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Donald W. Black, M.D., is Professor of Psychiatry at the University of Iowa Roy J. and Lucille A. Carver College of Medicine in Iowa City, Iowa. He is a graduate of Stanford University, where he received his undergraduate degree, and the University of Utah School of Medicine. He received his psychiatric training at the University of Iowa. He currently serves as Director of Residency Training. He is an authority on personality disorders and impulsive behavior and is author of *Bad Boys, Bad Men—Confronting Antisocial Personality Disorder*. He is a Distinguished Fellow of the American Psychiatric Association and President of the American Academy of Clinical Psychiatrists.

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What is psychiatry? It is the branch of medicine that focuses on the diagnosis and treatment of mental illnesses. Some of these illnesses are very serious, such as schizophrenia, Alzheimer’s disease, and the various mood disorders. Others may be less serious, but still very significant, such as anxiety disorders and personality disorders. Psychiatry differs from psychology by virtue of its medical orientation. Its primary focus is illness or abnormality, as opposed to normal psychological functioning; the latter is the primary focus of psychology. Of course, abnormal psychology is a small branch within psychology, just as understanding normality is necessary for the psychiatrist to recognize and treat abnormal functioning. The primary purposes of psychiatry as a discipline within medicine are to define and recognize illnesses, to identify methods for treating them, and ultimately to develop methods for discovering their causes and implementing preventive measures.
There are several reasons why psychiatry may be the most exciting discipline within medicine. First, psychiatrists are specialists who work with the most interesting organ within the body, the brain. The brain is intrinsically fascinating because it controls nearly all aspects of functioning within the rest of the body as well as the way people interact with and relate to one another. Psychiatry has rapidly advanced in recent years through the burgeoning of neuroscience, which has provided psychiatrists with the tools by which they can understand brain anatomy, chemistry, and physiology, thereby gradually developing a scientific base that will permit them to understand human emotion and behavior and to develop methods for treating abnormalities in these domains.

Yet as psychiatry evolves into a relatively high-powered science, it remains a very clinical and human branch within medicine. It can be an especially rewarding field for students who have chosen medicine because they wish to have contact with patients. The clinician working in psychiatry must spend time with his or her patients and learn about them as human beings as well as individuals who have illnesses or problems. Learning a person’s life story is fun and interesting; as one colleague once said, “It amazed me when I realized that I would get paid for asking people things that everybody always wants to know about anyway!”

Finally, psychiatry has enormous breadth. As a scientific discipline, it ranges from the highly detailed facts of molecular biology to the abstract concepts of the mind. As a clinical discipline, it ranges from the absorbingly complex disturbances that characterize illnesses such as schizophrenia to the understandable fearfulness shown by young children when they must separate from their parents and attend school or be left with a babysitter. It can be very scientific and technical, as in the frontier-expanding research currently occurring in molecular genetics or neuroimaging; but it can also be very human and personal, as when a clinician listens to a patient’s story and experiences the pleasure of being able to offer help by providing needed insights or even simple encouragement and support.

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Philippe Pinel, a leader of the French Revolution, is usually considered to be the founding father of modern psychiatry. In 1793, he was named director of the Bicêtre, the hospital in Paris for insane men. Soon afterward he instituted a grand, symbolic change by removing the chains that bound the patients to the walls at the Bicêtre and created a new type of treatment that he referred to as “moral treatment.” (This meant treating patients in ways that were morally and ethically sensitive.) He was later made director of the corresponding hospital for women, the Salpêtrière. In addition to treating the mentally ill with kindness and decency, Pinel also tried to approach the study of mental illness scientifically. He described his efforts in his Treatise on Insanity (1806):

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What does that mean? What does a psychiatrist actually do? Why do
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us have chosen to become psychiatrists because we want to understand
the human mind and spirit as well as the human brain. We chose to join
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to work with them as individuals. We like to think about people within
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What we contain within our memory stores forms the essence of our
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We are also unlocking the mysteries of brain development and aging
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Lastly, people study psychiatry and become psychiatrists because mental illnesses are among the most clinically important diseases from which human beings suffer. In 1996 two investigators at Harvard University, working in collaboration with the World Health Organization, published a pivotal book titled *The Global Burden of Disease*. This book captured the attention of leaders in the medical community because it provided the first objective summary of the costs of various types of illness to society throughout the world. One head-turning fact is the cost exacted by mental illnesses. For example, a mental illness—unipolar major depression—is the costliest illness in the world. Furthermore, four mental illnesses are among the top 10 diseases affecting people between ages 15 and 44 years: depression, alcohol misuse, bipolar disorder, and schizophrenia. Because self-inflicted injuries are also a consequence of mental illness, 5 of the 10 leading causes of disability in the world are attributable to psychiatric disorders. The message is clear: doctors can no longer afford to ignore mental illnesses. Every physician must learn to identify and diagnose mental illnesses and either provide treatment or referral to a specialist. Some must pursue a deeper understanding by becoming psychiatrists.

The study of psychiatry, the branch of medicine devoted to the study of mental illnesses, is therefore a discipline dedicated to the investigation of abnormalities in brain function manifested in diseases that afflict individuals in interesting and important ways. The clinical appearance of these abnormalities may be obvious and severe, as in the case of psychosis, or subtle and mild, as in the case of personality disorders. Ultimately the drive of modern psychiatry is to develop a comprehensive understanding of normal brain function at levels that range from mind to molecule and to determine how aberrations in these normal functions (produced either endogenously through genetic coding or exogenously through environmental influences) lead to the development of symptoms of mental illnesses.
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DURING THE TWENTY-FIRST CENTURY, all of medicine will experience a paradigm shift in the way that diseases are classified and defined. Our current diagnoses are primarily syndrome based. They rely heavily on clinical observations that signs and symptoms co-occur in groups of patients and also that they have a characteristic course and response to treatment. The twenty-first century will be the “era of the genome.” Thanks to ongoing advances in genomics and molecular biology, we will begin to have the opportunity to define diseases in terms of their etiologies rather than their signs and symptoms. Through this process, traditional medical classification—whether in pediatrics or psychiatry—will be challenged and revised over the ensuing decades. Today’s medical students and residents will need to follow these advances carefully and to be prepared to constantly revise the concepts that they are now being taught.

The fundamental purpose of diagnosis and classification is to isolate a group of discrete disease entities, each of which is characterized by a distinct pathophysiology and/or etiology. Ideally, all diseases in medicine would be defined in terms of etiology. For most illnesses, however, we do not know or understand the specific etiol-
ogy. By and large, a full understanding of etiology is limited to the infectious diseases, in which the etiology is exposure to some infectious agent to a degree sufficient that the body’s immune mechanisms are overwhelmed. (Even in this instance, our knowledge of immune mechanisms is incomplete.)

For most diseases, however, our understanding is at the level of pathophysiology rather than etiology. Diseases are defined in terms of the mechanisms that produce particular symptoms, such as infarction in the myocardium, inflammation in the joints, or abnormal regulation of insulin production.

In the areas of pathophysiology and etiology, psychiatry has more uncharted territory than the rest of medicine. Most of the disorders or diseases diagnosed in psychiatry are syndromes: collections of symptoms that tend to occur together and that appear to have a characteristic course and outcome. Much of the current investigative research in psychiatry is directed toward the goal of identifying the pathophysiology and etiology of major mental illnesses, but this goal has been achieved for only a few disorders (Alzheimer’s disease, vascular dementia, Huntington’s disease, and substance-induced syndromes such as amphetamine-related psychosis or the Wernicke-Korsakoff syndrome).

Why Diagnose Patients?

Diagnoses in psychiatry serve a variety of important purposes and are not just a “label.” Making a careful diagnosis is as fundamental in psychiatry as it is in the remainder of medicine.

Diagnosis introduces order and structure to our thinking and reduces the complexity of clinical phenomena. Psychiatry is a diverse field, and symptoms of mental illness encompass a broad range of emotional, cognitive, and behavioral abnormalities. The use of diagnoses introduces order and structure to this complexity. Disorders are divided into broad classes based on common features (e.g., psychosis, substance abuse, dementia, anxiety). Within each of the major classes, specific syndromes are then further delineated (e.g., dividing substance-related disorders in terms of the type of substance involved, dividing the dementias into Alzheimer’s disease and vascular dementia). The existence of broad groupings, subdivided into specific disorders, creates a structure within the apparent chaos of clinical phenomena and makes mental illnesses easier to learn about and understand. Although diag-
Diagnosis and Classification

Diagnoses are not necessarily defined in terms of etiology or pathophysiology, they are typically defined in terms of syndromal features.

**Diagnoses facilitate communication among clinicians.** When psychiatrists give a patient’s symptoms a specific diagnosis, such as bipolar disorder, they are making a specific statement about the clinical picture with which that particular patient presents. A diagnosis concisely summarizes information for all other clinicians who subsequently examine the patient’s records or to whom the patient is referred. A diagnosis of bipolar disorder, for example, indicates that

- The patient has had at least one episode of mania.
- During that episode of mania, the patient experienced a characteristic group of symptoms such as elated mood, increased energy, racing thoughts, rapid speech, grandiosity, and poor judgment.
- The patient probably has had episodes of depression as well, characterized by sadness, insomnia, decreased appetite, feelings of worthlessness, and other typical depressive symptoms.

The use of diagnostic categories gives clinicians a kind of “short-hand” through which they can summarize large quantities of information relatively easily.

**Diagnoses help to predict outcome.** Many psychiatric diagnoses are associated with a characteristic course and outcome. For example, bipolar disorder is usually episodic, with periods of relatively severe abnormalities in mood interspersed with periods of near normality or complete normality. Thus, patients with bipolar disorder have a relatively good outcome. Some other types of disorders, such as schizophrenia or personality disorders, typically have a more chronic course. Diagnoses are a useful way of summarizing the clinician’s expectations about the patient’s future course of illness.

**Diagnoses are often used to choose an appropriate treatment.** As psychiatry has advanced clinically and scientifically, relatively specific treatments for particular disorders or groups of symptoms have been developed. For example, antipsychotic drugs are typically used to treat psychoses. Thus they are used for disorders such as schizophrenia, in which psychosis is typically prominent, as well as for forms of mood disorder in which psychotic symptoms occur. A diagnosis of mania suggests the use of mood stabilizers such as lithium carbonate or valproate. Some relatively targeted medications are now available, such as the selective serotonin reuptake inhibitors for obsessive-compulsive disorder.
Diagnoses are used to assist in the search for pathophysiology and etiology. Clinical researchers use diagnoses to reduce heterogeneity in their samples and to separate groups of patients who may share a common mechanism or cause that produces their symptoms. Patients who share a relatively specific set of symptoms, such as severe schizophrenia characterized by negative symptoms, are often hypothesized to have a disorder that is mechanistically or etiologically distinct. Knowledge about specific groupings of clinical symptoms can be related to knowledge about brain specialization and function in order to formulate hypotheses about the neurochemical or anatomical substrates of a particular disorder. Ideally, the use of diagnoses defined on the basis of the clinical picture will lead ultimately to diagnoses that serve the fundamental purpose of identifying causes.

Other Purposes of Diagnosis

Beyond these clinical uses, diagnostic systems also have other purposes. Although physicians prefer to conceptualize their relationships with patients in terms of care and treatment, diagnoses are used by other health care providers, attorneys, epidemiologists, and insurance companies. Each time a clinician makes a diagnosis and records it, he or she must do so with an awareness of the other, nonclinical uses to which it may be put.

Diagnoses are used to monitor treatment and to make decisions about reimbursement. As health care has become increasingly managed, diagnoses are often used to determine the length of a hospital stay or the choice of a treatment course for a specific condition. Physicians or their assistants sometimes must spend hours speaking on the telephone with insurers to request additional days, or in writing letters to insurers appealing their decisions for denial of care if the patient’s course of treatment appears to exceed the preset guidelines. Depending on the insurer, some diagnoses may not be covered at all—for example, alcoholism and other drug use disorders. The range of diagnoses covered by insurers continues to change rapidly and may accelerate with the new health reform measures passed by the U.S. Congress in 2010.

Diagnoses are used by attorneys in malpractice suits and in other litigation. Although psychiatrists are the least frequently sued among medical specialists, lawsuits are a concern for all physicians in our litigious society. Some diagnoses, such as major depression, carry with
them a clear set of risks, such as suicide. Clinicians must be aware of those risks and clearly document that they have provided appropriate care. As the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) has made the diagnostic system of psychiatry more open and available, both lawyers and patients have learned much more about psychiatric classification. A physician called into court must expect to defend a recorded diagnosis with appropriate documentation that the various criteria have been assessed and are met.

**Diagnoses are used by health care epidemiologists to determine the incidence and prevalence of various diseases throughout the world.** Diagnoses recorded in hospital or clinic charts are translated into a standard system established by the World Health Organization (WHO), the International Classification of Diseases (ICD). This system is used to track regional differences in disease patterns as well as changes over time.

**Diagnoses are used to make decisions about insurance coverage.** A carelessly made diagnosis, be it of hypertension or major depression, may make it difficult for a patient to obtain life insurance or future health care insurance. Diagnoses also are sometimes used to make decisions about employment, admission to college, and other important opportunities. Because mental illnesses may be subject to discrimination and misunderstanding, these diagnoses involve a particular risk. The clinician obviously must walk a fine line—perhaps impossibly fine.

### The History Behind DSM

The process of diagnosis in psychiatry is partially simplified by the fact that the national professional organization to which most psychiatrists in the United States belong, the American Psychiatric Association, has formulated a manual that summarizes all of the diagnoses used in psychiatry, specifies the symptoms that must be present to make a given diagnosis, and organizes these diagnoses together into a classification system. This manual is titled the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).

The impetus to organize a DSM began during World War II. For the first time, psychiatrists from all over the United States were brought together in clinical settings that required them to communicate clearly with one another. It became apparent that diagnostic practices varied
widely throughout the United States, no doubt reflecting a diversity of training. Shortly thereafter, the American Psychiatric Association convened a task force to develop a diagnostic manual for use in all of American psychiatry. The product was DSM-I, which was published in 1952. Over the years, the DSM has undergone three major revisions (DSM-II, DSM-III, and DSM-IV). Currently, diagnoses in psychiatry are based on DSM-IV, which was published in 1994, and its text revision, DSM-IV-TR, which was published in 2000. A fifth edition, DSM-5, is now being developed and is expected to be published in 2013.

Compared with DSM-III and DSM-IV, DSM-I and DSM-II were relatively simple. For example, the definition of manic-depressive illness in DSM-II was as follows:

**Manic-Depressive Illnesses (Manic-Depressive Psychoses)**

These disorders are marked by severe mood swings and a tendency to remission and recurrence. Patients may be given this diagnosis in the absence of a previous history of affective psychosis if there is no obvious precipitating event. This disorder is divided into three major subtypes: manic type, depressed type, and circular type. (p. 8)

These early handbooks were relatively small. DSM-I contained 132 pages, and DSM-II contained 119 pages. DSM-III, which came out in 1980, was the first effort by a medical specialty to provide a comprehensive and detailed diagnostic manual in which all disorders were defined by specific criteria. DSM-III was a hefty tome—494 pages.

DSM-III represented a major change, which was subsequently carried forward in the next revisions, DSM-IV and DSM-IV-TR. Because of their vagueness and imprecision, the definitions in DSM-I and DSM-II did not adequately fulfill many of the purposes for making a diagnosis. In particular, the descriptions were not specific enough to facilitate communication among clinicians and to delineate one disorder from another. Research investigations made it clear that different clinicians using DSM-I or DSM-II guidelines would give different diagnoses to the same patient. The authors of DSM-III agreed to formulate specific diagnostic criteria that would be as objective as possible to define each of the disorders; would make their decisions about defining criteria and overall organizational structure on the basis of existing research data whenever possible; and would not resort to anecdotal approaches or simple clinical opinion if at all possible.

