We celebrate 65 years with you, our readers, by offering a series of special editorials on the future of psychiatry.

Editorial

The Molecular Medicine Revolution and Psychiatry: Bridging the Gap Between Basic Neuroscience Research and Clinical Psychiatry

Todd D. Gould, M.D., and Husseini K. Manji, M.D., F.R.C.P.C.

Recent years have witnessed a considerable increase in both fundamental knowledge and available experimental techniques in the basic neurosciences. Unfortunately, clinical translation of these findings vis-à-vis a direct benefit to patients who suffer from psychiatric diseases has not been as rapid. It is likely that this will change in the near future. We discuss some of the knowledge and expanding techniques of basic neuroscience, focusing on those that may be most promising regarding the future impact of the current molecular medicine revolution in psychiatry. Some of the more exciting findings (basic mechanisms, techniques, and clinical methodologies) that are expected to have a major impact on both our understanding of the biological underpinnings of psychiatric diseases and the development of novel and/or improved therapies include genetics, epigenetics, transcriptomics/proteomics, neuroimaging, animal models, and improved psychiatric endophenotypes.
(J Clin Psychiatry 2004;65:598–604)

The last decade has truly been a remarkable one for biomedical research. The "molecular medicine revolution" has brought to bear the power of sophisticated cellular and molecular biological methodologies to tackle many of society's most devastating illnesses. Psychiatry, like much of the rest of medicine, has entered a new and exciting age demarcated by current rapid advances and the future promises of genetics, molecular and cellular biology, and improving technologies. Unfortunately, clinical translation of these findings vis-à-vis a direct benefit to patients who suffer from severe psychiatric diseases has not been as rapid.

Complete sequencing of the human genome was officially announced in April of 2003,[1] coinciding with the 50th anniversary of the discovery of the structure of DNA.[2] It is now known that there are far fewer genes in the human genome than was originally thought, with current estimates ranging between 30,000 and 40,000. Although a complete functional understanding for many of these genes is still lacking, the completion of the sequencing of the human genome (at least to a certain point) undoubtedly marks the beginning of a new era in molecular medicine research. Perhaps more than any other event, this achievement represents both the massive progress and immeasurable wealth of opportunities subsequently available in all areas of medicine, but none more so than in neuropsychiatric research where even basic pathophysiology has thus far proven elusive. This is perhaps not altogether surprising given the sheer complexity of the central nervous system; current estimates suggest that the brain comprises 10^{11} neurons, each receiving 10^4 inputs and issuing 10^4 outputs. The number of synaptic contacts between neurons thus approaches 10^{15}! In spite of this complexity, it is our firm belief that the impact of molecular and cellular biology—which has been felt in every corner of clinical medicine—will ultimately also

Figure 1. From Genes to Diseases in Psychiatric Research—Sites of Current Research Efforts[a]
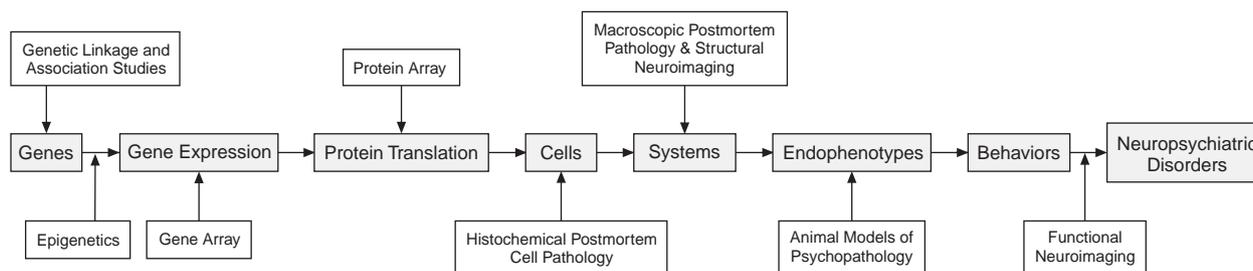
[a]Complex diseases, such as those in psychiatry, are perhaps best understood not by focusing on the disease at one level, but rather at multiple levels. Genetics, epigenetics, transcriptomics, proteomics, neuroimaging, animal models, and improved psychiatric endophenotypes represent areas that are likely to benefit most from the molecular revolution and are areas that will see a great deal of change in the forthcoming years.

have major repercussions for our understanding about the fundamental, core pathophysiology of major psychiatric disorders in this new millennium and that it will likewise be concomitant with the development of improved treatments.

