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EDITORIAL

Clinical Research in the Age of Neuroscience

Some time ago, I attended a meeting of a major patient advocacy organization to discuss priorities in mental illness research. During the discussion, a distinguished consumer advocate admonished me for overstating when I said, "It is within our capacity to discover the causes of mental illness (i.e., schizophrenia, manic depressive illness, major depression, and Alzheimer's disease) in our lifetime." Remembering the Shakespearean adage that "the better part of valor is discretion," I offered no rebuttal. However, while stifling my response, I began to consider the reasons for the advocate's skepticism. Surely, biomedical research is the best hope for the mentally ill to find relief from their symptoms and be able to lead enjoyable and productive lives. Of course, it could be said that until the latter half of this century, the field of psychiatry did little to distinguish itself as a scientific discipline and compiled an unenviable record of discovery and clinical progress. Even more recently, the major breakthroughs in psychiatric research (e.g., antipsychotics and antidepressants) were more a result of serendipity than hypothesis-driven investigation, and frequently the breakthroughs were facilitated by progress in other fields of medicine. Furthermore, when new treatments became available, they were introduced with exaggerated enthusiasm that inflated public expectations. Indeed, the dawn of the age of neuroscience found psychiatry still medicine's "stepchild," slow to embrace the new methods of molecular medicine.

In light of this, it is clear that for psychiatric research to assume a major role as a neuroscientific medical discipline, we must earn the respect and confidence of our patients and colleagues, we must understand whence we came, and the best means to proceed on the journey of scientific discovery. In previous issues of this journal, you have heard from my co-editors on the perspectives of their disciplines for the future of psychiatric research (Aston-Jones 1999; Berrettini 1999; Duman 1999; Tallman 1999). What follows in this issue is a perspective on the current role and types of clinical research in mental illness this journal sees as its mission to report to the field.

Historically, psychiatric researchers faced many limitations in their fields of endeavor. Chief among these was that mental illnesses had no clear and consistent neurobiology that would enable reliable and valid definitions of such disorders as Alzheimer's and other brain diseases. In addition, because the target organ of mental illness was the brain, which was assessable only through highly invasive procedures, direct in vivo examination of brain structure and function were virtually impossible until the advent of modern neuroimaging techniques. Finally, because the signs and symptoms of mental illness were largely behavioral, the use of animal models and other preclinical laboratory paradigms were problematic.

Given these limitations, psychiatric researchers have faced daunting challenges. Enter the field of neuropsychopharmacology. Perhaps more than any other medical discipline, psychiatry has used pharmacology, in a bootstrap approach, to develop treatments and pathophysiological models of mental disease. The observation that antitubercular drugs had mood-altering effects and were monoamine oxidase inhibitors led to the development of antidepressants and the monoamine theory of mood disorders. The discovery of neuroleptics and the psychotogenic effects of amphetamines led to the dopamine hypothesis of schizophrenia. The advent of the atypical neuroleptic clozapine resulted in modified theories of schizophrenia and a de-emphasis on the role of dopamine. (Should the putative antipsychotic drug M100907, a nondopamine-blocking 5HT-2A antagonist prove to be clinically effective, the role of dopamine will be further de-emphasized). Observations of the psychotogenic effects of phenecyclidine and NMDA receptor antagonists gave rise to the glutamatergic hypotheses of schizophrenia, which are influencing current drug development. If the substance P receptor subtype (NK_1 and NK_3) or the CRF (corti-

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cotropin releasing factor) antagonist drugs currently being tested prove to be clinically effective, this will, no doubt, bring wholesale revision of the pathophysiological models of depression and psychosis.

Thus, psychiatry has consistently used clinical pharmacologic research to inform pathological models and preclinical studies of mental disorders. It is, therefore, not surprising that when the American College of Neuropsychopharmacology was founded 38 years ago, it was named for the discipline of neuropsychopharmacology, which—at the time—virtually encompassed all that was psychiatric research. However, that was then, and now is now. We need only to read the scientific literature to know that psychiatric research currently derives its knowledge from the diverse disciplines of molecular and cellular biology, neurophysiology, behavioral pharmacology, molecular and behavioral genetics, cognitive neuroscience, and neuroimaging, in addition to clinical neuro- and psychopharmacology.

