Chapter 4

Mental Disorders and the Brain

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Studying the factors that play a role in mental disorders is like putting together a jigsaw puzzle. The pieces of the puzzle are bits of information about the workings of the human brain. This chapter considers the chemistry, structure, and function of the human brain in mental disorders. Another key piece in the puzzle is the heritability of these disorders, which is discussed in chapter 5.

The nature and amount of information available about the biology of mental disorders reflects the course of neuroscience research over the years. During the 1960s and 1970s there were advances in the methods used to study the chemistry of the brain and a resulting increase in knowledge about brain pharmacology and biochemistry. Many scientists therefore focused their work on the roles of natural chemicals and pharmaceuticals in mental disorders. The following decade, the 1980s, saw advances in molecular biology and imaging technologies, which in turn led to study of brain anatomy and activity and the molecules involved. The pace and extent of research into the biological components of mental disorders mirror these developments, with the body of knowledge concerning the chemistry of the brain being much larger than the growing database about other factors. Currently, some of the most active research involves techniques that enable investigators to study the activity of the brain in living subjects. These advances and the expectation of future discoveries have infused researchers in the area of mental disorders with optimism that further studies will pay off in a greater knowledge of the brain, a better understanding of disorders, and the development of new treatments for them.

Scientists examine the activity of the brain to determine its normal functioning and to see whether biological factors are associated with a given mental disorder. When a factor is identified, an important distinction must be made as to whether it is correlated with the disorder or in fact causes it. A correlated factor is one that is linked to the disorder and may result in some of its symptoms. For example, a perturbation of the chemical functioning of an area of the brain may be correlated with symptoms characteristic of a disorder. Understanding the perturbation can explain how the symptoms occur-that is, what the biological underpinnings are-but it does not explain what caused the chemical disturbance. Thus, a correlated factor—in this case the chemical perturbation-is secondary to the underlying cause of the disorder. The consistent association of either a causative or correlative factor with a disorder can provide a biological marker to aid in the diagnosis of the disorder, which in turn can be critical to research and treatment. The identification of factors that are associated with a disorder can also provide an understanding of the mechanisms underlying symptoms; this is crucial to the development of rational therapeutic interventions. Most basic of all is the identification of specific causes of mental disorders. To date, research into the biology of the mental disorders considered here has identified several factors that are associated with their symptoms; there is much less evidence regarding the causes of these disorders.

To solve the puzzle of what causes and contributes to mental disorders, all of the pieces have to be studied and fit together. It is important to note that not all of them will necessarily be biological. Although beyond the scope of this report, psychological and social factors also contribute. Thus, when a biological factor is identified, research must point out how it interacts with psychological and social factors that may produce, modify, or determine how mental disorders are expressed. For example, it may be that biological factors create a predisposition to certain disorders. The psychological and social experiences of an individual, such as exposure to stress or a negative life event, may then shape the likelihood that that factor will manifest itself as the clinical condition.

METHODS USED TO STUDY MENTAL DISORDERS

To understand the involvement of biological factors in mental disorders, researchers conduct experiments in animals, analyze biological samples from patients, and study patients' biochemistry, brain anatomy, behavior, and mental activities. In general, basic mechanisms of the brain's physiology, chemistry, and anatomy are studied in either animal models that approximate aspects of a disorder or in tissue samples from living persons and brain samples from deceased ones. Patient popula-

tions are examined to learn more about symptoms and characteristics associated with disorders. Understanding mental disorders depends on connecting information from these diverse observations. Ultimately, the most comprehensive information is derived from studies and techniques that permit direct measurements in humans, both those with and those without mental disorders. Although it is very difficult to study the working brain in humans, new techniques enable investigators to observe some physiological processes in living subjects. Refinement of these techniques, and the development of additional ones, will most likely enhance the understanding of mental disorders.

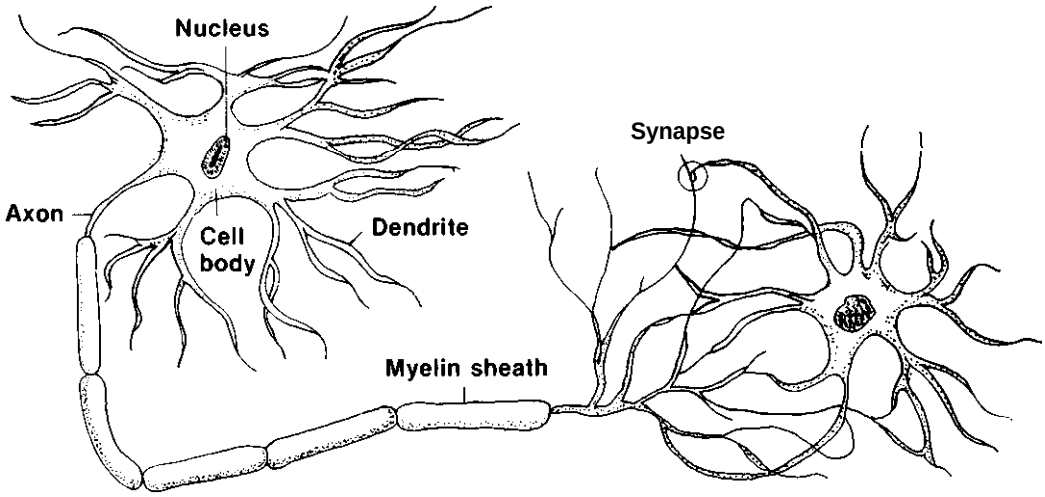
It is often difficult to put disparate biological pieces together into a unified hypothesis about the biological underpinnings of a mental disorder. Many times, results from studies contradict each other or are inconsistent, which further complicates this process. A number of factors contribute to these contradictions and inconsistencies. A better understanding of the workings of the healthy brain is essential to understanding what might go wrong in mental disorders. As a result, there is still much to be learned. Also, some older research techniques provide only crude measures of brain activity, producing less precise findings. Finally, the difficulty of distinguishing specific mental disorders may result in a heterogeneous research population, which can then produce difficult-to-interpret results. To some extent, the explosion in neuroscience research in recent years and the development of new, sophisticated techniques and methodologies for more precise, complex analysis have reduced, and will continue to alleviate, many of these problems.

Biochemistry

Study of the biochemistry of the brain involves examining the many chemicals involved in communication and processing of information in the brain. Neurotransmitters are chemicals released by nerve cells, or neurons, to communicate with each other. Neurons are the cells that process information in the brain. A neuron consists of a cell body with long extensions, much like the branches of a tree, called dendrites (figure 4-l). Also projecting out of the cell body is a single fiber called the axon, which can extend a great distance (figure 4-l). When a neuron is activated, it releases a neurotransmitter into the synapse, the gap between two neurons (figure 4-2). The molecules of the neurotransmitter move across the synapse and attach themselves, or bind, to proteins, called receptors, in the outer wall of an adjacent cell (figure 4-2). Usually, the axon terminal is the part of the cell that releases neurotransmitters into the synapse, and the dendrites and cell body are the areas of the neuron which contain receptors that form synapses with the axons of other neurons.

Once the neurotransmitter has activated a receptor, it unbinds from the receptor. It then has to be

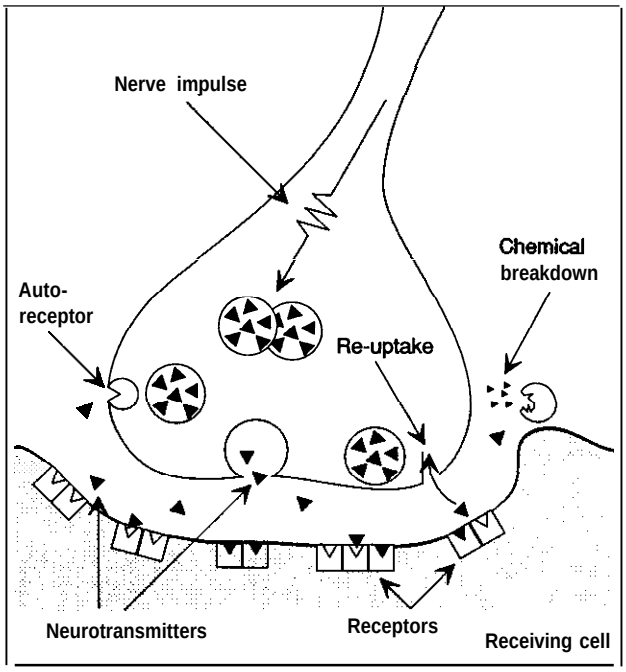
Figure 4-l—Neurons



Two neurons in synaptic contact.

SOURCE: R. Restak, *The Brain (New* York, NY: Bantam Books, 1984).

Figure 4-2—The Synapse



The synapse and associated structures.
SOURCE: Office of Technology Assessment, 1992.

removed from the synapse so the synapse will be available for a new message. This is done either by the neurotransmitter's being taken backup into the neuron that released it (a process called reuptake) or by it being broken down chemically into compounds called-metabolizes (figure 4-2).

For each neurotransmitter in the brain, there are specific receptors to which it can attach. Binding by the neurotransmitter activates the receptor, which can have different effects, depending on the receptor. Receptors can be linked to a variety of biochemical and cellular mechanisms that are turned on or off by the activation of the receptor. A neuron can have thousands of receptors for many different neurotransmitters. Some neurotransmitters activate neurons (excitatory neurotransmitters), while others decrease the activity of neurons (inhibitory neurotransmitters).

When a neuron is activated, changes occur in its membrane, resulting in a shift in the balance of ions (electrically charged molecules) between the inside and outside of the neuron. This change in ionic balance triggers an electrical impulse inside the neuron. The electrical impulse travels from the cell body, down the axon, to the axon terminal. At the axon terminal, the impulse causes the release of neurotransmitter from the neuron into the synapse.

Sometimes a receptor for one neurotransmitter can affect a receptor for another neurotransmitter. In such cases, the receptors are biochemically coupled: The activation of one modulates the functioning of the other, either increasing or decreasing its activity. A neuron can also have receptors for the neurotransmitter it releases; these are usually located near the site where the neurotransmitter is released into the synapse (figure 4-2). Such receptors are acted on by the neuron's own neurotransmitter to regulate the release of the neurotransmitter. Thus, these autoreceptors, as they are called, act as a feedback mechanism to regulate a neuron's activity. The activity of a neuron will be determined by the cumulative activity of all its various receptors.

While receptors are specific for a neurotransmitter, there may be a variety of receptor subtypes, linked to different cellular mechanisms, that all respond to the same neurotransmitter. In this way, one neurotransmitter can have diverse effects in various areas of the brain. Also, the number of receptors in the brain is not static. In response to increased production of a neurotransmitter, the number of receptors for that neurotransmitter will decrease; conversely, depletion of a neurotransmitter will result in an increase in the number of receptors for that neurotransmitter. This mechanism allows the brain to compensate for changes in neurotransmitter levels. Such receptor changes are important in therapeutics; some drugs mimic neurotransmitters by stimulating increases or decreases in receptor numbers. In some cases, these changes may be directly related to the drug's therapeutic effect.

Many chemicals have been identified as neurotransmitters, among them acetylcholine, the catecholamines (norepinephrine, epinephrine, dopamine), serotonin, various amino acids, and peptides, including certain hormones. Various chemicals in the brain other than neurotransmitters and their receptors are necessary for brain function. They may be associated with the biochemical mechanisms activated by neurotransmitter-receptor interactions, involved with the production and breakdown of neurotransmitters, or responsible for carrying out metabolic activity.

