

Viruses, Schizophrenia, and Bipolar Disorder

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INTRODUCTION

Schizophrenia and bipolar disorder are devastating disorders of the central nervous system with worldwide distribution. The etiology of these diseases is currently unknown. There is a body of evidence to indicate that infectious agents may play some role in the etiology of these disorders.

The hypothesis that schizophrenia and bipolar disorder are caused by infectious agents was first formulated in the 19th century. As early as 1845, the noted French neurologist Jean Esquirol wrote: "Many authors assure us that mental alienation is epidemic. It is certain that there are years when, independently of moral causes, insanity seems suddenly to extend to a great number of individuals" (53). In 1874, when bacteria were becoming known, the *American Journal of Insanity* published a long article, "On the Germ-Theory of Disease"

(47); the subsequent identification of spirochetes as the cause of neurosyphilis stimulated additional speculation among psychiatrists. By 1911, Eugen Bleuler was suggesting that "the connection of [schizophrenia] to infectious process equally needs further study" (20), and 8 years later, Emil Kraepelin added that "infections in the years of development might have a causal significance" (107).

The influenza pandemic of 1918 and 1919 provided an additional reason for speculation about the potential role of viruses because some affected individuals had symptoms resembling mania or schizophrenia following influenza. Karl Menninger, who had not yet begun his psychoanalytic training, summarized 39 such cases and claimed that he was "persuaded that dementia praecox [schizophrenia] is at least in most instances a somatopsychosis, the psychic manifestations of an encephalitis" (131, 132). Patients with encephalitis lethargica in the 1920s also frequently presented with symptoms of psychosis, and Kasanin and Petersen (91) suggested that "a thorough review of some of the early histories of atypical cases of schizophrenia or affective disorders may reveal a previous encephalitis."

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For the half-century following these speculations, remarkably little was written on a possible infectious etiology of serious mental illnesses. Biological approaches to psychiatry were modest in scope and confined to genetics. During these years American psychiatry was dominated by psychological theorizing, much of it based on Freudian ideas that assumed that serious mental illnesses originated etiologically in psychological experiences of early childhood. Since the 1970s, interest in the infectious hypothesis of serious mental illnesses has been revived, stimulated at least in part by work on slow and latent viruses by D. Carleton Gajdusek, Clarence J. Gibbs, and their colleagues. Most modern research attention has been focused on the possible role of viruses. This paper will review the infection hypothesis by examining the (i) clinical and epidemiological aspects, (ii) dysfunction of the immune system, and (iii) direct evidence of viral infection.

CLINICAL AND EPIDEMIOLOGICAL ASPECTS

Schizophrenia and bipolar disorder are chronic diseases of the central nervous system that usually begin in young adulthood and have various degrees of severity. Some cases relapse and remit, while others are continuously symptomatic. Bipolar disorder tends to stabilize with age, while many patients with schizophrenia exhibit clinical improvement in later years; in neither disease is it common to have a progressive downhill course such as is characteristic of many dementias. The predominant symptoms of schizophrenia and bipolar disorder are auditory hallucinations, delusional and illogical thinking, and affective symptoms that may range from mania to depression.

Changes in brain structure and function have been clearly established for these diseases. The structural changes include modest enlargement of the cerebral ventricles and loss of volume of medial temporal lobe structures, especially the hippocampus (19, 176). Functional changes include hypofrontality of cerebral blood flow as measured by positron emission tomography and other techniques, alterations of electrical activity, neuropsychological dysfunction, and neurological dysfunction (207). Although the most clearly described structural changes suggest neuropathology that is predominantly localized to medial temporal lobe structures, functional changes such as the neurological findings suggest that the disease process may be more widely distributed and involve integrative sensory function as well as motor coordination (79). There is substantial clinical variation from case to case.

Viruses should be considered possible agents in all chronic central nervous system diseases of unknown etiology because of their potential for neurotropism and latency (182). It is also known that occasional cases that later are proven to be viral encephalitis may present with symptoms of schizophrenia or bipolar disorder (198). Some viruses have been shown to alter dopamine metabolism (161), thought to be altered in schizophrenia, and several antipsychotic and antimanic drugs that are effective in treating serious mental illnesses have been shown to have antiviral properties both *in vitro* (108, 143) and *in vivo* (7, 34).

Epidemiologically, 12 specific risk factors for schizophrenia have been identified; many of them are also risk factors for bipolar disorder, although they have been less studied. These risk factors are described below.

Risk Factors

Genetic. It is clearly established that a person's risk of developing schizophrenia or bipolar disorder is increased if the

person has close relatives affected with these diseases and that the genetic risk factor is stronger for bipolar disorder than it is for schizophrenia. What is less clear is whether these diseases are actually transmitted on one or several genes, and are thus true genetic diseases (71), or whether it is a genetic predisposition that is transmitted. The pairwise concordance rate in carefully controlled monozygotic twin studies for schizophrenia is approximately 28%, virtually identical to the pairwise concordance rate for polio or multiple sclerosis (201). This finding suggests that the genetic component of schizophrenia is a predisposition rather than a necessary and sufficient determinant of disease. The pairwise concordance rate in monozygotic twin studies for bipolar disorder is approximately 56%, twice the rate as for schizophrenia (201). Many viral infections of the central nervous system are known to have genetic components (162). Possible mechanisms relating genetics and infection include genetic determinants of receptors, immune responsiveness, and underlying tissue pathology.

Age of onset. The mean age of onset for schizophrenia is in the early 20s, and for bipolar disorder it is approximately 30 years.

Gender. Schizophrenia affects males earlier in life and more severely. There are no significant gender differences in bipolar disorder, although women have more symptoms of depression and more commonly fall into the group of rapid cyclers who switch very quickly between mania and depression.

Season of birth. Over 40 studies have shown that individuals who later develop schizophrenia have a 5 to 15% excess of winter and spring births (22, 24). Experiments in animals have shown that viruses are more likely to infect the central nervous system in conditions of cold. A time series analysis of New York State data also reported a significant relationship between the seasonal birth patterns of schizophrenia and stillbirths (206). The majority of studies of bipolar disorder have reported a winter-spring seasonal excess similar to that found in schizophrenia, but there have been fewer such studies.