For the first time, the methods by which a psychiatric diagnosis could be made were relatively clear. Most of the time, the criteria require that a specified subset from a listed group of symptoms be present in order to make a diagnosis.
Psychiatry is the only specialty in medicine that has so consistently and comprehensively formalized the diagnostic processes for the disorders within its domain. This precision and structure are particularly important in psychiatry because it lacks specific laboratory diagnostic tests and confirmed etiologies for most disorders. Consequently, a DSM diagnosis relies largely on the patient’s presenting symptoms and history. Without the structure provided by diagnostic criteria, the diagnostic process could become imprecise and unclear.

The DSM system, as represented by all versions since DSM-III, has been an effective treatment for some of the previous lack of clarity of psychiatric diagnosis. But this treatment has not been without some untoward side effects as well.

Advantages and Disadvantages of the DSM System

Advantages

The advantages of the DSM system can be summarized as follows:

The DSM system has substantially improved the reliability of diagnosis. Reliability, a biometric concept, refers to the ability of two observers to agree on what they see. It is measured by a variety of statistical methods, such as percent agreement, correlation coefficients, and the kappa statistic, which corrects for chance agreement. The reliability of DSM-III was assessed in field trials and found to be relatively good. Even more extensive field trials and reliability studies were done for DSM-IV. These have been extensively summarized in the DSM sourcebooks. The kappa statistics for most diagnoses are approximately 0.8 or greater, which is considered very good.

The DSM system has clarified the diagnostic process and facilitated history taking. Because DSM-IV-TR specifies exactly which symptoms must be present to make a diagnosis, as well as the characteristic course of disorders whenever this is appropriate, it is highly objective. During the 1970s, many psychiatrists received predominantly psychodynamic training that de-emphasized a medical approach to diagnosis. This approach stressed the importance of recognizing underlying psychological processes rather than objective signs and symptoms. Although clinically useful, this approach was more subjective, was difficult to teach to beginners, and re-
quired substantial training. The DSM system provided a simpler approach that brought signs and symptoms back to the forefront of evaluation. Its criteria systematically specify which signs must be observed and which symptoms must be inquired about. This structured approach also makes it an excellent teaching tool for medical students and residents.

The DSM system has clarified and facilitated the process of differential diagnosis. Because it is so explicit, DSM helps clinicians decide which symptoms must be present to rule in or to rule out a particular diagnosis. For example, it specifies that a diagnosis of schizophrenia cannot be made if a full mood syndrome is present. Likewise, a diagnosis cannot be made if some type of drug of abuse, such as amphetamine, has led to the presence of psychotic symptoms. Not only are differential diagnostic issues embedded in the criteria, but the text of each DSM also contains a relatively detailed discussion of the differential diagnosis for each disorder.

Disadvantages

Every paradise has its serpent and poisoned apple. Every treatment has its unwanted side effects. Thus, the DSM system also has certain problems and disadvantages:

The increased precision sometimes gives clinicians and researchers a false sense of certainty about what they are doing. The DSM criteria are simple provisional agreements, arrived at by a group of experts, on what characteristic features must be present to make a diagnosis. Although the criteria are based on data whenever possible, the available data are often inadequate for building the criteria totally on a scientific database. Thus, the selection of signs and symptoms is often relatively arbitrary. The diagnoses themselves are certainly arbitrary. They will remain arbitrary as long as we are ignorant about pathophysiology and etiology. Medical students and residents often crave certainty (as do many physicians long out of training), so they want very much to believe that a given DSM diagnosis refers to some “real thing.” Thus the DSM system sometimes leads clinicians to lapse into petty and pointless debates about whether a patient “really” is depressed if he or she does or does not meet the DSM criteria. The criteria should be seen for what they are: useful tools that introduce structure but are arbitrary in essence, thus often requiring a healthy amount of skepticism.

The DSM system may sacrifice validity for reliability. Reliability refers to the capacity of individuals to agree on what they see, whereas validity refers to the capacity to predict prognosis and outcome, response to treatment, and ultimately etiology. Psychodynamically ori-
Diagnosis and Classification

11

ented clinicians have objected that the DSM system has sacrificed some of psychiatry’s most clinically important concepts because psychodynamic explanations and descriptions are generally excluded. Biologically oriented psychiatrists have objected to the lack of validity in DSM as well. In this instance, they point to the arbitrary nature of the definitions, which are not rooted in information about biological causes.

The DSM system may encourage clinicians to treat diagnosis as no more than a checklist and forget about the patient as a person. DSM-IV-TR can be used to streamline clinical interviews because it encourages the use of a checklist of symptoms in making a diagnosis. There is nothing wrong with the checklist approach, but the initial diagnostic interview should include many more aspects of the patient’s life as well. Perhaps the most important contribution that psychiatry makes to medicine in general is that it emphasizes the importance of establishing rapport with patients and knowing each patient as a unique person. The opportunity to establish a close doctor–patient relationship, based on asking about many facts of a person’s life, makes psychiatry a particularly interesting and enjoyable specialty in medicine—at least for those physicians who are interested in having a caring and human relationship with their patients. This emphasis on care and compassion in addition to “cure” has been the essence of medical care since the time of Hippocrates.

■ The Multiaxial System

The DSM classification system is multiaxial. The term multiaxial refers to a system that characterizes patients in multiple ways so that the clinician is encouraged to evaluate all aspects of the patient’s health and social background. The five axes used to code patient characteristics are summarized in Table 1–1.

<table>
<thead>
<tr>
<th>Table 1–1. Multiaxial system of DSM-IV-TR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axis I</strong></td>
</tr>
<tr>
<td>Clinical disorders</td>
</tr>
<tr>
<td>Other conditions that may be a focus of clinical attention</td>
</tr>
<tr>
<td><strong>Axis II</strong></td>
</tr>
<tr>
<td>Personality disorders</td>
</tr>
<tr>
<td>Mental retardation</td>
</tr>
<tr>
<td><strong>Axis III</strong></td>
</tr>
<tr>
<td>General medical conditions</td>
</tr>
<tr>
<td><strong>Axis IV</strong></td>
</tr>
<tr>
<td>Psychosocial and environmental problems</td>
</tr>
<tr>
<td><strong>Axis V</strong></td>
</tr>
<tr>
<td>Global assessment of functioning</td>
</tr>
</tbody>
</table>

ent
**Axis I** is used to indicate the major syndromes, such as schizophrenia, bipolar disorder, and panic disorder. If several diagnoses are present, all can be noted in order of importance.

**Axis II** is used to code disorders that arise relatively early in life and persist; specifically, mental retardation and personality disorders are coded on this axis. Patients may of course have both Axis I and Axis II diagnoses (e.g., major depressive disorder and borderline personality disorder).

**Axis III** is used to code the various medical conditions the patient has (e.g., hypertension, diabetes, thyroid disease). Axis III is an important component of diagnosis because it calls the clinician’s attention to medical conditions that might interact with the patient’s various psychiatric disorders. It also alerts the clinician to consider the impact of medications the patient may be taking to treat these conditions, which could interact with any psychoactive drugs prescribed.

**Axis IV** codes the various psychosocial and environmental problems that may interact with the patient’s psychiatric and general medical illnesses. Whenever possible, the clinician notes the specific stressor and codes its level of severity. Axis IV serves to alert the clinician to any personal factors that might be relevant to the patient’s diagnosis (e.g., the exacerbation of depression produced by living with an alcoholic spouse). Categories for the psychosocial and environmental problems to be listed on Axis IV are found in Table 1–2.

**Axis V** provides a global assessment of the patient’s overall level of functioning and psychological health. It includes various indices of social, psychological, and occupational functioning. These are coded on the Global Assessment of Functioning (GAF) Scale, which ranges from 1 to 100, with 100 representing superior functioning. The GAF Scale is summarized in Table 1–3. (The use of this scale also provides the clini-
TABLE 1–3.  DSM-IV-TR Global Assessment of Functioning (GAF) Scale

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health–illness. Do not include impairment in functioning due to physical (or environmental) limitations.

**Code**  
(Note: Use intermediate codes when appropriate, e.g., 45, 68, 72.)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>100</td>
<td>No symptoms.</td>
</tr>
<tr>
<td>91</td>
<td>Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members).</td>
</tr>
<tr>
<td>80</td>
<td>If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational, or school functioning (e.g., temporarily falling behind in schoolwork).</td>
</tr>
<tr>
<td>70</td>
<td>Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.</td>
</tr>
<tr>
<td>60</td>
<td>Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers).</td>
</tr>
<tr>
<td>50</td>
<td>Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).</td>
</tr>
<tr>
<td>40</td>
<td>Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).</td>
</tr>
<tr>
<td>30</td>
<td>Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job, home, or friends).</td>
</tr>
<tr>
<td>20</td>
<td>Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute).</td>
</tr>
<tr>
<td>10</td>
<td>Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.</td>
</tr>
<tr>
<td>0</td>
<td>Inadequate information.</td>
</tr>
</tbody>
</table>

cian with an indication of the patient’s overall prognosis, because high-functioning individuals typically have a better outcome.)

How to Become Familiar With the DSM System

The DSM system is obviously large and complex. Beginning students and residents should not attempt to master everything at once. Rather, they should focus on the major and common conditions that are frequently seen either in psychiatric practice or in primary care settings. They should become very familiar with the diagnostic criteria for a few common conditions, such as schizophrenia, major depression, dementia, anxiety disorders, and personality disorders. A few sets of symptom criteria (e.g., major depression) should be committed to memory, simply because they are used so often in so many different clinical settings. The system is too vast to commit all of it to memory, however, so the clinician should not feel concerned about the need to refer back to the criteria when evaluating patients’ symptoms and making diagnoses.

Self-Assessment Questions

1. What is the overall purpose of diagnosis and classification in medicine? Describe the extent to which it has been achieved in psychiatry.
2. Describe some of the specific purposes of psychiatric diagnosis.
3. Describe some of the changes introduced by DSM-III and carried forth to the present.
4. Define the concepts of reliability and validity. How is reliability measured?
5. Describe the advantages of the DSM approach. What are some of its disadvantages?
6. What is meant by the term multiaxial? List the five axes that are included in DSM-IV-TR.
CHAPTER 2

Interviewing and Assessment

Festina lente.
(Make haste slowly.)
*A Latin proverb*

THE FIRST ENCOUNTER with a patient begins with taking a clinical history, just as in other specialties. The novice may feel some anxiety about approaching and interviewing people with mental illnesses, but largely because they have been portrayed in the media in such disturbing ways. Think of Randall Patrick McMurphy in *One Flew Over the Cuckoo’s Nest*, or John Nash in *A Beautiful Mind*. Furthermore, psychiatric history-taking requires the interviewer to ask uncomfortable questions such as “Do you hear voices when no one is around?” or to ask about areas of life that are especially private and intimate, such as sexual preferences and practices. However, it is a bit like learning to ski or swim. Once you head down the mountain (or get in the water), you will find history-taking to be surprisingly easy, interesting, and even fun. Demands placed on the interviewer will vary, of course, depending on the type of illness the patient has and its severity. Patients with milder syndromes, such as anxiety disorders or personality disorders, are usually more capable of describing their symptoms and history clearly and articulately. The severely ill depressed, manic, or psychotic patient presents a real challenge, and
clinicians may have to depend on informants, such as family members or friends, in addition to the patient.

**The Psychiatric Interview**

An initial psychiatric evaluation serves several purposes. One is to formulate an impression as to the patient’s diagnosis or differential diagnosis and to begin to generate a treatment plan. The second purpose is to produce a document for the patient’s record that contains information organized in a standard, readable, and easily interpretable way. The initial interview is often therapeutic as well, in that it permits the clinician to establish a relationship with the patient and to reassure him or her that help will be provided.

The outline of that written record is summarized in Table 2–1. As the table indicates, a standard psychiatric evaluation is very similar to the evaluations used in the rest of medicine, with some minor modifications. The content of the present illness and past history is focused primarily on psychiatric symptoms, and the family history includes more information about psychiatric illnesses in family members. Family history and social history also include more social and personal information than is recorded in the standard medical history. An important part of the interview—the mental status examination—is typically included only in psychiatric and neurological evaluations.

**Identification of Patient and Informants**

Identify the patient by stating his or her age, race, gender, marital status, and occupational status. Indicate whether the patient was the sole informant or whether additional history was obtained from family members or previous psychiatric records. Indicate whether the patient was self-referred, was brought in at the request of family members, or was referred by a physician; if either of the latter two, specify which family members or physician. In addition, indicate how reliable the informant appears to be.

**Chief Complaint**

Begin by stating the patient’s chief complaint in his or her own words, using quotation marks (e.g., “I’m thinking of killing myself” or “I get
angry and want to hurt people”). An additional sentence or two of amplifying information also may be provided, particularly if the patient’s chief complaint is relatively vague.

**History of Present Illness**

Provide a concise history of the illness or problem that brought the patient in for treatment. Begin by describing the onset of the symptoms. If this is the patient’s first episode, first psychiatric evaluation, or first hospital admission, that should be stated early in the history of the present illness. Indicate how long ago the first symptoms began, the nature of their onset (e.g., acute, insidious), and whether the onset was precipitated by any particular life events or problems. If the latter, these events or problems should be described in some detail. Likewise, medical conditions that may have served as precipitants should be described. If drug or alcohol abuse was a potential precipitant, that also should be noted.

The evolution of the patient’s various symptoms should be described. A systematic summary of all symptoms present, in a form useful for making a differential diagnosis of the present illness, should be provided. This listing of symptoms should reflect the criteria included in DSM-IV-TR and should specify both which symptoms are present and which symptoms are absent. The description of symptoms should
not be limited to those included in the DSM-IV-TR diagnostic criteria, however, because these typically do not provide a full description of the range of symptoms that patients have (i.e., they are minimal, not comprehensively descriptive). The description of the present illness also should indicate the degree of incapacity that the patient is experiencing as a consequence of the symptoms, as well as the influence of the symptoms on personal and family life. Any treatments the patient has received for the present illness should be noted, including dosages, duration of treatment, and effectiveness of the specific medications, because these will often dictate the next step.

**Past Psychiatric History**

The past psychiatric history provides a summary of past illnesses, problems, and their treatment. In patients with complex histories and chronic psychiatric illnesses, this portion of the history will be quite extensive. It should begin by noting the age at which the patient was first seen for psychiatric evaluation and the number of past hospitalizations or episodes. Thereafter, past episodes should be described in chronological order, with some information about duration of episodes, types of symptoms present, severity of symptoms, treatments received, and response to treatment. If a characteristic pattern is present (e.g., episodes of mania are always followed by episodes of depression, or past depressive episodes have consistently responded to a particular medication), this should be noted because it provides useful prognostic treatment information. If the patient’s memory for past symptoms is relatively poor, or the bulk of the past history is obtained from old records rather than from the patient himself or herself, this also should be recorded. Confirmation by family members of types and patterns of symptoms and number of episodes also should be noted.

**Family History**

The age and occupation of both parents and all siblings should be noted, as should the age and education or occupation of all children (if applicable). If any of these first-degree relatives (parents, siblings, children) has a history of any mental illness, the specific illness should be mentioned, along with information about treatment, hospitalization, and long-term course and outcome. It may be necessary to describe specific disorders because many patients will not recognize alcoholism or criminality, for example, as relevant problems: “Do any blood relatives have a history of
alcoholism, criminality, drug abuse, severe depression, suicide attempts, or suicide? Have any ever been psychiatrically hospitalized or institutionalized? Do you know why? Have any ever taken ‘nerve pills’ or seen psychiatrists, psychologists, or counselors?” The interviewer should obtain as much information as possible about mental illness in the extended family as well. Any relevant information about the family’s social, cultural, or educational background also may be included in this section of the interview. It is often helpful to draw pedigrees in complicated cases.