Abnormalities in any of these chemicals, their receptors, or the cellular mechanisms that are turned on or off by the receptors could contribute to mental

disorders. For example, there may be too much or too little of a neurotransmitter, or the receptors for a neurotransmitter may not function properly. Mechanisms activated by receptors maybe defective, or the systems responsible for deactivating neurotransmitters maybe faulty. Also, breakdowns in the chemical systems responsible for the normal functioning of cells in the nervous system may play a role in mental disorders. Such alterations in neurotransmitter systems have been implicated in the symptoms of certain mental disorders (see later discussions).

Scientists use a variety of tools and methods to study these factors. Biochemical assays are available to measure receptor number and activity, concentrations of neurotransmitters, and many other biochemical parameters of brain function. The majority of these assays are used with tissue from animals or from patients (i.e., postmortem brain samples or tissue samples from living patients). For example, information about concentrations of neurotransmitters is derived from measuring these compounds or their metabolizes in samples of blood or cerebrospinal fluid (i.e., fluid inside and surrounding the brain and spinal cord). Nevertheless, such samples provide only an indirect measure of what is occurring in the brain. The inability to observe and measure the chemical activity of the brain directly has hampered investigators' understanding of how these processes may go awry in mental disorders. One new technique that enables scientists to study biochemistry in the living brain is positron emission tomography (PET) (see later discussion). In particular, it can be used to assay some biochemical measures, such as distribution and number of receptors, in living human subjects.

The last decade has also seen the application of molecular biological techniques to study the brain. Genetic information about the brain and its components is studied and manipulated to understand the cellular and molecular workings of the brain. While these new techniques are just beginning to have an impact on the study of mental disorders, they have already provided valuable information about receptor subtypes (box 4-A) and other aspects of the biochemistry of the brain.

Information about underlying biochemical abnormalities is also often derived from studying the actions of therapeutically effective drugs (i.e., psychopharmacology). In fact, many initial advances in understanding the biochemistry of mental disorders came from studies of drug actions in the brain. If a drug is found to be effective in treating a disorder, examination of that drug's chemical action in the brain may lead to the discovery of an intrinsic pathology. For example, the finding that effective antidepressant drugs act on catecholamines led to the study of these neurotransmitters in depression (see later discussion). Conversely, drug development may be guided by previously acquired knowledge about a disorder, which directs research efforts to create compounds that will act on an already identified pathology. If a specific neurotransmitter system is identified as being aberrant in a disorder, drugs can be designed to interact with some aspect of that system, such as the receptors, to try to reverse the abnormality.

Anatomy and Activity

Abnormalities in the structure of the brain or in its activity in specific locations can contribute to mental disorders. In the brain, neurons that share the same anatomical region, and to varying degrees the same function, are assembled into groups called nuclei. The brain is made up of hundreds of nuclei. Some consist of neurons that produce many different neurotransmitters, while others are predominantly of one type. Axons extending from nuclei convey information between and among them. Thus, the brain comprises many nuclei, which are connected by pathways of axons that contain various neurotransmitters. Information is conveyed and processed via networks made up of interconnected nuclei.

Some networks of nuclei are particularly relevant to mental disorders (figure 4-3). In general, these are networks that control cognitive (i.e., perception, recognition, reasoning, judgment, imagination), behavioral, and emotional functions. Disruptions of these areas are likely to be involved in the thinking and mood disturbances characteristic of severe mental disorders. The cerebral cortex (the portion of the brain that is critical in decisionmaking) is important in this regard, especially the frontal lobes, which are considered to be the seat of higher-order thinkmg and which enables humans to reason abstractly. The limbic system, a network of structures (e.g., hippocampus, amygdala, parts of the temporal lobe of the cortex) located in the upper part of the brain (figure 4-3) and involved in control of emotional behavior, is also important in mental disorders. Additional areas of the brain implicated in mental disorders are the basal ganglia, a group of

Box 4-A-Cloning Dopamine Receptors

Advances in the ability to manipulate and express genetic information provide an important new means of studying the brain. One area in which the tools of the molecular biologist have contributed significantly is the identification of receptor subtypes for neurotransmitters, These techniques have permitted the cloning of genes for specific receptors and have provided a detailed characterization of the receptor's three-dimensional structure. Not only is this information important for understanding better how the brain works, but it also aids the development of drugs specifically designed to act only on certain receptors. This specificity can increase the efficacy of a drug while decreasing the **side** effects it causes. The recent identification of several receptor subtypes for the neurotransmitter dopamine is an example of the contribution molecular biology is making to understanding the brain.

Previous to the use of molecular biological techniques, two dopamine receptors had been characterized, based on the ability of various drugs to bind to them. For example, drugs that are effective in treating schizophrenia (called typical antipsychotic drugs) ail bind to the same dopamine receptor--the D_2 receptor. In addition, another receptor that binds dopamine, but not typical antipsychotic drugs, was identified and called the D_1 receptor. Other evidence, derived using pharmacological techniques, suggested that there might be additional dopamine receptors, but it was not until the gene for each of the dopamine receptor subtypes was identified that their existence was confirmed.

Currently, six dopamine receptor subtypes have been identified and cloned using molecular biological techniques. Although all of these receptors are acted on by dopamine, they all have slightly different molecular structures. In addition, there are some differences in their location in the brain, the cellular mechanisms that they turn on when they are activated, and their ability to bind typical antipsychotic drugs. Both the D_1 and D_5 receptors are linked to the same cellular mechanism, are located in the hippocampus and cortex, and do not readily bind typical antipsychotic drugs. They differ in their ability to bind dopamine and dopamine-like drugs. There are two types of D_2 receptors: Both bind typical antipsychotic drugs, and both are found in parts of the limbic system, basal ganglia, and cortex. They differ in that each is linked to a different cellular mechanism, and one is a dopamine autoreceptor— a receptor that lies on the dopamine neuron itself, regulating the cell's activity (see text). The D_3 and D_4 receptors are found predominantly in the limbic system. While it is unclear what cellular mechanisms are activated by these receptors, the D_3 receptor is thought to be an autoreceptor. Neither binds typical antipsychotic drugs as effectively as D_2 receptors, and the D_4 receptor readily binds a new atypical antipsychotic drug, clozapine (see text).

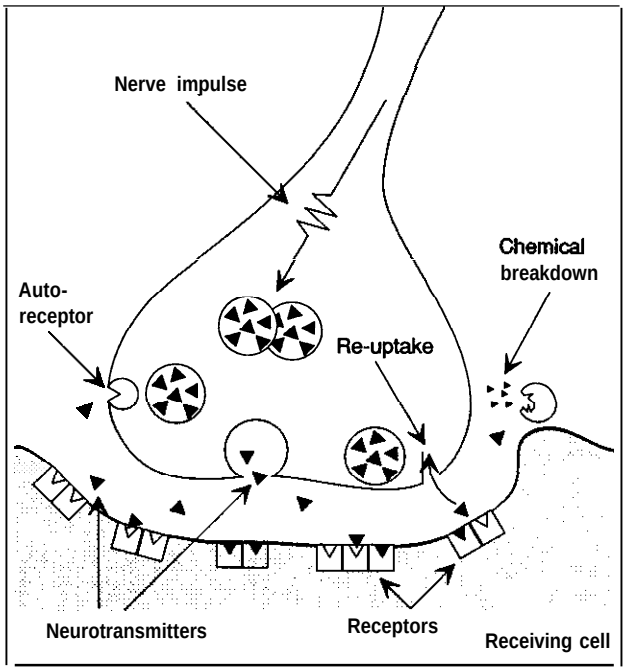
The identification of these dopamine receptor subtypes has provided new insights into how more efficacious antipsychotic medications can be designed. Since clozapine is a highly effective antipsychotic drug but produces fewer side effects than typical antipsychotics, it is thought that its mixture of strong binding to D_4 receptors and weak binding to D_2 receptors accounts for its action. Currently there is great interest in understanding the various dopamine receptor **subtypes** to determine their role in schizophrenia and how drugs can be designed to target them.

The complexity of the dopamine receptor system indicates the many ways that a single neurotransmitter can have myriad effects in the brain. Molecular biological techniques provide an important tool for clarifying these basic brain mechanisms, providing new information about how they maybe disturbed in mental disorders and leading the way for the development of more efficacious medications.

SOURCES: E. Kandel, J. Schwartz and T. Jessell (eds.), *Principles of Neuroscience (New* York NY: **Elsevier** Science publishing, 1991); P. Sokoloff, B. Giros, M. Martres, et al., ''Molecular Cloning and Characterization of a Novel Dopamine Receptor (D3) as a Target for Neuroleptics," Nature 347: 146-151, 1990; R Sunahara, H. Guarn, B. O'Dowd, et al., ''Cloning of the Gene for a Human Dopamine D5 Receptor With Higher Affinity for Dop amine Than Dl,' Nature 350:614-619, 1991; H. van Tol, J. Bunzow, H. Guan, et al., "Cloning of the Gene for a Human Dopamine D4 Receptor With High Affinity for the Antipsychotic Clozapine, ' Nature 350:610-614, 1991.

nuclei just below the cerebral cortex, some of which coordinate movement and others of which are part of the limbic system; the hypothalamus, a collection of nuclei at the base of the brain (figure 4-3) that regulate hormones and behaviors such as eating, drinking, and sex; the locus ceruleus, a nucleus in the brainstem (figure 4-3) made up of norepinephrine neurons that are intimately involved in the body's response to stressful situations (i.e., the fight-or-flight response); and the raphe nuclei, also found in the brainstem (figure 4-3), made up of serotonin neurons that regulate sleep, are involved with behavior and mood, and are connected to the limbic system. It must be kept in mind, however, that if any of these, or other brain structures, are impaired in a mental disorder, it is unlikely that only the function of that structure will be affected. Since the brain is organized as networks of nuclei, any structural or

Figure 4-2—The Synapse



The synapse and associated structures.
SOURCE: Office of Technology Assessment, 1992.

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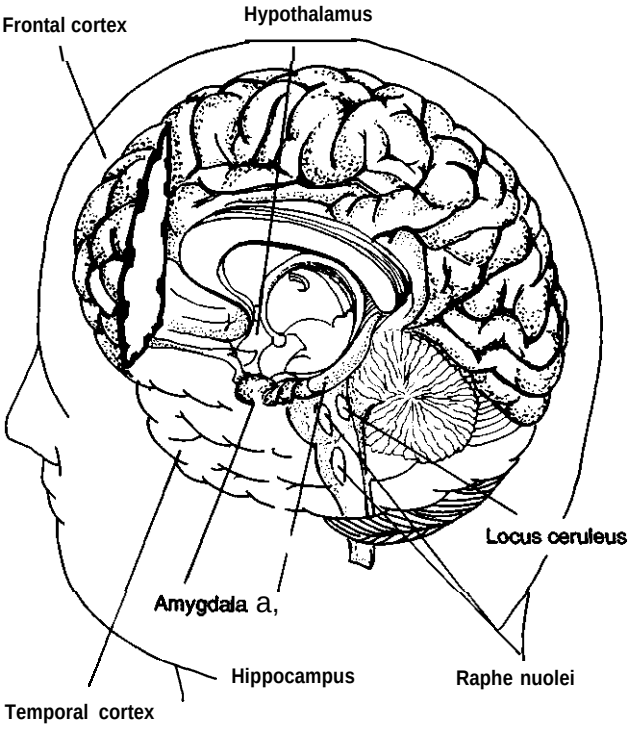
Figure 4-3—Brain Structures Involved in Mental Disorders



Three-dimensional drawing of the human brain.