Regional differences. Schizophrenia appears to be comparatively rare in most tropical countries and to increase in prevalence as one moves away from the equator, similar to the pattern seen in multiple sclerosis (197). Areas of comparatively high prevalence have been described in diverse places such as northern Sweden (21), western Ireland (208, 232), western Croatia (38), and some islands in Micronesia (82) and among West Indian immigrants in England (77, 224). Schizophrenia prevalence rates vary from a high of 17.0 per 1,000 persons in northern Sweden (21) to a low of 1.1 per 1,000 individuals among the rural Hutterites in the United States (50), although most studies report a prevalence in a range of 2 to 5 per 1,000 persons (199). In addition to these regional differences in prevalence, a study in Ireland reported statistically significant space-time clusters of births of individuals who later developed schizophrenia (233).

Urban birth. Two studies have shown that individuals who are born (190) or who are raised (115) in cities have an increased risk for developing schizophrenia compared with those born or raised in rural areas. This is consistent with studies of psychiatric hospitalization for serious mental illnesses carried out between 1880 and 1962 that showed higher hospitalization rates for states with more urbanized populations (204).

Household crowding. A study of psychiatric hospitalization rates for serious mental illnesses was carried out by Schweitzer and Su (168) in Brooklyn, N.Y. They utilized measures of persons per acre, buildings per acre, persons per household, and persons per room and concluded that "measures of household and family contact were found to be significantly

correlated to . . . rates of hospital utilization. . . . If density does produce mental illness its likely mechanism of action will be routed through household contact." Similarly, King et al. (100) in Northern Ireland found that prescriptions for antipsychotic medication were more frequent in areas with household crowding (persons per room). Household crowding was also common in the areas of northern Sweden (21) and western Ireland (208) that had high reported schizophrenia prevalence rates. However, studies done to ascertain possible adult transmission of schizophrenia among siblings (39) or from psychiatric patients to psychiatric nurses (37) have been negative. Therefore, insofar as household crowding is a risk factor, it is more likely to exert its effect in childhood than in adulthood.

Lower socioeconomic status. Studies of large cities have consistently found the prevalence rate of schizophrenia to be highest in the lowest socioeconomic class (105). At least part of the explanation for this finding is that preschizophrenic individuals tend to drift downwards socioeconomically. Other than this, it is unclear whether low socioeconomic status per se is a risk factor for serious mental illnesses, or whether the correlation is due to urban birth and/or household crowding that often coexists with lower socioeconomic status.

Prenatal and birth complications. The possibility that prenatal and birth complications may contribute to the etiology of serious mental illness has been extensively studied. Among the 11 controlled studies done since 1966, in 7 studies it was found that individuals with schizophrenia had had significantly more prenatal and birth complications, in 2 other studies there was a nonstatistically significant trend in the same direction, and in 2 studies no increase was found (129, 207). In these studies no single pregnancy or birth complication emerged as being especially noteworthy in predisposing the person to later schizophrenia.

Other evidence for a perinatal origin of some cases of serious mental illnesses has emerged from studies of minor physical anomalies and fingerprint patterns (dermatoglyphics). Minor physical anomalies, such as low-set ears and steeped palate, are thought to be affected by events in the first trimester of pregnancy. Dermatoglyphics are thought to be influenced by events of the first and second trimesters and are known to be affected by congenital viral infections (147, 228). Six studies of minor physical anomalies in adults all found significantly more anomalies in individuals with schizophrenia than in controls (72–74, 112, 124, 175). More than 20 studies of dermatoglyphics have been carried out on individuals with serious mental illnesses; most of them reported minor dermatoglyphic deviations in such individuals, although many of the studies were poorly controlled (23, 207).

The findings of excess prenatal and birth complications, minor physical anomalies, and dermatoglyphic deviations in individuals with serious mental illnesses are also consistent with emerging research on developmental and neuropathological aspects of their diseases. Developmentally, it has been reported for many years that a subset of individuals who later develop schizophrenia showed minor behavioral and/or neurological deviations in childhood. These reports have been corroborated by recent studies of children at high risk for developing schizophrenia (59) and of monozygotic twins discordant for schizophrenia and bipolar disorder (207). Neuropathologically, a few of the anatomical abnormalities reported in postmortem studies of brains from individuals with schizophrenia appear to have originated during development in utero, and this has given rise to the developmental hypotheses (222).

Prenatal exposure to influenza virus. In 1988, Mednick et al. (130) published a study showing that Finnish women who had

been in midtrimester of their pregnancies during the 1957 influenza epidemic gave birth to offspring who as adults had a modest, but statistically significant, increased risk of developing schizophrenia. By utilizing data from the 1957 and previous influenza epidemics, this association was subsequently replicated in Denmark (15), England (54, 139, 173), and Japan (111) and partially replicated in Scotland (95) and Australia (223). However, a large study ($n = 43,814$) (205) in the United States and studies in The Netherlands (170, 188) failed to find any association between pregnancy during influenza epidemics and the later development of schizophrenia in the offspring. In all of these studies it was known that the mother was pregnant during the influenza epidemic but not whether she had had influenza.

In order to further study this association, two studies of the offspring of women who were known to have had influenza during pregnancy were undertaken. In England, Crow et al. followed up children from the National Child Development Study who were born in March 1958 and in whom perinatal infections had been documented (40, 41). In Ireland, Cannon et al. (27) followed up 525 children whose mothers, pregnant during the 1957 influenza epidemic, were known to have been infected. Both studies found no increase in schizophrenia among the offspring.

What could explain an increased incidence of schizophrenia in the offspring of women who were pregnant during an influenza epidemic and who may or may not have actually had the disease, but no increased incidence among the offspring of pregnant women known to have had influenza? One possible explanation is that it is not the influenza virus per se that leads to later schizophrenia, but rather prenatal exposure to another virus that is more likely to be transmitted to the mother during concurrent viral infections that might occur during an influenza epidemic.

Having older siblings. Sham et al. (172), using data from a Swedish family study, reported that younger children in a family had a significantly increased risk of later developing schizophrenia if their siblings were 3 to 4 years older at the time the younger children were in utero. The researchers' suggested explanation for this phenomenon was that older children are a source of viral infections, which they may transmit to their pregnant mothers, and these infections in turn may cause schizophrenia in the offspring.

Famine during pregnancy. Susser and Lin (189) analyzed the incidence of schizophrenia among the offspring of women who were pregnant during the 1944 to 1945 war-induced severe famine in western Holland. They reported a statistically significant increase in schizophrenia among offspring who had been in the first trimester of development during the famine. Their original report found the increase for female offspring only, but subsequent research found it for both sexes (187). During the famine the researchers reported that "the strangest dishes were eaten," including cats and dogs. In addition to resulting in decreased intake of nutrients, famine conditions depress immune function and increase the spread of infectious diseases.

