

SCHIZOPHRENIA: Etiology and Course

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■ **Abstract** Decades of research on schizophrenia have not produced major breakthroughs, but gradual progress has been made in identifying risk factors and clarifying the nature of the etiologic process. This article provides an overview of trends in research findings as well as current assumptions about the interplay between environmental and genetic factors in the etiology of schizophrenia. Based on the cumulative findings, it appears that both genetic and prenatal factors can give rise to constitutional vulnerability. Subsequent neuromaturational processes, especially those that occur during adolescence, and exposure to stressful events can trigger the behavioral expression of this vulnerability.

CONTENTS

INTRODUCTION	402
History and Phenomenology	402
Cognitive and Socioemotional Aspects of Schizophrenia	405
THE ORIGINS OF VULNERABILITY	407
The Genetics of Schizophrenia	407
Prenatal and Postnatal Factors	410
COURSE AND PROGNOSIS	411
Premorbid Development	411
Illness Onset and Course	413
Environmental Stressors	414
BRAIN ABNORMALITIES	415
Structural and Functional Abnormalities	415
Neurotransmitters	417
THE TREATMENT OF SCHIZOPHRENIA	419
Antipsychotic Medications	419
Psychosocial Treatments	420
SUMMARY AND CONCLUSIONS	422

INTRODUCTION

Schizophrenia is a complex disorder. From the level of overt behavior, to intracellular processes, it has defied scientific explanation. Up to this point, investigators have not been able to identify a single factor that characterizes all patients with schizophrenia. Despite the challenges, however, many investigators have devoted their professional lives to research on schizophrenia. And, although we have not yet solved the puzzle, the persistent efforts of clinical researchers have put many pieces into place.

The fact that schizophrenia is among the most debilitating of mental illnesses is what compels researchers to continue the search for its causes. Most cases of the disorder are first diagnosed between the ages of 20 and 25, a stage of life when people typically attain independence from parents, develop intimate romantic relationships, and/or begin to pursue work or career goals (DeLisi 1992). The illness can, therefore, have a profound, negative impact on the person's opportunities for attaining social and occupational success, and the consequences can be devastating for the adult life course. Further, the illness knows no boundaries; it occurs in all countries and within all ethnic groups. Across cultures, estimates of the lifetime prevalence of schizophrenia are around 1% (Keith et al. 1991, Kulhara & Chakrabarti 2001, Torrey 1987), although the prognosis may differ among countries (Kulhara & Chakrabarti 2001).

In this article, we provide an up-to-date overview of the status of scientific knowledge and theory about schizophrenia. There is now a clear consensus that schizophrenia is a brain disease. The major pressing questions concern the nature of the etiological process. What are the origins and characteristics of the neural abnormality, and what interactional processes trigger its expression? With reference to these issues, three general themes are emphasized. The first is that the etiology of schizophrenia involves the interplay between brain vulnerabilities and environmental factors. A second theme is that the illness does not emerge from a defect in a specific brain region but rather from the dysfunction of circuits that are comprised of multiple brain regions. The third is that brain maturational processes play a critical role in the etiological process.

We begin with a discussion of history and phenomenology, then proceed to a description of some of the key findings that have shed light on the illness. In conclusion, we offer an integrative framework for conceptualizing the etiological process.

History and Phenomenology

Historical accounts of behavioral syndromes that parallel schizophrenia appear in records from ancient Mesopotamia, ancient India, ancient Greece and Rome, the Middle Ages, and Europe, from the fifteenth through the seventeenth century (Jeste et al. 1985). However, because psychotic symptoms can be a manifestation of a variety of disorders, it cannot be firmly established that all of these descriptions were comparable to what we now label "schizophrenia." In the mid-to-late nineteenth century, European psychiatrists investigated the etiology, classification,

and prognoses of the various types of psychosis. At that time, the most common cause of psychosis was tertiary syphilis, although researchers were unaware that there was any link between psychotic symptoms and syphilis. We now know that the psychological signs of tertiary syphilis frequently overlap with symptoms of what we call schizophrenia. This important discovery served to illustrate how a psychological syndrome can be produced by an infectious agent. It also sensitized researchers to the fact that similar syndromes can result from very different causes, and set the stage for the current assumption that the syndrome we call schizophrenia may have multiple etiologies.

Emil Kraepelin (1856–1926) was the first to differentiate schizophrenia, which he referred to as “dementia praecox” (dementia of the young), from manic-depressive psychosis (for a historical overview, see Howells 1991). He also lumped together “hebephrenia,” “paranoia,” and “catatonia” (previously thought to be distinct disorders), and classified all of them as subtypes of dementia praecox. Kraepelin based this on their similarities in age of onset and prognosis. He did not believe that any single symptom was diagnostic, but instead based the diagnosis on the total clinical picture, including a degenerative process. If a psychotic patient deteriorated over months and years, the disorder was assumed to be dementia praecox. The assumption that schizophrenia typically has a poor prognosis is still widespread, and research has confirmed that many patients manifest a chronic course that entails lifelong disability (Carpenter & Buchanan 1994). But, as described below, the course varies dramatically among patients, and these differences may reflect distinct etiological processes.

The term schizophrenia was introduced at the beginning of the twentieth century by Eugen Bleuler (1857–1939) (Howells 1991). The word is derived from two Greek words: “schizo,” which means to tear or to split, and “phren,” which means “the intellect” or “the mind,” and was sometimes used to refer to emotional functions. Thus, the word schizophrenia means the splitting or tearing of the mind and emotional stability of the patient. Bleuler classified the symptoms of schizophrenia into fundamental and accessory symptoms (Bleuler 1911). According to Bleuler, the fundamental symptoms are ambivalence, disturbance of association, disturbance of affect, and a preference for fantasy over reality. He postulated that these symptoms are present in all patients, at all stages of the illness, and are diagnostic of schizophrenia. Bleuler’s accessory symptoms of schizophrenia included delusions, hallucinations, movement disturbances, somatic symptoms, and manic and melancholic states. He believed that these symptoms often occurred in other illnesses and were not present in all schizophrenia patients. It is also noteworthy that Bleuler’s reconceptualization of dementia praecox as “the group of schizophrenias” is reflected in the contemporary view that schizophrenia is a heterogeneous group of disorders with varied etiologies but similar clinical presentations.

The most recent substantive changes in the diagnostic conceptualization of schizophrenia were proposed by Kurt Schneider in the mid 1900s (Schneider 1959). Schneider assumed that certain key symptoms were diagnostic of schizophrenia, and he referred to these as first-rank symptoms. Schneider’s first-rank symptoms are types of hallucinations and delusions that characterize the signs of psychosis.

Examples are thought echoing (thoughts are heard out loud), thought broadcasting (belief that others can hear one's thoughts), thought intrusion (feeling that some thoughts originate outside of one's own mind), thought withdrawal (belief that thoughts are taken), and delusional perceptions (a sudden, fixed, false belief about a particular everyday occurrence or perception). When compared to Bleuler's "fundamental" symptoms, Schneider's symptom descriptions were more detailed and specific. Subsequent diagnostic criteria for schizophrenia have been heavily influenced by Schneider's approach.

Beginning in the 1980s, investigators began to emphasize the distinction between "positive" and "negative" symptoms of schizophrenia (Harvey & Walker 1987). The positive symptoms are those that involve an excess of ideas, sensory experiences, or behavior. Hallucinations, delusions, and bizarre behaviors fall in this category. Most of the first-rank symptoms described by Schneider fall into the positive category. Negative symptoms, in contrast, involve a decrease in behavior, such as blunted or flat affect, anhedonia, and lack of motivation. These symptoms were emphasized by Bleuler (1911).

