as predictors of outcome, is considerable, and the non-invasiveness and potential wide availability of novel imaging technologies, such as functional magnetic resonance imaging, make these tools especially attractive. Facilitating the application of cognitive and affective neuroscience based imaging methods for use as potential biomarkers could lead to significant progress in the diagnosis and treatment of mood disorders.

The majority of work to date on biomarkers has examined peripheral markers, including catecholamine levels in plasma and urine, platelet markers such as the serotonin transporter, and plasma measures of the HPA axis such as cortisol and CRH. The studies on peripheral biomarkers in mood disorders were initially quite popular and well received by the research community. However, a strong counter-reaction to the catecholamine and platelet measures subsequently developed, in large part because they did not clearly reflect CNS activity or function. In contrast, studies of the HPA axis (including plasma cortisol) have continuously flourished, showing the role of extra-hypothalamic areas in regulating and being affected by cortisol.

Pharmacogenetics and Its Contributions to Drug Discovery and Drug Utilization

Pharmacogenetics seeks to find DNA markers for medication treatment outcome, including both response to and the potential for side effects from a particular treatment. One goal for pharmacogenetics is to have a set of polymorphisms that predict relative response and tolerability to specific classes of antidepressants and/or to specific members of classes. The suite of genetic variants could also help predict which people need longer-term maintenance treatment. Identification of polymorphisms predicting medication intolerance could help avoid unnecessary exposure to various drugs. Pharmacogenetics could also stimulate the development of new agents with even more specific or targeted modes of action. Many polymorphisms could be identified in public databases using candidate loci chosen based on current understanding of antidepressant mechanisms of action.

Research Priorities

1. Opportunities to Discover a Genetic Basis of Mood Disorders

OBJECTIVE 1. Enhance validity of mood disorder phenotypes by the identification of more heritable and homogeneous subtypes of mood disorders for use in molecular genetic studies.

Implementation:

■ Use existing and new data sets to identify highly heritable subtypes of mood disorders and intermediary biologic phenotypes (e.g., sleep parameters, circadian rhythm, hyperactivity, mood regulation, stress reactivity, psycho physiologic function, autonomic reactivity, and neural structure and function) for inclusion in molecular genetic studies of mood disorders.

■ Refine the classification of mood disorders by examining components of mood disorders and intermediary biological phenotypes in existing high-risk family studies and prospective longitudinal studies of mood disorders and related phenotypes.

OBJECTIVE 2. Identify genes that produce vulnerability and resilience to mood disorders and study gene x environment interactions, by capitalizing on existing resources and data sets, particularly population-based data.

Implementation:

■ Pool data and support meta-analyses of existing linkage studies of bipolar disorder to determine if positive linkage findings can be replicated using identical phenotypes and statistical methods across studies.

■ Identify the most heritable subtypes and endophenotypes of mood disorders (e.g., sleep patterns, atypical features, stress reactivity, mood regulation, and neuroendocrine function).

OBJECTIVE 3. Enhance the broad availability and coordination of core research resources in extramural and intramural genetics research programs for use in future genetic studies of mood disorders.

Implementation:

■ Continue to stimulate broad and free sharing with the scientific community of research resources, including clinical data and DNA, collected in genetic studies and clinical trials supported by NIMH.

2. Opportunities to Understand the Neural Basis of Mood and Emotion

OBJECTIVE 1. Identify measures of core symptoms of depression and mania that can be modeled in animals (e.g., indices of cognitive processes, sleep disturbances, or reward mechanisms) as an essential first step in model development.

Implementation:

■ Identify objective clinical measures, biomarkers, and relevant behavioral indicators of

depression and mania that are amenable to measurement in both clinical populations and animals (i.e., parallel measures).

— Identify and expand human and non-human experimental paradigms measuring processes associated with core cognitive symptoms.

— Develop other indicators of mood and affect including vegetative functions (e.g., sleep measures) and reward assessment, and discussion of ways to measure these in humans and in animals.

— Develop procedures to cross-validate measures employed in animal studies in clinical populations.

■ Develop cognitive measures in non-human primates.

— Develop a targeted initiative to encourage studies employing homologous models of neurocognitive deficits of human mood disorders in non-human primates.

■ Identify strategies for developing measures relevant to bipolar disorder to be used in animal models.

— Identify clinical markers indicative or predictive of manic and depressive episodes and rapid cycling in bipolar disorder that may be modeled in animals.

— Compare and refine desired attributes with existing models of depression and psychosis.

— Identify measures of both positive and negative affect.

OBJECTIVE 2. Establish how experiential and genetic factors interact to modulate neural and behavioral indicators of mood disorders.

Implementation:

■ Identify potential causes and compensatory changes in the development of mood disorders using longitudinal, prospective studies of brain structure and function, as well as examining environmental and psychological factors. Particular attention should be paid to an integrative review of risk factors and prospective design issues.

■ Identify progressive changes in brain activity and cognitive, emotional, and behavioral processes pre- and posttreatment for psychosocial and/or pharmacological interventions, and ancillary studies using both short-term longitudinal studies and later multisite studies.

OBJECTIVE 3. Expand resources in support of greater quality, availability, and use of postmortem brain tissues for studies of brain structures and circuitry related to mood disorders.

Implementation:

■ Create a national infrastructure for postmortem studies that promotes tissue preparation and clinical characterization, including medical disorders comorbid with depression.

■ Develop and apply markers of glial pathology in studies of brain regions implicated in mood disorders.

OBJECTIVE 4. Evaluate and extend cellular, anatomical, and electrophysiological models targeting brain circuits relevant to mood disorders.

Implementation:

■ Engage clinical neuroimaging investigators, along with systems neuroscientists, electrophysiologists, and scientists employing *in vitro* systems to:

— Identify mechanisms for validating cellular or circuit-based models.

— Explore circuit-based models for drug development.

■ Develop tools and reagents such as inducible and targeted mutant mice, selective ligands, and imaging techniques to facilitate model development and validation.

— Create pathophysiology-based animal models for mood disorders, especially mouse models that take advantage of advances in genomics.

OBJECTIVE 5. Develop parallel behavioral and neurobiological measures of affect and affect regulation that can be used across species to facilitate new models of mood disorders and the search for specific endophenotypes.

Implementation:

■ Initiate collaborations between animal researchers and clinical scientists to study specific model systems (e.g., hedonic and regulation of eating).

■ Increase the number of studies with non-human primates to better understand neural activity associated with complex systems of behavior.

OBJECTIVE 6. Develop a detailed understanding of the fundamental mental/emotional states and processes that characterize mood disorders as well as normal functioning.

Implementation:

■ Distinguish the positive and negative affectivity in emotion, mood, and temperament; and differentiate reactivity versus regulation of these processes in clinical vs. non-clinical populations.

■ Use multidisciplinary approaches that combine phenomenological, behavioral, and neurobiological measures, and explicate the heterogeneity of depressive disorders.

■ Develop and validate behavioral tasks to relate behavioral dysfunctions in mood disorders to specific aspects of brain function.

OBJECTIVE 7. Develop new etiological approaches to understanding bipolar disorder.

Implementation:

■ Identify the distinctive variations in cognition, social cognition, mood, and mood regulation that characterize bipolar disorder.

OBJECTIVE 8. Develop models to examine the behavioral and/or neurochemical impact of early life stressors on later susceptibility to adverse effects of stress in genetic mutant mice.

Implementation:

■ Phenotype differences in susceptibility and resilience of male and female mutant mice.

■ Examine the impact of environmental manipulations across several developmental periods (e.g., early peri/post natal, pre- and post-puberty).

3. Opportunities to Discover New Drug and Physiologic Treatments

OBJECTIVE 1. Establish quantitative outcome measures and biological markers for the diagnosis and assessment of disease progression and treatment of mood disorders.

Implementation:

■ Identify and validate quantitative outcome measures and instruments for assessing depression (e.g., cognitive, behavioral, psychometric measures, new rating scales).

— Ensure representative samples of women, children, the elderly, and racial and ethnic minority participants in the norming process.

■ Identify biological markers (e.g., imaging and genetic markers) for assessing risk, course of illness, and predicting treatment response or relapse.

— Develop guidelines for the validation of new quantitative outcome measures, instruments, and biological markers in clinical effectiveness trials in collaboration with representatives from the Food and Drug Administration (FDA), academia, and industry.

OBJECTIVE 2. Develop neurochemical tools for understanding disease pathophysiology and identify molecular targets for drug discovery.

Implementation:

■ Accelerate the development of novel ligands for PET, single photon emission computed tomography (SPECT), and functional brain imaging as probes to elucidate pathophysiology,

to identify disease targets, and as biological markers to assess disease progress and treatment response.

■ Expand chemical repositories to increase the availability of unlabeled imaging ligands/precursors for basic and clinical research.

OBJECTIVE 3. Model depression/depression-like and mania/mania-like symptoms that are side effects of pharmacological treatments for non-psychiatric disorders.

Implementation:

■ Create models for understanding the mechanisms whereby pharmacological treatments (e.g., interferon alpha, tumor necrosis factor (TNF), retinoic acid) for non-psychiatric disorders induce depression/depressive-like and mania/mania-like symptoms as side effects.

OBJECTIVE 4. Establish a drug development program that conducts proof of concept studies of innovative compounds for the treatment of mood disorders.

Implementation:

■ Support a targeted clinical trials network to conduct proof of concept studies of therapeutic compounds and to validate novel outcome measures, instruments, and biomarkers.

— Identify therapeutic candidates for proof of concept studies.

OBJECTIVE 5. Establish long-term partnerships between government, academia, and industry to accelerate innovative drug discovery and the development of behavioral assays for evaluating novel therapeutics.

Implementation:

■ Facilitate partnerships between NIMH, academia, and industry to support innovative approaches for drug discovery and the development of behavioral assays using NCI's National Cooperative Drug Discovery Group program as a model.

OBJECTIVE 6. Identify novel drug targets to assess differential treatment response.

Implementation:

■ Identify single nucleotide polymorphisms (SNPs) and haplotypes that index both therapeutic response and adverse events.

■ Collect DNA and other biological samples from ongoing large, multisite NIMH clinical trials in mood disorders, and make both DNA and clinical data available for pharmacogenomics research by the broader scientific community.

OBJECTIVE 7. Explore further development of somatic treatments for mood disorders.

Implementation:

■ Develop guidelines for appropriate control ("sham" or other) conditions, including adequate informed consent for the study of somatic treatments in collaboration with the FDA and academia.

■ Encourage collaboration among clinical, preclinical, and neurological investigators to: (a) delineate the mechanisms of action of new and existing somatic treatments; (b) apply knowledge gained from the use of somatic treatments for neurological disorders to inform research and practice for mental disorder treatments; and (c) develop promising animal model approaches, e.g., magnetic seizure induction for use as potential human clinical interventions.

I'm 13 years old and I'm really depressed. I love chatting on the computer, but think I am a little antisocial. I have had friends say they were going to kill themselves. One did. He had been my best friend for 3 years. I loved him so much and cried and begged, but he did it anyway so I am depressed about that. I think suicide would do it. I haven't told my parents yet. I'm afraid they will take my chat away. My parents are at work all day so I'm left alone. I'm stuck. I need your help and I need it fast.

Dimensions of Age and Disease

The prevalence of mood disorders is not constant throughout the human life span. In fact, the types of depression that occur early in life are likely to be different than those that occur late in life, when comorbid illnesses can play a significant role in psychological well-being. The influence of puberty, pregnancy, childbirth, and menopause also has a marked influence on the occurrence of mood disorders.

One picture of the natural history of mood disorders comes from the National Comorbidity Survey (NCS), which assessed a representative U.S. population sample of over 8,000 people, aged 15 through 54. The 30-day prevalence for an episode of major depression was 4.9 percent. It was highest (6.1 percent) in the youngest group surveyed (15-24 years) and lowest (3.9 percent) in the oldest group surveyed (45-54 years), suggesting that depression does not occur uniformly in all age groups. Prevalence rates also suggested more depression in younger participants; for example, the rate was scarcely higher in the oldest group (16.7 percent) than in the youngest (15.7 percent). A more detailed breakdown of the NCS data shows the highest 12-month prevalence in females during their late teens, and in males during their early 20s.

Prior to the 1980s, clinical and epidemiologic research on depression was confined almost entirely to adults. It was somewhat surprising, then, when national surveys noted that adults often reported onset of their depressive disorder in the late teens or earlier. Now that studies of children and adolescents are available, it is becoming clear that many—perhaps most—individuals with a depressive disorder began to experience serious symptoms early in adolescence, and that their vulnerability to develop these conditions may have been established even earlier.

An important aspect of the prevalence of unipolar depression is the marked gender-by-age change during adolescence. Until approximately age 13, depression is equally common in boys and girls. After that age, the rate increases two- to three-fold in females, in whom it continues to occur at a higher rate until after middle age. The rate also increases in boys, but not as much as in girls.

Classically defined bipolar disorder occurs infrequently in young people. The NCS estimated the lifetime prevalence of the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition revised (*DSM-III-R*), bipolar I disorder in 15- to 54-year-olds at 0.4 percent, and the 1-year prevalence at just under that figure. Recent surveys of adolescents report a 3-month prevalence of bipolar disorders (primarily hypomania) at 0.25 percent in children ages 9 to 13 and a "lifetime" prevalence of bipolar disorder of approximately 1 percent in older adolescents ages 14 through 18. However, these estimates are uncertain for various reasons. First, few studies possess adequate population samples to estimate prevalence accurately. Second, controversy remains concerning possible differences between clinical presentations of childhood versus adult bipolar disorder. Few studies have followed the same individuals over time to resolve this controversy by providing a careful, developmentally informed bipolar diagnosis. Hence, the actual population prevalence of prepubertal bipolar disorder is unknown.

Bipolar disorder exhibits little gender specificity or gender-by-age variation from adolescence to adulthood. Retrospective studies of adults report onset beginning in late adolescence. The similarity of 12-month and lifetime rates of bipolar disorder in adults from the NCS suggests that once established, this is a chronic disease. For clinically referred children and adolescents, it also appears that bipolar disorder is a chronic disease. However, the appropriate diagnosis for prepubertal children who may show symptoms of mood lability, extreme irritability, or rapid mood cycles remains an unresolved question. It is unclear, still, whether this is an early form of bipolar disorder or if it should be classified differently.

Late-life depression principally affects individuals with other medical and psychosocial problems, including cognitive dysfunction, disability, medical illnesses, and social isolation. The clinical associations of late-life depression have guided the development of hypotheses on mechanisms predisposing, initiating, and perpetuating specific mood syndromes.

Current Status of the Field

Mood Disorders in Children

Developmental Factors

Thirty years ago there was doubt about whether children could even experience depression; today the question is not whether children can suffer from depression but rather how many adult mood disorders are truly "adult onset," and how many are recurrent episodes of a disorder that had its onset in childhood or adolescence. Answering these questions is difficult, as there have been no published diagnostic studies of unipolar depression in population samples of children below ages 8 or 9. Indeed, there is a need for new diagnostic methods useful in children as young as preschool age, and for ways of

assessing possible early subthreshold manifestations of depression and monitoring their persistence over time.

Hormones

Puberty seems to be a time when children are most at risk of developing depression, particularly for girls. The changing levels of various hormones characteristic of puberty, including estrogen and testosterone, may affect brain function. Similarly, structural changes in the brain occur during puberty that may influence social roles. Other studies suggest that social changes may influence numbers of depression-triggering life events, or that mismatches may occur with the norms of the social group, as when some girls mature earlier than their peers. Evidence is also emerging that exposure to increased levels of testosterone and estrogen at puberty, especially in the context of social stress, independently predicts risk for depression among vulnerable girls. Clearly, high levels of estrogen and testosterone alone cannot "explain" depression, but understanding the manner in which hormones affect the brain could have great potential for preventing depression in girls at high risk.

Anxiety

Depression during childhood and adolescence is likely to be preceded, accompanied, or followed by other mental disorders. For example, anxiety disorders are some eight-fold more common in depressed than non-depressed children and adolescents, while conduct and oppositional disorders were 6.6 times more common. Similarly, attention-deficit/hyperactivity disorder (ADHD) was 5.5 times as common in children and adolescents with depression as in their unaffected peers. The onset of depression appears to follow the onset of other disorders, with the exception of substance abuse and panic disorder, which usually begin in the middle to late teens. The precise mechanisms by which comorbidity patterns change during development remain unclear. However, successful treatment and prevention programs may depend on a better understanding of the relationships of these other disorders and depression.