SOURCE: Adapted from Lewis E. Calver, University of Texas, Southwestern Medical Center, Dallas, TX, 1992.

functional impairment in part of a network can create a disturbance throughout the network.

Structural changes associated with mental disorders can include anatomical abnormalities in the structure of the brain or irregularities in the individual cells within a region of the brain. The classical techniques for gathering information about brain structure-the macroscopic and microscopic postmortem examination of normal brains and brains from individuals who have had mental disorders—have been augmented with a number of newer techniques and machines that make possible the study of the structure of the brain in living persons (table 4-l). Computerized axial tomography (CAT), which uses computers to combine a series of x-rays, provides clearer pictures of the brain than x-rays alone. Remarkably clear and detailed images of brain structure are obtained using magnetic resonance imaging (MRI) scans, which detect molecular changes in the brain that occur when an individual is exposed to a strong magnetic field. Abnormalities that can be detected by either CAT or MRI scans include structural brain abnormalities, changes in the volume of brain tissue, and enlargement of the cerebral ventricles.[1] Decreases in the volume of brain tissue and enlargement of the cerebral ventricles indicate either atrophy or underdevelopment of a brain region.

The activity of the brain can also be studied to determine damage or malfunctioning in a region of the brain. Neuropsychologica1 testing seeks to determine brain damage by measuring deficits in a person's performance on various tasks. For example, deficits on tests that measure language performance imply damage to the regions of the brain that subserve language skills, while poor performance on certain types of puzzles indicates abnormalities in regions devoted to various kinds of cognitive and sensory information processing. While neuropsychologica1 testing is helpful in identifying areas of brain pathology, the measures used are indirect, and exact locations of involved regions can only be inferred. However, when combined with more direct methods of looking at the brain, they provide a powerful tool for studying brain function and anatomy.

Measurement of electrical activity in the brain using the electroencephalograph (EEG) provides a more direct indication of brain function, and combining the EEG with computer analysis provides an even more detailed measure. Electrical activity can be measured while subjects are resting or engaging in some sort of sensory or cognitive task. By examining the electrical patterns of the brain, investigators can observe changes in normal brain responses and where they occur. A shortcoming of these measures is that they reflect the cumulative activity of broad areas of the brain, usually near the surface. This makes it more difficult to locate areas of possible pathology.

PET scanning and single-photon-emission computed tomography (SPECT) are imaging techniques that reveal brain activity. They do so by creating computerized images of the distribution of radioactively labeled materials in the brain. Researchers administer labeled materials to a subject either by injection or inhalation. Subsequent distribution of

[1] The cerebral ventricles are spaces in the brain that are filled with cerebrospinal fluid.

Table 4-l—Techniques for Imaging the Brain

Technique	How it works	What it images
Computerized axial tomography (CAT)	Computer construction of x-ray images	Structure
Magnetic resonance imaging (MRI)	Images molecular changes in brain cells when exposed to a strong magnetic field	Structure and activity (when used in conjunction with a magnetically active substance)
Computer analysis of electroencephalogram (EEG)	Creates maps of brain electrical activity by computer analysis of EEG	Activity
Single-photon-emission computed tomography (SPECT)	Creates images of the distribution of radioactively labeled substances in the brain following either injection into the blood or inhalation	Activity (regional cerebral blood flow)
Positron emission tomography (PET)	Creates images of the distribution of radioactively labeled substances following injection into the blood	Activity (regional cerebral blood flow, glucose utilization) and neurochemical activity (receptor number and distribution)

SOURCE: Office of Technology Assessment, 1992.

these materials reflects the activity of the brain. Recently, MRI scanning has also been adapted for this function. PET, SPECT, and MRI enable researchers to measure the utilization of glucose or the amount of blood flowing in a region of the brain (i.e., regional cerebral blood flow). Both glucose utilization and regional cerebral blood flow are indicators of brain activity: The more active a region is, the more blood will flow through it and the more glucose it will use. Abnormal activity levels in specific brain regions, in the whole brain, or in the normal asymmetry of activity between the two sides of the brain can be discerned with these techniques. Also, as previously mentioned, PET scanning can be done following the injection of labeled drugs that attach to specific receptors, making it possible to visualize the number and distribution of receptor populations. As with EEG measures, these scanning techniques can be done either while the subject is at rest or doing a task. While the imaging techniques now being used to study mental disorders will undoubtedly be refined, they provide for the first time a window through which to view the human brain at work.

SCHIZOPHRENIA

The symptoms of schizophrenia reflect a broad range of cognitive and emotional dysfunctions that are commonly categorized as either positive or negative symptoms (see ch. 3). Positive symptoms include hallucinations and delusions, paranoid psychosis, as well as bizarre behaviors and thought disorder. Negative symptoms include emotional flattening (i.e., flat affect), loss of motivation, general loss of interest, and social withdrawal. In some cases, specific alterations in the biochemistry or anatomy of the brain have been associated with either positive or negative symptoms. As with other severe mental disorders, there are many clues available regarding schizophrenia, and a number of hypotheses have been put forward in an attempt to unify this information into an explanation of the underlying pathology.

Biochemistry

Dopamine

The most prominent and enduring theory regarding the biochemistry of schizophrenia concerns the role of the neurotransmitter dopamine. This theory is based on two sets of observations about drug action. First, drugs that increase dopamine activity, such as amphetamine, L-dopa, cocaine, and methylphenidate, sometimes induce a paranoid psychosis in normal individuals that is similar to some aspects of schizophrenia. The same drugs, when administered to patients with schizophrenia, sometimes induce a transitory worsening of symptoms, particularly increasing psychosis and disturbance of thought. Second, and in contrast, drugs that block certain dopamine receptors often ease the symptoms, in particular the positive symptoms, of schizophrenia. In general, there is a close correlation between how well these drugs block dopamine receptors and their antipsychotic effect. The thera-

peutic effectiveness of dopamine-blocking drugs and the ability of dopamine-enhancing drugs to worsen the symptoms of schizophrenia provide evidence for the role of excessive concentrations or transmission of dopamine in at least some aspects of the disorder. Nevertheless, studies that have tried to measure dopamine activity in schizophrenia are less conclusive (81).

The concentrations of certain chemicals (e.g., homovanillic acid, a metabolize of dopamine) can be measured by scientists to provide information about dopamine activity. A number of investigators have measured these chemicals in the tissue and fluids of persons with and without schizophrenia. If higher concentrations of dopamine are associated with schizophrenia, then higher concentrations of these chemicals would be expected in persons with schizophrenia. The results are inconclusive. A review of this research (12) shows that in some studies higher dopamine concentrations were found in persons with schizophrenia; in others no such association was found. Conflicting results have also been found in studies of dopamine receptors, although one subtype of dopamine receptor (the D_2 receptor) may be increased in schizophrenia (12).

Thus, regardless of the index of dopamine activity examined in studies, results are variable. Data supporting the dopamine-excess hypothesis are usually contradicted by data that fail to find differences between persons with schizophrenia and controls. Part of this variability is undoubtedly due to the imprecision of some of the measures used. The use of newer, more sophisticated techniques may resolve some of these contradictions. For example, as previously described, there are a number of dopamine receptor subtypes (see box 4-A). As the ability to study these receptor subtypes improves, alterations in a specific receptor population may become evident. Part of the variability in results may also be due to differences in the characteristics of the patients with schizophrenia studied. Factors such as how long an individual has had the disorder and his or her age when it first appeared can affect findings.

There also is some evidence that dopamine activity may be associated with specific symptoms of schizophrenia. For example, when changes reflecting increased dopamine function are observed, they often occur in patients with prominent positive symptoms, particularly psychosis (12). Other studies support the proposition that dopamine deficiency is associated with the negative symptoms of schizophrenia. For example, a correlation between low levels of dopamine chemicals in cerebrospinal fluid and negative symptoms has been reported (59). In addition, dopamine-blocking drugs used to treat the positive symptoms of schizophrenia produce behaviors suggestive of the negative symptoms in animals and humans free of mental disorders (81,88). Thus, the contradictions between dopamine excess and dopamine deficiency as explanations for schizophrenia can be reconciled by proposing that each is associated with different symptoms of the disease—that is, positive and negative symptoms, respectively (12,60,88)-and that each involves different neural networks (see later discussion). However, these hypotheses are controversial and it is possible that one or both are incorrect. Nonetheless, most scientists agree that dopamine plays some role in schizophrenia.

Other Neurotransmitters

Alterations in the amount or function of other neurotransmitters in persons with schizophrenia have also been examined by researchers. Both increased and decreased levels of serotonin have been postulated as being associated with schizophrenia. The decreased-level hypothesis was based on the effects of LSD (lysergic acid diethylamide), which blocks serotonin activity in the brain and causes effects that are similar to some of the positive symptoms (e.g., hallucinations) seen inpatients with schizophrenia (21). These observations were not supported by other data; in particular, they were contradicted by evidence that some drugs effective against schizophrenia reduce serotonin activity. Also, as with the dopamine hypothesis, measures of serotonin in the blood, cerebrospinal fluid, and postmortem brain tissue do not provide clear answers. Both increased and decreased measures of serotonin and its metabolizes in blood and cerebrospinal fluid have been observed, and results from measures in postmortem brain tissue have been inconclusive (53). Thus, while there is some indication that serotonin activity may be altered in schizophrenia, the exact nature of its involvement is unclear.

Both an excess and a deficiency in the activity of the neurotransmitter norepinephrine have been associated with schizophrenia, although data indicate that an excess of norepinephrine is more likely to produce symptoms (80,90). Increased norepineph-

rine has been observed in the cerebrospinal fluid and blood of patients with schizophrenia (21,82). Since dopamine and norepinephrine have complex interactions, namely, that disturbances in one affect the other, it is unclear whether any observed increase in norepinephrine is primary to schizophrenia or secondary to changes in the dopamine system (53).

These neurotransmitters interact with and modulate the activity of many other neurotransmitter and neuropeptide systems; awareness of this fact has led to the study of these chemicals in schizophrenia. The opiate peptides are thought to affect dopamine neurons, and naloxone, a drug that blocks opiate receptors, may have antipsychotic properties (53). In addition, there have been findings relating other peptides to schizophrenia (53). Since alterations in such neuropeptides could facilitate, inhibit, or otherwise alter the pattern of activity of other nerve cells, further study of the status of peptides in schizophrenia is warranted.

Finally, a more specific neurotransmitter hypothesis involves the action of the drug phencyclidine (PCP) (31). PCP can produce symptoms that resemble both the positive and the negative symptoms of schizophrenia and can exacerbate these symptoms in people with the disorder. It is thought that PCP produces these dual effects by acting at different sites in the brain (21). PCP inhibits the activity of the excitatory neurotransmitter glutamate by interfering with the receptor for glutamate. From that observation, it has been speculated that inhibition of the glutamate receptor in the hippocampus results in the negative symptoms associated with schizophrenia (21). PCP also weakly blocks the reuptake of dopamine, and in other areas of the limbic system there is some evidence that PCP inhibition of glutamate secondarily causes an increase in dopamine activity. These effects on dopamine could result in the positive symptoms of schizophrenia. In both instances, there is implicit involvement of glutamate in the onset of symptoms of schizophrenia. While there is currently little experimental evidence to support this hypothesis, it represents a new avenue of investigation in schizophrenia research.

