Major Disorders of Mind and Brain

Schizophrenia and manic-depressive illness are shaped by heredity and marked by structural and biochemical changes in the brain. The predisposing genes remain unknown

by Elliot S. Gershon and Ronald O. Rieder

Madness was understood for centuries by religion and poetry as an affliction of the spirit and by medicine as a disorder of various humors and organs of the body. In the past century, physicians have recognized the most common forms of psychosis (our current word for madness) as two chronic disorders—schizophrenia and mania—and have begun to understand the abnormalities in brain structure and function that accompany them. Each affects about 1 percent of the population. Both flare episodically, although schizophrenia follows a deteriorating course, whereas patients with bipolar manic-depressive illness, who have episodes of mania and depression, are usually mentally normal between episodes.

The anatomic, biochemical and hereditary bases of these disorders are now emerging. Some research has already shaped the development of new treatments. These subjects form the focus of our article. First, however, it is useful to consider what these disorders are like for the people who have them.

When Mrs. T. was 16 years old, she began to experience her first symptom of schizophrenia: a profound feeling that people were staring at her. These bouts of self-consciousness soon forced her to end her public piano performances. Her self-consciousness led to withdrawal, then to fearful delusions that others were speaking of her and finally to suspicions that they were plotting to harm her. At first Mrs. T.’s illness was intermittent, and the return of her intelligence, warmth and ambition between episodes allowed her to complete several years of college, to marry and to bear three children. She had to enter a hospital for the first time at 28, after the birth of her third child, when she began to hallucinate.

Now, at 45, Mrs. T. is never entirely well. She has seen dinosaurs on the street and live animals in her refrigerator. While hallucinating, she speaks and writes in an incoherent, but almost poetic, way. At other times, she is more lucid, but even then her voices sometimes lead her to do dangerous things, such as driving very fast down the highway in the middle of the night, dressed only in a nightgown. As an episode winds down, Mrs. T. usually becomes deeply depressed and hopeless about her condition. Often she sits in her car with the engine running and contemplates committing suicide.

Over the past five years she has taken antipsychotic medications, such as haloperidol, that suppress the hallucinations and help her stay out of the hospital. Stress, however, can bring the hallucinations and delusions back for days or weeks, as happened after her recent separation from her husband and the subsequent sale of her home. At such times, her voices shout terrible criticisms. After her daughter left for college, they shouted, “You’ll never see her again, you have been a bad mother, she’ll die.” At other times and without any apparent stimulus, Mrs. T. has bizarre visual hallucinations. For example, she saw cherubs in the grocery store. These experiences leave her preoccupied, confused and frightened, unable to perform such everyday tasks as cooking or playing the piano. When feeling well, however, she does volunteer work at church.

The mood disorders, which are distinct from schizophrenia, are called unipolar when the patient has episodes of depression alone and bipolar when there are episodes of both mania and depression. (The term “manic-depressive illness” encompasses both the unipolar and the bipolar form; the term “bipolar” is also used for the rare cases in which mania occurs without depression.) The depressions are quite severe, and suicide is an all too frequent outcome. Mania, a state of excitement usually characterized by impulsive behavior, can, when untreated, ultimately ruin marriages, careers and fortunes.

Mania can develop suddenly and shockingly, as illustrated in a case cited by a group led by Robert L. Spitzer of Columbia University. Daryl, a 25-year-old dancer, was cast in a significant role in a theatrical production. Despite prolonged rehearsal, he could not memorize his lines. He could not function. He spent days in bed, staring into space, and his eyes were filled with tears. Always energetic and ambitious, he was now depressed, listless and hopeless. He spent most of his time brooding about the decline of his career. Over the past five years he has taken antidepressant medications, such as imipramine, that help him stay out of the hospital. Stress, however, can bring the hallucinations and delusions back for days or weeks, as happened after his recent separation from his husband and the subsequent sale of his home. At such times, his voices shout terrible criticisms. After his daughter left for college, they shouted, “You’ll never see her again, you have been a bad mother, she’ll die.” At other times and without any apparent stimulus, Mrs. T. has bizarre visual hallucinations. For example, she saw cherubs in the grocery store. These experiences leave her preoccupied, confused and frightened, unable to perform such everyday tasks as cooking or playing the piano. When feeling well, however, she does volunteer work at church.

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work to make a number of extravagant purchases.

At this time, two weeks after he had displayed his first symptoms, Daryl accepted hospitalization. He received one dose of a tranquilizer yet spent most of the night disrupting the ward. Then he signed out, against medical advice, in the morning. Eventually he responded well to lithium carbonate. Daryl's father has a similar but more prolonged history, losing many jobs over 20 years after episodes of excited confrontations with his bosses. Over the past five years, however, he too has responded well to lithium.