A variety of diagnostic taxonomies for mental disorders proliferated in the middle of the twentieth century, and many believe this had a detrimental effect on research progress. In response, subsequent diagnostic systems were developed with the intent of achieving uniformity and thereby improving diagnostic reliability. Among these were the Feighner or St. Louis diagnostic criteria (Feighner et al. 1972), and the Research Diagnostic Criteria developed by Robert Spitzer and his colleagues (Spitzer et al. 1978). These two approaches had a major impact on the criteria for schizophrenia contained in contemporary diagnostic systems, most notably, the Diagnostic and Statistical Manual of Mental Disorders (DSM).

The DSM is now the most widely used system for diagnosing schizophrenia and other mental disorders. The most recent version of the DSM is the DSM IV-TR (Am. Psychiatric Assoc. 2000). Using DSM IV-TR criteria, schizophrenia can be diagnosed when signs and symptoms of the disorder have been present for six months or more (including prodromal and residual phases). The characteristic symptom criteria for schizophrenia include (a) hallucinations, (b) delusions, (c) disorganized speech (e.g., frequent derailment or incoherence), (d) grossly disorganized or catatonic behavior, and (e) negative symptoms, i.e., affective flattening, alogia, or avolition. At least two or more of these symptoms must be present for at least one month. Only one of the above is necessary if the delusions are bizarre, or if the hallucinated voices consist of a running commentary or of two voices conversing (both of these are derived from Schneider's first-rank symptoms in Table 2). In addition to the clinical symptoms, there must be social/occupational dysfunction. Further, significant mood disorder, such as depression or manic symptoms, must not be present. (This would exclude individuals who meet criteria for major depressive disorder with psychotic symptoms, and bipolar disorder with psychotic symptoms.) Finally, general medical conditions or substance abuse that might lead to psychotic symptoms must be ruled out.

The four subtypes of schizophrenia described in DSM IV are *paranoid*, *disorganized*, *catatonic*, and *undifferentiated*. The paranoid type is characterized by a

preoccupation with delusions or hallucinations, but there is no disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect. This is the subtype with the best prognosis. The catatonic type involves a clinical syndrome that is dominated by postural and/or movement abnormalities, mutism, or echolalia. In the disorganized type, all of the following are prominent: disorganized speech, disorganized behavior, and flat or inappropriate affect, but the criteria for the catatonic subtype are not met. This is the subtype with the worst prognosis. Finally, the undifferentiated subtype is diagnosed when the patient does not meet criteria for the previous subtypes, yet does meet the general criteria for schizophrenia. The inclusion of this subtype reminds us that these categories are unlikely to represent distinct diagnostic entities with unique etiologies.

Two other diagnostic categories in the schizophrenia “spectrum” are worth noting. One category, the residual type, is for individuals who have met criteria for schizophrenia in the past, but no longer do. This diagnosis is applied when there is a prominence of negative symptoms, or two or more attenuated “characteristic” symptoms, but no prominent delusions, hallucinations, catatonic symptoms, or disorganized behavior or speech. The other category, schizophreniform disorder, is for individuals whose symptoms do not meet the six-month criterion. This diagnosis is frequently made as a prelude to the diagnosis of schizophrenia, when the patient presents for treatment early in the course of the disorder. Some individuals with this disorder, however, will recover completely and not suffer further episodes of psychosis.

It is important to emphasize that, despite advances in diagnosis, we still do not know the diagnostic boundaries of schizophrenia. Moreover, the boundaries between schizophrenia and mood disorders are obscure. Many individuals who meet criteria for schizophrenia show marked signs of depression. These symptoms are sometimes present before the onset of schizophrenia, and frequently occur in combination with marked psychotic symptoms. As a result, the DSM IV includes a diagnostic category called schizoaffective disorder. This disorder can be conceived of, conceptually, as a hybrid between the mood disorders (bipolar disorder or major depression with psychotic features) and schizophrenia. The two subtypes are the depressive subtype (if the mood disturbance includes only depressive episodes), and the bipolar subtype (where the symptoms of the disorder have included either a manic or a mixed episode). Interestingly, the prognosis for patients with schizoaffective disorder is, on average, somewhere between that of schizophrenia and the mood disorders.

Cognitive and Socioemotional Aspects of Schizophrenia

It is well established that, as a group, schizophrenia patients manifest deficits in virtually all domains of cognitive functioning. Research in this area first focused on higher level processes, such as those tapped by standardized intellectual tests (Aylward et al. 1984) and neuropsychological measures (Goldsamt 1994). More recently investigators have examined basic sensory processing abilities. The results are consistent: schizophrenia patients show performance deficits on cognitive tasks

that range from very simple to complex (Green et al. 2000). Further, the cognitive impairments are not merely side effects of treatment, because they are apparent in first-episode, nonmedicated patients.

One of the most basic deficits is in the very earliest stages of sensory information processing. Using a laboratory procedure called backward masking, researchers have shown that schizophrenia patients are slower in the initial processing of visual stimuli (Green et al. 1999). In fact, when brain activity is monitored during the presentation of visual or auditory stimuli, nonmedicated schizophrenia patients show a reduction of activity, relative to normals, in several brain regions, including the thalamus, prefrontal cortex, and parietal lobe (Braus et al. 2002).

Another measure of very basic aspects of information processing is *prepulse inhibition*, a paradigm that indexes the individual's startle responses to repeated sensory stimuli. The startle response, such as an eye blink, is typically inhibited when the startling event is preceded by a prestimulus that is weak and nonstartling; this is called prepulse inhibition. When tested within a few days of their first admission, and before medication, patients manifest a reduction in prepulse inhibition (Perry et al. 2002). Thus they respond to the target sensory stimulus as if it was not preceded by a prestimulus. Again, these findings indicate that some schizophrenia patients have a very basic cognitive impairment that is a consequence of brain dysfunction.

In addition to deficits in the early stages of processing sensory information, schizophrenia patients also manifest impairment in responding to stimuli. This appears to be due to both a deficit in the speed of response selection (Krieger et al. 2001) and the execution of motor responses (Flyckt et al. 2000). Deficits in manual motor speed and coordination are among the most consistently found impairments in schizophrenia (Flashman et al. 1996).

Among the higher level cognitive functions, schizophrenia patients show impairments in verbal and spatial memory, attention, and executive functions, such as abstract reasoning, and planning (Kuperberg & Heckers 2000). The executive functions, subserved by the frontal lobes, have been the focus of intense study because these cognitive abilities are predictive of prognosis (Green et al. 2000).

There are also deficits in thinking about social phenomena. Studies of social-cognitive abilities in schizophrenia patients have consistently shown that patients are impaired in their ability to comprehend and solve social problems (Penn et al. 1997). Deficits in social cognition may be partially due to limitations in more basic cognitive processes, such as memory and reasoning. However, evidence suggests that basic cognitive impairments do not account completely for the more pervasive and persistent social-cognitive deficits observed in schizophrenia.

Blunted and inappropriate affect are among the diagnostic criteria for schizophrenia. It is, therefore, not surprising that patients show abnormalities in the expression of emotion in both their faces and verbal communications; specifically, patients exhibit less intense facial emotion, and fewer positive and more negative expressions (Brozgold et al. 1998, Kring & Neale 1996). Further, patients are less accurate than normal comparison subjects in their ability to label facial expressions of emotion (Penn & Combs 2000, Walker 1981, Walker et al. 1980). Patients with more

severe impairments in their abilities to recognize and express emotion also have more problems in social adjustment.