DYSFUNCTION OF THE IMMUNE SYSTEM

Since the early years of this century, there have been reports of dysfunction of the immune system in individuals with serious mental illnesses. Most of the early reports focused on immune hyporeactivity as demonstrated by a diminished cutaneous response to exogenous intradermal antigens such as guinea pig serum (136) and pertussis vaccine (219) or to histamine (52, 225). The primary importance of such studies is that they suggested immune system dysfunction in seriously mentally ill

patients prior to the use of antipsychotic medications which, because they may also affect the immune system, have made such research more difficult. Studies of specific aspects of immune system dysfunction in individuals with serious mental illnesses have included lymphocyte abnormalities, protein abnormalities, autoantibodies, and cytokines.

Lymphocyte Abnormalities

An increased number of morphologically atypical peripheral lymphocytes, similar to those found in mononucleosis and other viral diseases, have been reported in patients with schizophrenia (57, 83, 84, 90), including some patients who had never taken antipsychotic medication (85). However, since antipsychotic medications may also cause morphological changes (58, 211), it is unclear how often such abnormalities are due to the disease rather than to the medication.

Alterations in peripheral lymphocyte subpopulations have been reported in schizophrenia, specifically, reduced T cells (35), increased B cells (42), and increased CD5⁺ B cells (128, 166), although such results have not been consistently replicated (65). There is also a report of increased T cells in the cerebrospinal fluid (CSF) of patients with schizophrenia (127). Peripheral lymphocyte activity has also been reported to be decreased in response to various mitogens in patients with schizophrenia (45, 217), although other researchers have reported the opposite result (138). A decreased lymphocyte response to mitogens has also been found in patients with mania (109) and severe depression (110). Although some of these studies included patients who were never medicated, the majority did not, and the significance of these findings remains undetermined.

Protein Abnormalities

Studies of CSF total protein in patients with serious mental illness have consistently found a subset of patients with elevated values. The largest such study, done prior to the availability of antipsychotic medications, reported elevated values in 54 (4%) of 1,281 patients (26). A study by Hunter et al. (86) reported elevated CSF total protein in 35 (14%) of 256 patients. More recently, Torrey (196) found elevated CSF total protein in 12 (7%) of 163 patients compared with 1 (2%) of 47 controls.

One known cause of CSF total protein elevation is an impaired blood-brain barrier, which permits serum proteins to pass more freely into the CSF. To date, four studies of blood-brain barrier permeability, utilizing the serum/CSF albumin ratio as a measure, have been done on patients with serious mental illnesses. Torrey et al. (202) found impairment in only 4 (7%) of 58 patients and in 0 of 7 controls. However, Kirch et al. (101) reported an abnormal blood-brain barrier in 10 (22%) of 46 patients compared with 1 (5%) of 20 controls; Axelsson et al. (11), in 7 (28%) of 25 patients; and Bauer and Kornhuber (17), in 5 (33%) of 15 patients. Kirch et al. assessed the same patients both on and off medication and found no difference, and two of the patients with impaired blood-brain barriers in the Bauer and Kornhuber study had never received medications; therefore, the impairment of the blood-brain barrier does not appear to be a medication effect. It is also apparent that impairment of the blood-brain barrier accounts for some but not all patients with elevated CSF total proteins; for example, in an unpublished study by Torrey (196), 4 of the 12 patients with elevated CSF total protein had impaired blood-brain barriers but 8 did not.

Studies of specific immunoglobulins (Ig) in patients with serious mental illnesses have yielded contradictory results.

Some studies of serum IgG, IgM, and IgA in patients with schizophrenia have reported them to be elevated, while other studies have found them to be normal or depressed (42). Two studies of serum immunoglobulins in patients with depression reported decreased levels (43, 226).

Studies of CSF immunoglobulins have also yielded contradictory findings; this may be due in part to a failure to utilize similar CSF fractions in patient and control groups as it is known that immunoglobulins may vary by at least 50% in different CSF fractions (60). DeLisi et al. (46) and Roos et al. (163) found no increase in CSF IgG in patients with schizophrenia or depression compared with controls. Torrey et al. (210) also found no statistically significant group differences, but 3 of 17 patients with schizophrenia and 2 of 14 patients with bipolar disorder had definite elevations of CSF IgG as a percentage of total protein. More recently, Kirch and Wyatt (102), using radial immunodiffusion and rate nephelometry, found a significantly higher ($P < 0.01$) CSF/serum IgG index for 46 patients with schizophrenia compared with 20 controls. The results could not be explained by impaired blood-brain barriers, and 9 (20%) of the 46 patients had evidence of intrathecal IgG production. One of the nine patients also had oligoclonal bands in CSF similar to those described by Ahokas et al. (1) for patients with schizophrenia. However, two other studies (163, 186) failed to find oligoclonal bands in the CSF of patients with schizophrenia.

Finally, there are two reports of abnormal CSF proteins detected by two-dimensional electrophoresis. In one study the abnormal proteins were found in 17 (32%) of 54 patients with schizophrenia compared with 0 of 99 normal controls (76); similar bands have also been detected in the CSF of patients with herpes simplex virus (HSV) encephalitis (90%), multiple sclerosis (13%), and Parkinson's disease (12%). In the other study increased amounts of three polypeptides were identified in the CSF of 27 patients with schizophrenia and 10 patients with Alzheimer's disease compared with controls (89); one of the polypeptides was identified by Western immunoblot as a haptoglobin.

Autoantibodies

Because of reports of immune dysfunction and autoantibodies in schizophrenia and bipolar disorder as well as the clinical aspects of these diseases (intermittent course, some improvement with age, and genetic predisposition), some researchers have theorized that there is an autoimmune component (103, 104). Antinuclear antibodies have been reported in several studies of patients with schizophrenia (42, 66, 181) and bipolar disorder (42, 113).

More pertinent to serious mental illnesses are autoantibodies to brain tissue. Early reports of antibrain antibodies in patients with schizophrenia date to the flocculation studies of Lehmann-Facius (114) and the immunofluorescence studies of Heath and Krupp (78). Baron et al. (14), using radioimmuno-fixation, found significantly higher antibody levels to brain septum in patients with schizophrenia than in controls. Vartanian et al. (217), using complement fixation, found antibodies to a brain glycoprotein fraction; and Pandey et al. (142), using hemagglutination, found that 48% of schizophrenia patients had antibrain antibody. On the other hand, using a radioimmune assay, DeLisi (42) found elevated antibodies to brain caudate in only 3 of 58 patients with schizophrenia and 2 of 11 patients with bipolar disorder, but also in 2 of 58 controls.