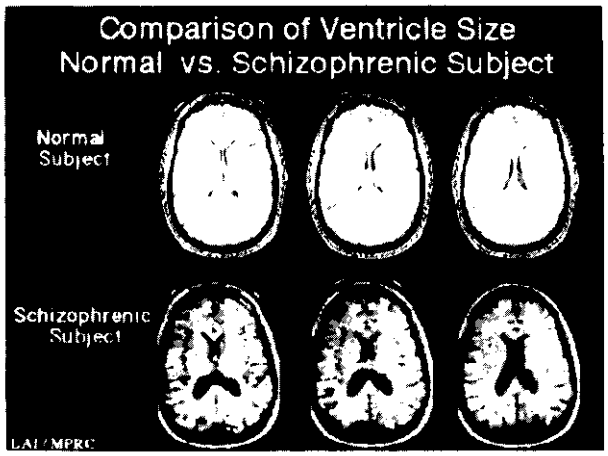
Thus, while it is likely that dopamine plays some role in schizophrenia, the involvement of other neurotransmitters is unclear. Since brain neurotransmitter systems interact with each other, it is often difficult to isolate a cause-effect relationship. The modulatory action that neurotransmitters exert suggests that there may be complex interactions in schizophrenia between dopamine systems and these other brain chemicals.

Anatomy and Activity

Alterations in a number of brain structures, notably the frontal cortex and limbic system, have been implicated in schizophrenia. In particular, ventricular enlargement and evidence of changes in the size of various brain regions have been observed in imaging studies and postmortem examinations (figure 4-4). Limbic structures, such as the hippocampus and parts of the temporal lobes, are most affected. However, the specificity of these findings for schizophrenia has been questioned because they also occur in normal aging and in a variety of other neurological and psychiatric conditions (10, 21).

Attempts to replicate these findings have yielded contradictory results. In some cases, evidence of changes in the volume of the frontal cortex and temporal lobes has been observed, but the data are not conclusive and additional studies are needed to confirm the results (10). Some PET studies have examined brain metabolism in schizophrenia and have observed decreased activity in the frontal cortex and limbic structures, as well as increased

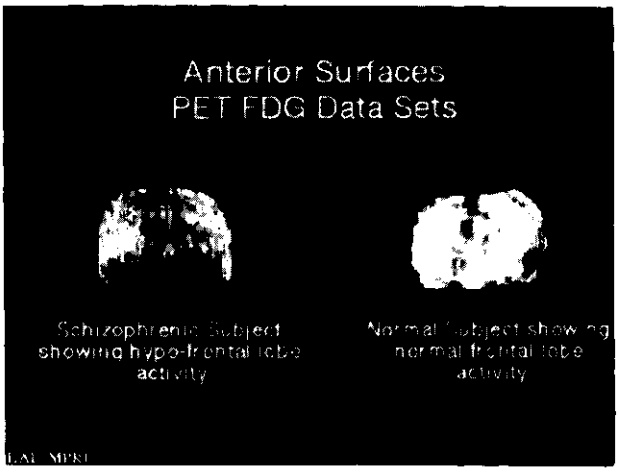
Figure 4-4—MRI Scan of an Individual With Schizophrenia



Brain structure shown of individual who does not have schizophrenia (top) and a person who does (bottom). The ventricles are enlarged in schizophrenia (black areas).

SOURCE: W. Carpenter, Maryland Psychiatric Research Center, and H. Loats, I_Oats Associates, Inc.

Figure 4-5-PET Scan of an Individual With Schizophrenia



Brain activity in an individual who does not have schizophrenia (right) and a person who does (left). The frontal cortex shows more activity in schizophrenia (white areas).

SOURGE: W. Carpenter, Maryland Psychiatric Research Center, and H. Loats, Loats Associates, Inc.

activity in the basal ganglia (10,21) (figure 4-5). In general, these studies indicate that decreased frontal cortex activity is associated with the negative symptoms of schizophrenia. This coincides with data from animal studies, which indicate that damage to the frontal lobes produces behaviors similar to the negative symptoms.

EEG studies that show a higher incidence of abnormal electrical activity in the brain of patients with schizophrenia than in normal subjects provide further evidence of the involvement of the frontal cortex. These abnormalities often appear in the temporal lobe as well. Impairments on neuropsychological tests, such as problem-solving and attention deficits, also indicate that these structures are affected in schizophrenia (34,39). For example, 65 percent of patients with schizophrenia often have difficulty visually following a moving object, compared to 8 percent of subjects who do not have schizophrenia (21) (see ch. 5). It is thought that defects in maintaining attention, as a result of a dysfunction in the frontal lobes and limbic system, contribute to these visual task defects.

These data have led to a number of hypotheses that attempt to unify the information regarding brain structures implicated in schizophrenia. In particular, these theories assign important functions to the limbic system and frontal cortex. The limbic system is integral to motivation, gratification, memory, and many other emotions and thought-processes whose disturbance is associated with psychosis and the other positive symptoms of schizophrenia. The frontal cortex has been implicated in the negative symptoms of schizophrenia. The proposed theories differ as to whether the two sets of dysfunctions should be viewed as dependent or independent and in the specific structures presumed to be involved.

One theory postulates that they are dependent and that an insult during the development of the brain that affected the functioning of the frontal cortex (see later discussion) can lead to negative symptoms (84). Since the frontal cortex and limbic system are interconnected, with the frontal cortex inhibiting activity in the limbic system, this theory posits that the dysfunction of the frontal cortex reduces the inhibition on the Iimbic system, leading to the positive symptoms.

Another theory suggests that positive and negative symptoms are mediated by two different networks within the frontal cortex and limbic system and that dysfunction in one of these networks is separate from dysfunction in the other (9). This coincides with data from PET studies which show that negative symptoms are only correlated with decreased activity in the frontal cortex.

A third theory implicates a disruption in the activity of the basal ganglia and its interaction with other brain structures (16,17). This theory is based on three experimental findings: First, there is increased metabolic activity in the basal ganglia of patients with schizophrenia; second, patients with schizophrenia have difficulty performing visual attention tasks, which are mediated by areas of the cortex; and third, animals with lesions in dopamine-containing areas of the brain that project to the basal ganglia display some of the behavioral impairments seen in schizophrenia. This evidence has led to the hypothesis that schizophrenia is related to impaired activity in a network composed of the basal ganglia, certain cortical areas, and other brain structures and that the impairment is secondary to decreased dopamine activity.

These hypotheses attempt to find a basis for the disturbed behaviors observed in schizophrenia; they are overlapping and not always mutually exclusive. The available data point to networks involving certain limbic structures in psychosis and networks involving the frontal cortex in negative symptoms.

The precise interaction between these networks and the possible involvement of other brain structures and areas still need to be clarified. Based on these theories, predictions (which can themselves be tested with additional studies) can be made about the involvement of various areas of the brain in schizophrenia.

Other Factors

Immune and Viral Factors

Viral theories for the cause of schizophrenia are derived from reports that a number of viral and immune indices, such as the number and function of immune system cells, are deviant inpatients with the disorder (13,32,83). Also, there is some epidemiological evidence to support a viral hypothesis. Schizophrenia may have a north-to-south prevalence gradient, may be endemic in a few areas (e.g., northern Sweden), and occurs somewhat more often in persons born in the winter. It has also been observed that fetuses in the second trimester of gestation during an influenza epidemic have an increased risk of developing schizophrenia as adults. However, it has been difficult to conduct definitive studies, since any potential marker of an immune or viral process associated with schizophrenia is applicable in only some cases and is subject to interpretation as secondary to conditions associated with the disease (e.g., crowding of hospitalized patients, exposure of individuals living in low socioeconomic circumstances, and poor health habits).

Developmental Factors

The observed changes in brain volume of persons with schizophrenia, and the cellular alterations that accompany these changes, are thought to be irreversible but not progressive (54). Current information suggests that the magnitude and nature of anatomical and morphological changes in schizophrenia are present at the onset of the disorder and do not vary over the lifetime of an individual. A possibility is that these abnormalities reflect changes that occurred very early in life or in utero, either as the result of some specific damage or a pathological alteration in the normal development of the brain.

Evidence that developmental factors may play a role derives from the observation that infants born after a complicated pregnancy or labor are at increased risk for developing schizophrenia as adults (41,42). One mechanism by which gestational or birth complications may alter brain development is diminished oxygen supply (i.e., hypoxia). This theory is attractive for two reasons. First, many pregnancy and birth complications are associated with temporary hypoxia. Second, limbic structures, especially the hippocampus, are among the most sensitive areas in the developing brain to the adverse consequences of hypoxia. Also, subtle deviations in neurological and psychological functioning have been observed from infancy in children who are at high risk of developing schizophrenia (11). Although far from established, it is possible that early, adverse gestational influences on the developing brain create a risk of both birth complications and, later, schizophrenia. A corollary to this proposition is that a pathological influence operating early in gestation alters the development of the brain to create subsequent vulnerability to schizophrenia. An intriguing possible instance of this proposition is the relationship, discussed earlier, between pregnancy during influenza epidemics and the development of schizophrenia.

What specific alterations in the brain may result from such insults is unknown; however, it is clear that subtle deviations in the development of the brain could create dysfunctions associated with specific behaviors. Furthermore, it is possible that such subtle brain abnormalities are not manifest until much later in life, when new demands are placed on the brain systems during adolescence and adulthood. Postmortem findings of abnormalities in the number and organization of some nerve cells (1,37) suggest that the developmental process of cell migration, by which the cells in the brain become organized into the normal pattern of neuronal networks, may have gone awry in schizophrenia. Altered cell migration could be a genetic result, might be caused by gestational insults, or might involve an interaction of both. Another process that might be involved is the pruning of nerve cells that occurs as the brain develops (18). During early development, the brain has more neurons than it needs; the fine-tuning necessary for efficient functioning involves eliminating certain nerve cells and many of the synapses connecting cells. Failure to prune nerve cells and synapses adequately, or an error in selecting which ones to prune, could underlie dysfunctions that lead to the manifestation of the symptoms of schizophrenia. Whatever developmental processes play a role in schizophrenia is still an open question.

Synthesis

Although various alterations in the biochemistry, anatomy, and activity of the brain have been observed in schizophrenia, there are several important points regarding these data (21). The high variability among patients on any one of the biological factors and the lack of agreement among studies about many of them suggest that schizophrenia is a heterogeneous disorder, with patients exhibiting different clusters of symptoms. This variability could also reflect the effects of other factors, such as psychosocial variables, on the biological components. The fact that some of the biological abnormalities observed in schizophrenia are also seen in other conditions calls into question their specificity to, and their role in, schizophrenia.

Despite the equivocal nature of the research findings, conclusions can still be drawn from them. Dopamine plays a role in at least some of the symptoms of schizophrenia; however, the characteristics of that involvement are unclear, and dopamine's precise relationship to the positive and negative symptoms of schizophrenia remains to be elucidated. The role of other neurotransmitters in schizophrenia, and if and how they interact with dopamine systems, needs to be clarified. Given the cognitive and emotional functions governed by the frontal cortex and limbic system, it is not surprising that alterations in these regions have been implicated in schizophrenia. Abnormal functioning of the frontal lobes has been one of the most consistent findings in schizophrenia, and, while less well documented, there does seem to be a relationship between decreased frontal cortex activity and negative symptoms. Positive symptoms appear to be associated with increased metabolic activity in the limbic system.

While completed studies furnish valuable information regarding what might be wrong in the brain of a person with schizophrenia, the question of why schizophrenia occurs remains unanswered. The role of abnormal brain development or an injury to the brain, either during development or early in life, is an important avenue of investigation. As with other factors associated with schizophrenia, the precise mechanisms that may be involved are subject to speculation. The interaction of such a precipitating event with genetic factors (see ch. 5) is another plausible cause.

