Infection and Autoimmunity as Etiologic Factors in Schizophrenia: A Review and Reappraisal

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Abstract

The focus of schizophrenia research has been turning from studies of structural and functional brain abnormalities to an increasing emphasis on possible etiologic factors. One etiologic hypothesis is that schizophrenia is the result of an infection (especially by a virus) or of an autoimmune reaction (perhaps following an infection) against central nervous system (CNS) tissue. Indirect evidence supporting this hypothesis includes possible geographic variance in the prevalence of schizophrenia, a season-of-birth effect, and observed associations between schizophrenia and prenatal exposure to viral epidemics. Several studies of cell-based and humoral immunity, as well as studies of cytokines, have indicated abnormalities in the immune function of schizophrenia patients, but many of these findings have not been replicated consistently. In addition, most observed alterations in immune function have been modest in degree and nonspecific. Attempts to identify a specific infectious agent or an antibody directed against CNS tissue have not produced a consistently replicable finding. In summary, no research evidence to date irrefutably indicates an infectious or autoimmune etiologic process in schizophrenia. It is probably unreasonable, however, to view schizophrenia as having a single cause. It is much more likely to be a heterogeneous disorder resulting from interactions between multiple factors, including the person's genetic endowment and various environmental influences. Infectious agents or CNS autoantibodies may well be among these environmental variables. A major current emphasis is on studying potential interactions between exposure to an infection or an autoimmune response and key early phases of brain development. A corresponding priority in the research agenda will be the development of animal models of CNS development that might elucidate the pathogenic mechanisms of such an interaction.

A major accomplishment of recent schizophrenia research has been to affirm the neurobiological basis of the disorder, largely by demonstrating multiple structural and functional abnormalities in the central nervous system (CNS) of schizophrenia patients (Kirch and Weinberger 1986; Gur and Pearlson 1993, this issue). Although these studies have confirmed that schizophrenia is a brain-based disorder, they have done much less, unfortunately, to reveal the etiology, or etiologies, of the schizophrenic syndrome. In terms of causative factors, there is general agreement that genetic predisposition plays a significant etiologic role in schizophrenia (Gottesman 1991; Kendler and Diehl 1993, this issue). It is equally obvious, however, that genes are only part of the explanation. The concordance rate for schizophrenia in monozygotic twins approaches 50 percent, and this evidence supports a genetic basis for schizophrenia. But some explanation is required for the equally important fact that half

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the monozygotic twins who have a genetically identical twin with schizophrenia do not develop the disorder. In fact, the majority of cases of schizophrenia are "sporadic," having no known history of the core diagnosis in first- or second-degree relatives.

Historically, several idiopathic disorders have ultimately been shown to be the result of infection. This includes disorders that share some clinical features with schizophrenia. One old and one very recent example illustrate this point. Tertiary neurosyphilis, or dementia paralytica, often presented with forms of psychosis resembling what we now call schizophrenia. The identification of the syphilis spirochete as the causative organism allowed these forms of "insanity" to be diagnostically separated out from other psychotic disorders. Much more recently, it has become apparent that infection with the human immunodeficiency virus (HIV) can (albeit rarely) present initially with CNS disturbances, including symptoms of psychosis (Jones et al. 1987; Elder and Sever 1988; Perry 1990). Although this retrovirus was proved to be the cause of the acquired immunodeficiency syndrome (AIDS), the precise pathogenic mechanisms by which some patients with HIV infection develop dementia, or more rarely psychosis, remain to be elucidated.

There has been longstanding interest in infection and the immune response as possible causative factors in schizophrenia. Without specifying a microbial cause, Esquirol in 1845 described the appearance of psychotic disorders in some cases as "epidemic." The eminent American psychiatrist, Karl Menninger (1919, 1926, 1928), observed the appearance of schizophrenia-like psychoses in victims of the vast influenza pandemics after World War I. In the 1930s, Lehmann-Facius (1937) produced data that suggested an immune reaction against brain tissue in schizophrenia patients. Shortly afterward, Molholm (1942) noted hyposensitivity to foreign proteins in schizophrenia patients. Thus, the idea that schizophrenia may involve infection or an abnormal immune response in the CNS is by no means new (for reviews see: Torrey and Peterson 1976; van Kammen and Sternberg 1980; Roos 1984; DeLisi et al. 1985; Knight 1985; DeLisi and Crow 1986; Torrey and Kaufmann 1986; DeLisi 1987; Kaufmann and Ziegler 1988; Pert et al. 1988; Torrey 1988; Waltrip et al. 1990; Rapaport and McAllister 1991; Kirch and Alexander 1992; Stevens and Hallick 1992; Ganguli et al., in press). New technical advances in virology and immunology, however, have dramatically enhanced our ability to test this hypothesis. Findings about markers of general immune activation, as well as studies of specific infectious agents and tissue-specific antibodies in schizophrenia patients, are reviewed below. This review is followed by a critical reappraisal of the infectious-autoimmune hypothesis of schizophrenia and suggestions for future research directions.

Variations of the Infectious-Autoimmune Hypothesis

In its simplest form, the hypothesis to be considered is that schizophrenia, in at least some cases, is the result of an infection of the CNS (most probably by a virus) or the result of activity against CNS tissue by autoantibodies (perhaps stimulated by a prior infection). Researchers working in this area have put forward several variations on this basic theme. Although not exhaustive, the following list summarizes some of the more specific hypotheses.

1. Schizophrenia may be the direct result of active infection by a pathogenic agent. This hypothesis assumes that the infectious agent is actively disrupting cellular and molecular function in the brain in a manner that directly causes the schizophrenic syndromes. The main focus of this hypothesis has been on viruses, as there are no data to support the involvement of more readily identified bacterial infections in schizophrenia. The concept of a viral infection is especially attractive because of the known neurotropism of some viruses, especially the deoxyribonucleic acid (DNA) viruses in the herpes virus family. Similarly, "unconventional" or "slow" viruses, such as the agents identified as the causes of kuru and Creutzfeldt-Jakob disease, have been shown to cause neurodegenerative syndromes. Finally, as noted above, studies showing that the newly identified human retroviruses also have CNS effects raise the possibility that a retrovirus is a causative agent in schizophrenia.

2. Rather than directly causing overt cytopathic effects, viral proteins may interfere with CNS function in a more subtle way. Pert and colleagues (1988) advanced the hypothesis that viral proteins may mimic endogenous CNS transmitters or block receptors in a manner that disrupts brain function and causes the schizophrenic syndrome.

3. Another variation of the viral infection hypothesis is that the causative agent is a latent virus that is periodically reactivated. A

scenario presented by Waltrip and associates (1990) proposed that stimulation of alpha-interferon by several different viruses, which may be latent in the brain and then reactivated, causes the CNS pathology in schizophrenia.

4. The ability of retroviral genomic material to become integrated into host-cell DNA led Crow (1984) to propose retroviral sequences as the causative agent in schizophrenia. His version of this hypothesis contended that these integrated retroviral sequences may interfere with normal CNS function—for example, the development of cerebral dominance—in a manner that results in schizophrenia.

5. Another variation emphasizes the immune response, rather than an initial infection (DeLisi et al. 1985). Autoimmunity, which may be the pathogenic result of the immune response to an earlier infection, may occur against CNS tissue. Systemic lupus erythematosus is one example of a disorder in which CNS autoantibodies may be associated with psychotic symptoms. Knight (1982, 1985) has been a major proponent of the theory that very low (i.e., difficult to detect) levels of autoantibodies, as observed in autoimmune thyroiditis and myasthenia gravis, may interact with endogenous receptors to disrupt normal CNS function.

Further refinement of these multiple variations on the infectious-autoimmune hypothesis is possible (Kaufmann and Ziegler 1988). Not only may several different pathogenic agents or tissue-specific autoantibodies be involved, but the regional specificity of their action in the brain may be important. One of the major thrusts of neuropathological and brain-imaging studies in schizophrenia has been to anatomically localize the CNS pathology of the disease. To the degree that structures such as the prefrontal cortex and the temporal lobes are highlighted by these studies, the specific CNS site of action of a virus or autoantibody may be crucial in an infectious-autoimmune model of schizophrenia. Similarly, the recent emphasis on "neurodevelopmental" models of schizophrenia (Murray and Lewis 1987; Weinberger 1987) may mean that the timing of an infectious or autoimmune insult is the crucial factor. As will be discussed, several lines of evidence indicate that prenatal insults may be especially disruptive to early CNS development and thus may be linked to the development of schizophrenia much later in life. Obviously, the infectious-autoimmune hypothesis of schizophrenia is far from a unitary concept. These variations should stimulate the development of more specific hypotheses and the research paradigms to test them.