Although schizophrenia and manic-depression can devastate patients' lives, the disorders do not preclude the performance of highly creative work. Schizophrenic patients confined in institutions have occasionally produced extraordinary works of graphic art [see illustration on page 126]. Manic-depressive illness often occurs in conjunction with extraordinary talent, even genius, in politics and military leadership, as well as in literature and music and the other performing arts. Among those thought to have had the disorder are William Blake, Lord Byron, Virginia Woolf, Robert Schumann, Oliver Cromwell and Winston Churchill. Many observers have suggested that extremes of mood and changes in outlook may spur creativity; they also speculate that the energy and facility of thought that typify the milder stages of mania can be a source of creativity.

Even though schizophrenia and severe mood disorders manifest themselves as intangible mental experiences, they are biologically determined to a major degree. (Only a few of the biological discoveries can be discussed in this brief article.) The first evidence of determinants came early in this century, when genetic studies showed that both schizophrenia and manic-depressive illness ran in families. Most workers discounted these correlations, however, on the grounds that families share environment as well as genes. To consider the two factors in isolation, researchers turned to adoptees, who, once adopted, have environmental families that are different from their genetic families.

In the best-known study, begun in the 1960s, Seymour S. Kety and his colleagues at the National Institute of Mental Health and at a psychological institute in Scandinavia identified schizophrenics adopted in infancy and traced their biological relatives through the adoption register. The study indicated that biological relatives had an
increased risk of developing the illness but adoptive relatives did not. The control group—biological relatives of nonpsychotic adoptees—faced no excess risk of schizophrenia or of any mental illness resembling it.

Twin studies are also revealing because different types of twins vary widely in their genetic relatedness. When schizophrenia or bipolar disease develops in one twin, the chance that it will develop in the other is much greater in identical twins, who share all their genes, than in fraternal twins, who share only about half. Moreover, although about half of the identical twins of schizophrenics never develop the illness, the children of even the well twins are at increased risk. These correlations imply two things. The risk of illness rises with increasing genetic similarity, but even a perfect identity of genes does not produce a perfect correspondence. Some environmental factor, or interaction of genes with the environment, must therefore push susceptible people over the threshold of illness. Studies have already implicated one possible factor: prenatal exposure to the influenza virus.

Mood disorders also stem from the interaction of genes with some aspect of the environment. Rates of major depression in every age group have steadily increased in several of the developed countries since the 1940s. This trend was first spotted some 10 years ago in an epidemiological study in Sweden. A similar increase in suicide over the same four decades occurred in Alberta, Canada. These findings have been firmly established as birth-cohort effects: suicide rates among 15- to 19-year-olds, for instance, were 10 times higher for those born in the late 1950s than for those born in the early 1930s. Similar birth-cohort increases appeared, over these decades, in suicide and unipolar disorder in the U.S., in bipolar disorder in the U.S. and Switzerland, and in alcoholism in males in the U.S. [see illustration on page 131].

Rates of depression, mania and suicide continue to rise as each new birth cohort ages, a pattern that harbors ominous public health consequences. Such birth-cohort effects are even more pronounced in the relatives of patients than in the general population—in other words, at comparable ages, the children of patients are far more susceptible to these disorders than are their ill parents’ siblings. This relation clearly implies an interaction between genes and some environmental factor, which must have been changing continuously over the past few decades. The factor remains a mystery.

The biological abnormalities that genes and environment somehow put into motion were quite mysterious until the 1970s, when new imaging technologies allowed physicians to visualize the living brain in great detail.

One imaging technique, computerized tomography (CT scanning), was first applied to the brains of schizophrenic patients in 1978 by Eve C. Johnstone and her colleagues at the Clinical Research Centre in Middlesex, England. They observed that the lateral cerebral ventricles were much larger than in normal subjects. If the ventricles or the spaces between convolutions are enlarged, one can conclude there has been a failure of development or a loss of brain tissue. Other x-ray evidence confirmed this conclusion by showing less tissue and more fluid-filled spaces around the convolutions in the cerebral cortex.

A nother technique, magnetic resonance imaging (MRI), confirmed the ventricular enlargement. Daniel R. Weinberger’s group at the National Institute of Mental Health used MRI to compare identical twins in which one twin had schizophrenia and the other did not. In 12 of 15 sets of such twins, the schizophrenic one had the larger cerebral ventricles. Relative diminution of specific brain structures has been demonstrated, too, in autopsies and by MRI scans of schizophrenic patients. The most striking examples of such diminution appear in the hippocampal region, part of the limbic system in the temporal lobe of the cerebrum, which modulates emotional response, memory and other functions [see illustration on opposite page].