One of the unresolved questions is whether schizophrenia is associated with a decline in cognitive functioning following the clinical onset of the illness. Although earlier research yielded inconsistent results, recent studies indicate that there is a cognitive decline in some patients (Harvey 2001). These findings have implications for our assumptions about the underlying pathological process, and we will return to this issue later when we address the course of schizophrenia.

Cumulative findings from many decades of research on cognitive functions in schizophrenia have shown that the deficits associated with the disorder are not specific to a particular sensory modality, stage of information processing, or cognitive domain (e.g., planning, memory, abstract reasoning). Instead, it appears that the impairments are generalized, although there is some evidence to suggest that certain domains, like working memory, may be more impaired than others (Green et al. 2000). But it is important to keep in mind that the aggregated data on patients obscure substantial individual differences in performance. In the vast majority of studies, there are some patients who perform at or above the average for normals, and others whose level of performance is so low it is outside the range for normals. To date, all cognitive measures, including those tapping the most basic processes, have yielded overlapping distributions for patients and controls. This has been interpreted by some to mean that there is no specific or unique cognitive deficit in schizophrenia. Instead, it may be that cognitive deficits in schizophrenia are nonspecific and secondary consequences of one or more of the etiologic factors that contribute to schizophrenia, such as pre- and perinatal insults. Of course, we cannot rule out the possibility that there is a specific cognitive deficit shared by almost all schizophrenia patients, and we have simply failed to identify it. Perhaps the cognitive deficit is at the level where “cold” cognitive processes interface with emotional processes (Gjerde 1983).

THE ORIGINS OF VULNERABILITY

Early writers on schizophrenia, such as Kraepelin (1913) and Eugen Bleuler (1911), did not offer explicit etiologic theories about the origins of schizophrenia, but they did suggest that there might be a biological basis for at least some cases of the illness. Although theories that emphasized psychosocial determinants gained some credence in the mid 1900s, contemporary theorists assume a biological vulnerability to schizophrenia that is present at birth. Researchers have identified two sources of this vulnerability: genetic factors and prenatal or delivery complications. Both appear to have implications for fetal brain development.

The Genetics of Schizophrenia

One of the most well-established findings in schizophrenia research is that vulnerability to the illness can be inherited (Gottesman 1991). Behavior genetic studies

utilizing twin, adoption, and family history methods have all yielded evidence that the risk for schizophrenia is elevated in individuals who have a biological relative with the disorder; the closer the level of genetic relatedness, the greater the likelihood the relative will also suffer from schizophrenia.

In a review of family, twin, and adoption studies conducted from 1916 to 1989, Gottesman (1991) outlined the compelling evidence for the role of genetic factors in schizophrenia. Monozygotic (MZ) twins, who share nearly 100% of their genes, have the highest concordance rate for schizophrenia. Among monozygotic cotwins of patients with schizophrenia, 25% to 50% will develop the illness. Dizygotic (DZ) twins and other siblings share, on average, only about half of their genes. About 10% to 15% of the DZ cotwins of patients are also diagnosed with the illness. Further, as genetic relatedness of the relative to the patient becomes more distant, such as from first-degree (parents, siblings) to second-degree relatives (grandparents, half siblings, aunts, and uncles), the lifetime risk for schizophrenia is reduced.

Adoption studies have provided strong evidence that the tendency for schizophrenia to run in families is primarily due to genetic factors, rather than the environmental influence of being exposed to a mentally ill family member. In a seminal study, Heston (1966) examined the rates of schizophrenia in adoptees with and without a biological parent who was diagnosed with the illness. He found higher rates of schizophrenia, and other mental illnesses, in the biological offspring of parents with schizophrenia, when compared to adoptees with no mental illness in biological parents. Similarly, in a Danish sample, Kety (1988) examined the relatives of adoptees with and without schizophrenia. He found that the biological relatives of adoptees who suffered from schizophrenia had a significantly higher rate of schizophrenia than the adoptive relatives who reared them. Also, the rate of schizophrenia in the biological relatives of adoptees with schizophrenia was higher than in the relatives (biological or adoptive) of healthy adoptees.

But more recent findings from an adoption study indicate that the genetic influences often act in concert with environmental factors. Tienari et al. (1994) conducted an adoption study in Finland, and found that the rate of psychoses and other severe disorders was significantly higher than in the matched control adoptees. However, genetic vulnerability was mainly expressed in association with disruptive adoptive environments, and an elevated rate of schizophrenia was not detected in adoptees reared in healthy family environments. These findings are consistent with the prevailing diathesis-stress models of etiology.

Taken together, the findings from behavioral genetic studies of schizophrenia lead to the conclusion that the disorder involves multiple genes, rather than a single gene (Gottesman 1991). This conclusion is based on several observations, most notably the fact that the pattern of familial transmission does not conform to what would be expected from a single genetic locus, or even a small number of genes. Rather, the genetic liability seems to involve multiple genes acting in concert, or numerous single susceptibility genes acting independently. Consistent with this assumption, attempts to identify a genetic locus that accounts for a significant

proportion of cases of schizophrenia have not met with success (Kato et al. 2002). Instead, researchers using molecular genetic techniques have identified an array of genes that seem to account for a very small proportion of cases or of variance in liability. Candidate gene analyses, genome scans, and linkage studies have provided some evidence for the involvement of several specific genes, such as the serotonin type 2a receptor (5-HT_{2a}) gene and the dopamine D₃ receptor gene, and several chromosomal regions (i.e., regions on chromosomes 6, 8, 13, and 22) (Badner & Gershon 2002, Mowry & Nancarrow 2001).

One of the most noteworthy genetic discoveries to date is the association between the 22q11 deletion and schizophrenia. The 22q11 deletion occurs in about 0.025% of the general population, and it involves a microdeletion on chromosome 22q11.2 that is often accompanied by physical syndrome that includes structural anomalies of the face, head, and heart. About 25% of individuals with the 22q deletion syndrome meet diagnostic criteria for schizophrenia, but only about 2% of schizophrenia patients have the 22q11 deletion genotype, although the rate of 22q11 deletion may be higher in patients with an earlier onset (Bassett et al. 1998, Karayiorgou et al. 1995).

Findings from molecular genetics also raise questions about the etiologic boundaries between schizophrenia and other psychotic disorders. Early behavioral genetic studies led to the conclusion that there were separable genetic liabilities for schizophrenia and the major affective disorders, namely, bipolar disorder and psychotic depression. But more recent evidence indicates that this is not the case. Using quantitative genetic techniques with large twin samples, researchers have shown that there is significant overlap in the genes that contribute to schizophrenia, schizoaffective disorder, and manic syndromes (Cardno et al. 2002). Other studies have yielded similar results, leading many in the field to conclude that the genetic vulnerability does not conform to the diagnostic boundaries listed in DSM and other taxonomies (e.g., Potash et al. 2001). Rather, it appears that there may be genetic vulnerabilities to psychosis in general, and that the expression of these vulnerabilities can take the form of schizophrenia *or* an affective psychosis, depending on other inherited and acquired risk factors.