Evidence From the Disorder

It is fair to ask which clinical features of schizophrenia are consistent with the involvement of infection or autoimmunity in the disease. At the outset, it is important to note that these clinical features in no way directly prove an infectious or immune cause. Nevertheless, they are clues that have stimulated a number of investigations.

It has already been noted that some psychotic syndromes with symptoms similar to schizophrenia have a known infectious etiology. Besides tertiary neurosyphilis and the psychosis that may occur with HIV infection, herpes simplex virus type 1 (HSV-1) is often cited as a known viral cause of psychosis resembling schizophrenia. Similarly, the postinfluenzal psychoses observed by Menninger (1919, 1926, 1928) are another model for viral induction of a schizophrenia-like syndrome.

Recently, some investigators have noted similarities in epidemiology and clinical course between schizophrenia and multiple sclerosis (Stevens 1988; Stevens and Hallick 1992), a disorder commonly thought to involve an infectious or autoimmune process. These investigators have highlighted possible common trends in geographic distribution (including an apparent north-south gradient) and similarities in age-of-onset and relapsing course between schizophrenia and multiple sclerosis. It should be noted that, although the possibility of an infectious-autoimmune cause is much more widely accepted for multiple sclerosis than for schizophrenia, there has been no direct proof of a viral agent or autoantibody as causative in multiple sclerosis.

It has been noted that schizophrenia patients show an increased prevalence of minor physical anomalies and dermatoglyphic changes (Green et al. 1989; Bracha et al. 1991). A recent study in monozygotic twins discordant for schizophrenia showed the twin affected with schizophrenia to be significantly more likely to display hand ectoderm dysmorphological signs than the unaffected twin (Bracha et al. 1991). Although several factors may contribute to these physical anomalies or dermatoglyphic changes, it is known that prenatal infection may be one causative factor.

Although neuropathological study of the brain in schizophrenia has revealed no pathognomonic lesion in the brain tissue of schizophrenia patients, a number of neuropathological findings have been reported (Kirch and Weinberger 1986). They include disruptions in cell morphology, number, and orientation, as well as rare reports of limited gliosis. Although the finding of gliosis has not been convincingly replicated, it is important because it may be a residual marker of an earlier inflammatory insult. In all fairness, it should be emphasized that there is no neuropathological evidence of an acute inflammatory process in the brain tissue of patients with schizophrenia, but it is equally important to note that, in general, these neuropathological studies are conducted on tissue from older patients who have been in the chronic stage of the illness for many years.

Thus, although these clinical features of schizophrenia are by no means specific for an infectious-autoimmune cause, they have stimulated investigators to search for more specific support for the hypothesis.

Evidence From Epidemiology

It is reasonable to assume that if infection is an environmental factor causing schizophrenia, this should be reflected in the epidemiology of the disorder. Several epidemiologic features have been examined that may support, albeit indirectly, a role for infection.

Geographic and Other Variations. Schizophrenia is typically cited as having a consistent geographic distribution throughout the world, with a prevalence ranging up to 1 percent (Eaton 1985, 1991; Torrey 1987). The variance between regions is often attributed to differences in the diagnostic criteria used or to socioeconomic factors affecting the distribution and recognition of patients with the disorder. Nevertheless, others have proposed that this geographic variation may represent a true underlying difference in prevalence (Torrey 1987). In a recent review of epidemiologic prevalence studies, Stevens and Hallick (1992) noted a tenfold to twentyfold variation in published prevalence data from around the world, raising the possibility that differences in prevalence may, in fact, reflect differences in immunity or exposure to a pathogenic agent. Similarly, a recent study of differences in schizophrenia rates between urban and rural areas noted a higher prevalence of schizophrenia among men raised in urban areas that appears to be independent of any socioeconomic drift of patients from rural to urban areas (Lewis et al. 1992). One possible explanation for such a distribution, if it does exist, is greater exposure to a pathogenic infectious agent in urban settings. An attempt to test the contagion hypothesis by studying age at onset for siblings, however, did not show conclusive evidence for horizontal transmission (Crow and Done 1986). It should be emphasized that although these lines of speculation are intriguing, the interpretation of putative epidemiologic findings must consider important methodological issues that might explain differences between studies (Eaton 1985).

Other epidemiologic variation in schizophrenia that might be relevant to an infectious-autoimmune hypothesis has been observed. For example, the known gender differences between male and female schizophrenia patients, with males having a significantly younger age-of-onset and more severe course, must be taken into account. It is possible, although by no means proven, that this may somehow reflect underlying differences between males and females in exposure to infection or in immune competence. Similarly, the intriguing observation exists that rheumatoid arthritis, an autoimmune disorder, is significantly less common in schizophrenia patients (Eaton et al. 1992). This finding has been replicated in several studies and cannot be attributed to neuroleptic exposure. Although this also raises the question of differences in immune competence in schizophrenia patients, it is equally important to consider that other factors may be involved in this negative association with rheumatoid arthritis, including genetic vulnerability and environmental variables.

Season of Birth. A much-discussed, and admittedly controversial, finding in schizophrenia research has been the observation of a significant seasonal effect, with more persons who later develop schizophrenia born in the late winter and early spring months (Torrey et al. 1977; Hare 1983; Bradbury and Miller 1985; Lewis 1989). This reported excess is modest, generally less than 10 percent, but has been replicated in several recent studies. Other studies have failed to find the increase. In addition, methodological issues have been proposed that could contribute to the artifactual finding of a seasonal excess of births. These have been reviewed in detail elsewhere (Bradbury and Miller 1985;

Lewis 1989), and the issue must be clarified by further study.

Studies of Epidemics. Perhaps the most compelling epidemiologic evidence implicating infection in the development of schizophrenia comes from recent research on the association between prenatal exposure to epidemics and later development of schizophrenia. Mednick and colleagues (1988) undertook an ambitious followup study of persons exposed in utero to the influenza epidemic that swept Helsinki, Finland, in 1957. Using the extensive clinical records available for this population, they were able to identify the relative risk of developing schizophrenia for persons exposed during different trimesters in utero. Their initial finding, which appeared even stronger in an extension of the study (Mednick et al. 1990), noted significantly more subsequent schizophrenia among those exposed to the epidemic during the second trimester of pregnancy than among those exposed during the first or third trimester. Because the second trimester is a crucial period of CNS development marked by extensive cortical neuronal migration, they proposed that the disruption of this phase of brain development leads to a predisposition for schizophrenia. Some investigators have reported similar findings (Kendell and Kemp 1989; O'Callaghan et al. 1991), but others (Torrey et al. 1988; Bowler and Torrey 1990; Crow et al. 1991) have failed to find a second-trimester effect after prenatal exposure to epidemics.

Although the association between schizophrenia and prenatal exposure to viral epidemics is intriguing, several points bear consideration. The positive studies simply indicate that second-trimester influenza exposure may be a cause of excess births of future schizophrenia patients. The studies in no way assert that influenza is the sole cause of schizophrenia. Moreover, it is possible that factors not directly related to the virus, such as fever, dehydration, or analgesic use, may be relevant to the finding. Another point is that, although the second trimester may be especially crucial for brain development, insults at other times may similarly predispose toward schizophrenia. Susser and Lin (1992) have recently reported the interesting finding of a gender-specific increase of schizophrenia among women exposed in utero during the first trimester to famine in Europe during World War II. Therefore, prenatal exposure to influenza may be simply one of many environmental factors contributing to later development of schizophrenia.

Markers of Immune Activation

If a past or current infection or autoimmune reaction is a pathogenic element in schizophrenia, some evidence of immune activation could be expected in schizophrenia patients. The following is a brief review of studies in schizophrenia patients of the three major aspects of the immune response: cellular components, antibodies, and the mediation of immunity by cytokines.