The new imaging devices also showed functional abnormalities for the first time. In 1974 David H. Ingvar of University Hospital in Lund, Sweden, found reduced blood flow in the frontal cerebrum of schizophrenic patients, implying decreased neuronal activity there. This finding has since been corroborated many times [see illustration at right].

Weinberger’s group presents evidence linking both structural and functional abnormalities in the brain to a schizophrenic cognitive trait. They found that normal subjects show increased blood flow in the prefrontal cerebral cortex while taking the Wisconsin Card Sort, a test of working memory and abstract thinking, whereas schizophrenic subjects show less of an increase in flow and do worse on the test. Moreover, those schizophrenic patients whose hippocampal structures are the smallest show the greatest deficit in prefrontal blood flow. The hippocampus connects to the prefrontal cortex, which manages working memory in primates [see “Working Memory and the Mind,” by Patricia S. Goldman-Rakic, page 110].

Postmortem studies of schizophrenic patients have also uncovered abnormalities in the number of brain cells and in their organization, particularly in the temporal lobe. Yet the tissue shows none of the scarring one would expect from an infection, nor do the abnormalities progress over time. Some researchers therefore speculate that the abnormalities stem from a developmental disorder, perhaps a failure of the growth of neurons and the development of their connections, or from a disturbance in the “pruning” of neurons that normally
Drugs may act on several points in the synapse. Antidepressants that affect the presynaptic cell include those that block the cell’s reuptake of monoamines (a). These drugs include tricyclic antidepressants, such as imipramine, which block reuptake of several monoamines, and more specific blockers, such as fluoxetine, for serotonin, and bupropion, for dopamine. Other antidepressants known as monoamine oxidase inhibitors (b) prevent the presynaptic cell from metabolizing monoamines. Drugs that affect the postsynaptic cell include agents that either block monoamine receptors or stimulate their ability to respond (c). Haloperidol, an antipsychotic, is a dopamine receptor blocker. Finally, some drugs affect the second messenger (d) that is normally produced after a receptor has been activated. For example, lithium carbonate, an antidepressant and antimanic agent, works by inhibiting the synthesis of phosphatidyl inositol. Here a postsynaptic receptor is shown coupled to a stimulatory G protein; this is its activated state, which causes more second-messenger chemicals to be synthesized, triggering molecular cascades that determine how the postsynaptic cell will respond.

Further research showed that the frontal parts of the temporal cortex receive highly processed and filtered sensory information from other parts of the cortex. That information eventually reaches the limbic system and other structures that mediate emotional response, or affect. Perhaps, then, some overactivation of the temporal cortex or abnormalities in the filtering process produce the common experiences of schizophrenic patients: auditory hallucinations and a sense of being overwhelmed by all the senses.

The first effective medications for schizophrenia and depression were discovered serendipitously, without any knowledge of their effects on brain chemistry. Chlorpromazine was developed in the 1950s as a surgical anesthetic but turned out to alleviate the symptoms of both schizophrenia and mania. It thus became the first widely used antipsychotic drug. Scientists then used it as a model for the synthesis of imipramine, which they expected would also serve as an antipsychotic agent. Instead it turned out to be very effective in the treatment of depression. Lithium was introduced into the treatment of manic-depressive illness after John Cade, an Australian psychiatrist, noted in 1949 that lithium salts sedated rodents in his laboratory.

Insight into the way antidepressant agents act began with the study of reser-
pine, a drug derived from the plant *Rauwolfia serpentina*, used in traditional medicine in India. Reserpine was one of the first effective medications for high blood pressure. Physicians noted, however, that the drug sometimes brought on severe depression in patients—a few even committed suicide.

Biochemists discovered that reserpine depletes certain neurotransmitters classed as monoamines, among them norepinephrine, dopamine and serotonin. All the antidepressant drugs known in the mid-1960s effectively concentrated these monoamines in the synapse, either by inhibiting their metabolic breakdown or by preventing cells from reabsorbing them from the synaptic space (a process known as reuptake).

This pattern led Joseph J. Schildkraut, then at the National Institute of Mental Health, to propose in 1965 that depression was associated with a reduction in synaptic availability of catecholamines (norepinephrine and dopamine), particularly dopamine, andmania with an increase of catecholamines. Nevertheless, there are antidepressant drugs, such as iprindole, that are associated with no observable change in norepinephrine reuptake or metabolism.