While knowledge of the full human genetic sequence is a major step forward, there are also many other advances of significant importance in our efforts to elucidate the pathophysiology of severe psychiatric illnesses. Recent years have witnessed a more wide-ranging understanding of the neural circuits and the various mechanisms of synaptic transmission, the molecular mechanisms of receptor and postreceptor signaling, a finer understanding of the process by which genes code for specific functional proteins, and the identification of causative genes in many neurologic disorders (e.g., Huntington's disease, early-onset Alzheimer's disease, and numerous seizure disorders) that in toto reduce the complexity in gene-to-behavior pathways.[3] Likewise, development of fundamental techniques has kept pace with these exciting discoveries. It is now commonplace to utilize cells in culture to model neurotransmission and neuroplasticity occurring in the intact brain, and, while such approaches clearly do not allow for a complete understanding of complex circuitry, they do permit the exquisite dissection of mechanisms at a cellular level. Current techniques also allow the ascertainment of thousands of single gene genotypes (in a single academic lab) within a period of 24 hours, and in a matter of months, the genome of a mouse can be altered such that any one of its genes is up-regulated in expression, removed, and/or controlled both temporally (for example, during development or adulthood) and regionally (e.g., hippocampus vs. striatum vs. frontal cortex) to help understand basic functioning or to model a specific supposed neuropsychiatric dysfunction.[4,5]

In other areas of medicine, the recent molecular medicine revolution has already had an immediate impact. Reasons for a lag in psychiatric medicine are multifold: in addition to the sheer complexity of the central nervous system, they include lack of a defined pathology, no direct tissue accessibility, the daunting fact that the complexity of behavior is not simply the sum of its parts, and monumental differences in public and medical acceptance of the severity and biological basis of psychiatric illnesses, ultimately affecting research goals and funding priorities. Some of the more exciting findings in the basic neurosciences (basic mechanisms, techniques, and clinical methodologies) that will most likely have a major impact on both our understanding of the biological underpinnings of psychiatric diseases and the development of novel and/or improved therapies include genetics, epigenetics, gene and protein expression profiling, neuroimaging, the defining of more specific and reproducible endophenotypes, and animal models (Figure 1).

GENETICS AND GENE REGULATION

Genetics

The genetic age is currently upon us, and the definitive (and causative) genes for the many but individually rare single gene diseases have been identified. Unfortunately, the paradigms that have proved so successful for the identification of genes in mendelizing disorders (diseases of dominant or recessive single gene inheritance such as Huntington's disease) have been of little use in the study of genetically "complex" disorders such as those in psychiatry.[6] These genetically complex disorders involve multiple genes, various environmental contributors, and multiple phenocopies and do not readily allow for a straightforward and reproducible genetic linkage analysis. What has become dogma in the study of disorders with complex genetics is that many genes, each with small additive effects, in different combinations interact with environmental, stochastic, and epigenetic mechanisms, lending susceptibility for the development of illness.