Another major issue confronting the field is the relative importance of inherited vulnerability versus external factors that impinge on the developing individual. At this point, researchers are not in a position to estimate the relative magnitude of the inherited and environmental contributors to the etiology of schizophrenia. Moreover, we do not yet know whether genetic vulnerability is present in all cases of schizophrenia. It is possible that some cases of the illness are solely attributable to environmental risk factors. Further, we do not know whether the genetic predisposition to schizophrenia is always expressed, although there is substantive evidence to indicate that it is not. The fact that the concordance rate for schizophrenia in MZ twins is nowhere near 100% suggests that some genetically vulnerable individuals do not develop the illness. It is possible, however, that the genetic liability for schizophrenia sometimes results from a mutation that occurs in only the affected member of discordant MZ pairs. But findings from

studies of discordant MZ twins indicate that the rate of schizophrenia is elevated in the offspring of nonaffected cotwins (Gottesman & Bertelsen 1989, Kringlen & Cramer 1989), which suggests that some individuals possess a genetic vulnerability for schizophrenia that they pass on to their offspring despite the fact that they are never diagnosed with the illness. Thus, unexpressed genetic vulnerabilities for schizophrenia may be common in the general population. The presence of unexpressed genetic vulnerability to schizophrenia makes the work of researchers much more difficult. At the same time, the evidence of unexpressed genotypes for schizophrenia leads us to inquire about factors that trigger the expression of illness in vulnerable individuals. This knowledge may, someday, lead to effective preventative interventions.

Prenatal and Postnatal Factors

Events that adversely affect fetal development are now considered to be potential environmental triggers of genetic vulnerability. It is also plausible that they are sufficient, on their own, to produce vulnerability to schizophrenia. There is extensive evidence that obstetrical complications (OCs) have an adverse impact on the developing fetal brain, and numerous studies have shown that schizophrenia patients are more likely to have a history of OCs (Buka et al. 1993, Dalman et al. 1999, McNeil et al. 2000). Included among these are pregnancy problems, such as toxemia and preeclampsia, as well as labor and delivery complications. A review of the OC literature by Cannon (1997) concluded that, among the different types of OCs, labor and delivery complications, which are often associated with hypoxia (fetal oxygen deprivation), were most strongly linked with later schizophrenia. In the National Collaborative Perinatal Project, which involved more than 9000 children followed from birth through adulthood, the odds of schizophrenia increased linearly with an increasing number of hypoxia-related OCs (Cannon et al. 2000, Cannon 1998).

Another prenatal event that has been linked with increased risk for schizophrenia is maternal infection. Researchers have found that the risk rate for schizophrenia is elevated for individuals born shortly after a flu epidemic (Barr et al. 1990, Murray et al. 1992) or after being prenatally exposed to rubella (Brown et al. 2001). The findings from research on viral infection are consistent with reports on the "season-of-birth" effect in schizophrenia. Several studies have found that a disproportionate number of schizophrenic patients are born during the winter months (Bradbury & Miller 1985, Torrey et al. 1997). This timing may reflect seasonal exposure to viral infections, which are most common in late fall and early winter. Thus the fetus would have been exposed to the infection during the second trimester. The second trimester is an important time for brain development, and disruptions during this stage may lead to developmental abnormalities.

Studies of rodents and nonhuman primates have shown that prenatal maternal stress can interfere with fetal brain development, and is associated with elevated glucocorticoid release and hippocampal abnormalities in the offspring (Smythe

et al. 1994, Weinstock 1996). Along the same lines, in humans, there is evidence that stressful events during pregnancy are associated with greater risk for schizophrenia and other psychiatric disorders in adult offspring. Researchers have found higher rates of schizophrenia in the offspring of women whose spouses died during their pregnancies (Huttunen 1989) or were exposed to a military invasion during pregnancy (van Os & Selten 1998). It is likely that prenatal stress triggers the release of maternal stress hormones, disturbing fetal neurodevelopment as well as disrupting subsequent functioning of the hypothalamic-pituitary-adrenal axis, which in turn influences behavior and cognition (Welberg & Seckl 2001).

Recent findings indicate that postnatal brain insults can also increase the risk for schizophrenia. There is a substantial body of literature showing that individuals who sustain head injury are at heightened risk for a variety of psychiatric disorders, including schizophrenia. The association between schizophrenia and head injury may be greater for injuries that occur in early childhood. AbdelMalik and colleagues (AbdelMalik et al. 2003) found that head injury before the age of 10 was more common in individuals who developed schizophrenia, and was linked with an earlier onset of illness.

One of the chief questions being pursued by researchers is whether OCs and postnatal brain trauma act independently to increase risk for schizophrenia, or have their effect in conjunction with a genetic vulnerability. It may be that the genetic vulnerability for schizophrenia involves an increased sensitivity to prenatal complications (Cannon 1997, 1998) and/or postnatal brain trauma (AbdelMalik et al. 2003). It is also plausible that prenatal and postnatal brain insults act independently of genetic vulnerabilities, although such effects would likely entail complex interactions among factors (Susser et al. 1999). For example, in order to produce the neurodevelopmental abnormalities that confer risk for schizophrenia, it may be necessary for a specific OC to occur during a critical period of cellular migration and/or in conjunction with other factors such as maternal fever or immune response.

COURSE AND PROGNOSIS

Assuming that genetic and obstetrical factors confer the vulnerability for schizophrenia, the diathesis must be present at birth. Yet, schizophrenia is typically diagnosed in late adolescence or early adulthood, with the average age of diagnosis in males about four years earlier than in females (Riecher-Rossler & Hafner 2000). This raises intriguing questions about the developmental course prior to the clinical onset.

Premorbid Development

There is compelling evidence that signs of schizophrenia are present long before the illness is diagnosed. Most of these signs are subtle, and do not reach the severity of clinical disorder. Nonetheless, when compared to children with healthy adult

outcomes, children who later develop schizophrenia manifest deficits in multiple domains. In some of these domains, the deficits are apparent as early as infancy.

In the area of cognitive functioning, children who later develop schizophrenia tend to perform below their healthy siblings and classmates. This is reflected in lower scores on measures of intelligence and achievement, and poorer grades in school (Aylward et al. 1984, Jones et al. 1994). It appears that the magnitude of the deficit becomes more pronounced in adolescence: The standardized achievement test scores of patients with adult-onset schizophrenia drop significantly between ages 13–16 years (Fuller et al. 2002).

Preschizophrenic children also show abnormalities in social behavior. They are less responsive in social situations, show less positive emotion (Walker & Lewine 1990, Walker et al. 1993), and have poorer social adjustment than children with healthy adult outcomes (Done et al. 1994). Further, preschizophrenic children with more serious adjustment problems have more brain and neuropsychological abnormalities after the onset of illness (Walker et al. 1996, Neumann et al. 1996). Studies of the childhood home movies of schizophrenia patients have shown that preschizophrenic children manifest more negative facial expressions of emotion than their siblings as early as the first year of life, indicating that the vulnerability for schizophrenia is subtly manifested in the earliest interpersonal interactions (Walker et al. 1993).

Vulnerability to schizophrenia is also apparent in motor functions. When compared to their siblings with healthy adult outcomes, preschizophrenic children show more delays and abnormalities in motor development, including deficits in the acquisition of early motor milestones such as bimanual manipulation and walking (Walker et al. 1994). Deficits in motor function extend throughout the premorbid period, and persist after the onset of the clinical illness (McNeil & Cantor-Graae 2000). It is important to note that neuromotor abnormalities are not pathognomonic for schizophrenia, in that they are observed in children at risk for a variety of disorders, including learning disabilities. But they are one of several important clues pointing to the involvement of dysfunctional brain circuitry in schizophrenia.

