Schizophrenia and Multiple Sclerosis

by Janice R. Stevens

Abstract

Similarities in clinical course, age of onset, geographical distribution, and immunological responses of patients with schizophrenia and multiple sclerosis (MS) suggest that these two common illnesses of young adults may belong to a similar class of disorders. This review examines some of the similarities and differences between these two disorders and suggests that epidemiological, immunological, and viral studies considered useful in the investigation of causal factors in multiple sclerosis may also be pertinent to the search for causes of schizophrenia.

The past several years have seen a resurgence of interest in schizophrenia as a disorder of the brain. Computerized tomographic (CT) studies have shown relative enlargement of the third and lateral ventricles of 15–20 percent of patients with a diagnosis of schizophrenia compared with controls (Johnstone et al. 1976; Weinberger et al. 1979; Boronow et al. 1985). Post-mortem measurements of subcortical nuclei show diminished size of hippocampus, amygdala, parahippocampal gyrus, globus pallidus, or periventricular nuclei in a significant percentage of studied cases compared with controls (Lesch and Bogerts 1984; Bogerts et al. 1985). Gliosis and nerve cell loss in diencephalon, limbic system, and basal ganglia have been described (Nieto and Escobar 1972; Stevens 1982). These data supporting morphological pathology in schizophrenia have stimulated the search for biological causes of this common and disabling psychosis.

There are a number of similarities between schizophrenia and multiple sclerosis (MS) that suggest that schizophrenia as well as MS may have an infectious or immunological etiology. Both disorders are characterized by onset in early adult life, and by progressive or remitting-exacerbating course with gradual increase in disability in many cases and spontaneous remission in others. Although schizophrenia and MS are pathologically and clinically very distinct disorders, some formal similarities of clinical course, epidemiology, and immune response suggest that both disorders may belong to a class of disturbances characterized by initial or persistent viral infection that can be followed by altered response of the immune system.

Onset and Course

Like MS, although 10-100 times more prevalent, schizophrenia is a disorder of young adults with a peak age of onset in the early to middle twenties (range 15–45 years, figure 1). Schizophrenia, like MS, has a unimodal age distribution which, as Johnson (1975) noted, is typical of, although not unique to infection acquired or activated in early adulthood. As in MS, the onset of schizophrenia may be either acute or subacute and is characterized by a steadily progressive course or by remissions and exacerbations resulting in increasing disability. In both disorders, the variable clinical picture and course are usually unaccompanied by signs or symptoms of systemic illness, although a history of chronic low-grade headache and of frequent somatic complaints is not unusual in early schizophrenia and easy
Fatigability is common in early MS. In both disorders, *formes frustes* occur, characterized by complete remission without residual symptoms.

**Geographic Distribution**

As is well known, MS is much more common in northern and temperate regions of the world than in the tropics, where it is quite rare. There is also a distinct north to south gradient of prevalence within Europe and North America (Acheson 1972). Differences in diagnostic requirements for schizophrenia in different parts of the world have greatly handicapped epidemiological studies. Schizophrenia incidence data reported from many developing countries, particularly in Africa, are nearly all based on hospital and clinic incidence rates rather than community- or country-wide surveys, and are inaccurately low due to shortages of medical facilities and to greater tolerance for some forms of schizophrenia in the community. However, even these relatively low numbers are erroneously high in many areas of the developing world due to widespread misdiagnosis of the “brief reactive psychoses,” which are very common in these regions, as schizophrenia (German 1972).

In a recent study undertaken in Harare, capital and largest city in Zimbabwe, 40–50 percent of all admissions to the mental wards of two university-affiliated hospitals were diagnosed as schizophrenia in 1983–84. However, when Research Diagnostic Criteria (Spitzer and Endicott 1978), requiring at least 2 weeks of illness for a diagnosis of schizophrenia, were applied, more than half of these patients failed to meet this duration criterion and were accordingly diagnosed as brief reactive psychosis. When the 6 months of illness specified by *DSM-III* (American Psychiatric Association 1980) were required, only 10–15 percent of admissions met criteria for schizophrenia (Stevens 1987).

