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## CHAPTER 1

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# HISTORY OF SCHIZOPHRENIA AS A PSYCHIATRIC DISORDER

HELEN LAVRETSKY

### HISTORY OF CLINICAL DIAGNOSIS OF SCHIZOPHRENIA

Schizophrenia is one of the most serious psychiatric disorders. It carries a lifetime risk of approximately 1%. The symptoms of schizophrenia remain perhaps the most mysterious form of human psychological experience. The early onset of the disease, most often occurring between ages 15 and 30 years, and its chronic course make this a particularly disabling disorder for patients and their families. Chronic disability results primarily from the negative and cognitive symptoms, whereas acute relapses result from exacerbations of the positive psychotic symptoms, such as delusions and hallucinations. The social and economic impact of the disorder on society and families is enormous.

Despite extensive research, the international psychiatric community still lacks diagnostic precision, clarity of etiology, and knowledge of underlying pathophysiology of schizophrenia. Disputes over concepts and appropriate models of mental illness extend back to classical times. Reports of schizophrenia-like illness can be found even in ancient literature. However, the first comprehensive description dates to the beginning of the 18th century. Schizophrenia was defined as an early dementia in the 19th century. French psychiatrist, Benedict Augustine Morel (1809–1873), coined the term *dementia praecox*, or “precocious dementia.”

The modern concept of schizophrenia was first formalized by the German psychiatrist Émil Kraepelin (1856–1927), who integrated contemporary descriptions of catatonia by Kahlbaum (1863), and hebephrenia by Hecker (1871), and his own “dementia paranoia” into a single disorder with an early onset, poor prognosis, and 36 “psychic” symptoms and 19 “bodily” or physical symptoms. Among the most common psychic symptoms were hallucinations occurring in all sensory modalities, but most commonly “hallucinations of hearing.” Although Kraepelin defined dementia praecox on the basis of the characteristic course and outcome of a cluster of symptoms and signs, he also

stated that it was a disorder with a specific neuroanatomical pathology and etiology. This statement generated an early and continuing interest in the anatomy of the central nervous system underlying schizophrenic process. The sixth edition of Kraepelin's *Textbook of Psychiatry* (1899/1990) distinguished between dementia praecox and manic–depressive disorder. He described one group of patients whose clinical picture was dominated by disordered mood and who followed a cyclical pattern of relapse and relative remission; for this condition, Kraepelin coined the term *manic depressive insanity*. Another group of patients had a deteriorating illness characterized by an acute onset of psychosis in adolescence, with a prolonged course marked by profound social and functional disability; this he called dementia praecox.

Kraepelinian concepts profoundly influenced European and American psychiatry. These diagnostic categories continue to guide our clinical practice and research in the 21st century, despite the fact that Kraepelin himself recognized their limitations, such as the existence of late-onset disorders and the possibility of reasonable functional remission in some individuals.

Kraepelin's (1899/1990) diagnostic concept of dementia praecox was expanded with the inclusion of Magnan and Legrain's (1895) notion of *délire chronique*. By the time of the seventh edition of Kraepelin's (1904) textbook, his concept embraced all disorders with a course leading to psychic invalidism of varying severity. Subsequently, however, he separated paranoid deteriorations (paraphrenias) with prevalent delusions, but without emotional and volitional psychopathology, from the paranoid form of dementia praecox. Then, he identified 10 different forms of dementia praecox: dementia simplex, silly deterioration (replacing the term *hebephrenia*), depressive deterioration, depressive deterioration with delusional manifestations, circular, agitated, periodic, catatonic, paranoid, and schizophasia. Finally, in the eighth edition of his textbook, Kraepelin (1913) described 10 different end states of the disease: cure; cure with defect; simple deterioration; imbecility with confusion of speech; hallucinatory deterioration; hallucinatory insanity; paranoid deterioration; flighty, silly deterioration; and dull, apathetic dementia. In the same edition, he defined *dementia praecox* as a series of clinical states that have as their common characteristic a peculiar destruction of the internal connections of the psychic personality, with the most marked damage to the emotional and volitional life. In 1959, Kurt Schneider further defined a list of relatively easily and reliably identified first-rank symptoms that were considered to be most consistent with the diagnosis of schizophrenia: audible thoughts; arguing or commenting voices; feeling controlled or influenced by an external force; thought withdrawal; diffusion of thought; and delusions.