Biochemical pharmacologists therefore looked beyond the neurotransmitters to the synaptic receptor molecules that bind with them. The workers knew that norepinephrine has several pharmacologically distinct receptors, called adrenoceptors, but their experiments in binding various antidepressant drugs to the receptors produced no consistent change.

Then, in 1975, Fridolin Sulser’s laboratory at Vanderbilt University found an answer by looking not at binding itself but at the intracellular response that one type of binding elicits. They studied how norepinephrine stimulates beta-receptors, a class of adrenoceptors that mediates the release of cyclic adenosine monophosphate inside the nerve cell. This molecule then serves as a second chemical messenger. But after long-term administration of certain antidepressants, including iprindole, this secondary response consistently decreases. Virtually all antidepressants, including those discovered after the finding was published, produce this result. So does electroconvulsive therapy, a very effective treatment for depression in which shocks are administered to the cerebral cortex to induce artificial seizures.

Post proposed that manic-depressive illness progresses in a similar fashion, each episode facilitating the next one. This mechanism would account for both the progression of the illness and the deleterious effects of interrupting treatment with lithium or anticonvulsant medication. After such an interruption, patients may fail to respond to a resumption of the medication, even if it had been effective earlier.

One can also infer aspects of the biology of schizophrenia from the biochemical action of the therapeutic neuroleptic drugs, which include chlorpromazine. Arvid Carlsson of the University of Göteborg sought to explain why these drugs cause animals to produce increased quantities of breakdown products of dopamine. He suggested the effect was a compensatory response of the presynaptic neuron to a postsynaptic blockade [see illustration on opposite page].

As the different molecular and pharmacologic forms of dopamine receptors became known, the D₂ dopamine receptor emerged as the principal site of action of antipsychotic medications. Some of the drugs seem to work by means of interactions with other neurotransmitter systems: among these interactions are the balance between the neural pathways containing the D₁ and the D₂ dopamine receptors and the balance between pathways containing certain serotonin receptors (SHT₂) and the D₃ dopamine receptors.

Maria and Arvid Carlsson recently proposed that schizophrenia is characterized by the disruption of a balance between dopamine neurons originating in the midbrain and glutamate neurons originating in the cerebral cortex. The imbalance could be an excess of dopamine or a deficit of glutamate, or both. A reduction in glutamate neurons would be consistent with the apparent cortical atrophy seen in schizophrenia. This theory fits with the effects of known psychosis-producing drugs of abuse: PCP,...
a hallucinogen, blocks glutamate receptors, whereas amphetamine, which can produce psychosis with chronic use, stimulates dopamine release.

Studies of the biochemical action of these drugs and related clinical research have brought us to an era of rationally based design of medications. Once neuropharmacologists understood that chlorpromazine works by blocking dopamine receptors, they were able to synthesize haloperidol, which strongly blocks dopamine receptors but has little effect on other receptors. Similarly, after scientists found that the antidepressant imipramine blocks reuptake of the neurotransmitter serotonin, they were able to design fluoxetine, which specifically blocks serotonin reuptake but has very little effect on the reuptake of other monoamines.

Pharmacology and neurobiology continue to feed off each other. Over the past few years, clinical trials have shown that clozapine helps about 30 percent of those schizophrenic patients who do not respond to other antipsychotic medications or who develop intolerable side effects. This drug’s unusual properties, such as its specific interaction with certain dopamine and serotonin receptors (D₄ and 5HT₂), may help in the effort to understand schizophrenia itself.

Depression turns out to involve hormonal systems of a much wider scope than had been realized. Cortisol, a hormone secreted by the adrenal glands, constitutes the main circulating steroid associated with stress in humans. Many severely depressed patients show persistently elevated blood cortisol, implying a malfunction in the system that normally governs it.

George P. Chrousos of the National Institute of Child Health and Development and Philip W. Gold of the National Institute of Mental Health interpret this failure as the result of a prolonged activation of the brain’s stress system. This system—a complex of neuronal, hormonal and immunologic responses—comes into play when some stress provokes the brain, causing its hypothalamic centers to secrete corticotropin-releasing hormone (CRH). This factor in turn stimulates the pituitary gland—just under the brain—to produce the hormone adrenocorticotropin, which circulates to the adrenal glands and stimulates their release of cortisol. This process normally turns itself off when the excess cortisol reaches its receptors (glucocorticoid receptors) in the brain and suppresses CRH production there. In depressed patients, however, Gold found that production of CRH is excessive and that this suppression fails.