Cellular Components of Immunity. As early as 1903, Bruce and Peebles (1903, 1904) published observations on white blood cell counts in schizophrenia patients. Their finding of increased leukocyte counts, especially during the acute phase of the illness, represents one of the first immunopathological studies of schizophrenia. Obviously, total white blood cell count is a crude measure that may be affected by factors such as stress and dehydration. Nevertheless, these studies paved the way for later, more sophisticated studies of cellular immunity. These included reports of morphologically atypical lymphocytes in blood samples from schizophrenia patients (Fessel and Hirata-Hibi 1963; Hirata-Hibi et al. 1982). However, early research on the effects of neuroleptics on lymphocyte populations (Fieve et al. 1966) raised the possibility that these abnormalities were artifactual. Other cellular immune abnormalities in schizophrenia patients were reported, including deficient activity in natural killer cells (DeLisi et al. 1983; Schindler et al. 1986), reduced cell-mediated immunity as measured by neopterin excretion in acutely ill patients (Sperner-Unterweger et al. 1992), decreased percentages of T lymphocytes (Coffey et al. 1983), and increased percentages of B lymphocytes (DeLisi et al. 1982). Lymphocytes were also studied to determine the ratio of helper to suppressor cells (Nyland et al. 1980; DeLisi et al. 1982), and abnormal ratios were observed in schizophrenia patients. Thus, using varied techniques, abnormalities in both number and function of circulating lymphocytes have been observed in schizophrenia.

The study of cell-based immunity has been advanced by using monoclonal antibodies to label more specific subsets of lymphocytes. The most striking finding by this technique is that the percentage of Differentiation Cluster

(CD)5-positive B cells, a lymphocyte subset thought to be involved in autoimmunity, appears to be elevated in patients with schizophrenia (McAllister et al. 1989*b*). The elevated CD5-positive percentage appears to be maintained both on and off neuroleptic treatment (McAllister et al. 1989*a*), although we have recent data (unpublished) that indicate this finding may be strongly influenced by exposure to drugs of abuse and may not be diagnostically specific to schizophrenia.

Antibodies. Before knowledge about and assays for specific antibodies were developed, studies of total proteins in the cerebrospinal fluid (CSF) demonstrated increased levels in CNS infections. An early study by Bruetsch and colleagues (1942) in a large cohort of schizophrenia subjects showed the patients, as a group, to have increased CSF total proteins. Although nonspecific, these elevations could have been consistent with increased CNS immunoglobulin production. Later methodological advances allowing the measurement of immunoglobulin subclasses as well as titers of antibodies to specific infectious agents made it possible to do more focused studies of antibodies in both blood and CSF of schizophrenia patients. Multiple studies have examined both immunoglobulin concentrations and specific antibody titers. Immunoglobulin M (IgM) may be an index of acute infection; immunoglobulin G (IgG) titers are more persistently elevated after infection. Whether they measure overall immunoglobulins or specific levels of IgM and IgG in blood, some investigators have reported increases that might be consistent with infection or autoimmunity, while others have noted normal levels or even decreased concentrations (Fessel 1962; Pearson 1973; Bock and Rafaelson 1974; Bock 1978; DeLisi et al. 1981).

Early findings from immunoglobulin studies in the CSF of schizophrenia patients were equally varied (Dencker and Malm 1968; Bock and Rafaelson 1974; Bock 1978; DeLisi et al. 1981). One potential problem was the failure of the studies to rigorously correct for possible differences in blood-CSF permeability in schizophrenia patients. Because the concentrations of proteins are much higher in blood than in CSF, increased permeability could artifactually elevate CSF levels of immunoglobulins. In fact, several studies using quantitative indices have shown increased blood-CSF permeability in schizophrenia subjects (Axelsson et al. 1982; Kirch et al. 1985, 1992*a*; Bauer and Kornhuber 1987). Using indices that correct for an altered blood-CSF barrier, however, there are signs that some patients may also have increased endogenous CNS IgG production (Kirch et al. 1985, 1992*a*), although this was not seen in at least one other study (Roos et al. 1985). In addition, despite some reports of oligoclonal IgG bands in the CSF of schizophrenia patients (Ahokas et al. 1985), this finding also has not been consistently replicated (Stevens et al. 1990).

The ambiguity in the data on immunoglobulin levels led many studies to focus on antibody titers to specific infectious agents, with particular emphasis on cytomegalovirus (CMV), HSV-1, and Epstein-Barr virus (EBV), members of the herpes virus family known for their neurotropism and their ability to achieve a latent state with periodic reactivation. Again, some investigators found increases in antibodies to CMV (especially in the CSF), but others did not replicate the finding (Albrecht et al. 1980; Gotlieb-Stematsky et al. 1981; Torrey et al. 1982, 1983; Kaufmann et al. 1983; van Kammen et al. 1984; King et al. 1985; Shrikhande et al. 1985; DeLisi et al. 1986; Rimon et al. 1986). Similarly mixed results have been obtained for antibodies to HSV-1, and investigators have also examined specific antiviral antibody titers for measles, mumps, vaccinia, and other viruses known to have CNS effects, with no consistently replicable increases among schizophrenia patients (Gotlieb-Stematsky et al. 1981; Libıkova 1983; DeLisi et al. 1986; Ahokas et al. 1987; Bartova et al. 1987; Rajcani et al. 1987). A problem in interpreting these analyses of antibody titers is that they deal with relatively common viruses for which seropositivity is the rule, rather than the exception, among adults.

Another form of antibody response relevant to the infectious-autoimmune hypothesis of schizophrenia is the possibility that schizophrenia patients have developed autoantibodies against CNS tissue. This hypothesis was supported by very early studies showing that serum proteins from schizophrenia patients bound to brain tissue (Lehmann-Facius 1937). It was popularized by the work of Heath in the 1960s reporting a component (taraxein) in serum from schizophrenia patients, a protein that appeared to bind to brain tissue (Heath and Krupp 1967). Heath and colleagues (1989) continued this work, recently reporting the identification of an IgG antibody in schizophrenia patients that binds to the septal region of the brain. Another group of inves-

tigators has produced a series of studies (Ganguli et al., in press) that identify multiple autoantibodies—including increased antinuclear antibody, anticardiolipin antibody, and antibodies to hippocampal antigens—in some schizophrenia patients. Other groups have also presented data indicating possible CNS autoimmunity in schizophrenia subjects, but the findings are by no means conclusive (Kuritzky et al. 1976; Baron et al. 1977; Pandey et al. 1981; Rimon et al. 1983; DeLisi et al. 1985; Kirchbach et al. 1987; Pelonero et al. 1990). A significant consideration in these studies is the possibility that schizophrenia patients have a type of CNS degenerative pathology that stimulates autoantibody formation as a secondary result of, rather than primary cause of, their disorder.

Cytokines. Several circulating factors have been identified that mediate immune response. Prominent among these are the interferons and the interleukins. These cytokines have multiple roles, including induction of an antiviral state, and abnormalities in cytokine concentrations may reflect the presence of an infectious or immune process.

Several studies of interferon in schizophrenia patients have reported no change in interferon concentrations or a decrease in interferon production by cultured lymphocytes (Rimon et al. 1983, 1985; Moises et al. 1985, 1986; Roy et al. 1985; Schindler et al. 1986; Ahokas et al. 1987; Rimon and Ahokas 1987). There is one report of increased serum interferon concentrations in a subgroup of schizophrenia patients who appeared to have more prominent psychotic symptoms (Preble and Torrey 1985). The findings on interleukins seem to have more consistently demonstrated abnormalities. There have been reports of decreased interleukin-2 production (Villemain et al. 1989), and two groups have cited increased levels of soluble interleukin-2 receptors (Ganguli and Rabin 1989; Rapaport et al. 1989). More recently, an increase in serum interleukin-6 has been noted in some schizophrenia patients (Ganguli et al., in press).

There is no shortage of reported abnormalities of cellular immunity, antibodies, or cytokines in schizophrenia patients. The problem is the lack of consistent replicability of the findings, as well as the relatively modest degree of the abnormalities observed. For example, the level of interferon elevation reported by Preble and Torrey (1985) is well below that seen in acute infectious states. Thus, any critical appraisal of these immunologic findings must acknowledge that they in no way appear to extend to all patients and that they also do not seem to reflect a fully active infection or autoimmune response. In addition, most studies in the literature involved patients with considerable neuroleptic exposure. An important element of future research on immune function in schizophrenia will be distinguishing drug effects from a primary underlying immunologic abnormality.