Although study of these disorders is daunting, progress is clearly being made—especially so in schizophrenia,

Figure 2. Psychiatric Genetics Deals With Probabilism, Not Determinism[a]
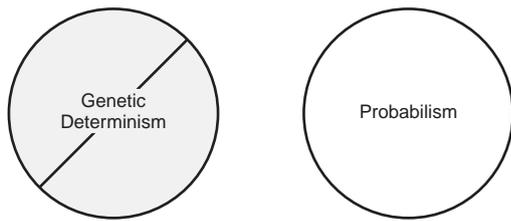
[a]Copyright 2004, Irving I. Gottesman, M.D., reprinted with permission. Psychiatric genetics, and indeed the genetics of all complex diseases, is not deterministic but rather probabilistic.[8] One salient example: monozygotic twins share exactly the same genes, but are 50% discordant for schizophrenia,[34] suggesting that genes are only part of the story. Epigenetics (Figure 3 and text) represents one putative mechanism that may control diversity in these genetically identical but phenotypically different populations.[35]

where multiple susceptibility genes have been reproducibly implicated, including catechol-O-methyl transferase (COMT), neuregulin, and dysbindin, among others (see reference 7 for review). But it is critically important to remember that polymorphisms in these genes (and those to be discovered) are simply associated with schizophrenia[8]; these genes do not invariably determine outcome, but only lend a higher probability for the subsequent development of illness (Figure 2). In fact, genes will never code for abnormal behaviors per se, but rather code for proteins that make up cells, forming circuits that in combination determine facets of both abnormal and normal behavior.[9] These expanding levels of interaction are among the factors that have made the study of psychiatric diseases so difficult.

The next task of psychiatric genetic research is to study how and why variations in these genes impart a greater probability of developing schizophrenia (understanding pathophysiology) and then to direct therapeutics at that pathophysiology. Hence, there is no doubt that knowledge of the genetics, and subsequent understanding of their relevant biology, will have a tremendous impact on diagnosis, classification, and treatment of psychiatric disease; it must be cautioned, however, that to be efficiently successful, studies of the genetics of complex disorders must be prudent in study design and interpretation (see reference 10 for a relevant discussion). As we discuss in the endophenotype section, there is hope that the biological processes more closely regulated by genes can be studied, resulting in a better understanding of the principal components of psychiatric diseases on the level of interacting circuits or simpler behaviors (Figure 1).

Epigenetics

While traditional genetics generally deals with nucleotide (the A's, T's, C's, and G's) sequence variation,

epigenetics (as it is currently applied in molecular biology) refers to regulation of gene activity that is controlled by heritable but potentially reversible changes in DNA methylation and chromatin structure[11,12] (Figure 3).

Epigenetics purports to define the molecular mechanisms by which different cells from different tissues of the same organism, despite their DNA sequence identity, exhibit very different cellular phenotypes and perform very different functions. Even the cells from the same tissue are not identical, although, again, they all carry the same DNA code. All of these phenotypic and functional differences are the cumulative result of a large number of developmental, environmental, and stochastic events, some of which are mediated through epigenetic modifications of DNA, histones, and changes in chromatin structure.

DNA methylation involves covalent binding of a methyl group to cytosines by enzymes called DNA methyltransferases; following promoter methylation, gene transcription is generally (but not always) suppressed (Figure 3). Methylation of DNA also interacts with a second, and perhaps more dynamic, level of epigenetic regulation, namely a large variety of posttranslational modifications to histones, such as acetylation, methylation, phosphorylation, and ubiquitination (see reference 13 for review). It is then through alterations in the accessibility/affinity of transcription factors to DNA promoter regions that epigenetic modifications have profound effects upon gene expression, both temporally and regionally (Figure 3).

Epigenetics represents one mechanism to explain why genetically identical monozygotic twins are often discordant for psychiatric illness. It further provides a putative mechanism whereby environmental stressors early in life can alter behavior later in life. Research data with experimental animals demonstrate that some patterns of maternal care can result in the epigenetic regulation of specific genes.[14] Numerous similar scenarios could exist in which epigenetic changes in responsive genes induced by external stimuli have far-ranging effects on behavior (Figure 3). In conclusion, molecular epigenetics is an area of important research that may help illuminate the molecular substrates of genome-environment interactions (please see a recent review by Arturas Petronis[13] for a more extensive discussion of the putative roles of epigenetics in psychiatric disorders).