There does appear to be a significant association between major depression and abuse, maltreatment, and related forms of environmental adversity, though it cannot be assumed that because children are depressed that they were abused. Further systematic investigation of depressed children with histories of maltreatment and depressed children without histories of adversity should help to delineate the unique risk and protective factors associated with the onset of depression in children.

Exposure to stress during childhood and adolescence appears to have the potential to produce long-lasting effects on human physiology, brain structure, and brain function. In a variety of animals, exposure to adversity during critical periods of pre- or postnatal brain development appears to induce changes, leading to permanent alterations of their perceptions of and responsiveness to environmental events. Nevertheless, complications arise in relating animal behavior to human conditions such as depression. Clinical studies

have linked stress exposure to various developmental psychopathologies; however, the frequent occurrence of two or more comorbid conditions in the wake of such exposure has made it difficult to ascertain if there is a specific link to depression.

Problems also arise in attempting to understand how genetic vulnerabilities and stress exposure interact over the course of development. Although stress may differentially affect children at increased genetic risk, family stress may only increase risk in children without family history of depression. However, some children may be genetically more liable to stress exposure, as well as to depression.

Family Risk Factors for Early-Onset Depression

Studies of families at high risk for depression have shown that there is a considerable heritable component to depression. Children of parents with depression are three times more likely to have a lifetime episode of depression than offspring of parents who did not have depression, and the first-degree relatives (i.e., fraternal twins, siblings, parents) of depressed children have been found to have significantly elevated rates of major depression. In contrast, two adoption studies and a growing number of twin studies provide inconsistent support for the role of genetic factors in the early-onset depressive symptoms. In twin studies, for example, while heritability estimates of parent-rated depressive symptoms of children tend to be high, heritability estimates based on self-reported depressive symptoms are often substantially lower.

Parents may transmit genes that directly predispose toward depression; genes that are functional in some environments but confer vulnerability in others; or genes associated with cognitive styles, such as ruminating, that can lead to depression. Some children may carry a genetic liability to other mental disorders, such as anxiety disorders, that increase the risk of depression. Alternatively, depression may represent an early manifestation of another disease to which a child has a genetic liability, such as bipolar disorder. Parental genes may also influence not just the risk of disease, but the age at which the disease occurs.

Parents also provide the atmosphere in which a child grows up. Aspects of parenting and the home environment that may not be directly associated with a genetic risk appear to influence the risk of, but not the direct cause for, mental disorders in general, including depression.

The Influence of Gender on Mood Disorders

One of the hallmark observations about depression is that women are twice as likely as men to experience a depressive episode within a lifetime. Depression can occur at any stage of a woman's life, and it occurs across educational, economic, and racial and ethnic groups.

Clinicians have long known that mood disorders vary in their expression among women and men and during periods of reproductive endocrine change. The reproductive-

related variability should not be surprising, as the reproductive steroids estrogen, testosterone, and progesterone not only regulate neural function, but also organize the development of the brain. During development, reproductive steroids play a significant role in how neurons connect to one another by regulating which neurons and how many survive, how they differentiate into different types of neurons and migrate through the brain as they grow, and how they form synapses with neighboring nerve cells.

The effects of the developmental influences of the reproductive hormones do not end once the brain's development is complete, however, for these processes also create brain circuitry that remains sensitive to the influence of reproductive hormones. Thus, when puberty arrives, the sudden influx of these hormones can activate this circuitry, and in turn, influence behavior. It may be that mood disorders affect women and men differently at the time of puberty as a result of fundamental differences in neural circuitry laid down during brain development. This hypothesis is supported by observations of mood changes occurring in some women in concert with three periods of change in reproductive hormones: the luteal phase of the menstrual cycle, after the birth of a child, and in the initial stages of menopause.

Studies involving the artificial manipulation of hormone levels suggest that normal changes in reproductive steroids are capable of triggering mood disregulation in some, but not all, women. Women with a history of premenstrual dysphoric disorder (PMDD), but not women lacking the diagnosis, experience elimination of their dysphoria during gonadal suppression and return of their dysphoria when exposed to progesterone or estrogen. Similarly, euthymic women with a history of postpartum depression (PPD), but not women without a history of PPD, become depressed when exposed to and withdrawn from high levels of estrogen and progesterone. In neither of these disorders is there compelling evidence for abnormal levels of reproductive steroids; hence, the depression that is precipitated appears to represent an abnormal response to otherwise normal levels or changes in levels of reproductive steroids. The source of this differential response is unknown and represents an area of great promise for future research, one that may help identify the biological underpinnings of vulnerability to other, non-reproductive endocrine-related mood disorders.

There was a period in the 1970s when researchers believed that the hormonal changes occurring during menopause were irrelevant in considering the causes of depression that occur during this stage of life. Today, however, we know that reproductive function plays a critical role in depression that occurs during menopause. In fact, estrogen itself is an effective antidepressant for women who first experience depression at the onset of menopause. While it is likely that a variety of psychological, environmental, historical, and adaptive factors influence the expression of depressions associated with changes in reproductive function, it is no longer tenable to deny the importance of reproductive steroids in the regulation of brain and affect.

Aging and Depression

Geriatric depression occurs in the context of other events, such as cognitive dysfunction, disability, comorbid medical illnesses, and psychosocial adversity. These dimensions of health have offered an experimental opportunity for advancing and testing hypotheses on the development of geriatric depression. Some of these hypotheses and models may also prove to be applicable to depression in younger adults. The clinical complexity of geriatric depression has also begun to guide the development of comprehensive models of care for elderly people with heterogeneous depressive syndromes. The areas described below are examples of topics of interest.

Cognition and Depression in the Elderly

A significant percentage of depressed elderly individuals also have cognitive impairment. The combination of impaired cognition and depressive symptoms doubles in frequency by 5-year intervals after age 70 in those living in the community, so that by the time a person reaches 85, they have a 25 percent chance of experiencing both cognitive dysfunction and depressive symptoms. Individuals with depression have disturbances in attention, speed of processing, and executive function even when they are not demented. These clinical associations have generated important hypotheses on the pathophysiology of geriatric depression and its relationship to treatment response.

A limitation to this line of research is the dependence on clinical tests of cognitive function. These tests are reliable, but having been developed from clinical traditions, they tend to be nonspecific indicators of function. At the moment, the tests and methods that are tied closest to brain function have not been adapted for use in clinical studies of late life.

The point prevalence of major depression or clinically significant depressive symptomatology is approximately 17 percent for people with Alzheimer's disease and is even higher for those with subcortical dementias. However, discrepancies in reporting symptoms of depression contribute to reduced or incorrect identification of depression in people with dementia. A history of depression is also associated with increased incidence of Alzheimer's disease, and indeed, depressive symptoms often precede the appearance of dementia. Individuals with late-life depression and cognitive impairment frequently develop dementia within a few years after the onset of depression.

There are probably many causes for the cognitive impairment seen in geriatric depression, with contributions from neurodegenerative and vascular processes likely playing an important role. For example, depression may lead to atrophy of the hippocampus, which in turn could contribute to cognitive decline. Given that subcortical lesions are common in the elderly who have both depression and vascular disease, it may be that some types of depression might come from critical lesions or an accumulation of lesions leading to disruption of frontostriatal pathways or their modulating systems.

Depression onset for the first time later in life may represent a distinct subtype of depressive illness.

Improper functioning in frontal and striatal regions of the brain may be an important indicator of the course of geriatric depression. A measure of executive dysfunction, the neuropsychological expression of frontostriatal impairment, was shown to predict poor or delayed antidepressant response, and has been associated with relapse and recurrence in geriatric major depression. Again, the use of more sophisticated assessments will help establish this link more precisely.

Psychosocial Factors in Geriatric Depression

Researchers have known for nearly a decade that social factors are not only related to the risk of depression, but may also influence the course of depression and play a role in suicide risk among the elderly. Depression is the most common risk factor for suicide among the elderly, and the elderly have the highest rates of suicide in the Nation, with elderly males having a suicide rate six times the national average.

Advanced age, history of depression, death of a spouse, health-related factors, and comorbid anxiety all show significant associations with late-life depression. Financial problems in later life are also associated with increased depressive symptoms. However, the effects of stress on depression can be ameliorated by environmental factors such as having a marital partner and if unmarried, having a good network of social support. In fact, research has shown conclusively that social support significantly reduces the impact of functional disabilities on the incidence of depression.

Older persons who experience a large number of negative life events in the past year experience a wide range of depressive symptoms. For example, elders who experience a death in their family during the past year tend to experience more symptoms of depression than do older adults who did not have a family member die. Approximately 10 to 20 percent of persons who lose their spouse develop clinically significant depression in the first year of bereavement. If left untreated, the depression persists and may lead to further chronic disability. Widows in particular experience more depression than their married peers, though within a year those symptoms usually resolve themselves. In addition, recent widowhood increases the risk for suicide among older men, though not among older women.

Depressed elders are often socially isolated—they often lack confiding relationships and perceive their friends as less supportive and reliable. Older adults who do not have close social ties report higher depressed mood than elders who are actively engaged in a supportive social network. In fact, research has shown that measures of social support show a strong correlation with mental health measures in a cross-sectional survey of rural elders. The availability of a confidant was found to be the single most protective factor for four dimensions of depression—depressed affect, low positive affect, medical complaints, and interpersonal problems.

Cognitive theory suggests that how elders perceive their social contact is more important than absolute isolation. Loneliness is associated with social isolation and social support, poor or perceived health, and depression, and both depression and loneliness compromise quality of life. Older women who experience loneliness, for example, report more hopelessness, self-focus, and poor health.

Depression and Caregiving

Depression is a common consequence of family caregiving, a burden most often borne by women. Depression is most likely to occur during long-term caregiving and during transitions such as institutionalization. Research has shown that caregivers are at risk for experiencing clinically significant depression and that a significant percentage of caregivers have been shown to meet diagnostic criteria for depression. This holds true even for caregivers who had never been diagnosed with depression prior to assuming the role of taking care of an elderly loved one. Prevalence rates of depression, ranging from 30 percent to as high as 83 percent, among community dwelling caregivers of persons with dementia have consistently been reported. Several studies have shown that increased social support from family and friends can decrease the stress placed on caregivers and lessen depressive symptoms. Psychological and educational interventions have helped caregivers effectively manage problem behaviors and reduce depression. Individual and family counseling sessions, participation in support groups, and availability of counselors to assist with crises may also reduce depressive symptoms in caregivers.

Depression and Illness in the Elderly

The prevalence of geriatric depression is higher in medical settings than in the community. Epidemiological studies show that major depression occurs in 1 percent of the general elderly population, while 3 percent of community residing elderly individuals suffer from dysthymia and 8 to 15 percent have clinically significant depressive symptoms. In contrast, studies have found that clinically significant depressive symptoms occur in 17 to 37 percent of people who are hospitalized.

Depression in the elderly is a burden to both the consumer/patient and the Nation's health care system. Depressed medical patients with chronic diseases, such as diabetes, arthritis, hypertension, and chronic lung disease, stay in bed more days compared to similar patients without depression. In addition to medical morbidity, depression increases the perception of poor health and utilization of medical services. Depressed primary care patients have almost twice the number of appointments with a doctor per year compared to non-depressed patients, and depressed patients have more than twice the number of hospital days over the expected length of stay compared to non-depressed patients. In addition, 65 percent of depressed patients receive more than five medications compared to 36 percent of non-depressed patients.

Research on the association between depression and increased mortality has been equivocal. Health may be a confounding factor, as depression is associated with poor health in elders. One longitudinal study examining the association between depression and mortality in nursing home and apartment residents found that the effects of depression on mortality were attributable to the correlation of depression with ill health, and another investigation found that major depression increased the likelihood of death by 59 percent, independently of medical health parameters.

Despite problems associated with depression among hospitalized older adults, the detection and treatment of depression in this population is inadequate. One study, for example, found that only a quarter of depressed patients were identified as such by their physicians, with correspondingly low use of antidepressants even following the diagnosis of depression. Detection and treatment of depression in primary care and long-term care settings are also poor. These studies suggest that detecting and treating depression promptly could have a major effect on the health of the elderly.

The reasons for underdiagnosis of depression are complex, but poor reporting of depressive symptoms may be a contributing factor. Older individuals report fewer symptoms of depression to their family members than younger individuals. Another factor may be the time constraints of physicians that prevent in-depth discussion of depressive symptoms and related psychosocial factors, and age bias. Underreporting of depression is particularly common in traditionally underserved racial and ethnic minority communities.

Comorbidity: Depression and Other Medical Illnesses

Coronary Heart Disease

Depression is common in people with coronary heart disease (CHD) and other cardiac illnesses, a dangerous situation since depression increases the risk by as much as six-fold of dying from heart disease. Approximately one in five cardiac patients has major depression at the time of diagnostic cardiac catheterization or following acute myocardial infarction (MI). Another one in five has minor depression at these times. Many people who are not depressed in the first few days and weeks following an acute MI go on to experience an episode of depression within a year, with approximately one out of three developing major depression at some time during the 12 months following an MI. Although there have been relatively few follow-up studies of depression in post-MI patients, there is evidence that it tends to follow a chronic course during the first year after the heart attack. In patients with congestive heart failure, estimates of the prevalence of major depression have ranged from 17 to 37 percent. In the first year following heart transplantation, an estimated 17 percent of patients have major depression.

Depressed CHD patients are slower to return to work and are more likely to return to the hospital, to report more stress and emotional instability, to be disabled, and to incur higher costs for their medical care than CHD patients who are not depressed. Depression is

also associated with poorer psychosocial adjustment and less symptom relief following coronary bypass surgery.

Depression increases the risk that patients with newly diagnosed coronary artery disease will experience a cardiac event following diagnostic cardiac catheterization. It is also a significant risk factor for cardiac mortality and medical morbidity following an acute heart attack, in patients with unstable angina, and in patients with a transplanted heart. In addition, several large, prospective studies have shown that depressed individuals without clinical evidence of coronary disease are more likely to develop CHD in the ensuing years than are otherwise comparable individuals who are not depressed. It is unclear whether depression contributes to the precipitation of cardiac events, contributes directly to the underlying artherosclerotic process, or both. The mechanism or mechanisms underlying the relationship between depression and cardiac morbidity and mortality are unknown, though investigators have proposed several hypotheses that are being tested including alteration in heart rate variability and serotonin-induced platelet aggregation.

Diabetes

Depression occurs more frequently in adults with diabetes than in otherwise healthy control subjects, and it takes a more serious course in diabetic patients. For example, people with comorbid diabetes and depression have an eight times greater relapse rate than those with depression but without other medical conditions. Conversely, depression is associated with an increased rate of medical complications from diabetes and poor control of blood sugar levels. Indeed, the relative severity of depression among elderly diabetics, for example, correlates with difficulty controlling blood glucose levels. In primary care patients, comorbid depression increases health care costs and the use of health services. One estimate pegs the total health care costs for diabetes and comorbid depression at $192 million per year.

One complication of comorbid depression and diabetes is that both monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) can negatively interfere with glucose metabolism, and therefore worsen diabetes. In contrast, the serotonin reuptake inhibitors (SSRIs) may actually improve both depressive symptoms and glucose control. Researchers have also noted that improvements in mood, regardless of the therapy chosen, are associated with better compliance with the dietary and medical restrictions needed to treat diabetes.

Neurological Disorders and Stroke

The prevalence of depression in neurological disorders is best characterized in patients who have suffered a stroke. In contrast to degenerative diseases such as Parkinson's disease and Alzheimer's disease in which disease onset is often hard to pinpoint, the timing and the location of a stroke make the association of changes in mood and onset more exact. The mean prevalence of major depression and minor depression in patients after a stroke is

approximately 20 percent and 19 percent, respectively. In Parkinson's disease, the best estimate is approximately 15 to 20 percent, and for vascular disease it is perhaps 20 to 25 percent, with another 25 percent of patients in each group suffering from minor depression.

Depression has a significant impact on functional recovery from stroke. While the average duration of depression in patients who have suffered a stroke is approximately 1 year, as many as 25 percent of these patients with minor or major depression at baseline may remain depressed for up to 3 years. Further, these depressed patients have a more prolonged and limited recovery from the stroke and have an increased mortality. As with cardiovascular disease, both minor and major depression have an impact on recovery and mortality.