The CRH-producing neurons of the
hypothalamus are principally regulated by neurons containing norepinephrine, which originate in the hindbrain. These CRH and norepinephrine neurons serve the stress system as central stations. Each set of neurons stimulates the other. In addition, each responds similarly to many neurotransmitters and peptide modulators of neurotransmission. Because many antidepressant drugs affect these neurotransmitters, they must also influence the regulation of the stress system.

The stress system of the brain sets the level of arousal and the emotional tone, alters the ease with which various kinds of information can be retrieved and analyzed, and aids in the initiation of specific actions. All these functions are disordered in depressed patients, and as a result they become sad, have trouble concentrating and become incapable of making decisions.

The anatomy of the stress system starts with the locus coeruleus in the hindbrain (the major source of norepinephrine-producing neurons) and the paraventricular nucleus of the hypothalamus (the brain's major CRH-producing region). From there the connections reach into the cerebrum; these connections include dopamine-producing neurons that project into the mesolimbic dopamine tract, which helps to control motivation, reward and reinforcement. A connection of CRH neurons to the amygdala and hippocampus is important for memory retrieval and emotional analysis of information pertinent to the environmental events that induced the stress.

The general concepts of stress system dysregulation apply to many psychiatric and other diseases, and it will require a considerable amount of basic and clinical research to determine whether a causal relation exists between mood disorders and this kind of stress response dysregulation.

Molecular genetics can test hypotheses on the biology of these diseases because the predisposition to them is almost certainly inherited. The task is made difficult, however, by the complexity of inheritance in schizophrenia and manic-depression. Neither illness is inherited through one dominant or recessive gene. Analysts must take into account that illness might result from coordinated actions of several genes at several different locations (loci) or, alternatively, from genetic heterogeneity (in which the same illness can be caused by a mutation at any one of several loci).

There are two major strategies for finding pathogenic genes. One can systematically search each chromosome, or one can investigate a candidate gene—such as that for a given receptor—which is known to code for proteins related to the disease.

DNA markers now exist for nearly every segment of every chromosome. In any family, each parent contributes to the child a single segment from either one or the other chromosome in a given pair of chromosomes. The illness is linked to a marker location on the genetic map if, and only if, one ancestral chromosome segment is consistently inherited with illness throughout a pedigree. Whenever there is a linkage to the marker, one can be sure that a gene for the illness resides somewhere on that chromosome segment.

Such mapping has consistently shown that a proportion of the families of Alzheimer's patients have illness linked to markers on the long arm of chromosome 21. No such linkages have been demonstrated conclusively for manic-depressive illness or schizophrenia. One widely publicized study of a large Amish pedigree linked manic-depressive illness to markers on chromosome 11; another study of a series of pedigrees in Iceland and England linked schizophrenia to markers on chromosome 5. But later analyses led the investigators to withdraw their conclusions, and no other researchers have confirmed the findings.

Linkage to manic-depressive illness has been reported more than once at the tip of the long arm of the X chromosome, but the linkage remains controversial. One can expect more definitive results from several large-scale international efforts, now under way, to scan the entire gene map of families touched by either schizophrenia or manic-depressive illness.

Many genes encoding the molecules involved in neurotransmission are candidates for the defects underlying manic-depressive illness or schizophrenia. A study of several such candidates for manic-depressive illness was performed on a series of 20 pedigrees at the National Institute of Mental Health by Margret R. Hoebel, Sevilla D. Detera-Wadleigh, Wade H. Berrettini, Pablo V. Gejman and one of us (Gershon). The group tested structural genes for many of the receptors we have described, including norepinephrine (three alpha-receptor genes and two beta-receptor genes), dopamine (D2 and D4) and corticosteroid receptors, and the gene of a G protein subunit (Gsa). Other investigators have studied the D2 dopamine receptor in schizophrenia pedigrees. Linkage was strongly excluded for each of these genes.

When linkage of a candidate gene to illness can be ruled out, one can conclude that no mutation in the candidate gene determines inheritance of the susceptibility to the illness. The only qualification to this general rule is the statistical and technical limits on our power to detect or rule out linkage. Methods other than linkage can also scan for mutations in candidate genes, and many genes remain to be examined.

W e expect our understanding of the biology of schizophrenia and mood disorders to expand dramatically, fueled by the impressive advances in neurobiology, cognitive neuroscience and genetics. Precise diagnostic tests for persons at risk for illness, treatments based on knowledge of molecular alterations that lead to illness, understanding of how environmental events interact with the brain to produce illness and, eventually, the development of gene therapy are all goals that may be achieved.

FURTHER READING