Thus, although it is often stated that prevalence of schizophrenia is similar throughout the world (e.g., Sartorius et al. 1986), available data do not permit this conclusion. Indeed, the few population-based surveys that do exist indicate an approximately tenfold variation with much lower rates in Africa and parts of southwest Asia than in western Europe or the United States (Eaton 1985). As is the case with MS, reported cases of schizophrenia also appear to have their highest distribution in northern and eastern Europe, but are comparatively less common in southern Europe and in Africa, even in areas where schizophrenia has been looked for systematically by trained European personnel (see Torrey, this issue). This trend remains true for schizophrenia as for MS when prevalence data are presented only for the population at risk—i.e., over age 15. Just as the British Isles and northern Europe have the highest prevalence of MS in the world, western Ireland, Sweden, and western Croatia reportedly have the highest prevalence of schizophrenia, with Ireland alone showing a rate 44 times that of Guyana (Walsh and Walsh 1970). There are also considerable differences in hospital admissions for schizophrenia in the United States that cannot be wholly accounted for by “drift” hypothesis but could reflect admission policies or genuine geo-
SCHIZOPHRENIA RATES PER 100,000 FOR ADMISSION TO
STATE AND COUNTY HOSPITALS USA 1981 (DSM III)

Data from Survey and Reports Branch, NIMH (1981).

Sentence:

1 Data from Survey and Reports Branch, NIMH (1981).

Figure 2. Number of admissions for schizophrenia to State and county hospitals in United States in 1981.

Graphical differences as in MS (figure 2).

Sartorius et al. (1986) did not set minimum duration criteria for the diagnosis of schizophrenia. The inclusion of brief psychoses may thus have contributed to their conclusion that schizophrenia occurs with equal incidence throughout the world. For want of adequate population data, this important article also omitted three of the four developing countries studied from their incidence statistics. Finally, their conclusion that there is a similar incidence of schizophrenia in all the countries studied and hence world-wide, relied on incidence data derived with the Present State Examination and CATEGO's "narrow" definition of schizophrenia (S+). The narrow definition, which only requires one of Schneider's first-rank symptoms for diagnosis, is highly reliable (reproducible among observers) but does not distinguish schizophrenia from many acute psychoses, and gives essentially zero heritability and very poor final diagnosis predictability for the "nuclear" schizophrenia so diagnosed (Brockington et al. 1978; McGuffin et al. 1984). Hence, the validity of the diagnosis may be questioned.

These facts are stressed here because accurate epidemiology is so important to any hypothesis attempting to explain schizophrenia. An unequal geographical distribution with pockets of very high incidence is compatible with the hypothesis that, as in MS, an environmental event in addition to a genetic predisposition best explains the known epidemiology of the illness. Although epidemiological data for schizophrenia are less than adequate, the available information indicates that the dictum that schizophrenia is more or less equally distributed throughout the world is a premature extension of the observation that schizophrenia-like illnesses exist in all parts of the world.

In contrast to MS, which has a poorer prognosis in the tropics (Liebowitz and Alter 1973), the prognosis of schizophrenia is said to be significantly better in the developing world than in the developed (largely temperate) lands (World Health Organization 1973; Sartorius et al. 1986). The better prognosis in developing countries may, like the prevalence, be erroneously exaggerated by inclusion of the brief schizophreniform psychoses that contribute significantly to all admissions to psychiatric hospitals in these countries. The better prognosis in these areas could also signal greater immunity to a schizophrenia-inducing agent or agents. Alternatively, better outcome could be related to the much wider use of electroconvulsive therapies, to the less prolonged and smaller doses of neuroleptics, to much less psychotherapy, or as is usually assumed, to local cultural factors of care and aftercare.

Migration and Risk of MS and Schizophrenia

Adults who emigrate from countries of high risk for MS (e.g.,
Epidemics

For both schizophrenia and MS, there are reports of clusters of increased prevalence in space and time. Kurtzke and Hyllested (1986) documented the abrupt appearance of MS in the previously MS-free Faeroe Islands following the British occupation in World War II. A recent survey in Micronesia presented similar findings for schizophrenia (Dale 1981). Fortes and Mayer (1969) studied a group of villages in Ghana in the 1950's and found only one case of schizophrenia in a population of 5,000. On his return 26 years later to resurvey the area, Mayer found 13 cases per 5,000. Between his first and second visits, the population had for the first time experienced considerable exposure to Western civilization.

Genetic Factors

Heridity has long been considered of primary importance in schizophrenia and of much less significance in MS. However, concordance figures for twins and siblings are surprisingly similar for both disorders: 40-80 percent (MS) and 50-60 percent (schizophrenia) for monozygotic twins, 5-10 percent for siblings and DZ twins, and negligible risk for spouses in both disorders. Parents and children have a risk almost equal to sibs in both disorders (Gottesman and Carey 1983; Bundey 1985). Since the population risk for schizophrenia is at least 20 times higher than for MS, heritability of MS may be at least equal to that of schizophrenia. In both disorders the heritability factor is, however, considerably less than required for a purely genetic disorder unless one introduces the incomplete penetrance explanation. Differences in geographical distributions and migration patterns of the disease are thus critical evidence of environmental factors in these disorders.