The Swiss psychiatrist Eugen Bleuler coined the term *schizophrenia* in 1911, and that term rapidly replaced dementia praecox. Although Bleuler subtitled his book on dementia praecox *The Group of Schizophrenias*, his major argument was that the concept of schizophrenia was unified by a single defining phenotype that was present in all patients with the illness. Bleuler thought of schizophrenia in psychological rather than in neuropathological terms. He chose the name *schizophrenia* because it meant literally “a mind that is torn asunder.” He developed a hierarchy that distinguished between fundamental and accessory symptoms. *Fundamental symptoms* were shared by all schizophrenia subtypes as a common endophenotype, and included “fragmented” disturbed associations, or what we now term *cognitive disturbances*. Psychic schisis or split, ambivalence, cognitive features of “loose associations,” avolition, inattention, autism, and incongruent features signified primary deficits for Bleuler, whereas florid psychotic symptoms of delusions and hallucinations were conceptualized as secondary or *accessory* to the core cognitive disturbances. Bleuler's advanced cognitive theory of schizophrenia was ahead of its time, and difficult to prove and define reliably due to a lack of measurement tools, partic-

ularly for the “softer” concepts of “simple” or “latent” types of schizophrenia that addressed personality characteristics of “odd individuals.” It required another 100 years of neurocognitive research to narrow down the fundamental schizophrenic deficit of cognitive dysmetria, which Bleuler hypothesized as a disruption of the fluid, coordinated sequences of thought and action that are the hallmark of normal cognition (Andreasen, 1999).

The conceptual confusion at the beginning of the 20th century was compounded by clinical heterogeneity of schizophrenia, lack of clear prognostic features, and failure to discover any definitive pathological abnormalities. Bleuler’s approach led to an expansion of the diagnostic concept of schizophrenia that incorporated many other neuropsychiatric disorders, particularly, in the United States during the early development of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I and II) through the 1970s, and in the former Soviet Union.

Another prominent influence on the concept of schizophrenia in the United States was provided by the theories of Adolph Meyer, who emphasized the impact of the individual history of each particular patient on the schizophrenia syndrome (Peteres, 1991). Other important broad diagnostic concepts included schizoaffective psychosis (Kasanin, 1933), ambulatory schizophrenia (Zilboorg, 1956), and “pseudoneurotic schizophrenia” (Hoch & Polatin, 1949). DSM-II (American Psychiatric Association, 1968) presented schizophrenia in its broadest interpretation. In 1966, the World Health Organization sponsored the International Pilot Study of Schizophrenia (IPSS; 1973), which investigated the illness in several centers around the world and found a high degree of consistency in the clinical features of schizophrenia when using strict diagnostic criteria. This finding led to the critical revision of diagnostic categories during the 1970s in the United States, with narrowing of its definitions and development of the core symptoms criteria. DSM-III became a turning point for U.S. psychiatry, reintroducing a neo-Kraepelinian approach toward the diagnosis of mental disorders that brought U.S. and European concepts closer. Further revisions of both DSM (III-R and IV) and the *International Classification of Diseases* (ICD-10) brought these systems even closer. Both systems identify a number of subtypes of schizophrenia, and both use only cross-sectional disease status for diagnostic purposes. These diagnostic systems differ only in the affective categorization of psychosis, with mood-incongruent features subsumed under affective psychosis in DSM-IV, and under schizophrenias in the ICD-10.

In addition to the improved clinical diagnostic boundaries, major advances have been made in the psychopharmacological and psychosocial treatments of schizophrenia, providing new hope for improved outcomes of this disabling disease.

## HISTORY OF TREATMENT OF SCHIZOPHRENIA

For decades following Kraepelin’s seminal description of schizophrenia there was no effective medical treatment. Unfortunate patients were treated with some “desperate” methods, such as prolonged barbiturate-induced sleep therapy, insulin coma, or psychosurgery (Valenstein, 1986). Insulin coma involved creating a hypoglycemic state through administration of large doses of insulin that resulted in loss of consciousness and seizures. A few reports suggested that a series of such insulin shocks might reduce patients’ psychotic episodes. However, the technique was never carefully evaluated, and posed risks of heart attack and stroke.

