

01 - 7.1 Schizophrenia

7.1 Schizophrenia

Schizophrenia Spectrum and Other Psychotic Disorders 7.1 Schizophrenia Although schizophrenia is discussed as if it is a single disease, it probably comprises a group of disorders with heterogeneous etiologies, and it includes patients whose clinical presentations, treatment response, and courses of illness vary. Signs and symptoms are variable and include changes in perception, emotion, cognition, thinking, and behavior. The expression of these manifestations varies across patients and over time, but the effect of the illness is always severe and is usually long lasting. The disorder usually begins before age 25 years, persists throughout life, and affects persons of all social classes. Both patients and their families often suffer from poor care and social ostracism because of widespread ignorance about the disorder. Schizophrenia is one of the most common of the serious mental disorders, but its essential nature remains to be clarified; thus, it is sometimes referred to as a syndrome, as the group of schizophrenias, or as in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the schizophrenia spectrum. Clinicians should appreciate that the diagnosis of schizophrenia is based entirely on the psychiatric history and mental status examination. There is no laboratory test for schizophrenia. HISTORY Written descriptions of symptoms commonly observed today in patients with schizophrenia are found throughout history. Early Greek physicians described delusions of grandeur, paranoia, and deterioration in cognitive functions and personality. It was not until the 19th century, however, that schizophrenia emerged as a medical condition worthy of study and treatment. Two major figures in psychiatry and neurology who studied the disorder were Emil Kraepelin (1856–1926) and Eugene Bleuler (1857–1939). Earlier, Benedict Morel (1809–1873), a French psychiatrist, had used the term *démence précoce* to describe deteriorated patients whose illnesses began in adolescence. Emil Kraepelin Kraepelin (Fig. 7.1-1) translated Morel's *démence précoce* into *dementia precox*, a term that emphasized the change in cognition (dementia) and early onset (*precox*) of the disorder. Patients with *dementia precox* were described as having a long-term deteriorating course and the clinical symptoms of hallucinations and delusions.

Kraepelin distinguished these patients from those who underwent distinct episodes of illness alternating with periods of normal functioning, which he classified as having manic-depressive psychosis. Another separate condition called paranoia was characterized by persistent persecutory delusions. These patients lacked the deteriorating course of *dementia precox* and the intermittent symptoms of manicdepressive psychosis. FIGURE 7.1-1 Emil Kraepelin, 1856–1926. (Courtesy of National Library of Medicine, Bethesda, MD.) Eugene Bleuler Bleuler (Fig. 7.1-2) coined the term schizophrenia, which replaced *dementia precox* in the literature. He chose the term to express the presence of schisms among thought, emotion, and behavior in patients with the disorder. Bleuler stressed that, unlike Kraepelin's concept of *dementia precox*, schizophrenia need not have a

deteriorating course. This term is often misconstrued, especially by lay people, to mean split personality. Split personality, called dissociative identity disorder, differs completely from schizophrenia (see Chapter 12).

FIGURE 7.1-2 Eugene Bleuler, 1857–1939. (Courtesy of National Library of Medicine, Bethesda, MD.) The Four As. Bleuler identified specific fundamental (or primary) symptoms of schizophrenia to develop his theory about the internal mental schisms of patients. These symptoms included associational disturbances of thought, especially looseness, affective disturbances, autism, and ambivalence, summarized as the four As: associations, affect, autism, and ambivalence. Bleuler also identified accessory (secondary) symptoms, which included the symptoms that Kraepelin saw as major indicators of dementia precox: hallucinations and delusions. Other Theorists Ernst Kretschmer (1888–1926). Kretschmer compiled data to support the idea that schizophrenia occurred more often among persons with asthenic (i.e., slender, lightly muscled physiques), athletic, or dysplastic body types rather than among persons with pyknic (i.e., short, stocky physiques) body types. He thought the latter were more likely to incur bipolar disorders. His observations may seem strange, but they are not inconsistent with a superficial impression of the body types in many persons with schizophrenia.

Kurt Schneider (1887–1967). Schneider contributed a description of first-rank symptoms, which, he stressed, were not specific for schizophrenia and were not to be rigidly applied but were useful for making diagnoses. He emphasized that in patients who showed no first-rank symptoms, the disorder could be diagnosed exclusively on the basis of second-rank symptoms and an otherwise typical clinical appearance. Clinicians frequently ignore his warnings and sometimes see the absence of first-rank symptoms during a single interview as evidence that a person does not have schizophrenia. Karl Jaspers (1883–1969). Jaspers, a psychiatrist and philosopher, played a major role in developing existential psychoanalysis. He was interested in the phenomenology of mental illness and the subjective feelings of patients with mental illness. His work paved the way toward trying to understand the psychological meaning of schizophrenic signs and symptoms such as delusions and hallucinations. Adolf Meyer (1866–1950). Meyer, the founder of psychobiology, saw schizophrenia as a reaction to life stresses. It was a maladaptation that was understandable in terms of the patient's life experiences. Meyer's view was represented in the nomenclature of the 1950s, which referred to the schizophrenic reaction. In later editions of DSM, the term reaction was dropped. **EPIDEMIOLOGY** In the United States, the lifetime prevalence of schizophrenia is about 1 percent, which means that about one person in 100 will develop schizophrenia during their lifetime. The Epidemiologic Catchment Area study sponsored by the National Institute of Mental Health reported a lifetime prevalence of 0.6 to 1.9 percent. In the United States, about 0.05 percent of the total population is treated for schizophrenia in any single year, and only about half of all patients with schizophrenia obtain treatment, despite the severity of the disorder. **Gender and Age** Schizophrenia is equally prevalent in men and women. The two genders differ, however, in the onset and course of illness. Onset is earlier in men than in women. More than half of all male schizophrenia patients, but only one-third of all female schizophrenia patients, are first admitted to a psychiatric hospital before age 25 years. The peak ages of onset are 10 to 25 years for men and 25 to 35 years for women. Unlike men, women display a bimodal age distribution, with a second peak occurring in middle age. Approximately 3 to 10 percent of women with schizophrenia present with disease onset after age 40 years. About 90 percent of patients in treatment for schizophrenia are between 15 and 55 years old. Onset of schizophrenia before age 10 years or after age 60 years

is extremely rare. Some studies have indicated that men are more likely to be impaired by negative symptoms (described later) than are women and that women are

more likely to have better social functioning than are men before disease onset. In general, the outcome for female schizophrenia patients is better than that for male schizophrenia patients. When onset occurs after age 45 years, the disorder is characterized as late-onset schizophrenia.

Reproductive Factors The use of psychopharmacological drugs, the open-door policies in hospitals, the deinstitutionalization in state hospitals, and the emphasis on rehabilitation and community-based care for patients have all led to an increase in the marriage and fertility rates among persons with schizophrenia. Because of these factors, the number of children born to parents with schizophrenia is continually increasing. The fertility rate for persons with schizophrenia is close to that for the general population. First-degree biological relatives of persons with schizophrenia have a ten times greater risk for developing the disease than the general population.

Medical Illness Persons with schizophrenia have a higher mortality rate from accidents and natural causes than the general population. Institution- or treatment-related variables do not explain the increased mortality rate, but the higher rate may be related to the fact that the diagnosis and treatment of medical and surgical conditions in schizophrenia patients can be clinical challenges. Several studies have shown that up to 80 percent of all schizophrenia patients have significant concurrent medical illnesses and that up to 50 percent of these conditions may be undiagnosed.

Infection and Birth Season Persons who develop schizophrenia are more likely to have been born in the winter and early spring and less likely to have been born in late spring and summer. In the Northern Hemisphere, including the United States, persons with schizophrenia are more often born in the months from January to April. In the Southern Hemisphere, persons with schizophrenia are more often born in the months from July to September. Season-specific risk factors, such as a virus or a seasonal change in diet, may be operative. Another hypothesis is that persons with a genetic predisposition for schizophrenia have a decreased biological advantage to survive season-specific insults. Studies have pointed to gestational and birth complications, exposure to influenza epidemics, maternal starvation during pregnancy, Rhesus factor incompatibility, and an excess of winter births in the etiology of schizophrenia. The nature of these factors suggests a neurodevelopmental pathological process in schizophrenia, but the exact pathophysiological mechanism associated with these risk factors is not known. Epidemiological data show a high incidence of schizophrenia after prenatal exposure to influenza during several epidemics of the disease. Some studies show that the frequency of schizophrenia is increased after exposure to influenza—which occurs in the

winter—during the second trimester of pregnancy. Other data supporting a viral hypothesis are an increased number of physical anomalies at birth, an increased rate of pregnancy and birth complications, seasonality of birth consistent with viral infection, geographical clusters of adult cases, and seasonality of hospitalizations. Viral theories stem from the fact that several specific viral theories have the power to explain the particular localization of pathology necessary to account for a range of manifestations in schizophrenia without overt febrile encephalitis.

Substance Abuse Substance abuse is common in schizophrenia. The lifetime prevalence of any drug abuse (other than tobacco) is often greater than 50 percent. For all drugs of abuse (other than tobacco), abuse is associated with poorer function. In one population-based study, the lifetime prevalence of alcohol within schizophrenia was 40 percent. Alcohol abuse increases risk of hospitalization and, in some patients, may increase psychotic symptoms. People with schizophrenia have an increased

prevalence of abuse of common street drugs. There has been particular interest in the association between cannabis and schizophrenia. Those reporting high levels of cannabis use (more than 50 occasions) were at sixfold increased risk of schizophrenia compared with nonusers. The use of amphetamines, cocaine, and similar drugs should raise particular concern because of their marked ability to increase psychotic symptoms. Nicotine. Up to 90 percent of schizophrenia patients may be dependent on nicotine. Apart from smoking-associated mortality, nicotine decreases the blood concentrations of some antipsychotics. There are suggestions that the increased prevalence in smoking is due, at least in part, to brain abnormalities in nicotinic receptors. A specific polymorphism in a nicotinic receptor has been linked to a genetic risk for schizophrenia. Nicotine administration appears to improve some cognitive impairments and parkinsonism in schizophrenia, possibly because of nicotine-dependent activation of dopamine neurons. Recent studies have also demonstrated that nicotine may decrease positive symptoms such as hallucinations in schizophrenia patients by its effect on nicotine receptors in the brain that reduce the perception of outside stimuli, especially noise. In that sense, smoking is a form of self-medication. Population Density The prevalence of schizophrenia has been correlated with local population density in cities with populations of more than 1 million people. The correlation is weaker in cities of 100,000 to 500,000 people and is absent in cities with fewer than 10,000 people. The effect of population density is consistent with the observation that the incidence of schizophrenia in children of either one or two parents with schizophrenia is twice as high in cities as in rural communities. These observations suggest that social stressors in urban settings may affect the development of schizophrenia in persons at risk.

Socioeconomic and Cultural Factors Economics. Because schizophrenia begins early in life; causes significant and longlasting impairments; makes heavy demands for hospital care; and requires ongoing clinical care, rehabilitation, and support services, the financial cost of the illness in the United States is estimated to exceed that of all cancers combined. Patients with a diagnosis of schizophrenia are reported to account for 15 to 45 percent of homeless Americans. Hospitalization. The development of effective antipsychotic drugs and changes in political and popular attitudes toward the treatment and the rights of persons who are mentally ill have dramatically changed the patterns of hospitalization for schizophrenia patients since the mid-1950s. Even with antipsychotic medication, however, the probability of readmission within 2 years after discharge from the first hospitalization is about 40 to 60 percent. Patients with schizophrenia occupy about 50 percent of all mental hospital beds and account for about 16 percent of all psychiatric patients who receive any treatment. ETIOLOGY Genetic Factors There is a genetic contribution to some, perhaps all, forms of schizophrenia, and a high proportion of the variance in liability to schizophrenia is due to additive genetic effects. For example, schizophrenia and schizophrenia-related disorders (e.g., schizotypal personality disorder) occur at an increased rate among the biological relatives of patients with schizophrenia. The likelihood of a person having schizophrenia is correlated with the closeness of the relationship to an affected relative (e.g., first- or second-degree relative). In the case of monozygotic twins who have identical genetic endowment, there is an approximately 50 percent concordance rate for schizophrenia. This rate is four to five times the concordance rate in dizygotic twins or the rate of occurrence found in other first-degree relatives (i.e., siblings, parents, or offspring). The role of genetic factors is further reflected in the drop-off in the occurrence of schizophrenia among second- and third-degree relatives, in whom one would hypothesize a decreased genetic loading. The finding of a higher rate of schizophrenia among the biological relatives of an adopted-away person who develops schizophrenia, compared with the adoptive,

nonbiological relatives who rear the patient, provides further support to the genetic contribution in the etiology of schizophrenia. Nevertheless, the monozygotic twin data clearly demonstrate the fact that individuals who are genetically vulnerable to schizophrenia do not inevitably develop schizophrenia; other factors (e.g., environment) must be involved in determining a schizophrenia outcome. If a vulnerability-liability model of schizophrenia is correct in its postulation of an environmental influence, then other biological or psychosocial environment factors may prevent or cause schizophrenia in the genetically vulnerable

individual. Some data indicate that the age of the father has a correlation with the development of schizophrenia. In studies of schizophrenia patients with no history of illness in either the maternal or paternal line, it was found that those born from fathers older than the age of 60 years were vulnerable to developing the disorder. Presumably, spermatogenesis in older men is subject to greater epigenetic damage than in younger men. The modes of genetic transmission in schizophrenia are unknown, but several genes appear to make a contribution to schizophrenia vulnerability. Linkage and association genetic studies have provided strong evidence for nine linkage sites: 1q, 5q, 6p, 6q, 8p, 10p, 13q, 15q, and 22q. Further analyses of these chromosomal sites have led to the identification of specific candidate genes, and the best current candidates are α -7 nicotinic receptor, DISC 1, GRM 3, COMT, NRG 1, RGS 4, and G 72. Recently, mutations of the genes dystrobrevin (DTNBP1) and neureglin 1 have been found to be associated with negative features of schizophrenia.