MOOD DISORDERS

Mood disorders include major depression and bipolar disorder. As the name indicates, major depression is marked by a deep depression that can be unremitting. Bipolar disorders are characterized by periods of depression alternating with manic episodes. Sadness is a normal human emotion in response to various life events, but depression that has no known cause or unremitting depression that interferes with normal activity is pathological. Available data regarding the role of biological factors in major depression and bipolar disorder often overlap. This reflects the fact that these disorders may be closely linked. The depressed state may be mediated by the same brain regions in both conditions. However, different brain mechanisms may be involved in the manic state and the swing from depression to mania that is characteristic of bipolar disorder.

Biochemistry

Neurotransmitter Systems

Prominent hypotheses concerning depression have focused on altered function of the group of neurotransmitters called monoamine (i.e., norepinephrine, epinephrine, serotonin, dopamine), particularly norepinephrine (NE) and serotonin (25,51,70). Evidence that monoamines are involved comes from the knowledge of the mechanism of action of the two classes of clinically effective antidepressant medications—tricyclic antidepressants and monoamine oxidase inhibitors (MAOIS). Tricyclic antidepressants block the reuptake of neurotransmitters, and MAOIs block the action of monoamine oxidase, the enzyme involved in the chemical breakdown of the monoamine transmitters once they are released into the synapse. The net effect of both of these types of drugs is to prolong the activity of these neurotransmitters in the synapse.

In the 1960s, the clinical observation that patients who were taking a norepinephrine-blocking drug for high blood pressure developed depression led to the hypothesis that depression was the result of low concentrations of monoamine, in particular NE (25). Some experiments have shown that patients with bipolar disorder have decreased NE metabolizes during depression and increased amounts during mania, which supports the NE imbalance hypothesis; other studies, however, have shown that patients

Box 4-B—Serotonin and Suicide

More than 30,000 Americans commit suicide each year, making it the eighth leading cause of death in the Nation. It is the second leading cause of death among adolescents. Changes in a number of indices of serotonin activity are correlated with suicide attempts and suicide completions. Suicidal behavior is associated with decreased concentrations of serotonin and its metabolizes in cerebrospinal fluid and the brain. Among successful suicides, decreased concentrations are usually found in the brainstem, where the raphe nuclei, the major serotonin-containing nuclei in the brain, are located. Also, increased numbers of serotonin receptors have been observed in the brains of suicide victims, usually in the frontal cortex. Since certain frontal cortex neurons receive connections from those of the raphe nuclei, it is possible that the receptor increase is a compensatory response to decreased serotonin activity in the raphe neurons. A decrease in the number of serotonin autoreceptors in suicide victims has been reported in some studies. Finally, suicide attempters, as compared to nonattempters, show decreased release of the hormone prolactin following administration of a serotonin-stimulating drug. This blunted prolactin response is indicative of a low level of serotonin activity. These data indicate that a net decrease in serotonin activity in the brain is associated with suicidal behavior.

These data do not mean that decreased serotonin causes a person to commit suicide. First of all, not every suicide victim exhibits decreased serotonin. For example, serotonin metabolize concentrations are not reduced in individuals with bipolar disorder who attempt suicide, compared to individuals with bipolar disorder who do not attempt suicide. Also, there is some evidence that among suicide attempters, measures of decreased serotonin activity correlate with the lethality of the method us@ that is, the more violent the attempted suicide method (e.g., cutting arteries v. drug overdose), the more depressed the serotonin activity. In addition, some of these same measures of serotonin activity, such as low levels of serotonin metabolizes in the cerebrospinal fluid and blunted response to prolactin, can be observed in individuals who exhibit impulsive and aggressive behavior. This suggests that, rather than causing suicide, decreased serotonin activity is correlated with a behavioral predisposition that can lead to suicide. If individuals who are burdened with feelings of despondency also have depressed serotonin activity, the propensity for aggression may be directed internally, tragically resulting in a successful suicide attempt.

SOURCES: E.F. Coccaro and J.L. Astill, ''Central Serotonergic Function in Parasuicide,' *Progress in Neuro-Psychop harmacology & Biological Psychiatry 14:663-674,* 1990; K.Y. Little and D.L. Sparks, "Brain Markers and Suicide: Can a Relationship Be Found?" *Journal of Forensic Sciences* 35:1393-1403, 1990; J.J. Mann, V. Arango, M.D. Underwood, *et* al., "Neurochemical correlates of suicidal Behavior Involv ement of Serotonergic and Non-Serotonergic Systems," *Pharmacology and Toxicology* 3:37-60, 1990; J.J. Mann, V. Arango, and M.D. Underwood, ' 'Serotonin and Behavior, ''Annals *of the New York Academy of Sciences* 60&476-484, 1990; L.C. Ricci and M.M. Wellman, ''Monoamines: Biochemical Markers of Suicide?" *Journal of Clinical Psychology 46:106-116,* 1990.

with major depression exhibit increased concentrations of NE metabolizes (51,70).

As more information has been gathered, it has become clear that the chemistry of depression is more complex and that other neurotransmitters, especially serotonin, maybe involved. For example, fluoxetine, a highly effective antidepressant drug that is widely prescribed, acts exclusively on serotonin.

Although the results from studies of serotonin metabolizes are not conclusive, there is some indication that concentrations of serotonin are decreased in mood disorders (25). Also, low concentrations of serotonin metabolizes have been observed in people who commit suicide (box 4-B). As a result of these findings, it has been hypothesized that decreased serotonin plays a role in mood disorders (25,46). In addition, decreased dopamine metabolizes have been observed in some, but not all, studies of depression.

One fact that argues against the monoamine imbalance hypothesis is the time lag between administration of antidepressant medications and their clinical effect. These medications increase neurotransmitter levels almost immediately upon administration, but their therapeutic effects often do not appear until 2 or 3 weeks after initiation of drug therapy. This time lag has led to the suggestion that the receptors for monoamines may be involved—specifically, that the clinical effects of these drugs are due to reductions in the number of receptors to compensate for the drug-induced increased levels of monoamine neurotransmitters. It would take weeks for such compensatory changes to come about.

One hypothesis related to drug-induced changes in receptors involves a receptor for NE (25). There

are **a** number of NE receptor subtypes. One is an autoreceptor that decreases the release of NE into the synapse when it is activated. It has been hypothesized that these NE autoreceptors are overly active in depression. The therapeutic effects of antidepressant drugs are the result of exposing the autoreceptors to higher concentrations of neurotransmitter, which decreases their number, ultimately increasing the activity of the NE-containing neurons. While this hypothesis would explain the delayed appearance of clinical effects of antidepressant dregs, studies of the NE autoreceptor in depression have found no specific evidence of an abnormality to date.

Currently, no clear evidence links abnormal serotonin receptor activity in the brain to depression (51). Increased receptors for serotonin have been observed in the brains of suicide victims (box 4-B), but there are conflicting results from studies that have examined serotonin receptors in depressed persons (25). Changes in serotonin receptor activity have been measured indirectly in mood disorders, notably bipolar disorder, using blood platelets (a type of cell found in the blood) which also contain serotonin and are used to investigate mechanisms related to serotonin and its receptors (46). Both increased numbers of a subtype of serotonin receptor and decreased sites for the reuptake of serotonin into the platelets have been seen in the platelets of persons with depression (46). However, it is unclear how these changes relate to serotonin activity in the brain of persons with major depression and bipolar disorder.

While there is sufficient evidence to support the notion that abnormalities in monoamine systems are an important component of depression, the data currently available do not provide consistent evidence either for altered neurotransmitter levels or for disruption of normal receptor activity. This has led to a dysregulation hypothesis, which states that there is a more general perturbation in the mechanisms that regulate the activity of the monoamine neurotransmitters and that clinically effective drugs restore efficient regulation (70). Linked to this hypothesis is the fact that the monoamine systems interact with each other-the activity of one affects and modulates the activity of another. Based on available data, it has been proposed that decreased activity within the NE-serotonin component of the system is associated with depression, while increased activity of the NE-dopamine component tends to promote mania (25).

Complicating the picture is the fact that other neurotransmitters have been implicated in bipolar disorder. Based on evidence that agents which activate acetylcholine systems can induce depression and that agents which block such activity have some ability to alleviate depression (51), it has been postulated that increased acetylcholine activity induces depression and decreased activity induces mania (15,25,30,70). Furthermore, a number of investigators have proposed that the salient mechanism may be the balance between NE and acetylcholine systems, with a predominance of acetylcholine activity associated with depression and a predominance of NE activity associated with mania (25,28,51,70). A role for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has also been put forth, based on the paradoxical finding that increased GABA activity has both an antidepressant and an antimanic effect (25,40,51). Given that GABA is a ubiquitous inhibitory neurotransmitter, it is possible that increasing its activity can result in the modulation of a number of other neurotransmitter systems, which could explain its broad range of effects. Finally, there is evidence that some neuropeptides may also be involved in mood disorders (6,23,25). In particular, decreased levels of somatostatin and increased levels of corticotropin-releasing factor are associated with depression.

Thus, a number of neurotransmitters have been implicated in mood disorders, with NE and serotonin being the most prominent. Lithium is the most effective drug for the treatment of mania and for controlling the mood swings between depression and mania that characterize bipolar disorder. It is not known how lithium affects the activity of neurons, but like many other chemicals that are important to normal brain functioning, lithium is an ion—that is, a molecule that has an electrical charge. It is thought that, whatever its action on neurons, lithium has many different effects in the brain (8). It increases serotonin activity, decreases acetylcholine activity, affects the activity of both norepinephrine and dopamine, and inhibits some of the intracellular mechanisms that are initiated by activation of receptors. Since lithium has such a broad range of actions that can affect the neurotransmitter systems implicated in mood disorders, its therapeutic effect may be due to its capacity to correct the neurotransmitter abnormalities associated with mania and depression, and to prevent the changes in neuro-

chemical balance that are thought to be responsible for the mood swings of bipolar disorder.

Neuroendocrine Systems

Abnormalities in hormone regulation are common in depression (7,25,70,71), perhaps because regulation of hormones and the glands that secrete them is under the control of the same neurotransmitters in the brain that are thought to be dysfunctional in depression. In particular, the activities of the pituitary, adrenal, and pineal glands are affected. Many of the symptoms associated with depression (e.g., changes in appetite, sleep, and sex drive) may be related to these hormonal changes, which means that the hormonal abnormalities may be secondary to the neurotransmitter alterations of the disorder (7). Nonetheless, there is great interest in studying these changes in hopes of discovering a biological marker and developing diagnostic tests for depression.

A number of hormones have been studied to determine if depressed persons consistently exhibit abnormal concentrations of them or show an abnormal release of them in response to some sort of pharmacological challenge. Current information indicates that while some of these hormones are altered in depression, variability in baselines and pharmacological response, as well as the possibility of changes due to other causes, makes them unreliable markers for depression (7,70,71).

Depressed persons often have elevated concentrations of the hormone cortisol (7,25,70,71), which results from increased concentrations of corticotropin-releasing factor. In healthy individuals, administration of the drug dexamethasone suppresses the concentration of cortisol in the blood. The dexamethasone-suppression test (DST), developed as a test of hormone functioning, has been studied as a possible diagnostic tool in depression. Approximately 40 to 50 percent of persons diagnosed with major depression have an abnormal DST in that they do not suppress cortisol in response to dexamethasone (70). In very severe cases, particularly psychotically depressed patients, the percentage ranges from 60 to 80. It is not known why only some patients show an abnormal DST. Whether this reflects variability in response to DST or a subpopulation of depressed patients has yet to be resolved. Therefore, there are several problems with using the DST as a diagnostic tool (7,25,70,71). Aside from the fact that not all depressed patients show an abnormal DST, a number of other clinical (e.g., Alzheimer's disease, anorexia nervosa) and nonclinical conditions (e.g., fasting, ingestion of caffeine) can result in abnormal DSTs. Although its effectiveness as a diagnostic tool is limited, the test maybe useful in predicting which patients are likely to relapse following cessation of drug therapy: If DST results remain abnormal during therapy, the patient is more likely to relapse once the antidepressant is withdrawn (7).