Frontal lobotomies, or leukotomies, involved neurosurgery that cut the nerve tracts of the frontal lobes, thereby reducing agitation and impulsive behavior, but causing addi-

tional cognitive impairment. Large numbers of patients underwent the operation, with little demonstrable benefit and little concern for ethical requirements such as informed consent for treatment.

Limited therapeutic options and prospects during the first half of the 20th century meant that thousands of patients with schizophrenia were warehoused in huge psychiatric hospitals. By the mid-1950s, the United States and Canada alone had over 500,000 psychotic inpatients who were hospitalized indefinitely. Despite the efforts of the pioneers of psychiatry to address treatment of schizophrenia, patients' quality of life did not improve. Modern psychopharmacology was started serendipitously. A French naval surgeon, Henry Laborit, was testing a new drug, promethazine, to determine its effect on autonomic nervous system. He was looking for a treatment for circulatory shock after surgeries. However, the secondary properties of the drug included drowsiness, reduced pain, and feelings of euphoria. Laborit published observations of the psychotropic effects of promethazine that stimulated interest of researchers at the laboratories of the firm Rhone-Poulenc. They, in turn, modified the promethazine formula, resulting in the creation of the first effective antipsychotic drug, chlorpromazine. The initial observations of promethazine and chlorpromazine in psychiatric patients reflected the drugs' short-term antipsychotic and sedating effects. Later, a number of clinical trials, especially those by Delay, Deniker, and Harl (1952), and Sigwald and Bouttier (1953) in Europe, Lehmann and Hanrahan (1954) in Canada, and finally, the large, collaborative National Institute of Mental Health (NIMH; Cole, Goldberg, & Klerman, 1964) study in the United States, demonstrated the efficacy of new medications. Chlorpromazine reduced agitation and mood disturbance, as well as positive psychotic symptoms of delusions, hallucinations, and thought disorder, and even some negative symptoms. Patients who received this medication spent less time in the hospital, had fewer relapses, and showed enhanced life functioning compared to untreated patients.

Although psychopharmacological interventions revolutionized care for patients with chronic schizophrenia and changed the cost of care for society, they did not provide a cure. A minority of patients responded poorly to antipsychotic drugs, and even responsive patients had to deal with unpleasant and occasionally disabling side effects. Many patients relapsed, if the drug was discontinued. In addition, even in improved patients, a lack of occupational and daily living skills or social support undermined successful functioning after discharge from the hospital. Such services were not available to a vast majority of chronically mentally ill patients. Deinstitutionalization of patients with severe mental illness, beginning in the mid-1950s, without adequate follow-up care resulted in a social drift to poverty and stigma despite improvement in treatment outcomes.

The main form of psychotherapy used for schizophrenia in the United States and the United Kingdom until the early 1960s was psychoanalysis or dynamically oriented psychotherapy. The NIMH-sponsored 1964 study showed that such psychotherapy (as well as electroconvulsive therapy) was significantly less effective than antipsychotic drugs. At the same time, it became clear that the medications were only useful for reducing severity of symptoms and for preventing relapse. Supportive psychotherapy was therefore considered an essential adjunct to pharmacotherapy. Subsequently, other forms of psychosocial interventions, such as cognitive-behavioral therapy (CBT), social skills training, supported employment, and family intervention programs, were developed and tested for usefulness in people with schizophrenia. It is now well accepted that medications alone are inadequate for management of schizophrenia, and that a combined psychopharmacological-psychosocial approach is a must for improving long-term outcome in persons with schizophrenia.

## PSYCHOPHARMACOLOGY AND NEUROSCIENCE OF SCHIZOPHRENIA

The revolution in psychopharmacology and biological psychiatry started by the introduction of chlorpromazine provided the first effective treatment for schizophrenia, as well as ideas and evidence about the pathophysiology of the illness. There is evidence for a variety of neurochemical abnormalities, ranging from excessive to deficient concentrations of dopamine, serotonin, and glutamate, in studies comparing patients with schizophrenia and controls.