The Search for an Infectious Agent

As noted in the description of studies searching for virus-specific antibodies, there are "usual suspects" that have received the most attention in studies of the viral hypothesis of schizophrenia. The neurotropic viruses, especially the DNA viruses of the herpes virus family, as well as other agents known to have the ability to cause persistent CNS infection, such as measles virus, have been studied most extensively. Another general class of viruses receiving much recent attention is the retroviruses. The apparent neurotropism of HIV and its ability to produce neuropsychiatric syndromes strongly support interest in this class of viruses. Other characteristics of retroviruses that make their study especially attractive in relation to schizophrenia are their ability to become incorporated into the germ cell line and be vertically transmitted, as well as their ability to remain latent and then be reactivated years later. The study of the dementias brought attention to the so-called unconventional or slow viruses, such as the agents responsible for kuru and Creutzfeldt-Jakob disease. There may be heretofore undiscovered, unconventional agents associated with other disorders, including schizophrenia. Regardless of the specific pathogenic suspect, however, several different methodological approaches may be used to identify a causative infectious agent in schizophrenia. These approaches are outlined below.

Transmission. If an infectious agent has entered the brain and is responsible for causing schizophrenia, it may be possible to transmit the disease by inoculating research animals with brain tissue or CSF from schizophrenia patients. This approach was used successfully in proving the transmissibility of the spongiform encephalopathies caused by unconventional viruses. Several transmission experiments have

been conducted in schizophrenia. These involve not only the inoculation of animals, but also in vitro inoculation of tissue cultures. Despite some early, encouraging data on the cytopathic effects on cultured cells of CSF from schizophrenia patients (Tyrrell et al. 1979) and on the behavioral effects of CNS injection of patient CSF into marmosets (Baker et al. 1983), no definitive neuropathological changes were subsequently identified in the brains of the inoculated animals. Kaufmann and colleagues (1988) could not demonstrate neuropathological effects after inoculating several different species with brain tissue from schizophrenia patients. Rajcani and associates (1987) reported seeing structures resembling a herpes virus in brains of animals inoculated with CSF and with brain tissue from schizophrenia patients. More recently, Stevens and colleagues inoculated neuronal cell cultures with CSF and brain tissue from schizophrenia patients. They sequentially passaged these cell lines and observed a transmissible effect—growth of cells to increased density—which they were able to passage by cell-free media (Schwartz and Stevens 1988; Stevens and Hallick 1992). Work to confirm and extend this finding is in progress (J.R. Stevens, personal communication).

It should be noted that a key assumption in transmission experiments is that the infectious agent remains present in brain tissue or CSF in a form competent for transmission. In essence, they assume persistent active or latent infection. Obviously, the experiments would be negative if the causative process in schizophrenia is an earlier infection with no residual infectious particles.

Antigen Hybridization. If viral proteins are present in the brain tissue of schizophrenia patients, it may be possible to identify these antigenic proteins (even in the absence of fully competent viral particles) using antibody-antigen binding techniques. Antibody specificity is a crucial methodological issue in these studies. Such techniques have been used to search for CMV and other herpes virus antigens in the brain tissue of schizophrenia patients with essentially negative results (Stevens et al. 1983, 1984). Once again, the underlying assumption of such studies is the persistence of some antigenic viral proteins. Their absence does not rule out an etiologic role for an earlier infection that left no residual viral antigen.

Seeking Genomic Material. An alternative to looking for viral proteins in the brain is to look for either ribonucleic acid (RNA) or DNA (depending upon the agent) from the viral genome itself. Two approaches have been used. One has involved nucleic acid hybridization techniques in which a nucleic acid probe complementary to the target viral nucleic acid sequence is tagged and used in an attempt to label genomic viral nucleic acids in brain tissue in situ or in nucleic acids extracted from this tissue. This hybridization approach has been marked by rare positive findings, although the technique is very susceptible to artifactual nonspecific binding (Aulakh et al. 1981; Taylor et al. 1985; Carter et al. 1987; Moises et al. 1988).

A more sensitive and specific method for identifying viral genomic material in the CNS uses the recently developed polymerase chain reaction (PCR) (Saiki et al. 1988). In this method, oligonucleotide primers complementary to viral nucleic acid sequences will generate multiple copies of the target viral sequences if they are present in the tissue being studied. The technique has been modified to amplify either DNA or RNA. We have used a PCR method to search for cytomegalovirus DNA (Alexander et al. 1992*b*) and both HSV-1 and varicella-zoster DNA (Alexander et al. 1992*a*) in brain tissue from schizophrenia patients. Neither study revealed persistent viral DNA in the brain. Torrey and colleagues (E.F. Torrey, personal communication) have conducted preliminary studies using PCR amplification of patient RNA that indicate possible infection in some schizophrenia patients by a pestivirus. The power of the PCR technique is its extreme sensitivity: it may detect the target viral nucleic acids even if they are present in only one of several thousand cells. The technique may be used not only for specific viruses such as those described above, but also, depending on the specificity of primers used, for a group of viruses that share nucleic acid homology.

The Retroviral Challenge. The discovery of human retroviruses, including HIV, has caused considerable refinement in our notions of viral pathogenesis. Of particular interest is the ability of retroviruses to become incorporated into the host cell genome and be vertically transmitted as a genomic element. After their discovery, human retroviruses quickly became suspects as etiologic agents in schizophrenia (Crow 1984).

Initial studies searched either for antibodies to retroviruses or for retroviral antigens in schizophrenia

patients, with negative results (DeLisi and Sarin 1985; Robert-Guroff et al. 1985). In a more recent series of experiments (Feenstra et al. 1988, 1989; Coggiano et al. 1991), we used a series of techniques to look for reverse transcriptase, the key enzyme associated with retrovirus replication. Using varied stimulation paradigms on lymphocyte cultures from schizophrenia patients, no evidence of reverse transcriptase activity was observed. It is important to note, however, that although this is evidence against the presence of an active, replicating retrovirus in chronic schizophrenia patients, it does not rule out the presence of a fully incorporated, nonreplicating retroviral genome. In fact, it has become clear that numerous retroviral sequences may have been incorporated into the human genome long ago and that these sequences may now function as endogenous genomic elements. It is conceivable that incorporated retroviral sequences relevant to schizophrenia do exist and that their activity consists of either their own expression or their regulatory effects on other genes.

Treatment. Obviously, antiviral therapies are limited. Given the possibility of an active viral infection in schizophrenia, however, the rationale does exist for therapeutic trials of antiviral drugs. Once again, however, an underlying assumption is the presence of an active, replicating virus. In such a trial, DeLisi and colleagues (1987) observed no benefit from treatment of schizophrenia patients with acyclovir.

In summary, although several different methodological approaches have been used, no specific infectious agent has been conclusively identified as causative in schizophrenia. It does appear, however, that new techniques, especially gene amplification using PCR, will allow an ongoing search for viral genomic components in the brain tissue of schizophrenia patients with an unprecedented level of specificity and sensitivity.

Weighing the Evidence

Several pieces of indirect evidence and research findings point toward a possible role for an infectious or autoimmune process in at least some cases of schizophrenia. As in many other areas of schizophrenia research, the problem has been inconsistent or unreplicated findings. The lack of overt inflammatory neuropathology in schizophrenia, as well as the modest degree of the reported immunologic abnormalities, makes it highly unlikely that schizophrenia in its typical chronic adult form involves an active, ongoing infection. It is equally apparent, however, that direct cytopathic infection is only one form of viral pathogenesis. Some authors have recently stressed our need to dramatically expand our notions about how viruses and the immune response cause disease (Oldstone 1984; Co et al. 1986; Kaufmann and Ziegler 1988). An infectious agent, or autoantibodies generated in response to an infection, may have much more subtle effects. They may alter the synthesis of neurotransmitters or interact with cellular receptors for neuropeptides and neurotransmitters (Lycke and Roos 1974). In addition, the subtle effects of viral pathogenesis may vary according to host factors, especially the genotype of the infected person, the location of the infection within the CNS, and the timing of the infection in relation to CNS development.

Immunologic studies of schizophrenia have focused primarily on patients with a chronic form of the illness. Because of this focus, the findings observed may be epiphenomenal, resulting from chronicity, exposure to a hospital environment, use of neuroleptics, or other factors. The ability of future research to rule out such artifactual causes of immune abnormalities is crucial to distinguishing state from trait findings.