Another aspect of endocrine function related to depression is the association between depression and reproduction-related events in women (2). Hormonal alterations related to menstruation, pregnancy, childbirth, and menopause can affect neurotransmitters that regulate mood and behavior. The evidence regarding the relationship between these hormonal fluctuations and the occurrence of depression is mixed. Nevertheless, the clear association of mood alterations with these reproductive events in some women suggests an area for additional investigation. Understanding these biochemical interactions could provide new insights into the pathology of depression.

Anatomy and Activity

It is unclear which areas of the brain may be involved in mood disorders. The data regarding anatomical defects and activity in the brain of persons with mood disorders are equivocal. Given that few studies have been conducted and that their results have varied, it is impossible to come to any conclusions regarding relationships between the data and the cause and symptoms of mood disorders. Overall, the data suggest an association between mood disorders and abnormalities of large regions of the brain, especially the frontal and temporal lobes; they also imply an abnormal difference between the left and right sides of the brain. Normally, the left and right sides of the brain are involved in different, although overlapping, functions. For example, the left is usually more specialized for language and logical thinking, while the right is more involved with spatial processing. As a result of these different functions, the two halves of the brain often exhibit different levels of activity. In mood disorders, some of the normal differences in activity level between the right and left sides of the brain appear to be altered.

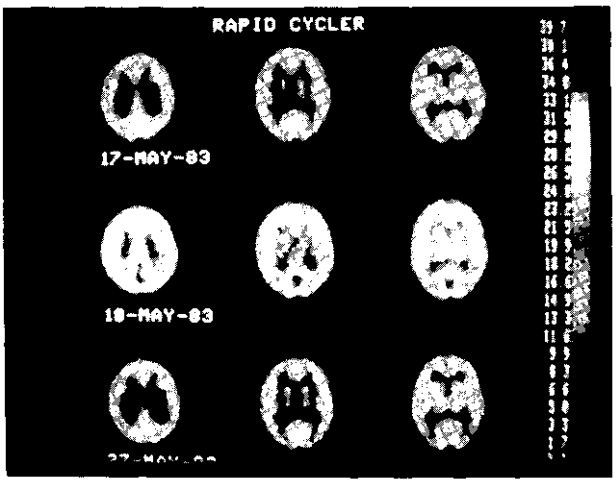
Few postmortem studies have investigated anatomical alterations in the brains of persons with mood disorders, although a number of studies have

examined depression and mania that are secondary to other insults to the brain (e.g., tumors, stroke, wounds) (25). Often, the trauma-induced alteration in mood occurs as a single episode of either depression or mania; there are only a few reports of bipolar disorder occurring as a result of brain damage. Although the secondary nature of the disorders severely limits the usefulness of these studies, some anatomical patterns can be discerned. In general, depression and mania are associated with damage to the frontal and temporal lobes of the brain, while bipolar disorders are associated with diverse areas of the brain. Depression tends to be associated with damage to the left side of the brain and mania with damage to the right (25).

Additional information has been derived from studies using CAT and MRI scans (25). While not conclusive, data from CAT scans indicate that patients with mood disorders, especially bipolar disorder, have decreased cortical volume. The clinical features most frequently correlated with decreased cortical volume are psychotic symptoms and poor response to treatment. The few MRI studies of persons with bipolar disorder indicate that there may be some structural abnormalities present, especially in the frontal and temporal lobes (25).

Studies measuring cerebral blood flow and glucose utilization have also produced some evidence of abnormal activity in mood disorders (25,85) (figure 4-6). The available data suggest that persons with bipolar disorder, as well as persons with major depression, show decreased activity in a specific portion of the frontal lobes called the prefrontal cortex; persons with bipolar disorder also show a more general decrease in activity involving the whole cortex and the left frontal lobes (25). Thus, these studies implicate the left side of the brain. However, results of studies using neuropsychological testing and observations of electrical activity in the brain caused by performing a task implicate a deficit in the right side (25,74,86). Neuropsychological testing consistently finds deficits in tasks related to right-hemisphere functioning, such as spatial learning and memory, among persons with mood disorders (25). The imaging data, which are consistent with the postmortem studies, are from studies of the brain in its resting state, whereas the neuropsychological testing and electrophysiological studies measured the active functioning of the brain in response to a task. It is unclear whether the divergence in observations represents discrete abnormalities that are detected selectively by the different methods. Additional data need to be collected, using imaging techniques in conjunction with performance tasks, to clarify this issue and to determine the significance of these differences in activity on the two sides of the brain.

Figure 4-&PET Scans of an Individual With Bipolar Disorder



Brain activity in a person when depressed (top and bottom rows) and when in the manic state (middle row).

SOURCE: L. Baxter, M. Phelps, J. Mazziotta, et al., "Cerebral Metabolic Rates for Glucose in Mood Disorders: Studies With Positron Emission Tomography and Fluorodeoxyglucose F1 8," *Archives of Genera/ Psychiatry* 42:441-447, *1985* (copyright 1985 © American Medical Association).

Other Factors

Sleep and Biological Rhythms

Sleep disturbances are common in persons with major depression (25,38,68,70) and, like the alterations in endocrine function discussed earlier, are likely to be secondary to a primary pathology. Sleep consists of rapid eye movement (REM) sleep (the time during which dreaming takes place) and non-REM sleep. Both REM and non-REM sleep can be monitored with the EEG. In the course of a night, REM and non-REM sleep cycle approximately every 90 minutes. In depression, the first REM period occurs earlier than normal after sleep begins, the time spent in REM sleep is increased, and the length of non-REM sleep decreases. In 80 to 85 percent of depressed persons, sleep is broken by frequent awakenings, while the remaining percentage show features of hypersomnia. It has been suggested that depressed persons can be differentiated from other individuals on the basis of the

abnormalities in REM sleep (70). The early occurrence of REM sleep has been repeatedly demonstrated in depression. Based on these observations, it has been suggested that shortened REM latency, and possibly other REM sleep measures, can be used to diagnose depression (70); others question the specificity of these changes to depression (25).

The sleep of persons with bipolar disorder is often disturbed and varies with clinical state, severity, and stage of the disorder (25). When depressed, bipolar patients may sleep excessively, and when manic, may sleep little or not at all. Sleep can also influence the switch from one phase to another. Sleep loss often precedes, and may trigger, a manic episode. Also, one or two nights of sleep deprivation can have a short-term antidepressant effect (25,79). This evidence indicates that in some cases mania can be prevented and depression treated by appropriate manipulation of the sleep-wake cycle (25).

The sleep cycles previously described are an example of a biological rhythm. The preceding report in the Office of Technology Assessment's neuroscience series (79) describes and discusses biological rhythms-the changes in various physiological and behavioral functions that repeat at regular intervals and provide a framework of temporal organization for those functions-and their effects. and consequences. While sleep stages are measured in minutes, many biological rhythms (e.g., body temperature, secretion of hormones, sleep-wake cycle, alertness, memory) have a 24-hour cycle and are called circadian rhythms. For example, body temperature fluctuates over 24 hours, with peak body temperature occurring during the day and lowest body temperature occurring at night.

The cyclic pattern of bipolar disorder and the fact that people with depression exhibit daily and seasonal fluctuations in mood suggest a link between mood disorders and biological rhythms. Whether that link is causative or correlative is unknown (79). Changes in biological rhythms have been observed in some persons with mood disorders (25,72). The fact that animal studies have indicated that some antidepressant medications have an effect on the organization of circadian rhythms provides a further link between mood disorders and biological rhythms. Finally, a seasonal variation in the occurrence of depression has been observed. A specific syndrome of winter depression, which remits during the summer, has been identified and named seasonal affective disorder (SAD). Although it is not clear whether SAD is associated with altered biological rhythms, it is related to changes in the length of daylight across the seasons. Exposure to additional light during the winter is an effective treatment for SAD.

Kindling and Sensitization

Recurrences of mania and depression in bipolar disorder tend to increase in frequency overtime. The neurobiological phenomena of electrical kindling and behavioral sensitization observed in animals may provide clues to the physiological mechanisms underlying this pattern of cycling (25). Repeated administration of low-level electrical stimulation to an area of the brain results in kindling, or increased responsiveness to electrical stimulus that leads to the development of seizures. If the stimulation is repeated frequently enough, the area becomes so sensitive that seizures will occur spontaneously. Similarly, behavioral sensitization refers to the increasing behavioral response that results from repeated administration of the same dose of a stimulant drug.

While these phenomena are not directly analogous to the mood disturbances of bipolar disorder, they do share certain characteristics (62). For example, in each, early episodes require a precipitating event, while later ones can occur spontaneously. Also, repeated exposure to precipitating events leads to more frequent occurrence of episodes. These characteristics coincide with the concept that early episodes of mania or depression result from some sort of psychosocial stress but later episodes can occur in the absence of such a stimulus, and with the observation that episodes tend to occur with a shorter and shorter cycle.

Thus, the same or similar brain mechanisms controlling kindling and sensitization could play a role in the cycling of bipolar disorder. Some evidence for this is seen in the fact that serotonin, norepinephrine, and GABA, neurotransmitters implicated in mood disorders, all inhibit the kindling phenomenon (25). Also, lithium, which is efficacious in treating bipolar disorder, blocks behavioral sensitization, while carbamazepine, an antiseizure medication that is also effective in bipolar disorder, blocks kindling.

Immune and Viral Factors

Results from some studies have raised the possibility that mood disorders may be associated with abnormalities in the body's immune system or with viral infection (25). For example, some studies indicate that persons with major depression may have a compromised immune system, as indicated by their diminished response to infectious challenges. Also, some studies have found increased antibodies to certain viruses that infect the nervous system (i.e., cytomegalovirus, herpes, and Borna disease virus) in some persons with mood disorders. Thus, there is limited evidence that immune system dysfunction or viral infection may be associated with mood disorders in some persons, although the available data are far from conclusive. If such associations exist, it is unclear what relationship they may have to the onset and symptoms of the disorder.

Synthesis

There are many disparate pieces to the puzzle of mood disorders, and fitting the available ones together is difficult. Early theories that depression and bipolar disorder are the result of a simple imbalance in norepinephrine or that a specific anatomical locus could be identified are now recognized as simplistic. Clinically effective drugs have shown that adjusting the activity in monoamine-containing regions of the brain has an antidepressant effect. Whether this indicates there is a primary dysfunction in these regions in depression has yet to be proved. The implications of the other factors described in this section are also unclear.

An approach that encompasses the diversity of experimental data and is at the same time harmonious with the clinical profile of the disorders is needed in order to construct a meaningful hypothesis. As discussed in chapter 3, it is unclear whether depression is a single disorder or a collection of disorders. This possible heterogeneity complicates attempts to delineate biological factors that might be involved. It is likely that the same regions of the brain mediate depression in both major depression and bipolar disorder. If separate subtypes of depression exist, this same network of structures is likely to be involved; what differentiates the disorders may be the factors that disrupt the network. This idea coincides with information suggesting that mood disorders occur because integrated control systems in the brain are disrupted, rather than because of defects in specific regions. The explanations that there is an overall dysregulation in the balance between the different monoamine neurotransmitter systems and that the brain mechanisms which control biological rhythms may be involved in mood disorders are examples of hypotheses involving disruptions of integrated control systems. As more information is gathered about these and other systems, researchers will gain a clearer understanding of how they maybe disrupted in mood disorders.