Gene and Protein Expression Profiling

Tremendous advances have been made in the last decade in our ability to study an entire transcriptome (all the genes transcribed at one time) and proteome (all the genes translated at one time, as well as their various posttranslational modifications) (Figure 1). These methodologies are providing not only important new leads in our understanding of the molecular and cellular pathophysiology of severe psychiatric disorders but also insights into novel treatment development.

Figure 3. Epigenetics: A Putative Role in Cellular Memory[a]

A. Pre-Stimuli Exposure

B. Environmental Stimuli

C. Post-Stimuli Exposure
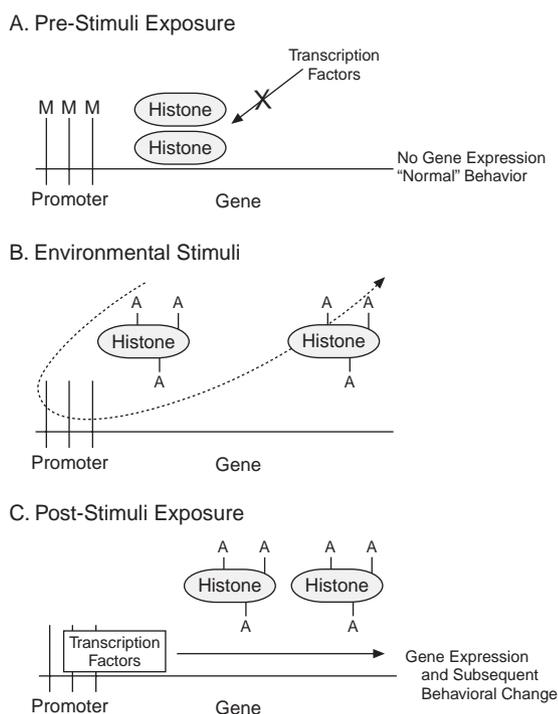
[a]Epigenetic changes represent a mechanism that can permanently alter gene expression, thus subsequently affecting behavior. Both decreased methylation of DNA and increased acetylation of histones modify the local chromatin structure, providing access to transcription factors that results in up-regulation of the gene transcription. Such epigenetic changes are stable but potentially reversible over time. The figure depicts environmental stimuli increasing gene expression, but it is equally likely in some circumstances that gene expression is decreased.
Abbreviations: A = acetylation of histones, M = methylation of DNA.

The advent of methodologies such as subtractive hybridization, mRNA differential display, and microarrays has illustrated the importance of hypothesis-generating (as opposed to hypothesis-dependent) techniques, particularly when dealing with disorders whose pathophysiology remains largely unknown. These technologies are utilized to study gene expression; microarray, the newest of the techniques, utilizes sequences of DNA arranged on a slide that generate a quantifiable signal in response to cDNA (complementary DNA) binding (cDNA is synthesized from RNA and thus directly proportional to the amount of RNA present).

Primarily because of its markedly reduced labor intensiveness, microarrays are largely replacing differential display and subtractive hybridization as the method of choice to interrogate the whole transcriptome. There have been rapid advances in these methodologies, and investigators have already begun to focus on expression profiles obtained from particular brain cell types, using methodologies like laser capture microdissection. Using this

technology, investigators have already begun to study how plasticity-related mRNAs are regulated locally within dendrites and how the process of "synaptic tagging" contributes to long-term, enduring changes in discrete dendrites; the further refinement of these methodologies offers much promise to study gene expression changes in specific cell populations and circuits in severe psychiatric illnesses.

It is likely that as the technology improves, current problems are eliminated, and as new applications are developed, microarrays are likely to become an essential, indispensable tool for the neuroscience-psychiatric community. Notably, the application of these methods to the study of postmortem human brain tissue has already provided clues about the involvement of oligodendrocytes (glial cells that generate the myelin sheath) in schizophrenia and bipolar disorder[15,16] and synaptic pathology in schizophrenia.[17] Furthermore, their application to the study of treatment-induced changes has identified a number of hitherto unexpected genes involved in regulating cellular plasticity and resilience (including bcl-2, Bag-1, GRP78) as long-term targets of mood stabilizers (see reference 18 for discussion). Indeed, as we discuss in the concluding remarks, the use of the differential display methodology to identify bcl-2 as a long-term target for lithium led to clinical neuroimaging studies demonstrating neurotrophic effects of lithium in bipolar disorder patients.