Biochemical Factors Dopamine Hypothesis. The simplest formulation of the dopamine hypothesis of schizophrenia posits that schizophrenia results from too much dopaminergic activity. The theory evolved from two observations. First, the efficacy and the potency of many antipsychotic drugs (i.e., the dopamine receptor antagonists [DRAs]) are correlated with their ability to act as antagonists of the dopamine type 2 (D2) receptor. Second, drugs that increase dopaminergic activity, notably cocaine and amphetamine, are psychotomimetic. The basic theory does not elaborate on whether the dopaminergic hyperactivity is due to too much release of dopamine, too many dopamine receptors, hypersensitivity of the dopamine receptors to dopamine, or a combination of these mechanisms. Which dopamine tracts in the brain are involved is also not specified in the theory, although the mesocortical and mesolimbic tracts are most often implicated. The dopaminergic neurons in these tracts project from their cell bodies in the midbrain to dopaminoceptive neurons in the limbic system and the cerebral cortex. Excessive dopamine release in patients with schizophrenia has been linked to the severity of positive psychotic symptoms. Position emission tomography studies of dopamine receptors document an increase in D2 receptors in the caudate nucleus of drug-free patients with schizophrenia. There have also been reports of increased dopamine concentration in the amygdala, decreased density of the dopamine transporter, and increased numbers of dopamine type 4 receptors in the entorhinal cortex.

Serotonin. Current hypotheses posit serotonin excess as a cause of both positive and negative symptoms in schizophrenia. The robust serotonin antagonist activity of clozapine and other second-generation antipsychotics coupled with the effectiveness of clozapine to decrease positive symptoms in chronic patients has contributed to the validity of this proposition.

Norepinephrine. Anhedonia—the impaired capacity for emotional gratification and the decreased ability to experience pleasure—has long been noted to be a prominent feature of schizophrenia. A selective neuronal degeneration within the norepinephrine reward neural system could account for this aspect of schizophrenic symptomatology. However, biochemical and pharmacological data

bearing on this proposal are inconclusive. GABA. The inhibitory amino acid neurotransmitter γ -aminobutyric acid (GABA) has been implicated in the pathophysiology of schizophrenia based on the finding that some patients with schizophrenia have a loss of GABAergic neurons in the hippocampus. GABA has a regulatory effect on dopamine activity, and the loss of inhibitory GABAergic neurons could lead to the hyperactivity of dopaminergic neurons. Neuropeptides. Neuropeptides, such as substance P and neurotensin, are localized with the catecholamine and indolamine neurotransmitters and influence the action of these neurotransmitters. Alteration in neuropeptide mechanisms could facilitate, inhibit, or otherwise alter the pattern of firing these neuronal systems. Glutamate. Glutamate has been implicated because ingestion of phencyclidine, a glutamate antagonist, produces an acute syndrome similar to schizophrenia. The hypotheses proposed about glutamate include those of hyperactivity, hypoactivity, and glutamate-induced neurotoxicity. Acetylcholine and Nicotine. Postmortem studies in schizophrenia have demonstrated decreased muscarinic and nicotinic receptors in the caudate-putamen, hippocampus, and selected regions of the prefrontal cortex. These receptors play a role in the regulation of neurotransmitter systems involved in cognition, which is impaired in schizophrenia. Neuropathology In the 19th century, neuropathologists failed to find a neuropathological basis for schizophrenia, and thus they classified schizophrenia as a functional disorder. By the end of the 20th century, however, researchers had made significant strides in revealing a potential neuropathological basis for schizophrenia, primarily in the limbic system and the basal ganglia, including neuropathological or neurochemical abnormalities in the cerebral cortex, the thalamus, and the brainstem. The loss of brain volume widely reported in schizophrenic brains appears to result from reduced density of the axons, dendrites, and synapses that mediate associative functions of the brain. Synaptic density is highest at age 1 year and then is pared down to adult values in early adolescence. One theory, based in part on the observation that patients often develop schizophrenic symptoms during adolescence, holds that schizophrenia results from excessive pruning of synapses during this phase of development.

Cerebral Ventricles. Computed tomography (CT) scans of patients with schizophrenia have consistently shown lateral and third ventricular enlargement and some reduction in cortical volume. Reduced volumes of cortical gray matter have been demonstrated during the earliest stages of the disease. Several investigators have attempted to determine whether the abnormalities detected by CT are progressive or static. Some studies have concluded that the lesions observed on CT scan are present at the onset of the illness and do not progress. Other studies, however, have concluded that the pathological process visualized on CT scan continues to progress during the illness. Thus, whether an active pathological process is continuing to evolve in schizophrenia patients is still uncertain. Reduced Symmetry. There is a reduced symmetry in several brain areas in schizophrenia, including the temporal, frontal, and occipital lobes. This reduced symmetry is believed by some investigators to originate during fetal life and to be indicative of a disruption in brain lateralization during neurodevelopment. Limbic System. Because of its role in controlling emotions, the limbic system has been hypothesized to be involved in the pathophysiology of schizophrenia. Studies of postmortem brain samples from schizophrenia patients have shown a decrease in the size of the region, including the amygdala, the hippocampus, and the parahippocampal gyrus. This neuropathological finding agrees with the observation made by magnetic resonance imaging studies of patients with schizophrenia. The hippocampus is not only smaller in size in schizophrenia but is also functionally abnormal as indicated by disturbances in glutamate transmission. Disorganization of the neurons within the

hippocampus has also been seen in brain tissue sections of schizophrenia patients compared with healthy control participants without schizophrenia. Prefrontal Cortex. There is considerable evidence from postmortem brain studies that supports anatomical abnormalities in the prefrontal cortex in schizophrenia. Functional deficits in the prefrontal brain imaging region have also been demonstrated. It has long been noted that several symptoms of schizophrenia mimic those found in persons with prefrontal lobotomies or frontal lobe syndromes. Thalamus. Some studies of the thalamus show evidence of volume shrinkage or neuronal loss, in particular subnuclei. The medial dorsal nucleus of the thalamus, which has reciprocal connections with the prefrontal cortex, has been reported to contain a reduced number of neurons. The total number of neurons, oligodendrocytes, and astrocytes is reduced by 30 to 45 percent in schizophrenia patients. This putative finding does not appear to be due to the effects of antipsychotic drugs because the volume of the thalamus is similar in size between patients with schizophrenia treated chronically with medication and neuroleptic-naïve subjects. Basal Ganglia and Cerebellum. The basal ganglia and cerebellum have been of

theoretical interest in schizophrenia for at least two reasons. First, many patients with schizophrenia show odd movements, even in the absence of medication-induced movement disorders (e.g., tardive dyskinesia). The odd movements can include an awkward gait, facial grimacing, and stereotypies. Because the basal ganglia and cerebellum are involved in the control of movement, disease in these areas is implicated in the pathophysiology of schizophrenia. Second, the movement disorders involving the basal ganglia (e.g., Huntington's disease, Parkinson's disease) are the ones most commonly associated with psychosis. Neuropathological studies of the basal ganglia have produced variable and inconclusive reports about cell loss or the reduction of volume of the globus pallidus and the substantia nigra. Studies have also shown an increase in the number of D2 receptors in the caudate, the putamen, and the nucleus accumbens. The question remains, however, whether the increase is secondary to the patient having received antipsychotic medications. Some investigators have begun to study the serotonergic system in the basal ganglia; a role for serotonin in psychotic disorder is suggested by the clinical usefulness of antipsychotic drugs that are serotonin antagonists (e.g., clozapine, risperidone). Neural Circuits There has been a gradual evolution from conceptualizing schizophrenia as a disorder that involves discrete areas of the brain to a perspective that views schizophrenia as a disorder of brain neural circuits. For example, as mentioned previously, the basal ganglia and cerebellum are reciprocally connected to the frontal lobes, and the abnormalities in frontal lobe function seen in some brain imaging studies may be due to disease in either area rather than in the frontal lobes themselves. It is also hypothesized that an early developmental lesion of the dopaminergic tracts to the prefrontal cortex results in the disturbance of prefrontal and limbic system function and leads to the positive and negative symptoms and cognitive impairments observed in patients with schizophrenia. Of particular interest in the context of neural circuit hypotheses linking the prefrontal cortex and limbic system are studies demonstrating a relationship between hippocampal morphological abnormalities and disturbances in prefrontal cortex metabolism or function (or both). Data from functional and structural imaging studies in humans suggest that whereas dysfunction of the anterior cingulate basal ganglia thalamocortical circuit underlies the production of positive psychotic symptoms, dysfunction of the dorsolateral prefrontal circuit underlies the production of primary, enduring, negative or deficit symptoms. There is a neural basis for cognitive functions that is impaired in patients with schizophrenia. The observation of the relationship among impaired working memory performance, disrupted prefrontal neuronal integrity, altered prefrontal, cingulate,

and inferior parietal cortex, and altered hippocampal blood flow provides strong support for disruption of the normal working memory neural circuit in patients with schizophrenia. The involvement of this circuit, at least for auditory hallucinations, has been documented in a number of functional imaging studies that

contrast hallucinating and nonhallucinating patients. Brain Metabolism Studies using magnetic resonance spectroscopy, a technique that measures the concentration of specific molecules in the brain, found that patients with schizophrenia had lower levels of phosphomonoester and inorganic phosphate and higher levels of phosphodiester than a control group. Furthermore, concentrations of N-acetyl aspartate, a marker of neurons, were lower in the hippocampus and frontal lobes of patients with schizophrenia. Applied Electrophysiology Electroencephalographic studies indicate that many schizophrenia patients have abnormal records, increased sensitivity to activation procedures (e.g., frequent spike activity after sleep deprivation), decreased alpha activity, increased theta and delta activity, possibly more epileptiform activity than usual, and possibly more left-sided abnormalities than usual. Schizophrenia patients also exhibit an inability to filter out irrelevant sounds and are extremely sensitive to background noise. The flooding of sound that results makes concentration difficult and may be a factor in the production of auditory hallucinations. This sound sensitivity may be associated with a genetic defect. Complex Partial Epilepsy. Schizophrenia-like psychoses have been reported to occur more frequently than expected in patients with complex partial seizures, especially seizures involving the temporal lobes. Factors associated with the development of psychosis in these patients include a left-sided seizure focus, medial temporal location of the lesion, and an early onset of seizures. The first-rank symptoms described by Schneider may be similar to symptoms of patients with complex partial epilepsy and may reflect the presence of a temporal lobe disorder when seen in patients with schizophrenia. Evoked Potentials. A large number of abnormalities in evoked potential among patients with schizophrenia has been described. The P300 has been most studied and is defined as a large, positive evoked-potential wave that occurs about 300 milliseconds after a sensory stimulus is detected. The major source of the P300 wave may be located in the limbic system structures of the medial temporal lobes. In patients with schizophrenia, the P300 has been reported to be statistically smaller than in comparison groups. Abnormalities in the P300 wave have also been reported to be more common in children who, because they have affected parents, are at high risk for schizophrenia. Whether the characteristics of the P300 represent a state or a trait phenomenon remains controversial. Other evoked potentials reported to be abnormal in patients with schizophrenia are the N100 and the contingent negative variation. The N100 is a negative wave that occurs about 100 milliseconds after a stimulus, and the contingent negative variation is a slowly developing, negative-voltage shift following the