ANXIETY DISORDERS

Anxiety is a normal human emotion that can help people cope with certain situations. It is only when anxiety or its manifestations become excessive and interfere with normal performance or health that they are considered pathological and termed a disorder (see ch. 3). Anxiety disorders include generalized anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), social and simple phobias, and posttraumatic stress disorder (PTSD). This discussion will be limited to the disorders in which biological factors have been most extensively studied, namely, OCD and panic disorder.

Obsessive-Compulsive Disorder

Idiosyncratic daily rituals and odd personal habits are ubiquitous. It is only when obsessions or compulsions, or both, cause marked distress, occupy more than 1 hour a day, and cause significant social or occupational dysfunction that the diagnosis of OCD is made (63) (see ch. 3). OCD is commonly accompanied by depression. Symptoms include recurrent obsessions with fears of contamination, harming others, and worries that doors are not locked or lights have not been turned off. Compulsions such as washing, checking, counting, and rearranging are common. Though most patients know that these thoughts and behaviors are irrational, they cannot put them out of their mind. The involuntary, repetitive nature of the cognitive or motor behaviors associated with OCD, coupled with recent experimental findings, suggests a role for biological factors in OCD.

Biochemistry

Drugs that are effective in treating OCD act by blocking the reuptake of serotonin into the neuron from which it was released (49,50,87). Not all persons with OCD respond to these drugs (91),

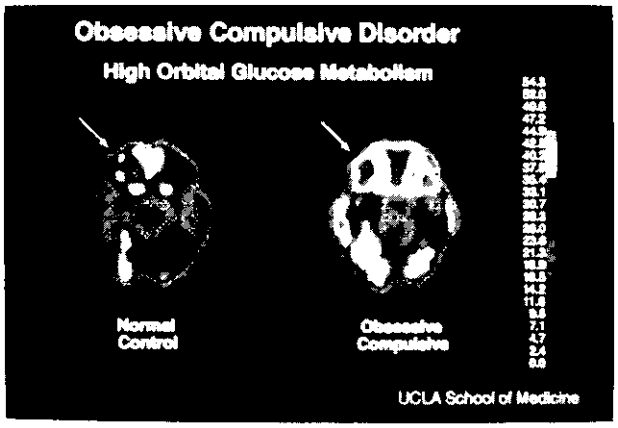
however, and it is unclear whether these persons represent a subgroup of patients with OCD (91). The potency of drugs that block serotonin reuptake suggests that persons who do respond may have abnormal serotonin functioning, but supporting evidence is meager. Like other neurotransmitter systems, the serotonin system is complex. Serotonin is found in a number of specific areas of the brain, and several receptor subtypes have been identified. While a few studies have shown that drugs that block serotonin receptors can exacerbate OCD symptoms, no abnormalities in the synthesis, release, reuptake, metabolism, or receptors of serotonin in patients with OCD have been identified in other studies (87). Also, while the reuptake-blocking effects of drugs occur immediately, the therapeutic response usually does not develop until after several weeks of treatment (24,87). This delay suggests that the clinical effect could be the result of adaptive changes in the serotonin or other neurotransmitter systems in response to the changes in serotonin levels induced by the drugs (87). Thus, it is not certain whether these drugs act directly on a primary defect of the disorder or whether they act indirectly, via the serotonin system, to counteract the effects of a primary defect.

It has also been proposed that dopamine systems play a role in OCD (24). Symptoms of OCD sometimes result from damage to the basal ganglia, which have high concentrations of dopamine. Tourette's syndrome, a disorder characterized by motor and vocal tics, and often symptoms of OCD as well, is thought to result from a dysfunction of the dopamine system in the basal ganglia. Based on observations that serotonin can inhibit the activity of dopamine systems and that the basal ganglia receive input from serotonin-containing neurons, a hypothesis has been put forward that an alteration in the normal interaction of these neurotransmitter systems in the basal ganglia may be involved in OCD (24). There are some preliminary findings that drugs that act on dopamine may have an effect on OCD (24), and data from anatomical studies also indicate a role for the basal ganglia in OCD. This hypothesis is considered in greater detail in the next section, which describes the basal ganglia and some of their anatomical connections.

Anatomy and Activity

Persons with OCD exhibit a variety of abnormalities on neuropsychological tests (91). In general, these tests point to dysfunctions in the frontal lobes, basal ganglia, and hippocampus. For example, persons with OCD often perform poorly on tests that measure memory and attention. PET studies of glucose utilization have shown greater than normal activity in parts of the basal ganglia and an area of the frontal cortex, the orbital cortex, in OCD (4,5,91) (figure 4-7). Data from the few CAT studies that have been 'done indicate that the only difference between the brains of OCD patients and controls is a decrease in the size of various regions in the basal ganglia (64,91). These data, coupled with those previously discussed, lead to the hypothesis that OCD is the result of an abnormal interaction between the basal ganglia and other areas of the brain, principally the orbital cortex (4,5,35,64,91). These areas work together to coordinate movement in response to thought. If the basal ganglia are damaged, involuntary movements such as tics occur.

Figure 4-7—PET Scan of an Individual With Obsessive-Compulsive Disorder



Brain activity in the brain of a person with OCD (right) and the brain of a person without OCD (left). In OCD, there is increased activity in the frontal cortex.

SOURCE: L. Baxter, UCLA Center for Health Sciences, Los Angeles, CA.

The thoughts and impulses that often make up obsessions (e.g., those related to aggression, hygiene, sex, and danger) are thought to be generated in the frontal cortex. In normal individuals, the basal ganglia-orbital system filters these impulses, putting them aside so that they are not acted upon. According to this theory of OCD, the filtering effect that keeps an individual from acting on thoughts or impulses does not work properly. As a result, a thought occurs and the person takes action. Again, the association with Tourette's syndrome is striking. Individuals with this disorder exhibit not only motor

tics, but involuntary vocalizations, often of an obscene or socially unacceptable nature (such as racial epithets). The basal ganglia-orbital cortex hypothesis posits a dysfunction in the normal control of thoughts (obsessions), which can lead to reactive motor activity (compulsions).

Panic Disorder

Panic disorder is marked by recurrent periods of intense fear that last for several minutes. The attacks are not triggered by anxiety-provoking situations, and patients often report that they occur ''out of the blue. ' Many persons with panic disorder experience varying degrees of anxiety between attacks in anticipation of the next panic attack (57). This ''fear of fear' often results in patients with panic disorder developing agoraphobia, the fear of being in public places.

Several theories have been postulated to explain panic disorder (57). One views panic as the result of hyperactivity of the physiological mechanisms that are normally activated in stressful situations (i.e., the sympathetic nervous system). Another posits that individuals have an increased psychological sensitivity to normal fluctuations in physiological responses. This theory suggests that patients may misinterpret normal physiological changes as dangerous, inducing more anxiety and precipitating a panic attack. Another theory suggests that there is a primary defect in brain mechanisms related to the neurotransmitter norepinephrine, which is associated with the sympathetic response. A role for sensitivity to the chemicals lactate and carbon dioxide, for hyperventilation, and for dysfunction in the temporal lobe of the brain have also been proposed. There is experimental evidence to support, or in some cases refute, these various theories. Thus, while there are a lot of puzzle pieces, there is currently no unified theory of panic disorder.

Biochemistry

Information about the pharmacology associated with panic disorder can be derived both from drugs that are effective in treating the disorder and from agents that induce a panic attack when given to a patient. The most effective drugs for treating anxiety are the benzodiazepines. In high doses, these drugs are also effective in controlling panic disorder. Benzodiazepines exert their antianxiety effects indirectly, by increasing the action of the inhibitory neurotransmitter GABA. The discovery that there are specific receptors in the brain for benzodiazepines indicates that there must be a chemical produced by the brain that would normally attach to these receptors (although such a chemical has yet to be discovered). Benzodiazepine receptors are coupled to GABA receptors, and activation of the former accentuates the effects of GABA, which turns off overly active brain cells (14,76).

Unlike GABA and its receptors, which are found throughout the brain, benzodiazepine receptors are located in only a few brain structures. Thus, not all GABA receptors are coupled with benzodiazepine receptors. The GABA receptors that are coupled to benzodiazepine receptors and that respond to the drug are known as $GABA_A$ receptors. The areas of the brain that contain both benzodiazepine and $GABA_A$ receptors include the hippocampus and the amygdala, both limbic system structures (76). As described previously, the Limbic system plays a role in controlling emotional behavior. Thus, it is thought that the antianxiety effect of benzodiazepines results from their action on $GABA_A$ receptors in the hippocampus and amygdala.

Another compound, buspirone, is effective for treating general anxiety, but instead of affecting GABA, it acts on other chemical systems in the brain. Buspirone decreases the activity of the neurotransmitter serotonin in some areas of the brain and activates receptors for the neurotransmitter dopamine in other areas (76). Buspirone acts on serotonin systems through a complex interaction with a number of different subtypes of serotonin receptors. This action, coupled with other experimental findings, has led to the speculation that increased activity in serotonin-containing areas, particularly the raphe nuclei, maybe involved in anxiety (55). It is thought that the raphe nuclei, via their connections with the limbic system, may be involved in mediating anxious behavior and that activation would cause anxiety.

The most effective drugs for treating panic disorder are the drugs used to treat depression, although they exert a therapeutic action in panic that is different from that in depression (76). The efficacy of these drugs has led to the theory that panic results from overactivity of the norepinephrine systems in the brain that mediate the fight-or-flight response,

principally the locus ceruleus (3,43,55,65). It should be kept in mind, however, that the neurons in the locus ceruleus make connections with neurons in the limbic system and can affect their activity. The hypothesis is that a panic attack is the result of inappropriate activation of the norepinephrine system in the locus ceruleus. Studies have shown that panic attacks can be caused by drugs that increase either the activity of cells in the locus ceruleus or the release of norepinephrine from them, whereas the antidepressants used to treat panic decrease the activity of the locus ceruleus (29,55,61,76).

Any number of agents can provoke panic attacks in persons who suffer from panic disorder, including the chemical lactate (administered intravenously) and carbon dioxide (inhaled). At a high enough concentration, carbon dioxide will also induce panic in controls. The mechanism by which these agents cause panic attacks is unknown (22,27,73,76). Lactate has complex actions in the brain, including effects on serotonin, norepinephrine, and other transmitter systems, as well as areas of the brain that respond to changes in blood chemistry and regulate respiration (73). Inhalation of carbon dioxide upsets the balance of oxygen in the blood and can affect its acidity (27). The areas of the brain that monitor and control functions such as respiration and the cardiovascular system are connected with the locus ceruleus as part of the fight-or-flight response. One theory holds-that the norepinephrine system in the locus ceruleus is unusually sensitive in persons with panic disorder. Thus, according to this theory, lactate and carbon dioxide cause changes in either the body or the brain that indirectly activate the norepinephrine system in the locus ceruleus, precipitating a panic attack (27,55,73,92). Lactate induces a panic attack in about 80 percent of persons with panic disorder (55). This high correlation has led to the suggestion that lactate response can be considered a diagnostic marker for the disorder (20), although variability in the characteristics of the response among patients has called this into question (55).