More recent studies of antibrain antibodies in patients with serious mental illnesses have continued to give mixed results. Pelonero et al. (144), using an enzyme-linked immunosorbent

assay (ELISA) technique, failed to find differences in autoantibodies to brain lipids between patients with schizophrenia and controls. Kelly et al. (94), also using ELISA, failed to find elevated antibodies against hippocampal antigens in patients with schizophrenia. On the other hand, Kilidireas et al. (96), using Western blot, detected antibodies against an extract of human neuroblastoma cells later identified as the 60-kDa heat shock protein in 14 (44%) of 32 patients with schizophrenia compared with 8 (8%) of 100 controls. In addition, Henneberg et al. (80), using indirect immunofluorescence, found anti-brain antibodies in 35 (70%) of 50 patients with schizophrenia compared with 12% of controls. Follow-up studies found antibodies in another 11 (44%) of 25 patients with schizophrenia (including 3 patients who were drug naive) compared with 3 (6%) of 49 controls (81).

Cytokines

Cytokines are factors in the blood that mediate immune responses and are associated with many infectious and immune diseases. Interferon and interleukin are the two cytokines that have been studied most intensively in patients with serious mental illnesses.

Interferon was initially reported to be elevated in both the serum and CSF of patients with schizophrenia in two studies by Libikova et al. (119, 121). Preble and Torrey (146) confirmed serum interferon elevations in 24% of patients with schizophrenia, while Kirch and Wyatt (102) found it to be elevated in 33% of patients. No CSF interferon was detected in patients in the Preble and Torrey study. On the other hand, studies of the serum by Schindler et al. (167) and Becker et al. (18), studies of the CSF by Roy et al. (164), and studies of both the serum and CSF by Ahokas et al. (2) and Rimon and Ahokas (154) all failed to find elevated interferon levels in seriously mentally ill patients, some of whom were drug naive. Moises et al. (135), in fact, reported that, *in vitro*, leukocytes from patients with schizophrenia were deficient in interferon production. Medication effects probably account for some of the discrepant findings, but it is also clear that there are methodological problems because some of the same samples reported to have high levels of interferon by Preble and Torrey had undetectable levels when tested in the laboratory of Schindler, Moises, and Kirchner (196).

Interleukin studies have yielded somewhat more consistent findings. Three studies, including one utilizing drug-naive patients, have reported decreased interleukin-2 (IL-2) in patients with schizophrenia as measured directly in serum or by *in vitro* mitogen stimulation of lymphocytes (106, 180, 220), while two other studies failed to replicate this finding (67, 140). In further studies, Ganguli et al. (63) showed an association between decreased IL-2 and autoantibodies in patients with schizophrenia. Studies of IL-2 in the CSF have reported it to be significantly increased (122), decreased (150), or the same as controls (51) in individuals with serious mental illnesses.

In addition to studies of IL-2, four studies have also been carried out on serum-soluble IL-2 receptors, 45-kDa proteins normally present in low levels in the peripheral blood. In three studies, including one done on monozygotic twins discordant for schizophrenia, significantly increased levels of serum-soluble IL-2 receptors were found in individuals with schizophrenia (64, 149, 151), while the fourth study, which included 31 patients with schizophrenia who were not on medications, reported a trend ($P = 0.07$) in the same direction (140).

DIRECT EVIDENCE OF VIRAL INFECTION

Direct testing of a viral hypothesis of serious mental illnesses began in the 1950s. Utilizing the technology that was then available, Morozov (137) and his colleagues in the Soviet Union claimed to have microscopically seen "virus-like corpuscles" in the CSF and nasal secretions of many patients with schizophrenia. In Italy, Mastrogiovanni and Scarlato (126) inoculated CSF from patients with schizophrenia into chicken embryos and also claimed to have microscopically visualized "virus-like particles." Since that time, the only researchers who have claimed to have found virus particles in patients with serious mental illnesses have been Castillo and his colleagues in Havana, Cuba. They have described intracytoplasmic encapsulated structures similar to herpesviruses in freshly obtained postmortem brain tissue from patients with schizophrenia (30) and also in brain tissue from aborted fetuses from mothers with schizophrenia (31).

Other direct evidence of viral infection in individuals with serious mental illnesses have included studies of viral antibodies, viral antigens, viral genomes, cytopathic effect (CPE) of specimens on cell cultures, and animal transmission experiments.

Viral Antibodies

As summarized in Table 1, there have been more than 30 studies of viral antibodies in blood from individuals with serious mental illnesses and more than 15 studies of viral antibodies in the CSF. The majority of these studies have focused on herpesviruses, especially HSV type 1 (HSV-1), cytomegalovirus (CMV), and Epstein-Barr virus. Earlier studies included large numbers of individuals with depression and bipolar disorder, but later studies have focused more on individuals with schizophrenia.

These studies have yielded varied results. Individuals with affective disorders were initially reported as having increased serum HSV antibody titers (156, 157), although other studies failed to replicate this finding. Two studies have reported increased serum antibody titers to borna disease virus in individuals with depression and bipolar disorder (6, 8). Individuals with schizophrenia have been found to have increased CSF CMV antibody titers in some studies (3, 93, 213, 216) but not in others (2, 155, 178). There have also been suggestions of abnormal CSF antibody titers to measles (210) and mumps (99) viruses. Of special interest is the study by Ahokas et al. (2) in which paired acute- and convalescent-phase sera and CSF from 54 patients with "acute functional psychiatric disorders" were tested for 16 viruses by complement fixation and enzyme immunoassay; 33% of the patients had a fourfold or greater change in serum antibody levels and 13% had a twofold or greater change in CSF antibody level to a wide variety of viruses.

Finally, a recent study by Yolken et al. (230) found that the sera and CSF of individuals with schizophrenia displayed increased reactivity to a 33-kDa peptide derived from a baculovirus clone of the nonstructural protein of the pestivirus bovine viral diarrhea virus; the significance of this reactivity is the subject of ongoing investigations.

Viral Antigens

Few studies using immunocytochemical techniques to identify viral antigens in brain tissue from individuals with serious mental illnesses have been done. Rhodes et al. (152) reported HSV-1 antigen in widespread intranuclear inclusions in neurons and glial cells in a woman with psychotic depression.