### Dopamine

The early 1960s implicated monoamines in the effects of the antipsychotic drugs and in the pathophysiology of schizophrenia and related drug side effects. Dopamine was one of the approximately 10 neurotransmitters distributed diffusely throughout the brain considered for pathophysiology of schizophrenia. The strongest support for a connection between dopamine function and schizophrenia came from studies showing that the clinical efficacy of drugs depends on their ability to block dopamine receptors, especially the dopamine D<sub>2</sub> receptor subtype. These studies, carried out in the 1970s, used postmortem brain tissue samples. The studies of dopamine metabolites in the cerebrospinal fluid and dopamine receptor binding that used *in vivo* functional neuroimaging provided additional evidence for dopamine abnormalities in schizophrenia.

### Serotonin

In 1943, Swiss chemist Albert Hoffman ingested a new chemical compound—an ergot derivative called lysergic acid diethylamide (LSD). He experienced psychotic delusions and vivid hallucinations. That experience led him to the studies of drugs that produce psychotic symptoms. LSD seemed to enhance and potentiate the effects of serotonin in the brain. This finding initiated interest in the role of serotonin in schizophrenia, which was rekindled in the late 1980s and early 1990s with the development of atypical antipsychotic drugs, starting with clozapine and risperidone. These compounds appeared to work by blocking both dopamine D<sub>2</sub> and serotonin S<sub>2</sub> receptors. This dual activity distinguished these newer, atypical antipsychotics from the older, typical antipsychotics that only blocked dopamine receptors. The serotonin-blocking action seemed to be an important part of the demonstrated efficacy for positive and, to some extent, negative symptoms of schizophrenia, as well as a reduction in the risk of tardive dyskinesia with atypical compared with typical antipsychotics. Other, newer atypical antipsychotic agents developed since then, such as olanzapine, quetiapine, ziprasidone, and aripiprazole, share this dual neurotransmitter action. However, direct evidence for a primary role of serotonin in the pathophysiology of schizophrenia remains less convincing compared to that for dopamine.

### Glutamate

The search for other altered neurotransmitter systems involved in the pathophysiology of schizophrenia continues. Glutamate is a principal excitatory neurotransmitter distributed in the brain structures implicated in schizophrenia, such as the frontal cortex, hippocampus, and entorhinal cortex. Dopamine antagonizes the glutamate system, reducing glutamate release. The most suggestive evidence for the role of glutamate comes from the

effects of a drug of abuse, phencyclidine (PCP), which serves as one of the putative neurochemical models for schizophrenia (Kornhuber, 1990). PCP binds to a specific site on the N-methyl-D-aspartate (NMDA) receptor and blocks the action of glutamate, which is considered to be responsible for its analgesic, anesthetic, and physiological effects. Supportive evidence comes from postmortem neuropathological studies reporting reduction in the glutamate transmitter binding in brains of people with schizophrenia. Deficient glutamate neurotransmission may be a primary or secondary, underlying mechanism in schizophrenia.

Other candidate neurotransmitters include aspartate, glycine, and gamma-aminobutyric acid (GABA), collectively dominating excitatory and inhibitory neurotransmission. Eventually, we might discover that dysregulation of several neurotransmitter systems is the unifying underlying mechanism of the disease. Brain imaging studies of receptor densities in young adults and children, or in patients with first-episode schizophrenia may be helpful in identifying early vulnerability factors.

## HISTORY OF THE NEUROSCIENCE OF SCHIZOPHRENIA

Over the last two decades, with the rapid development of the neurosciences, new hope and confidence have arisen that schizophrenia will soon be cured or, at least, that its outcome will be dramatically improved. It is our hope that knowledge of the structure and function of the brain yields breakthroughs in science and treatment.

In 1989, the U.S. Congress declared the coming “Decade of the Brain,” in expectation of a major victory in conquering serious mental illness by the new millennium. The resulting “explosion” of neuroscience and drug development research did lead to improved schizophrenia treatment portfolios, but unfortunately failed to lead to dramatic changes in the disease course and long-term outcomes. The failure to achieve this goal reflects the complexity of schizophrenia and the limitations of our conceptual understanding of its pathophysiology and diagnostic classification, as well as the limitations of new technologies and research methodology.