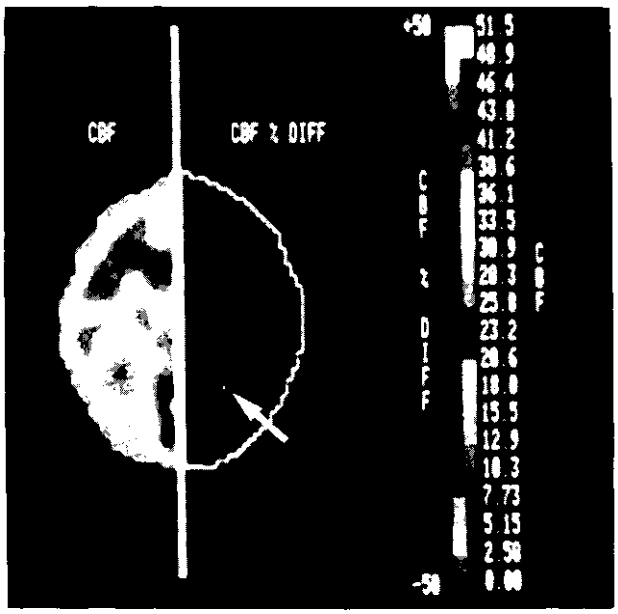
While it seems likely that the locus ceruleus is involved in panic disorder, other experimental evidence raises the question as to whether that role is primary or secondary to the cause of the disorder and whether other brain systems are also involved (76). For example, serotonin has also been implicated in the genesis of panic attacks (55,58,76). Serotonin connections to the locus ceruleus inhibit the activity of locus ceruleus cells, and drugs that potentate the action of serotonin suppress panic attacks (76). It has been postulated that a primary decrease in activity in this serotonin-inhibiting system may play a role in inducing panic attacks (58) and that the role of the locus ceruleus is secondary to this effect. In addition, the action of caffeine indicates that other brain systems besides the locus ceruleus may be involved. Caffeine can precipitate a panic attack in persons with panic disorder (55,76,77). As a result, people who suffer from panic attacks often learn, on their own, to avoid caffeine-laden products such as coffee and chocolate. Caffeine's principal action in the brain is to block the receptors for the inhibitory neurotransmitter adenosine. However, caffeine also has some effect on norepinephrine, dopamine, and benzodiazepine systems. It is not known whether caffeine produces panic by inhibiting adenosine activity, some other action, or a combination of these (77). It is also unclear how or whether caffeine's panic-inducing action relates to the occurrence of panic disorder.

Anatomy and Activity

The few CAT and MRI studies that have examined the brain structure of persons with panic disorder provide evidence of brain atrophy or underdevelopment, particularly in the frontal and temporal lobes (33). However, given the limited number of studies that have been done, the signifcance of these results is unclear and must be considered preliminary (33).

Abnormal activity has also been observed in the brains of persons with panic disorder (26,44,45,67). At rest, panic disorder patients who are sensitive to lactate exhibited increased cerebral blood flow to the parahippocampal gyrus (PHG), an area of the cerebral cortex that is associated with the limbic system (figure 4-8). Normal controls or lactate-insensitive panic patients did not show these changes. Based on these results, it was proposed that a PHG abnormality was involved in a predisposition to panic, and it was further hypothesized that activation of a norepinephrine pathway to the PHG initiates an attack (67). However, this hypothesis is based on limited data, and conflation will require additional studies. Furthermore, it does not explain what mechanism might be present in lactate-insensitive panic disorder patients. Other studies have demon-

Figure 4-8-PET Scan of an Individual With Panic Disorder



Whole brain activity (left side) and abnormal activity in the parahippocampal gyrus (right side) in the brain of a person with panic disorder in the nonpanic state.

SOURCE: E. Reiman, Good Samaritan Hospital, Phoenix, AZ.

strated that there is an increase in cerebral blood flow during lactate-induced panic attacks (67).

Synthesis

There is evidence that a number of different biological factors play a role in OCD and panic disorder. The possible role of the basal ganglia-orbital cortex system in OCD is an intriguing theory, coupling areas of the brain involved in cognitive and motor activity. Further examination of these brain regions, the role of dopamine mechanisms, and their interactions with serotonin systems are important areas for future research related to OCD. Both limbic structures and the locus ceruleus are implicated in panic disorder. Data suggest that the limbic structures mediate generalized feelings of anxiety, influenced by the activity of GABA, while the locus ceruleus controls an active response to anxiety-provoking stimuli (i.e., panic attacks). The anatomical connections between these two regions of the brain suggest that there might be some interaction of these systems in panic disorder, but additional study of these systems and their interaction is necessary.

IMPLICATIONS FOR TREATMENT

One of the **greatest** promises of research into the biology of mental disorders is the development of more efficacious treatments-particularly drugs. At the same time, effective treatment of a mental disorder must take into consideration all aspects of the disorder—biological, psychological, and social. Thus, developments related to biological factors associated with a disorder contribute to the total therapeutic protocol available to treat patients.

The antipsychotic drug chlorpromazine, used to treat persons with schizophrenia, provides an example of the development of a biological treatment. The discovery that chlorpromazine was an antipsychotic drug was serendipitous (36). The drug was originally developed in the search for an effective antihistamine; the chance clinical observation that it had an antipsychotic effect led to its use in schizophrenia. Once chlorpromazine's effect was established, research into its mechanism of action led to the finding that it exerted its effect by blocking the D_2 dopamine receptor subtype (see earlier discussion). This led in turn to the development of additional antipsychotic drugs, called typical antipsychotics, that also act by blocking D_2 dopamine receptors.

The chlorpromazine story also illustrates the point that most therapeutic advances in psychopharmacology have occurred by chance. A drug discovered to be efficacious was then examined further, to advance researchers' understanding of the biological mechanisms underlying a disorder (36).

The impetus for developing new drugs comes from the fact that current drugs are imperfect (89). Side effects are common, and not all patients respond to a given drug. In general, these problems result from existing drugs' inability to act selectively on the symptoms of a disorder. For example, while typical antipsychotic drugs act by blocking D_2 receptors in areas of the brain involved with schizophrenia symptoms, they also block D_2 receptors in other areas of the brain, which produces the movement side effects characteristic of these drugs. Another example is the side effects associated with antidepressant drugs, which result when the antidepressants act on other neurotransmitter systems besides the monoamine systems thought to be involved with depression.

Beyond the need for more efficacious drugs with fewer side effects, the financial impact that more effective treatments can have is another factor driving the search for new drugs. Improved treatments can decrease total treatment costs by reducing the need for hospitalization; they can decrease other financial effects as well, such as lost wages due to disability. For example, a study conducted in 1980 estimated that the introduction of lithium in 1969, for the treatment of bipolar disorder, resulted in an average yearly savings in treatment costs of $290 million in the United States (66). It was also estimated that in the first year following the introduction of lithium, $92 million in lost wages was regained (66).

By attaining a better understanding of what neurochemical systems are affected in a disorder and how those systems interact with others, more effective drugs can be developed to treat the symptoms of a disorder while minimizing side effects. The recent strides that have been made in basic neuroscience research, particularly advances in molecular and cellular neurobiology, will facilitate this process (75,78). The ability to clone receptor subtypes and identify precisely the molecular structure of receptors and other biochemical constituents of the brain will enable scientists to construct drugs that act more precisely. Thus, the development of drugs for mental disorders is entering a new phase in which both clinical and basic research findings will be applied to the design of more efficacious medications.

The antipsychotic drug clozapine and the antidepressant fluoxetine are examples of this new generation of drugs. Clozapine, a so-called atypical antipsychotic drug, not only blocks D_2 receptors but also acts on other dopamine receptors (see box 4-A) and on serotonin receptors to create different effects on these systems in different areas of the brain (47). Clozapine is thought to block sufficient dopamine in appropriate areas of the brain to control psychosis, while acting on other areas of the brain to avert the blanket D_2 blockade that produces side effects. Unlike traditional antidepressants, which have a broad effect on catecholamine and other neurotransmitter systems, fluoxetine (Prozac) was designed specifically to block serotonin reuptake (69). As a result, it has an antidepressant action equivalent to that of older drugs, but without many of their side effects.

Table 4-2—Drugs in Development for Mental Disorders

Disorder	United States	Other countries
Schizophrenia	76	42
Mood disorders	83	61
Anxiety disorders	91	46

SOURCE: PJB Publications, *Pharmaprojects* (Surrey, England: PJB Publications, 1992).

Both of these drugs are improvements on older medications, but neither is totally without problems. Although clozapine does not produce the movement side effects associated with typical antipsychotic drugs, it is associated with an even more dangerous side effect. About 2 percent of persons taking clozapine develop a potentially deadly blood disease, agranulocytosis. As a result, anyone taking the drug must be tested regularly; if there is any indication of the disease, treatment must be stopped. The need for constant monitoring makes administration of clozapine costly, ranging between $6,000 and $9,000 a year (19). While fluoxetine has many fewer side effects than older antidepressants, it is associated with such adverse reactions as nausea, nervousness, insomnia, and headache (56).

Despite these problems, the advantages of these drugs make them highly popular. For example, in spite of the costs associated with clozapine, results from a study demonstrated that over a 2-year period there was a savings of approximately $16,000 per patient, per year, as a result of decreased hospitalization among 37 patients who had taken the drug (48). Total U.S. sales of clozapine in 1991 were estimated to be $60 million (19), while 1990 sales for fluoxetine were put at $500 million (52). Currently, a number of other drugs, which may represent further improvements on the medications that have been used in the past to treat mental disorders, are being developed and tested (table 4-2). These new drugs represent the latest efforts to apply information derived from the study of the biology of mental disorders to treatment of patients.

SUMMARY AND CONCLUSIONS

Evidence exists for the activity of a variety of biological factors in each disorder reviewed in this report. However, it is difficult to put the strands of evidence together in a unified hypothesis about the role of biological factors in a given disorder.

Most of the biological factors that have been identified relate to changes in the brain that are correlated with a disorder. These include alterations in neurotransmitter systems, such as the association of increased or decreased levels of dopamine with the various symptoms of schizophrenia and the role of monoamines in mood disorders. Disruptions in brain activity are associated with disorders as well, such as the decreased activity found in the frontal lobes of persons with schizophrenia and the increased activity in the basal ganglia of persons with OCD. These factors, and the others discussed in this chapter, provide insights into the mechanisms underlying the symptoms displayed by patients. A better understanding of such mechanisms should enable scientists to develop more effective treatments.

Less is known about the causes of mental disorders. The influence of various factors, such as developmental and viral factors, has been hypothesized, but as yet there is no definitive explanation for any of these disorders. To understand what leads to the onset of mental disorders, researchers must consider the role of psychological and social factors and how they may interact with a pathological biological condition. For example, the alterations in the limbic system and locus ceruleus associated with panic disorder may represent a biological predisposition that is shaped by an individual's experiences to determine whether and how the disorder is manifested, while the kindling-sensitization model of bipolar disorder suggests that life events can modify abnormal brain activity.

It is essential to learn how the healthy brain works. Research in the basic neuroscience provides the foundation for research on the biology of mental disorders. Advances in the neuroscience have resulted in the development of new techniques and improvements on old ones that greatly increase our ability to study the brain. Combining such techniques as neuropsychological testing or biochemical analysis with brain imaging techniques extends that ability even further. Current research is increasingly taking multidimensional approaches to the study of mental disorders, integrating data concerning different aspects of brain functioning and behavior into testable hypotheses. That trend is expected to accelerate.

Essential to this effort will be strategies for studying the integrated networks of brain structures that control behaviors. Some mental disorders may be collections of disorder subtypes, indicating that the normal functioning of a network that mediates a behavior can be disrupted at various points. The ultimate goals of research are to understand how brain structures work in concert to produce behavior, how this process is disrupted in mental disorders, and what factors cause it to go awry.

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