Looking forward, what can clinical research provide that will bridge the gap between molecular and preclinical behavioral research and the descriptive phenomenology of psychiatric research? I do not believe it is unfair to say that the traditional methods of neuroendocrinology and neurochemistry, which use the secretory patterns of the hypothalamic pituitary hormones and CSF and plasma levels of neurotransmitters and their metabolites, are not likely to be sufficiently informative to warrant continued emphasis. In their place, clinical investigators will ride the accelerated super-engine of drug discovery and use new, more pharmaco-dynamically specific and diverse compounds to treat and pharmacologically characterize mental disorders. In previous issues of this journal, Field Editor Duman and Senior Editor Tallman described new molecular targets for such therapeutic agents as receptor subtypes using oligo and antisense nucleotides, signal transduction proteins and enzymes, gene transcription factors, trophic factors and gene modulators, including inducible and region-specific knock-out and knock-in transgenic strategies that will ultimately become available for clinical investigation. We can also use rapidly developing imaging techniques to dissect brain structure and to examine its function and biochemistry in mental illness. Brain-imaging methods, along with genetics, will be important in the development and use of surrogate markers of drug activity. In addition, clinical research must focus on valid and precise characterization of disease pathology, refining the clinical phenotypes for genetics studies and testing clinical hypotheses through the assessment of treatment, longitudinal course, neurophysiology and neuropsychology, and neuroimaging studies. Epidemiological studies and, particularly, genetic epidemiology will continue to be important in psychiatric research. Finally, pharmacology will still be used in various paradigms: standard clinical trials and treatment efficacy studies, treatment effectiveness and outcome studies (both controlled and quasinaturalistic), and pharmacological challenge studies.

It is the results of such studies that this journal seeks to communicate, rapidly and effectively, to the diverse field that is the constituency of mental illness research. We are particularly interested in and invite submissions of new drug development, ranging from proof of concept studies to phase II, III, and IV clinical trials, and pharmacogenetics. We are also keenly interested in therapeutics studies using surrogate biomarker markers of efficacy and safety. We are also encouraging the submission and publication of studies employing modern methods of clinical neuroscience, including electrophysiology, nuclear medicine, and neuropsychology. Finally, we hope eventually to see reports of studies in the field of molecular epidemiology. We are open to inquiries from prospective authors about the suitability of their work for the journal and what would be the most appropriate format in which to report it.

Exciting as these scientific developments are and bright as these prospects may seem, serious concerns also pervade the field of psychiatric research. There is concern that clinical research is waning because of the emphasis on molecular biology and genetics and the declining numbers of physician investigators. Moreover, there is vigorous debate among scientists, policy makers, and lay advocates about whether there is sufficient emphasis on what is termed "disease-oriented" research. Recent reports by the NIH and Institute of Medicine address these issues and make recommendations on funding priorities and research training needs. Some of the recommendations have already been translated into action in the form of NIH-sponsored research on relevant topics and the generation of new funding mechanisms, including a series of RFAs, a revamped series of K awards, and research training fellowship programs for clinical intervention.

At the same time, we are challenged by specific questions regarding research designs that have been traditionally used in medical and psychiatric research but are considered "high risk," such as the use of placebo, drug washout, and symptom-provoking challenge studies. Concern about assuring patient protection has generated various types of professional and governmental activities that will almost certainly lead to additional regulatory guidelines and possibly new legislation. Clinical researchers will have to adapt to these developments and hope that they do not increase too greatly the difficulty of clinical research. These issues notwithstanding, pharmacological research will continue to be important, along with the other strategies mentioned earlier, for clinical research in mental illness.

As the journal of the premier multidisciplinary psychiatric research organization, *Neuropsychopharmacology* plans to play a significant role in disseminating the

results of such studies and reports of the events that have an impact on the research enterprise. Thus, the journal seeks from members of the College and the fields of clinical neuroscience and neuropsychopharmacology reports of their research. Specifically, we invite submissions of new research, scholarly critical reviews, viewpoints, commentaries, and brief reports.

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