There is considerable evidence for an association between several HLA factors and MS in certain but not all populations studied (Stewart and Kirk 1983). Although, in general, HLA studies have not supported predominance of one or more HLA factors in unclassified schizophrenia (McGuffin et al. 1983), in all six centers where a paranoid subgroup was delineated, HLA A9 was increased; HLA A1 was significantly increased in hebephrenic patients compared with controls in three of four centers (McGuffin et al. 1981). Miyanaga et al. (1984) also reported elevated incidence of DRW8 in a group of Japanese patients with schizophrenia.

Season of Onset

The principal interest in season-of-onset differences for diseases of unknown etiology is to relate such disorders to known fluctuations in incidence of recognized infections or toxic syndromes. Analysis of admissions to mental hospitals in England and Wales during the 1970's demonstrated a 4.7 percent rise in admission rate of schizophrenic patients in July and August and a 9.5 percent excess of admissions for mania during the same period (Hare 1983). From Japan, Abe (1963) reported a 9 percent excess of schizophrenic admissions in July among 90,000 patients admitted to hospitals between 1955 and 1961.

Although seasonal correlations with onset or relapse of MS are less well demonstrated, Bamford et al (1983) reported a slight predominance of attacks in the summer months in Arizona and a difference in time of onset in several other parts of the world. Sibley et al (1985) reported that more than 25 percent of clinical exacerbations of MS are associated with upper respiratory infections.

Season of Birth

There has been great interest in the unequal yearly distribution of births in a number of disorders because this may indicate exposure...
of the fetus or infant to special risks at time of conception, birth, or during a critical intrauterine period. An approximately 8 percent excess of births of future schizophrenic patients was shown during winter months and a 4 percent excess in early spring months in the large English-Wales population studied by Hare (1983). A relative excess of winter-early spring births has also been reported for Scandinavian countries, the United States, Japan, and Australia (Dalen 1975; Parker and Balze 1977). In a recent study from Finland, Mednick et al. (1987) found that the incidence of schizophrenia was nearly doubled in a cohort of schizophrenic patients who were in their second trimester of gestation during the widespread influenza A epidemic of 1957. The data concerning preferred season of birth for future MS victims are controversial. Dalen (1975) cites a single report from the Netherlands indicating an elevated optic neuritis incidence in individuals born in February and March.

**Immunological Factors**

The strongest evidence that MS is an infectious or immunological disorder stems from the reports of intrathecal IgG synthesis, oligoclonal bands in cerebrospinal fluid (CSF), and decrease in T-cells during only partially supported by all studies of diagnosed schizophrenics, a finding only partially supported by Kirch et al. (1985). Coffey et al. (1983) reported a reduction in T-lymphocytes in patients with acute, including never-treated, schizophrenic and a rise to normal ratio following treatment with neuroleptics. DeLisi et al. (1982, 1983) did not find a reduction in total T-cells in *chronically* hospitalized schizophrenic patients, most of whom were taking neuroleptics, but did observe a decrease in natural killer (NK) cells, a finding also reported for MS (Merrill et al. 1982). Decreased lymphocyte migration to measles or other antigens has been inconsistently reported in MS (Van Meulen and Stephenson 1977) and in schizophrenia (Vartanian et al. 1978).

Hirata Hibi et al. (1982) reported abnormal lymphocytes resembling those of infectious mononucleosis in the peripheral blood of schizophrenic patients, a finding not confirmed or attributed to phenothiazine effects by others (DeLisi et al. 1982). Again, studies of a relatively acute population by one group and chronic or drug-treated patients by another could explain the discrepancy. Ultrastructural abnormalities in lymphocyte nuclei (Bonartsev 1971) and other peripheral lymphocyte and serologic abnormalities including increased antibrain antibodies (Kuritzky et al. 1976; Kolyaskina 1983), abnormal protein in the CSF (Harrington et al. 1985), and an inhibitory effect of schizophrenic serum on phytohemagglutinin-stimulated lymphocytes (Vartanian et al. 1978) have been reported. Heath and Krupp (1967) described an IgG component in schizophrenic serum directed against the septal region of the brain that induced behavioral and electroencephalographic changes in systemically injected monkeys. Although a similar protein cross-reacting with brain was identified from schizophrenic serum in several other laboratories (Baron et al. 1977; Bergen et al. 1980), in most hands, autoantibodies against brain have been found with equal frequency in schizophrenic and control subjects (Whittingham et al. 1968; Boehme et al. 1974; DeLisi et al. 1985). Using immunocytochemical methods, we have not succeeded in our laboratory in demonstrating antibrain antibodies in serum or CSF of *chronic* schizophrenic patients against normal or schizophrenic brain specimens from septal regions, hypothalamus, or hippocampus (unpublished observations). The effects of medication and the great differences in the stage of illness in which patients are studied are likely to be very important barriers to achieving coherent results.