Despite the subtle signs of abnormality that have been identified in children at risk for schizophrenia, most do not manifest diagnosable mental disorders in early and middle childhood. But the picture often changes in adolescence. During postpubescence, many subjects who go on to develop schizophrenia show a pattern of escalating adjustment problems (Walker et al. 1998). This gradual increase in problems includes feelings of depression, social withdrawal, irritability and noncompliance. But this developmental pattern is not unique to schizophrenia; adolescence is also the critical period for the expression of the first signs of mood disorders, substance abuse, and some other behavioral disorders. As a result, researchers view adolescence as a critical period for the emergence of a broad range of psychiatric disorders (Walker 2002).

Among the behavioral risk indicators sometimes observed in preschizophrenic adolescents are subclinical signs of psychotic symptoms. These signs are also the defining features of a DSM Axis II disorder, namely, schizotypal personality

disorder (SPD). The diagnostic criteria for SPD include social anxiety or withdrawal, affective abnormalities, eccentric behavior, unusual ideas (e.g., persistent belief in extrasensory phenomena), and unusual sensory experiences (e.g., repeated experiences with confusing noises with peoples' voices, or seeing objects move). Although the individual's unusual ideas and perceptions are not severe or persistent enough to meet criteria for delusions or hallucinations, they are recurring. An extensive body of research demonstrates genetic and developmental links between schizophrenia and SPD. The genetic link between SPD and schizophrenia has been well established through twin and family history studies (Kendler et al. 1995a,b; Raine & Mednick 1995). Recently, several research groups have documented the developmental transition from schizotypal signs to schizophrenia in young adulthood.

Longitudinal studies indicate that 20% to 40% of youth with schizotypal signs eventually show an Axis I schizophrenia spectrum disorder (Miller et al. 2002, Yung et al. 1998). The remainder either show other adjustment problems or a complete remission of symptoms in young adulthood. Given the high rate of progression to schizophrenia, researchers are now attempting to determine whether schizotypal youth who will eventually manifest schizophrenia can be identified prior to the onset of the illness. This is considered a pivotal step in efforts to develop secondary prevention programs.

Recent investigations have revealed that adolescents with SPD manifest some of the same functional abnormalities observed in patients with schizophrenia. For example, SPD youth show motor abnormalities (Walker et al. 1999), cognitive deficits (Diforio et al. 2000), and an increase in cortisol, a stress hormone that is elevated in several psychiatric disorders (Weinstein et al. 1999).

Illness Onset and Course

The onset of the clinical symptoms of schizophrenia can be abrupt or gradual, but it is usually preceded by escalating signs of behavioral dysfunction and subclinical psychotic symptoms, a period referred to as the prodromal phase (Lieberman et al. 2001). Longer untreated psychotic episodes may be harmful for schizophrenia patients and result in a worse course of illness (Davidson & McGlashan 1997). Although some researchers have questioned the validity of this conclusion (Larsen et al. 2001), it has prompted many researchers to focus greater attention on the prodromal period.

Following the clinical onset of schizophrenia, patients vary significantly in their illness course. Some patients experience a full recovery, whereas others show chronic debilitation. It has been estimated that only 20% to 30% of patients are eventually able to lead relatively normal lives, meaning they live independently and/or maintain a job (Cancro 1989). But the majority experience a more debilitating course, with 20% to 30% manifesting continued moderate symptoms, and more than half experiencing significant impairment throughout their adulthood.

Given the chronicity of the illness, it is not surprising that suicide is a leading cause of death among people with schizophrenia (Schwartz & Cohen 2001). Moreover, patients with schizophrenia often suffer from other comorbid conditions. For example, the rate of substance abuse among schizophrenia patients is very high, with as many as 47% in the community and 90% of patients in prison settings meeting criteria for substance abuse or dependence (Regier et al. 1990).

What determines the course of schizophrenia? Male sex, gradual onset, early age of onset, poor premorbid functioning, and family history of schizophrenia are all associated with poorer prognosis (Gottesman 1991). In addition, as would be predicted by the diathesis-stress model, exposure to environmental stressors can exacerbate the course of schizophrenia.

Environmental Stressors

Several lines of research provide support for the hypothesis that stressful events can worsen the course of schizophrenia (for a review, see Norman & Malla 1993). For example, the number of stressful life events increases in the months immediately preceding a schizophrenia relapse (Ventura et al. 1992). Also, patients are more likely to relapse if they live in homes where family members express more negative attitudes and emotion (Butzlaff & Hooley 1998). Given these findings, it is not surprising that intervention programs aimed at reducing stress are beneficial for patients (Norman et al. 2002).

Indirect evidence indicates that stress exposure can also contribute to the onset of symptoms in vulnerable individuals. In a study that examined the interaction between parental psychiatric status and child maltreatment, the offspring of schizophrenic parents manifested significantly greater increases in behavior problems over time if they were also victims of neglect and/or abuse (Walker et al. 1989). Another study showed that high-risk offspring were more likely to develop schizophrenic symptoms if they were raised in institutional settings, rather than by parents or extended family members (Walker et al. 1981). Along the same lines, adopted-away children of biological mothers with schizophrenia are at greater risk for the disorder if their adoptive families are dysfunctional (Tienari et al. 1994) or show "communication deviance" (Wahlberg et al. 1997).

It is well established that stress exposure impacts brain function. This effect is partially mediated by activation of the hypothalamic-pituitary-adrenal (HPA) axis, one of the chief neural systems involved in the biological response to stress. Activation of the HPA axis results in a cascade of neurohormonal events that culminates in the release of cortisol from the adrenal gland. Cortisol has pervasive effects on brain function, and can alter the activity of neurotransmitter systems. When stress hormones are chronically elevated, structural brain changes can occur, such as reductions in hippocampal volume (Lombroso & Sapolsky 1998).

Elevations in cortisol are linked with more severe symptoms and cognitive deficits in schizophrenia (Walder et al. 2000). Walker & Diforio (1997) have reviewed evidence of HPA dysregulation in schizophrenia. In their "neural

diathesis-stress model,” they describe how heightened cortisol release has the potential to exacerbate schizophrenia symptoms by augmenting dopamine activity. The chronic stress inherent in suffering from a psychotic illness may also contribute to degenerative brain changes.

BRAIN ABNORMALITIES

Structural and Functional Abnormalities

With the advent of neuroimaging techniques in the 1960s, it became possible to document what many had long suspected: that schizophrenia was associated with brain abnormalities. The earliest reports, based on computerized axial tomography, showed that patients had enlarged brain ventricles, especially increased volume of the lateral ventricles (Dennert & Andreasen 1983). As new imaging techniques were developed, these findings were replicated, and additional abnormalities were detected (Henn & Braus 1999). Magnetic resonance imaging (MRI) revealed decreased frontal, temporal, and whole-brain volume (Lawrie & Abukmeil 1998). More fine-grained analyses demonstrated reductions in the size of structures such as the thalamus and hippocampus. In fact, of all the regions studied, the hippocampus is one that has most consistently been identified as distinguishing schizophrenia patients from healthy controls (Schmajuk 2001).