**Social History**

The social history provides a concise narrative description of the patient’s life history. It includes information about where the patient was born, where he or she grew up, and the nature of his or her early life adjustment. Any problems during childhood, such as temper tantrums, school phobia, or delinquency, should be noted. The patient’s relationships with his or her parents and siblings should be described. Psychosexual development, such as age at first sexual experience, also should be described. Information about familial religious or cultural attitudes that is relevant to the patient’s condition should be noted. Educational history should be summarized, including information about how many years of school the patient completed, quality of school performance, and nature of academic interests. Some description should be provided of the patient’s interest and participation in extracurricular activities and interpersonal relationships during adolescence and early adulthood. Work history and military history also should be summarized. Certain areas may need more emphasis and detail, depending on the chief complaint and diagnostic formulation.

This section also contains a summary of the patient’s current social situation, including marital status, occupation, and income. With patients who are unemployed or disabled, it may be helpful to ask, “What was your usual (or past) occupation?” The location of the patient’s residence should be described, as well as the specific family members who live with the patient. This section of the history should provide information about the various social supports currently available to the patient. Habits (e.g., smoking, use of alcohol) should be recorded as well.

**General Medical History**

The patient’s current and past state of health should be summarized. Any existing illness for which the patient is currently receiving treat-
ment should be noted, as well as the types of treatments, medications, and their dosages. Include vitamins, supplements, herbals, or other nontraditional treatments (e.g., acupuncture, chiropractic, dietary supplements). Allergies, past surgeries, traumatic injuries, or other serious medical illnesses should be summarized. Head injuries, headaches, seizures, and other problems involving the central nervous system are particularly relevant.

**Mental Status Examination**

The mental status examination is the psychiatric equivalent of the physical examination in medicine. It includes a comprehensive evaluation of the patient’s appearance, thinking and speech patterns, memory, and judgment.

The components of the mental status examination are summarized in Table 2–2. Some domains are determined simply by observing the patient (e.g., appearance, affect). Other portions are determined by asking the patient relatively specific questions (e.g., mood, abnormalities in perception). Still others are assessed by asking the patient a specified set of questions (e.g., memory, general information). The interviewer should develop his or her own repertoire of techniques to assess functions such as memory, general information, and calculation. He or she should consistently use this same repertoire for all patients so that he or she develops a good sense of the range of normal and abnormal responses in individuals of various ages, educational levels, and diagnoses.

**Appearance and Attitude**

Describe the patient’s general appearance, including grooming, hygiene, and facial expression. Note whether the patient looks his or her stated age, younger, or older. Note type and appropriateness of dress. Describe whether the patient’s attitude is cooperative, guarded, angry, or suspicious.

**Motor Activity**

Note the patient’s level of motor activity. Does he or she sit quietly, or is he or she physically agitated? Note any abnormal movements, tics, or mannerisms. If relevant, evaluate for and note any indications of catatonia, such as waxy flexibility (described later in the chapter under “Catatonic Motor Behavior”). Determine whether any indications of ab-
normal movements are present, such as the oral-buccal movements seen in persons with tardive dyskinesia.

**Thought and Speech**

Psychiatrists often speak about “thought disorder” or “formal thought disorder.” This concept refers to the patient’s pattern of speech, from which abnormal patterns of thought are inferred. It is, of course, not possible to evaluate thought directly. Note the rate of the patient’s speech—whether it is normal, slowed, or pressured. Note whether the patient’s speech indicates a pattern of thought that is logical and goal directed or whether any of a variety of abnormalities in form of thought is present (e.g., derailment, incoherence, poverty of content of speech). Summarize the content of the thought, noting in particular any delusional thinking that is present. Delusions, when present, should be described in detail. (If already noted in the history of the present illness, this can be indicated with a simple statement such as “Delusions were present as described above.”)

**Mood and Affect**

The term *mood* refers to an emotional attitude that is relatively sustained; it is typically determined through the patient’s own self-report, although some inferences can be made from the patient’s facial expression. Note whether the patient’s mood is neutral, euphoric, depressed, anxious, or irritable.

*Affect* is inferred from emotional responses that are usually triggered by some stimulus. *Affect* refers to the way that a patient conveys his or her emotional state, as perceived by others. The examiner watches the response of the patient’s face to a joke or a smile, determines whether
the patient shows appropriate or inappropriate emotional reactions, and notes the degree of reactivity of emotion. Affect is typically described as full, flat, blunted, or inappropriate. Flat or blunted affect is inferred when the patient shows very little emotional response and seems emotionally dulled, whereas inappropriate affect refers to emotional responses that are not appropriate to the content of the discussion, such as silly laughter for no apparent reason.

Perception
Note any abnormalities in perception. The most common perceptual abnormalities are hallucinations: abnormal sensory perceptions in the absence of an actual stimulus. Hallucinations may be auditory, visual, tactile, or olfactory. Sometimes hypnagogic or hypnopompic hallucinations occur when the patient is falling asleep or waking from sleep; these are not considered true hallucinations. An illusion is a misinterpretation of an actual stimulus—for example, seeing a shadow and believing it is a man.

Orientation
Describe the patient’s level of orientation. Normally, this includes orientation to time, place, and person. Orientation is assessed by asking the patient to describe the day, date, year, time, place where he or she is currently residing, his or her name and identity, and why he or she is in the hospital (or clinic).

Memory
Memory is divided into very short term, short term, and long term. All three types should be described. Very-short-term memory involves the immediate registration of information, which is usually assessed by having the patient repeat back immediately a series of digits or three pieces of information (e.g., the color green, the name Mr. Williams, and the address 1915 High Street). The examiner determines whether the patient can recall these items immediately after he or she is told them. If the patient has difficulty, he or she should be given the items repeatedly until he or she is able to register them. If he or she is unable to register them after three or four trials, this should be noted. The patient should then be warned that he or she will be asked to recall these items in 3–5 minutes. His or her ability to remember them after that time interval is an indication of his or her short-term memory. Long-term memory is assessed by asking the patient to recall events that occurred
in the past several days, as well as events that occurred in the more remote past, such as months or years ago.

**General Information**

General information is assessed by asking the patient a specific set of questions covering topics such as the names of the last five presidents, current events, or information about history or geography (e.g., “Can you tell me what happened on September 11, 2001?”; “Who is our president?”). The patient’s fund of general information should be noted in relation to his or her level of educational achievement. This is particularly important in assessing the possibility of dementia.

**Calculations**

The standard test of calculations is serial 7s. This test involves having the patient subtract 7 from 100, then 7 from that product, and so on for at least five subtractions. Some chronic patients become relatively well trained in this exercise, so it is a good idea to have other tools in one’s repertoire. One that is quite useful involves asking the patient to make calculations necessary in daily living (e.g., “If I went to the store and bought six oranges, priced at three for a dollar, and gave the clerk a $10 bill, how much change would I get back?”). Calculations can be modified for the patient’s educational level. Poorly educated patients may need to calculate serial 3s. Likewise, real-life calculations can be simplified or made more complex.

**Capacity to Read and Write**

The patient should be given a simple text and asked to read it aloud. He or she also should be asked to write down a specific sentence, either of the examiner’s choice or of his or her own choice. The patient’s ability to read and write should be assessed relative to his or her level of education.

**Visuospatial Ability**

The patient should be asked to copy a figure. This figure can be quite simple, such as a square inside a circle. An alternative task is to ask the patient to draw a clock face and set the hands at some specified time, such as 10 minutes past 11 o’clock.

**Attention**

Attention is assessed in part by several of the tasks just described, such as calculations or clock setting. Additional tests of attention can be used, such
as asking the patient to spell a word backward (e.g., “world”). The patient also can be asked to name five things that start with a specific letter, such as *d*. The latter is a good test of cognitive and verbal fluency.

**Abstraction**

The patient’s capacity to think abstractly can be assessed in a variety of ways. One favorite method is asking the patient to interpret proverbs, such as “A rolling stone gathers no moss” or “Don’t cry over spilt milk.” Alternatively, the patient can be asked to identify commonalities between two items (e.g., “How are an apple and an orange alike?”; “How are a fly and a tree alike?”).

**Judgment and Insight**

Assess overall judgment and insight by noting how realistically the patient has appraised his or her illness and various life problems. Insight can be ascertained relatively directly—for example, by asking “Do you believe you are mentally ill?” or “Do you believe that you need treatment?” Judgment may not be as easily assessed, but the patient’s recent choices and decisions will help in its determination. Sometimes simple questions may be helpful. The following are frequently used: “If you found a stamped, addressed envelope, what would you do?” and “If you were in a movie theater and smelled smoke, what would you do?”

**General Physical Examination**

The general physical examination should follow the standard format used in the rest of medicine, covering organ systems of the body from head to foot. Examinations of patients of the opposite sex (e.g., male physician examining a female patient) should always be chaperoned.

**Neurological Examination**

A standard neurological examination should be performed. A detailed neurological evaluation is particularly important in psychiatric patients to rule out focal signs that might help to explain the patient’s symptoms.

**Diagnostic Impression**

The clinician should note his or her diagnostic impression based on all five DSM-IV-TR axes whenever possible. When appropriate, more than
one diagnosis should be made. When the diagnosis is uncertain, the qualifier *provisional* should be added. Not infrequently, it is difficult to make a definitive diagnosis at the time of the index evaluation. When this situation occurs, differential diagnostic possibilities should be listed.

**Treatment and Management Plan**

The treatment and management section will vary, depending on the level of diagnostic certainty. If the diagnosis is quite uncertain, the first step in treatment and management will involve additional assessments to determine the diagnosis with more certainty. Thus the treatment and management plan may include a list of laboratory tests appropriate to assist in the differential diagnosis listed above. Alternatively, when the diagnosis is straightforward, a specific treatment plan can be outlined, including a proposed medication regimen, plans for vocational rehabilitation, a program for social skills training, occupational therapy, marital counseling, or other ancillary treatments appropriate to the patient’s specific problems.

**Interviewing Techniques**

Although the demands of the interview may vary depending on the patient and his or her illness, some techniques are common to most interviewing situations.

**Establish rapport as early in the interview as possible.** It is often best to begin by asking the patient about him- or herself (e.g., What kind of work do you do? What do you do for fun? How old are you?). Questions about these topics should not be asked in a manner that seems to “grill” the patient but rather in a way that indicates that the interviewer is genuinely interested in getting to know the patient. Interest can be indicated through follow-up questions. The overall tone of the opening of the interview should convey warmth and friendliness. Once rapport has been established, the interviewer should then inquire about what kind of problem the patient has been having, and what brought him or her to the clinic or hospital.

**Determine the patient’s chief complaint.** Sometimes this complaint will be helpful and explicit (e.g., “I’ve been feeling very depressed,” or “I’ve been having a pain in my head that other doctors can’t explain”).
At other times, the chief complaint may be relatively vague and require several follow-up questions (e.g., “I don’t know why I’m here—my family brought me,” or “I’ve been having trouble at work”). When the replies are not particularly explicit, the interviewer will need to follow up his or her initial questions with others that will help determine the nature of the patient’s problem (e.g., “What kinds of things have been bothering your family?” “What kind of trouble at work?”). The initial portion of the interview, devoted to eliciting the chief complaint, should take as long as is necessary to determine the patient’s primary problem. When the patient is a clear, logical informant, he or she should be allowed to tell his or her story as freely as possible without interruption. When he or she is a relatively poor informant, the interviewer will need to be active and directive.

**Use the chief complaint to develop a provisional differential diagnosis.** As in the rest of medicine, once the patient’s primary problem has been determined, the interviewer begins to construct in his or her mind a range of explanations as to the specific diagnosis that might lead to that particular problem. For example, if the patient indicates that he or she has been hearing voices, the differential diagnosis includes a variety of disorders that produce this type of psychotic symptom, such as schizophrenia, schizophreniform disorder, psychotic mania, substance abuse involving hallucinogens, or alcoholic hallucinosis. It may be comforting to realize that the fundamental process of interviewing and diagnosing is the same in psychiatry as it is in internal medicine or neurology.

**Rule the various diagnostic possibilities in or out by using more focused and detailed questions.** The existence of DSM-IV-TR is particularly helpful in this regard. If the patient’s chief complaint has suggested three or four different possible diagnoses, the interviewer can determine which is most relevant by referring to the diagnostic criteria for those disorders. Thus the interviewer elicits additional symptoms beyond those already enumerated when discussing the chief complaint. The interviewer inquires about the course and onset of the symptoms and about the presence of physical or psychological precipitants, such as drugs, alcohol, or personal losses.

**Follow up vague or obscure replies with enough persistence to accurately determine the answer to the question.** Some patients, particularly psychotic patients, have great difficulty answering questions clearly and concisely. They may say “yes” or “no” to every question asked. When a pattern of this sort is observed, the patient should be re-
Repeatedly ask the patient to describe his or her experiences as explicitly as possible. For example, if the patient says that he or she hears voices, he or she should be asked to describe them in more detail—whether they are male or female, what they say, and how often they occur. The greater the level of detail the patient is able to provide, the more confident the clinician can feel that the symptom is truly present. Because making a diagnosis of schizophrenia or another major psychiatric disorder has important prognostic implications, the clinician should not hastily accept an answer that suggests vaguely that the patient may have a particular symptom of a disorder.

Let the patient talk freely enough to observe how tightly his or her thoughts are connected. Most patients should be allowed to talk for at least 3 or 4 minutes without interruption in the course of any psychiatric interview. The very laconic patient, of course, will not be able to do this, but most can. The coherence of the pattern in which the patient’s thoughts are presented may provide major clues to the type of problem that he or she is experiencing. For example, patients with mania, schizophrenia, or depression may have any one of a variety of types of “formal thought disorder” (see section “Definitions of Common Signs and Symptoms and Methods for Eliciting Them” later in this chapter). Coherence of thought also may be helpful in making a differential diagnosis between dementia and depression.

Use a mixture of open and closed questions. Interviewers can learn a great deal about patients by mixing up their types of questions, just as a good pitcher mixes up his or her pitches. Open-ended questions permit the patient to ramble and become disorganized, whereas closed questions determine whether the patient can come up with the specifics when pressed. These are important indicators as to whether the patient is conceptually disorganized or confused, whether he or she is being evasive, or whether he or she is answering randomly or falsely. The content of the questions should be mixed as well. For example, at some point in the interview, the interviewer will probably want to drop his or her objective style of interviewing and focus on some personal topic that is affect laden, such as sexual or interpersonal relationships (e.g., “Can you tell me about your relationship with your mother?” or “Tell me about your marriage”). These questions will give the interviewer important clues about the patient’s capacity to show emotional responsiveness. Evaluating the patient’s mood and affect is a fundamental aspect of the psychiatric evaluation, just as is evaluating the coherence of his or her thinking and communication.
Do not be afraid to ask about topics that you or the patient might find difficult or embarrassing. Beginning interviewers sometimes find it difficult to ask about topics such as sexual relationships, sexual experiences, or even use of alcohol or drugs. Yet all this information is part of a complete psychiatric interview and must be included. Nearly all patients expect doctors to ask these questions and are not offended. Likewise, beginning interviewers are sometimes embarrassed to ask about symptoms of psychosis, such as hearing voices. To the interviewer, these symptoms seem so "crazy" that the patient might be insulted by being asked about them. Again, however, information of this type is basic and cannot be avoided. If the patient seems "obviously" not psychotic, questions about psychotic symptoms still should be asked—and in an unapologetic manner. If the patient seems amused or annoyed, then the interviewer can explain that it is necessary to cover all kinds of questions to provide a comprehensive evaluation of each patient.

Do not forget to ask about suicidal thoughts. This is another topic that may seem to fall into the "embarrassing" category. Nevertheless, suicide is a common outcome of many psychiatric illnesses, and it is incumbent on the interviewer to ask about it. The subject can be broached quite tactfully by a question such as "Have you ever felt life isn’t worth living?" The topic of suicide can then be broached, leading to questions such as "Have you ever thought about taking your life?" Further tips on interviewing the suicidal patient are provided in Chapter 15.

Give the patient a chance to ask questions at the end. From the patient’s point of view, there is nothing more frustrating than being interviewed for an hour and then ushered out of the office or examining room with his or her own questions unanswered. The questions that patients ask often tell a great deal about what is on their mind. A patient might be prompted by asking, "Is there anything you feel is important that we haven’t talked about?" Even if their questions are not helpful to the diagnostic process, they are significant to the patient and therefore intrinsically important.