**Search for Virus**

Investigation of serum and CSF antibodies to a number of common viruses have been carried out in both MS and schizophrenia. Elevated titers against measles are most commonly specified for MS, but antibodies to herpes simplex (HSV), influenza A, mumps, Epstein Barr, rubella, and vaccinia have also been reported (Norrby 1978; Cook and Dowling 1980; Cremer et al. 1980). Increased serum and/or CSF titers against HSV, influenza A, measles, and cytomegalovirus (CMV) have also been reported in schizophrenia from some laboratories (Halonen et al. 1974; Albrecht et al. 1980; Torrey et al. 1982; Libikova 1983) but unfortunately have not stood up to replications (Lycke et al. 1974; Gottlieb-Stematsky et al. 1981; King et al. 1985; Rimón et al. 1986). Tests for HTLV-III antibody in schizophrenic serum and
reverse transcriptase in CSF have thus far yielded negative results (Robert-Guroff et al. 1985; DeLisi and Saran 1986). Serum interferon elevation was found by Preble and Torrey (1985) but not by Rimon et al. (1983).

Following the publications of Albrecht et al (1980) and Torrey et al (1982) of increased CMV antibody in CSF of patients with schizophrenia, we began a search for CMV and HSV antigen in the brains of schizophrenic patients, many of whom had died at a relatively early age during both acute and chronic stages of their illnesses. Although our early immunohistochemical studies with crude CMV antisera yielded positive results in a series of patients, with later use of affinity purified CMV antisera, we could not replicate our own initial positive results. Only 1 patient out of the 22 we have studied demonstrated immunoreactivity against CMV (in several large neurons of the vestibular nucleus) (Stevens et al. 1984). In other studies, high titer antisera to CMV, HSV-1 and HSV-2, mumps, measles, rubella, and rubeola were incubated with frozen specimens of 10 schizophrenic and 13 control brains. In one case, a 21-year-old woman, ill for less than 5 years before her death by suicide, there were scattered large neurons in amygdala and hippocampus that showed a distinct diffuse granular staining of the cytoplasm but sparing of nucleus following incubation with HSV-1 antibody.

Although a number of different viruses have reportedly been isolated from MS tissue, attempts to culture, cocultivate, or transmit virus from MS plaques or nervous tissue have had generally disappointing results. A few similar investigations have been carried out with schizophrenic material. Libikova (1983) reported growth of a herpes virus in cell cultures from a schizophrenic brain specimen. Tyrrell et al. (1979) described a cytopathic effect on human embryonic fibroblasts of CSF from schizophrenic patients and from individuals with a number of neurodegenerative disorders, but were unable to passage the agent or inhibit its effect with metabolic or DNA and RNA antagonists. Intracerebral inoculation of marmosets with the cytopathic CSF reportedly caused behavioral changes (Baker et al. 1983). Cytopathic effects of schizophrenic CSF were also reported by Libikova (1983). No cytopathic effects were observed by Mered et al. (1983), who attempted to replicate the Tyrrell et al. experiments with CSF from a new group of patients.

In 1979, a group of workers at the National Institutes of Health injected material from 20 brain specimens of patients diagnosed (mostly chronic) schizophrenia and from 19 controls with other neurological disorders, including MS, into guinea pigs (n = 22) and subhuman primates (n = 37). Animals were sacrificed or died 2-4 years later. With the exception of one guinea pig that developed a paralysis of the hindlimbs 18 months after inoculation with material from a patient who committed suicide during the first year of his schizophrenia, no illness ensued in the other animals. Examination of central nervous system (CNS) tissue from these animals with light and electron microscopy generally failed to reveal significant pathology (Kaufmann et al. 1983).