presentation of a sensory stimulus that is a warning for an upcoming stimulus. The evoked-potential data have been interpreted as indicating that although patients with schizophrenia are unusually sensitive to a sensory stimulus (larger early evoked potentials), they compensate for the increased sensitivity by blunting the processing of information at higher cortical levels (indicated by smaller late evoked potentials). Eye Movement Dysfunction The inability to follow a moving visual target accurately is the defining basis for the disorders of smooth visual pursuit and disinhibition of saccadic eye movements seen in patients with schizophrenia. Eye movement dysfunction may be a trait marker for schizophrenia; it is independent of drug treatment and clinical state and is also seen in first-degree relatives of probands with schizophrenia. Various

studies have reported abnormal eye movements in 50 to 85 percent of patients with schizophrenia compared with about 25 percent in psychiatric patients without schizophrenia and fewer than 10 percent in nonpsychiatrically ill control participant. Psychoneuroimmunology Several immunological abnormalities have been associated with patients who have schizophrenia. The abnormalities include decreased T-cell interleukin-2 production, reduced number and responsiveness of peripheral lymphocytes, abnormal cellular and humoral reactivity to neurons, and the presence of brain-directed (antibrain) antibodies. The data can be interpreted variously as representing the effects of a neurotoxic virus or of an endogenous autoimmune disorder. Most carefully conducted investigations that have searched for evidence of neurotoxic viral infections in schizophrenia have had negative results, although epidemiological data show a high incidence of schizophrenia after prenatal exposure to influenza during several epidemics of the disease. Other data supporting a viral hypothesis are an increased number of physical anomalies at birth, an increased rate of pregnancy and birth complications, seasonality of birth consistent with viral infection, geographical clusters of adult cases, and seasonality of hospitalizations. Nonetheless, the inability to detect genetic evidence of viral infection reduces the significance of all circumstantial data. The possibility of autoimmune brain antibodies has some data to support it; the pathophysiological process, if it exists, however, probably explains only a subset of the population with schizophrenia. Psychoneuroendocrinology Many reports describe neuroendocrine differences between groups of patients with schizophrenia and groups of control subjects. For example, results of the dexamethasone-suppression test have been reported to be abnormal in various subgroups of patients with schizophrenia, although the practical or predictive value of the test in schizophrenia has been questioned. One carefully done report, however, has correlated persistent nonsuppression on the dexamethasone-suppression test in

schizophrenia with a poor long-term outcome. Some data suggest decreased concentrations of luteinizing hormone or folliclestimulating hormone, perhaps correlated with age of onset and length of illness. Two additional reported abnormalities may be correlated with the presence of negative symptoms: a blunted release of prolactin and growth hormone on gonadotropinreleasing hormone or thyrotropin-releasing hormone stimulation and a blunted release of growth hormone on apomorphine stimulation. PSYCHOSOCIAL AND PSYCHOANALYTIC THEORIES If schizophrenia is a disease of the brain, it is likely to parallel diseases of other organs (e.g., myocardial infarctions, diabetes) whose courses are affected by psychosocial stress. Thus, clinicians should consider both psychosocial and biological factors affecting schizophrenia. The disorder affects individual patients, each of whom has a unique psychological makeup. Although many psychodynamic theories about the pathogenesis of schizophrenia seem outdated, perceptive clinical observations can help contemporary clinicians understand how the disease may affect a patient's psyche. Psychoanalytic Theories. Sigmund Freud postulated that schizophrenia resulted from developmental fixations early in life. These fixations produce defects in ego development, and he postulated that such defects contributed to the symptoms of schizophrenia. Ego disintegration in schizophrenia represents a return to the time when the ego was not yet developed or had just begun to be established. Because the ego affects the interpretation of reality and the control of inner drives, such as sex and aggression, these ego functions are impaired. Thus, intrapsychic conflict arising from the early fixations and the ego defect, which may have resulted from poor early object relations, fuel the psychotic symptoms. As described by Margaret Mahler, there are distortions in the reciprocal relationship between the infant and the mother. The child is unable to separate from, and progress beyond, the closeness and complete dependence that characterize the mother-child relationship in

the oral phase of development. As a result, the person's identity never becomes secure. Paul Federn hypothesized that the defect in ego functions permits intense hostility and aggression to distort the mother– infant relationship, which leads to eventual personality disorganization and vulnerability to stress. The onset of symptoms during adolescence occurs when teenagers need a strong ego to function independently, to separate from the parents, to identify tasks, to control increased internal drives, and to cope with intense external stimulation. Harry Stack Sullivan viewed schizophrenia as a disturbance in interpersonal relatedness. The patient's massive anxiety creates a sense of unrelatedness that is transformed into parataxic distortions, which are usually, but not always, persecutory. To Sullivan, schizophrenia is an adaptive method used to avoid panic, terror, and disintegration of the sense of self. The source of pathological anxiety results from cumulative experiential traumas during development. Psychoanalytic theory also postulates that the various symptoms of schizophrenia have symbolic meaning for individual patients. For example, fantasies of the world coming to an end may indicate a perception that a person's internal world has broken down. Feelings of inferiority are replaced by delusions of grandeur and omnipotence. Hallucinations may be substitutes for a patient's inability to deal with objective reality and may represent inner wishes or fears. Delusions,

similar to hallucinations, are regressive, restitutive attempts to create a new reality or to express hidden fears or impulses (Fig. 7.1-3). Regardless of the theoretical model, all psychodynamic approaches are founded on the premise that psychotic symptoms have meaning in schizophrenia. Patients, for example, may become grandiose after an injury to their self-esteem. Similarly, all theories recognize that human relatedness may be terrifying for persons with schizophrenia. Although research on the efficacy of psychotherapy with schizophrenia shows mixed results, concerned persons who offer compassion and a sanctuary in the confusing world of schizophrenia must be a cornerstone of any overall treatment plan. Long-term followup studies show that some patients who bury psychotic episodes probably do not benefit from exploratory psychotherapy, but those who are able to integrate the psychotic experience into their lives may benefit from some insight-oriented approaches. There is renewed interest in the use of long-term individual psychotherapy in the treatment of schizophrenia, especially when combined with medication.

FIGURE 7.1-3 This patient wore suits too large for him in the delusional belief that he would appear taller to others. (Courtesy of Emil Kraepelin, M.D.) Learning Theories. According to learning theorists, children who later have schizophrenia learn irrational reactions and ways of thinking by imitating parents who have their own significant emotional problems. In learning theory, the poor interpersonal relationships of persons with schizophrenia develop because of poor models for learning during childhood. Family Dynamics In a study of British 4-year-old children, those who had a poor mother–child relationship

had a sixfold increase in the risk of developing schizophrenia, and offspring from schizophrenic mothers who were adopted away at birth were more likely to develop the illness if they were reared in adverse circumstances compared with those raised in loving homes by stable adoptive parents. Nevertheless, no well-controlled evidence indicates that a specific family pattern plays a causative role in the development of schizophrenia. Some patients with schizophrenia do come from dysfunctional families, just as do many nonpsychiatrically ill persons. It is important, however, not to overlook pathological family behavior that can significantly increase the emotional stress with which a vulnerable patient with schizophrenia must cope. Double Bind. The double-bind

concept was formulated by Gregory Bateson and Donald Jackson to describe a hypothetical family in which children receive conflicting parental messages about their behavior, attitudes, and feelings. In Bateson's hypothesis, children withdraw into a psychotic state to escape the unsolvable confusion of the double bind. Unfortunately, the family studies that were conducted to validate the theory were seriously flawed methodologically. The theory has value only as a descriptive pattern, not as a causal explanation of schizophrenia. An example of a double bind is a parent who tells a child to provide cookies for his or her friends and then chastises the child for giving away too many cookies to playmates.

Schisms and Skewed Families. Theodore Lidz described two abnormal patterns of family behavior. In one family type, with a prominent schism between the parents, one parent is overly close to a child of the opposite gender. In the other family type, a skewed relationship between a child and one parent involves a power struggle between the parents and the resulting dominance of one parent. These dynamics stress the tenuous adaptive capacity of the person with schizophrenia.

Pseudomutual and Pseudohostile Families. As described by Lyman Wynne, some families suppress emotional expression by consistently using pseudomutual or pseudohostile verbal communication. In such families, a unique verbal communication develops, and when a child leaves home and must relate to other persons, problems may arise. The child's verbal communication may be incomprehensible to outsiders.

Expressed Emotion. Parents or other caregivers may behave with overt criticism, hostility, and overinvolvement toward a person with schizophrenia. Many studies have indicated that in families with high levels of expressed emotion, the relapse rate for schizophrenia is high. The assessment of expressed emotion involves analyzing both what is said and the manner in which it is said.

DIAGNOSIS The DSM-5 diagnostic criteria include course specifiers (i.e., prognosis) that offer clinicians several options and describe actual clinical situations (Table 7.1-1). The

presence of hallucinations or delusions is not necessary for a diagnosis of schizophrenia; the patient's disorder is diagnosed as schizophrenia when the patient exhibits two of the symptoms listed in symptoms 1 through 5 of Criterion A in Table 7.1-1 (e.g., disorganized speech). Criterion B requires that impaired functioning, although not deteriorations, be present during the active phase of the illness. Symptoms must persist for at least 6 months, and a diagnosis of schizoaffective disorder or mood disorder must be absent. Table 7.1-1 DSM-5 Diagnostic Criteria for Schizophrenia

Subtypes Five subtypes of schizophrenia have been described based predominantly on clinical presentation: paranoid, disorganized, catatonic, undifferentiated, and residual. DSM-5 no longer uses these subtypes but they are listed in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). They are included in this text because the authors believe them to be of clinical significance and they are still used by most clinicians in the United States and around the world to

describe the phenomenology of schizophrenia.

Paranoid Type. The paranoid type of schizophrenia is characterized by preoccupation with one or more delusions or frequent auditory hallucinations. Classically, the paranoid type of schizophrenia is characterized mainly by the presence of delusions of persecution or grandeur (Fig. 7.1-4). Patients with paranoid schizophrenia usually have their first episode of illness at an older age than do patients with catatonic or disorganized schizophrenia. Patients in whom schizophrenia occurs in the late 20s or 30s have usually established a social life that may help them through their illness, and the ego resources of paranoid patients tend to be greater than those of patients with catatonic and disorganized schizophrenia. Patients with the

paranoid type of schizophrenia show less regression of their mental faculties, emotional responses, and behavior than do patients with other types of schizophrenia. FIGURE 7.1-4 This patient had an artificial eye that he believed had special powers when removed from the socket. (Courtesy of Emil Kraepelin, M.D.) Patients with paranoid schizophrenia are typically tense, suspicious, guarded, reserved, and sometimes hostile or aggressive, but they can occasionally conduct themselves adequately in social situations. Their intelligence in areas not invaded by their psychosis tends to remain intact. Disorganized Type. The disorganized type of schizophrenia is characterized by a marked regression to primitive, disinhibited, and unorganized behavior and by the

absence of symptoms that meet the criteria for the catatonic type. The onset of this subtype is generally early, occurring before age 25 years. Disorganized patients are usually active but in an aimless, nonconstructive manner. Their thought disorder is pronounced, and their contact with reality is poor. Their personal appearance is disheveled, and their social behavior and their emotional responses are inappropriate. They often burst into laughter without any apparent reason. Incongruous grinning and grimacing are common in these patients, whose behavior is best described as silly or fatuous. Patient AB, a 32-year-old woman, began to lose weight and became careless about her work, which deteriorated in quality and quantity. She believed that other women at her place of employment were circulating slanderous stories concerning her and complained that a young man employed in the same plant had put his arm around her and insulted her. Her family demanded that the charge be investigated, which showed not only that the charge was without foundation but also that the man in question had not spoken to her for months. One day she returned home from work, and as she entered the house, she laughed loudly, watched her sister-in-law suspiciously, refused to answer questions, and at the sight of her brother began to cry. She refused to go to the bathroom, saying that a man was looking in the windows at her. She ate no food, and the next day she declared that her sisters were "bad women," that everyone was talking about her, and that someone had been having sexual relations with her, and although she could not see him, he was "always around." The patient was admitted to a public psychiatric hospital. As she entered the admitting office, she laughed loudly and repeatedly screamed in a loud tone, "She cannot stay here; she's got to go home!" She grimaced and performed various stereotyped movements of her hands. When seen on the ward an hour later, she paid no attention to questions, although she talked to herself in a childish tone. She moved about constantly, walked on her toes in a dancing manner, pointed aimlessly about, and put out her tongue and sucked her lips in the manner of an infant. At times she moaned and cried like a child but shed no tears. As the months passed, she remained silly, childish, preoccupied, and inaccessible, grimacing, gesturing, pointing at objects in a stereotyped way, and usually chattering to herself in a peculiar high-pitched voice, with little of what she said being understood. Her condition continued to deteriorate, she remained unkempt, and she presented a picture of extreme introversion and regression, with no interest either in the activities of the institution or in her relatives who visited her. (Adapted from case of Arthur P. Noyes, M.D., and Lawrence C. Kolb, M.D.) Catatonic Type. The catatonic type of schizophrenia, which was common several decades ago, has become rare in Europe and North America. The classic feature of the catatonic type is a marked disturbance in motor function; this disturbance may involve