For these reasons, in the recent years, schizophrenia research has expanded the search for markers to include behavior, neuroanatomy, neuropathology, and most recently, genetics to define vulnerability to the disease. A genuine marker must be prevalent and occur at high frequency in patients with the disease, and at very low frequencies in people with other disorders or in healthy controls. Next, we review the major historical milestones in schizophrenia research that have led toward identification of biological markers.

### Neuroanatomy and Structural Neuroimaging

Since the time of Émil Kraepelin and Alois Alzheimer (who first described what is now considered the most common form of dementia), many investigators have examined neuropathological and neuroanatomical brain changes in schizophrenia. The initial work in this area concerned coarse brain structure, and reported lower brain weight, frontal atrophy, lacunae, pyknotic neuronal atrophy, focal demyelination, and metachromatic bodies. However, the relative lack of gliosis in patients’ brains has generated considerable interest, supporting the idea of the neurodevelopmental origin of schizophrenia. Abnormalities in neuronal distribution, cell size, and laminar density in schizophrenic brain tissue have been reported. At the same time, a frequent absence of consistency in findings and small effect sizes have diminished enthusiasm about histopathological findings.



The next technological development, pneumoencephalography, an early precursor of the modern structural neuroimaging techniques, by the American neurosurgeon Dandy in 1919 was applied to the studies of neuroanatomical brain changes in schizophrenia. The main findings were cortical atrophy and ventricular enlargement in patients compared to controls. Pneumoencephalography is a complex, invasive procedure with enormous variations in technical details and potentially serious adverse effects due to the draining of the different amounts of cerebrospinal fluid, and volume-for-volume exchange with air. This technique was replaced with noninvasive computerized axial tomography (CAT) developed in the early 1970s.

CAT findings have supported those of pneumoencephalography, reporting increased cortical atrophy and lateral ventricular enlargement, as well as increased ventricle-to-brain ratio. The effects of medications and other somatic treatments were not examined. Although CAT was a great improvement in neuroimaging tools, with its gradual enhancement of resolution, it did not allow for distinction between gray and white matter, thus precluding precision in localizing pathology and standardization of procedures during rescanning.

In 1984, the first magnetic resonance imaging (MRI) scan study in schizophrenia was published. The images were much clearer than those with CAT, and allowed differentiation of the white and gray matter. MRI studies of schizophrenia consistently reported ventricular enlargement, decreased cortical volume, and disproportionate volume loss in the temporal lobe.

Neuroimaging studies of schizophrenia are limited by their use of convenience clinical samples that are generally small and a lack of specificity of findings (compared to those of other serious mental illnesses). Despite these limitations, the MRI techniques brought an understanding of the neuroanatomical substrates of schizophrenia in sight. Newer MRI techniques, such as magnetic resonance proton spectroscopy, or magnetization transfer and diffusion tensor imaging (DTI) continue to improve the range of investigation from white matter tract connectivity to biochemical changes in the brain, approaching the goals of *in vivo* functional imaging. Enhanced by the new computational brain atlases and statistical algorithms, the morphometric methods offer an advantage of mapping structural abnormalities and correlating them with any other functional, metabolic, spectroscopic, and architectonic data. Furthermore, cortical mapping can also identify deficit patterns associated with genetic risk for schizophrenia, which may provide researchers with the neuroimaging-defined rather than pure clinical endophenotypes.

## Functional Neuroimaging

### *Functional MRI*

The first report by Belliveau and colleagues (1991) of localized changes in cerebral blood oxygenation in the occipital cortex following visual stimulation in humans was of seminal importance to neuropsychiatric research. This technological development enabled noninvasive visualization of *in vivo* human brain function (based on investigation of changes in oxyhemoglobin) in response to specific cognitive tasks in patients with schizophrenia compared to age-matched controls. The techniques have the advantage of optimal spatial resolution, and (in comparison to the functional imaging techniques described below) lower cost.

Functional MRI (fMRI) research in schizophrenia has explored a broad range of cognitive functioning, especially executive function, attention, working memory, psychomotor function, and basic sensory processing. fMRI studies further define the hypothe-

sized hypofrontality in the activation studies of schizophrenia, evaluating the subject performance on the executive cognitive tasks. The fMRI approach is well suited for use in the within-subject longitudinal design evaluating changes over time and the effects of treatment and for developing more disease-specific cognitive probes.