The research to date has certainly failed to identify a "schizovirus" (Torrey 1988). We must seriously question at this point whether it is realistic to assume that a single pathogenic organism will be identified as the cause of a significant number of cases of schizophrenia. An analogy might be drawn to the current status of genetic research in schizophrenia (Kendler and Diehl 1993, this issue). There was initially great enthusiasm for the concept of identifying a single major gene locus as the cause of schizophrenia (Sherrington et al. 1988). The failure to replicate initial evidence of gene linkage (Kennedy et al. 1988; Kendler and Diehl 1993, this issue) has led to a much greater emphasis on the likelihood of complex genetic mechanisms being involved. Researchers have become much more willing to consider the possibility that schizophrenia involves multiple genetic loci contributing in varying degrees and with varying penetrance in different individuals to the schizophrenic syndrome through interactions with multiple environmental factors. Just as mathematical genetics is now emphasizing these complex models for disorders like schizophrenia, it seems reasonable

for proponents of the infectious-autoimmune hypothesis to acknowledge this complexity. Ultimately, it may be that multiple infectious agents, and even multiple autoantibodies, contribute in different ways and in different cases to the development of a schizophrenic syndrome. The clinical heterogeneity of schizophrenia is an inescapable fact that must be acknowledged by accepting the very real possibility of etiologic heterogeneity.

A Research Agenda

Given the findings reviewed above and the weight of the evidence against identifying a single specific virus or autoantibody as a predominant etiologic factor in schizophrenia, it is important to define a research agenda that takes these facts into account. The following would seem to be important issues in further research on an infectious-autoimmune hypothesis of schizophrenia.

It seems that focusing on patients with chronic schizophrenia might be counterproductive. As noted above, there is little to support the idea of chronic schizophrenia involving an active infection or autoimmune process. The chronic disorder is more likely the long-term result of a much earlier infectious or autoimmune insult. Therefore, a strategy of identifying and focusing primarily on schizophrenia patients with multiple immune abnormalities might be more productive. Patients who are dysfunctional on multiple immune parameters might be a high-yield group for viral-immunologic studies. In particular, these patients might be studied longitudinally, especially on and off neuroleptics, to determine how much their immunologic abnormalities vary over time and how they relate both to severity of illness and to neuroleptic exposure. A second strategy, which would probably be even more productive, is to pay attention to the earlier stages of the illness. Studies could focus on children at high risk for schizophrenia, including cohorts currently being followed because of their genetic "load" for the disorder. Another important target population is patients experiencing their first episode of psychosis; this group certainly would be best studied immunologically before any exposure to neuroleptics. There has been a recent emphasis on studies of first-episode psychosis (Kirch et al. 1992*b*), and at least one group has focused on immunologic function in these patients (Ganguli et al., in press). Other populations that might be productively studied are groups of patients known to have had early exposure to an infection. We have previously proposed that cohorts of individuals identified at birth as seropositive for CMV might be one group meriting longitudinal followup regarding their risk for schizophrenia (Alexander et al. 1992*b*).

As our concepts of schizophrenia become more complex, several researchers have emphasized the model of a "neurodevelopmental" disorder (Murray and Lewis 1987; Weinberger 1987). The combined evidence regarding possible prenatal and perinatal insults in schizophrenia patients, together with the striking time course of late adolescent and early adult emergence of symptoms, have led some investigators to propose that a genetic predisposition to schizophrenia combined with an early insult to brain development may result much later in disrupted CNS function expressed as schizophrenia. As investigators explore in more detail the effects of early insults on later CNS maturation, it will be important to continue to study the possibility that infection or an autoantibody response can affect CNS maturation. Schizophrenia research has suffered from a lack of animal models of the syndrome itself. Nevertheless, the use of animal models of prenatal and perinatal insults, which might replicate some of the neuropathological and neurochemical deficits observed in schizophrenia (if not the symptoms of the disorder) may be crucial in our expanding understanding of this illness.

Finally, close coordination is vital between those studying other etiologic factors, especially genetic predisposition, and researchers interested in viral-immunologic causes of schizophrenia. The likelihood of an interaction between genes and environment in this disorder makes communication between researchers studying these two different kinds of etiologic factors highly important.

History should never be ignored. A century ago many of those labeled as "insane" and institutionalized in our mental hospitals had symptoms consistent with schizophrenia but caused by syphilis. When the infectious organism causing their psychosis was identified and treated, a subgroup of patients who could have been labeled as having schizophrenia had the etiology of their illness solved. Given the rapid recent advances in virology and immunology, the etiologic answers for further subgroups of schizophrenia patients may be at hand.

References

Ahokas, A.; Koskiniemi, M.; Vaheri, A.; and Rimon, R. Altered white cell count, protein concentration and oligoclonal IgG bands in the cerebrospinal fluid of many patients with acute psychiatric disorders. *Neuropsychobiology,* 14:1–4, 1985.

Ahokas, A.; Rimon, R.; Koskiniemi, M.; Vaheri, A.; Julkunen, I.; and Sarna, S. Viral antibodies and interferon in acute psychiatric disorders. *Journal of Clinical Psychiatry,* 48:194–196, 1987.

Albrecht, P.; Boone, E.; Torrey, E.F.; Hicks, J.; and Daniel, N. Raised cytomegalovirus-antibody in cerebrospinal fluid of schizophrenic patients. *Lancet,* II:769–772, 1980.

Alexander, R.C.; Cabirac, G.; Lowenkopf, T.; Casanova, M.; Kleinman, J.; Wyatt, R.J.; and Kirch, D.G. Search for evidence of herpes simplex virus type 1, or varicella-zoster infection in postmortem brain tissue from schizophrenia patients. *Acta Psychiatrica Scandinavica,* 86:418–420, 1992*a*.

Alexander, R.C.; Spector, S.A.; Casanova, M.; Kleinman, J.; Wyatt, R.J.; and Kirch, D.G. Search for cytomegalovirus in the postmortem brains of schizophrenic patients using the polymerase chain reaction. *Archives of General Psychiatry,* 49:47–53, 1992*b*.

Aulakh, G.S.; Kleinman, J.E.; Aulakh, H.S.; Albrecht, P.; Torrey, E.F.; and Wyatt, R.J. Search for cytomegalovirus in schizophrenic brain tissue. *Proceedings of the Society for Experimental Biology and Medicine,* 167:172–174, 1981.

Axelsson, R.; Martensson, E.; and Alling, C. Impairment of the blood-brain barrier as an aetiological factor in paranoid psychosis. *British Journal of Psychiatry,* 141:273–281, 1982.

Baker, H.F.; Ridley, R.M.; Crow, T.J.; Bloxham, C.A.; Parry, R.P.; and Tyrrell, D.A.J. An investigation of the effects of intracerebral injection in the marmoset of cytopathic cerebrospinal fluid from patients with schizophrenia or neurological disease. *Psychological Medicine,* 13:499–511, 1983.

Baron, M.; Stern, M.; Anavi, R.; and Witz, I.P. Tissue-serum affinity in schizophrenia: A clinical and genetic study. *Biological Psychiatry,* 12:199–219, 1977.

Bartova, L.; Rajcani, J.; and Pogady, J. Herpes simplex virus antibodies in the cerebrospinal fluid of schizophrenic patients. *Acta Virologica,* 31:443–446, 1987.

Bauer, K., and Kornhuber, J. Blood-cerebrospinal fluid in schizophrenic patients. *European Archives of Psychiatry and Neurological Sciences,* 236:257–259, 1987.

Bock, E. Immunoglobulins, prealbumin, transferrin, albumin, and alpha$_2$-macroglobulin in cerebrospinal fluid and serum in schizophrenic patients. *Birth Defects,* 14:283–295, 1978.

Bock, E., and Rafaelson, O.J. Schizophrenia: Proteins in blood and cerebrospinal fluid. *Danish Medical Bulletin,* 21:93–105, 1974.

Bowler, A.E., and Torrey, E.F. Letter to the editor. *Archives of General Psychiatry,* 47:876–877, 1990.

Bracha, H.S.; Torrey, E.F.; Bigelow, L.B.; Lohr, J.B.; and Linington, B.B. Subtle signs of prenatal maldevelopment of the hand ectoderm in schizophrenia: A preliminary monozygotic twin study. *Biological Psychiatry,* 30:719–725, 1991.

Bradbury, T.N., and Miller, G.A. Season of birth in schizophrenia: A review of evidence, methodology and etiology. *Psychological Bulletin,* 98:569–594, 1985.

Bruce, L.C., and Peebles, A.M.S. Clinical and experimental observations on catatonia. *Journal of Mental Science,* 49:614–628, 1903.

Bruce, L.C., and Peebles, A.M.S. Quantitative and qualitative leukocyte counts in various forms of mental disease. *Journal of Mental Science,* 50:409–417, 1904.

Bruetsch, V.L.; Bahr, M.A.; Skobba, J.S.; and Dieter, V.J. The group of dementia praecox patients with an increase of the protein content of the cerebrospinal fluid. *Journal of Nervous and Mental Disorders,* 95:669–679, 1942.