stupor, negativism, rigidity, excitement, or posturing. Sometimes the patient shows a rapid alteration between extremes of excitement and stupor. Associated features include stereotypies, mannerisms, and waxy flexibility. Mutism is particularly common. During catatonic excitement,

patients need careful supervision to prevent them from hurting themselves or others. Medical care may be needed because of malnutrition, exhaustion, hyperpyrexia, or self-inflicted injury. AC, age 32 years, was admitted to the hospital. On arrival, he was noted to be an asthenic, poorly nourished man with dilated pupils, hyperactive tendon reflexes, and a pulse rate of 120 beats/min. He showed many mannerisms, laid down on the floor, pulled at his foot, made undirected violent striking movements, struck attendants, grimaced, assumed rigid and strange postures, refused to speak, and appeared to be having auditory hallucinations. When seen later in the day, he was found to be in a stuporous state. His face was without expression, he was mute and rigid, and he paid no attention to those about him or to their questions. His eyes were closed, and his eyelids could be separated only with effort. There was no response to pinpricks or other painful stimuli. He gradually became accessible, and when asked concerning himself, he referred to his stuporous period as sleep and maintained that he had no recollection of any events occurring during it. He said, "I didn't know anything. Everything seemed to be dark as far as my mind is concerned. Then I began to see a little light, like the shape of a star. Then my head got through the star gradually. I saw more and more light until I saw everything in a perfect form a few days ago." He explained his mutism by saying that he had been afraid he would "say the wrong thing" and that he "didn't know exactly what to talk about." From his obviously inadequate emotional response and his statement that he was "a scientist and an inventor of the most extraordinary genius of the 20th century," it was plain that he was still far from well. (Adapted from case of Arthur P. Noyes, M.D., and Lawrence C. Kolb, M.D.)

Undifferentiated Type. Frequently, patients who clearly have schizophrenia cannot be easily fit into one type or another. These patients are classified as having schizophrenia of the undifferentiated type.

Residual Type. The residual type of schizophrenia is characterized by continuing evidence of the schizophrenic disturbance in the absence of a complete set of active symptoms or of sufficient symptoms to meet the diagnosis of another type of schizophrenia. Emotional blunting, social withdrawal, eccentric behavior, illogical thinking, and mild loosening of associations commonly appear in the residual type. When delusions or hallucinations occur, they are neither prominent nor accompanied by strong affect.

Other Subtypes The subtyping of schizophrenia has had a long history; other subtyping schemes appear in the literature, especially literature from countries other than the United States.

Bouffée Déliante (Acute Delusional Psychosis). This French diagnostic concept differs from a diagnosis of schizophrenia primarily on the basis of a symptom duration of less than 3 months. The diagnosis is similar to the DSM-5 diagnosis of schizophreniform disorder. French clinicians report that about 40 percent of patients with a diagnosis of bouffée délirante progress in their illness and are eventually classified as having schizophrenia.

Latent. The concept of latent schizophrenia was developed during a time when theorists conceived of the disorder in broad diagnostic terms. Currently, patients must be very mentally ill to warrant a diagnosis of schizophrenia, but with a broad diagnostic concept of schizophrenia, the condition of patients who would not currently be thought of as severely ill could have received a diagnosis of schizophrenia. Latent schizophrenia, for example, was often the diagnosis used for what are now called borderline, schizoid, and schizotypal personality disorders. These patients may occasionally show peculiar behaviors or thought disorders but do not consistently manifest psychotic symptoms. In the past, the syndrome was also termed borderline schizophrenia.

Oneiroid. The oneiroid state refers to a dream-like state in which patients may be deeply perplexed and not fully oriented in time and place. The term oneiroid schizophrenia has been used for patients who are engaged in their hallucinatory experiences to the exclusion of involvement in the real world. When an oneiroid state is present,

clinicians should be particularly careful to examine patients for medical or neurological causes of the symptoms. After a 20-year-old female college student had recovered from her schizophrenic breakdown, she wrote the following description of her experiences during the oneiroid phase: This is how I remember it. The road has changed. It is twisted and it used to be straight. Nothing is constant—all is in motion. The trees are moving. They do not remain at rest. How is it my mother does not bump into the trees that are moving? I follow my mother. I am afraid, but I follow. I have to share my strange thoughts with someone. We are sitting on a bench. The bench seems low. It, too, has moved. “The bench is low,” I say. “Yes,” says my mother. “This isn’t how it used to be. How come there are no people around? There are usually lots of people and it is Sunday and there are no people. This is strange.” All these strange questions irritate my mother who then says she must be going soon. While I continue thinking I’m in a kind of nowhere....

There are no days; no nights; sometimes it is darker than other times—that’s all. It is never quite black, just dark gray. There is no such thing as time—there is only eternity. There is no such thing as death—nor heaven and hell—there is only a timeless—hateful—spaceless—worsening of things. You can never go forward; you must always regress into this horrific mess.... The outside was moving rather swiftly, everything seemed topsy-turvy—things were flying about. It was very strange. I wanted to get back to the quiet very badly but when I got back I couldn’t remember where anything was (e.g., the bathroom).... (Courtesy of Heinz E. Lehmann, M.D.) Paraphrenia. The term paraphrenia is sometimes used as a synonym for paranoid schizophrenia or for either a progressively deteriorating course of illness or the presence of a well-systemized delusional system. The multiple meanings of the term render it ineffectual in communicating information. Pseudoneurotic Schizophrenia. Occasionally, patients who initially have such symptoms as anxiety, phobias, obsessions, and compulsions later reveal symptoms of thought disorder and psychosis. These patients are characterized by symptoms of pananxiety, panphobia, panambivalence, and sometimes chaotic sexuality. Unlike persons with anxiety disorders, pseudoneurotic patients have free-floating anxiety that rarely subsides. In clinical descriptions, the patients seldom become overtly and severely psychotic. This condition is currently diagnosed as borderline personality disorder. Simple Deteriorative Disorder (Simple Schizophrenia). Simple deteriorative disorder is characterized by a gradual, insidious loss of drive and ambition. Patients with the disorder are usually not overtly psychotic and do not experience persistent hallucinations or delusions. Their primary symptom is withdrawal from social and work-related situations. The syndrome must be differentiated from depression, a phobia, a dementia, or an exacerbation of personality traits. Clinicians should be sure that patients truly meet the diagnostic criteria for schizophrenia before making the diagnosis. An unmarried man, 27 years old, was brought to the mental hospital because he had on several occasions become violent toward his father. For a few weeks, he had hallucinations and heard voices. The voices eventually ceased, but he then adopted a strange way of life. He would sit up all night, sleep all day, and become very angry when his father tried to get him out of bed. He did not shave or wash for weeks, smoked continuously, ate very irregularly, and drank enormous quantities of tea. In the hospital, he adjusted rapidly to the new environment and was found to be generally cooperative. He showed no marked abnormalities of mental state or behavior, except for his lack of concern for just about anything. He kept to himself as

much as possible and conversed little with patients or staff. His personal hygiene had to be supervised by the nursing staff; otherwise, he would quickly become dirty and untidy. Six years after his admission to the hospital, he is described as shiftless and careless, sullen and

unreasonable. He lies on a couch all day long. Although many efforts have been made to get the patient to accept therapeutic work assignments, he refuses to consider any kind of regular occupation. In the summer, he wanders about the hospital grounds or lies under a tree. In the winter, he wanders through the tunnels connecting the various hospital buildings and is often seen stretched out for hours under the warm pipes that carry the steam through the tunnels. (Courtesy of Heinz E. Lehmann, M.D.)

Postpsychotic Depressive Disorder of Schizophrenia. After an acute schizophrenia episode, some patients become depressed. The symptoms of postpsychotic depressive disorder of schizophrenia can closely resemble the symptoms of the residual phase of schizophrenia and the adverse effects of commonly used antipsychotic medications. The diagnosis should not be made if they are substance induced or part of a mood disorder due to a general medical condition. These depressive states occur in up to 25 percent of patients with schizophrenia and are associated with an increased risk of suicide.

Early-Onset Schizophrenia. A small minority of patients manifest schizophrenia in childhood. Such children may at first present diagnostic problems, particularly with differentiation from mental retardation and autistic disorder. Recent studies have established that the diagnosis of childhood schizophrenia may be based on the same symptoms used for adult schizophrenia. Its onset is usually insidious, its course tends to be chronic, and the prognosis is mostly unfavorable.

Late-Onset Schizophrenia. Late-onset schizophrenia is clinically indistinguishable from schizophrenia but has an onset after age 45 years. This condition tends to appear more frequently in women and tends to be characterized by a predominance of paranoid symptoms. The prognosis is favorable, and these patients usually do well on antipsychotic medication.

Deficit Schizophrenia. In the 1980s, criteria were promulgated for a subtype of schizophrenia characterized by enduring, idiopathic negative symptoms. These patients were said to exhibit the deficit syndrome. This group of patients is now said to have deficit schizophrenia (see the criteria for that putative disease diagnosis in Table 7.1-2). Patients with schizophrenia with positive symptoms are said to have nondeficit schizophrenia. The symptoms used to define deficit schizophrenia are strongly interrelated, although various combinations of the six negative symptoms in the criteria can be found.

Table 7.1-2 Diagnostic Criteria for Deficit Schizophrenia Deficit patients have a more severe course of illness than nondeficit patients, with a higher prevalence of abnormal involuntary movements before administration of antipsychotic drugs and poorer social function before the onset of psychotic symptoms. The onset of the first psychotic episode is more often insidious, and these patients show less longterm recovery of function than do nondeficit patients. Deficit patients are also less likely to marry than are other patients with schizophrenia. However, despite their poorer level of function and greater social isolation, both of which should increase a patient's stress and, therefore, the risk of serious depression, deficit patients appear to have a decreased risk of major depression and probably have a decreased risk of suicide as well. The risk factors of deficit patients differ from those of nondeficit patients; whereas deficit schizophrenia is associated with an excess of summer births, nondeficit patients have an excess of winter births. Deficit schizophrenia may also be associated with a greater familial risk of schizophrenia and of mild, deficit-like features in the nonpsychotic relatives of deficit probands. Within a family with multiple affected siblings, the deficit-nondeficit categorization tends to be uniform. The deficit group also has a higher prevalence of men. The psychopathology of deficit patients impacts treatment; their lack of motivation, lack of distress, greater cognitive impairment, and asocial nature undermine the efficacy of psychosocial interventions, as well as their adherence to medication regimens. Their cognitive impairment, which is greater than that of nondeficit subjects, also contributes to this lack of efficacy.

PSYCHOLOGICAL TESTING. Patients with schizophrenia generally perform poorly on a wide

range of neuropsychological tests. Vigilance, memory, and concept formation are most affected and consistent with pathological involvement in the frontotemporal cortex. Objective measures of neuropsychological performance, such as the Halstead-Reitan battery and the Luria-Nebraska battery, often give abnormal findings, such as bilateral frontal and temporal lobe dysfunction, including impairments in attention, retention time, and problem-solving ability. Motor ability is also impaired, possibly related to brain asymmetry. INTELLIGENCE TESTS. When groups of patients with schizophrenia are compared with groups of psychiatric patients without schizophrenia or with the general population, the schizophrenia patients tend to score lower on intelligence tests.