Depression also has an adverse effect on quality of life, cognitive functioning, and motor symptoms in Parkinson's disease, and it increases functional disability in people with Alzheimer's disease. Although some have argued that depression in Parkinson's disease is simply a reaction to the disability of the illness, the incidence of depression in Parkinson's disease is higher than in other illnesses with similar disability. The association of depression and Alzheimer's disease is complicated by the fact that late-onset depression in cognitively intact individuals may be a risk factor for later development of Alzheimer's disease. In general, researchers have concluded that depression in Alzheimer's disease can occur during any stage of the illness and is a source of increased disability and mortality.

Researchers have proposed two theories on the etiology of depression in neurological disease. The first assumes that depression is a reaction to disability, and, as pointed out above, this can become a circular argument with depression causing increased disability. Clearly, disability has a role in the development of depression, but there is evidence that the relationship may not be a simple one. The second theory is that depression is the result of the neurodegenerative process. Studies examining glucose metabolic rates or blood flow changes in regional brain areas of patients with neurological disorders—including stroke, Parkinson's disease, and Huntington's disease—and comorbid depression demonstrate that these disorders showed a similar pattern to that found in primary depression: decreased activity or brain lesions in the orbital frontal cortex and basal ganglia.

Cancer

The symptoms of depression are common among cancer patients, occurring in as many as half of all cancer patients. There is evidence, though, that depression in individuals with cancer has been underdiagnosed and undertreated. In part, this is because of the belief that depression is a normal and universal reaction to serious disease, but it also arises because physicians mistake physical symptoms, such as weight loss and sleep disturbance, or the emotional and cognitive signs of depression as symptoms of the medical illness itself.

Factors associated with greater prevalence of depression are pain, a higher level of medical disability, and more severe illness. More rapid progression and increased symptoms of cancer, especially pain, are associated with more severe depression. Having cancer and depression simultaneously is associated with increased functional impairment and poorer quality of life over the course of cancer therapy and recovery.

Studies of cancer patients suggest that the severity of depression may have a deleterious effect on the number of leukocytes, a class of immune cell, over short periods of time. For example, mood disturbances are associated with lower white blood cell counts in women with cancer. Symptoms of depression and a lack of social support also predict reduced immune cell activity measured at a 3-month follow-up in breast cancer patients.

The diminished immune system activity experienced by patients with depression may explain another grim fact: depressed mood heightens the risk of developing cancer and of dying after developing cancer. This finding is stronger in people who have been chronically depressed.

HIV/AIDS

Depression affects a significant proportion of individuals living with HIV/AIDS, with estimates of lifetime rates of depression among persons living with HIV, ranging from 22 to 45 percent. There is, however, a dearth of research regarding the intersection of depression, HIV/AIDS, and aging, which is particularly troubling because HIV/AIDS surveillance data indicate that persons over age 50 represent 10 percent of reported cases in the United States. Furthermore, trends in incidence rates suggest that AIDS will increasingly affect older adults as people already living with HIV are living longer due to advances in antiretroviral treatments.

Depression may affect disease progression in HIV/AIDS through its influence on the immune functioning or through its effects on behavioral issues such as treatment adherence. Although a clear causal relationship between depression and disease progression has not been demonstrated, researchers have accumulated data suggesting that the presence of depressive symptoms and severe life stress may contribute to immunosuppression and HIV disease progression.

Numerous studies have documented the myriad problems with adherence to treatment, substance use, and declines in quality of life that are associated with depression in HIV disease. The mechanisms responsible for these behaviors in depression are complex, but recent conceptual models suggest that cognitive, affective, and contextual components, such as simple forgetting, apathy, and isolation, respectively, can adversely affect adherence to complicated antiretroviral medications and may also be related to general poor health care. There is some initial evidence that maintenance of effective antiretroviral therapy may be related to improvement of depressive symptoms, and several studies are now under way to test the direct and indirect effects of interventions to improve mood on adherence to treatment.

Opportunities for Progress

One of the major gaps in mood disorders research is the need for a more complete understanding of the natural history and developmental course of depression and bipolar disorder—when they first appear, what course these illnesses take as a person ages, and how the manifestations of depression and bipolar disorder change over the course of time. A complete picture of these disorders would also include how they affect, and in turn are affected by, the various medical problems that a person experiences throughout the course of a lifetime.

Opportunities to Identify Depression and Bipolar Disorder During Development

Advances that are occurring in deciphering the human genome raise exciting possibilities for integrative programs of research designed to evaluate developmental models of depression in the context of interactions between genetic predispositions and environmental stresses. Although no specific set of genes, proteins, or environmental factors has been linked unambiguously to the origins of the mood disorders, several promising hypotheses have emerged. It appears, for example, that the genetic contribution to these diseases is likely to be significant and complex, that perinatal complications or exposure to adverse environmental circumstances serve to sensitize stress-responsive systems during development, that subsequent exposure to trauma may precipitate the expression of these diseases in genetically vulnerable individuals, and that specific neurobiological systems are involved at different times of development.

To date, however, far more research examines these ideas in animal models than in developing children. Specifically, there is a clear need to conduct the same structural and functional neuroimaging studies in pre-adolescents and adolescents as in adults with major depression to determine developmental differences in the neuroanatomical correlates of depression across the life cycle. Indeed, the few neuroimaging studies in depressed children and adolescents offer preliminary evidence that some neuroanatomical correlates of depression may be evident from early in life, while others may emerge later in development or secondary to biological alterations associated with the persistence and recurrence of disorder. The wealth of emerging non-invasive neuroimaging techniques that are suitable for use in children also make this an ideal time to invest in this area of research.

Because so little is known about the development of bipolar disorder in children, and considering that genetic factors significantly increase the risk of developing bipolar disorder, it would be useful to conduct longitudinal studies of young offspring of bipolar parents. Such studies would enable researchers to spot the earliest symptoms of bipolar disorder and to correlate them with other behavioral and physical traits that may precede the development of bipolar disorder. This information would be invaluable in

understanding the origins of bipolar disorder and in determining if this illness, like depression, first appears during childhood in many people.

Longitudinal studies of this sort would also help researchers and clinicians to develop more appropriate diagnostic labels for children presenting to clinics with symptoms of extreme mood lability or irritability. Indeed, there is considerable controversy about the most appropriate means for distinguishing bipolar disorder in young children from a range of other possible comorbid conditions, including both depression and a disruptive behavior disorder. For example, comorbidity, typically with disruptive behavior disorders, usually complicates the diagnosis in many children where there is a question of a bipolar disorder diagnosis. Bipolar disorder's symptomatic overlap with ADHD is also a leading source of diagnostic confusion. Systematic studies of children and adolescents show that rates of comorbid ADHD range from 60 to 90 percent in youth classified as bipolar. Conduct disorder is also strongly associated with pediatric-onset bipolar disorder, and although anxiety is frequently overlooked in studies of pediatric-onset bipolar disorder, studies of youth with panic disorder and youth with mania document an important overlap of symptoms.

Careful family-based and longitudinal studies are needed to clarify diagnostic boundaries and the relationships between these disorders. Since the diagnosis of bipolar disorder appears easier to make in adolescents or adults than in children, it will be important to conduct longitudinal studies examining developmental changes in symptoms among children of parents classically defined as bipolar. For example, a developmental change in a common symptom, like irritability, needs to be examined in large diverse samples of community-identified children as they age into adulthood.

Recent studies of adult bipolar disorder have also generated important research questions. Bipolar disorder is recognized as among the most strongly genetic of the complex mental syndromes, which should encourage efforts to identify the earliest stages of this disorder during childhood. Recent studies among adults also have begun to elucidate neural circuits implicated in bipolar disorder as compared to depression. Future longitudinal studies of children at high risk for bipolar disorder should begin as early as possible and include measures that monitor these potential early forms of the disorder, as well as cognitive and affective mechanisms involved in the behavioral expression of this disorder. These studies will complement ongoing genetic studies and may elucidate markers of increased biological risk in vulnerable children before they develop symptoms of bipolar illness.

Opportunities to Develop New Therapies for Children and Adolescents

Because there has been general acceptance for less than three decades that children can experience mood disorders, the state of knowledge regarding mood disorder treatments in children remains quite primitive. What is known is that TCAs do not work well in pediatric

depression. Studies to date are uniformly negative and are probably sufficient to conclude that these agents are likely to be ineffective or much less effective in childhood and adolescent depression than they are in acute adult depression. SSRIs, however, show more promise in treating pediatric depression.

CBT and IPT are effective therapies for pediatric depression, as shown by over a dozen randomized controlled studies. Ongoing psychotherapy studies on pediatric depression include studies of psychotherapy for dysthymic children, the Adolescent Coping with Depression course compared to mentoring in adolescents with comorbid depression and conduct disorder, and Internet-based approaches to treating adolescent depression.

Several structured psychotherapeutic interventions developed for adults have been found effective in treating older children and adolescents who come to clinical settings. Data from randomized controlled trials support the use of both CBT and IPT for depressed adolescents. On the other hand, systemic family therapy and non-specific supportive psychotherapy did not prove as successful at speedily reducing depression. The response rates for short-term treatment were comparable to adult psychotherapy and pediatric trials with SSRIs; likewise, follow-up studies of psychotherapeutic interventions showed a high relapse rate. Thus, as with medication, trials of longer-term, more intensive interventions are needed to determine whether it is possible to increase response and decrease relapse rates. In addition, there is an urgent need to develop and test age-appropriate psychotherapeutic interventions for depressed pre-pubertal children.

There are no controlled trials or ongoing studies on treatment of preschool depression. Outcomes with available treatments in school-age children are not impressive. Development of more robust treatments, both pharmacotherapy and psychotherapy, and demonstration of the effectiveness in community settings are essential.

There are ongoing NIMH studies of the combination of psychotherapy and pharmacotherapy for pediatric depression. The Treatment for Adolescents with Depression Study (TADS), a multisite study, compares placebo, an SSRI, CBT, and an SSRI plus CBT in the treatment of acute adolescent depression. Another ongoing study is examining a collaborative care model of CBT within a health maintenance organization as an adjunct to antidepressant treatment.

Work on preventing child and adolescent depression has followed two general pathways. One approach has been on treatment or prevention of postpartum and maternal depression as a potential risk factor for childhood depression, while the other approach has been to develop programs targeted at children specifically at risk of developing depression or on all children through school-based programs. The first, more common approach has reduced maternal depression, but the effects on depression in children have been less clear than the effects on other areas, such as cognitive development or behavioral problems. In part this may result from short follow-up periods that do not extend into periods when childhood depression becomes most prevalent. As several prevention studies

are currently under way, longer-term follow-up data should become available in the next decade.

Programs directly targeting children and adolescents at risk of developing depression have had some success. However, programs addressed to unselected populations, such as classroom interventions designed to prevent suicidal behaviors through awareness curriculums, have produced mixed results, in some cases even causing potential harm. Some studies have established a temporal relationship between early anxiety and later depression, especially in adolescent girls. Since effective cognitive-behavioral and pharmacological treatments for pediatric anxiety disorders are now available, the opportunity exists to conduct prevention-intervention trials in adolescents with anxiety disorder as a means for heading off future depressive episodes.

There are few controlled studies on the pharmacotherapy of adolescent bipolar disorder. One group found that lithium was superior to placebo in the treatment of adolescents with comorbid bipolar disorder and substance dependency. In a study of depressed children with a family history of bipolar disorder, there was no evidence of lithium efficacy.

Given that many psychopharmacological treatments for behavior disorders can exacerbate mania in adults, research is needed that carefully examines the impact of such treatments on children. Although recent studies examining short-term SSRI effects in children with depression or anxiety disorders document very low rates of manic "switching," longer-term studies in clinically referred patients suggest that the number of depressed children that switch may be high. Moreover, in clinical samples treated acutely with SSRIs, a sizable group of children showed signs of "activation" or irritability. These findings raise questions regarding the predictive relationship between such responses to an SSRI and later risk for bipolar disorder, but the power of these phenomena as risk factors for bipolar depression has not yet been tested in representative population samples.

Opportunities to Understand the Influence of Gender

A recent World Health Organization report indicates that depression presents the greatest disease burden for women when compared to other diseases. Consequently, it is critically important to understand what has been learned from empirical studies about the gender influences on the course of depression, its treatment, and prevention; and apply that knowledge to reduce the environmental, social, and cultural risk factors for depression and to optimize interventions. It also is important to incorporate this new knowledge into a research agenda that will advance our understanding of how gender and depression influence each other.

Biological differences in women and men are likely to play a role in the differential development of depressive episodes between genders. There is some evidence that genes may play a larger role in the development of depression in women. Studies underway present the opportunity to determine whether this initial observation holds true, and if so,

whether the same genes have a differential impact on women versus men in the development of depression. Certainly, the obvious difference in sex hormones between women and men, and the link between increased rates of depression for women after puberty, as well as the link between mood and the menstrual cycle or reproduction, suggest that sex hormones may contribute to differences in the onset of depression.

One possibility is that a disturbance in the interaction between the HPA axis and neurotransmitters such as serotonin is a key contributor to depression in women. Women may be vulnerable to such disregulation because the neuroendocrine rhythmicity in the menstrual cycle or reproduction may make them more sensitive to psychosocial, environmental, and other psychological risk factors. Although the direct and indirect effects among these factors have not been clearly linked to the onset of mood disorders, ongoing research into these connections should provide important insights into the development and treatment of mood disorders in women.

Psychological and social variables are of particular importance to researchers attempting to understand the sex-linked differences in the development of depression. Gender differences in the response to stress and the impact of stress are likely to play a role in the course of depression, though few studies have examined sex differences in regard to stress and depression. However, initial research in this area has demonstrated that women are three times more likely than men to experience depression in response to stressful events. One cognitive style that confers increased risk for depression and that is more common in women is ruminative thinking. Another important cognitive difference between genders is that relationships are more central to women's self-concept than men's, and there is evidence that this may account for some of the gender differences in depressive symptoms. Certainly, there are important insights to be learned from studies of how gender affects such psychological and social factors.

There is no clear evidence that women respond less or more positively to treatments for depression. However, treatment interventions alone may not be sufficient to reduce the high prevalence of major depression in women. Instead, researchers need to increase their efforts to develop, evaluate, and implement interventions that will prevent the onset of depressive episodes. Future prevention research should target women across the life span. Identifying groups at imminent risk for depressive episodes may be effective in increasing the utility of preventive interventions. Studies should explicitly observe effects on collateral public health problems, such as smoking, other substance abuse, unplanned pregnancies, marital problems, school performance, job performance, and physical health. These preventive interventions may need to address multiple outcomes, including healthy development as well as the prevention of psychopathology, and involve the collaboration with community to provide the maximal benefit for participants.

Looking toward the future, there is a tremendous opportunity to advance our understanding of depression and how to treat and prevent it by examining, rather than ignoring, gender differences. Researchers must begin to consider the effects of gender when designing and implementing studies and reporting results. Women are a heterogeneous

group, and this heterogeneity and the context of women's lives must also be considered in research design and the interpretation of experimental results.

Depression and the Reproductive Cycle

PMDD is diagnosed in approximately 5 percent of menstruating women and is distinguished from the much more common premenstrual syndrome (PMS) by its more severe symptoms and impairment. Clinical trials have consistently shown that SSRIs taken during the luteal phase of the menstrual cycle can treat the symptoms of PMDD. Little has been done, however, to study the benefits of non-pharmacological therapies, including exercise and psychotherapy, in treating or preventing PMDD.

An ongoing challenge to the women who suffer from moderate to severe premenstrual conditions is the detection of the illness and treatment with empirically proven therapies. For a variety of reasons, including stigma, women will neglect to consult a physician when they have moderate to severe premenstrual symptoms, including PMDD. On the other hand, clinicians frequently fail to ask women whether moderate to severe premenstrual symptoms are affecting their mood and well-being. Given the substantial personal burden of PMDD, increased attention to this illness by the primary care community could translate into pronounced personal and societal benefits.

Depression during and after pregnancy can have serious effects on both mother and child. Depression during pregnancy is associated with biological disregulation that can be detrimental to fetal development, while depression in the period after birth can disrupt the attachment of mother and child. Treatment options usually exclude medication, though IPT is effective in both pregnancy and the postpartum period because of its focus on role transition and interpersonal functioning. ECT appears to be safe and effective and is one of the most important interventions for the most serious depressions, especially psychotic depression during the postpartum period.