Conclude the initial interview by conveying a sense of confidence and, if possible, of hope. Thank the patient for providing so much information. Compliment him or her, in whatever way it can be done sincerely, on having told his or her story well. Indicate that you now have a much better understanding of his or her problems, and conclude by stating that you will do what you can to help him or her. If you already have a relatively good idea that his or her problem is one that is amenable to treatment, explain
that to the patient. At the end of the initial interview, if you are uncertain about diagnosis or treatment, indicate that you have learned a great deal but that you need to think about the problem some more and perhaps gather more information before arriving at a recommendation.

■ Definitions of Common Signs and Symptoms and Methods for Eliciting Them

A vast panoply of signs and symptoms characterizes major mental illnesses. The following are some of the more common ones seen in psychiatric patients. Where appropriate, some suggested questions are provided that can be used to probe for these symptoms. Follow-up questions appear in parentheses.

Symptoms That Frequently Occur in Psychotic Disorders

The term psychosis has several different meanings, which may be especially confusing to beginning students. In the broadest sense, the term refers to the group of symptoms that characterize the most severe mental illnesses, such as schizophrenia or mania, and that involve an impairment in the ability to make judgments about the boundaries between what is real and unreal (sometimes called “impaired reality testing”). At a more operational level, psychosis refers to a specific group of symptoms that are common in these severe disorders. In the narrowest sense, psychosis is synonymous with having delusions and hallucinations. A somewhat broader operational definition also includes bizarre behavior, disorganized speech (“positive formal thought disorder”), and inappropriate affect. This group of symptoms is also known as positive symptoms; they may occur in any psychotic disorder, but are most common in schizophrenia. A second group of symptoms, referred to as negative symptoms, occur primarily in schizophrenia; they include alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attentional impairment.

Delusions

Delusions represent an abnormality in content of thought. They are false beliefs that cannot be explained on the basis of the patient’s cultural
background. Although delusions are sometimes defined as fixed false beliefs, in their mildest form delusions may persist for only weeks to months, and the patient may question his or her beliefs or doubt them. The patient’s behavior may or may not be influenced by the specific delusions. The assessment of the severity of delusions and of the global severity of delusional thinking should take into account their persistence, their complexity, the extent to which the patient acts on them, the extent to which the patient doubts them, and the extent to which the beliefs deviate from those that nonpsychotic people might have. Beliefs held with less than a delusional intensity are often referred to as overvalued ideas.

**Persecutory delusions.** People with persecutory delusions believe that they are being conspired against or persecuted in some way. Common manifestations include the belief that one is being followed, that one’s mail is being opened, that one’s room or office is bugged, that the telephone is tapped, or that one is being harassed by police, government officials, neighbors, or fellow workers. Persecutory delusions are sometimes relatively isolated or fragmented, but in some cases the person has a complex system of delusions involving both a wide range of forms of persecution and a belief that there is a well-planned conspiracy behind them: for example, that the patient’s house is bugged and that he or she is being followed because the government wrongly considers him or her a secret agent of a foreign government. This delusion may be so complex that at least to the patient, it explains almost everything that happens to him or her.

- Have you had trouble getting along with people?
- Have you felt that people are against you?
- Has anyone been trying to harm you in any way?
- (Do you think people have been conspiring or plotting against you? Who?)

**Delusions of jealousy.** The patient believes that his or her spouse or partner is having an affair with someone. Random bits of information are construed as “evidence.” The person usually goes to great effort to prove the existence of the affair, searching for hair in the bedclothes, the odor of shaving lotion or smoke on clothing, or receipts or checks indicating that a gift has been bought for the lover. Elaborate plans are often made to trap the two together.

- Have you worried that your (husband, wife, boyfriend, girlfriend) might be unfaithful to you?
- (What evidence do you have?)
Delusions of sin or guilt. The patient believes that he or she has committed some terrible sin or done something unforgivable. Sometimes the patient is excessively or inappropriately preoccupied with things he or she did as a child that were perceived to be wrong, such as masturbating. Sometimes the patient feels responsible for causing some disastrous event, such as a fire or an accident, with which he or she in fact has no connection. Sometimes these delusions have a religious flavor, involving the belief that the sin is unpardonable and that the patient will suffer eternal punishment from God. Sometimes the patient simply believes that he or she deserves punishment by society. The patient may spend a good deal of time confessing these sins to whoever will listen.

- Have you felt that you have done some terrible thing?
- Is there anything that is bothering your conscience?
- (What is it?)
- (Do you feel you deserve to be punished for it?)

Grandiose delusions. The patient believes that he or she has special powers or abilities or is a famous person, such as a rock star, Napoleon, or Christ. The patient may believe he or she is writing some definitive book, composing a great piece of music, or developing some wonderful new invention. The patient is often suspicious that someone is trying to steal his or her ideas and may become quite irritated if his or her abilities are doubted.

- Do you have any special powers, talents, or abilities? Great wealth?
- Do you feel you are going to achieve great things?

Religious delusions. The patient is preoccupied with false beliefs of a religious nature. Sometimes these exist within the context of a conventional religious system, such as beliefs about the Second Coming, the Antichrist, or possession by the Devil. At other times, they may involve an entirely new religious system or a pastiche of beliefs from a variety of religions, particularly Eastern religions, such as ideas about reincarnation or Nirvana. Religious delusions may be combined with grandiose delusions (if the patient considers him- or herself a religious leader), delusions of guilt, or delusions of being controlled. Religious delusions must be outside the range of beliefs considered normal for the patient’s cultural and religious background.

- Are you a religious person?
- Have you had any unusual religious experiences?
- Have you become closer to God?
Somatic delusions. The patient believes that somehow his or her body is diseased, abnormal, or changed. For example, the patient may believe that his or her stomach or brain is rotting, that his or her hands have become enlarged, or that his or her facial features are ugly or misshapen (this belief is referred to as dysmorphophobia). Sometimes somatic delusions are accompanied by tactile or other hallucinations, and when this occurs, both should be considered to be present. (For example, a patient believes that he has ball bearings rolling about in his head, placed there by a dentist who filled his teeth, and can actually hear them clanking against one another.)

- Is there anything wrong with the way your body is working?
- Have you noticed any change in your appearance?

Ideas and delusions of reference. The patient believes that insignificant remarks, statements, or events have some special meaning for him or her. For example, the patient walks into a room, sees people laughing, and suspects that they were just talking about him or her. Sometimes items read in the newspaper, heard on the radio, or seen on television are considered special messages to the person. In the case of ideas of reference, the patient is suspicious but recognizes that his or her idea may be erroneous. When the patient actually believes that the statements or events refer to him or her, then this is considered a delusion of reference.

- Have you walked into a room and thought that people were talking about you or laughing at you?
- Have you seen things in magazines or on TV that seem to refer to you or contain a special message for you?
- Have you received special messages in any other ways?

Delusions of passivity (being controlled). The patient has a subjective experience that his or her feelings or actions are controlled by some outside force. The central requirement for this type of delusion is an actual strong subjective experience of being controlled. It does not include simple beliefs or ideas, such as that the patient is acting as an agent of God or that friends or parents are trying to coerce him or her into doing something. Rather, the patient must describe, for example, that his or her body has been occupied by some alien force that is making it move in peculiar ways, or that messages are being sent to his or her brain by radio waves and causing him or her to experience particular feelings that the person recognizes are not his or her own.
Interviewing and Assessment

- Have you felt that you were being controlled by some outside person or force?
- (Do you feel like a puppet on a string?)

**Delusions of mind reading.** The patient believes that people can read his or her mind or know his or her thoughts—that is, the patient subjectively experiences and recognizes that others know his or her thoughts, but he or she does not think that they can be heard out loud.

- Have you had the feeling that people could read your mind or know what you are thinking?

**Thought broadcasting/Audible thoughts.** The patient believes that his or her thoughts are broadcast so that he or she or others can hear them. Sometimes the patient experiences his or her thoughts as a voice outside his or her head; this is an auditory hallucination as well as a delusion. Sometimes the patient feels that his or her thoughts are being broadcast, although he or she cannot hear them himself- or herself. Sometimes he or she believes that his or her thoughts are picked up by a microphone and broadcast on the radio, the television, or through the Internet.

- Have you heard your own thoughts out loud, as if they were a voice outside your head?
- Have you felt that your thoughts were broadcast so that other people could hear them?

**Thought insertion.** The patient believes that thoughts that are not his or her own have been inserted into his or her mind. For example, the patient may believe that a neighbor is practicing voodoo and planting alien sexual thoughts into his or her mind. This symptom should not be confused with experiencing unpleasant thoughts that the patient recognizes as his or her own, such as delusions of persecution or guilt.

- Have you felt that thoughts were being placed into your head by some outside person or force?

**Thought withdrawal.** The patient believes that thoughts have been taken away from his or her mind. He or she is able to describe a subjective experience of beginning a thought and then suddenly having it removed by some alien force. This symptom does not include the mere subjective recognition of alogia.

- Have you felt that your thoughts were taken away by some outside person or force?
Hallucinations

Hallucinations represent an abnormality in perception. They are false perceptions occurring in the absence of an identifiable external stimulus. They may be experienced in any of the sensory modalities, including hearing, touch, taste, smell, and vision. True hallucinations should be distinguished from illusions (which involve a misperception of an external stimulus), hypnagogic and hypnopompic experiences (which occur when a patient is falling asleep and waking up, respectively), or normal thought processes that are exceptionally vivid. If the hallucinations have a religious quality, then they should be judged within the context of what is normal for the patient’s social and cultural background.

Auditory hallucinations. The patient reports hearing voices, noises, or sounds. The most common auditory hallucinations involve hearing voices speaking to the patient or calling his or her name. The voices may be male or female, familiar or unfamiliar, and critical or complimentary. Typically, patients with schizophrenia experience the voices as unpleasant and negative. Less frequently patients report that the voices are comforting or provide companionship. Hallucinations involving sounds other than voices, such as noises or music, should be considered less characteristic and less severe.

- Have you heard voices or other sounds when no one was around or when you could not account for them?
- (What did they say?)

Voices commenting. These hallucinations involve hearing a voice that makes a running commentary on the patient’s behavior or thought as it occurs (e.g., “Carl is brushing his teeth. Carl is about to eat breakfast”).

- Have you heard voices commenting on what you are thinking or doing?
- (What do they say?)

Voices conversing. These hallucinations involve hearing two or more voices talking with each other, usually discussing something about the patient.

- Have you heard two or more voices talking with each other?
- (What do they say?)

Somatic or tactile hallucinations. Somatic or tactile hallucinations involve experiencing peculiar physical sensations in the body. They in-
include burning, itching sensations, or tingling sensations or the perception that the body has changed in shape or size.

- Have you had burning sensations or other strange sensations in your body?
- (What were they?)

**Olfactory hallucinations.** The patient experiences unusual smells that are typically quite unpleasant. Sometimes the patient may believe that he or she smells bad. This belief should be considered a hallucination if the patient can actually smell the odor but should be considered a delusion if he or she believes that only others can smell the odor.

- Have you experienced any unusual smells or smells that others do not notice?
- (What were they?)

**Visual hallucinations.** The patient sees shapes or people that are not actually present. Sometimes these are shapes or colors, but most typically they are figures of people or humanlike objects. They also may be characters of a religious nature, such as the Devil or Christ. As always, visual hallucinations involving religious themes should be judged within the context of the patient’s cultural background.

- Have you had visions or seen things that other people cannot?
- (What did you see?)

**Bizarre or Disorganized Behavior**

The patient’s behavior is unusual, bizarre, or fantastic. The information for this symptom will sometimes come from the patient, sometimes come from other sources, and sometimes come from direct observation. Bizarre behavior due to the immediate effects of intoxication with alcohol or drugs should not be considered a symptom of psychosis. Social and cultural norms must be considered in making the determination of bizarre behavior, and detailed examples should be elicited and noted.

**Clothing and appearance.** The patient dresses in an unusual manner or does other strange things to alter his or her appearance. For example, the patient may shave off all his or her hair or paint body parts different colors. The patient’s clothing may be quite unusual; for example, he or she may choose to wear some outfit that appears generally inappropriate and unacceptable, such as a baseball cap backward with rubber ga-
loshes and long underwear covered by denim overalls. The patient may dress in a fantastic costume representing some historical personage or a person from outer space. He or she may wear clothing completely inappropriate to the climatic conditions, such as heavy wools in summer.

- Has anyone made comments about the way you dress?
- (What did they say?)

**Social and sexual behavior.** The patient may do things that are considered inappropriate according to usual social norms. For example, he or she may masturbate in public, urinate or defecate in inappropriate receptacles, walk along the street muttering to him- or herself, or begin talking to people whom he or she has never before met about intimate personal matters (as when riding on a subway or standing in some public place). He or she may drop to his or her knees praying and shouting or suddenly assume a fetal position when in the midst of a crowd. He or she may make inappropriate sexual overtures or remarks to strangers.

- Have you done anything that others might think is unusual or that has called attention to yourself?
- Has anyone complained or commented about your behavior?
- (What were you doing at the time?)

**Aggressive and agitated behavior.** The patient may behave in an aggressive, agitated manner, often quite unpredictably. He or she may start arguments inappropriately with friends or members of his or her family or accost strangers on the street and begin haranguing them angrily. He or she may write letters or send e-mails of a threatening or angry nature to government officials or others with whom he or she has some quarrel. Occasionally, patients may perform violent acts, such as injuring or tormenting animals or attempting to injure or kill human beings.

- Have you been unusually angry or irritable with anyone?
- (How did you express your anger?)
- Have you done anything to try to harm animals or people?

**Ritualistic or stereotyped behavior.** The patient may develop a set of repetitive actions or rituals that he or she must perform over and over. Sometimes he or she will attribute some symbolic significance to these actions and believe that they are either influencing others or preventing himself or herself from being influenced. For example, he or she may
eat jelly beans every night for dessert, assuming that different consequences will occur depending on the color of the jelly beans. He or she may have to eat foods in a particular order, wear particular clothes, or get dressed in a certain order. He or she may have to write messages to him- or herself or to others over and over, sometimes in an unusual or occult language.

- Are there any things that you do over and over?
- Are there any things that you have to do in a certain way or in a particular order?
- (Why do you do it?)
- (Does it have any special meaning or significance to you?)

**Disorganized Speech (Positive Formal Thought Disorder)**

Disorganized speech, which is also referred to as positive formal thought disorder, is fluent speech that tends to communicate poorly for a variety of reasons. The patient tends to skip from topic to topic without warning; is distracted by events in the nearby environment; joins words together because they are semantically or phonologically alike, even though they make no sense; or ignores the question asked and answers another. This type of speech may be rapid, and it frequently seems quite disjointed. Unlike alogia (negative formal thought disorder; see subsection “Alogia” later in this chapter), a wealth of detail is provided, and the flow of speech tends to have an energetic rather than an apathetic quality to it.

To evaluate thought disorder, the patient should be permitted to talk without interruption for as long as 5 minutes. The interviewer should observe closely the extent to which the patient’s sequencing of ideas is well connected. Close attention should also be paid to how well the patient can reply to various types of questions, ranging from simple (“When were you born?”) to more complicated (“Why did you come to the hospital?”). If the ideas seem vague or incomprehensible, the interviewer should prompt the patient to clarify or elaborate.

**Derailment (loose associations).** The patient has a pattern of spontaneous speech in which the ideas slip off the track onto another that is clearly but obliquely related or onto one completely unrelated. Things may be said in juxtaposition that lack a meaningful relationship, or the patient may shift idiosyncratically from one frame of reference to another. At times, there may be a vague connection between the ideas, and at other times, none will be apparent. This pattern of speech is often characterized as sounding “disjointed.” Perhaps the most common manifestation of this disorder is a slow, steady slippage, with no single
derailment being particularly severe, so that the speaker gets farther and farther off the track with each derailment without showing any awareness that his or her reply no longer has any connection with the question that was asked. This abnormality is often characterized by lack of cohesion between clauses and sentences and by unclear pronoun references.