A landmark study of monozygotic twins discordant for schizophrenia was the first to demonstrate that these brain abnormalities were not solely attributable to genetic factors (Suddath et al. 1990). When compared to their healthy identical cotwins, twins with schizophrenia were found to have reduced temporal lobe volumes, with the hippocampal region showing the most dramatic difference between the affected and nonaffected cotwins. Subsequent studies have confirmed smaller brain volumes in affected twins when compared to their healthy identical cotwins (Baare et al. 2001), and thus lend support to the hypothesis that the brain abnormalities may be partially due to factors that interfere with brain development.

Longitudinal studies of brain morphology in schizophrenia have yielded striking evidence of volumetric reductions over time. Decreases in gray matter volume and increases in ventricular size have been documented in the early stages of the illness in patients with young-adult onset (Cahn et al. 2002, DeLisi 1999), and in adolescents with schizophrenia (Rapoport et al. 1999). Although normal adolescents also manifest a developmental reduction in gray matter volume, it is more pronounced in those with schizophrenia. Moreover, adolescents with schizophrenia show volumetric reduction in total cortical and hippocampal volume that is not observed in normal adolescents (Giedd et al. 1999). It appears that brain changes precede the onset of schizophrenia. In a study of individuals with prodromal symptoms, those who subsequently developed schizophrenia showed a decrease in gray matter in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyrus (Pantelis et al. 2003). Taken together, these findings suggest

that abnormal brain changes predate the onset of schizophrenia, and may begin in adolescence.

In addition to structural abnormalities, schizophrenia patients also differ from normals in functional brain characteristics. The most consistent findings from fMRI and PET are reductions in activity in the frontal and temporal regions, especially during the performance of cognitive tasks (Kindermann et al. 1997, Pearlson 1997). Recent findings indicate that reduced brain activity is also observed in the limbic system in schizophrenia patients during the processing of facial emotion (Gur et al. 2002).

While the results of neuroimaging research on schizophrenia are impressive, an important caveat should be kept in mind. Despite the plethora of research findings indicating the presence of gross morphological and functional abnormalities in the brains of schizophrenia patients, no abnormality has been shown to be either specific to schizophrenia or to characterize all patients. Therefore, like the generalized cognitive deficits manifested by patients, the brain abnormalities are viewed as nonspecific indicators of brain dysfunction. In an effort to identify more precisely the origins of the dysfunction, some investigators have looked at the cellular level.

Postmortem studies of the brains of patients have revealed a number of abnormalities in neural density, structure, and interconnections. These include reductions in neuron density, and abnormal neuronal morphology, cytoarchitecture, dendritic arbors and spines, but with no signs of gliosis (Arnold 1999). The absence of gliosis, which typically develops following postnatal brain injury, has led to the conclusion that the cellular abnormalities reflect early developmental abnormalities.

In addition, the widespread nature of the cellular abnormalities observed in schizophrenia have led many researchers to conceptualize the disorder as one that involves malfunction of neural circuits. For example, it has been suggested that schizophrenia may involve abnormal function of "cortico-striatal circuits" that link various regions of the cortex and the limbic system with the striatum (Walker 1994). These circuits involve several neurotransmitter systems, and abnormalities in multiple segments of the circuit could be functionally equivalent with respect to the behavioral disturbance they produce. Further, the brain regions that distinguish these circuits mature at different rates. It is possible that disruption in one or more of the circuits characterized by neuromaturation in adolescence/early adulthood may subserve the onset of symptoms.

Along the same lines, Benes (2000) has suggested that schizophrenia may involve mis-wirings in intrinsic circuits (microcircuitry) within certain brain regions, as well as changes at the level of interconnections between two or more regions within a network (macrocircuitry). Normal postnatal maturational changes, at the level of both macro- and microcircuitry, within the limbic system may then serve as triggers for the onset of schizophrenia during adolescence. Finally, others have suggested that there is a disruption in the cortical-thalamic-cerebellar-cortical circuit that leads to an impairment in synchrony, or coordination of mental processes. Impairment in this basic cognitive process is assumed to produce the diversity of symptoms seen in schizophrenia (Andreasen et al. 1999).

The notion that schizophrenia involves dysfunction of one or more neural circuits, as opposed to a specific brain region, converges with the evidence from other lines of investigation, including phenomenology, cognitive functions, genetics, and the neuroanatomy of schizophrenia. Given that neural circuits involve multiple neurotransmitters and multiple segments, including some that provide inhibitory feedback, their function could be disrupted in numerous ways. Moreover, the disruption of a specific circuit could have relatively broad and nonspecific effects on behaviors.

Neurotransmitters

Brain circuit activity is driven by neurotransmitters. The idea that schizophrenia involves an abnormality in neurotransmission has a long history. Initial neurotransmitter theories focused on epinephrine and norepinephrine. Subsequent approaches have hypothesized that serotonin, glutamate, and/or GABA abnormalities are present in schizophrenia patients. But, compared to other neurotransmitters, dopamine has played a more enduring role in theories about the biochemical basis of schizophrenia.

Dopamine is widely distributed in the brain and is one of the neurotransmitters that enables communication in the circuits that link subcortical with cortical brain regions (Jentsch et al. 2000). Since the 1950s, support for the idea that dopamine might play a central role in schizophrenia has waxed and waned. In the past decade, however, interest in dopamine has resurged, largely because research findings have offered a new perspective.

The initial support for the role of dopamine in schizophrenia was based on two indirect pieces of evidence (Carlsson 1988): (a) drugs that reduce dopamine activity also serve to diminish psychotic symptoms, and (b) drugs that heighten dopamine activity exacerbate or trigger psychotic episodes. It was eventually discovered that antipsychotic drugs have their effect by blocking dopamine receptors, especially the D2 subtype that is prevalent in subcortical regions of the brain. The newer antipsychotic drugs, or “atypical” antipsychotics, have the advantage of causing fewer motor side effects. Nonetheless, they also act on the dopamine system by blocking various subtypes of dopamine receptors.

Early studies of dopamine in schizophrenia failed to find evidence of excess dopamine or its metabolites in fluids from schizophrenia patients. When investigators examined dopamine receptors, however, they found some evidence of increased densities. Both postmortem and functional MRI studies of patients’ brains yielded evidence that the number of dopamine D2 receptors tends to be greater in patients than in normal controls (Kestler et al. 2001). Controversy has surrounded this literature because antipsychotic drugs can change dopamine receptor density. Nonetheless, even studies of never-medicated patients with schizophrenia have shown elevations in dopamine receptors (Kestler et al. 2001).

Other abnormalities in dopamine transmission have also been found. It appears, for example, that dopamine synthesis and release may be augmented in the brains

of schizophrenia patients (Lindstrom et al. 1999). When schizophrenia patients and normal controls are given amphetamine, a drug that enhances dopamine release, the patients show more augmented dopamine release (Abi-Dargham et al. 1998, Soares & Innis 1999).

Glutamate is an excitatory neurotransmitter. Glutamatergic neurons are part of the pathways that connect the hippocampus, prefrontal cortex, and thalamus, all regions that have been implicated in the neural circuitry of schizophrenia. Investigators have found evidence of diminished activity at glutamatergic receptors among schizophrenia patients in these brain regions (Carlsson et al. 1999, Goff & Coyle 2001, Tsai & Coyle 2002). One of the chief receptors for glutamate in the brain is the N-methyl-D-aspartic acid (NMDA) subtype of receptor. It has been suggested that these receptors may be abnormal in schizophrenia. Blockade of NMDA receptors produces the symptomatic manifestations of schizophrenia in normal subjects, including negative symptoms and cognitive impairments. For example, administration of NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, induces a broad range of schizophrenic-like symptomatology in humans, and these findings have contributed to a hypoglutamatergic hypothesis of schizophrenia. Conversely, drugs that indirectly enhance NMDA receptor function can reduce negative symptoms and improve cognitive functioning in schizophrenia patients. It is important to note that the idea of dysfunction of glutamatergic transmission is consistent with the dopamine hypothesis of schizophrenia because there are reciprocal connections between forebrain dopamine projections and systems that use glutamate. Thus dysregulation of one system would be expected to alter neurotransmission in the other.