TABLE 1. Studies of viral antibodies in individuals with serious mental illnesses^a

Reference(s)	Patients ^b	Virus(es) and test(s) used	Finding(s)
Serum			
Rimon and Halonen, 1969 (156)	61 schizophrenic, 28 psychotic depression, and 34 controls	HSV by CF	HSV antibody significantly more prevalent and in higher titer in psychotic depression
Rimon et al., 1971 (157)	32 schizophrenic, 72 psychotic depression, and 12 controls	HSV by CF	HSV antibody significantly more prevalent in psychotic depression
Torrey and Peterson, 1973 (209)	16 schizophrenic	10 common viruses by CF and HI	Negative
Pokorny et al., 1973 (145)	68 schizophrenic, 13 psychotic depression, and 38 controls	HSV-1 by CF and neutralization	Negative
Lycke et al., 1974 (125)	327 schizophrenic, 35 psychotic depression, and 140 controls	HSV, CMV, VZV, and measles by CF and neutralization	HSV, CMV, and VZV antibody significantly more prevalent in psychotic depression
Halonen et al., 1974 (75)	75 schizophrenic, 88 psychotic depression, and 32 controls	HSV-1, rubella, and measles by HI and neutralization	HSV antibody titer significantly higher in both patient groups
Chacon et al., 1975 (33)	32 schizophrenic and 43 "affective disorders"	HSV, mumps, measles, influenza, parainfluenza, RSV, and adenovirus by CF	Negative
Rimon et al., 1978 (159)	12 schizophrenic and 10 controls	HSV-1, measles, and rubella by HI	Negative
Torrey et al., 1978 (210)	52 schizophrenic, 14 manic depression, and 90 controls	HSV-1, CMV, rubella, and measles by HI and plaque neutralization	Negative
Cappel et al., 1978 (28)	21 psychotic depression and 22 controls	HSV, CMV, measles, and rubella by CF and HI	HSV antibody significantly higher in patients
Rimon et al., 1979 (158)	16 schizophrenic and 18 controls	HSV-1 by RIA	Negative
Albrecht et al., 1980 (3)	60 schizophrenic and 26 controls	HSV-1, CMV, vaccinia, and influenza A by plaque neutralization	CMV and vaccinia antibody titers significantly lower in schizophrenics
Gotlieb-Stematsky et al., 1981 (70)	41 schizophrenic, 27 affective disorders, and 25 controls	HSV-1, EBV, CMV, and measles by IF and HI	EBV elevated in both patient groups
Libikova 1983, (117)	265 schizophrenic and 420 controls	HSV-1, CMV, VZV, measles, LCM virus, arbovirus, and orbivirus by neutralization, plaque neutralization, CF, and HI	HSV-1 antibody titer significantly higher in schizophrenics
King et al., 1985 (98)	222 schizophrenic, 60 affective disorder, and 143 controls	HSV-1, CMV, VZV, EBV, mumps, measles, rubella, and adenovirus by EIA	Mumps antibody significantly lower in schizophrenics
King et al., 1985 (99)	20 schizophrenic and 36 controls	HSV, CMV, VZV, mumps, measles, rubella, and adenovirus by EIA	Antibody levels higher in schizophrenics for all viruses except mumps, but not statistically significant
Amsterdam et al., 1985 (8)	265 unipolar and bipolar depression and 105 controls	Borna disease virus by IF	0.5% (12 of 265) of patients and 0 of 105 controls had antibody
Vasilyev et al., 1986 (218)	77 schizophrenic and 44 controls	Measles, vaccinia, influenza, LCM, and arenaviruses by CF and HI	Vaccinia antibody significantly higher in schizophrenics
Rimon et al., 1986 (155)	40 schizophrenic and 40 controls	CMV by CF and EIA	Negative
Schindler et al., 1986 (167)	30 schizophrenic and 30 controls	HSV-1 and CMV by EIA	Negative
DeLisi et al., 1986 (45)	38 schizophrenic and 41 controls	HSV-1, HSV-2, CMV, and EBV by IF and EIA	Questionable increase in EBV antibody in schizophrenics
Cazzullo et al., 1987 (32)	127 schizophrenic and 52 controls	HSV, CMV, EBV, VZV, and measles by IF and HSV-1 and EBV by IF	Negative

Continued on following page

TABLE 1—Continued

Reference(s)	Patients ^b	Virus(es) and test(s) used	Finding(s)
Gotlieb-Stematsky et al., 1987 (69)	21 schizophrenic and schizophreniform and 21 controls	HSV-1 and ERV by IF	Negative
Ahokas et al., 1987 (2)	54 "acute functional psychiatric disorders"; paired acute- and convalescent-phase specimens	16 viruses by CF and EIA	33% (18 of 54) had >4-fold rise or fall: 9 to one virus only and 9 to two or more viruses
Dvorakova et al., 1990 (49)	84 schizophrenic and 80 controls	LDH virus by leukocyte adherence inhibition	LDH virus antibody significantly higher in schizophrenics
Pelonero et al., 1990 (144)	38 schizophrenic and 22 controls	HSV, CMV, EBV, mumps, and measles by EIA	HSV antibody higher in schizophrenics
Rajcani et al., 1991 (148)	183 schizophrenic and 100 controls	HSV-1 by EIA	Negative
Amsterdam et al., 1992 (6)	138 "depressives" and 117 controls	Two specific epitopes, borna disease virus antibodies by Western immunoblot	(a) 38% of patients and 16% of controls positive; (b) 12% of patients and 4% of controls positive
Fux et al., 1992 (61)	48 schizophrenic and 48 controls	HSV and CMV by immunoperoxidase assay	Negative
CSF			
Torrey et al., 1978 (210)	52 schizophrenic, 14 manic depression, and 90 controls	HSV-1, CMV, rubella, and measles by HI and plaque neutralization	8% (4 of 52) schizophrenics had increased antibodies to measles as measured by serum/CSF ratio
Rimon et al., 1978 (159)	12 schizophrenic and 10 controls	HSV-1, measles, and rubella by HI	Negative
Rimon et al., 1979 (158)	16 schizophrenic and 18 controls	HSV-1 by RIA	Negative
Libikova et al., 1979 (119); Libikova, 1983 (117)	194 schizophrenic	HSV-1, measles, LCM virus, arboviruses, and orbivirus by neutralization, plaque neutralization, CF, and HI	42% had antibodies to HSV-1; 4% had multiple antibodies
Albrecht et al., 1980 (3); Torrey et al., 1981 (203) and 1983 (212)	60 schizophrenic and 26 controls	HSV-1, CMV, EBV, measles, mumps, rubella, influenza, polio, parvoviruses, arboviruses, adenoviruses, vaccinia, and hepatitis B by HI, neutralization, plaque neutralization, enhanced neutralization, EIA, RIA, and IF	31% (19 of 60) CMV positive; influenza A and vaccinia antibodies significantly elevated in schizophrenics over controls; 2% (1 of 60) measles positive
Libikova et al., 1981 (120)	57 schizophrenic	Hepatitis B by EIA	14% had antibodies
Gotlieb-Stematsky et al., 1981 (70)	19 schizophrenic, 10 affective disorder, and 20 controls	HSV-1, EBV, CMV, and measles by IF and HI	61% (11 of 18) schizophrenics and 40% (4 of 10) affectives had HSV-1 antibody; 6% (1 of 18) schizophrenics and 30% (3 of 10) affectives had EBV antibody
Torrey et al., 1982 (213)	178 schizophrenic, 17 bipolar, and 41 controls	CMV by EIA	11% (20 of 178) schizophrenics, 18% (3 of 17) bipolar, and no controls had antibody to CMV
Kaufmann et al., 1983 (93)	35 schizophrenic	CMV by EIA	17% (6 of 35) positive
van Kammen et al., 1984 (216)	27 schizophrenic	CMV by EIA	19% (5 of 27) positive
Shrikhande et al., 1985 (178)	32 schizophrenic and 10 controls	CMV by EIA	Negative
King et al., 1985 (99)	20 schizophrenic and 36 controls	HSV, CMV, VZV, mumps, measles, rubella, and adenovirus by EIA	Antibody to mumps significantly lower in schizophrenics; CSF/serum ratios significantly lower in schizophrenics for mumps, measles, and rubella