**Interviewer:** Did you enjoy college?
**Subject:** Um-hm. Oh hey well I, oh, I really enjoyed some communities. I tried it, and the, and the next day when I’d be going out, you know, um, I took control, like, uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago and she was going to the junior college. And we lived in the Y.W.C.A., so she wanted to put it, um, peroxide on my hair, and she did, and I got up and I looked at the mirror and tears came to my eyes. Now do you understand it—I was fully aware of what was going on but why couldn’t I, I…why the tears? I can’t understand that, can you?

**Tangentiality.** The patient replies to a question in an oblique, tangential, or even irrelevant manner. The reply may be related to the question in some distant way, or the reply may be unrelated and seem totally irrelevant.

**Interviewer:** What city are you from?
**Subject:** Well, that’s a hard question to answer because my parents… I was born in Iowa, but I know that I’m white instead of black, so apparently I came from the North somewhere and I don’t know where, you know, I really don’t know whether I’m Irish or Scandinavian, or I don’t, I don’t believe I’m Polish, but I think I’m, I think I might be German or Welsh.

**Incoherence (word salad, schizophasia).** The patient has a pattern of speech that is essentially incomprehensible at times. Incoherence is often accompanied by derailment. It differs from derailment in that with incoherence the abnormality occurs at the level of the sentence or clause, which contains words or phrases that are joined incoherently. The abnormality in derailment involves unclear or confusing connections between larger units, such as sentences or clauses. This type of language disorder is relatively rare. When it occurs, it tends to be severe or extreme, and mild forms are quite uncommon. It may sound quite similar to Wernicke’s aphasia or jargon aphasia, and in these cases the disorder should only be called incoherence definitively when history and laboratory data exclude the possibility of a past stroke and clinical testing for aphasia has negative results.

**Interviewer:** What do you think about current political issues like the energy crisis?
Subject: They’re destroying too many cattle and oil just to make soap. If we need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should, get pop but the best thing to get, is motor oil, and, money. May, may as, well go there and, trade in some, pop caps and, uh, tires, and tractors to group, car garages, so they can pull cars away from wrecks, is what I believed in.

Illogicality. The patient has a pattern of speech in which conclusions are reached that do not follow logically. Illogicality may take the form of non sequiturs (meaning “it does not follow”), in which the patient makes a logical inference between two clauses that is unwarranted or illogical. It may take the form of faulty inductive inferences. It may also take the form of reaching conclusions based on faulty premises without any actual delusional thinking.

Subject: Parents are the people that raise you. Anything that raises you can be a parent. Parents can be anything—material, vegetable, or mineral—that has taught you something. Parents would be the world of things that are alive, that are there. Rocks—a person can look at a rock and learn something from it, so that would be a parent.

Circumstantiality. The patient has a pattern of speech that is very indirect and delayed in reaching its goal ideas. In the process of explaining something, the speaker brings in many tedious details and sometimes makes parenthetical remarks. Circumstantial replies or statements may last for many minutes if the speaker is not interrupted and urged to get to the point. Interviewers will often recognize circumsstantiality on the basis of needing to interrupt the speaker to complete the process of history taking within an allotted time. When not called circumstantial, these people are often referred to as long-winded.

Although it may coexist with instances of poverty of content of speech or loss of goal, circumstantiality differs from poverty of content of speech in containing excessive amplifying or illustrative detail and from loss of goal in that the goal is eventually reached if the person is allowed to talk long enough. It differs from derailment in that the details presented are closely related to some particular goal or idea and that the particular goal or idea must, by definition, eventually be reached (unless the patient is interrupted by an impatient interviewer).

Pressure of speech. The patient has an increase in the amount of spontaneous speech as compared with what is considered ordinary or socially customary. The patient talks rapidly and is difficult to interrupt. Pressured speech is often seen in mania but can be found in other syndromes.
as well. Some sentences may be left uncompleted because of eagerness to get on to a new idea. Simple questions that could be answered in only a few words or sentences are answered at great length so that the answer takes minutes rather than seconds and indeed may not stop at all if the speaker is not interrupted. Even when interrupted, the speaker often continues to talk. Speech tends to be loud and emphatic. Sometimes speakers with severe pressure will talk without any social stimulation and talk even though no one is listening. When patients are receiving antipsychotics or mood stabilizers, their speech is often slowed down by medication, and then it can be judged only on the basis of amount, volume, and social appropriateness. If a quantitative measure is applied to the rate of speech, then a rate greater than 150 words per minute is usually considered rapid or pressured. This disorder may be accompanied by derailment, tangentiality, or incoherence, but it is distinct from them.

**Distractible speech.** During the course of a discussion or an interview, the patient stops talking in the middle of a sentence or idea and changes the subject in response to a nearby stimulus, such as an object on a desk, the interviewer’s clothing or appearance, and so forth.

*Subject:* Then I left San Francisco and moved to...where did you get that tie? It looks like it's left over from the '50s. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba diving?

**Clanging.** The patient has a pattern of speech in which sounds rather than meaningful relations appear to govern word choice, so that the intelligibility of the speech is impaired and redundant words are introduced in addition to rhyming relationships. This pattern of speech also may include punning associations, so that a word similar in sound brings in a new thought.

*Subject:* I'm not trying to make a noise. I'm trying to make sense. If you can make sense out of nonsense, well, have fun. I'm trying to make sense out of sense. I'm not making sense [cents] anymore. I have to make dollars.

**Catatonic Motor Behavior**

Catatonic motor symptoms are not common and should only be considered present when they are obvious and have been directly observed by the clinician or some other professional.

**Stupor.** The patient has a marked decrease in reactivity to the environment and reduction of spontaneous movements and activity. The patient may appear to be aware of the nature of his or her surroundings.
Rigidity. The patient shows signs of motor rigidity, such as resistance to passive movement.

Waxy flexibility (catalepsy). The patient maintains postures into which he or she is placed for at least 15 seconds.

Excitement. The patient has apparently purposeless and stereotyped excited motor activity not influenced by external stimuli.

Posturing and mannerisms. The patient voluntarily assumes an inappropriate or a bizarre posture. Manneristic gestures or tics also may be observed. These involve movements or gestures that appear artificial or contrived, are not appropriate to the situation, or are stereotyped and repetitive. (Patients with tardive dyskinesia may have manneristic gestures or tics, but these should not be considered manifestations of cata-tonia.)

Inappropriate Affect
The patient’s affect expressed is inappropriate or incongruous, not simply flat or blunted. Most typically, this manifestation of affective disturbance takes the form of smiling or assuming a silly facial expression while talking about a serious or sad subject. For example, the patient may laugh inappropriately when talking about thoughts of harming another person. (Occasionally, patients may smile or laugh when talking about a serious subject that they find uncomfortable or embarrassing. Although their smiling may seem inappropriate, it is due to anxiety and therefore should not be rated as inappropriate affect.)

Alogia
Alogia is a general term coined to refer to the impoverished thinking and cognition that often occur in patients with schizophrenia (from the Greek α, “no”; λόγος, “mind, thought”). Patients with alogia have thinking processes that seem empty, turgid, or slow. Because thinking cannot be observed directly, it is inferred from the patient’s speech. The two major manifestations of alogia are nonfluent empty speech (poverty of speech) and fluent empty speech (poverty of content of speech). Blocking and increased latency of response also may reflect alogia.

Poverty of speech. The patient has a restricted amount of spontaneous speech, so that replies to questions tend to be brief, concrete, and unelaborated. Unprompted additional information is rarely provided. Replies may be monosyllabic, and some questions may be left unanswered altogether. When confronted with this speech pattern, the inter-
viewer may find him- or herself frequently prompting the patient, to encourage elaboration of replies. To elicit this finding, the examiner must allow the patient adequate time to answer and to elaborate his or her answer.

Interviewer: Can you tell me something about what brought you to the hospital?
Subject: A car.
Interviewer: I was wondering about what kinds of problems you’ve been having. Can you tell me something about them?
Subject: I dunno.

Poverty of content of speech. Although the patient’s replies are long enough so that speech is adequate in amount, it conveys little information. Language tends to be vague, often overabstract or overconcrete, repetitive, and stereotyped. The interviewer may recognize this finding by observing that the patient has spoken at some length but has not given adequate information to answer the question. Alternatively, the patient may provide enough information but require many words to do so, so that a lengthy reply can be summarized in a sentence or two. This abnormality differs from circumstantiality in that the circumstantial patient tends to provide a wealth of detail.

Interviewer: Why is it, do you think, that people believe in God?
Subject: Well, first of all because He, uh, He are the person that is their personal savior. He walks with me and talks with me. And, uh, the understanding that I have, um, a lot of people, they don’t readily, uh, know their own personal self. Because, uh, they ain’t, they all, just don’t know their personal self. They don’t, know that He, uh—seemed like to me, a lot of ‘em don’t understand that He walks and talks with ‘em.

Blocking. The patient’s train of speech is interrupted before a thought or an idea has been completed. After a period of silence, which may last from a few seconds to minutes, the person indicates that he or she cannot recall what he or she has been saying or meant to say. Blocking should be judged to be present only if a person voluntarily describes losing his or her thought or if, on questioning by the interviewer, the person indicates that that was his or her reason for pausing.

Subject: So I didn’t want to go back to school so I…(1-minute silence while the patient stares blankly)
Interviewer: What about going back to school? What happened?
Subject: I dunno. I forgot what I was going to say.
Increased latency of response. The patient takes a longer time to reply to questions than is usually considered normal. He or she may seem distant, and sometimes the examiner may wonder whether he or she has heard the question. Prompting usually indicates that the patient is aware of the question but has been having difficulty formulating his or her thoughts to make an appropriate reply.

**Interviewer:** When were you last in the hospital?
**Subject:** (30-second pause) A year ago.
**Interviewer:** Which hospital was it?
**Subject:** (30-second pause) This one.

Perseveration. The patient persistently repeats words, ideas, or phrases so that once a patient begins to use a particular word, he or she continually returns to it in the process of speaking. Perseveration differs from “stock words” in that the repeated words are used in ways inappropriate to their usual meaning. Some words or phrases are commonly used as pause-fillers, such as “you know” or “like,” and these should not be considered perseverations.

**Interviewer:** Tell me what you are like—what kind of person you are.
**Subject:** I’m from Marshalltown, Iowa. That’s 60 miles northwest, northeast of Des Moines, Iowa. And I’m married at the present time. I’m 36 years old; my wife is 35. She lives in Garwin, Iowa. That’s 15 miles southeast of Marshalltown, Iowa. I’m getting a divorce at the present time. And I am at present in a mental institution in Iowa City, Iowa, which is 100 miles southeast of Marshalltown, Iowa.

Affective Flattening or Blunting

Affective flattening or blunting manifests itself as a characteristic impoverishment of emotional expression, reactivity, and feeling. Affective flattening can be evaluated by observation of the patient’s behavior and responsiveness during a routine interview. The evaluation of affective expression may be influenced by the patient’s use of prescription drugs, because the parkinsonian side effects of antipsychotics may lead to mask-like facies and diminished associated movements. Other aspects of affect, such as responsivity or appropriateness, will not be affected, however.

Unchanging facial expression. The patient’s face does not change expression, or changes less than normally expected, as the emotional content of the discourse changes. His or her face appears wooden, me-
chanical, and frozen. Because antipsychotics may partially mimic this effect, the interviewer should be careful to note whether the patient is taking medication.

**Decreased spontaneous movements.** The patient sits quietly throughout the interview and shows few or no spontaneous movements. He or she does not shift position, move his or her legs, or move his or her hands or does so less than normally expected.

**Paucity of expressive gestures.** The patient does not use his or her body as an aid in expressing his or her ideas through means such as hand gestures, sitting forward in his or her chair when intent on a subject, or leaning back when relaxed. Paucity of expressive gestures may occur in addition to decreased spontaneous movements.

**Poor eye contact.** The patient avoids looking at others or using his or her eyes as an aid in expression. He or she appears to be staring into space even when he or she is talking. The interviewer should consider the quality as well as the quantity of eye contact.

**Affective nonresponsivity.** The patient fails to smile or laugh when prompted. This function may be tested by smiling or joking in a way that would usually elicit a smile from a psychiatrically normal individual.

**Lack of vocal inflections.** While speaking, the patient fails to show normal vocal emphasis patterns. Speech has a monotonic quality, and important words are not emphasized through changes in pitch or volume. The patient also may fail to change volume with changes of content, so that he or she does not drop his or her voice when discussing private topics or raise it as he or she discusses things that are exciting or for which louder speech might be appropriate.

**Avolition-Apathy**

Avolition-apathy manifests itself as a characteristic lack of energy and drive. Patients become inert and are unable to mobilize themselves to initiate or persist in completing many different kinds of tasks. Unlike the diminished energy or interest of depression, the avolitional symptom complex in schizophrenia usually is not accompanied by saddened or depressed affect. The avolitional symptom complex often leads to severe social and economic impairment.

**Grooming and hygiene.** The patient pays less attention to grooming and hygiene than is normal. Clothing may appear sloppy, outdated, or
soiled. He or she may bathe infrequently and not care for his or her hair, nails, or teeth—leading to manifestations such as greasy or uncombed hair, dirty hands, body odor, or unclean teeth and bad breath. Overall, the appearance is dilapidated and disheveled. In extreme cases, the patient may even have poor toilet habits.

**Impersistence at work or school.** The patient has difficulty in seeking or maintaining employment (or doing schoolwork) as appropriate for his or her age and gender. If a student, he or she may have registered for courses but dropped several or all of them. If of working age, the patient may have found it difficult to work at a job because of an inability to persist in completing tasks and apparent irresponsibility. He or she may go to work irregularly, wander away early, fail to complete expected assignments, or complete them in a disorganized manner. He or she may simply sit around the house and not seek any employment or seek it only in an infrequent or desultory manner. If a homemaker or a retired person, the patient may fail to complete chores, such as shopping or cleaning, or complete them in a careless and half-hearted way. If in a hospital or an institution, he or she does not attend or persist in vocational or rehabilitative programs effectively.

- Have you been able to (work, go to school) during the past month?
- Have you been attending vocational rehabilitation or occupational therapy sessions (in the hospital)?
- What have you been able to do?
- (Do you have trouble finishing what you start?)
- (What kinds of problems have you had?)

**Physical anergia.** The patient tends to be physically inert; he or she may sit in a chair for hours at a time and not initiate any spontaneous activity. If encouraged to become involved in an activity, he or she may participate only briefly and then wander away or disengage him- or herself and return to sitting alone. He or she may spend large amounts of time in some relatively mindless and physically inactive task such as watching television or playing solitaire. Family members may report that the patient spends most of his or her time at home “doing nothing except sitting around.” Either at home or in an inpatient setting, he or she may spend much of his or her time sitting unoccupied.

- How have you been spending your time?
- Do you have any trouble getting yourself going?
Anhedonia-Asociality

Anhedonia-asociality encompasses the patient’s difficulties in experiencing interest or pleasure. It may express itself as a loss of interest in pleasurable activities, an inability to experience pleasure when participating in activities normally considered pleasurable, or a lack of involvement in social relationships of various kinds.

Recreational interests and activities. The patient may have few or no interests, activities, or hobbies. Although this symptom may begin insidiously or slowly, there will usually be some obvious decline from an earlier level of interest and activity. Patients with relatively milder loss of interest will engage in some activities that are passive or non-demanding, such as watching television, or will show only occasional or sporadic interest. Patients with the most extreme loss will appear to have a complete and intractable inability to become involved in or enjoy activities. The evaluation in this area should take both the quality and the quantity of recreational interests into account.

- What do you do for enjoyment?
- (How often do you do those things?)
- Have you been attending recreational therapy?
- (What have you been doing?)
- (Do you enjoy it?)