Statistically, the evidence suggests that low intelligence is often present at the onset, and intelligence may continue to deteriorate with the progression of the disorder. PROJECTIVE AND

PERSONALITY TESTS. Projective tests, such as the Rorschach test and the Thematic Apperception Test, may indicate bizarre ideation. Personality inventories, such as the Minnesota Multiphasic Personality Inventory, often give abnormal results in schizophrenia, but the contribution to

diagnosis and treatment planning is minimal. CLINICAL FEATURES A discussion of the clinical signs and symptoms of schizophrenia raises three key issues. First, no clinical sign or symptom is pathognomonic for schizophrenia; every sign or symptom seen in schizophrenia occurs in other psychiatric and neurological disorders. This observation is contrary to the often-heard clinical opinion that certain signs and symptoms are diagnostic of schizophrenia. Therefore, a patient's history is essential for the diagnosis of schizophrenia; clinicians cannot diagnose schizophrenia simply by results of a mental status examination, which may vary. Second, a patient's symptoms change with time. For example, a patient may have intermittent hallucinations and a varying ability to perform adequately in social situations, or significant symptoms of a mood disorder may come and go during the course of schizophrenia. Third, clinicians must take into account the patient's educational level, intellectual ability, and cultural and subcultural membership. An impaired ability to understand abstract concepts, for example, may reflect either the patient's education or his or her intelligence. Religious organizations and cults may have customs that seem strange to outsiders but are normal to those within the cultural setting. Premorbid Signs and Symptoms In theoretical formulations of the course of schizophrenia, premorbid signs and symptoms appear before the prodromal phase of the illness. The differentiation implies that premorbid signs and symptoms exist before the disease process evidences itself and that the prodromal signs and symptoms are parts of the evolving disorder. In the typical, but not invariable, premorbid history of schizophrenia, patients had schizoid or schizotypal personalities characterized as quiet, passive, and introverted; as children,

they had few friends. Preschizophrenic adolescents may have no close friends and no dates and may avoid team sports. They may enjoy watching movies and television, listening to music, or playing computer games to the exclusion of social activities. Some adolescent patients may show a sudden onset of obsessive-compulsive behavior as part of the prodromal picture. The validity of the prodromal signs and symptoms, almost invariably recognized after the diagnosis of schizophrenia has been made, is uncertain; after schizophrenia is diagnosed, the retrospective remembrance of early signs and symptoms is affected. Nevertheless, although the first hospitalization is often believed to mark the beginning of the disorder, signs and symptoms have often been present for months or even years. The signs may have started with complaints about somatic symptoms, such as headache, back and muscle pain, weakness, and digestive problems. The initial diagnosis may

be malingering, chronic fatigue syndrome, or somatization disorder. Family and friends may eventually notice that the person has changed and is no longer functioning well in occupational, social, and personal activities. During this stage, a patient may begin to develop an interest in abstract ideas, philosophy, and the occult or religious questions (Fig. 7.1-5). Additional prodromal signs and symptoms can include markedly peculiar behavior, abnormal affect, unusual speech, bizarre ideas, and strange perceptual experiences.

FIGURE 7.1-5 Schizophrenia patient schema. This illustrates his fragmented, abstract, and overly inclusive thinking and preoccupation with religious ideologies and mathematical proofs. (Courtesy of Heinz E. Lehmann.)

Mental Status Examination General Description. The appearance of a patient with schizophrenia can range from that of a completely disheveled, screaming, agitated person to an obsessively groomed, completely silent, and immobile person. Between these two poles, patients may be talkative and may exhibit bizarre postures. Their behavior may become agitated or violent, apparently in an unprovoked manner, but usually in response to hallucinations. In contrast, in catatonic stupor, often referred to as catatonia, patients seem completely lifeless and may exhibit such signs as muteness, negativism, and automatic obedience. Waxy flexibility, once a common sign in catatonia, has become rare, as has manneristic behavior. A person with a less extreme subtype of catatonia may show marked social withdrawal and egocentricity, a lack of spontaneous speech or movement, and an absence of goal-directed behavior. Patients with catatonia may sit immobile and speechless in their chairs, respond to questions with only short answers, and move only when directed to move. Other obvious behavior may include odd clumsiness or stiffness in body movements, signs now seen as possibly indicating a disease process in the basal ganglia. Patients with schizophrenia are often poorly groomed, fail to bathe, and dress much too warmly for the prevailing temperatures. Other odd behaviors include tics; stereotypies; mannerisms; and, occasionally, echopraxia, in which patients imitate the posture or the behavior of the examiner.

PRECOX FEELING. Some experienced clinicians report a precox feeling, an intuitive experience of their inability to establish an emotional rapport with a patient. Although the experience is common, no data indicate that it is a valid or reliable criterion in the diagnosis of schizophrenia.

Mood, Feelings, and Affect Two common affective symptoms in schizophrenia are reduced emotional responsiveness, sometimes severe enough to warrant the label of anhedonia, and overly active and inappropriate emotions such as extremes of rage, happiness, and anxiety. A flat or blunted affect can be a symptom of the illness itself, of the parkinsonian adverse effects of antipsychotic medications, or of depression, and differentiating these symptoms can be a clinical challenge. Overly emotional patients may describe exultant feelings of omnipotence, religious ecstasy, terror at the disintegration of their souls, or paralyzing anxiety about the destruction of the universe. Other feeling tones include perplexity, a sense of isolation, overwhelming ambivalence, and depression.

Perceptual Disturbances

HALLUCINATIONS. Any of the five senses may be affected by hallucinatory experiences in patients with schizophrenia. The most common hallucinations, however, are auditory, with voices that are often threatening, obscene, accusatory, or insulting. Two or more voices may converse among themselves, or a voice may comment on the patient's life or behavior. Visual hallucinations are common (Fig. 7.1-6), but tactile, olfactory, and gustatory hallucinations are unusual; their presence should prompt the clinician to consider the possibility of an underlying medical or neurological disorder that is causing the entire syndrome.

FIGURE 7.1-6 A symbolic representation of the strange perceptions of the schizophrenia patient. (Courtesy of Arthur Tress.) A 48-year-old man,

who had been diagnosed with schizophrenia while in the army at age 21 years, led an isolated and often frightened existence, living alone and supported by disability payments. Although he would confirm that he had chronic auditory hallucinations, he was never comfortable with discussing the content of these hallucinations, and a review of records showed this was a long-term pattern for the patient. Otherwise the patient had good rapport with his psychiatrist and was enthusiastic about the possibility of participating in a study of a novel antipsychotic agent. During the informed consent procedure, the patient asked about the possibility that the new medication might decrease his chronic auditory hallucinations. When it was acknowledged that any response was possible, including decreases in his

hallucinations, the patient broke off the discussion abruptly and left the office. At a later visit, he reported that his most reliable pleasure in life was nightly discussions of gossip with hallucinations of voices he believed belonged to 17th- century French courtiers, and the chance that he might lose these conversations and the companionship they offered was too frightening for him to consider. (Adapted from Stephen Lewis, M.D., P. Rodrigo Escalona, M.D., and Samuel J. Keith, M.D.)

Cenesthetic Hallucinations. Cenesthetic hallucinations are unfounded sensations of altered states in bodily organs. Examples of cenesthetic hallucinations include a burning sensation in the brain, a pushing sensation in the blood vessels, and a cutting sensation in the bone marrow. Bodily distortions may also occur.

ILLUSIONS. As differentiated from hallucinations, whereas illusions are distortions of real images or sensations, hallucinations are not based on real images or sensations. Illusions can occur in schizophrenia patients during active phases, but they can also occur during the prodromal phases and during periods of remission. Whenever illusions or hallucinations occur, clinicians should consider the possibility of a substance-related cause for the symptoms, even when patients have already received a diagnosis of schizophrenia.

Thought Disorders. Disorders of thought are the most difficult symptoms for many clinicians and students to understand, but they may be the core symptoms of schizophrenia. Dividing the disorders of thought into disorders of thought content, form of thought, and thought process is one way to clarify them.

THOUGHT CONTENT. Disorders of thought content reflect the patient's ideas, beliefs, and interpretations of stimuli. Delusions, the most obvious example of a disorder of thought content, are varied in schizophrenia and may assume persecutory, grandiose, religious, or somatic forms. Patients may believe that an outside entity controls their thoughts or behavior or, conversely, that they control outside events in an extraordinary fashion (such as causing the sun to rise and set or by preventing earthquakes). Patients may have an intense and consuming preoccupation with esoteric, abstract, symbolic, psychological, or philosophical ideas. Patients may also worry about allegedly life-threatening but bizarre and implausible somatic conditions, such as the presence of aliens inside the patient's testicles affecting his ability to father children. The phrase loss of ego boundaries describes the lack of a clear sense of where the patient's own body, mind, and influence end and where those of other animate and inanimate objects begin. For example, patients may think that other persons, the television, or the newspapers are referring to them (ideas of reference). Other symptoms of the loss of ego boundaries include the sense that the patient has physically fused with an outside object (e.g., a tree or another person) or that the patient has disintegrated and fused with the entire universe (cosmic identity). With such a state of mind, some

patients with schizophrenia doubt their gender or their sexual orientation. These symptoms should not be confused with transvestism, transsexuality, or other gender identity problems.

FORM OF THOUGHT. Disorders of the form of thought are objectively observable in patients' spoken and

written language (Fig. 7.1-7). The disorders include looseness of associations, derailment, incoherence, tangentiality, circumstantiality, neologisms, echolalia, verbigeration, word salad, and mutism. Although looseness of associations was once described as pathognomonic for schizophrenia, the symptom is frequently seen in mania. Distinguishing between looseness of associations and tangentiality can be difficult for even the most experienced clinicians. FIGURE 7.1-7 Sample of noncommunicative writing by a patient with chronic paranoid schizophrenia. This letter, written to the patient's psychiatrist, illustrates manneristic writing, verbigeration, and neologisms. The following sample is taken from a memo typed by a secretary with schizophrenia who was still able to work part time in an office. Note her preoccupation with the mind, the Trinity, and other esoteric matters. Also note that peculiar restructuring of concepts by hyphenating the words germ-any (the patient had a distinct fear of germs) and infer-

no (inferring that there will be no salvation). The "chain reaction" is a reference to atomic piles. Mental health is the Blessed Trinity, and as man cannot be without God, it is futile to deny His Son. For the Creation understand germ-any in Voice New Order, not lie of chained reaction, spawning mark in temple Cain with Babel grave'n image to wanton V day "Israel." Lucifer fell Jew prostitute and lambeth walks by roam to sex ritual, in Bible six million of the Babylon woman, infer-no Salvation. The one common factor in the thought process above is a preoccupation with invisible forces, radiation, witchcraft, religion, philosophy, and psychology and a leaning toward the esoteric, the abstract, and the symbolic. Consequently, the thinking of a person with schizophrenia is characterized simultaneously by both an overly concrete and an overly symbolic nature. THOUGHT PROCESS. Disorders in thought process concern the way ideas and languages are formulated. The examiner infers a disorder from what and how the patient speaks, writes, or draws. The examiner may also assess the patient's thought process by observing his or her behavior, especially in carrying out discrete tasks (e.g., in occupational therapy). Disorders of thought process include flight of ideas, thought blocking, impaired attention, poverty of thought content, poor abstraction abilities, perseveration, idiosyncratic associations (e.g., identical predicates, clang associations), overinclusion, and circumstantiality. Thought control, in which outside forces are controlling what the patient thinks or feels, is common, as is thought broadcasting, in which patients think others can read their minds or that their thoughts are broadcast through television sets or radios. Impulsiveness, Violence, Suicide, and Homicide. Patients with schizophrenia may be agitated and have little impulse control when ill. They may also have decreased social sensitivity and appear to be impulsive when, for example, they grab another patient's cigarettes, change television channels abruptly, or throw food on the floor. Some apparently impulsive behavior, including suicide and homicide attempts, may be in response to hallucinations commanding the patient to act. VIOLENCE. Violent behavior (excluding homicide) is common among untreated schizophrenia patients. Delusions of a persecutory nature, previous episodes of violence, and neurological deficits are risk factors for violent or impulsive behavior. Management includes appropriate antipsychotic medication. Emergency treatment consists of restraints and seclusion. Acute sedation with lorazepam (Ativan), 1 to 2 mg intramuscularly, repeated every hour as needed, may be necessary to prevent the patient from harming others. If a clinician feels fearful in the presence of a schizophrenia patient, it should be taken as an internal clue that the patient may be on the verge of acting out violently. In such cases, the interview should be terminated or be conducted with an attendant at the ready.