Despite the obvious connection between dramatic changes in hormone levels and postpartum depression, relatively few studies have examined the role that hormones play in triggering postpartum depression or the place that hormone therapy might have in treating or preventing depression after childbirth. This should become an important avenue for research. In addition, more work needs to be done to determine how best to deliver depression-related services to women during pregnancy and after childbirth. This is a time when more women seek out medical care than at any other point in their lives, so this may represent a unique opportunity to identify and treat mood disorders regardless of their specificity for childbearing-related events.

The belief that women suffer severe mood disturbances or depression during the period surrounding the onset of menopause is not supported by epidemiological data. What remains unanswered, however, is whether some women may be more vulnerable to the mood effects of hormonal changes. Some evidence suggests that women with a history of PMDD or other premenstrual mood changes may have an increased sensitivity to the

hormonal changes that occur at perimenopause, and that women with previously diagnosed mood disorders that are cyclic or associated with reproductive events may be at higher risk for depressive symptoms at the onset of menopause. Further research is needed to explore these suggestive findings.

Opportunities to Improve Mental Health for the Elderly

Overall, there remain numerous significant opportunities for research to help reduce the burden of depression in late life. The past decade has seen the emergence of primary efficacy studies of antidepressant treatment; yet, we do not know which antidepressants are the most appropriate for older adults, when considering both their safety and their effectiveness. Studies that provide comparative information of multiple medications and studies that try to identify the algorithms for optimal treatment are needed. Without this information to guide care, older adults end up receiving variable care. These issues are equally applicable to psychosocial treatment research.

Given that most treatment of late-life depression occurs in primary care settings, greater efforts can be made to improve the care received there. To date, there have been modest gains establishing the challenges to treating depression in primary care, with the emphasis on establishing that an effective treatment, regardless of cost, can be provided. Over time, more sustainable programs will require validation. Multilevel studies are needed to identify effective and cost-efficient methods for identification and treatment of depression in both assisted living facilities and nursing home residents. All of these studies can help advance the validation and development of time efficient screening instruments for routine clinical care.

The range and variability of depression appears greater in late life, such that there remains a need to better characterize its manifestations. For example, the depression seen in Alzheimer's disease appears different than major depression. This has led to the development of provisional diagnostic criteria, which can help foster treatment research. Our knowledge of the depressive symptoms that co-occur with other mental illnesses, including psychosis in late life and anxiety disorders, is more modest. Longitudinal studies that can better characterize mood disturbance will ultimately lead to treatment development. Underlying the development of treatments that can reduce these burdens is the need to further develop basic models of depression in late life, given the known relationship with neurobiological function.

The variability of depression in late life also includes psychotic depression and bipolar disorder. Both of these illnesses, though less common, place a greater burden on society and the individual. Our gains in understanding and treating these conditions are more limited, in part due to the added challenges that come with treatment. Studies that can characterize and validate treatment are most needed.

To date, research has not been able to determine whether and to what extent depression increases disability among the elderly and how much disability contributes to

depression in the elderly. Longitudinal treatment studies need to clarify these relationships and identify the target of interventions focused on both depressive symptoms and functional deficits.

Cognitive aspects of depression may play a significant role, and there is a lack of consensus regarding the role of cognition in the severity and treatment of depression. The development of more sensitive and meaningful measures of cognition is probably the most critical step to making gains in this area. Translational research that integrates cognitive neuroscience, neuropsychology, and clinical trials theory would hopefully lead to better tools.

An important research task is to identify the specific mechanisms by which social factors promote or protect older adults from depression and influence its longitudinal course. The role of stress and its biological correlates, including immune function and cardiovascular reactivity, as well as the complex interactions between social factors, depression, and medical illness, needs to be better articulated. Such studies can guide the development of targeted psychosocial and biological interventions.

Interventions aimed at improving caregivers' capabilities and well-being need investigation, too. Fostering coping skills, and encouraging use of formal help, including adult day care and respite services, and informal help may prove effective. Focused studies need to examine whether premature or inappropriate institutionalization can be prevented through use of pharmacotherapy for behavioral and cognitive symptoms in people with dementia and through psychotherapeutic interventions, including short-term cognitive, behavioral, psychodynamic therapy, for caregivers.

Opportunities to Understand Mood Disorders as Diseases of the Brain and Body

The development of standardized criteria for the diagnosis of depression in the *DSM* was a significant advancement in the treatment of mental illness. The diagnosis of depression in the context of comorbid medical disorders is poorly developed within this framework, however. Indeed, research in this area is minimal and lacks coordination even though it is clear that mood disorders have an effect on and are affected by other medical conditions that may alter the symptoms of depression and perhaps bipolar disorder. For example, comorbid depression may be a symptom in a patient with a neurological disorder that is responsive to treatment and with treatment may have a significant impact on functional outcome. Yet, the diagnosis of depression in neurological disorders remains challenging, and few trials define the potential risks and benefits of somatic therapies in this population. Clearly, new thought—and research—is needed to rectify this situation.

Depression and depressive symptoms have a profound effect on the longitudinal course of neurological disorders. Despite being poorly understood, the diagnosis and treatment of comorbid depression could provide immediate improvement to long-term functional outcomes of a significant percentage of individuals with neurological disease.

I'm 32 years old and expecting my third child. I'm worried about developing postpartum depression since I suffered from it twice before. Four days after my last delivery, I became suicidal and also experienced irritability, sleep disruption, weight loss, and racing thoughts. I don't want that to happen again. Previously, I was treated with an SSRI, but it didn't help at all and in fact seemed to make me worse. Following a consultation with my husband, doctor, and mother, I began taking a mood stabilizer and felt better in about 3 weeks. Although I was diagnosed with bipolar disorder, I hope that doesn't stigmatize me and interfere with my life's goals of being a good mother and a teacher.

The diagnosis of depression could be standardized, enabling researchers and clinicians to develop easily administered diagnostic scales. These scales could be used to assess depression and made available to clinicians in routine practice. Algorithms could be developed to determine optimal antidepressant medications, as well as physical and rehabilitative therapies and other behavioral treatments of depression.

Understanding depression in neurological disorders can also increase our understanding of the pathophysiology of depression. The groundbreaking work linking depression to cerebrovascular disease in the left frontal cortex and specific subcortical structures and the recent findings of depression induced by deep brain stimulators in Parkinson's disease are two examples of critical findings that have increased our understanding of depression in neurological disorders.

There also is a need to coordinate clinical research with basic science research in areas such as neuropathology of well-characterized neurological diseases. There are few animal models of depression and neurological disorders even though animal models could provide important insights into such interactions as the role of degeneration of specific subcortical nuclei and depression in neurological disorders.

Numerous studies have provided preliminary evidence for a directional relationship between depressive symptoms and aspects of the immune system in groups homogeneous for gender and type of disease. However, the link between such measures of immunity and clinically meaningful immune function is unclear. More research with cancer patients is needed that examines specific functional aspects of cellular immunity in association with depression. There is an intriguing recent report in a small sample of cancer patients showing a correlation between response to pharmacological treatment for depression and natural killer cell counts.

Similarly, more research is needed that examines specific endocrine and immunological correlates of depression for their effects on the health status of cancer patients. Gross measures of disease progression do not show an association with depression; however, a recent study demonstrated an association between severe depression and subsequent risk of being diagnosed with breast cancer. More prospective research could begin to systematically identify any effects of depression on the health status of cancer patients that may have an impact on disease incidence, course, and longevity.

For persons living with HIV/AIDS, mental health issues have proven to be an integral part of adaptation to illness, and an unfortunate but powerful predictor of maladaptive coping with the disease, poor adherence to treatment, and decreased quality of life. Integrated mental health and HIV/AIDS treatment is the exception rather than the norm. Research is needed to test various structural interventions, such as how best to encourage and integrate service delivery that could improve access and adherence to treatments for both HIV/AIDS and depression.

Although there has been excellent work on developing effective treatments for depression in HIV/AIDS patients, this research needs to be extended to develop, adapt, and assess theory-based interventions for treating depression among underserved, high-risk, or special need populations with HIV/AIDS. Few trials, for example, have included representative samples of women, children, ethnic and racial minorities, or older persons living with HIV.

More translational research would enhance our understanding of the mechanisms for depression to affect the course of HIV disease, which might also improve our selection of treatments. Such studies would help to disentangle the influence of affective and cognitive dimensions on mood in HIV disease, including the effects of apathy, lack of initiation, neurocognitive problems, and fatigue.

Effective tools are needed to screen for depressive disorders among patients already in care for HIV/AIDS and those at high risk for HIV, such as patients at clinics for sexually transmitted diseases. Strategies are also needed to increase the incentives for appropriate diagnosis and treatment of mood disorders in medical treatment, since such approaches would likely increase appropriate identification and treatment.

Research Priorities

1. Opportunities to Identify Depression and Bipolar Disorder During Development

OBJECTIVE 1. Expand basic preclinical and human research on the development of neurobiological, cognitive, emotional, and social processes associated with temperament and mood regulation.

Implementation:

■ Identify critical gaps and research opportunities in current knowledge about the development of these basic processes in normative and high-risk populations.

OBJECTIVE 2. Improve the diagnostic validity of mood disorders in children and adolescents.

Implementation:

■ Improve assessment and treatment of mood disorders in primary care settings and school settings.

■ Assess functioning levels in children and adolescents with diagnosed mood disorders.

■ Delineate differential diagnosis, causes, course, treatment, and prevention of early-onset bipolar and depressive disorders using collaborative multidisciplinary networks of researchers.

OBJECTIVE 3. Understand the effects of sex and gender on etiology, diagnosis, treatment, and prevention of depression and bipolar disorder in women.

Implementation:

■ Investigate periods for high risk for mood disorders in women (e.g., puberty, the childbearing years, the postpartum period, and perimenopause), traumatic life events (e.g., childhood sexual assault), and other conditions placing women at higher risk.

■ Explore role of hormones (e.g., cortisol, estrogen, progesterone, and dehydro-epiandrosterone) in relation to the neurobiology of depression in women throughout the life span and integrate biological and psychosocial models of depression.

■ Examine the role of stress, including early trauma and stressors throughout the life span of women, in mood disorders.

■ Examine the relationship between substance use/abuse and mood disorders in women.

■ Investigate the effectiveness of short- and longer-term gender-specific treatments and secondary initiatives to reduce relapse, recurrent depression, and refractory depression.

■ Determine effective strategies to increase access to services, particularly for ethnic and racial minority women and for populations who underutilize available services (e.g., older women).

OBJECTIVE 4. Determine the developmental pathophysiology of mood disorders.

Implementation:

■ Identify the neurobiological mechanisms underlying the development of mood disorders and clinical and biological predictors of relapse in children and adolescents.

■ Determine the neurobiological mechanisms underlying differential pharmacological responsiveness in child and adult mood disorders. Structural and functional neuroimaging are among the suggested tools to be used.

OBJECTIVE 5. Improve identification of precursors to, and subsyndromes of, mood disorders.

Implementation:

■ Conduct longitudinal studies aimed at young children with prominent early mood symptoms (e.g., negative affect, mood lability, extreme irritability, explosiveness, chronic anger) that do not meet *DSM* diagnostic criteria for mood disorders.

■ Study short- and long-term consequences (positive and negative) associated with acute, recurrent, and chronic exposure of pharmacological interventions used for mood disorders on the developing brain.

■ Expand longitudinal studies of diagnosed and high-risk children to incorporate genetic, brain imaging, and other neurobiological and basic behavioral measures.

■ Assess the acute and long-term mental health effects of exposure to trauma in children and adolescents.

OBJECTIVE 6. Determine when changes in interventions are needed to accommodate psychological or physiological life phase changes.

Implementation:

■ Identify potential differences in treatment response at major developmental and life transitional points (e.g., pre-puberty to puberty; pregnancy; biological changes with aging).

■ Support secondary analyses of funded treatment trials to explore predictors of treatment response during life phases (e.g., studies comparing individual developmental history with prior treatment history and outcomes).

OBJECTIVE 7. Develop effective treatments for children and adolescents with mood disorders.

Implementation:

■ Support studies of long-term maintenance treatments (pharmacological, psychosocial, and family psychoeducational) to determine the course of the disorder (e.g., affect on relapse) and the development of comorbid conditions, etc.

■ Establish the efficacy and effectiveness of adding manualized CBT and IPT to pharmacological treatment and management of adolescent bipolar disorder.

■ Identify and determine the differential effectiveness of pharmacotherapies for children and adolescents with mood disorders.

■ Develop and test promising combination and sequenced treatment strategies for child and adolescent mood disorders, including strategies to address common comorbid disorders.

■ Develop interventions or service delivery models that are sensitive to differences in the neuropathophysiology of pre-pubertal children who are depressed or have mania, with attention to factors such as cognitive capacity, family culture, environmental adversity, comorbid conditions, or other factors that may influence treatment and outcome course.

OBJECTIVE 8. Prevent mood disorders in children and adolescents.

Implementation:

■ Determine the long-term impact of successful treatment of juvenile depression and anxiety disorders on functioning and on the subsequent development of new episodes and other disorders.

■ Establish whether pharmacological agents used to treat ADHD and mood disorders increase the risk of hypomania and bipolar disorder.

■ Identify benefits of parent education and parent-mediated interventions to improve outcomes and prevent relapse in childhood mood disorders.

■ Ascertain the acute and long-term effects of interventions for depression on children and adolescents exposed to trauma.

2. Opportunities to Improve Mental Health for the Elderly

OBJECTIVE 1. Develop a comprehensive understanding of the risk and protective factors in late-life mood disorders that can lead to new preventive and treatment interventions.

Implementation:

■ Determine well-established risk factors that can be used for rapid development of new interventions through support of secondary analyses of epidemiological data sets.

■ Support trans-institute longitudinal studies to reveal the roles and interactions of specific life history, psychosocial, and neurobiological risk factors in morbidity and course of disorder.

OBJECTIVE 2. Establish the role of cognitive functioning in late-life mood disorders.

Implementation:

■ Delineate specific behavioral and neurobiological aspects of cognitive dysfunction in late-life mood disorders, including the use of new measures development.

■ Validate diagnoses and treatments for cognition-related disease models (e.g., depression in Alzheimer's disease, depression in Parkinson's disease).

OBJECTIVE 3. Establish the factors involved in the pathophysiology of late-life mood disorders.

Implementation:

■ Identify subtypes of depression that are heavily characterized by large- and small-artery disease and related cardiovascular morbidity such as hypertension (in conjunction with the National Institute on Aging and the National Heart, Lung, and Blood Institute).

■ Identify other biological factors that contribute to depression (e.g., neuro- degenerative diseases that affect the midbrain dopaminergic system).

■ Develop innovative and precisely targeted therapeutics that would address the vascular mechanisms involved in the depressive disorder.

■ Develop novel interventions that target both neurobiological and psychosocial factors contributing to depression.

OBJECTIVE 4. Expand the knowledge base of safe and effective treatments for late-life depression and associated suicide risk.

Implementation:

■ Establish "Treatment Research Units – Geriatric" network (TRU-G), similar to the child RUPP program. Areas of emphasis could include:

– Effectiveness
– Relapse prevention
– Determining maintenance algorithms
– Understudied areas (bipolar, dysthymia, psychotic depression, suicide)

■ Validate treatments for acute efficacy while simultaneously exploring factors that contribute to sustained remission, reduced relapse, and recurrence.

■ Actively expand research into nursing home, assisted living facilities, and broader community settings.

3. Opportunities to Understand Mood Disorders as Diseases of the Brain and Body

OBJECTIVE 1. Improve the ability to diagnose and assess depression comorbid with other medical disorders.

Implementation:

■ Establish the criteria and decision rules used to diagnose major depression, dysthymia, and adjustment reactions in persons with other medical illnesses.

■ Based on gaps and needs identified, support development of reliable and valid measures for depression in persons with other medical illnesses.

OBJECTIVE 2. Identify the mechanisms and processes that have a relatively large influence on the development of comorbid disorders (i.e., explain a relatively large amount of variance in the outcomes) and can also be modified through intervention.

Implementation:

■ Discover potentially modifiable biological substrates that link comorbid disorders, including research on neurotransmitters, neuropeptides, neuromodulators, hormones and other proteins, neural circuits, and neural systems (to include nervous, endocrine, and immune system pathways, e.g., the HPA axis).