### *Single Photon Emission Computed Tomography and Positron Emission Tomography*

The reconstruction of three-dimensional images deriving from radiotracer distribution in the human brain was achieved by Kuhl and Edwards (1964). This achievement gave birth to both single photon emission computed tomography (SPECT) and positron emission tomography (PET).

Functional neuroimaging studies with PET and SPECT have demonstrated three patterns of abnormal cerebral blood flow in schizophrenia. First, abnormal blood flow and glucose utilization in the dorsolateral prefrontal cortex (DLPFC) have been associated with impaired executive functions and working memory. Second, dysfunction of temporal–limbic circuits has been associated with disinhibition of subcortical dopamine release and the manifestation of positive symptoms. Third, positive symptoms, such as auditory hallucinations, have been associated with increased blood flow in subcortical, medial temporal, and limbic brain areas. These findings support the 19th-century theory of Hughling Jackson, the renowned English neurologist. According to this hypothesis, the evolution of the brain increases vulnerability of the frontal or temporal–limbic cortex to the disease. The resulting loss of neuronal function is thought to cause negative symptoms. As a result, evolutionarily older brain areas may become disinhibited, leading to a manifestation of positive symptoms, such as hallucinations and delusions.

PET and SPECT are powerful techniques that enable exploration of the neurochemistry of the living brain. They have been instrumental in testing the hyperdopaminergic theory of schizophrenia, as well as the dopaminergic occupancy theory of antipsychotic drugs. PET and SPECT have also proven to be invaluable tools for measuring drug occupancy at D<sub>2</sub> and other receptors *in vivo*, and exploring relationships between occupancy and clinical measures. This observation presents a clear opportunity for drug development and for further understanding of the psychopharmacological effects of antipsychotic medications and the pathophysiology of schizophrenia.

The development of new and exciting technologies of neuroimaging advances our understanding of the pathophysiological substrates of schizophrenia, generally supporting earlier clinical–neuropathological observations. However, a pattern of brain dysfunction that would serve as a biological trait marker or predict treatment response has not emerged to date. A combination of genetics, cognitive neuropsychology, and multimodal structural–functional neuroimaging can further elucidate vulnerability factors and help define endophenotypes. Despite great advances in technology, neuroimaging remains a research tool for schizophrenia, with no utility for clinical practice at the present time.

### **Cognitive Neuroscience**

While psychoanalysts theorized about psychological causes of schizophrenia, suggesting psychotherapy to resolve infantile traumas and early rejection experiences believed to cause the disease, the search continued for behavioral vulnerability markers. Stemming from the ideas of Bleuler and Kraepelin, it is increasingly believed that impaired cognitive processing may be a marker of vulnerability to schizophrenia, including deficits in attention and concentration, in sustained mental effort, and in selecting and processing information. Physiological indicators can be used as objective markers of cognitive disturbances.



Since the turn of the 20th century, theories of frontal dysfunction have provided a framework that may be helpful in understanding the consequences of injury to the brain. Neuropsychological tests serve as probes of brain dysfunction. The extent to which schizophrenia is a disorder of executive dysfunction remains an object of extensive investigation. Structural and functional imaging, combined with neuropsychological testing, can improve the precision of the search for markers.

## Genetics

The first theory about the role of heredity in mental illness was proposed by Morel (1857). He postulated that insanity was the result of an innate biological defect, and that the severity of mental syndromes increased in lineal descents. Morel's theory of hereditary brain degeneration remained in mainstream psychiatry for several decades. Its proponents included Krafft-Ebing (1868) in Austria, Maudsley (1870) in England, Magnan and Legrain (1895) in France, and many others. In the eighth edition of his textbook, Kraepelin (1919/1971) noted that about 70% of his patients with dementia praecox at the Heidelberg Clinic (1891–1899) had family histories of psychosis. His findings set the stage for research in the genetics of the disease. Findings in family studies are consistent with a genetic etiology of schizophrenia. The risk of developing schizophrenia was found to be consistently higher in the relatives of patients with schizophrenia than in the general population, with greater risk for first-degree relatives than for second-degree relatives. In Zerbin-Rudin's (1967) pooled data, the risk for children with one parent with schizophrenia was nearly 15 times greater (12.3%) than that in the general population (0.85%); with siblings and parents, about 10 times greater (8.5% and 8.2%, respectively); and with uncles and aunts (2%), nephews and nieces (2.2%), grandchildren (2.8%), and half-siblings (3.2%), roughly three times greater than the general population rate.