Sexual interest and activity. The patient may show a decrement in sexual interest and activity or enjoyment as compared to what would be judged healthy for the patient’s age and marital status. Individuals who are married may manifest disinterest in sex or may engage in intercourse only at the partner’s request. In extreme cases, the patient may not engage in sex at all. Single patients may go for long periods without sexual involvement and make no effort to satisfy this drive. Whether married or single, patients may report that they subjectively feel only minimal sex drive or that they take little enjoyment in sexual intercourse or in masturbatory activity even when they engage in it.

- What has your sex drive been like?
- Have you been able to enjoy sex lately?
- (What is your usual sexual outlet?)
- (When was the last time you engaged in sexual activity?)

Ability to feel intimacy and closeness. The patient may be unable to form intimate and close relationships of a type appropriate for his or her
age, gender, and family status. In the case of a younger person, this area should be evaluated in terms of relationships with the opposite sex and with parents and siblings. In the case of an older person who is married, the relationship with the spouse and with children should be evaluated, whereas unmarried individuals should be judged in terms of opposite-or same-sex relationships or relationships with family members who live nearby. Patients may show few or no feelings of affection to available family members, or they may have arranged their lives so that they are completely isolated from any intimate relationships, live alone, and make no effort to initiate contacts with family or others.

- Do you feel close to your family (husband, wife, partner, children)?
- Is there anyone outside your family to whom you feel especially close?
- (How often do you see [them, him, her]?)

Relationships with friends and peers. Patients also may be relatively restricted in their relationships with friends and peers of either gender. They may have few or no friends, make little or no effort to develop such relationships, and choose to spend all or most of their time alone.

- Do you have many friends?
- (Are you very close to them?)
- (How often do you see them?)
- (What do you do together?)
- Have you gotten to know any patients in the hospital?

Attention

Attention is often poor in patients with severe mental illnesses. The patient may have trouble focusing his or her attention or may be able to focus only sporadically and erratically. He or she may ignore attempts to converse with him or her, wander away while in the middle of an activity or a task, or appear to be inattentive when engaged in formal testing or interviewing. He or she may or may not be aware of the difficulty in focusing attention.

Social inattentiveness. While involved in social situations or activities, the patient appears inattentive. He or she looks away during conversations, does not pick up the topic during a discussion, or appears uninvolved or disengaged. He or she may abruptly terminate a discussion or a task without any apparent reason. He or she may seem “spacey” or “out of it.” He or she may seem to have poor concentration when playing games, reading, or watching television.
Inattentiveness during mental status testing. The patient may perform poorly on simple tests of intellectual functioning despite adequate education and intellectual ability. Inattentiveness should be assessed by having the patient spell world (or some equivalent five-letter word) backward and by serial 7s (at least a 10th-grade education) or serial 3s (at least a 6th-grade education) for a series of five subtractions.

Manic Symptoms

Euphoric mood. The patient has had one or more distinct periods of euphoric, irritable, or expansive mood not due to alcohol or drug intoxication.

- Have you been feeling too good or even high—clearly different from your normal self?
- (Do your friends or family think this is more than just feeling good?)
- Have you felt irritable and easily annoyed?
- (How long has this mood lasted?)

Increase in activity. The patient shows an increase in involvement or activity level associated with work, family, friends, sex drive, new projects, interests, or activities (e.g., telephone calls, letter writing).

- Are you more active or involved in things compared with the way you usually are?
- (How about at work, at home, with your friends, or with your family?)
- (What about your involvement in hobbies or other interests?)
- Have you been unable to sit still, or have you had to be moving or pacing back and forth?

Racing thoughts/Flight of ideas. The patient has the subjective experience that his or her thinking is markedly accelerated. For example, “My thoughts are ahead of my speech.”

- Have your thoughts been racing through your mind?
- Do you have more ideas than usual?

Inflated self-esteem. The patient has increased self-esteem and appraisal of his or her worth, contacts, influence, power, or knowledge (may be delusional) as compared with his or her usual level. Persecutory delusions should not be considered evidence of grandiosity unless
the patient feels persecution is due to some special attributes (e.g., power, knowledge, or contacts).

- Do you feel more self-confident than usual?
- Do you feel that you are a particularly important person or that you have special talents or abilities?

**Decreased need for sleep.** The patient needs less sleep than usual to feel rested. (This rating should be based on the average of several days rather than a single severe night.)

- Do you need less sleep than usual to feel rested?
- (How much sleep do you ordinarily need?)
- (How much sleep do you need now?)

**Distractibility.** The patient’s attention is too easily drawn to unimportant or irrelevant external stimuli. For example, the patient gets up and inspects some item in the room while talking or listening, shifts his or her topic of speech, and so forth.

- Are you easily distracted by things around you?

**Poor judgment.** The patient shows excessive involvement in activities that have a high potential for painful consequences that are not recognized (e.g., buying sprees, sexual indiscretions, foolish business investments, reckless giving).

- Have you done anything that caused trouble for you or your family or friends?
- Looking back now, have you done anything that showed poor judgment?
- Have you done anything foolish with money?
- Have you done anything sexually that was unusual for you?

**Depressive Symptoms**

**Dysphoric mood.** The patient feels sad, despondent, discouraged, or unhappy; significant anxiety or tense irritability also should be rated as a dysphoric mood. The evaluation should be made irrespective of length of mood.

- Have you been having periods of feeling depressed, sad, or hopeless? When you didn’t care about anything or couldn’t enjoy anything?
• Have you felt tense, anxious, or irritable?  
• (How long did this last?)

**Change in appetite or weight.** The patient has had significant weight change. This should not include change due to dieting, unless the dieting is associated with some depressive belief that approaches delusional proportions.

• Have you had any changes in your appetite—either increased or decreased?  
• Have you lost or gained much more weight than is usual for you?

**Insomnia or hypersomnia.** Insomnia may include waking up after only a few hours of sleep as well as difficulty in getting to sleep. Patterns of insomnia include initial (trouble going to sleep), middle (waking in the middle of the night but eventually falling asleep again), and terminal (waking early—e.g., 2:00 A.M. to 5:00 A.M.—and remaining awake).

• Have you had trouble sleeping?  
• (What was it like?)  
• (Do you have trouble falling asleep?)  
• (Do you wake up too early in the morning?)  
• Have you been sleeping more than usual?  
• How much sleep do you get in a typical 24-hour period?

**Psychomotor agitation.** The patient is unable to sit still, with a need to keep moving. (Do not include mere subjective feelings of restlessness.) Objective evidence (e.g., hand wringing, fidgeting, pacing) should be present.

• Have you felt restless or agitated?  
• Do you have trouble sitting still?

**Psychomotor retardation.** The patient feels slowed down and experiences great difficulty moving. (Do not include mere subjective feelings of being slowed down.) Objective evidence (e.g., slowed speech) should be present.

• Have you been feeling slowed down?

**Loss of interest or pleasure.** The patient has loss of interest or pleasure in usual activities or a decrease in sexual drive. This may be similar
to the anhedonia seen in psychosis. In the depressive syndrome, loss of interest or pleasure is invariably accompanied by intense, painful affect, whereas in psychosis, the affect is often blunted.

- Have you noticed a change in your interest in things you normally enjoy?
- (What have you been less interested in?)

**Loss of energy.** The patient has a loss of energy, becomes easily fatigued, or feels tired. These energy comparisons should be based on the person’s usual activity level whenever possible.

- Have you had a tendency to feel more tired than usual?
- (Have you been feeling as if all your energy is drained?)

**Feelings of worthlessness.** In addition to feelings of worthlessness, the patient may report feelings of self-reproach or excessive or inappropriate guilt. (Either may be delusional.)

- Have you been feeling down on yourself?
- Have you been feeling guilty about anything?
- (Could you tell me about some of the things for which you feel guilty?)

**Diminished ability to think or concentrate.** The patient complains of diminished ability to think or concentrate, such as slowed thinking or indecisiveness, not associated with marked derailment or incoherence.

- Have you had trouble thinking?
- What about your concentration?
- Have you had trouble making decisions?

**Recurrent thoughts of death/suicide.** The patient has thoughts about death and dying, plus possible wishes to be dead or to take his or her life.

- Have you been thinking about death or about taking your own life?
- (How often have these thoughts occurred?)
- (What were you thinking of doing?)

**Distinct quality to mood.** The patient’s depressed mood is experienced as distinctly different from the kind of feelings experienced after
the death of a loved one. If the patient has not lost a loved one, ask him or her to compare the feelings with those after some significant personal loss appropriate to his or her age and experience.

- The feelings of (sadness) you are having now—are they the same as the feelings you would have had when someone close to you died, or are they different?
- (How are they similar or different?)

**Nonreactivity of mood.** The patient does not feel much better, even temporarily, when something good happens.

- Do your feelings of depression go away or get better when you do something you enjoy, such as talking with friends, visiting your family, or playing with a pet (engaging in some other favorite activity)?

**Diurnal variation.** The patient’s mood shifts during the course of the day. Some patients feel terrible in the morning but feel steadily better as the day goes on and even near normal in the evening. Others feel good in the morning and worse as the day progresses.

- Is there any time of the day that is especially bad for you?
- (Do you feel worse in the morning? In the evening? Or is it about the same all the time?)

**Anxiety Symptoms**

**Panic attacks.** The patient has discrete episodes of intense fear or discomfort in which a variety of symptoms occur, such as shortness of breath, dizziness, palpitations, or shaking.

- Have you ever experienced a sudden attack of panic or fear, in which you felt extremely uncomfortable?
- (How long did it last?)
- (Did you notice any other symptoms occurring at the same time?)
- (Did you feel as if you were going to die or go crazy?)

**Agoraphobia.** The patient has a fear of going outside (literally “a fear of the marketplace”). In many patients, however, the fear is more generalized and involves being afraid of being in a place or situation from which escape might be difficult.

- Have you ever been afraid of going outside, so that you tended to just stay home all the time?
• Have you been afraid of getting caught or trapped somewhere so that you would be unable to escape?

Social phobia. The patient has a fear of being in some social situation in which he or she will be seen by others and may do something that he or she might find to be humiliating or embarrassing. Some common social phobias include fear of public speaking, fear of eating in front of others, and fear of using public bathrooms.

• Do you have any special fears, such as a fear of public speaking?
• Of eating in front of others?

Specific phobia. The patient is afraid of some specific circumscribed stimulus, such as animals (e.g., snakes, insects), seeing blood, being at high places, or being afraid to fly on airplanes.

• Are you afraid of snakes?
• The sight of blood?
• Air travel?
• Do you have any other specific fears?

Obsessions. The patient experiences persistent ideas, thoughts, or impulses that are unwanted and experienced as unpleasant. The patient tends to ruminate and worry about them. The patient may try to ignore or suppress them but typically finds this difficult. Some common obsessions include repetitive thoughts of performing some violent act or becoming contaminated by touching other people or inanimate objects, such as a doorknob.

• Are you ever bothered by persistent ideas that you can’t get out of your head, such as being dirty or contaminated?
• (Can you give me some specific examples?)

Compulsions. The patient has to perform specific acts over and over in a way that he or she recognizes to be senseless or inappropriate. The compulsions are usually performed to ease some worry or obsession or to prevent some feared event from occurring. For example, a patient may have the worry that he or she has left the door unlocked and must return to check it repeatedly. Obsessions about contamination may lead to repetitive hand washing. Obsessions about thoughts of violence may lead to ritualistic behavior designed to prevent injury to the person about whom violence has been imagined.
• Are there any types of actions that you have to perform over and over, such as washing your hands or checking the stove?
• (Can you give me some examples?)

Self-Assessment Questions

1. Describe the way in which the patient’s chief complaint can be used to take a history and to develop a differential diagnosis.
2. Describe several techniques that are important for concluding the initial interview with a patient.
3. Enumerate the components of a standard psychiatric history, giving each of the main headings of the overall outline.
4. Summarize the major components of the mental status examination.
5. Enumerate and describe at least four of the positive symptoms of psychosis. Give examples of some typical kinds of delusions and hallucinations.
6. Enumerate and describe at least four negative symptoms.
7. Enumerate and define some of the symptoms observed in depression.
8. Enumerate and define some of the symptoms observed in mania.
9. Enumerate and define some of the symptoms observed in anxiety disorders.
CHAPTER 3

The Neurobiology and Genetics of Mental Illness

Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter, and jests, as well as our sorrows, pains, griefs, and fears. Through it, in particular, we think, see, hear…

Hippocrates

STUDENTS OF PSYCHIATRY are privileged to study diseases that affect the most interesting and important organ in the body: the miraculous human brain. The human brain has created and invented the myriad achievements that surround us every day—skyscrapers, computers, complex economic markets, advances in medical science ranging from vaccines to antibiotics to magnetic resonance scanners, an understanding of quantum mechanics and chaos theory, and art, music, and literature. These achievements have been accomplished because the human brain is one of the most complex systems in the universe. Composed of more than 100 billion neurons (more nerve cells than the stars in the Milky Way), the brain expands its communicating and thinking power by multiplying connectivity through an average of 1,000–10,000 synapses per nerve cell. The synapses are “plastic” in that they remodel themselves continuously in response
to changes in their environment and the inputs that they receive. The whole human brain system is composed of feedback loops and circuits composed of multiple neurons, further expanding the fine-tuning and thinking capacities. The abilities that we all have to think, feel emotions, and relate to other people in normal ways depend on the activity of this complex organ. The disturbances in thought, emotion, and behavior that we observe in the mentally ill also are ultimately due to aberrations in the brain. Understanding those brain aberrations—and correcting them—is our ultimate challenge.

Modern psychiatry stretches from mind to molecule and from clinical neuroscience to molecular biology as it attempts to understand how aberrations in thinking and behavior are rooted in underlying biological mechanisms. During the past several decades neuroscience has grown to become one of the largest domains of scientific research. This chapter provides a selective overview of a few topics from neurobiology that are relevant to understanding either the symptoms or treatment of mental illnesses.

Anatomical and Functional Brain Systems

The human brain may be divided into a variety of systems that mediate many different cognitive, emotional, and perceptual functions, such as the motor system, the visual system, the auditory system, and the somatosensory system. The systems that are of special interest to psychiatry are those that represent circuitry or functions that are particularly disturbed in mental illnesses. These systems represent some of the “last frontiers” in the study of the human brain. Three important anatomical systems are the prefrontal system, the limbic system, and the basal ganglia system. Important functional systems include the executive function, memory, language, attention, and reward systems.

Any method for dividing the brain into parts or systems is somewhat arbitrary because the three anatomical systems are all interconnected with one another and work interactively. The functional systems are also highly interdependent with one another and with the prefrontal, limbic, and basal ganglia systems as well. Furthermore, the division of the brain into “functional and anatomical systems” and “neurochemical systems” is also arbitrary. These oversimplifications are introduced purely for conceptual convenience, providing a strategy for reducing
the overwhelming complexity of the central nervous system (CNS) to a level that permits discussion and analysis. Ultimately, however, a full understanding of the brain can only occur by an ongoing process of analysis (or breakdown and simplification) as well as synthesis (or rebuilding and unifying).

One must add a word of caution about our existing level of ignorance. We do not as yet have a complete map of the human brain, summarizing accurately its various neural circuits and chemical anatomy. This process is ongoing and becoming much more sophisticated, particularly with the aid of neuroimaging techniques such as structural and functional magnetic resonance imaging (sMRI and fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), magnetoencephalography (MEG), and positron emission tomography (PET). These technologies permit in vivo study of the anatomy and physiology of the human brain in ways that were previously impossible. Prior to the availability of neuroimaging, our knowledge about circuitry and functional systems was based primarily on lesion and postmortem studies. Directly visualizing how the brain performs mental work with fMRI or PET imaging is clearly more accurate than trying to infer indirectly how it works by observing what it cannot do when parts are missing.

The Prefrontal System and Executive Functions

The prefrontal system, or prefrontal cortex, is one of the largest cortical subregions in the human brain. It constitutes 29% of the cortex in human beings, compared with 17% in chimpanzees, 7% in dogs, and 3.5% in cats. The relative development of the prefrontal cortex in various animal species is shown in Figure 3–1.