■ Elucidate the genetic, other biological, behavioral, psychosocial, and environ-mental risk and protective processes that contribute to these comorbid disorders, especially the most potent (those that account for the most variance in outcomes) and potentially modifiable processes so interventions may be designed to alter them.

OBJECTIVE 3. Determine variations in prevalence and incidence rates on comorbid depression and other medical disorders in women, members of racial and ethnic minority groups, children and adolescents, and the elderly.

Implementation:

■ Determine prevalence and incidence rates by age, gender, racial/ethnic background, and income level for mood, anxiety, and psychotic disorders comorbid with the leading causes of death in the United States, such as heart disease, cancers, strokes, chronic obstructive pulmonary diseases, and diabetes.

■ Promote epidemiologic studies of depression comorbid with other medical disorders to facilitate knowledge of prevalence; to identify potentially modifiable risk and protective processes; and to monitor trends in prevention, treatment, and rehabilitation.

OBJECTIVE 4. Support innovative pharmacological, behavioral, psychosocial, or environmental interventions aimed at comorbid disorders (e.g., discover potentially modifiable biological substrates that link comorbid mental and other medical disorders, target functional and symptomatic outcomes, study impact of separate organizational and financial systems for mental and general medical illnesses).

Implementation:

■ Expand research on the efficacy, effectiveness, long-term outcome, and safety of preventive, treatment, and rehabilitative interventions across the life span on the potent, modifiable risk and protective processes contributing to comorbid disorders.

■ Increase the number of clinical trials and intervention studies on pharmacological, psychosocial, behavioral, or environmental approaches (individually or in combination) that target functional and symptomatic outcomes in depressed individuals with comorbid disorders.

In 1996, it was the beginning of my senior year in high school. Things were going great. I was an honor student, vice president of the student body, and a speech and debate team member. Then one day things changed. I started thinking I wanted to die and planned exactly how I would do it. My mom found a note that I had written stating how I wanted to kill myself, which turned out to be a blessing. I was not diagnosed as having manic-depression until 3 years later, after I had begun hearing voices, self-multilating, and still wanting to just disappear. In 2000, my medications were finally adjusted where I was doing great in life—working, attending college, and taking care of my apartment. Then a year later, I decided that I did not need medication and could make it on my own. Boy, was I ever wrong! I did fine for 4 months, but then I hit rock bottom and had to be hospitalized again. The worse part is that the medications I was taking before did not work again, so we had to start all over and it took another 5 months to find a different set of medications. If I had known someone with manic depression, I probably would not have quit my medications,but I felt embarrassed when I had to take them in front of others.

Treatment, Prevention, and Services: Improving Outcomes

For people suffering from a mood disorder, the outlook has never been better. Effective therapies, both pharmacological and behavioral, can help them recover from potentially devastating episodes of depression or mania and prevent possible relapses. Why, then, is NIMH putting such a heavy emphasis on the development and dissemination of new therapies for mood disorders? The answer is that despite acknowledged progress, many people with depression or bipolar disorder go untreated. Despite the availability of a reasonably safe and effective therapeutic armamentarium, untreated and less-than-optimally treated depression, for example, are both common and associated with profound societal costs. Only half of individuals with anxiety and depressive disorders are accurately diagnosed, and of those diagnosed, only 25 to 50 percent receive guideline-level pharmacotherapy and less than 10 percent receive evidence-based psychotherapeutic treatments. Even when they do receive treatment, only slightly more than half of all of them respond well to therapy, defined as experiencing a 50 percent or greater reduction from baseline symptom severity. If complete symptom remission or restoration of function is the outcome, then the proportion is even lower.

Investigators have learned a good deal about the efficacy of pharmacological and behavioral treatments applied in academic settings to relatively homogeneous populations of almost exclusively Caucasian people without complicated general medical or mental disorders. Now, researchers need to determine which treatments are effective and cost-effective among all members of our society in real-life settings. There is also a dramatic need for a better understanding of how to deliver effective therapies to the very people who need them most, regardless of their socioeconomic, racial, or ethnic background.

In today's world of constantly shifting health care organizations and a rapidly expanding array of treatments, the challenge for intervention research in mood disorders is

to select research priorities and design trials that will have high public health significance. Public health-based intervention trials prove the value of new treatments and show how to translate the delivery of treatments to best meet the needs of all people who seek care for a disorder that interferes with their healthy functioning. To accomplish these goals, researchers must develop and validate markers of treatment outcome—genetic, neuroimaging, physiological, cognitive, functional, and behavioral—that represent the mental health status of all members of our society. To include all members of society, researchers will have to work with community members to engage them in research so that persons representative of all Americans will want to participate in such trials.

Current Status of the Field

Clinical Trials

The modern standard for clinical trials used to determine the intrinsic efficacy of any treatment (whether pharmacological or psychotherapeutic) is the randomized, double blind, placebo-controlled trial. These are usually carried out in academic settings by well-trained clinical investigators, and to maximize the likelihood of a finding, the participants under study are invariably narrowly defined. For example, in a trial of a treatment for depression, the age range of the subjects would be limited—the elderly might be excluded, for example—and individuals with a medical illness such as heart disease or diabetes would be excluded, as would anyone who used more than a specified amount of alcohol. In addition, the endpoints are usually limited to symptom reduction based on well-validated rating scales.

Such "efficacy" trials are crucial if we are to know that a treatment has value and is worth pursuing. Such trials are not, however, enough. When the testing of an intervention is limited to such classic clinical trials, we should not be surprised to find that the intervention may not work as expected when applied in broad community populations, in "real world" settings, and among diverse practitioners operating under real world constraints. The results often fail to meet the intent of providers, the expectations of consumers, or the demands of health care payers. We regard this gap as a reflection of the difference in the yield of research that follows a "regulatory" model and research that adheres to a "public health" model of studying interventions for mental disorders. One of NIMH's most important goals in the years ahead is to collaborate with the clinical and health services research communities, in consultation with basic scientists, advocates, and other federal agencies, to bridge that gap.

The outcomes of real world patient care often hinge on questions that are not addressed in studies based on a regulatory model. Payers want to know the best ways to determine what interventions work for what populations and which are the most cost-effective. Clinicians want data that will help them plan and implement treatment for consumers who may present with co-occurring mental disorders, substance abuse, or

medical problems; who can be at various stages of an illness; and who are culturally, ethnically, or racially diverse. Health care consumers, who are increasingly savvy about treatment options and often carry high expectations, want to know what treatment is best for their particular condition while presenting clinicians with varying concerns about adherence to a treatment regimen.

The public health model attempts to address these needs. In this type of trial, age, gender, co-occurring illnesses, and many other characteristics are no longer the basis for exclusion, but rather present important dimensions to ensure that studies are representative of the American population and will generalize to many clinical and community settings. Treatment intervention is defined to encompass a full range of pharmacotherapy and other somatic interventions, psychotherapy and other psychosocial approaches, and mixed modality approaches. It can extend to research on rehabilitative interventions and preventive interventions, including those focused on prevention of relapse and recurrence. Outcomes are not limited to symptom remission but can encompass performance, family and interpersonal relationships, disability, health care resource use, and quality of life. Settings are selected from a full range of academic and nonacademic institutions, specialty and primary care, and public and private facilities, with sample sizes sufficiently large to ensure adequate power. In these ways, the public health model permits studies to be designed to evaluate the effectiveness of clinical interventions, as they are likely to be delivered in community and specialized practice.

These new types of treatment intervention studies will require the development of studies that combines the designs of traditional clinical and services research. This will necessitate a compromise between the strict randomized studies traditionally used in clinical research and the more observational designs used in services research. One attempts to maximize internal validity while the other tries to ensure external validity. In order to bridge this gap, there is a need to bring together methodologists with expertise across these fields to delineate what we currently know and what we don't. A great deal of knowledge exists, but it has not been applied to the types of studies proposed here in the mental health field. It is also quite likely that new methods and statistical analytic approaches will need to be developed to address studies in the mental health area. NIMH is committed to fostering development of this new methodology and is exploring the best ways to proceed with this endeavor.

Pharmacological Therapy

Depression

Medications for the treatment of depression were introduced in the late 1950s and early 1960s as part of what is commonly referred to as the "psychopharmacology revolution." Two classes of antidepressant medications were developed, TCAs and MAOIs. A second major wave of new antidepressants occurred in 1988 with the introduction of the first SSRI, a class of drugs that prevents neurons from removing serotonin from the synapse,

which has the effect of increasing the duration of a nerve signal. However, at best only 65 percent of individuals with depression or bipolar illness respond adequately to available drugs, and many experience intolerable side effects. Furthermore, for both antidepressants and mood stabilizers, there is a time lag of weeks to months in the desired therapeutic response.

The SSRIs have become the clear drug treatment of choice for all forms of depression. Five are now available and these drugs are approximately equivalent to each other. The SSRIs have a much more benign side-effect profile, including safety after overdose, than the TCAs and largely for this reason have replaced the earlier drugs as first-line therapy. Sexual dysfunction is a major problem of the SSRIs—and indeed of all drugs that block the reuptake of serotonin and may affect treatment adherence.

There are several other effective antidepressants that are frequently used but do not fall conveniently into any single category. One, for example, is a dual serotonin and norepinephrine reuptake inhibitor, while another increases presynaptic release of both serotonin and norepinephrine and is also a serotonin receptor antagonist. Because of advantages in the side-effect profile and possibly in efficacy, these drugs are often used as first-line agents.

Most people with depression do not exhibit a therapeutic response until they have taken the drug for at least several weeks. A number of agents have been used as add-ons to established antidepressants in an attempt to reduce this latency to response. So far, systematic evidence that any such agent is effective in this regard is lacking.

Slightly more than half the people receiving antidepressant therapy achieve adequate response to treatment. NIMH has launched a very large, multisite public health-oriented trial, "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D), to identify the most effective approaches using available drugs and psychotherapy to address treatment-resistant depression.

"Off the shelf" herbal remedies are self-prescribed by many individuals for the relief of depression, but they are not regulated by the FDA. Therefore, there is virtually no information on efficacy, adverse events, or drug-drug interactions of these agents, nor is there any regulation of drug composition. Moreover, in most cases the possible mechanism of action of these compounds is obscure. Recently, a controlled study failed to demonstrate that one of these herbal preparations, St. John's Wort, was any more effective than placebo in the treatment of major depression of moderate severity.

There is some limited evidence that drugs that enhance dopaminergic neurotransmission may have antidepressant properties. For example, one dopamine receptor agonist has been reported to be as effective as an SSRI in treating depression. Other dopamine reuptake inhibitors, including some that are also serotonin and/or norepinephrine reuptake inhibitors, are under development, however.

Bipolar Disorder

Until about 10 years ago, bipolar disorder was in danger of becoming an orphan disorder with respect to treatment research and clinical trials. A period of enormous complacency had followed the introduction of lithium carbonate in the United States, and only a tiny number of trials were conducted between its introduction and the early 1990s, when both new clinical trial and naturalistic data indicated surprisingly poor outcomes showing that fewer than half of all individuals go 2 years without a new episode of mania or depression. This has led to a resurgence of interest in the treatment of this devastating disorder, including the recognition that psychosocial interventions, virtually absent from prior research endeavors, might have a role to play as adjunct treatments.

Efforts to develop new pharmacologic strategies for bipolar disorder have included trials of a variety of different compounds with different biochemical activities, such as anticonvulsants. Although some evidence is available to support the use of each of these agents in lithium-resistant bipolar disorder, few studies have carefully evaluated the maintenance efficacy of such strategies. Only scant research attention has been given to the possibility that psychosocial interventions may be useful adjuncts to maintenance pharmacotherapy.

Most recently, NIMH has funded the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a large multicenter, multifaceted long-term clinical trial. By following thousands of people over several years in a semi-naturalistic "best practices" design, STEP-BD investigators will provide the field with an unprecedented amount of data on the longitudinal course and effectiveness of modern, multimodal acute and maintenance interventions for different phases of bipolar disorder. A subset of the participants maintained on pharmacotherapy will be randomized to one of three specific adjunctive psychosocial treatment arms (cognitive therapy, family-focused therapy, or interpersonal and social rhythm therapy), and its effectiveness at reducing residual symptoms and promoting the recovery of adults with bipolar illness will be compared to that afforded by more usual, minimal psychosocial intervention. Embedded randomized trials will permit the controlled evaluation of common clinical practices, e.g., combined antidepressant and mood stabilizer versus mood stabilizer alone for bipolar depression. Related women's health studies within STEP-BD will examine the relationship of valproate to polycystic ovary syndrome and the effectiveness and safety of omega-3 fatty acids for mood stabilization in women with bipolar disorder who discontinue traditional medications due to planned or actual pregnancy.

Somatic Treatments for Mood Disorders

In many respects the study of somatic treatments is comparable to that of other interventions for mental disorders, utilizing clinical trials methodology that includes specified treatment parameters, duration, and standard outcome measures. However, certain characteristics of somatic treatments distinguish them, to varying degrees, from

standard drug and psychotherapeutic interventions, and present special challenges to the performance of scientific research.

Because of the relatively invasive nature of some somatic therapies, their use is skewed toward sicker mood disorder populations, and studies involving random assignment to treatment are problematic. For example, ECT is specifically indicated in cases of severe depression accompanied by psychosis or catatonia. This also means that a disproportionate number of individuals available for study or clinical treatment using ECT will be treatment resistant. The need to study very ill people also means that it is difficult to establish a medication free baseline, which would be ideal to study the true effects of a somatic intervention and essential for meaningful mechanism of action research. This has been less of an obstacle to pharmacotherapy research, where the use of multiple medications has become the norm in severe mood disorders. The only controlled trial of ECT in mania, for example, was published more than a dozen years ago. Some investigators have moved instead toward combined treatment studies of somatic treatments plus drug treatment.

However, NIMH-supported research has found ways of improving the outcome of ECT while minimizing side effects. For example, placing electrodes on one side of the head and using a stronger electrical pulse reduces the memory loss usually associated with ECT while retaining its efficacy. A variety of ongoing studies are aimed at further increasing the safety of ECT while maximizing its therapeutic effects. Recent NIMH-supported research demonstrated that aggressive pharmacotherapy following successful completion of a course of ECT can substantially reduce the common problem of relapse in the year following ECT. The first controlled trial of maintenance ECT is currently underway.

Researchers are currently exploring another promising somatic therapy known as regional transcranial magnetic stimulation (rTMS). In contrast to ECT, which applies an electrical stimulation to the scalp, rTMS generates a more precisely localized electromagnetic pulse by using a magnetic coil placed over the person's head. To date, the antidepressant effect of rTMS has been modest, but studies continue in an attempt to improve this therapy, which does not require anesthesia and has rarely been associated with adverse effects beyond a mild headache. Other more invasive somatic treatments, including vagus nerve stimulation and deep brain stimulation, are under study, but have not yet shown efficacy in refractory depression in controlled trials. At the milder end of the depressive spectrum, a structured aerobic exercise program has shown efficacy similar to that of antidepressant medication in one NIMH-supported trial. Research over the past two decades supports the efficacy of daily exposure to bright artificial light in individuals with an exclusive and repeated seasonal pattern of mood disturbance over multiple years.

Psychosocial Therapy Development

Depression

Depression responds to several different psychotherapies. IPT and CBT have the strongest

empirical support. Both have demonstrated efficacy in the acute treatment of depressed outpatients, although questions remain about the efficacy of CBT among people with more severe depression. Traditional psychodynamic and experiential interventions, including eclectic approaches to therapy, have been tested in relatively few studies and have not proven particularly effective in most of these trials.

Both IPT and CBT appear to reduce risk for relapse or recurrence so long as they are continued. Moreover, CBT appears to have an enduring effect that extends beyond the end of treatment. Acute treatment with CBT has been shown to reduce risk for subsequent relapse, and adding CBT to medications during continuation treatment reduced risk for both relapse and recurrence. There are also indications that CBT can prevent the initial onset of the disorder in persons at risk. These indications deserve to be pursued; it would be important to determine if CBT has a preventive effect.

IPT may have a specific effect on interpersonal functioning and the quality of relationships. Given that interpersonal relationships are themselves important and that problems in this domain may contribute to onset and prolongation of mood disorders, these preliminary findings suggest that further research is needed to determine whether IPT improves the quality of social and vocational life for those with mood disorders.