SUICIDE. Suicide is the single leading cause of premature death among people with schizophrenia. Suicide attempts are made by 20 to 50 percent of the patients, with longterm rates of suicide estimated to be 10 to 13 percent. According to DSM-5 approximately 5 to 6 percent of schizophrenic patients die by suicide, but this is probably an underestimation. Often, suicide in schizophrenia seems to occur “out of the blue,” without prior warnings or expressions of verbal intent. The most important factor is the presence of a major depressive episode. Epidemiological studies indicate that up to 80 percent of schizophrenia patients may have a major depressive episode at some time in their lives. Some data suggest that those patients with the best prognosis (few negative symptoms, preservation of capacity to experience affects, better abstract thinking) can paradoxically also be at highest risk for suicide. The profile of the patient at greatest risk is a young man who once had high expectations, declined from a higher level of functioning, realizes that his dreams are not likely to come true, and has lost faith in the effectiveness of treatment. Other possible contributors to the high rate of suicide include command hallucinations and drug abuse. Two-thirds or more of schizophrenic patients who commit suicide have seen an apparently unsuspecting clinician within 72 hours of death. A large pharmacological study suggests that clozapine (Clozaril) may have particular efficacy in reducing suicidal ideation in schizophrenia patients with prior hospitalizations for suicidality. Adjunctive antidepressant medications have been shown to be effective in alleviating co-occurring major depression in schizophrenia. The following is an example of an unpredictable suicide in a patient with schizophrenia who had been responding to psychiatric treatment: The patient had been an autistic child and did not speak until he was 7 years old. He had responded well to psychiatric treatment, and at age 13 his IQ was reported as 122. At age 17 he became violent toward his parents, shaved all his hair off, and made such statements as, “I like bank robbers knocking people unconscious” and “I think tough gangs are funny because they beat down people.” While saying this, he laughed loudly. He was admitted to a mental hospital, where he responded with definite improvement to pharmacotherapy and psychotherapy, and he went home regularly for weekends. He left various notes on his desk before committing suicide. Among these notes was an eight-page list giving 211 “inexcusable mistakes throughout my life.” Each one was dated, for example, “1952, 2nd of November: throwing up in my friend’s house on a shoe-box. 1953, 17th August: accidentally wearing a watch that wasn’t water-proof in the bath-tub. 1956, 23rd of September: slamming back-door of Meteor after getting in.” He then proceeded in his notes to give “the causes of the mistakes:” “Montreal having a mountain; I have a receding hair-line; my height since I was nine years old; Canada having two languages....” He also wrote: “My feelings of tension since 1962 is getting worse most of the time. I planned the date of my death without the slightest

trace of emotion....” The boy hanged himself at age 18 in the family garage. An experienced psychiatrist who had repeatedly interviewed him noted no signs of depression only a week before. (Courtesy of Heinz E. Lehmann, M.D.) **HOMICIDE.** Despite the sensational attention that the news media provides when a patient with schizophrenia murders someone, the available data indicate that these patients are no more likely to commit homicide than is a member of the general population. When a patient with schizophrenia does commit homicide, it may be for unpredictable or bizarre reasons based on hallucinations or delusions. Possible predictors of homicidal activity are a history of previous violence, dangerous behavior while hospitalized, and hallucinations or delusions involving such violence. **Sensorium and Cognition Orientation.** Patients with schizophrenia are usually oriented to person, time, and place. The lack of such orientation should prompt clinicians to investigate the possibility of a medical or neurological brain disorder. Some

patients with schizophrenia may give incorrect or bizarre answers to questions about orientation, for example, "I am Christ; this is heaven; and it is AD 35." Memory. Memory, as tested in the mental status examination, is usually intact, but there can be minor cognitive deficiencies. It may not be possible, however, to get the patient to attend closely enough to the memory tests for the ability to be assessed adequately. Cognitive Impairment. An important development in the understanding of the psychopathology of schizophrenia is an appreciation of the importance of cognitive impairment in the disorder. In outpatients, cognitive impairment is a better predictor of level of function than is the severity of psychotic symptoms. Patients with schizophrenia typically exhibit subtle cognitive dysfunction in the domains of attention, executive function, working memory, and episodic memory. Although a substantial percentage of patients have normal intelligence quotients, it is possible that every person who has schizophrenia has cognitive dysfunction compared with what he or she would be able to do without the disorder. Although these impairments cannot function as diagnostic tools, they are strongly related to the functional outcome of the illness and, for that reason, have clinical value as prognostic variables, as well as for treatment planning. The cognitive impairment seems already to be present when patients have their first episode and appears largely to remain stable over the course of early illness. (There may be a small subgroup of patients who have a true dementia in late life that is not due to other cognitive disorders, such as Alzheimer's disease.) Cognitive impairments are also present in attenuated forms in nonpsychotic relatives of schizophrenia patients. The cognitive impairments of schizophrenia have become the target of

pharmacological and psychosocial treatment trials. It is likely that effective treatments will become widely available within a few years, and these are likely to lead to an improvement in the quality of life and level of functioning of people with schizophrenia. Judgment and Insight. Classically, patients with schizophrenia are described as having poor insight into the nature and the severity of their disorder. The so-called lack of insight is associated with poor compliance with treatment. When examining schizophrenia patients, clinicians should carefully define various aspects of insight, such as awareness of symptoms, trouble getting along with people, and the reasons for these problems. Such information can be clinically useful in tailoring a treatment strategy and theoretically useful in postulating what areas of the brain contribute to the observed lack of insight (e.g., the parietal lobes). Reliability. A patient with schizophrenia is no less reliable than any other psychiatric patient. The nature of the disorder, however, requires the examiner to verify important information through additional sources. Somatic Comorbidity Neurological Findings. Localizing and nonlocalizing neurological signs (also known as hard and soft signs, respectively) have been reported to be more common in patients with schizophrenia than in other psychiatric patients. Nonlocalizing signs include dysdiadochokinesia, astereognosis, primitive reflexes, and diminished dexterity. The presence of neurological signs and symptoms correlates with increased severity of illness, affective blunting, and a poor prognosis. Other abnormal neurological signs include tics, stereotypies, grimacing, impaired fine motor skills, abnormal motor tone, and abnormal movements. One study has found that only about 25 percent of patients with schizophrenia are aware of their own abnormal involuntary movements and that the lack of awareness is correlated with a lack of insight about the primary psychiatric disorder and the duration of illness. Eye Examination. In addition to the disorder of smooth ocular pursuit (saccadic movement), patients with schizophrenia have an elevated blink rate. The elevated blink rate is believed to reflect hyperdopaminergic activity. In primates, blinking can be increased by dopamine agonists and reduced by dopamine antagonists. Speech. Although the disorders of speech in schizophrenia (e.g.,

looseness of associations) are classically considered to indicate a thought disorder, they may also indicate a forme fruste of aphasia, perhaps implicating the dominant parietal lobe. The inability of schizophrenia patients to perceive the prosody of speech or to inflect their own speech can be seen as a neurological symptom of a disorder in the nondominant parietal lobe. Other parietal lobe-like symptoms in schizophrenia include the inability to carry out tasks (i.e., apraxia), right-left disorientation, and lack of concern about the

disorder. Other Comorbidity Obesity. Patients with schizophrenia appear to be more obese, with higher body mass indexes (BMIs) than age- and gender-matched cohorts in the general population. This is due, at least in part, to the effect of many antipsychotic medications, as well as poor nutritional balance and decreased motor activity. This weight gain, in turn, contributes to an increased risk of cardiovascular morbidity and mortality, an increased risk of diabetes, and other obesity-related conditions such as hyperlipidemia and obstructive sleep apnea. Diabetes Mellitus. Schizophrenia is associated with an increased risk of type II diabetes mellitus. This is probably due, in part, to the association with obesity noted previously, but there is also evidence that some antipsychotic medications cause diabetes through a direct mechanism. Cardiovascular Disease. Many antipsychotic medications have direct effects on cardiac electrophysiology. In addition, obesity; increased rates of smoking, diabetes, hyperlipidemia; and a sedentary lifestyle all independently increase the risk of cardiovascular morbidity and mortality. HIV. Patients with schizophrenia appear to have a risk of HIV infection that is 1.5 to 2 times that of the general population. This association is thought to be due to increased risk behaviors, such as unprotected sex, multiple partners, and increased drug use. Chronic Obstructive Pulmonary Disease. Rates of chronic obstructive pulmonary disease are reportedly increased in schizophrenia compared with the general population. The increased prevalence of smoking is an obvious contributor to this problem and may be the only cause. Rheumatoid Arthritis. Patients with schizophrenia have approximately one-third the risk of rheumatoid arthritis that is found in the general population. This inverse association has been replicated several times, the significance of which is unknown. DIFFERENTIAL DIAGNOSIS Secondary Psychotic Disorders A wide range of nonpsychiatric medical conditions and a variety of substances can induce symptoms of psychosis and catatonia (Table 7.1-3). The most appropriate diagnosis for such psychosis or catatonia is psychotic disorder due to a general medical condition, catatonic disorder due to a general medical condition, or substance-induced psychotic disorder.

Table 7.1-3 Differential Diagnosis of Schizophrenia-Like Symptoms

When evaluating a patient with psychotic symptoms, clinicians should follow the general guidelines for assessing nonpsychiatric conditions. First, clinicians should aggressively pursue an undiagnosed nonpsychiatric medical condition when a patient exhibits any unusual or rare symptoms or any variation in the level of consciousness. Second, clinicians should attempt to obtain a complete family history, including a history of medical, neurological, and psychiatric disorders. Third, clinicians should consider the possibility of a nonpsychiatric medical condition, even in patients with previous diagnoses of schizophrenia. A patient with schizophrenia is just as likely to have a brain tumor that produces psychotic symptoms as is a patient without schizophrenia. Other Psychotic Disorders The psychotic symptoms of schizophrenia can be identical with those of schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, and delusional disorders. Schizophreniform disorder differs from schizophrenia in that the symptoms have a

duration of at least 1 month but less than 6 months. Brief psychotic disorder is the appropriate diagnosis when the symptoms have lasted at least 1 day but less than 1 month and when the patient has not returned to the premorbid state of functioning within that time. There may also be a precipitating traumatic event. When a manic or depressive syndrome develops concurrently with the major symptoms of schizophrenia, schizoaffective disorder is the appropriate diagnosis. Nonbizarre delusions present for at least 1 month without other symptoms of schizophrenia or a mood disorder warrant the diagnosis of delusional disorder. Mood Disorders A patient with a major depressive episode may present with delusions and hallucinations, whether the patient has unipolar or bipolar mood disorder. Delusions seen with psychotic depression are typically mood congruent and involve themes such as guilt, self-depreciation, deserved punishment, and incurable illnesses. In mood disorders, psychotic symptoms resolve completely with the resolution of depression. A depressive episode that is this severe may also result in loss of functioning, decline in self-care, and social isolation, but these are secondary to the depressive symptoms and should not be confused with the negative symptoms of schizophrenia. A full-blown manic episode often presents with delusions and sometimes hallucinations. Delusions in mania are most often mood congruent and typically involve grandiose themes. The flight of ideas seen in mania may, at times, be confused with the thought disorder of schizophrenia. Special attention during mental status examination of a patient with a flight of ideas is required to note whether the associative links between topics are conserved, although the conversation is difficult for the observer to follow because of the patient's accelerated rate of thinking.

Personality Disorders Various personality disorders may have some features of schizophrenia. Schizotypal, schizoid, and borderline personality disorders are the personality disorders with the most similar symptoms. Severe obsessive-compulsive personality disorder may mask an underlying schizophrenic process. Personality disorders, unlike schizophrenia, have mild symptoms and a history of occurring throughout a patient's life; they also lack an identifiable date of onset. Malingering and Factitious Disorders For a patient who imitates the symptoms of schizophrenia but does not actually have the disorder, either malingering or factitious disorder may be an appropriate diagnosis. Persons have faked schizophrenic symptoms and have been admitted into and treated at psychiatric hospitals. The condition of patients who are completely in control of their symptom production may qualify for a diagnosis of malingering; such patients usually have some obvious financial or legal reason to want to be considered mentally ill. The condition of patients who are less in control of their falsification of psychotic symptoms may qualify for a diagnosis of factitious disorder. Some patients with schizophrenia, however, may falsely complain of an exacerbation of psychotic symptoms to obtain increased assistance benefits or to gain admission to a hospital. COURSE AND PROGNOSIS Course A premorbid pattern of symptoms may be the first evidence of illness, although the importance of the symptoms is usually recognized only retrospectively. Characteristically, the symptoms begin in adolescence and are followed by the development of prodromal symptoms in days to a few months. Social or environmental changes, such as going away to college, using a substance, or a relative's death, may precipitate the disturbing symptoms, and the prodromal syndrome may last a year or more before the onset of overt psychotic symptoms. The classic course of schizophrenia is one of exacerbations and remissions. After the first psychotic episode, a patient gradually recovers and may then function relatively normally for a long time. Patients usually relapse, however, and the pattern of illness during the first 5 years after the diagnosis generally indicates the patient's course. Further deterioration in the patient's baseline functioning follows each relapse of the psychosis. This failure to return to baseline

functioning after each relapse is the major distinction between schizophrenia and the mood disorders. Sometimes a clinically observable postpsychotic depression follows a psychotic episode, and the schizophrenia patient's vulnerability to stress is usually lifelong. Positive symptoms tend to become less severe with time, but the socially debilitating negative or deficit symptoms may increase in severity. Although about one-third of all schizophrenia patients have some