This huge association region in the brain integrates input from much of the neocortex, limbic regions, hypothalamic and brainstem regions, and (via the thalamus) most of the rest of the brain. Its high degree of development in human beings suggests that it may mediate a variety of specifically human functions often referred to as executive functions, such as high-order abstract thought, creative problem solving, and the temporal sequencing of behavior. Lesion and trauma studies, supplemented by experimental studies in nonhuman primates, have substantially added to this view of the functions of the prefrontal cortex. It is now clear that the prefrontal cortex mediates a large variety of functions, including attention and perception, moral judgment, temporal integration, and affect and emotion.
FIGURE 3–1. Phylogenetic development of the prefrontal cortex.
a.s. = arcuate sulcus; c.s. = cingulate sulcus; g.pr. = gyrus proreus; i.p.f. = inferior precentral fissure; p.f. = presylvian fissure; pr.f. = proreal fissure; p.s. = principal sulcus.

The intactness of the prefrontal cortex can be assessed by a variety of cognitive tasks, and it has been explored through neuroimaging as well. The Wisconsin Card Sorting Test, the Continuous Performance Test, the Sternberg Working Memory Task, and the Tower of London are standard “frontal lobe” tests in neuropsychology. Several of these tests have been explored using fMRI and PET and have been shown to produce frontal lobe activation. Because the negative symptoms of schizophrenia reflect an impairment in many frontally mediated functions, investigators have proposed that some patients with schizophrenia might have frontal lobe abnormalities, a finding that has been supported in numerous anatomical and functional neuroimaging studies. Abnormalities in frontal lobe structure and function have also been observed in many other disorders, such as mood disorders, obsessive-compulsive disorder, and autism spectrum disorders.

The Limbic System

The word *limbic* means “border” in Latin. This term was first used by Paul Broca, a French neurologist, to refer to the circular ring of tissue that appears to “hem” the prefrontal, parietal, and occipital neocortex when the brain is viewed from a midsagittal perspective. There is still no consensus as to what constitutes a clear definition of the limbic system or its components. As in other brain systems, boundaries can be defined on the basis of cytoarchitectonics, interconnections, or inputs. Walle Nauta later proposed, as a unifying concept, that the various structures in the limbic system share circuitry that connects them to the hypothalamus. He pointed out that the interconnections between the hypothalamus (via the mamillary bodies), the amygdala, the hippocampus, and cingulate gyrus are reciprocal. The hypothalamus collects visceral sensory signals from the spinal cord and brainstem, while input also comes to this circuit through two major neocortical association regions, the prefrontal cortex and the inferior temporal association cortex.

The functions of the limbic system are of great importance to the understanding of human emotion. The various interconnections suggest functions related to integrating visceral sensation and the experience of the external environment through multiple modalities (e.g., visual, sensory, auditory). Lesion, animal, and neuroimaging studies have shown that the amygdala and hippocampus mediate aspects of learning and memory. The amygdala is known as “the hub in the wheel of fear” and is implicated in the neurobiology of a variety of anxiety disorders.
The Basal Ganglia

The major structures of the basal ganglia include the caudate, putamen, and globus pallidus, which are shown schematically in Figure 3–2. A triplanar view of the caudate and other basal ganglia structures as seen with sMRI is shown in Figure 3–3. The substantia nigra, located in the midbrain, is not visualized. The caudate is a C-shaped mass of gray matter tissue that has its head at the lateral anterior borders of the frontal horns of the ventricles. It arches back posteriorly in a circular fashion and then curls forward again, ending in the amygdala bilaterally. Separated from it, and lateral to it, is the lentiform nucleus, so called because it is shaped like a lens. The medial portion of the lentiform nucleus, which is darker and more densely full of gray matter, is the putamen, whereas the globus pallidus is lateral to it. The caudate is separated from the lentiform nucleus by the anterior limb of the internal capsule, but the sMRI scan shows clearly that bands of gray matter interconnect these two nuclei; posteriorly the lentiform nucleus is separated from the thalamus by the posterior limb of the internal capsule. Because these structures contain a combination of gray and white matter, they have a striped appearance in postmortem brains and on sMRI scans, causing them to be referred to as the “corpus striatum” (striped body).

This brain region is of importance to the understanding of mental illness for several reasons. First, there are several major syndromes involving abnormalities in these regions that manifest psychiatric symptoms. Huntington’s disease, characterized by severe atrophy in the caudate nucleus, typically presents with a variety of delusional and depressive symptoms. Severe dementia may also develop. Parkinson’s disease is another syndrome affecting the basal ganglia; it is due to neuronal loss in the substantia nigra, which uses dopamine as its primary neurotransmitter. Loss of pigmented neurons and a decrease in dopaminergic activity produce a variety of symptoms similar to the negative symptoms of schizophrenia, including affective blunting and loss of volition.

The basal ganglia are also relevant to psychiatry because of their chemical anatomy. The caudate and putamen contain a very high concentration of dopamine receptors, particularly D2 receptors. The efficacy of antipsychotic medications is highly correlated with their ability to block D2 receptors (see “Neurochemical Systems” later in the chapter). Because D2 receptors have a very high density in these regions, the caudate and putamen may be important sites for antipsychotic drug action.
FIGURE 3–2. Interconnections of the basal ganglia.

The Memory System

The memory system is a major functional brain system that may be impaired in some mentally ill patients. Deficits in learning and memory are the hallmark of the dementias. Although patients with psychotic disorders do not typically have severe memory deficits, some investigators have speculated that the neural mechanisms of delusions and hallucinations might be based on either abnormal excitability or abnormal connectivity in the neural circuitry used for the encoding, retrieval, and interpretation of memories. Within psychoanalytic theory, it has long been believed that the various “neuroses,” such as anxiety disorders or hysteria (i.e., somatization disorder), might represent the painful stimulus of repressed memories that have not been psychologically integrated. The process of psychotherapy involves the process of learning, which is based in turn on memory; patients who successfully complete a course of psychotherapy have learned new ways of understanding their past experiences and relating to other people.

Memory is in fact a diverse set of functions that are mediated in different ways. Typically, memory is now thought of as a two-stage process. The first stage involves working memory; this is the form we use...
when we “learn” a telephone number long enough to dial it or a driver’s license number long enough to write it down. This type of memory is accessible in short-term storage and is used as a mental scratchpad that we call on when we perform mental operations such as arithmetic calculations from numbers that have been quoted to us. Long-term memory, on the other hand, consists of information that we have learned and retained for periods of time greater than a few minutes. This type of memory is sometimes referred to as “consolidated” memory and is currently being employed by the students reading this textbook.

Normal human experience, as well as research in neuroscience, indicates that a variety of techniques can be used to facilitate learning, or consolidation of memory. These include such things as repetition, rehearsal, or mnemonic devices. This type of memory is mediated by a different set of mechanisms that lead to long-term storage of information. The work of Eric Kandel, using the gill withdrawal reflex in the snail *Aplysia* as a model, has shown that long-term memory depends on the synthesis of proteins in neurons that are synaptically connected during the time that short-term learning has been occurring; this process creates a molecular consolidation of memory that is more permanently stored. Kandel, a psychiatrist, received the Nobel Prize in Physiology or Medicine in 2000 for this work, which explains the extraordinary capacity of the human brain for neuroplastic remodeling throughout the lifespan.

**The Language System**

As far as we know, the capacity to communicate in a highly developed and complex language is limited to human beings. Although porpoises, dolphins, and a few other creatures are believed to communicate specific messages to one another, human beings alone appear to have a syntactically complex language that exists in both oral and written forms. The ability to record our history and to communicate scientifically and culturally has permitted us to repeatedly build complex civilizations and social systems, and to destroy them as well.

The capacity to communicate in oral and written language is facilitated by dedicated brain regions that probably occur only in human beings. These language systems are localized in the neocortex. A simplified schematic diagram of the human brain circuitry traditionally considered to mediate language functions appears in Figure 3–4. Lesion studies suggest that this system is located primarily in the left hemi-
sphere in most individuals, although functional imaging studies have revealed some bilaterality. About one-third of left-handers use either their right hemisphere or both hemispheres to perform language functions.

Within the left hemisphere there are two major language regions as well as some subsidiary ones. Broca’s area is the region dedicated to the production of speech. It contains information about the syntactical structure of language, provides the “little words” such as prepositions that tie the fabric of language together, and is the generator for fluent speech. Lesions to Broca’s area, which occur in stroke victims (often with an accompanying right hemiparesis), lead to halting, stammering, and ungrammatical speech. Wernicke’s area is often referred to as the “auditory association cortex.” It encodes the information that permits us to “understand” the sounds expressed in speech. The perception of sound waves, which encode speech, occurs through transducers in the ear that convert the information to neural signals. The signals are received in the auditory cortex, but the meaning of the specific signals cannot be understood (i.e., perceived as constituting words with specific meanings—as opposed, for example, to the wordless music of a symphony) without being compared to “templates” in Wernicke’s area. An analogous process occurs when we understand written language. In
this case the information is collected through our eyes, relayed via the optic tracts back to the primary visual cortex in the occipital lobe, and then forwarded on to the angular gyrus, a visual association cortex that contains the information or templates that permit us to recognize language presented in visual form.

Patients with major mental illnesses have a variety of disruptions in their capacity to communicate in language. Some of these incapacities are similar to those observed in the aphasias, but none is precisely identical. Some patients with schizophrenia have impoverished speech reminiscent of Broca’s aphasia but lacking its halting, agrammatical quality. Likewise, some patients with schizophrenia or mania produce very disorganized, abundant speech similar to Wernicke’s aphasia, but (unlike the patient with Wernicke’s aphasia) they appear to have intact comprehension. Auditory hallucinations (hearing “voices”) are abnormal auditory perceptions of language—that is, the individual perceives auditory speech when none is present. The reasons for these various disruptions and aberrations in language function in psychosis (and in many of the dementias as well) are still not clear. They may represent specific abnormalities in specialized language regions in the brain, but more likely they represent a disorganization at some higher integrative level.

**The Attention System**

Attention is the cognitive process through which the brain identifies stimuli within the context of time and space and selects what is relevant for both input and output. We are bombarded continually with sensory information in multiple modalities as well as with the information within our internal cognitive repertoire. A person driving a car on a busy highway is receiving information about other cars, the road, and the surrounding terrain from the visual system and auditory input from the car motor or the sound of other vehicles as they pass; there is also tactile input from hands on the steering wheel and the foot on the gas pedal and the physical sensations experienced by the rest of the body as the car grips the road or bounces and sways. The person may also be talking on a cell phone, listening to music, or thinking about a recent conversation. Attention is the cognitive process that permits the person to suppress irrelevant stimuli (e.g., to ignore most of the landscape), to notice important stimuli (e.g., that the car in front is putting on the brakes and slowing down suddenly), and to shift from one stimulus to another (e.g., from thoughts about the recent conversation to the traffic). If we lacked this capacity, we would be overwhelmed with stimuli. Attention is sometimes compared to a spotlight that the brain uses to highlight what is important.
Attention is mediated through multiple brain systems. Input to the brain is first provided by the reticular activating system, which arises in the brainstem. Midline circuitry passes this information through the thalamus, which plays a major role in “gating” or “filtering.” Many other brain regions also play a major role in attention, including the cingulate gyrus, the hypothalamus, the hippocampus and amygdala, and the prefrontal, temporal, parietal, and occipital cortices. Neuroimaging studies using both fMRI and PET have demonstrated that the cingulate gyrus shows increases in activity during tasks that place heavy demands on the attentional system, such as those that involve competition and interference between stimuli. Attention is impaired in many mental illnesses, ranging from schizophrenia to attention-deficit/hyperactivity disorder (ADHD) to the mood disorders.

The Reward System

As behaviorists have noted for many years, human beings are strongly motivated by positive reinforcement. Put more simply, they are prone to seek pleasure and to avoid pain. Therefore, it is not surprising that the brain also possesses a reward system—a network that is used for the experience of pleasure. Its major components are the ventral tegmental area, the nucleus accumbens, the prefrontal cortex (particularly the anterior cingulate and ventral frontal cortex), the amygdala, and the hippocampus.

The reward system is relevant to many types of psychiatric disorders. It is often said that substance abuse develops when exposure to a drug such as cocaine “hijacks the brain reward system” by inducing an intense experience of pleasure that stimulates craving and repeated drug-seeking behavior. This system has been implicated in all types of dependence on both illegal (e.g., amphetamines, opiates) and legal (e.g., nicotine, alcohol) substances. It is also thought to provide the basis for other types of pleasure-seeking or addictive behaviors and their consequences, such as pathological gambling or compulsive overeating and obesity.

■ Neurochemical Systems

In addition to the functional and anatomical systems described earlier, the brain also consists of a grouping of neurochemical systems. These systems provide the “fuel” that permits the functional and anatomical systems to run (or run poorly, when an abnormality occurs). The neuro-
chemical systems are interwoven and interdependent with the anatomical and functional systems. Any anatomic subsystem within the brain usually runs on multiple classes of neurotransmitters. Clearly, this complexity of anatomic and neurochemical organization permits much greater fine tuning of the entire system.

The Dopamine System

Dopamine, a catecholamine neurotransmitter, is the first product synthesized from tyrosine through the enzymatic activity of tyrosine hydroxylase. Its synthetic pathway, as well as the subsequent ones of norepinephrine and epinephrine, is shown in Figure 3–5.
There are three subsystems within the brain that use dopamine as their primary neurotransmitter. These all arise in the ventral tegmental area. One group, arising in the substantia nigra, projects to the caudate and putamen and is referred to as the nigrostriatal pathway. Its terminations appear to be rich in both D₁ and D₂ receptors. A second major tract, called the mesocortical or mesolimbic (or mesocorticolumbic), arises in the ventral tegmental area and projects to the prefrontal cortex and temporolimbic regions such as the amygdala and hippocampus. The concentration of D₂ receptors in these regions is minimal, whereas D₁ receptors predominate. The third component of the dopamine system originates in the arcuate nucleus of the hypothalamus and projects to the pituitary. The first two of these dopamine subsystems are summarized in Figure 3–6. As the figure indicates, the dopamine system is fairly specifically localized in the human brain. Because its projections include only a limited part of the cortex and focus primarily on brain regions important to cognition and emotion, it is considered to be one of the most important neurotransmitter systems for the understanding of these functions and potentially for the understanding of their disturbances in many types of mental illnesses.

For many years schizophrenia, the most important among the various psychotic disorders, was explained by the dopamine hypothesis, which proposed that the symptoms of this illness were due to a functional excess of dopamine. Because the efficacy of many of the antipsychotic drugs used to treat psychosis is highly correlated with their ability to block D₂ receptors, the dopamine hypothesis also suggested that the abnormality in this illness might specifically lie with D₂ receptors. There is a modest but much weaker correlation with their ability to block D₁ receptors. The dopamine hypothesis is currently being reappraised, however, in the light of several new lines of evidence that have emerged. First, the distribution of D₁ and D₂ receptors has been more specifically mapped, and there appears to be a rather sparse density of D₂ receptors in critical brain regions that mediate cognition and emotion, such as the prefrontal cortex, amygdala, and hippocampus. These regions are, however, high in D₁ and serotonin type 2 receptors (5-HT₂). These observations, coupled with the prominent effects on serotonin and D₁ by the new second-generation antipsychotics, suggest that the traditional dopamine hypothesis needs revision.

Understanding the projections of the dopamine system, as well as the differential localization of D₁ and D₂ receptors, clarifies some of the other effects of antipsychotic drugs. Some of these drugs have potent extrapyramidal side effects as a consequence of blocking D₂ receptors in the nigrostriatal pathway. Drugs that have a weak D₂ effect (of which
clozapine and quetiapine are examples) thus are more likely to have fewer extrapyramidal (“parkinsonian”) side effects.

Dopamine is sometimes called the “pleasure neurotransmitter,” because it is the primary neurotransmitter in the brain reward system and is associated with adventuresome and exploratory behaviors. Many drugs of abuse (e.g., amphetamines, cocaine) exert their psychoactive effects by increasing dopaminergic tone.