Recent research has identified genetic variations associated with schizophrenia. The primary goal of modern genetic research is first to characterize how genes associated with schizophrenia affect brain development and function, and second, to see how this translates into the clinical manifestation of the disorder. This will ultimately have implications for the prevention and treatment of the disease. The goal has become more immediate as we witness a shift in psychiatric genetics from mapping illness loci to identifying gene effects on information processing in the brain.

Genomic approaches to schizophrenia are also becoming increasingly feasible as data from the Human Genome Project accumulate. However, studies aiming to identify susceptibility genes for schizophrenia and other complex psychiatric disorders are faced with confounds of subjective clinical criteria, commonly occurring phenocopies, significant between-subject variability of candidate traits, and a likelihood of allelic and locus heterogeneity.

Over the past couple of years, several specific genes have been shown to be associated with schizophrenia risk in a number of populations around the world. Some of the genes that have been studied more extensively include catechol-O-methyltransferase (*COMT*; chromosome 22q), *dysbindin-1* (chromosome 6p), *neuregulin 1* (chromosome 8p), metabotropic glutamate receptor 3 (*GRM-3*; chromosome 7q), *glutamate decarboxylase 1* (chromosome 2q), and disrupted-in-schizophrenia 1 (*DISC1*; chromosome 1q). A functional polymorphism in the *COMT* gene, which affects prefrontal cortical function by changing dopamine signaling in the prefrontal cortex, has probably been studied most extensively. Data suggest that these susceptibility genes influence the cortical information processing that characterizes the schizophrenic phenotype.

Taken together, the new and improved methods of neuroscience are dazzling in their ability to display the biology of the brain. They offer new avenues for developing trans-

genic animal models of the disease and further advancing our understanding of the pathophysiology of the disease. Genetic influence on neurobiological mechanisms of schizophrenia may be a key to developing future prevention strategies and new “individualized” treatments. The next decade is shaping up to become the “Decade of Translational Neuroscience.”

### KEY POINTS

- The history of schizophrenia as a psychiatric disorder represents the history of modern neuropsychiatry, neuropsychopharmacology, and neuroscience.
- French psychiatrist Benedict Augustine Morel (1809–1873) coined the term *dementia praecox*, describing clinical features of schizophrenia and postulating that insanity was the result of an innate biological defect, and that the severity of mental syndromes increased in lineal descents as a sign of “degeneration.”
- Émil Kraepelin (1856–1927) integrated the contemporary concept of dementia praecox on the basis of the characteristic course and outcome of a cluster of symptoms and signs, but also stated that the disorder had a specific neuroanatomical pathology and etiology.
- The Swiss psychiatrist, Eugen Bleuler, coined the term *schizophrenia* in 1911. Bleuler developed a hierarchy that distinguished between *fundamental* and *accessory* symptoms; fundamental symptoms were shared by patients with schizophrenia and included “fragmented,” disturbed associations or neurocognitive disturbances; positive psychotic symptoms were conceptualized as “accessory” symptoms—a product of fundamental symptoms.
- In 1966 the World Health Organization sponsored the International Pilot Study of Schizophrenia, which suggested a high degree of consistency in the clinical features of schizophrenia across the world and led to the critical revision of U.S. diagnostic categories during the 1970s, with narrowing of definitions and development of the core symptom criteria in DSM-III.
- By the end of the 20th century, major advances in neuroscience, neuroimaging, and psychopharmacological and psychosocial treatments of the disease provided new hope for improved outcomes.
- However, a lack of precision of clinical endophenotypes of schizophrenia continues to impede further advances in the development of novel psychopharmacological agents and in disease prevention.
- The new and improved scientific methods combining genetic, neuroimaging, and neurocognitive approaches offer exciting avenues for developing transgenic animal models and advancing our understanding of the pathophysiology of the disease, potentially, leading to the development of new “individualized” treatments.

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