Carter, G.; Taylor, G.; and Crow, T. Search for viral nucleic acid sequences in the post mortem brains of patients with schizophrenia and individuals who have committed suicide. *Journal of Neurology, Neurosurgery and Psychiatry,* 50:247–251, 1987.

Co, M.S.; Fields, B.N.; and Greene, M.I. Viral receptors serving host functions. In: Notkins, A.L., and Oldstone, M.B.A., eds. *Concepts in Viral Pathogenesis II.* New York, NY: Springer-Verlag, 1986. pp. 126–131.

Coffey, C.E.; Sullivan, J.L.; and Rice, J.R. T-lymphocytes in schizophrenia. *Biological Psychiatry,* 18:113–119, 1983.

Coggiano, M.; Alexander, R.C.; Kirch, D.G.; Wyatt, R.J.; and Kulaga, H. The continued search for evidence of retroviral infection in schizophrenic patients. *Schizophrenia Research,* 5:243–247, 1991.

Crow, T.J. A re-evaluation of the viral hypothesis: Is psychosis the

result of retroviral integration at a site close to the cerebral dominance gene? *British Journal of Psychiatry,* 145:243–253, 1984.

Crow, T.J., and Done, D.J. Age of onset of schizophrenia in siblings: A test of the contagion hypothesis. *Psychiatry Research,* 18:107–117, 1986.

Crow, T.J.; Done, D.J.; and Johnstone, E.C. Influenza and schizophrenia. *Lancet,* 338:116–117, 1991.

DeLisi, L.E. Viral and immune hypotheses for schizophrenia. In: Meltzer, H.Y., ed. *Psychopharmacology: The Third Generation of Progress.* New York, NY: Raven Press, 1987. pp. 765–771.

DeLisi, L.E., and Crow, T.J. Is schizophrenia a viral or immunologic disorder? *Psychiatric Clinics of North America,* 9:115–132, 1986.

DeLisi, L.E.; Goldin, L.R.; Nurnberger, J.I.; Simmons-Alling, S.; Hamovit, J.; and Dingman, C.W. Failure to alleviate symptoms of schizophrenia with the novel use of an antiviral agent, acyclovir (Zovirax). *Biological Psychiatry,* 22:216–220, 1987.

DeLisi, L.E.; Goodman, S.; Neckers, L.M.; and Wyatt, R.J. Lymphocyte subpopulations in schizophrenic patients. *Biological Psychiatry,* 17:1003–1007, 1982.

DeLisi, L.E.; Ortaldo, J.R.; Maluish, A.E.; and Wyatt, R.J. Deficient natural killer cell (NK) activity and macrophage functioning in schizophrenic patients. *Journal of Neural Transmission,* 58:96–106, 1983.

DeLisi, L.E., and Sarin, P.S. Lack of evidence for retrovirus infection in schizophrenic patients. [Letter] *British Journal of Psychiatry,* 146:674, 1985.

DeLisi, L.E.; Smith, S.; Hamovit, J.; Maxwell, M.; Goldin, L.R.; Dingman, C.; and Gershon, E. Herpes simplex virus, cytomegalovirus and Epstein-Barr virus antibody titers in sera from schizophrenic patients. *Psychological Medicine,* 16:757–763, 1986.

DeLisi, L.E.; Weber, R.J.; and Pert, C.B. Are there antibodies against brain in sera from schizophrenic patients? Review and prospectus. *Biological Psychiatry,* 20:94–119, 1985.

DeLisi, L.E.; Weinberger, D.R.; Potkin, S.; Neckers, L.M.; Shiling, D.J.; and Wyatt, R.J. Quantitative determination of immunoglobulins in CSF and plasma of chronic schizophrenic patients. *British Journal of Psychiatry,* 139:513–518, 1981.

Dencker, S.J., and Malm, U. Protein pattern of cerebrospinal fluid in mental disease. *Acta Psychiatrica Scandinavica,* 203(Suppl.):105–109, 1968.

Eaton, W.W. Epidemiology of schizophrenia. *Epidemiologic Reviews,* 7:105–126, 1985.

Eaton, W.W. Update on the epidemiology of schizophrenia. *Epidemiologic Reviews,* 13:320–328, 1991.

Eaton, W.W.; Hayward, C.; and Ram, R. Schizophrenia and rheumatoid arthritis: A review. *Schizophrenia Research,* 6:181–192, 1992.

Elder, G.A., and Sever, J.A. AIDS and neurological disorders: An overview. *Annals of Neurology,* 23:S4–S6, 1988.

Esquirol, J.E. *Mental Maladies, a Treatise on Insanity.* Philadelphia, PA: Lea and Blanchard, 1845.

Feenstra, A.; Kirch, D.G.; Bracha, H.; and Wyatt, R. Lack of evidence for a role of T-cell associated retroviruses in the etiology of schizophrenia. *Biological Psychiatry,* 25:421–430, 1989.

Feenstra, A.; Kirch, D.G.; Coggiano, M.A.; and Wyatt, R.J. Reverse transcriptase activity in 5-azacytidine-treated lymphocyte cultures of patients with schizophrenia. *Schizophrenia Research,* 1:385–389, 1988.

Fessel, W.J. Blood proteins in functional psychoses. *Archives of General Psychiatry,* 6:40–56, 1962.

Fessel, W.J., and Hirata-Hibi, M. Abnormal leukocytes in schizophrenia. *Archives of General Psychiatry,* 9:601–603, 1963.

Fieve, R.R.; Blumenthal, B.; and Little, B. The relationship of atypical lymphocytes, phenothiazine and schizophrenia. *Archives of General Psychiatry,* 15:529–534, 1966.

Ganguli, R.; Brar, J.S.; Chengappa, K.N.R.; Yang, Z.W.; Nimgaonkar, V.L.; and Rabin, B.S. Autoimmunity in schizophrenia: A review of recent findings. *Annals of Medicine,* in press.

Ganguli, R., and Rabin, B.S. Increased serum interleukin 2 receptor concentration in schizophrenic and brain-damaged subjects. [Letter] *Archives of General Psychiatry,* 46:292, 1989.

Gotlieb-Stematsky, T.; Zonis, J.; Arlazoroff, A.; Mozes, T.; Sigal, M.; and Szekely, A. Antibodies to Epstein-Barr virus, herpes simplex type 1, cytomegalovirus and measles virus in psychiatric patients. *Archives of Virology,* 67:333–339, 1981.

Gottesman, I.I. *Schizophrenia Genesis: The Origins of Madness.* New York, NY: W.H. Freeman, 1991.

Green, M.F.; Satz, P.; Gaier, D.; Ganzell, S.; and Kharabi, F. Minor physical anomalies in schizophrenia. *Schizophrenia Bulletin,* 15:91–99, 1989.

Gur, R.E., and Pearlson, G.D. Neuroimaging in schizophrenia re-

search. *Schizophrenia Bulletin,* 19:337–353, 1993.

Hare, E.H. Epidemiological evidence for a viral factor in the etiology of the functional psychoses. *Advances in Biological Psychiatry,* 12:52–75, 1983.

Heath, R.G., and Krupp, I.M. Schizophrenia as an immunologic disorder: I. Demonstration of antibrain globulins by fluorescent antibody techniques. *Archives of General Psychiatry,* 16:1–9, 1967.

Heath, R.G.; McCarron, K.L.; and O'Neil, C.E. Antiseptal brain antibody in IgG of schizophrenic patients. *Biological Psychiatry,* 25:725–733, 1989.

Hirata-Hibi, M.; Higashi, S.; Tachibana, T.; and Vatanabi, N. Stimulated lymphocytes in schizophrenia. *Archives of General Psychiatry,* 39:82–87, 1982.

Jones, G.H.; Kelly, C.L.; and Davies, J.A. HIV and onset of schizophrenia. [Letter] *Lancet,* I:982, 1987.

Kaufmann, C.A.; Weinberger, D.R.; Stevens, J.R.; Asher, D.M.; Kleinman, J.E.; Sulima, M.P.; Gibbs, C.J.; and Gadjusek, D.C. Intracerebral inoculation of experimental animals with brain tissue from patients with schizophrenia: Failure to observe consistent or specific behavioral and neuropathological effects. *Archives of General Psychiatry,* 45:648–652, 1988.

Kaufmann, C.A.; Weinberger, D.R.; Yolken, R.H.; Torrey, E.F.; and Potkin, S.G. Viruses and schizophrenia. [Letter] *Lancet,* II:1136–1137, 1983.