Despite this tremendous progress, the current trancriptomics methodologies do have important limitations. Foremost among these is the inability to distinguish between splice variants, the fact that only transcripts in high to medium abundance can be accurately profiled, and additional uncertainties that are inherent in the study of postmortem brain tissue.[19] Finally, for gene expression changes to be related to functional neuronal changes, expression at the protein level must be examined (the genome is the script and the proteins are the actors). For these reasons, the use of advanced proteomics methodologies in conjunction with transcriptomics is most likely to yield critical information about psychiatric disorders. Indeed, proteomics technologies provide a strategy for studying the critical functional output of diseases by integrating genetic, epigenetic, and environmental contributions.

Protein analysis is, however, considerably more complicated than determining the linear sequence of transcribed RNA and often involves the identifying and quantifying of proteins and their localization, modifications, and interactions.[20] For these reasons, proteomics has lagged somewhat behind transcriptomics, although rapid technological advances are being made (for example, high throughput protein arrays).[20] With respect to psychiatric disorders, the study of postmortem human brain tissue introduces additional obstacles in proteomic analysis, since many posttranslational modifications such as phosphorylation are rapidly lost in the early postmortem period.[21]

Despite these formidable obstacles, important knowledge gained from proteomic studies is already being applied to the development of new medicines based on a more mechanistically based and target-driven drug discovery process. Indeed, since the vast majority of drug targets are proteins, target identification and characterization at the protein level will facilitate the selection of relevant therapeutic targets.[20] It is anticipated that, in coming years, the concerted use of genomic and proteomic strategies to refine complex psychiatric diseases into mechanism-based subcategories may ultimately allow for the matching of particular target-based therapies to particular markers in subgroups of patients.

ENDOPHENOTYPES: CLINICAL AND PRECLINICAL APPLICATIONS

Endophenotypes

Endophenotypes are quantifiable measures that may have the ability to reduce the heterogeneity (both genetic and biological) inherent in psychiatric diseases.[24,25] This important concept has long been utilized in the study and diagnosis of non-psychiatric diseases.[26] For example, in coronary artery disease, the disorder phenotype is represented by such signs and symptoms as shortness of breath, obesity, and chest pain with exertion. However, abnormal endophenotypes (in the genes-to-phenotype causal chain) may be measured as elevated cholesterol levels or changes on electrocardiogram (ECG). There can be multiple causes of shortness of breath, obesity, or chest pain; however, both the biology and genetics of increased cholesterol and ECG changes are much easier to study.

An endophenotype in psychiatry may be neurophysiologic, biochemical, endocrinologic, neuroanatomical, cognitive, or neuropsychological (including configured self-report data) in nature.[26] As one example, schizophrenia is associated with disorganized thinking, hallucinations, and delusions. Endophenotypes in schizophrenia include working memory deficits, impairments in prepulse inhibition, and smooth pursuit eye movement abnormalities.[27] Recent work has utilized these endophenotypes to implicate gene regions and specific genes and to develop animal models.[26]

It is likely that many susceptibility genes may result in differing variations along a continuum, with endophenotypes representing one mechanism to discern the pathological antecedents to psychiatric disease. For instance, COMT, as previously discussed, is a gene in which variations are associated with schizophrenia. However, these same COMT variations have been associated more strongly with working memory performance at both the psychological (neuropsychological testing) and physiologic (functional neuroimaging) level.[9] While all groups of individuals have variations in performance on these tasks, only a portion of this variation can be attributed to the COMT genotype, and only a small percentage of individuals with the COMT variation develop schizophrenia. It is anticipated that the genetics of working memory performance will be simpler to decipher than schizophrenia per se, and thus by studying working memory we will be better able to elucidate the biology and genetics of the disease.[9] While endophenotypes in schizophrenia are in the process of becoming well established,[28,29] they remain nondiagnostic; unfortunately, other psychiatric disorders are far behind in terms of progress. An endophenotype approach has a number of clinical and preclinical applications. As we discuss, these applications include neuroimaging as a means to visualize both the structure and real-time functioning of neural systems (responsible for both normal and abnormal behavior), and the utility of endophenotypes for improvement of animal models for psychiatric illness (Figure 1).