Continued on following page

TABLE 1—Continued

Reference(s)	Patients ^b	Virus(es) and test(s) used	Finding(s)
Rimon et al., 1986 (155)	40 schizophrenic and 40 controls	CMV by CF and EIA	Negative
Bartova et al., 1987 (16)	262 schizophrenic	HSV-1 by neutralization and EIA	18% (48 of 262) positive by neutralization; 61% (161 of 262) positive by ELISA
Ahokas et al., 1987 (2)	54 "acute functional psychiatric disorders"; paired acute- and convalescent-phase specimens	16 viruses by CF and EIA	13% (7 of 54) had >2-fold rise or fall: 1 HSV, 2 parainfluenza, 3 influenza A, and 1 influenza A and adenovirus
Serum and lymphocyte studies of retroviruses			
Robert-Guroff et al., 1985 (160)	30 schizophrenic	HTLV-I-III by EIA	3% (1 of 30) positive to HTLV-I and 3% (1 of 30) positive to HTLV-II
DeLisi and Sarin, 1985 (44)	15 schizophrenic and 15 controls	Antibodies to retroviral reverse transcriptase and to HTLV-I and -III	Negative
Feenstra et al., 1988 (56)	11 schizophrenic and 6 controls	Antibodies to retroviral reverse transcriptase	Negative
Feenstra et al., 1989 (55)	17 schizophrenic and 10 controls	Antibodies to retroviral reverse transcriptase	Negative
Coggiano et al., 1991 (36)	15 schizophrenic and 9 controls	Antibodies to retroviral reverse transcriptase	Negative

^a CF, complement fixation; EIA, enzyme immunoassay; HI, hemagglutination inhibition; IF, indirect immunofluorescence; RIA, radioimmunoassay; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; LCM, lymphocytic choriomeningitis; RSV, respiratory syncytial virus; LDH, lactate dehydrogenase; HTLV, human T-cell lymphotropic virus.

^b The diagnoses listed in Tables 1 and 2 are those used in the published papers. Psychotic depression implies episodes of depression only and is approximately the same as unipolar depression. Bipolar disorder requires episodes of both depression and mania. Manic depressive illness may have depression, mania, or both. Affective disorders is a nonspecific term and may include any of the above.

Stevens et al. used the peroxidase-antiperoxidase method to look for viral antigens in postmortem brain tissue from individuals with schizophrenia and from controls. In their initial study using antisera for HSV, CMV, and varicella-zoster virus, they reported staining in the nucleus basalis or hippocampus in 4 of 6 patients compared with 2 of 12 controls (183). A follow-up study of 25 patients and 41 controls, using more purified antisera, found only 1 patient and no controls with faint immunoreactivity to CMV in the hippocampus (185).

In a third study, Stevens and Hallick (184) tested brain tissue from 10 individuals with schizophrenia and 13 controls with high-titer antisera to HSV-1, HSV-2, CMV, and mumps, measles, and rubella viruses. Tissue from three of the patients reacted to two or more antisera, while two control tissues reacted to a single antiserum. The most clearly positive patient showed diffuse granular cytoplasmic staining in the amygdala and hippocampus to HSV-2 antibody and less dramatic reaction to HSV-1, CMV, and varicella-zoster virus.

Viral Genome

Studies of viral genomes in individuals with serious mental illnesses are summarized in Table 2. To date, eight studies using hybridization techniques have been carried out and four studies using PCR techniques have been done. With a few exceptions (134), these studies have failed to find viral genomic sequences in individuals with serious mental illnesses, including an extensive study by Taller et al. (191) that examined postmortem brain material from 63 patients and 7 controls for 13 viruses, including measles virus, influenza virus, retrovi-

rus, and herpesviruses. The negative results may indicate that these viruses are not involved in the etiology of serious mental illnesses, that the viruses are present in brain regions other than those tested, or that the primers that were used were from regions of the genome that are not conserved in the human infections.

CPE of Specimens on Cell Cultures

Several research groups have attempted to demonstrate viruses in the CSF or brain from individuals with serious mental illnesses by showing CPE on cell cultures. Tyrrell et al. (214) reported CPE in human fibroblasts treated with the CSF of 13 of 38 patients with schizophrenia; they later replicated these results (195). However, Mered et al. (133) and Cazzullo et al. (32) were not able to replicate these findings. In further attempts to characterize the agent responsible for their observed CPE, Taylor et al. (192) found that it was extremely resistant to UV light; it was not affected by inhibitors of DNA, RNA, or protein synthesis; it was associated with increased CSF enolase levels; and it was not accompanied by *de novo* synthesis of specific proteins or antigens detectable with antibodies in pooled human serum. Taylor et al. (192) concluded that "it seems more likely that the cytopathogenic agent is a toxin rather than a virus."