GABA is an inhibitory neurotransmitter. Some have suggested that its inhibitory effects may be increased in psychotic disorders (Squires & Saederup 1991). On the other hand, the uptake and the release of GABA were reduced in some studies of postmortem brain tissue from schizophrenia patients (Lewis et al. 1999), and there are abnormalities in the interconnections among GABA neurons (Benes & Berretta 2001). More specifically, there is evidence of a loss of cortical GABA interneurons. Current theories about the role of GABA in schizophrenia assume that it is important because cortical processes require an optimal balance between GABA inhibition and glutamatergic excitation.

Other neurotransmitters that have been implicated in schizophrenia include serotonin and noradrenaline (Pralong et al. 2002). However, the evidence to support their role in schizophrenia is more limited.

The true picture of the neurochemical abnormalities in schizophrenia may be more complex than we would like to assume. Neurotransmitter systems interact in intricate ways at multiple levels in the brain's circuitry (Carlsson et al. 2001). Consequently, an alteration in the synthesis, reuptake, receptor density, or receptor affinity for any one of the neurotransmitter systems would be expected to have implications for one or more of the other neurotransmitter systems. Further, because neural circuits involve multiple segments that rely on different transmitters, it is easy to imagine how an abnormality in even one specific subgroup of

receptors could result in the dysfunction of all the brain regions by a particular brain circuit.

THE TREATMENT OF SCHIZOPHRENIA

Findings from research on the treatment of schizophrenia have advanced both clinical practice and theories of etiology. Based on the evidence, the contemporary treatment “ideal” is a combination of medication, psychological therapy, and community support. In reality, however, medication is both the first and the *only* treatment received by many patients.

Antipsychotic Medications

The mainstay of contemporary treatment of schizophrenia is antipsychotic medication. Antipsychotic medication can be divided into two major classes. Conventional antipsychotic medications, first introduced in the 1950s, are usually referred to as either “typical” or “first-generation” antipsychotics. (These drugs preceded the release of clozapine (Clozaril) into the North American market in the 1980s.) Chlorpromazine (Thorazine), was the first antipsychotic medication, and the following three decades witnessed the release of various other typical neuroleptics. All of these medications reduce dopamine activity by blocking dopamine receptors, especially the D2 subtype, and these drugs have similar efficacy for the positive symptoms of schizophrenia. They differ from each other, however, in side-effect profiles.

Drug-induced movement abnormalities are the main side effect associated with the typical antipsychotics. There are both early- and late-emerging motor side effects (Sadock & Sadock 2000). Early emerging “extrapyramidal” syndromes include pseudoparkinsonism (clinically similar to Parkinson’s disease), dystonic reactions (sudden onset of sustained intense muscle contraction), and akathisia (restlessness).

The most common late-emerging syndrome is tardive dyskinesia (irregular twisting or writhing movements). The cause of these motor side effects is not established, but is assumed to be due to excessive dopamine D2 receptor blockade. The motor symptoms typically decline following the discontinuation of medication.

The side effects caused by the typical antipsychotics have led most clinicians to abandon them in favor of second-generation medications. Nonetheless, they contributed to our understanding of the neurochemistry of schizophrenia, and offered many patients the first opportunity to live outside an institution.

Clozapine and the subsequently introduced antipsychotics are a heterogeneous group of medications that are commonly referred to as the “atypical” or “second-generation” antipsychotics. The atypicals differ significantly from one another in terms of the neurotransmitter receptors that they occupy. However, they all act as

dopamine antagonists to some extent, in addition to affecting other neurotransmitter systems, and they have a reduced risk of both the early and late emerging movement disorders (Marder et al. 2002). In addition, clozapine has been shown to be highly effective for treatment-resistant schizophrenia. However, its use is generally confined to the refractory patients because of its potentially serious side-effects (including agranulocytosis), and the requirement for frequent blood monitoring (Alphs & Anand 1999, Naheed & Green 2001). With the exception of clozapine, the atypicals have become the first line in the treatment of schizophrenia and other psychotic disorders. The most commonly prescribed atypical antipsychotics in the United States include Risperdal (risperidone), Zyprexa (olanzapine), Seroquel (quetiapine), and Geodon (ziprasidone).

There are several theories about why the atypical antipsychotics are less likely than the typical neuroleptics to cause extrapyramidal side effects. The potency of the atypicals, which block both dopamine D2 and serotonin 5-HT_{2A} receptors, might be responsible. It has been suggested that reduced serotonergic function in the brain, which can be achieved by blocking the 5-HT_{2A} receptor, reduces extrapyramidal side effects (Richelson 1999). Others have theorized that the unique action of the atypical antipsychotics derives from their low affinity for the dopamine D2 receptor. These drugs, compared to dopamine itself, are loosely bound to, and rapidly released from, the dopamine D2 receptors, whereas the typical antipsychotics bind to the D2 receptors with greater affinity than dopamine (Seeman 2002).

Another new horizon in the treatment of schizophrenia is the future potential to tailor medication to patients' genetic profiles. The new and rapidly developing fields of pharmacogenomics and pharmacogenetics are seeking to uncover the genetic basis of differences in medication response and toxicity. The goal is to be able to individualize therapy based on a patient's genetic makeup (Basile et al. 2002). The field of pharmacogenomics looks at the determinants of drug response at the level of the entire human genome using DNA microarray (DNA chip) analysis, which allows researchers to examine changes in the expression of genes that result from medication (Kawanishi et al. 2000). Pharmacogenetic investigations study DNA sequence variations in candidate genes, which might affect drug response or toxicity (i.e., drug metabolism pathways, receptor gene variants). It is not yet clear whether phenotyping or genotyping will be able to predict an optimal dosage range for a given patient. However, as the technology advances and knowledge is gained, we will continue to move closer to the development of clinically meaningful tests that will be useful for determining the optimal drug, and perhaps also an optimal dosage range for each patient (Basile et al. 2002).

Psychosocial Treatments

When used in conjunction with medication, a variety of psychological therapies have improved prognosis and reduced rates of relapse in schizophrenia. For example, a large body of literature supports the use of family therapy, which includes

psychoeducational and behavioral components, in the treatment of schizophrenia (Bustillo et al. 2001). Family therapy has been shown to reduce caregiver burden and improve family members' coping and knowledge about schizophrenia, thus reducing the risk of relapse.

Among the therapies that focus directly on the patient, social skills training seeks to improve functioning by teaching the skills necessary to enhance performance in interpersonal interactions, involvement in leisure activities, and employment. Overall, social skills training has been shown to improve social competence in the laboratory and in the clinic. However, it remains unclear to what extent, if any, this translates into better functioning within the community (Bustillo et al. 2001, Penn & Mueser 1996).