Combined treatment involving medication and evidence-based psychotherapy typically provides a modest increment over either single type of treatment alone with respect to the reduction of acute distress, and appears to retain the specific additional advantages produced by each. For example, medications typically produce more rapid symptom relief than IPT, whereas IPT has the broader effect on the quality of inter-personal life. Similarly, combining CBT with medication appears to compensate for any relative limitations CBT may have in the treatment of more severely depressed people while retaining its enduring effects.

As with antidepressant medications, not all individuals respond to psychosocial therapy, and only a minority achieve full remission. Incomplete response increases the risk of relapse, and many will have chronic or recurring problems if they do not stay in ongoing treatment. Even with such treatment, some individuals will suffer relapse or recurrences. Individuals with a history of chronic depression or long-standing personality disorders appear to be particularly unlikely to respond to brief interventions. Moreover, little is known about the effects of existing treatments on work disabilities and other dysfunction that often constitute the primary concerns of people with depression. Clearly, new treatments must be developed and existing interventions strengthened to deal with these limitations.

Work is under way on adapting existing evidence-based interventions for use with chronic or treatment-resistant forms of depression and in other more specific indications around prophylaxis or relapse prevention. Other research is directed toward adapting existing therapeutic approaches for new applications, such as dialectical behavior therapy for depressed elders with personality disorders, problem-solving approaches for depression

in the primary care setting, and behavioral activation as a more simply behavioral form of CBT. Additional research is needed to further develop and establish the properties and optimal uses of new psychotherapeutic approaches that have shown initial promise in the treatment of mood disorders, such as supportive-expressive psychodynamic psychotherapy, Cognitive Behavioral Analysis System of Psychotherapy in treatment of chronic forms of depression, and mindfulness-based cognitive therapy in prevention of depressive relapse and recurrence.

Bipolar Disorder

The treatment of bipolar disorder remains problematic. The pharmacological guidelines for treating people with bipolar disorder during acute, continuation, and maintenance phases are well established. Nonetheless, most individuals have break-through episodes or significant residual symptoms even while on medications. Problems with adherence further undermine the stability of response. Episodes of the illness are associated with significant social and occupational problems, and functional deficits often remain even when the person is not having an occurrence of the illness.

Though there is little evidence as yet that these approaches can forestall the emergence of mania, over recent years researchers have shown a renewed interest in applying psychosocial therapies to the treatment of individuals on medication for bipolar disorder. Family-focused therapy aimed at reducing high levels of emotion, especially criticism, and enhancing the frequency of positive family or marital interactions appears to reduce the risk for subsequent relapse in people on medication. Similarly, IPT modified to incorporate attention to stabilizing people's social rhythms has shown considerable promise. Likewise, CBT has demonstrated potential for reducing the frequency of depressive relapse and delaying manic relapses, when aimed at early recognition and treatment of prodromal symptoms in medicated individuals.

More must be done to refine existing treatments and develop novel interventions for bipolar disorder. The fact that many people do poorly even while on medications speaks to the importance of developing or extending other types of treatment. This might include developing brief educational interventions for young people at risk for early onset by virtue of family history or mood fluctuations. Psychosocial interventions also should be developed to enhance individuals' adherence to mood stabilizing medication regimens and their ability to cope with stress that contributes to illness recurrence. Such interventions have the potential to alleviate impairments in social and occupational functioning not addressed by medication. Sequential models need to be developed that parallel the changing course of the illness. Research is needed to determine the optimal composition and sequencing of an overall, empirically based treatment approach and to validate preliminary clinical observations that behavioral activation, family support, and cognitive restructuring may be useful during the depressed phase, whereas medication regularity and social rhythm stabilization may be particularly important to prevent cycles into mania.

Issues for Treatment

Measurement

Advances in depression research and treatment development are highly dependent on the quality of research procedures to measure, assess, or classify the pathology and its expressed symptomatology. No reliable biological markers or valid behavioral tests exist to define the exact nature of depression and disentangle issues of comorbid pathologies, or co-occurring syndromes or clusters of symptoms; accordingly, diagnostic and classification systems have principally relied upon clinical description and the naming of behavioral signs and symptoms to define the syndrome (e.g., sad mood, sleep difficulties, diminished interest). The traditional assessment and diagnosis of depression has proved insensitive for the identification of likely responders to existing psychosocial and psychopharmacological treatments.

Historically, diagnostic measures of depression have utilized two modes: patient self-report of symptoms or clinician rating of patient symptoms. Measures in each of these traditions have been widely used for multiple purposes with broad public health implications, including validating the use of new medications for treatment and identifying people who might respond to various treatments of depression. However, the most widely used instruments in clinical settings have generally failed to provide clear documentation of the symptoms experienced by individuals and instead typically have offered only global indices of depression.

Assessment tools (both self-report and clinician administered) need to deal effectively with the heterogeneity of depression for several reasons. First, different forms of depression may respond differentially to various treatment modalities, or have a different course. Second, the complete mapping of the human genome raises the possibility of relating disorder subtypes to specific genetic vulnerabilities. Third, advances in techniques to study neuropathophysiological processes facilitate the study of associations between clinical phenomena and the neural substrates and circuitry of mood and emotion. Refined measurement is a prerequisite for studies that examine such associations, link genetic diatheses to particular forms of disorder, or guide the precise tailoring of future therapeutics.

The tools developed will need to be tailored to a wide audience of consumers and should reflect validated components of depression such as depressed mood, hopelessness, psychomotor retardation, sleep disruption, fatigue or loss of energy, diminished ability to think or concentrate, disturbed self-image (i.e., feelings of worthlessness or excessive guilt), and suicidal ideation. They also need to be appropriate for individuals of diverse cultural backgrounds, valid for individuals at various stages of development (i.e., children, adults, elderly), suitable for use in diverse settings (e.g., clinical trials based in academic centers and community-based mental health), and sensitive to individuals with various comorbid medical conditions.

Prevention of Suicidal Behavior

Suicide is a complex behavior usually caused by a combination of factors. Research shows that almost all people who kill themselves have a diagnosable mental or substance abuse disorder or both, and that the majority have depressive illness. Researchers know little about the prevention of suicidal behavior. Suicidal people are routinely excluded from controlled trials, and few studies have targeted such behavior. While it is practice to reduce imminent risk for suicide through hospitalization, few studies have examined whether this practice reduces suicidality over the long term. Existing interventions for depression have done little to reduce the incidence of death by suicide, although this may be changing with the advent of newer and safer medications.

Psychosocial interventions that target suicidal behaviors may reduce risk for morbidity and mortality. There are indications that the availability of crisis intervention services can reduce risk for suicidal behaviors for some subgroups, and simply maintaining a correspondence with people who refuse treatment has been found to reduce rates of suicide. Further research is needed to determine whether suicide is best prevented by reducing the general level of distress, by targeting the suicidal behaviors directly, or both.

Delivery of Services

Primary Care

Primary care represents a strategically important setting for the identification and treatment of depression and other mental disorders, especially for children and older adults. It offers the advantages of continuity of health care, early identification and, importantly, coordination of care for mental and somatic disorders given the frequency of comorbidity.

Research indicates that approximately one-third of depressed patients in primary settings receive inadequate treatment, and more than half (55 percent) receive no treatment. The deficiencies are attributable to a complex set of factors. Primary care physicians are hampered by an inability to address multiple problems and concerns in a time-limited visit; the lack of clear biological markers with diagnostic utility; and limitations in necessary knowledge and skills in mental health care. Patients contribute to the problem by an inability or unwillingness—the latter often prompted by the person's beliefs about mental illness and stigma—to articulate their reasons for seeking care and by lack of appreciation of the importance of treatment adherence. The health care system also erects multiple barriers to effective diagnoses and treatment; these include lack of availability of providers and treatments; limitations of third-party insurance coverage, including restrictions on specialists, medication, and psychotherapeutic care; and competing demands of other medical illnesses in terms of costs for procedures and drugs. Often crosscutting these physician, patient, and system obstacles are cultural and language barriers in expressing and translating symptoms.

The reality that the preponderance of treatment for mental disorders occurs in the general medical/primary care sector, and the limitations of that care, underscore the need for more intensive research addressing these issues. The complex interplay between financial/economic incentives, health care provider and patient behavior, and its impact on the delivery of effective treatment for depression or bipolar disorder must be understood to improve clinical outcomes and realize the full potential of the primary care setting.

Barriers to Care

Too often, clinical practices and service system innovations validated by research are not fully adopted in treatment settings and service systems for individuals with mood disorders. Health services must be improved by focusing on a continuum of knowledge translation: from basic science to development of new treatments, from treatment development to clinical trials, and from clinical trials to practice. The model, in its most extreme form, seems to assume that the universe of patient care rotates around the earth of scientific knowledge, but clinical practice must proceed even in the absence of data from randomized controlled trials. The process of translating science to practice is neither a one-way flow from basic to services research, nor a linear process but instead a process that has a series of loops whereby at one point practice may stimulate the ideas for treatment development and at another time be the recipient of the change.

The more serious problem is that there also are many common clinical situations where people require treatment and there is clear experimental evidence to indicate what the clinician should do, but that treatment is not provided. Research funds fail to improve public health unless research results become part of routine practice through education or re-education of practitioners, administrators, policymakers, and consumers/patients.

The mood disorders research field can no longer ignore the mounting evidence that new information—the central product of research—has only a very limited impact on the decision-making behavior of those who receive it. This fact and the resultant chasm between treatments selected and carried out in clinical trials and those selected and carried out in real world settings have led to considerable tension between clinical researchers and practitioners. This chasm must be bridged if we are to improve the health of the Nation. In an ideal world, researchers would choose to study highly efficacious treatments that are also very generalizable, but this has rarely occurred.

The data on the efficacy of a few carefully studied psychotherapies and of appropriately dosed medication treatment support both forms of therapy for most unipolar mood disorders. How have patterns of care shifted as this information became available? It is evident that the introduction of the SSRIs has had dramatic and pervasive effects on care for depression. The impact of the evidence on the effectiveness of CBT, IPT, and other empirically supported psychotherapies is equivocal at best. However, this is hardly surprising since neither form of treatment is efficacious with all persons suffering from depression, and there are almost no data on how to select among treatments when faced

with a given patient. It is difficult to know what contribution is made through the advertising created by drug companies on the positive effects of their products, an advantage, if it is one, that the psychotherapies do share.

To date, treatment research priorities have not balanced new knowledge generation with questions about information needs and opportunities and mechanisms to improve care. Future research priorities will need to emphasize "how" to deliver the treatment as well as "what" treatment. They will also need to emphasize the cost-effectiveness of treatments across populations and care settings.

The burden of an illness refers to its total direct and indirect consequences across stakeholders of interest—consumers and their families, clinicians, payers, and society. Different stakeholders face different consequences of mood disorders and benefit differentially from interventions to reduce the burden of these disorders. As a result, "externalities" exist, where the consequences of decisions are experienced by stakeholders other than the decision maker. For example, pain and suffering is largely borne by affected individuals and their families, while health care costs may be borne initially by providers, payers, and plans. In this situation, providers and purchasers may be reluctant to support the level of care that might be desired by families. More generally, externalities can result in substantial barriers to treatment and to changing consumer and provider behavior. Information on how costs and benefits of an illness and marginal effects of interventions are distributed across stakeholders can be used to formulate policies to correct incentives.

It is likely that barriers to care contribute significantly to the unmet needs for appropriate care. For example, low socioeconomic status and poverty increase the risk for mood disorders and reduce access to specialty or general medical and mental health services. In studies of perceived unmet need, financial barriers predominate. One study found that 14 percent of the National Depressive and Manic-Depressive Association (NDMDA) members with bipolar disorder indicated they might discontinue medication due to costs. Other factors that erect barriers to care include family dysfunction; lack of family resources; comorbid general medical and mental disorders; consumer attitudes, knowledge, and behavior; clinician and practice factors; lack of insurance coverage; community factors; and societal stigma. Breaking down these barriers in effective ways will require new interventions developed through research.

Issues Facing Racial and Ethnic Minority Groups

Among the many challenges facing our Nation in the 21st century, one of the most urgent is to address health and health care disparities experienced by many citizens and disproportionately by members of racial and ethnic minority groups. Racial and ethnic minority groups make up 29 percent of the U.S. population and by 2050 will account for nearly 50 percent of the population. Yet despite having similar needs for mental health care, members of the Nation's racial and ethnic minority groups often fail to receive appropriate care. For example, two national studies found that racial and ethnic minority

treatment populations were less likely to receive appropriate care for depression or anxiety than were Caucasians.

Americans of ethnically and racially diverse backgrounds also face unique cultural barriers to care. For example, although African Americans make up nearly 12 percent of the U.S. population, only 2 percent of psychiatrists and 2 percent of psychologists are African Americans; a similar pattern applies to other racial and ethnic minority groups. Racially and ethnically diverse Americans are also more apt than Caucasians to be uninsured. Studies have also shown that African Americans are terminated sooner from treatment by Caucasian therapists, and are also more likely to be perceived stereotypically by inpatient staff as violent or dangerous.

African Americans with bipolar disorder are at higher risk for being misdiagnosed as having schizophrenia than are Caucasians, are less likely to receive lithium therapy, and are more likely to have lithium side effects. African Americans are also more likely than Caucasians to receive antipsychotics across diagnostic groups and to receive higher doses, contributing to high risk for tardive dyskinesia.

In late 2001, NIMH in collaboration with consultants and public comment developed a 5-year strategic plan to address mental health outcome disparities through research that aims to describe, understand, and remedy the disproportionate impact on minority populations of mental disorders and behaviorally influenced medical conditions such as HIV/AIDS (http://www.nimh.nih.gov/strategic/strategicplanmenu.cfm). This research takes into consideration relevant contextual frameworks, including interpersonal, sociocultural, and organizational factors. The plan prioritizes ongoing research, research training/capacity building, and public information outreach and dissemination activities as well as new initiatives. NIMH has also created an additional plan for mental health research career development of racial/ethnic minority investigators (http://www.nimh.nih.gov/council/diversity.pdf).

Children and Adolescents

The literature on burden of mood disorders is undeveloped for children and adolescents. The conceptualization and evaluation of barriers is complicated by the diversity of service systems for youths, including schools, foster care, and juvenile justice systems, in addition to general medical, mental health, and substance abuse systems. Professionals differ within and across systems in training, experience, and responsibility for youths with mood disorders.

One of the chief problems is that there is no consensus on diagnostic criteria for youth mood disorders. Provider recognition is lower for internalizing disorders, such as depression and anxiety, than externalizing disorders, such as conduct disorder, in youth, and parents may be less likely to seek services for children with internalizing problems. Barriers to referral and treatment in primary care include delays in obtaining appointments, lack of specialists, payment problems, managed care restrictions, and complex

appeal processes. Among children seeking behavioral health care under managed Medicaid, 25 percent of their families reported not getting enough approved visits and 15 to 20 percent reported waiting more than 4 weeks for an appointment.

Children are also over-represented among the uninsured. Some initiatives offer promise, but benefits vary across states and enrollment rates are low. In the private sector, most children are covered by managed specialty carve-out companies. Variation in financing and management may affect use of mental health services for children, but effects of specific policies are unknown. One consumer survey suggests that children with severe mental illness frequently end up in the juvenile justice or child welfare systems due to unavailable or inadequate treatment under limits imposed by managed care. While achieving parity of annual and lifetime dollar limits for mental health and medical health services could increase mental health service use by children, the effects of mandated coverage on this age group have not been studied. Policy initiatives affecting mental health care for children are implemented with few efforts to track results.

Opportunities for Progress

Novel interventions may be created from scratch or refined from existing treatments. Innovation often builds on existing knowledge and theory about the processes that initiate and maintain the disorders of interest. This knowledge may come from basic research on normal populations or psychopathology research on clinical populations; efforts to use this information for clinical purposes have come to be called translational research. Similarly, basic research on the change process can be used to test theory and refine existing interventions, as can efforts to examine mechanisms of change within the confines of controlled clinical trials. Finally, innovation can arise from the experience of clinical practitioners.