Libikova et al. (119), in a series of experiments, reported that the CSF from 1 of 13 patients with schizoaffective psychosis produced CPE "in 3 or 4 but not more subsequent passages" and identified the agent as HSV-1 by immunofluorescence. Brain tissue from biopsies taken while patients were

TABLE 2. Studies of viral genomes in postmortem brain tissue from individuals with serious mental illnesses^a

Reference(s)	Patients ^b	Virus(es) and test used	Finding(s)
Sequiera et al., 1979 (171)	1 schizophrenic and 1 "acute psychotic reaction"	HSV-1 by solution and in situ hybridization	Patient with schizophrenia positive
Aulakh et al., 1981 (10)	6 schizophrenic and 6 controls	CMV in hippocampus by solution hybridization	Negative
Taylor et al., 1985 (194); Taylor and Crow, 1986 (193)	32 schizophrenic and 23 controls	CMV and HSV-1 in temporal lobe by dot blot hybridization	Negative
Carter et al., 1987 (29)	20 schizophrenic and 21 controls	CMV, HSV-1, VZV, and JC and BK papovaviruses in caudate, putamen, hippocampus, temporal cortex, and frontal cortex by dot blot hybridization	Negative
Moises et al., 1988 (134)	12 schizophrenic and 9 controls	CMV in mixed temporal cortex by Southern blot hybridization	8% (1 of 12) patients strongly positive
Hayward et al., reported in Torrey, 1988 (200)	18 schizophrenic and 17 controls	CMV, HSV-1, HSV-2, and EBV in temporal cortex (auditory region) by Southern blot hybridization	Negative
King and Cooper, 1989 (97)	23 schizophrenic and 23 controls	Measles, mumps, and rubella in brains (site not specified) by in situ hybridization	Negative
Rajcani et al., 1991 (148)	Biopsy specimens from 18 schizophrenic and postmortem specimens from 26 controls	HSV-1 in amygdala by dot blot hybridization	17% (3 of 18) of patients and 15% (4 of 26) of controls positive
Shankar et al., 1992 (174)	16 schizophrenic, 5 affective, and 64 controls	Borna disease virus in brains (site not specified) by PCR	Negative
Alexander et al., 1992 (4, 5)	8 schizophrenic, 8 suicide victims, and 8 controls	CMV, HSV-1, and VZV in temporal cortex by PCR	Negative
Taller et al., 1994 (191)	63 schizophrenic and 7 controls	HSV-1, HSV-2, CMV, EBV, VZV, HHV-6, influenza, polio, measles, rubella, mumps, HTLV-I, and St. Louis encephalitis virus in temporal cortex by PCR	All negative except 1 HSV-1 and 2 HTLV-I
Sierra-Honigmann et al., 1994 (179)	Brain material from 3 schizophrenic and 3 controls and CSF from 55 schizophrenic, 5 bipolar, and 13 controls	CMV, influenza A, HIV, borna disease virus, and BVDV in CSF and hippocampus by PCR	Negative

^a VZV, varicella-zoster virus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; HTLV-I, human T-cell lymphotropic virus; BVDV, bovine viral diarrhea virus.

^b The diagnoses listed in Tables 1 and 2 are those used in the published papers. Psychotic depression implies episodes of depression only and is approximately the same as unipolar depression. Bipolar disorder requires episodes of both depression and mania. Manic depressive illness may have depression, mania, or both. Affective disorders is a nonspecific term and may include any of the above.

undergoing stereotaxic neurosurgery was also available from three patients with schizophrenia; explants from one of these patients "exerted pronounced growth of various cell types and the culture fluid killed a part of cerebrally inoculated baby mice in three subsequent passages" (117, 118).

More recently, Stevens and Hallick (184) and Shirabe et al. (177) have demonstrated "a growth-promoting agent" from the CSF of seven patients with schizophrenia. On the human neuroblastoma cell line SK-N-SH(EP), this agent accelerates the growth rate, increases cell density at confluence, changes the cell shape, and increases colony formation in soft agar. The change in growth properties was found to be transmissible and permanent. The agent is filterable and is destroyed by proteases, heat, and chloroform. They conclude that "such prop-

erties resemble those seen following viral transformation of cells" (177).

Animal Transmission Experiments

The successful transmission of kuru (62) and Creutzfeldt-Jakob disease (68) from infected humans to chimpanzees stimulated two attempts to transmit schizophrenia to primates. Researchers in England utilized CPE-inducing CSF from patients with schizophrenia (see above), neurological diseases (multiple sclerosis and Huntington's disease), and normal controls and inoculated it intracerebrally into marmosets. No differences in behavior were observed for the first 6 months, but thereafter the marmosets who had been inoculated with

CSF from the patients with schizophrenia and with neurological diseases "engaged in fewer activities and spent more time huddled together" (13, 153). These behavioral alterations remained statistically significant, as measured by an automated behavior-monitoring device, for 2.5 years, at which time the marmosets were sacrificed and examined neuropathologically. No specific pathological differences were found; analytical methods included an assay for dopamine D-2 receptors in the caudate and molecular hybridization techniques for the CMV genome. The researchers, however, were unable to replicate the behavioral changes in other marmosets when they repeated the experiment with other CSF samples with observations for 2.5 years (13).

In the other transmission experiment, researchers in the United States inoculated postmortem brain tissue from 10 patients with schizophrenia into 35 primates and 22 guinea pigs. Primates and guinea pigs that had been injected with brain tissue from patients with other diseases were used as controls. The animals were monitored for 2 to 6 years, after which they were sacrificed. No consistent behavioral or neuropathological changes were noted in the animals inoculated with tissue from the patients with schizophrenia (92).

DISCUSSION

Although clinical and epidemiological aspects of schizophrenia and bipolar disorder are consistent with a possible infectious etiology, there are no studies that provide a definite link between an infectious agent and these diseases. In this respect schizophrenia and bipolar disorder are similar to multiple sclerosis and Parkinson's disease, both of which are suspected of having a viral etiology but for both of which definite proof is still lacking.

If one or more infectious agents do cause schizophrenia and/or bipolar disorder, there are several reasons why this may be difficult to prove.

(i) The agent may cause infection in utero or in the early postnatal period and then disappear. It would therefore be very difficult to directly detect the agent when the disease manifested itself ≥ 20 years later. The original infection may initiate neurochemical damage without visible pathological change, similar to that described by Oldstone et al. (141) for lymphocytic choriomeningitis virus infection in newborn mice. Alternatively, the infection may initiate an autoimmune disease process that takes 20 years or more to become manifest.

(ii) A common infectious agent could cause disease by inducing an uncommon reaction, such as measles virus causing subacute sclerosing panencephalitis. In such cases it would be difficult to identify the agent since almost everyone would have been exposed.

(iii) A rare or unknown infectious agent could cause disease and would not be identified until it was specifically tested for. Thus, hepatitis C was not identified as a major etiological agent of transfusion hepatitis until the agent was identified by molecular cloning techniques. Similarly, human immunodeficiency virus was not identified as the etiological agent of AIDS until the conditions for viral replication in lymphoid cell lines were defined.