The Norepinephrine System

The norepinephrine system arises in the locus coeruleus and sends projections diffusely throughout the entire brain. These projections are summarized in Figure 3–7. As that figure illustrates, norepinephrine appears to exert effects on almost every brain region in the human brain, including the entire cortex, the hypothalamus, the cerebellum, and the brainstem. This distribution suggests that it may have a diffuse modulatory or regulatory effect within the CNS.

There is some evidence that norepinephrine may play a major role in mediating symptoms of major mental illnesses, especially mood disorders. Soon after they were developed, it was demonstrated that tricyclic antide-
Pressants inhibit norepinephrine reuptake, thereby enhancing the amount of norepinephrine available to stimulate postsynaptic receptors. Likewise, monoamine oxidase inhibitor antidepressants also enhance noradrenergic transmission by inhibiting neurotransmitter breakdown. However, it is also clear that many antidepressants have mixed noradrenergic and serotonergic activities or purely serotonergic effects (i.e., the selective serotonin reuptake inhibitors [SSRIs]). Thus, the original catecholamine hypothesis of mood disorders, which suggested that depression was due to a functional deficit of norepinephrine at crucial nerve terminals, whereas mania was due to a functional excess, was clearly an oversimplification.

The Serotonin System

Serotonergic neurons have a distribution strikingly similar to that of norepinephrine neurons. This is summarized in Figure 3–8. Serotonergic neurons arise in the raphe nuclei, localized around the aqueduct in
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they project to a similarly wide range of CNS regions, including the entire neocortex, the basal ganglia, temporolimbic regions, the hypothalamus, the cerebellum, and the brainstem. As is the case with the norepinephrine system, the serotonin system appears to be a general modulator.

Serotonin plays a role in modulating mood, anxiety, and aggressive or violent behavior. A serotonin hypothesis of depression has been proposed, largely because many antidepressant medications (e.g., fluoxetine) facilitate serotonergic transmission by blocking reuptake. These medications are also used in the treatment of anxiety disorders. A high serotonergic tone has been shown to be associated with impulsive, violent, or suicidal behavior. Serotonin is probably also involved in schizophrenia and other psychotic disorders, because clozapine and the newer second-generation antipsychotics (e.g., olanzapine) have significant effects on the serotonin system. As these examples indicate, there are no simple single-neurotransmitter to single-illness relationships.
The Cholinergic System

Like dopamine, acetylcholine has a relatively more specific localization in the human brain, as shown schematically in Figure 3–9. The cell bodies of a major group of acetylcholine neurons are located in the nucleus basalis of Meynert, which lies in the ventral and medial regions of the globus pallidus. Neurons from the nucleus basalis of Meynert project throughout the cortex. The second group of acetylcholine projections originating in the diagonal band of Broca and the septal nucleus project to the hippocampus and cingulate gyrus. A third group of cholinergic neurons are local circuit neurons that enter main structures within the basal ganglia.

The acetylcholine system plays a major role in the encoding of memory, although the precise mechanisms are not understood. Patients with Alzheimer’s disease show losses of acetylcholine projections both to the cortex and to the hippocampus, and blockade of muscarinic receptors produces memory impairment. Dopamine and acetylcholine share heavy concentrations of activity within the basal ganglia, and the drugs used to block the extrapyramidal side effects of antipsychotics are cholinergic agonists; this suggests a possible reciprocal relationship between dopamine and acetylcholine in the modulation of motor activity and possibly of psychosis as well. Cholinergic agonists also may impair cognitive functions such as learning and memory in individuals for whom they are prescribed.

The GABA System

γ-Aminobutyric acid (GABA) is an amino acid neurotransmitter, as is glutamate. These two major amino acid neurotransmitters serve complementary functions, with GABA playing an inhibitory role and glutamate playing an excitatory role.

GABAergic neurons are a mix of local circuit and long-tract systems. Within the cerebral cortex and the limbic system, GABAergic neurons are predominately local circuit. The cell bodies of GABAergic neurons in the caudate and putamen project to the globus pallidus and substantia nigra, making them relatively long tract, and long-tract GABA neurons also occur in the cerebellum.

The GABA system has substantial importance for the understanding of the neurochemistry of mental illness. Many of the anxiolytic drugs (e.g., diazepam) act as GABA agonists, thereby increasing the inhibitory tone within the CNS. Loss of the long-tract GABA neurons con-
necting the caudate to the globus pallidus releases the later structure from inhibitory control, thereby permitting the globus pallidus to “run free” and produce the choreiform movements that characterize Huntington’s disease.

The Glutamate System

Glutamate, an excitatory amino acid neurotransmitter, is produced by pyramidal cells throughout the cerebral cortex and hippocampus. For example, the projections from the prefrontal cortex to the basal ganglia are glutamatergic.

The glutamate system is very complex and has many functions. It plays a role in synapse formation and stabilization, long-term potentiation (LTP), and learning and memory. Maintaining an adequate balance between excessive and inadequate levels of glutamate tone is crucial for CNS function. At high levels it is neurotoxic (as occurs in stroke). On the other hand, a hypoactive glutamate system leads to impaired LTP, synaptic plasticity, and cognitive performance. Two drugs that block N-methyl-D-aspartate (NMDA) receptors within the glutamate system, phencycli-
dine (PCP) and ketamine, produce a syndrome that closely resembles schizophrenia. Both can cause a psychosis characterized by withdrawal, stupor, disorganized thinking and speech, and hallucinations. This has suggested an alternative to the dopamine hypothesis, the NMDA receptor hypofunction hypothesis, and that the NMDA receptor could be a potential target for antipsychotic drug development. Some potential agents that modulate NMDA receptor function are currently under development.

The Genetics of Mental Illnesses

Thanks to the completion of the mapping of the human genome, we now know that it is composed of approximately 30,000 genes, about 70,000 fewer than the number that appeared in textbooks just a few years ago. More than half of these genes are expressed in the brain. During the next several decades, all physicians will be living in the “Era of the Genome”—a time when we will begin to discover the mechanisms of major mental disorders at the molecular level. Increasingly, we will begin to understand how gene expression and gene products produce the manifestations of a variety of diseases. We also will increasingly recognize that most major medical disorders are complex—that is, that very few illnesses are simple Mendelian disorders. The opportunity to understand illnesses at the genetic and genomic levels offers great promise for the future. Understanding mechanisms offers the opportunity to intervene early and perhaps ultimately implement preventive measures by modifying gene expression and gene products. This is the “holy grail” of psychiatric genetics.

Epidemiological Approaches

It has been recognized for many years that mental illnesses have a significant genetic component. A variety of studies have used the tools of psychiatric epidemiology and demonstrated that mental illnesses tend to run in families. Such studies are usually divided into three broad groups: family studies, twin studies, and adoption studies. Each of these types of studies offers different perspectives on the genetics of disorders.

Family Studies

Family studies examine the pattern of aggregation within a family, beginning with the identification of a proband (or index case) who has a partic-
ular disorder of interest, such as bipolar disorder or schizophrenia. Thereafter, all available first-degree relatives (parents, siblings, children) are also evaluated using structured interviews and diagnostic criteria. The prevalence of the specific disorder under investigation is compared with the prevalence in a carefully selected control group. If an increased rate of the specific mental illness under study is observed in the first-degree relatives of the probands as compared with the first-degree relatives of the control subjects, then these results suggest that a disorder is familial and possibly genetic. These studies cannot exclude the possibility that the disorder has prominent nongenetic causes. Disorders can also run in families because of learned behavior, role modeling, or predisposing social environments. The following disorders have been found to “run in families”: major depression, bipolar disorder, schizophrenia, panic disorder, social phobia, obsessive-compulsive disorder, antisocial personality disorder, borderline personality disorder, autistic disorder, and ADHD. Family studies have also led to the understanding that a spectrum of disorders is related to schizophrenia, including schizotypal personality disorder.

**Twin Studies**

Twin studies offer a better perspective on the extent to which a disorder is actually genetic. Twin studies typically compare the rate of a specific disorder in monozygotic (identical) versus dizygotic (nonidentical) twins. The rationale behind twin studies is that monozygotic twins have identical genetic material, whereas dizygotic twins theoretically share an average of 50% of their genetic material. The higher the rate of concordance in monozygotic twins, as compared with dizygotic twins, the greater the degree of genetic influence. Thus if a disorder were totally genetic and fully penetrant, the concordance rate in monozygotic twins would theoretically be 100%, whereas in dizygotic twins it would be 50%. In fact, actual rates for both groups are lower for most major mental illnesses. Table 3–1 shows the concordance rates for a variety of medical conditions that have been evaluated through twin studies. It is noteworthy that mental illnesses appear to be more highly genetic, as indicated by the twin method, than other medical disorders.

Although powerful, twin studies are not a perfect method for studying the genetics of major mental illnesses, because nongenetic psychological factors may play a significant role. Because twins are reared together, role modeling can be an influential factor. Furthermore, this factor is likely to be greater in monozygotic than in dizygotic twins because monozygotic twins are often treated as identical by their parents and peers, even being given the same toys and being dressed in the same clothing.
Adoption Studies

Adoption studies are the most refined technique for disentangling environmental and genetic influences. In adoption studies, the focus is on children born to parents with a major mental illness and then adopted at birth and reared by parents without the disorder. These children are compared with a control group consisting of children born to psychiatrically well mothers, similarly adopted at birth, and reared by psychiatrically well parents. To whatever extent the rate of illness is higher in the adopted children of the mothers with a specific mental illness, that mental illness can be considered to be transmitted genetically rather than environmentally. In this model, learned behavior and role modeling of parents with mental illness are excluded, because the child is reared apart from the ill parent. Adoption studies have been conducted for schizophrenia and mood disorders and clearly demonstrate a significant genetic component.

Simple Versus “Complex” Illnesses

Researchers “gene hunting” for brain diseases were overly optimistic during its early era because of the success in finding the gene for Huntington’s disease, a Mendelian autosomal dominant disorder caused by a single gene that is highly penetrant. Using classic positional cloning techniques, linkage was relatively quickly established on chromosome 4 through the study of a large Venezuelan pedigree. This quickly led to the development of a premorbid test for the disease. Thus individuals from families with Huntington’s disease could determine if they possessed the disease-causing gene, refrain from having children at risk if
they chose, and plan their lives for an unfortunate outcome. We also know that the gene causes trinucleotide repeats, that 40 or more repeats result in disease occurrence, and that a greater number of repeats leads to an earlier age at onset. Nevertheless, illustrating the intransigent puzzles inherent in human biology, we still do not know what the abnormal structural or regulatory protein is that produces this illness, and we still are unable to either treat or prevent the illness. Even with a clear, relatively simple autosomal dominant disease for which the genetic abnormality has been identified, the final answer that we seek has not come easily.

Most mental illnesses, like other common disorders in medicine such as hypertension or diabetes, are complex illnesses. They are clearly non-Mendelian and are generally considered to be due to multiple genes of small effect that interact with multiple nongenetic factors, causing the disease to emerge if enough cumulative genetic and nongenetic risk factors co-occur. Further complicating the search for these genes, mental illnesses are relatively common in the general population, making it difficult to find families in which a specific disease breeds true.

**Finding the Genes**

Several approaches have been used to locate genes for mental illnesses and identify their functions.

**Linkage Studies**

Linkage studies were the earliest approaches to be applied in the search for genes. Although linkage studies have yielded significant results for a few disorders (e.g., the identification of a locus on chromosome 4 for Huntington’s disease), they have been considerably less successful for other types of mental illness, which are most likely to be genetically complex. Linkage studies of mental illnesses have sometimes been said to have a “manic-depressive history.” Early reports identify a linkage between a site on a given chromosome and a specific illness, leading to enthusiasm and excitement, followed by replication studies that are unable to reproduce the initial finding in a different population of subjects, leading to depression. Examples are the initial reports of linkage for bipolar illness on chromosome 11 or the X chromosome, or linkages between schizophrenia and sites on chromosomes 6, 8, and 22. Consequently, linkage studies have largely been supplanted by other methods.
Candidate Gene Studies

Candidate gene studies provide an alternative approach. Typically, these studies begin with hypothesis-driven selection of a candidate gene. Candidate genes are chosen because they have single nucleotide polymorphisms (SNPs) and because they code for a protein that could have some effect leading to a specific mental illness. Examples of candidate genes include proteins regulating brain development such as brain-derived neurotrophic factor (BDNF), enzymes that affect neurotransmitter synthesis such as catechol-O-methyltransferase (COMT), or hormones that regulate brain activity such as neuropeptide Y. The strength of the candidate gene approach is that it directly permits investigators to determine whether a particular protein has any relevance to a specific mental illness. In the candidate gene approach, a group of patients with the specific disorder is usually compared with a group of normal control subjects to determine whether a specific allele occurs more frequently in the patients.

Candidate gene studies have some of the same limitations as the linkage studies. They may yield false-positive results, particularly if samples are not carefully chosen, and like linkage studies, their credibility depends on repeated replications. Despite these disclaimers, several candidate genes have been identified and replicated as potential vulnerability genes for schizophrenia. These include BDNF, COMT, dysbindin, Disrupted-in-Schizophrenia (DISC), and neuregulin 1. Several candidate genes that confer vulnerability to autism also have been identified, such as neurexin and ubiquitin, and the serotonin transporter gene has been implicated in mood disorders. In addition to examining disease association, investigators also have begun to do “deep phenotyping” of some genes using a variety of techniques such as animal models or neuroimaging. The Met allele in the BDNF promoter region is associated with schizophrenia, and individuals with this particular genotype also show decreased hippocampal activity during fMRI studies, smaller volume of frontal gray matter and hippocampus as measured with sMRI, progressive gray matter loss over the course of the disease, and poorer episodic memory than normal control subjects.

Copy Number Variants

Until relatively recently, it was assumed that all autosomal genes are present in two faithfully duplicated copies, with one allele inherited from each parent. We now know that large-scale variations in copy number are common and have the potential to confer disease liability. Copy number variants (CNVs) are mutations in DNA that are large
(1 kilobase or larger) and can include deletions, insertions, and duplications. It is estimated that there are an average of 12 CNVs per individual, that they cover approximately 12% of the human genome, and that at least half occur in protein-coding regions. This finding has launched a search for their possible relationship to a variety of diseases, including mental illnesses. They have now been found to be associated with rare disorders such as Prader-Willi and Angelman syndromes, but also with Alzheimer’s disease and schizophrenia.

Genome-Wide Association Studies

Genome-wide association studies are another approach to finding genes for mental illnesses, made possible through advances such as the haplotype map of the entire human genome and the assembly of large databases containing DNA from thousands of individuals who suffer from specific disorders. To date, none of these genome-wide surveys has produced robust results. They have generated some evidence for genes on chromosomes 9, 10, and 12 for the dementias and chromosomes 1, 6, 8, 10, 11, 13, and 22 for the psychoses. However, evidence for linkage is often across a broad region, with different groups mapping to nonoverlapping areas of the same chromosome arm. Nonetheless, as statistical methods improve, and as haplotype map data are integrated with the method, genome-wide association studies may provide significant additional information about the location of the various genes over the next decade.

■ Self-Assessment Questions

1. Describe the functions performed by the prefrontal cortex.
2. Describe the locations and functions of the two major language regions in the brain.
3. Identify the anatomic components of the reward system and discuss its relationship to at least two psychiatric disorders.
4. Discuss the role of serotonin in modulating behavior and the ways that this role is associated with mental illnesses.
5. Describe the location and function of the dopamine system and discuss its relationship to at least two mental illnesses.
6. Describe the functions of glutamate and its possible relation to the symptoms of psychosis.
7. Describe the relative strengths of family studies, twin studies, and adoption studies as methods for determining the familiality of mental illnesses and the degree to which purely genetic factors play a causal role.

8. Discuss the possible interaction between genes and environmental factors in producing mental illness.

9. What are single nucleotide polymorphisms? Copy number variants? Genome-wide association studies? What have we learned from them about genetic mechanisms of mental illnesses?