Opportunities to Improve and Expand Clinical Trials

In recent years there has been an increasing emphasis on extending clinical trials research—research that examines how well treatments work in people—from tightly controlled, academic settings out into community settings. Many past studies have established the safety and efficacy of various treatments for mental disorders—that is, how well they work in very specific groups of people under ideal conditions. However, few studies have adequately tested the effectiveness of particular treatments or treatment strategies—how well they work, for example, in people who live in the community, come from diverse backgrounds, have co-occurring disorders, or experience atypical patterns of illness. In addition, quality of life, ability to work, social functioning, treatment adherence, and treatment cost-effectiveness are among the important, real world issues that only effectiveness research can adequately assess. In contrast to efficacy research, effectiveness studies have very few exclusionary criteria and enroll large numbers of participants—

several hundred to thousands—so that the findings will be representative of and broadly applicable to an entire population group.

To improve the standards of treatment for mental disorders, NIMH has taken the lead in developing treatment effectiveness research on a number of clinical issues of major public health significance. Three major, multisite, NIMH-funded effectiveness trials that relate to mood disorders are ongoing.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is the largest and longest treatment study for bipolar disorder ever conducted. STEP-BD focuses on finding the most effective strategies for treating episodes of depression and mania and for preventing recurrent episodes over time. Almost anyone with bipolar disorder who is age 15 or older and living near a study center can participate. There are currently 15 STEP-BD study centers recruiting individuals, with an expected total enrollment of 5000 participants. STEP-BD is evaluating all the best-practice treatment options used for bipolar disorder: mood-stabilizing medications, antidepressants, atypical antipsychotics, and psychosocial interventions—or "talk" therapies. Findings from STEP-BD will help improve the treatment standards for bipolar disorder used by doctors in everyday clinical practice.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) focuses on non-psychotic major depressive disorder in adults who are seen in outpatient settings. The primary purpose of this research study is to determine which treatments work best if the first treatment with medication does not produce an acceptable response. There are currently more than 30 STAR-D sites recruiting, with an expected total enrollment of 4000. Participants will first receive citalopram, an SSRI medication; if symptoms remain after 8-12 weeks of treatment, up to four other levels of treatment will be offered, including cognitive therapy and other medications. There are no placebo treatments. Some individuals may require a combination of two or more treatments to obtain full benefit. Participation could last from 15 to 27 months and involve up to 30 clinic visits. Participants will be interviewed by telephone throughout the study about their symptoms, daily functioning, treatment side effects, use of the health care system, and satisfaction with treatment. There will be a 1-year follow-up for participants once their depression has been successfully treated.

The Treatment for Adolescents with Depression Study (TADS) is a research study of treatments for major depressive disorder in teenagers. TADS will compare the short- and long-term effectiveness of an antidepressant medication (fluoxetine), psychotherapy (CBT), and the combination of these treatments in teens ages 12-17 with major depression. This is a 36-week study with a 1-year follow-up period. There are 12 TADS sites currently recruiting participants, for a total expected enrollment of 432.

Increasing Participation Diversity in Clinical Trials

The participation of racial and ethnic minority groups in clinical and public health research is essential for addressing disparities in health status. However, for many different

reasons, racial and ethnic minority group participation is low in most research studies. Many authors have documented numerous barriers to participation in research. Those barriers fall into four categories: broader health care system issues; cultural and social attitudes; public knowledge, perceptions, and attitudes toward researchers and research; and behaviors and attitudes of providers and researchers. Most research takes place at university medical centers that tend to have an underrepresentation of racial and ethnic minority faculty, researchers, students, and patients who ordinarily comprise the research scenario. The absence of familiar social and cultural accommodations could account for the sense of discomfort racial and ethnic minorities feel in the medical research center, and hence their reluctance to enter this setting, particularly as clinical trial participants. Several authors describe researcher and physician biases as barriers to recruitment of racially and ethnically diverse participants. Despite ethical standards that would prohibit such actions, researchers may limit racial and ethnic minority group participation in clinical trials because of their beliefs that these participants will prove difficult because of linguistic or other social and cultural barriers and impediments.

Failure to accommodate cultural and economic diversity of potential study participants, failure to recognize that restrictive studies do not fully assess safety and efficacy of new treatments or preventive interventions for all populations, claims that statistical power will be reduced if racial and ethnic minority participants are included, inaccurate beliefs that certain populations are not at risk for specific conditions or illnesses, and failure to establish research clinics in institutions that have historically served racially and ethnically diverse populations, all limit the generalizability of results and perpetuate health disparities. With the encouragement of NIMH, clinical researchers must dramatically increase the ethnic and racial diversity of their clinical trials populations. At the very least, all trials must reflect the diversity of the communities in which clinical research is being conducted. NIMH has recently formed partnerships with institutions that have historically served predominantly racial and ethnic minority groups, such as Howard University.

Opportunities to Develop New Psychosocial and Behavioral Therapies

Basic research in the areas of cognitive science, neuroscience, behavioral science, and developmental psychopathology provides an obvious source of innovation, largely by suggesting possible targets for intervention. This has clearly been the case, for example, for the existing evidence-based psychosocial interventions for depression: IPT drew heavily on attachment theory, and CBT was strongly influenced by social-cognitive theories of emotion and information processing. It is striking that the two psychosocial interventions with the strongest empirical support so closely parallel two of the major animal models of depression, separation-loss and learned helplessness.

The recent report of the National Advisory Mental Health Council's Behavioral Science Workgroup Translating Behavioral Science into Action (http://www.nimh.nih.gov/tbsia/tbsiatoc.cfm) describes ways in which basic research can inform clinical innovation. Better understanding how people process emotionally relevant information can be used to identify "what" to target, and recent advances in developmental psychopathology that have identified periods of risk for mood disorders and suicide can tell us "when" to intervene. Much has been learned about the structure and function of the nervous system in the last several decades, and the development of imaging technologies allows studies of human neural function *in vivo*. These advances and others yet to come may be parlayed into new and more powerful psychosocial interventions by linking basic research to intervention development.

Research on the structure of affect parallels the growing understanding of the structure and function of brain neural systems. For example, one new model suggests that anxiety and depression share a common core of negative affect, whereas depression is further distinguished by an absence of positive affect. Whether this distinction proves helpful in refining interventions remains to be seen. One line of research has extended CBT to include greater attention to positive affect and a sense of well-being.

Cognitive science also suggests a number of targets for intervention development. For example, research has shown that people with histories of depression think differently under stress or in states of mild distress—they become more negative and rigid in their thinking and have difficulty generating solutions to the problems they face. These propensities are shaped in part by negative life experiences, and both predict risk for symptom onset and appear to mediate the preventive effects observed for CBT. Work is underway to better understand how these cognitive propensities relate to underlying neural mechanisms and how they are shaped by early interpersonal context.

Research on the mechanisms that underlie interpersonal attachment and vulnerability to disruptions in those bonds may illuminate additional ways to intervene. Interpersonal loss and disappointment can play an important role in the onset and maintenance of depression, and criticism from important others has been shown to increase the risk for relapse. As an example, one group is using MRI techniques to explore the brain regions that are activated among recovered depressed persons in response to maternal criticism.

Finally, understanding better the protective mechanisms that allow resilience in the face of life stress may facilitate the development of innovative interventions. For example, researchers need to study the development of emotion regulation, for new knowledge about the mechanisms that underlie these phenomena may allow investigators to develop new and more effective interventions for depression, bipolar illness, and suicide.

Opportunities for the Prevention of Mood Disorders

Depression has come to be recognized as a chronic recurrent disorder in which the majority of people with the illness will experience multiple episodes across their lifetimes. Clinical practice is evolving toward maintaining such individuals on medications indefinitely to reduce the risk of relapse. Given that life-long treatment regimens are costly, as well as the costs in human misery and lost productivity when people do not obtain treatment, there is much to gain by preventing the onset of the disorder and providing the tools to slow its progression. Perhaps it is not surprising, then, that the Institute of Medicine Committee on the Prevention of Mental Disorders identified depression as the most preventable disorder and called for a substantial increase in prevention research in high-risk samples.

Extending the duration of evidenced-based interventions appears to reduce subsequent risk of recurrence—IPT, CBT, and antidepressant medication all reduce risk for relapse or recurrence so long as they are continued. Moreover, CBT appears to have an enduring effect that lasts beyond the end of treatment. This enduring effect appears to be robust regardless of whether the intervention is provided during acute or continuation treatment and with or without medications. Clearly, some mechanism must be operating that reduces subsequent risk, and research should be directed to determining the nature of that mechanism.

For bipolar disorder, brief psycho-educational interventions should be developed for younger persons who have not yet been diagnosed but are at risk because of family history or dramatic mood fluctuations. Components of these preventive interventions might include education about the disorder and its triggers, mood charting, identification of early warning signs, sleep/wake cycle monitoring, cognitive restructuring, and other tools. Similarly, there may be a role for psychosocial interventions whose primary focus is on medication adherence, particularly during the maintenance phase. Components might include teaching people how to recognize drug side effects and how to communicate with their mental health providers about them. Such preventive therapies could address beliefs regarding the meaning of taking medications or the tendency to over-glamorize the "high" periods or provide useful discussions about family conflicts pertinent to medication taking.

Research that leads to a detailed account of how cognitive, behavioral, and affective vulnerabilities influence the onset and prolongation of mood disorders can contribute to the development of effective preventive interventions. For example, adolescence is associated with a striking increase in the incidence of depression and associated suicide attempts, as well as the emergence of sex differences in depression rates, with females greatly outnumbering males. Better understanding of the mechanisms underlying these changes might provide clues to the nature and timing of preventive interventions.

Prevention research should also test theories about normal development, the course of psychopathology, and change processes that alter the course of mood disorders. Well-

designed prevention studies can test whether high- and low-risk groups actually differ in targeted risk factors, whether and how interventions change these factors, and whether these changes are related to improved mood regulation and reduction in episode incidence. Prevention trials provide an opportunity to test theories regarding the mechanisms that lead to onset and the strategies that avert it.

Preventive interventions need not be targeted directly at depression to reduce its incidence. For example, exposure to job-search skills and inoculation against setbacks not only resulted in higher levels of reemployment and monthly income, but also reduced levels of depression and the onset of diagnosable depressive episodes among the recently unemployed. Similarly, programs designed to increase reading in grade school youngsters also reduced symptoms of depression.

Many depressed and suicidal individuals do not receive efficacious treatment. The problem is most severe for members of racial and ethnic minority groups, individuals with low incomes, people with different sexual orientations, and children and the elderly. In fact, as mentioned above, members of racial and ethnic minority groups are so poorly represented in randomized controlled trials that we know very little about the effectiveness of "evidence-based interventions" in these groups. Efforts must be made, then, to sample populations in a representative fashion, determine whether heterogeneity influences outcomes, and identify the responsible mechanisms. Although this might be done through conventional means, it likely will require developing new interventions, adapting existing ones, and utilizing novel delivery methods, whether targeted at prevention or treatment. It will also require new partnerships, more grassroots participation, and working with the community.

It is unclear whether interventions efficacious in controlled trials generalize to everyday clinical practice; sometimes they do and sometimes they do not. If an intervention is efficacious under controlled conditions but is less effective in applied settings, researchers need to ask if that resulted from the patients, therapists, implementation, or other aspects of the context and setting. Such variability represents an opportunity to explore the processes that lie behind that treatment's effect or lack of it.

Transporting interventions to new populations may require new modes of delivery. A growing body of literature suggests that interventions for racial and ethnic minority groups need to be culturally sensitive so that they take into consideration the role of culture and context, with the result that culturally enhanced or adapted treatments may differ significantly from the original treatments. For example, involving families in treatment decisions appears to be especially important when working with Latino populations, while adding a case management component to deal with concrete real-life problems may be necessary to reduce attrition in low-income, medically ill populations, regardless of race or ethnic background. When treatments must be modified to retain their effects, it provides an opportunity to explore relevant processes and deepen our understanding of the mechanisms involved. The complexity in assessing what will work best for whom is both a

science and an art that is going to require the development of new methods of assessment and the creation of new scientific disciplines.

Using Non-Traditional Dissemination Methods to Increase Accessibility to Psychosocial Interventions

Non-traditional dissemination methods hold special promise for increasing access to effective interventions. Various non-traditional methods have been employed in community settings, but they have not been studied systematically. Strategies that have been tested include telephone contacts, community-wide television programming, and use of computers and web-based questionnaires and teaching modules.

The Internet affords the opportunity to make psychosocial interventions that can be implemented appropriately, reliably, and with proper security available to large segments of the public. Web-based educational and assessment tools can be developed that could be used for interventions such as acquainting people with bipolar disorder with the early warning signs of manic episodes, and providing access to early intervention and self-monitoring forms commonly used in clinical practice. Self-rated assessment scales can be used to screen widely for bipolar spectrum disorders, as the web site of the NDMDA is currently doing. A similar approach could be used to educate families and friends about suicide risk and suggest ways to obtain crisis intervention.

The web and other non-traditional dissemination methods also can be used to reach providers. It can provide training in evidence-based methods, information about the latest research findings, collegial support to clinicians who are leading the way in the provision of evidence-based methods in their professional community, scales useful for monitoring patient progress, and even consultation on difficult cases.

Researchers often think about development of new psychosocial interventions in terms of "market segmentation." By developing a variety of alternative delivery methods, we should be able to tailor interventions for increasing segments of the population in need, including those in rural areas and non-English-speakers. None of these methods will reach everyone, and none will be universally effective; but together they can expand prevention and treatment of mood disorders to a larger proportion of the population and provide a framework for prioritizing resources.

Research Priorities

1. Opportunities to Improve and Expand Clinical Trials

OBJECTIVE 1. Determine the efficacy of interventions in populations underrepresented in previous trials and determine the effectiveness and cost-effectiveness of already proven efficacious treatments for mood disorders.

Implementation:

■ Determine in what underrepresented populations clinical trials may be needed based on evidence of potential differential response by those populations compared to the general population.

■ Test the efficacy of psychosocial and pharmacological treatment interventions in underrepresented populations and clinical subgroups suspected of having a differential response from the general population (e.g., racial and ethnic minority populations, prepubertal children with unipolar depression, children and adolescents with bipolar disorder, women with postpartum depression, people with depression and medical comorbidity).

■ Determine specific approaches to enhance recruitment, participation, and retention of underrepresented populations to expand the generalizability of findings from clinical trials.

■ Initiate trials to test the effectiveness and cost-effectiveness of treatment interventions in mood disorders that have been little studied or are not currently under investigation (e.g., major depressive disorder with psychotic features, depression with comorbid substance abuse and/or personality disorder).

OBJECTIVE 2. Develop new methodology and statistical analytic procedures to enhance the ability of clinical trials to provide data relevant to community populations.

Implementation:

■ Incorporate epidemiological strategies and sampling approaches to better characterize those who do not participate in clinical trials and dropouts from a trial.

■ Develop new methodologies for trial designs that improve relevance of the trial results to community populations.

■ Test ways of incorporating preferences and needs of community providers and consumers into treatment designs.

■ Evaluate the adequacy of current assessment tools for measurement of mood disorders as outcomes in treatment trials across the life span.

■ Increase communication and interaction between clinicians treating individuals with mood disorders and basic and clinical researchers to enhance two-way exchange of information regarding researchable problems and applicability of findings to settings.

OBJECTIVE 3. Assess the long-term effects of treatment interventions on physiological and functional status.

Implementation:

■ Monitor long-term beneficial and adverse effects of treatment interventions in currently funded clinical trials (e.g., possible changes in brain structure due to therapies).

■ Determine the long-term effects of treatments in selected populations with particular vulnerabilities to disease recurrence or adverse effects (e.g., racial and ethnic minority groups, woman, children, and the elderly).

2. Opportunities to Develop New Psychosocial and Behavioral Therapies

OBJECTIVE 1. Determine the basic mechanisms by which psychosocial interventions operate to produce therapeutic change to increase opportunities for innovative developments.

Implementation:

■ Test proposed theories of change that have been drawn from identified common key dimensions and potential mechanism of action in currently used mood disorder intervention protocols.

■ Support translational research on emotion as a means of stimulating development of treatments that draw on the interplay between emotion, cognitive functioning, and motivational systems.

■ Use advances in cognitive neuroscience, imaging, emotion, memory, and learning to develop targeted interventions that address known deficits in cognitive functioning in depression and bipolar disorder.

■ Identify dimensions of the mood disorders spectrum (e.g., affect regulation, irritability, neuroticism, rumination) that may be features of other diseases (e.g., Parkinson's) where the psychosocial treatments already developed might be transportable to mental disorders.