(iv) Two infectious agents may be required to cause disease synergistically; for example, the viruses of hepatitis B and the hepatitis delta agent are both necessary to cause hepatitis delta.

(v) It is possible that one of several infectious agents could cause disease. In this case the critical factor may be either the timing of the infection, the precise cerebral location of replication, or genetic predisposition.

(vi) Infectious agents may account for only a certain percentage of cases if schizophrenia and bipolar disorder are heterogeneous diseases. It would therefore require studies of large numbers of patients and controls to identify those who are infected.

(vii) The infectious agent may be incorporated into the genome, as some retroviruses can be, making identification difficult using standard virological methods.

(viii) Identification of viral antigen or genome from brain tissue is known to be extremely difficult for many infectious agents even in cases of known disease, such as measles virus in subacute sclerosing panencephalitis or CMV in known CMV encephalitis. Viral agents will be particularly difficult to identify if they are present in low concentrations and have an uneven distribution in the brain.

FUTURE DIRECTIONS

Schizophrenia and bipolar disorder have features that make infectious and autoimmune hypotheses attractive. Epidemiologic studies should be pursued to try to identify putative infectious agents and possible modes of transmission. In addition, the development of new methods for the detection and analysis of viral infection offers a number of new opportunities for exploring the relationship between viral infection and human disease. These methods include ones directed at the analysis of previously recognized pathogens as well as the identification of novel viral agents. Some examples of such techniques are described below.

Immunoassays Utilizing Synthetic Antigens

Many of the experimental approaches directed at the establishment of a relationship between viral agents and chronic forms of human disease are based on the detection of antibodies in the blood and body fluids of affected individuals. The reliance on serology is based on the fact that the pathological consequences of infection may become manifest long after the primary infection has occurred. In such circumstances, the detection of antibodies with long half-lives can provide the most efficient method for disease identification.

In the past, serological methods have been used to detect antibodies to antigens derived from viruses propagated in cell culture. While potentially sensitive, such methods may generate nonspecific reactions because of the interaction of antibodies with extraneous antigens derived from the cell culture system (231). Such nonspecific interactions can reduce assay sensitivity and result in misleading reactions. The recent development of methods for the generation of specific antigens by molecular techniques has markedly improved the potential sensitivity and specificity of immunological assays. One method of particular importance for the measurement of human antibodies is the construction of antigens by molecular cloning techniques and the production of large quantities of the cloned antigens in expression systems. In the case of assays involving human antigens, expression systems employing eukaryotic cells such as primate or insect cells are of particular importance since they minimize possible cross-reactions with antibodies directed at contaminating bacterial proteins. In another technique for producing purified antigens, synthetic peptides with the amino acid sequences of target epitopes are prepared. These peptides are generally 10 to 30 amino acids in length.

Assays that use cloned and synthetic antigens have become widely available for the detection of antibodies to a large number of viral antigens. In the case of chronic human diseases, such assays have been used to establish associations

between viral infection and chronic conditions such as autoimmune diseases (25) and neoplasia (221). It can be expected that as additional viral antigens are cloned and coding sequences are elucidated, sensitive and specific immunoassays will be developed for increasing numbers of human pathogens. Such assays may prove to be ideally suited for population-based studies of the relationship between viral infections and human neuropsychiatric diseases.

Nucleic Acid Detection

While serological assays are important for establishing possible associations between viral infection and disease, the direct identification of the infecting agent in human tissue represents a crucial step in the definition of the infectious process. In the past the detection of viral agents in human tissue has been limited by the fact that many important human viral pathogens grow poorly, if at all, in cell culture systems. While such organisms can be detected by antigen detection methods, the sensitivity of available immunoassay techniques is limited (229). Sensitivity is a particularly important issue in the analysis of chronic diseases such as schizophrenia and bipolar disorder since it is likely that the level of organisms in target areas of the brain is quite low. The recent development of methods for the direct detection of viral nucleic acids in human tissue represents a major advance in this regard. Of particular interest is PCR (165), a method that employs alternating reactions of specific target nucleotides with oligonucleotide primers and thermostable forms of DNA polymerase. PCR allows for the amplification of small amounts of viral nucleic acids from human body fluids and tissues. The PCR method has already been employed to identify viruses in individuals with chronic neurological diseases such as chronic myelopathy (87) and amyotrophic lateral sclerosis (227). It can be anticipated that PCR and other sensitive methods for nucleic acid detection will be increasingly employed for the detection of viral nucleic acids in the body fluids of individuals with schizophrenia, bipolar disorder, and other neuropsychiatric diseases.

Identification of Novel Infecting Viruses

The above methods are extremely useful for the detection of infections with viruses that have been previously identified and characterized. However, they are difficult to apply to the detection of infections caused by organisms that have not been well characterized. In such cases, data regarding nucleotide or amino acid sequences are generally insufficient to construct efficient immunoassays or nucleic acid amplification procedures. In addition, immunoassay and PCR methods are not easily applied to the discovery of new viral agents. Fortunately, a number of techniques that allow for the direct detection of novel viral agents in human tissues have now been developed. These techniques generally involve the extraction of nucleic acids from human tissue, the cloning of the nucleic acids into a suitable expression system, and the screening of individual clones to identify ones that may be associated with disease. For example, clones can be screened with sera from individuals with a particular disease in order to identify antigenic proteins. Reactive clones are subsequently sequenced and characterized for genomic organization and potentially encoded proteins. The information derived from these procedures can be used to construct immunoassays or nucleic acid amplification assays, and these assays can be used for large-scale studies of disease epidemiology. This process has already been employed for the initial identification and study of a number of novel viral agents including hepatitis C (9), hepatitis E (215), and human calici-

viruses (88). Of note is the fact that none of these viruses had been previously propagated in cell culture systems.

One limitation of standard nucleic acid library methods is that they are labor-intensive and require extended periods of time for the characterization of the target genomes. Recently, additional methods for the more efficient identification of nucleic acids associated with human diseases have been devised. Several of these methods, such as subtraction cloning (48), differential display PCR (116), and representational difference analysis (123), allow for the rapid identification and characterization of DNA or RNA found in affected individuals as opposed to controls. In addition, cloning techniques involving filamentous bacteriophage that express cloned proteins on the phage surface (169) can be used for the large-scale screening of potential disease-associated epitopes. It is highly likely that the application of these and additional techniques to the study of schizophrenia and bipolar disorder will result in the identification of novel target viruses. The association of these agents with the target disease can then be analyzed by carefully controlled trials involving large numbers of affected and control individuals. The application of this approach offers great promise in terms of the identification of new agents of disease and their eventual eradication.

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