Neuroimaging

Neuroimaging has advanced considerably beyond the early pneumoencephalogram (x-rays of the brain and ventricles following depletion of cerebrospinal fluid), wherein current techniques allow the discovery of the functional and structural foundations of human brain function and dysfunction as never previously possible. The available technology includes methods based on nuclear magnetic resonance such as magnetic resonance imaging (MRI; used for structural imaging and also in diffusion tensor imaging [DTI] to measure water movement along white matter pathways),[22] functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS; measures specific neurochemicals).[23] The utilization of radiotracers in positron emission tomography (PET) or single-photon emission computed tomography (SPECT) allows the study of neurochemistry, blood flow, or metabolism.[23] Understanding of molecular biology is greatly influencing neuroimaging methodology. For example, it is within molecular and cellular biology labs that PET and SPECT ligands are envisioned, derived, and validated. Efforts are already underway to develop PET ligands to study second messenger intracellular signaling pathways in the living human brain (e.g., protein kinase C and cAMP phosphodiesterases). As technology advances, MRS is becoming more specific for biological molecules and functionally more temporally and regionally specific, necessitating a greater interaction between neuroimaging and molecular biology to thereafter understand on a cellular level what is taking place.

These improvements in the sensitivity and specificity of imaging measures are enabling assessment of progressively smaller brain structures and allowing an enhanced capability to obtain measurements previously considered of marginal validity and reliability. Utilization of these recent improvements in brain imaging technolo-

gies is providing enhanced opportunities for identifying neuromorphological, neurophysiologic, and neurochemical alterations (putative endophenotypes) in psychiatric disorders. The ability to image brain function more directly has advanced considerably the prospect that reproducible endophenotypes may one day lead to a better understanding of disease pathology, disease classification, and the potential to measure or predict efficacy of novel drugs.

Animal Models of Psychiatric Illnesses

The lack of well-validated animal models for most psychiatric disorders that can be utilized for in-depth biochemical, histological, and behavioral analyses has greatly hindered progress both in understanding neurobiology and developing novel medications.[30] One of the primary advantages of an endophenotype approach to understanding psychiatric illness is that, while complex behavioral phenotypes (e.g., psychosis) are difficult to study in animal models, endophenotypes are generally more straightforward, on the level of both biology and genetics, and therefore lend themselves more readily to modeling in animals. There are 3 generally accepted criteria for validating animal models for human psychiatric disorders: face validity, construct validity, and predictive validity.[31,32] Face validity refers to the outward appearance of the model, i.e., does the animal's behavior adequately reflect the human behavior being modeled? Construct validity refers to the fundamental causality and etiology of the behavior (perhaps a mouse with decreased levels of synaptic serotonin to model depression). Predictive validity is the ability of a model to predict the effect that pharmacologic or other manipulations will have on the condition being modeled.

Anxiety is one area in which models on all 3 axes are comparably well developed. It is usually quite apparent if an animal is easily startled, thus lending face validity. Compare this with the assessment of whether an animal is displaying psychotic-like or manic-like behavior, for example, which is much more difficult. Regarding construct validity, the function and underlying anatomical (locus ceruleus and amygdala) and neurochemical (norepinephrine) substrates of anxiety are well conserved. Additionally, a number of anxiety models are utilized to test efficacy of different classes of drugs including serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and benzodiazepines. However, while the general modeling of fear and anxiety has reasonable face, construct, and predictive validity, models of specific disorders are much more meager in these respects, and a great deal more experimentation is required.[5]