marginal or integrated social existence, most have lives characterized by aimlessness; inactivity; frequent hospitalizations; and, in urban settings, homelessness and poverty. Prognosis Several studies have shown that over the 5- to 10-year period after the first psychiatric hospitalization for schizophrenia, only about 10 to 20 percent of patients can be described as having a good outcome. More than 50 percent of patients can be described as having a poor outcome, with repeated hospitalizations, exacerbations of symptoms, episodes of major mood disorders, and suicide attempts. Despite these glum figures, schizophrenia does not always run a deteriorating course, and several factors have been associated with a good prognosis (Table 7.1-4). Table 7.1-4 Features Weighting Toward Good to Poor Prognosis in Schizophrenia Reported remission rates range from 10 to 60 percent, and a reasonable estimate is that 20 to 30 percent of all schizophrenia patients are able to lead somewhat normal lives. About 20 to 30 percent of patients continue to experience moderate symptoms, and 40 to 60 percent of patients remain significantly impaired by their disorder for their entire lives. Patients with schizophrenia do much poorer than patients with mood disorders, although 20 to 25 percent of mood disorder patients are also severely disturbed at long-term follow-up. TREATMENT Although antipsychotic medications are the mainstay of the treatment for schizophrenia,

research has found that psychosocial interventions, including psychotherapy, can augment the clinical improvement. Just as pharmacological agents are used to treat presumed chemical imbalances, nonpharmacological strategies must treat nonbiological issues. The complexity of schizophrenia usually renders any single therapeutic approach inadequate to deal with the multifaceted disorder. Psychosocial modalities should be integrated into the drug treatment regimen and should support it. Patients with schizophrenia benefit more from the combined use of antipsychotic drugs and psychosocial treatment than from either treatment used alone. Hospitalization Hospitalization is indicated for diagnostic purposes; for stabilization of medications; for patients' safety because of suicidal or homicidal ideation; and for grossly disorganized or inappropriate behavior, including the inability to take care of basic needs such as food, clothing, and shelter. Establishing an effective association between patients and community support systems is also a primary goal of hospitalization. Short stays of 4 to 6 weeks are just as effective as long-term hospitalizations, and hospital settings with active behavioral approaches produce better results than do custodial institutions. Hospital treatment plans should be oriented toward practical issues of self-care, quality of life, employment, and social relationships. During hospitalization, patients should be coordinated with aftercare facilities, including their family homes, foster families, board-and-care homes, and halfway houses. Day care centers and home visits by therapists or nurses can help patients remain out of the hospital for long periods and can improve the quality of their daily lives. Pharmacotherapy The introduction of chlorpromazine (Thorazine) in 1952 may be the most important single contribution to the treatment of a psychiatric illness. Henri Laborit, a surgeon in Paris, noticed that administering chlorpromazine to patients before surgery resulted in an unusual state in which they seemed less anxious regarding the procedure. Chlorpromazine was subsequently shown to be effective at reducing hallucinations and delusions,

as well as excitement. It was also noted that it caused side effects that appeared similar to parkinsonism. Antipsychotics diminish psychotic symptom expression and reduce relapse rates. Approximately 70 percent of patients treated with any antipsychotic achieve remission. The drugs used to treat schizophrenia have a wide variety of pharmacological properties, but all share the capacity to antagonize postsynaptic dopamine receptors in the brain. Antipsychotics can be categorized into two main groups: the older conventional antipsychotics, which have also been called first-generation antipsychotics or dopamine receptor antagonists, and the newer drugs, which have been called second-generation antipsychotics or serotonin dopamine antagonists (SDAs). Clozapine (Clozaril), the first effective antipsychotic with negligible extrapyramidal side effects, was discovered in 1958 and first studied during the 1960s. However, in

1976, it was noted that clozapine was associated with a substantial risk of agranulocytosis. This property resulted in delays in the introduction of clozapine. In 1990, clozapine finally became available in the United States, but its use was restricted to patients who responded poorly to other agents.

PHASES OF TREATMENT IN SCHIZOPHRENIA

Treatment of Acute Psychosis Acute psychotic symptoms require immediate attention. Treatment during the acute phase focuses on alleviating the most severe psychotic symptoms. This phase usually lasts from 4 to 8 weeks. Acute schizophrenia is typically associated with severe agitation, which can result from such symptoms as frightening delusions, hallucinations, or suspiciousness, or from other causes (including stimulant abuse). Patients with akathisia can appear agitated when they experience a subjective feeling of motor restlessness. Differentiating akathisia from psychotic agitation can be difficult, particularly when patients are incapable of describing their internal experience. If patients are receiving an agent associated with extrapyramidal side effects, usually a first-generation antipsychotic, a trial with an anticholinergic anti-Parkinson medication, benzodiazepine, or propranolol (Inderal) may be helpful in making the discrimination. Clinicians have a number of options for managing agitation that results from psychosis. Antipsychotics and benzodiazepines can result in relatively rapid calming of patients. With highly agitated patients, intramuscular administration of antipsychotics produces a more rapid effect. An advantage of an antipsychotic is that a single intramuscular injection of haloperidol (Haldol), fluphenazine (Prolixin, Permitil), olanzapine (Zyprexa), or ziprasidone (Geodon) will often result in calming effect without excessive sedation. Low-potency antipsychotics are often associated with sedation and postural hypotension, particularly when they are administered intramuscularly. Intramuscular ziprasidone and olanzapine are similar to their oral counterparts in not causing substantial extrapyramidal side effects during acute treatment. This can be an important advantage over haloperidol or fluphenazine, which can cause frightening dystonias or akathisia in some patients. A rapidly dissolving oral formulation of olanzapine (Zydis) may also be helpful as an alternative to an intramuscular injection. Benzodiazepines are also effective for agitation during acute psychosis. Lorazepam (Ativan) has the advantage of reliable absorption when it is administered either orally or intramuscularly. The use of benzodiazepines may also reduce the amount of antipsychotic that is needed to control psychotic patients.

Treatment During Stabilization and Maintenance Phase

In the stable or maintenance phase, the illness is in a relative stage of remission. The goals during this phase are to prevent psychotic relapse and to assist patients in improving their level of functioning. As newer medications have been introduced with a

substantively reduced risk of tardive dyskinesia, one of the major concerns about longterm treatment has been diminished. During this phase, patients are usually in a relative state of

remission with only minimal psychotic symptoms. Stable patients who are maintained on an antipsychotic have a much lower relapse rate than patients who have their medications discontinued. Data suggest that 16 to 23 percent of patients receiving treatment will experience a relapse within 1 year, and 53 to 72 percent will relapse without medications. Even patients who have had only one episode have a four in five chance of relapsing at least once over the following 5 years. Stopping medication increases this risk fivefold. Although published guidelines do not make definitive recommendations about the duration of maintenance treatment after the first episode, recent data suggest that 1 or 2 years might not be adequate. This is a particular concern when patients have achieved good employment status or are involved in educational programs because they have a lot to lose if they experience another psychotic decompensation. It is generally recommended that multipisode patients receive maintenance treatment for at least 5 years, and many experts recommend pharmacotherapy on an indefinite basis. Noncompliance.

Noncompliance with long-term antipsychotic treatment is very high. An estimated 40 to 50 percent of patients become noncompliant within 1 or 2 years. Compliance increases when long-acting medication is used instead of oral medication. When beginning long-acting drugs, some oral supplementation is necessary while peak plasma levels are being achieved. Fluphenazine and haloperidol have been formulated as long-acting injectables. Long-acting forms of risperidone, paliperidone, aripiprazole, and olanzapine are also available. There are a number of advantages to using long-acting injectable medication. Clinicians know immediately when noncompliance occurs and have some time to initiate appropriate interventions before the medication effect dissipates; there is less day-to-day variability in blood levels, making it easier to establish a minimum effective dose; and finally, many patients prefer it to having to remember dosage schedules of daily oral preparations. **STRATEGIES FOR POOR RESPONDERS** When patients with acute schizophrenia are administered an antipsychotic medication, approximately 60 percent will improve to the extent that they will achieve a complete remission or experience only mild symptoms; the remaining 40 percent of patients will improve but still demonstrate variable levels of positive symptoms that are resistant to the medications. Rather than categorizing patients into responders and nonresponders, it is more accurate to consider the degree to which the illness is improved by medication. Some resistant patients are so severely ill that they require chronic institutionalization. Others respond to an antipsychotic with substantial suppression of their psychotic

symptoms but demonstrate persistent symptoms, such as hallucinations or delusions. Before considering a patient a poor responder to a particular drug, it is important to assure that they received an adequate trial of the medication. A 4- to 6-week trial on an adequate dose of an antipsychotic represents a reasonable trial for most patients. Patients who demonstrate even a mild amount of improvement during this period may continue to improve at a steady rate for 3 to 6 months. It may be helpful to confirm that the patient is receiving an adequate amount of the drug by monitoring the plasma concentration. This information is available for a number of antipsychotics, including haloperidol, clozapine, fluphenazine, trifluoperazine (Stelazine), and perphenazine (Trilafon). A very low plasma concentration may indicate that the patient has been noncompliant or, more commonly, only partially compliant. It may also suggest that the patient is a rapid metabolizer of the antipsychotic or that the drug is not being adequately absorbed. Under these conditions, raising the dose may be helpful. If the level is relatively high, clinicians should consider whether side effects may be interfering with therapeutic response. If the patient is responding poorly, one may increase the dose above the usual therapeutic level; however, higher doses are not usually associated with greater improvement than conventional doses. Changing to

another drug is preferable to titrating to a high dose. If a patient has responded poorly to a conventional DRA, it is unlikely that this individual will do well on another DRA. Changing to an SDA is more likely to be helpful. Clozapine is effective for patients who respond poorly to DRAs. Double-blind studies comparing clozapine with other antipsychotics indicated that clozapine had the clearest advantage over conventional drugs in patients with the most severe psychotic symptoms, as well as in those who had previously responded poorly to other antipsychotics. When clozapine was compared with chlorpromazine in a severely psychotic group of individuals who had failed in trials with at least three antipsychotics, clozapine was significantly more effective in nearly every dimension of psychopathology, including both positive symptoms and negative symptoms.

MANAGING SIDE EFFECTS Patients frequently experience side effects of an antipsychotic before they experience clinical improvement. Whereas a clinical response may be delayed for days or weeks after drugs are started, side effects may begin almost immediately. For low-potency drugs, these side effects are likely to include sedation, postural hypotension, and anticholinergic effects, whereas high-potency drugs are likely to cause extrapyramidal side effects. Extrapyramidal Side Effects Clinicians have a number of alternatives for treating extrapyramidal side effects. These include reducing the dose of the antipsychotic (which is most commonly a DRA), adding an anti-Parkinson medication, and changing the patient to an SDA that is less likely to cause extrapyramidal side effects. The most effective anti-Parkinson medications are the

anticholinergic anti-Parkinson drugs. However, these medications have their own side effects, including dry mouth; constipation; blurred vision; and, often, memory loss. Also, these medications are often only partially effective, leaving patients with substantial amounts of lingering extrapyramidal side effects. Centrally acting β -blockers, such as propranolol, are also often effective for treating akathisia. Most patients respond to dosages between 30 and 90 mg per day. If conventional antipsychotics are being prescribed, clinicians may consider prescribing prophylactic anti-Parkinson medications for patients who are likely to experience disturbing extrapyramidal side effects. These include patients who have a history of extrapyramidal side effect sensitivity and those who are being treated with relatively high doses of high-potency drugs. Prophylactic anti-Parkinson medications may also be indicated when high-potency drugs are prescribed for young men who tend to have an increased vulnerability for developing dystonias. Again, these patients should be candidates for newer drugs. Some individuals are highly sensitive to extrapyramidal side effects at the dose that is necessary to control their psychosis. For many of these patients, medication side effects may seem worse than the illness itself. These patients should be treated routinely with an SDA because these agents result in substantially fewer extrapyramidal side effects than the DRAs. However, these highly sensitive individuals may even experience extrapyramidal side effects on an SDA. Risperidone may cause extrapyramidal side effects even at low doses—for example, 0.5 mg—but the severity and risk are increased at higher doses—for example, more than 6 mg. Olanzapine and ziprasidone are also associated with dose-related parkinsonism and akathisia. Tardive Dyskinesia About 20 to 30 percent of patients on long-term treatment with a conventional DRA will exhibit symptoms of tardive dyskinesia. About 3 to 5 percent of young patients receiving a DRA develop tardive dyskinesia each year. The risk in elderly patients is much higher. Although seriously disabling dyskinesia is uncommon, it can affect walking, breathing, eating, and talking when it occurs. Individuals who are more sensitive to acute extrapyramidal side effects appear to be more vulnerable to developing tardive dyskinesia. Patients with comorbid cognitive or mood disorders may also be more vulnerable to tardive dyskinesia than those with only schizophrenia. The onset of the abnormal movements usually