Kaufmann, C.A., and Ziegler, R.J. The viral hypothesis of schizophrenia. In: Sen, A.K., and Lee, T., eds. *Receptors and Ligands in Psychiatry.* Cambridge, England: Cambridge University Press, 1988. pp. 187–208.

Kendell, R.E., and Kemp, I.W. Maternal influenza in the etiology of schizophrenia. *Archives of General Psychiatry,* 46:878–892, 1989.

Kendler, K.S., and Diehl, S.R. The genetics of schizophrenia: A current, genetic-epidemiologic perspective. *Schizophrenia Bulletin,* 19:261–285, 1993.

Kennedy, J.L.; Guiffra, L.A.; Moises, H.W.; Cavilla-Sforza, L.L.; Pakstis, A.J.; Kidd, J.R.; Castiglione, C.M.; Sjogren, B.; Wetterberg, L.; and Kidd, K.K. Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree. *Nature,* 336:167–170, 1988.

King, D.J.; Cooper, S.J.; Earle, J.A.P.; Martin, S.J.; McFerran, N.V.; and Wisdom, G.B. Serum and CSF antibody titers to seven common viruses in schizophrenic patients. *British Journal of Psychiatry,* 147:145–149, 1985.

Kirch, D.G., and Alexander, R.C. Viruses, autoimmunity, and psychiatric disorders. In: Tasman, A., and Riba, M.B., eds. *Annual Review of Psychiatry,* Vol. 11. Washington, DC: American Psychiatric Press, 1992. pp. 202–218.

Kirch, D.G.; Alexander, R.C.; Suddath, R.L.; Papadopoulos, N.M.; Kaufmann, C.A.; Daniel, D.G.; and Wyatt, R.J. Blood-CSF barrier permeability and central nervous system immunoglobulin G in schizophrenia. *Journal of Neural Transmission,* 89:219–232, 1992*a*.

Kirch, D.G.; Kaufmann, C.A.; Papadopoulos, N.M.; Martin, B.; and Weinberger, D.R. Abnormal cerebrospinal fluid protein indices in schizophrenia. *Biological Psychiatry,* 20:1039–1046, 1985.

Kirch, D.G.; Keith, S.J.; and Matthews, S. Research on first episode psychosis: Report on a National Institute of Mental Health workshop. *Schizophrenia Bulletin,* 18:179–184, 1992*b*.

Kirch, D.G., and Weinberger, D.R. Anatomical neuropathology in schizophrenia: Post mortem findings. In: Nasrallah, H., and Weinberger, D.R., eds. *Handbook of Schizophrenia; The Neurology of Schizophrenia.* Vol. 1. Amsterdam, The Netherlands: Elsevier, 1986. pp. 325–348.

Kirchbach, A.V.; Fischer, E.G.; and Kornhuber, H.H. Failure to detect dopamine receptor IgG autoantibodies in sera of schizophrenic patients. *Journal of Neural Transmission,* 70:175–179, 1987.

Knight, J.G. Dopamine-receptor-stimulating autoantibodies: A possible cause of schizophrenia. *Lancet,* II:1073–1076, 1982.

Knight, J.G. Possible autoimmune mechanisms in schizophrenia. *Integrative Psychiatry,* 3:134–143, 1985.

Kuritzky, A.; Livni, E.; Munitz, H.; Englander, T.; Tyano, S.; Wijsenbeek, H.; Joshua, H.; and Kott, E. Cell-mediated immunity to human myelin basic protein in schizophrenic patients. *Journal of the Neurological Sciences,* 30:369–373, 1976.

Lehmann-Facius, H. Über die Liquordiagnose der Schizophrenien. *Klinische Wochenschrift,* 16:1646–1648, 1937.

Lewis, G.; David, A.; Andreasson, S.; and Allbeck, P. Schizophrenia and city life. *Lancet,* 340:137–140, 1992.

Lewis, M.S. Age incidence and schizophrenia: Part I. The season of birth controversy. *Schizophrenia Bulletin,* 15:59–73, 1989.

Libikova, H. Schizophrenia and viruses: Principles of etiologic studies. *Advances in Biological Psychiatry,* 12:20–51, 1983.

Lycke, E., and Roos, B.-E. Influence of changes in brain monoamine metabolism on behavior of herpes simplex-infected mice. *Journal of Neurological Science,* 22:277–289, 1974.

McAllister, C.G.; Rapaport, M.H.; Pickar, D.; and Paul, S.M. Effects of short-term administration of antipsychotic drugs on lymphocyte subsets in schizophrenic patients. *Archives of General Psychiatry,* 46:957–958, 1989*a*.

McAllister, C.G.; Rapaport, M.H.; Pickar, D.; Podruchny, T.A.; Christison, G.; Alphs, L.D.; and Paul, S.M. Increased numbers of CD5+ B lymphocytes in schizophrenic patients. *Archives of General Psychiatry,* 46:890–894, 1989*b*.

Mednick, S.A.; Machon, R.A.; and Huttunen, M.O. An update on the Helsinki influenza project. [Letter] *Archives of General Psychiatry,* 47:292, 1990.

Mednick, S.A.; Machon, R.A.; Huttunen, M.O.; and Bonett, D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry,* 45:189–192, 1988.

Menninger, K.A. Psychoses associated with influenza. *Journal of the American Medical Association,* 72:235–241, 1919.

Menninger, K.A. Influenza and schizophrenia: An analysis of post-influenza "dementia praecox" as of 1918 and five years later. *American Journal of Psychiatry,* 5:469–529, 1926.

Menninger, K.A. The schizophrenia syndrome as a product of acute infectious disease. *Archives of Neurological Psychiatry,* 20:464–481, 1928.

Moises, H.W.; Beck, J.; Schindler, L.; and Kirchner, H. Decreased interferon in schizophrenic patients. *Pharmacopsychiatry,* 19:226–227, 1986.

Moises, H.; Ruediger, R.; Reynolds, G.; and Fleckenstein, B. Human cytomegalovirus DNA in the temporal cortex of a schizophrenic patient. *European Journal of Psychiatry and Neurological Sciences,* 238:110–113, 1988.

Moises, H.W.; Schindler, L.; Leroux, M.; and Kirchner, H. Decreased production of interferon alpha and interferon gamma in leucocyte cultures of schizophrenic patients. *Acta Psychiatrica Scandinavica,* 72:42–50, 1985.

Molholm, H.B. Hyposensitivity to foreign protein in schizophrenic patients. *Psychiatric Quarterly,* 16:565–571, 1942.

Murray, R.M., and Lewis, S.W. Is schizophrenia a neurodevelopmental disorder? *British Medical Journal,* 295:681–682, 1987.

Nyland, H.; Naess, A.; and Lunde, H. Lymphocyte subpopulations in peripheral blood from schizophrenic patients. *Acta Psychiatrica Scandinavica,* 61:313–318, 1980.

O'Callaghan, E.; Sham, P.; Takei, N.; Glover, G.; and Murray, R.M. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet,* 337:1248–1250, 1991.

Oldstone, M.B.A. Virus can alter cell function without causing cell pathology: Disordered function leads to imbalance of homeostasis and disease. In: Notkins, A.L., and Oldstone, M.B.A., eds. *Concepts in Viral Pathogenesis.* New York, NY: Springer-Verlag, 1984. pp. 269–276.

Pandey, R.S.; Gupta, A.K.; and Chaturvedi, U.C. Autoimmune model of schizophrenia with special reference to antibrain antibodies. *Biological Psychiatry,* 16:1123–1136, 1981.

Pearson, E.K. Study of cerebrospinal fluid in schizophrenics: A review of the literature. *Psychopharmacology Bulletin,* 9:59–62, 1973.

Pelonero, A.L.; Pandurangi, A.K.; and Calabrese, V.P. Autoantibodies to brain lipids in schizophrenia. *American Journal of Psychiatry,* 147:661–662, 1990.

Perry, S.W. Organic mental disorders caused by HIV: Update on early diagnosis and treatment. *American Journal of Psychiatry,* 147:696–710, 1990.

Pert, C.B.; Knight, J.C.; Laing, P.; and Markwell, M.A.K. Scenarios for a viral etiology of schizophrenia. *Schizophrenia Bulletin,* 14:243–247, 1988.

Preble, O.T., and Torrey, E.F. Serum interferon in patients with psychosis. *American Journal of Psychiatry,* 142:1184–1186, 1985.