In addition to the general development of new models that fulfill these 3 validity criteria, the future of animal models of psychiatric diseases will increasingly rely on the ability to change the expression (both temporally and regionally) of specific genes in rodent (currently primarily mouse) models[4,5] to recapitulate developmental and brain region–specific pathologies. One recent example of this conditional knockout technology relied on both temporal and regional modulation of expression of one of the serotonin receptors, $5\text{-}HT_{1A}$, in mice.[33] These authors were able to show that anxiety-like behavior, which is increased in $5\text{-}HT_{1A}$ knockout mice, is rescued by re-expression of this receptor in the hippocampus and cortex but not in the raphe nuclei. They were additionally able to show, by removing (knocking out) the gene during only certain periods, that the early postnatal period appears to be critical to the development of the increased anxiety-like behavior in their model.[33] In addition to the increasingly more sophisticated knockout and transgenic strategies, there has also been progress in other methodologies to selectively regulate gene expression in discrete areas of the brain, including viral delivery of genes and siRNA (small inhibitory RNA) approaches to knockdown genes; these methodologies offer much promise for the future investigation of the concerted effects of modifying multiple putative susceptibility genes simultaneously. Such approaches will undoubtedly be invaluable to the development of improved animal models.

CONCLUSIONS

In this brief perspectives paper, we have attempted to highlight some of the advances in molecular and cellular neuroscience and genetics that are rapidly changing our understanding of both the normal and abnormal functioning of the human brain. Despite this remarkable progress, the application of this recent knowledge to the practice of clinical psychiatry is in its early stages, and it remains a critical task to translate these basic neuroscience findings to those that will benefit our patients and their families and help attenuate the massive overall impact of psychiatric illnesses.

Nevertheless, progress is being made, as evidenced by the growing appreciation that the major psychiatric illnesses are disorders of synapses and circuits rather than purely abnormalities in individual neurotransmitters. Similarly, results from transcriptomic studies, which identified neurotrophic signaling as a target for the long-term actions of lithium, have played a role (along with neuroimaging and postmortem brain studies) in a reconceptualization about the pathophysiology, course, and optimal long-term treatment of severe psychiatric disorders. These data suggest that, while bipolar disorder is clearly not a classic neurodegenerative disease, it is, in fact, associated with impairments of cellular plasticity and resilience. As a consequence, there is a growing appreciation that optimal long-term treatment will very likely be achieved by attempting to prevent the underlying disease progression and its attendant cellular dysfunction rather

than exclusively focusing on the treatment of signs and symptoms.

We are optimistic that the advances outlined in this article are likely to increase our knowledge of the pathophysiology of severe psychiatric illnesses; these advances will result in a dramatically different diagnostic system based on etiology and ultimately will lead to the discovery of new approaches to the prevention and treatment of some of mankind's most devastating and least-understood illnesses.

Drug name: lithium (Lithobid, Eskalith, and others).