occurs either while the patient is receiving an antipsychotic or within 4 weeks of discontinuing an oral antipsychotic or 8 weeks after the withdrawal of a depot antipsychotic. There is a slightly lower risk of tardive dyskinesia with new-generation drugs. However, the risk of tardive dyskinesia is not absent with the SDAs. Recommendations for preventing and managing tardive dyskinesia include (1) using the lowest effective dose of antipsychotic; (2) prescribing cautiously with children, elderly patients, and patients with mood disorders; (3) examining patients on a regular basis for evidence of tardive dyskinesia; (4) considering alternatives to the antipsychotic

being used and considering dosage reduction when tardive dyskinesia is diagnosed; and (5) considering a number of options if the tardive dyskinesia worsens, including discontinuing the antipsychotic or switching to a different drug. Clozapine has been shown to be effective in reducing severe tardive dyskinesia or tardive dystonia. Other Side Effects Sedation and postural hypotension can be important side effects for patients who are being treated with low-potency DRAs, such as perphenazine. These effects are often most severe during the initial dosing with these medications. As a result, patients treated with these medications—particularly clozapine—may require weeks to reach a therapeutic dose. Although most patients develop tolerance to sedation and postural hypotension, sedation may continue to be a problem. In these patients, daytime drowsiness may interfere with a patient's attempts to return to community life. All DRAs, as well as SDAs, elevate prolactin levels, which can result in galactorrhea and irregular menses. Long-term elevations in prolactin and the resultant suppression in gonadotropin-releasing hormone can cause suppression in gonadal hormones. These, in turn, may have effects on libido and sexual functioning. There is also concern that elevated prolactin may cause decreases in bone density and lead to osteoporosis. The concerns about hyperprolactinemia, sexual functioning, and bone density are based on experiences with prolactin elevations related to tumors and other causes. It is unclear if these risks are also associated with the lower elevations that occur with prolactinelevating drugs.

Health Monitoring in Patients Receiving Antipsychotics Because of the effects of the SDAs on insulin metabolism, psychiatrists should monitor a number of health indicators, including BMI, fasting blood glucose, and lipid profiles. Patients should be weighed and their BMIs calculated for every visit for 6 months after a medication change.

Side Effects of Clozapine Clozapine has a number of side effects that make it a difficult drug to administer. The most serious is a risk of agranulocytosis. This potentially fatal condition occurs in approximately 0.3 percent of patients treated with clozapine during the first year of exposure. Subsequently, the risk is substantially lower. As a result, patients who receive clozapine in the United States are required to be in a program of weekly blood monitoring for the first 6 months and biweekly monitoring for the next 6 months. After 1 year of treatment without hematological problems, monitoring can be performed monthly. Clozapine is also associated with a higher risk of seizures than other antipsychotics. The risk reaches nearly 5 percent at doses of more than 600 mg. Patients who develop seizures with clozapine can usually be managed by reducing the dose and adding an

anticonvulsant, usually valproate (Depakene). Myocarditis has been reported to occur in approximately five patients per 100,000 patient-years. Other side effects with clozapine include hypersalivation, sedation, tachycardia, weight gain, diabetes, fever, and postural hypotension.

OTHER BIOLOGICAL THERAPIES Electroconvulsive therapy (ECT) has been studied in both acute and chronic schizophrenia. Studies in recent-onset patients indicate that ECT is about as effective as antipsychotic medications and more effective than psychotherapy. Other studies suggest that supplementing antipsychotic medications with ECT is more effective than antipsychotic

medications alone. Antipsychotic medications should be administered during and after ECT treatment. Although psychosurgery is no longer considered an appropriate treatment, it is practiced on a limited experimental basis for severe, intractable cases.

PSYCHOSOCIAL THERAPIES

Psychosocial therapies include a variety of methods to increase social abilities, selfsufficiency, practical skills, and interpersonal communication in schizophrenia patients. The goal is to enable persons who are severely ill to develop social and vocational skills for independent living. Such treatment is carried out at many sites, including hospitals, outpatient clinics, mental health centers, day hospitals, and home or social clubs.

Social Skills Training

Social skills training is sometimes referred to as behavioral skills therapy. Along with pharmacological therapy, this therapy can be directly supportive and useful to the patient. In addition to the psychotic symptoms seen in patients with schizophrenia, other noticeable symptoms involve the way the person relates to others, including poor eye contact, unusual delays in response, odd facial expressions, lack of spontaneity in social situations, and inaccurate perception or lack of perception of emotions in other people. Behavioral skills training addresses these behaviors through the use of videotapes of others and of the patient, role playing in therapy, and homework assignments for the specific skills being practiced. Social skills training has been shown to reduce relapse rates as measured by the need for hospitalization.

Family-Oriented Therapies

Because patients with schizophrenia are often discharged in an only partially remitted state, a family to which a patient returns can often benefit from a brief but intensive (as often as daily) course of family therapy. The therapy should focus on the immediate situation and should include identifying and avoiding potentially troublesome situations. When problems do emerge with the patient in the family, the aim of the therapy should be to resolve the problem quickly.

In wanting to help, family members often encourage a relative with schizophrenia to resume regular activities too quickly, both from ignorance about the disorder and from denial of its severity. Without being overly discouraging, therapists must help both the family and the patient understand and learn about schizophrenia and must encourage discussion of the psychotic episode and the events leading up to it. Ignoring the psychotic episode, a common occurrence, often increases the shame associated with the event and does not exploit the freshness of the episode to understand it better. Psychotic symptoms often frighten family members, and talking openly with the psychiatrist and with the relative with schizophrenia often eases all parties. Therapists can direct later family therapy toward long-range application of stress-reducing and coping strategies and toward the patient's gradual reintegration into everyday life. Therapists must control the emotional intensity of family sessions with patients with schizophrenia. The excessive expression of emotion during a session can damage a patient's recovery process and undermine potentially successful future family therapy. Several studies have shown that family therapy is especially effective in reducing relapses.

National Alliance on Mental Illness (NAMI)

The NAMI and similar organizations offer support groups for family members and friends of patients who are mentally ill and for patients themselves. These organizations offer emotional and practical advice about obtaining care in the sometimes complex health care delivery system and are useful sources to which to refer family members. NAMI has also waged a campaign to destigmatize mental illness and to increase government awareness of the needs and rights of persons who are mentally ill and their families.

Case Management

Because a variety of professionals with specialized skills, such as psychiatrists, social workers, and occupational therapists, among others, are involved in a treatment program, it is helpful to have one person aware of all the forces acting on the patient. The case manager ensures that their efforts are coordinated and that the patient keeps

appointments and complies with treatment plans; the case manager may make home visits and even accompany the patient to work. The success of the program depends on the educational background, training, and competence of the individual case manager, which vary. Case managers often have too many cases to manage effectively. The ultimate benefits of the program have yet to be demonstrated. Assertive Community Treatment The Assertive Community Treatment (ACT) program was originally developed by researchers in Madison, Wisconsin, in the 1970s, for the delivery of services for persons with chronic mental illness. Patients are assigned to one multidisciplinary team (e.g., case manager, psychiatrist, nurse, general physicians). The team has a fixed caseload of patients and delivers all services when and where needed by the patient, 24 hours a

day, 7 days a week. This is mobile and intensive intervention that provides treatment, rehabilitation, and support activities. These include home delivery of medications, monitoring of mental and physical health, in vivo social skills, and frequent contact with family members. There is a high staff-to-patient ratio (1:12). ACT programs can effectively decrease the risk of rehospitalization for persons with schizophrenia, but they are labor-intensive and expensive programs to administer. Group Therapy Group therapy for persons with schizophrenia generally focuses on real-life plans, problems, and relationships. Groups may be behaviorally oriented, psychodynamically or insight oriented, or supportive. Some investigators doubt that dynamic interpretation and insight therapy are valuable for typical patients with schizophrenia. But group therapy is effective in reducing social isolation, increasing the sense of cohesiveness, and improving reality testing for patients with schizophrenia. Groups led in a supportive manner appear to be most helpful for schizophrenia patients. Cognitive Behavioral Therapy Cognitive behavioral therapy has been used in schizophrenia patients to improve cognitive distortions, reduce distractibility, and correct errors in judgment. There are reports of ameliorating delusions and hallucinations in some patients using this method. Patients who might benefit generally have some insight into their illness. Individual Psychotherapy Studies of the effects of individual psychotherapy in the treatment of schizophrenia have provided data that the therapy is helpful and that the effects are additive to those of pharmacological treatment. In psychotherapy with a schizophrenia patient, developing a therapeutic relationship that the patient experiences as safe is critical. The therapist's reliability, the emotional distance between the therapist and the patient, and the genuineness of the therapist as interpreted by the patient all affect the therapeutic experience. Psychotherapy for a schizophrenia patient should be thought of in terms of decades, rather than sessions, months, or even years. Some clinicians and researchers have emphasized that the ability of a patient with schizophrenia to form a therapeutic alliance with a therapist is predictive of the outcome. Schizophrenia patients who are able to form a good therapeutic alliance are likely to remain in psychotherapy, to remain compliant with their medications, and to have good outcomes at 2-year follow-up evaluations. The relationship between clinicians and patients differs from that encountered in the treatment of nonpsychotic patients. Establishing a relationship is often difficult. Persons with schizophrenia are desperately lonely, yet defend against closeness and trust; they are likely to become suspicious, anxious, or hostile or to regress when someone attempts to draw close (Fig. 7.1-8). Therapists should scrupulously respect a patient's distance

and privacy and should demonstrate simple directness, patience, sincerity, and sensitivity to social conventions in preference to premature informality and the condescending use of first names. The patient is likely to perceive exaggerated warmth or professions of friendship as attempts at

bribery, manipulation, or exploitation. FIGURE 7.1-8 Patients with schizophrenia live in a state of chronic anxiety and fear. The environment is seen as hostile and threatening as symbolized in this illustration. (Courtesy of Arthur Tress.) In the context of a professional relationship, however, flexibility is essential in establishing a working alliance with the patient. A therapist may have meals with the patient, sit on the floor, go for a walk, eat at a restaurant, accept and give gifts, play table tennis, remember the patient's birthday, or just sit silently with the patient. The major aim is to convey the idea that the therapist is trustworthy, wants to understand the patient and tries to do so, and has faith in the patient's potential as a human, no matter how disturbed, hostile, or bizarre the patient may be at the moment. Personal Therapy A flexible type of psychotherapy called personal therapy is a recently developed form of individual treatment for schizophrenia patients. Its objective is to enhance personal and social adjustment and to forestall relapse. It is a select method using social skills and

relaxation exercises, psychoeducation, self-reflection, self-awareness, and exploration of individual vulnerability to stress. The therapist provides a setting that stresses acceptance and empathy. Patients receiving personal therapy show improvement in social adjustment (a composite measure that includes work performance, leisure, and interpersonal relationships) and have a lower relapse rate after 3 years than patients not receiving personal therapy. Dialectical Behavior Therapy This form of therapy, which combines cognitive and behavioral theories in both individual and group settings, has proved useful in borderline states and may have benefit in schizophrenia. Emphasis is placed on improving interpersonal skills in the presence of an active and empathic therapist. Vocational Therapy A variety of methods and settings are used to help patients regain old skills or develop new ones. These include sheltered workshops, job clubs, and part-time or transitional employment programs. Enabling patients to become gainfully employed is both a means toward, and a sign of, recovery. Many schizophrenia patients are capable of performing high-quality work despite their illness. Others may exhibit exceptional skill or even brilliance in a limited field as a result of some idiosyncratic aspect of their disorder. Art Therapy Many schizophrenia patients benefit from art therapy, which provides them with an outlet for their constant bombardment of imagery. It helps them communicate with others and share their inner, often frightening world with others. Cognitive Training Cognitive training or cognitive remediation is a technique introduced recently for the treatment of schizophrenia. Utilizing computer generated exercises, neural networks are influenced in such a way that cognition, including working memory, is improved which translates into more effective social functioning. The field is in its infancy and further work and replication of studies is needed; however, it is a technique that is easily learned and administered and holds great promise. REFERENCES Beck AT, Rector NA, Stolar N, Grant P. Schizophrenia: Cognitive Theory, Research, and Therapy. New York: Guilford Press; 2009. Deserno L, Sterzer P, Wüstenberg T, Heinz A, Schlagenhauf F. Reduced prefrontal-parietal effective connectivity and working memory deficits in schizophrenia. *J Neurosci*. 2012;32:12. Diederer KMJ, Neggers SFW, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IEC. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry*. 2010;167:427.

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