Rajcani, J.; Libikova, H.; Smerekova, J.; Mucha, V.; Kudelova, M.; Pogady, J.; Breier, S.; and Skodacek, I. Investigations on the possible role of viruses affecting the CNS in the etiology of schizophrenia and related mental disorders. In: Kurstak, E.; Lipowski, Z.J.; and Morozov, P.V., eds. *Viruses, Immunity, and Mental Disorders.* New York, NY: Plenum Press, 1987. pp. 135–148.

Rapaport, M.H., and McAllister, C.G. Neuroimmunological factors in schizophrenia. In: Gorman, J.M., and Kertzner, R.M., eds. *Psychoimmunology Update.* Washington, DC: American Psychiatric Press, 1991. pp. 31–51.

Rapaport, M.H.; McAllister, C.G.; Pickar, D.; Nelson, D.L.; and Paul, S.M. Elevated levels of soluble interleukin 2 receptors in schizophrenia. [Letter] *Archives of General Psychiatry*, 46:291–292, 1989.

Rimon, R.H., and Ahokas, A. Interferon in schizophrenia. In: Kurstak, E.; Lipowski, Z.J.; and Morozov, P.V., eds. *Viruses, Immunity, and Mental Disorders*. New York, NY: Plenum Press, 1987. pp. 379–382.

Rimon, R.; Ahokas, A.; Hintikka, J.; and Heikkila, L. Serum interferon in schizophrenia. *Annals of Clinical Research*, 17:139–140, 1985.

Rimon, R.H.; Ahokas, A.; and Palo, J. Serum and cerebrospinal fluid antibodies to cytomegalovirus in schizophrenia. *Acta Psychiatrica Scandinavica*, 73:642–644, 1986.

Rimon, R.H.; Halonen, P.; Lebon, P.; Heikkila, L.; Frey, H.; Karhula, P.; Hintikka, J.; and Salmela, L. Antibrain antibodies and interferon in the serum and the cerebrospinal fluid of patients with schizophrenia. *Advances in Biological Psychiatry*, 12:161–167, 1983.

Robert-Guroff, M.; Torrey, E.F.; and Brown, M. Retroviruses and schizophrenia. [Letter] *British Journal of Psychiatry*, 146:326, 1985.

Roos, B.-E. Schizophrenia and viral and autoimmune issues. *Psychopharmacology Bulletin*, 20:514–518, 1984.

Roos, R.P.; Davis, K.; and Meltzer, H.Y. Immunoglobulin studies in patients with psychiatric diseases. *Archives of General Psychiatry*, 42:124–128, 1985.

Roy, A.; Pickar, D.; Ninan, P.; Hooks, J.; and Paul, S.M. A search for interferon in the CSF of chronic schizophrenic patients. [Letter] *American Journal of Psychiatry*, 142:269, 1985.

Saiki, R.K.; Gelfand, D.H.; and Stoffel, S. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science*, 239:487–491, 1988.

Schindler, L.; Leroux, M.; Beck, J.; Moises, H.W.; and Kirchner, H. Studies of cellular immunity, serum interferon titers, and natural killer cell activity in schizophrenic patients. *Acta Psychiatrica Scandinavica*, 73:651–657, 1986.

Schwartz, J.P., and Stevens, J.R. Transmissible agent in schizophrenic CSF. [Abstract] *Neurology*, 38(Suppl.):119, 1988.

Sherrington, R.; Brynjolfsson, B.; Petursson, H.; Potter, M.; Dudleston, K.; Barraclough, B.; Wasmuth, J.; Dobbs, M.; and Gurling, H. Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, 336:164–167, 1988.

Shrikhande, S.; Kirsh, S.; Coleman, J.; Reveley, M.; and Dayton, R. Cytomegalovirus and schizophrenia: A test of the viral hypothesis. *British Journal of Psychiatry*, 146:503–506, 1985.

Sperner-Unterweger, B.; Barnas, C.; Fuchs, D.; Kemmler G.; Wachter, H.; Hinterhuber, H.; and Fleischhacker, W.W. Neopterin production in acute schizophrenic patients: An indicator of alterations of cell-mediated immunity. *Psychiatry Research*, 42:121–128, 1992.

Stevens, J.R. Schizophrenia and multiple sclerosis. *Schizophrenia Bulletin*, 14:231–241, 1988.

Stevens, J.R.; Albrecht, P.; Godfrey, L.; and Krauthamer, E. Viral antigen in the brain of schizophrenic patients? *Advances in Biological Psychiatry*, 12:76–96, 1983.

Stevens, J.R., and Hallick, L.M. Viruses and schizophrenia. In: Specter, S.; Bendinelli, M.; and Friedman, H., eds. *Neuropathogenic Viruses and Immunity*. New York, NY: Plenum Press, 1992. pp. 303–316.

Stevens, J.R.; Langloss, J.M.; Albrecht, P.; Yolken, R.; and Wang, Y.-N. A search for cytomegalovirus and herpes viral antigen in brains of schizophrenic patients. *Archives of General Psychiatry*, 41:795–801, 1984.

Stevens, J.R.; Papadopoulos, N.M.; and Resnick, M. Oligoclonal bands in acute schizophrenia: A negative search. *Acta Psychiatrica Scandinavica*, 81:262–264, 1990.

Susser, E.S., and Lin, S.P. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. *Archives of General Psychiatry*, 49:983–988, 1992.

Taylor, G.; Crow, T.; Higgins, T.; and Reynolds, G. Search for cytomegalovirus in postmortem brain tissue from patients with Huntington's chorea and other psychiatric disease by molecular hybridization using cloned DNA. *Journal of Neuropathology and Experimental Neurology*, 44:176–184, 1985.

Torrey, E.F. Prevalence studies in schizophrenia. *British Journal of Psychiatry*, 150:598–608, 1987.

Torrey, E.F. Stalking the schizovirus. *Schizophrenia Bulletin*, 14:223–229, 1988.

Torrey, E.F., and Kaufmann, C.A. Schizophrenia and neuroviruses. In: Nasrallah, H.A., and Weinberger, D.R., eds. *Handbook of Schizophrenia: The Neurology of Schizophrenia*. Vol. 1. Amsterdam, The Netherlands: Elsevier, 1986. pp. 361–376.

Torrey, E.F., and Peterson, M.R. The viral hypothesis of schizophrenia. *Schizophrenia Bulletin*, 2:136–146, 1976.

Torrey, E.F.; Rawlings, R.; and Waldman, I. Schizophrenic births and viral diseases in two states. *Schizophrenia Research*, 1:73–77, 1988.

Torrey, E.F.; Torrey, B.B.; and Peterson, M.R. Seasonality of schizophrenic births in the United States. *Archives of General Psychiatry*, 34:1065–1070, 1977.

Torrey, E.; Yolken, R.; and Albrecht, P. Cytomegalovirus as a possible etiologic agent in schizophrenia. *Advances in Biological Psychiatry*, 12:150–160, 1983.

Torrey, E.; Yolken, R.; and Winfrey, C. Cytomegalovirus antibody in cerebrospinal fluid of schizophrenic patients detected by enzyme immunoassay. *Science*, 216:892–894, 1982.

Tyrrell, D.A.J.; Crow, T.J.; Parry, R.P.; Johnstone, E.; and Ferrier, I.N. Possible virus in schizophrenia and some neurological disorders. *Lancet*, I:839–844, 1979.

van Kammen, D.; Mann, L.; Scheinin, M.; van Kammen, W.; and Linnoila, M. Spinal fluid metabolites and anti-cytomegalovirus antibodies and brain scan evaluation in schizophrenia. *Psychopharmacology Bulletin*, 20:519–522, 1984.

van Kammen, D.P., and Sternberg, D.E. Cerebrospinal fluid studies in schizophrenia. In: Wood, J.H., ed. *Neurobiology of Cerebrospinal Fluid*. New York, NY: Plenum Press, 1980. pp. 719–742.

Villemain, F.; Chatenoud, L.; Galinowski, A.; Homo-Delarche, F.; Ginestet, D.; Loo, H.; Zarifian, E.; and Bach, J.-F. Aberrant T cell-mediated immunity in untreated schizophrenic patients. Deficient interleukin-2 production. *American Journal of Psychiatry*, 146:609–616, 1989.

Waltrip, R.W.; Carrigan, D.R.; and Carpenter, W.T., Jr. Immunopathology and viral reactivation. *Journal of Nervous and Mental Disease*, 178:729–738, 1990.

Weinberger, D.R. Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, 44:660–669, 1987.

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