OBJECTIVE 2. Establish for whom and under what conditions therapy is likely to be most effective.

Implementation:

■ Identify and develop non-traditional outcome targets that reflect the extent of functional impairment (e.g., work and social disability) and use these to guide treatment development.

3. Opportunities for the Prevention of Mood Disorders

OBJECTIVE 1. Expand studies that test interventions for the prevention of suicide.

Implementation:

■ Establish consensus on measurement of suicidality (or proxies such as hopeless-ness) and protective factors that will increase consistent use of measures across trials.

■ Establish safe and ethical approaches to screening and referral for suicidality across settings, including schools, primary care, prisons, and Internet web sites.

■ Determine service use patterns and long-term suicidality outcomes in already funded clinical trials.

■ Determine interventions to reduce suicidality in community settings (e.g., emergency departments, primary care, psychiatric day treatment programs, residential treatment facilities, home visiting nurse services).

OBJECTIVE 2. Increase and strengthen preventive interventions research.

Implementation:

■ Promote prevention design methodologies that utilize defined populations to provide a more complete analysis of mediators and moderators of intervention impact.

■ Study models of emotion regulation (e.g., recovery from emotionally activating events) in bipolar disorder and depression as a prevention strategy for relapse.

■ Explore the potential of nontraditional psychosocial interventions delivered by nontraditional means (e.g., mood management campaigns or courses via television or the web) for both treatment and preventive interventions.

OBJECTIVE 3. Determine what interventions are needed during various phases of an illness to help prevent the recurrence and relapse of mood disorders.

Implementation:

■ Expand definitions of treatment outcome (e.g., durable recovery, partial response).

■ Test acute interventions that produce longer recovery periods for those most at risk for relapse in community populations.

■ Determine optimal combinations and sequencing of interventions over time, to address questions such as:

– What approaches are most effective after inadequate response to acute treatment for alleviating residual symptoms and dysfunctions in treated individuals?

– What approaches are most effective for integrating multiple treatments for individuals with substance abuse or other comorbid disorders?

■ Identify predictors to treatment response at various points throughout illness course (e.g., address questions such as what are the best approaches to treat a 3rd episode).

■ Conduct secondary analyses of funded treatment trials to explore predictors of treatment response by individual illness history, life events, treatment preferences, and prior treatment history.

4. Opportunities to Improve Delivery of Services

OBJECTIVE 1. Increase the development of practice-level interventions that are based on research tested theoretical models.

Implementation:

■ Test theoretically informed practice-level interventions for mood disorders (e.g., interventions based on sociological theories of family-centered care, interventions based on economic theories that inform how incentives might reduce bipolar disease burden and improve care), including existing trials.

OBJECTIVE 2. Understand the processes by which theoretically based research information on mood disorders is effectively disseminated and implemented or utilized by clinicians or delivery systems.

Implementation:

■ Assess providers' perspectives on mood disorders, beliefs about efficacy and treatments, and studies of approaches that increase the use of research-based treatments (e.g., study of what motivates mental health care practice decisions).

■ Use models from research in disciplines that are rarely used in mental health to develop new approaches to dissemination and implementation (e.g., engineering, social marketing).

■ Develop and test dissemination strategies that increase the understanding of basic behavioral processes such as motivation, decision making, adherence, emotion, cognition, and social interactions between health care providers and consumers.

OBJECTIVE 3. Translate multidisciplinary decision theories into community interventions to reduce the burden of mood disorders.

Implementation:

■ Specify how mental health policy decisions are made at higher organizational and funding levels (e.g., insurers, employers, state mental health directors, legislators) to identify levers and barriers to using research evidence by decision makers.

OBJECTIVE 4. Identify the individual, social, and cultural determinants of stigma and develop interventions to change these determinants.

Implementation:

■ Based on review of stigma research in other health areas, apply relevant findings and models to new research on people with mood disorders.

■ Enlist interdisciplinary group of researchers, health care organization decision makers (e.g., employers, insurers, state officials), and other Federal groups (e.g., Center for Mental Health Services) to develop unique strategies and collaborations in this area to change the individual, social, and cultural determinants of stigma against mood disorders.

At age 6, Mike's irritable, distractible, and belligerent behavior prompted his parents to seek a psychiatric evaluation. Diagnosed with ADHD and oppositional defiant disorder (ODD), he was prescribed Ritalin. By the time he was 9 years old, Mike began to experience periods of excessively sad mood, often for 2 to 3 weeks at a stretch. He lost interest in normally fun activities, including playing with his friends, and preferred to sleep through much of the day. One day, after telling his mom that he should never have been born, he attempted to jump from a moving car. At age 10, Mike began to have 3-5 day periods of rapidly shifting mood, alternating between irritability and feeling "totally the best." His sleep became erratic—one night he stayed up until 3:00 a.m., rearranging furniture in his room, then got up 3 hours later full of energy. After contacting one of his dad's friends to ask for a job at NASA because he believed he was a famous scientist, Mike was hospitalized and diagnosed with bipolar disorder. Today, on a regular regimen of an anticonvulsant, an antidepressant, and an atypical antipsychotic medication, Mike is a 5th grade student in his neighborhood school and is keeping up with classwork and homework.

Expanding and Strengthening the Research Foundation

The utility of the scientific agenda that holds center stage throughout the pages of this mood disorders research strategic plan ultimately will be measured by the extent to which it improves the lives of individuals who themselves have a mood disorder or who deal with the impact of mood disorders in the context of family, work, or other social groupings. The centrality of the human element in planning, conduct, and application of research was recognized by every workgroup that contributed to the strategic plan. Clearly, the needs of individuals with mood disorders are a driving force behind develop-ment of the plan. But many other persons are equally critical: educators who play a vital role in training young scientists in the techniques and nuances of research relevant to mood disorders; researchers and communicators whose primary responsibility is to disseminate the knowledge generated through research; and clinicians and other health and social service professionals who apply the products of research in diverse settings.

Challenges in two particular arenas—training tomorrow's researchers and putting the fruits of research in the hands of public health practitioners, clinicians, and members of the general public—crosscut the entire strategic planning process. Absent a solid foundation in these areas, even the most innovative scientific agenda becomes a sterile exercise. In compiling this final document, NIMH staff culled from the workgroup reports an array of implicit and explicit recommendations for research training that encompass disciplinary as well as demographic gaps in the contemporary research community and, importantly, that anticipate the impact of future scientific advances and shifts in the Nation's age and racial/cultural composition in the years ahead. A second category of needs and opportunities involves educating front-line clinicians and the public at large about mood disorders, using a mix of media and language and formats that will be broadly accessible. An example of a more specific educational challenge is that of informing

interested individuals—clinicians as well as patients—how to learn about and participate in clinical services and prevention trials.

Research Training

At these promising times for research on the brain and its disorders, we are faced with unparalleled scientific opportunities and the consequent need to attract and retain the best and the brightest individuals to research careers aimed at understanding mood disorders and developing efficacious treatments and prevention strategies. NIMH is committed to creating viable career paths for junior investigators whose research training and career goals are in areas of program relevance. To accomplish its goal of training future generations of mental health researchers, NIMH has long been among the leading NIH institutes in supporting National Research Service Award (NRSA) training and Research Career Development programs (K-awards).

As a proportion of its budget, the NIMH investment in NRSA institutional training grants, individual fellowships, and career development awards is the highest among NIH institutes that support research on the brain and its disorders. This fact requires us to look at training and career development issues from a broader NIH and national needs perspective. NIMH is committed to training that prepares junior, early-to-mid-career, and to a certain extent more established scientists in multidisciplinary and interdisciplinary research on mental health and mental illness.

To train future generations of mental health researchers, several issues need particular attention: focusing on research areas most likely to hold promise in the future; ensuring that training and career development support meet future needs in terms of the research work force; encouraging and helping women scientists in their chosen research career track; and attracting and retaining underrepresented racial and ethnic minority groups in research fields relevant to mental health and mental illness.

Disseminating Research Results

The goal of dissemination and implementation research is to bridge the gap between clinical research and everyday practice by building a knowledge base about how mental health care information and new practices are transmitted and translated for health care service use in specific settings. One of the major issues about the applicability of basic and clinical research to mental health practice settings surrounds how research findings spread throughout the field. Research is needed to understand how and why information on mental health treatments reaches stakeholders within the field, as a necessary prerequisite to determining how the information leads to practice change. Dissemination research relates specifically to research topics underlying the creation, transmission, and reception

of “messages” providing information on psychopharma-cological and psychosocial treatments.

Research is needed, too, on factors that influence the adoption of new psychopharmacological and psychosocial interventions within real world mental health care systems. Previous efforts to understand implementation have often assumed that interventions can be successfully implemented into specific contexts, and have relied on an assessment of patient outcomes instead of examining whether implementation was faithful to the originally conceived treatment. In addition, previous research has often quite effectively demonstrated the ability of a specific treatment to fit into a specific setting, but has not explored more fundamental issues that can be generalized beyond a specific treatment paradigm.

Dissemination and implementation research can utilize theories and empirical findings from a variety of fields, many not often traditionally associated with mental health research. Relevant fields include: information science, clinical decision-making, organizational theory, finance, strategic and behavioral change, anthropology, learning theory, and marketing. In addition, meaningful research will likely include collaboration with stakeholders from multiple mental health settings.

Research Priorities

1. Opportunities to Expand and Strengthen the Research Foundation

IN TRAINING:

OBJECTIVE 1. Address the shortage of new and established investigators in various disciplines to conduct mood disorders research, particularly racial and ethnic minority investigators, and those focusing on child and elderly populations.

Implementation:

■ Develop a trans-institute plan to support the multidisciplinary training of clinical and preclinical investigators interested in pursuing research careers in the fields of childhood-onset mood disorders and late-life mood disorders.

■ Develop a mood disorders mentorship program devoted to training racial and ethnic minority investigators.

OBJECTIVE 2. Create training programs and interdisciplinary opportunities to foster precision and validity in investigations that extend beyond the boundaries of individual disciplines.

Implementation:

■ Encourage individual career enhancement and training in molecular genetics, genetic epidemiology, statistical genetics, and population genetics for researchers with basic and clinical research expertise in mood disorders.

■ Increase efforts to recruit basic scientists representing a range of disciplines (from molecular genetics to behavioral and systems neuroscience) to mood disorders research. Emphasis should be placed on training individuals in an interdisciplinary manner and on integrating disease-oriented research with basic neuroscience.

■ Further endorse translational research centers through development of specialized initiatives to attract new scholars to rapidly test new targets implicated by basic research.

– Sponsor conferences in which junior investigators generate proposals for translational research that are reviewed by senior researchers in the field.

– Provide administrative supplements modeled on minority supplements to place junior investigators (postdoctoral) with a basic research background in clinical research settings and vice versa.

■ Establish interdisciplinary training programs to develop clinical and social science investigators skilled in conducting applied research for populations with mood disorders in communities and community-based delivery settings. Such programs would include training in interdisciplinary methods; qualitative and quantitative methodologies; and application of diverse theoretical approaches to changing behavior of individuals, institutions, and communities.

IN PUBLIC EDUCATION:

OBJECTIVE 1. Expand the dissemination and translation of mood disorders risk factors, diagnosis, and treatment knowledge to the community.

Implementation:

■ Develop evidence-based web sites that focus on information on mood disorders in specific populations (e.g., late life, childhood, women) to serve as resource clearinghouses for researchers, clinicians, and other individuals.

■ Coordinate with NIMH's Office of Communications and Public Liaison and relevant providers to develop materials that can be used to improve recognition of depression and bipolar disorder in community settings.

■ Support efforts by investigators to increase dissemination efforts.

■ Coordinate with the Substance Abuse and Mental Health Services Administration and the services community to instantiate new practice models in both primary care and institutional settings.

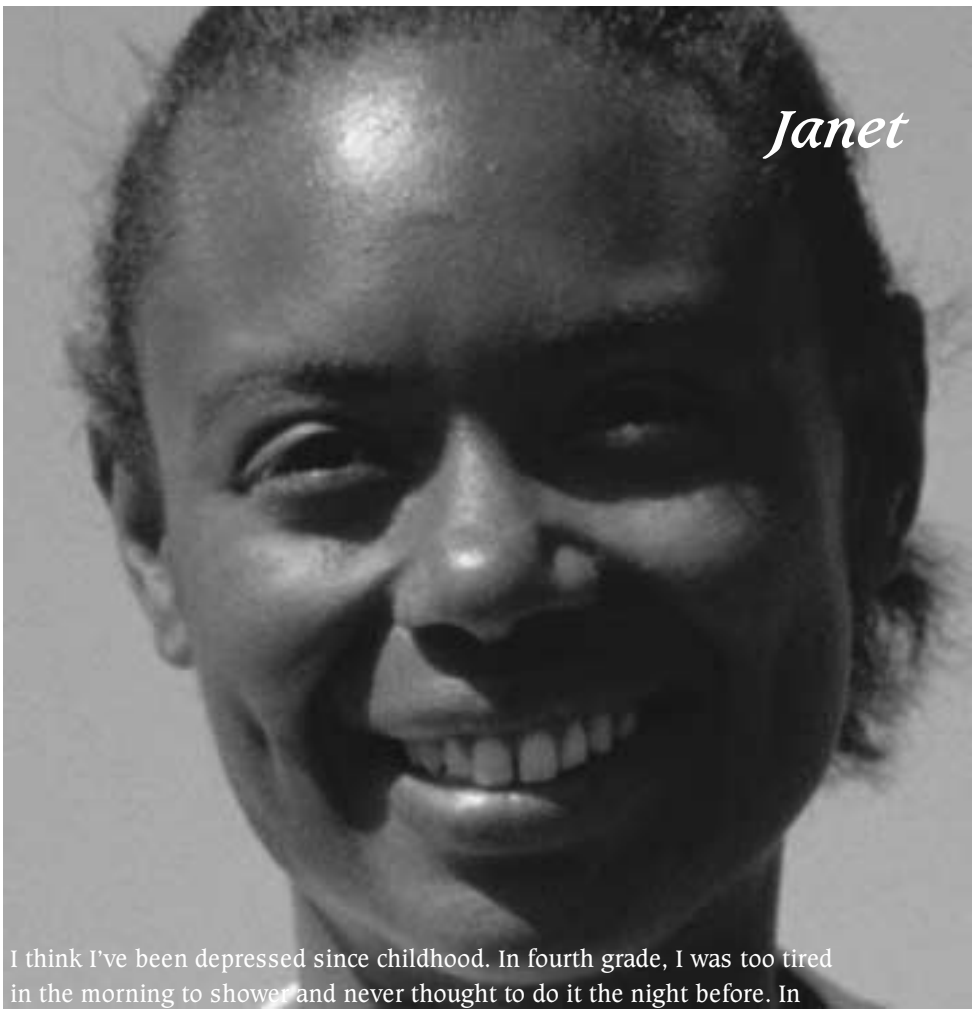
OBJECTIVE 2. Enhance public awareness, understanding, and participation in genetic risk factor research on mood disorders.

Implementation:

■ Develop an initiative with the Ethical, Legal, and Social Implications Program of the National Human Genome Research Institute to produce guidelines for the inclusion of children in genetic studies of mood disorders.

OBJECTIVE 3. Provide information about clinical trials to evaluate prevention and treatment regimens that will enable individuals and their health care providers to make informed choices.

OBJECTIVE 4. Develop culturally sensitive public awareness information on mood disorders for consumers, families, and health care providers of diverse races and ethnicities.



I think I've been depressed since childhood. In fourth grade, I was too tired in the morning to shower and never thought to do it the night before. In high school I cried almost every day and thought this was what everyone did. I believed that my "moods" were a state of mind that could be overcome without assistance. When I was in my twenties, I sank into the deepest depression ever. I thought constantly of suicide, not so much because I wanted to die, but because I wanted to end the pain and break the vicious circle where depression made it difficult for me to do my job, which added stress and increased my depression. This time, I sought out a therapist, who prescribed medication and suggested that I attend a support group for people with depression. I went to local National Depressive and Manic-Depressive Association meetings regularly for almost 2 years. Today, I remain convinced that those meetings helped save my life. My husband also belongs to a support group for families and friends of persons with depression. We both are learning how to develop more effective coping skills. I continue to marvel that I now embrace life when only a few years ago I could not get out of bed.

Appendix A
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NIH Publication No. 03-5121
January 2003