REFERENCES

1. National Human Genome Research Institute. Human Genome Project. Available at: www.genome.gov
2. Watson JD, Crick FH. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. Nature 1953;171:737–738
3. Manji HK, Gottesman II, Gould TD. Signal transduction and genes-to-behaviors pathways in psychiatric diseases. Sci STKE 2003;207:pe49
4. Morozov A, Kellendonk C, Simpson E, et al. Using conditional mutagenesis to study the brain. Biol Psychiatry 2003;54:1125–1133
5. Tecott LH. The genes and brains of mice and men. Am J Psychiatry 2003;160:646–656
6. McGuffin P, Owens MJ, Gottesman II. Psychiatric Genetics and Genomics. Oxford, England: Oxford University Press; 2002:472
7. Owen MJ, Williams NM, O'Donovan MC. The molecular genetics of schizophrenia: new findings promise new insights. Mol Psychiatry 2004;9:14–27
8. Gottesman II. Psychopathology through a life span-genetic prism. Am Psychol 2001;56:867–878
9. Weinberger DR, Egan MF, Bertolino A, et al. Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 2001;50:825–844
10. Bertram L, Tanzi RE. Alzheimer's disease: one disorder, too many genes? Hum Mol Genet 2004;13(suppl 1):R135–R141
11. Henikoff S, Matzke MA. Exploring and explaining epigenetic effects. Trends Genet 1997;13:293–295
12. Petronis A. Human morbid genetics revisited: relevance of epigenetics. Trends Genet 2001;17:142–146
13. Petronis A. The origin of schizophrenia: genetic thesis, epigenetic antithesis, and resolving synthesis. Biol Psychiatry 2004;55:965–970
14. Weaver IC, Szyf M, Meaney MJ. From maternal care to gene expression: DNA methylation and the maternal programming of stress responses [abstract]. Endocr Res 2002;28:699
15. Tkachev D, Mimmack ML, Ryan MM, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003; 362:798–805
16. Hakak Y, Walker JR, Li C, et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A 2001;98:4746–4751
17. Mirnics K, Middleton FA, Marquez A, et al. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. Neuron 2000;28:53–67
18. Gray NA, Zhou R, Du J, et al. The use of mood stabilizers as plasticity enhancers in the treatment of neuropsychiatric disorders. J Clin Psychiatry 2003;64(suppl 5):3–17
19. Ryan MM, Huffaker SJ, Webster MJ, et al. Application and optimization of microarray technologies for human postmortem brain studies. Biol Psychiatry 2004;55:329–336
20. Rohlff C, Hollis K. Modern proteomic strategies in the study of complex neuropsychiatric disorders. Biol Psychiatry 2003;53:847–853
21. Li J, Gould TD, Yuan P, et al. Post-mortem interval effects on the phosphorylation of signaling proteins. Neuropsychopharmacology 2003;28:1017–1025
22. Taylor WD, Hsu E, Krishnan KR, et al. Diffusion tensor imaging: background, potential, and utility in psychiatric research. Biol Psychiatry 2004;55:201–207
23. Seibyl JP, Scanley BE, Krystal JH, et al. Neuroimaging methodologies: utilizing radiotracers or nuclear magnetic resonance. In: Charney DS, Nester EJ, eds. Neurobiology of Mental Illness. New York, NY: Oxford University Press; 2004
24. Gottesman II, Shields J. Schizophrenia and Genetics: A Twin Study Vantage Point. New York, NY: Academic Press, Inc; 1972
25. Gottesman II, Shields J. Genetic theorizing and schizophrenia. Br J Psychiatry 1973;122:15–30
26. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636–645
27. Braff DL, Freedman R. Endophenotypes in studies of the genetics of schizophrenia. In: Davis KL, Charney DS, Coyle JT, et al, eds. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia, Pa: Lippincott Williams & Wilkens; 2002
28. Egan MF, Goldberg TE. Intermediate cognitive phenotypes associated with schizophrenia. Methods Mol Med 2003;77:163–197
29. Callicott JH, Weinberger DR. Brain imaging as an approach to phenotype characterization for genetic studies of schizophrenia. Methods Mol Med 2003;77:227–247
30. Nestler EJ, Gould E, Manji HK, et al. Preclinical models: status of basic research in depression. Biol Psychiatry 2002;52:503–528
31. Crawley JN. What's Wrong With My Mouse? Behavioral Phenotyping of Transgenic and Knockout Mice. New York, NY: Wiley-Liss; 2000:xiii, 329
32. Einat H, Manji HK, Belmaker RH. New approaches to modeling bipolar disorder. Psychopharmacol Bull 2003;37:47–63
33. Gross C, Zhuang X, Stark K, et al. Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. Nature 2002;416:396–400
34. Gottesman II. Schizophrenia Genesis: The Origins of Madness. New York, NY: W.H. Freeman; 1991:296
35. Petronis A, Gottesman II, Kan P, et al. Monozygotic twins exhibit numerous epigenetic differences: clues to twin discordance? Schizophr Bull 2003;29:169–178