Cognitive behavior therapy (CBT) for schizophrenia draws on the tenets of cognitive therapy (Beck 1976). CBT is used to help psychotic patients deal directly with their symptoms. Specific psychotic symptoms such as hallucinations and delusions are identified for intervention by the patient and therapist (Dickerson 2000). The few published randomized controlled trials of CBT with schizophrenia patients indicate that it is effective in reducing hallucinations and delusions in medication-resistant patients, and as a complement to pharmacotherapy in acute psychosis (Bustillo et al. 2001).

The vulnerability-stress model suggests that specific training in stress management techniques might benefit patients with schizophrenia. A recently published study comparing the outcome of patients randomly assigned to either stress management or a social activities group revealed that the subjects who participated in the stress management program had fewer hospital admissions in the year following treatment (Norman et al. 2002). This effect was most apparent for those who showed a high level of attendance. Thus, stress management training may provide patients with the skills to cope more effectively with acute stressors and reduce the likelihood of symptom exacerbation necessitating hospital admission.

Occupational functioning has been another focus of treatment. The rate of competitive employment for the severely mentally ill has been estimated at less than 20% (Lehman 1995). Vocational rehabilitation programs have a positive influence on work-related activities, but have not been shown to have a substantial impact on patients' abilities to obtain employment independently in the community (Lehman 1995). There is some evidence to suggest that "supported employment programs" produce better results than traditional vocational rehabilitation programs; however, job retention remains a significant problem (Lehman et al. 2002). Also, there is little evidence to support the contention that the employment obtained produces improved self-esteem or quality of life (Bustillo et al. 2001).

Finally, a multifaceted approach to treatment is assertive community treatment (ACT), which was originally developed in the 1970s by researchers in Madison, Wisconsin (Bustillo et al. 2001). This is a comprehensive treatment approach for the seriously mentally ill living in the community. Patients are assigned to a multidisciplinary team (nurse, case manager, general physician, and psychiatrist) that delivers all services to the patient when and where he or she needs them. Services

include home delivery of medication, monitoring of physical and mental health status, *in vivo* social skills training, and frequent contact with family members. The ACT model has been shown to reduce time spent in the hospital, to improve housing stability, and to increase patient and family satisfaction. However, studies have failed to show improvement in social functioning, employment, or other measures of quality of life.

In summary, as mentioned above, evidence that longer duration of untreated psychotic episodes is related with the poorer prognosis has led to more aggressive efforts to provide treatment as soon as possible after the clinical onset. Some even advocate treatment of individuals in the prodromal phase of schizophrenia. Because the atypical antipsychotics have fewer side effects, many believe it is now more reasonable to consider preventive medication for individuals in the prodromal phase. However, researchers have not established reliable criteria for identifying the prodrome, and investigators have raised questions about the long-term consequences of preventive pharmacological and/or psychosocial interventions (Cornblatt et al. 2002). Because treatment with antipsychotic medication, even the atypical antipsychotics, is sometimes associated with serious side effects, there is reason to be cautious about preventive medication until we are able to identify at-risk individuals with greater accuracy (Marder et al. 2002).

SUMMARY AND CONCLUSIONS

In this article we have offered an overview of research findings on the nature and origins of schizophrenia. Progress has been slow, and there is no doubt that investigators have traversed countless blind alleys. Inappropriate paradigms and conceptualizations have been part of the problem. The notion that schizophrenia is a single disease with discrete phenomenological boundaries and a specific cause no longer seems plausible. Rather, the contemporary view assumes that we have not yet clearly defined the boundaries of the disorder, and that the etiologies are diverse, with multiple genetic and environmental contributors. Although this may not strike some as progress, the contemporary view actually reflects the more sophisticated psychobiological perspective that now characterizes scientific thinking about a range of mental and physical illnesses, from depression to cancer.

The picture that has emerged from research on schizophrenia, as well as other psychotic disorders, is best described in an expansion of the diathesis-stress model that has dominated the field for several decades.

Figure 1 illustrates a contemporary version of the diathesis-stress model that encompasses all of the factors that are currently considered to play a significant etiologic role in schizophrenia. This model postulates that constitutional vulnerability to schizophrenia (i.e., the diathesis) can result from both inherited and acquired constitutional factors. The inherited factors are genetically determined characteristics of the brain that influence its structure and function. Acquired vulnerabilities can arise from prenatal events that alter fetal neurodevelopment and

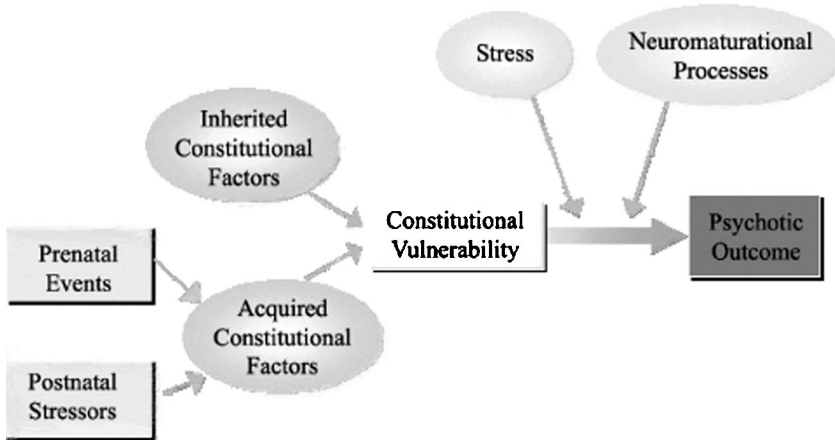


Figure 1 A diathesis-stress model of the etiology of schizophrenia.

postnatal stressors, broadly defined to include brain trauma. Both are assumed to compromise brain structure and function.

Whether the constitutional vulnerability is a consequence of genetic factors, or environmental factors, or a combination of both, the model assumes that vulnerability is, in most cases, congenital. But the assumption that vulnerability is present at birth does not imply that it will be clinically expressed as psychosis at any point in the life span. Rather, we assume that two sets of factors determine the postnatal course of the vulnerable individual.

Adolescent neuromaturation is assumed to be one key element. It is well established that adolescence/early adulthood is a critical period for the expression of the vulnerability for schizophrenia. Rapidly accumulating data indicate that brain changes occur in adolescence and extend into early adulthood (Walker 2002). Thus some aspect(s) of brain maturational processes during the postpubertal period are likely playing an important role in triggering the clinical expression of latent liabilities. It is plausible that the genetic liability for schizophrenia involves an abnormality in genes that govern this maturational process. Alternatively, a latent abnormality in the brain circuitry that matures during this period may be gradually behaviorally expressed during the course of adolescence, culminating in the clinical onset of schizophrenia.

Further, external stress is assumed to influence the expression of the vulnerability. This is a long-standing assumption among theorists, although it is important to qualify this notion. Empirical research has provided evidence that episodes of schizophrenia tend to follow periods of increased life stress (Walker & Diforio 1997). Nonetheless, there is no reliable evidence that schizophrenia patients experience more psychosocial stress during the premorbid period than normals, but rather that they are more sensitive to stress when it occurs. At the biological level, enhanced sensitivity to stress may result from the disruptive effects

of stress hormone release on the function of abnormal brain circuitry. This is the essence of the model—it is the interaction between vulnerability and stress that is critical.

In summary, although we have not identified all the pieces of the puzzle, we have made significant progress in moving toward a comprehensive account of the etiology of schizophrenia. In the coming years, we can expect research to yield important information about the precise nature of the brain vulnerabilities associated with schizophrenia, and the mechanisms involved in the interaction of congenital vulnerability with subsequent life stress and neuromaturation.

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