During the past 2 years, we have inoculated fresh and frozen brain and CSF from 24 schizophrenic patients and 10 controls on cultures of human dorsal root ganglia, human neuroblastoma, and medulloblastoma cells. Although no cytopathic effects have been observed, one line of neuroblastoma cells inoculated with fresh CSF from schizophrenic patients has shown changes in growth characteristics and increased cyclic adenosine monophosphate (AMP) production compared with controls. The responsible agent has been passaged in subcultures and cell-free media. CSF from additional patients and controls is under investigation (J.P Schwartz and J.R. Stevens, unpublished).

**Electron Microscopy and Genome Hybridization**

Electron microscopic studies of MS have yielded controversial results. Although several workers have described viral-like particles, these findings have generally not been confirmed (DuBois-Dalq et al. 1973; Melnick et al. 1982; Lampert and Lamport 1975). Most recently, Koprowski et al. (1985) reported finding both serum antibodies to HTLV and genomic material of a retrovirus related to HTLV-1 in CSF T-cells of patients with MS. This work awaits replication.

Although much less extensively investigated than in MS, virus-like particles resembling herpes simplex have also been described in schizophrenic brain specimens by Mesa and Cabrera (1979). As in MS, there are no convincing replications and further studies are required. In situ hybridization for CMV viral genome has been negative in MS and in schizophrenic brain specimens in our hands and others (Aulakh et al. 1980, 1982, Taylor and Crow 1986). Reported HSV genome in schizophrenic brains
(Sequiera et al. 1979) may be due to spurious hybridization with human DNA (Jones and Hyman 1983).

Discussion

Similarities between the course of illness and of several epidemiological features of MS and schizophrenia suggest that both disorders may be of infectious or immunological origin. This concept has long received wide acceptance among neurologists for MS, but is generally viewed with some incredulity for schizophrenia.

There are also, of course, very important differences between MS and schizophrenia. MS is associated with characteristic neuropathological changes in the brain and spinal cord that generally correspond to and account for the clinical signs and symptoms of the disease. The more modest and variable neuropathological and radiological abnormalities of schizophrenia are still subjects of argument among investigators. Thus, Roberts et al. (1986), using an optical densitometry method to measure glial fibrillary acid protein in schizophrenic and control material, concluded that there is no evidence for the gliosis of schizophrenic brains reported by others. Inspection of their data, however, reveals that although their method is very insensitive to reactive inflammation, but may be associated with only altered cell metabolism or membrane properties (Knight 1982; Oldstone et al. 1984; Manuelides et al. 1987).

There is solid evidence for decreased T-suppressor cells in peripheral blood, coincident with exacerbations of MS, and for the presence of oligoclonal bands in CSF in 85–90 percent of MS patients. There is a single report of decreased T-suppressor cells in peripheral blood in schizophrenia (Coffey et al. 1983) and a single instance of oligoclonal bands found in CSF (Kirch et al. 1985). This area needs further investigation in untreated patients early in the disease process. In both schizophrenia and MS, there are inconsistent reports of an autoimmune process directed against the brain. Recent advances in molecular and immunological techniques offer new opportunities to resolve the earlier controversial data. The viral hypothesis of schizophrenia (or MS) does not require that the disorder itself be contagious. Indeed, there is no evidence of this for either schizophrenia or MS. Spouses of patients with either disease have no greater incidence of the illness than the general population. The strong evidence for genetic predisposition in both illnesses suggests that if a virus initiates the illness, this complication is related to the unique genetic characteristics of the individual response.

This essay does not suppose or suggest that schizophrenia and MS have similar etiologies, but only proposes that as for MS there are good reasons to seek infectious or immunological factors as causal agents in schizophrenia. Nor does this hypothesis propose a single cause for all cases of schizophrenia. Comprehensive epidemiological studies, especially in the developing countries, evaluation of immunolog-
ical and potential infectious factors, especially during the acute disease process, and ultrastructural and molecular investigations of brain tissue are areas needing further investigation.

References


Ahokas, A.; Koskimemi, M.-L.; Vaheiri, A.; and Rimón, 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


Biton, V., and Abramsky, O Newer study fails to support environmental factors in etiology of MS. Neurology, 36 (Suppl. 1):184, 1986.


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


Survey and Reports Branch, Division of Biometry and Epidemiology, National Institute of Mental Health. Additions and Resident Patients at End of Year: State and County Mental Hospitals by Age and Diagnosis, by State. U.S. Rockville, MD: NIMH, 1981.


The Author

Janice R. Stevens, M.D., is Professor of Neurology and Psychiatry, Oregon Health Sciences University, Portland, OR, and Senior Staff Physician, Intramural Research Program, NIMH, Neuropsychiatric Research Hospital at St. Elizabeths, Washington, DC.