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Comment

How a Poliovirus Might Cause Schizophrenia: A Commentary on Eagles' Hypothesis

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John M. Eagles suggested that polioviruses might cause schizophrenia because 1) several reports of a recent decline in the incidence of schizophrenia coinciding with the introduction of polio vaccination, 2) the observed winter excesses in schizophrenic births (in temperate climates) could be explained by fetal exposure to poliovirus during the second trimester of gestation which would occur during the summer when polio epidemics are most frequent, 3) there are increased rates of schizophrenia among immigrants to the UK from regions of the world with low frequencies if immunity to polioviruses, 4) there may be genetic variants in the poliovirus receptor gene that could increase susceptibility to poliovirus infection (1). The large discordance rates for schizophrenia in monozygotic twin pairs indicate the existence of both genetic and environmental factors. Numerous genetic studies indicate an interaction of several genes in the etiology of schizophrenia. These genes may encode a family of poliovirus receptor subunits, various active combinations of which are expressed on T-immunocytes, monocytes, endothelial cells, and limited populations of (glutamatergic?) neurons. The poliovirus receptor on the T-cell may require both a specific combination of V segments of the T-cell antigen receptor, as well as a specific major histocompatibility (MHC) antigen, acting in concert to infect monocytes, the primary transporter of poliovirus from blood into the brain. The very large discordance rates for schizophrenia that probably exist for dichorionic-monozygotic twins (about 90%), as well as the much smaller discordance rates for monochorionic-monozygotic twins (about 40%), may be due to several allelic exclusion events expressed both in T-cells and possibly in certain neurons. A child who has lost some glutamatergic neurons due to viral infection during the second trimester of gestation, may be able to compensate for this deficit to a large extent by the super-abundance of excitatory synapses that exists in the brain until sexual maturity, at which time a selective loss of excitatory (mainly glutamatergic) synapses occurs together with hormonally induced changes in behavior, leading to a much increased risk of a psychotic episode.

KEY WORDS: Poliovirus; schizophrenia; Eagle's hypothesis.

John M. Eagles has made a convincing argument for polioviruses being a cause of schizophrenia (1). Earlier, we reviewed the evidence for GABergic predominance/glutamatergic deficit as a common etiological factor in the "functional" psychoses (2,3). An important cause of such a neurotransmitter imbalance was considered to be selective destruction by a neurotropic virus of some types of excitatory glutamatergic and/or cholinergic neurons, leaving a predominance of inhibitory GABergic neurons (2–5).

Three major findings in biological psychiatry (large discordance rates for the major psychoses in monozygotic twins; an uneven distribution, over time, of births of individuals who will become psychotic later in life; the presence of cerebral atrophies and neuronal losses in

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many psychotic individuals), that link schizophrenia and affective psychoses, are also consistent with an etiological role for neurotropic pathogens in these psychoses (2). Although the accumulated circumstantial evidence over the years for a viral infection of the fetal brain, probably during the second trimester of gestation is compelling, the virus remains to be identified (6,7).

The postulated pathogens should have the following properties: 1) they should be neurotropic with a high specificity for certain types of neurons, 2) they should be present worldwide, 3) they should cause seasonal epidemics in temperate climates. Several enteroviruses, including the polioviruses, exhibit these properties, and there has been some speculation that polioviruses could play a role in the etiology of schizophrenia (1,4). In particular, there have been several reports of a declining incidence in schizophrenia, coinciding with the introduction of polio vaccination (1). However, there is no direct evidence, so far, to implicate any enterovirus or other pathogen. For example, intracerebral inoculation of non-human primates and guinea pigs with postmortem brain tissue from schizophrenic patients did not result in behavioral differences or neuropathological abnormalities, compared to control animals, followed up for six years (8). Further, an extensive search for enterovirus (and other viral) RNA in postmortem schizophrenic brain samples, using polymerase chain reaction techniques to amplify such RNA, was negative (9).

Nevertheless, a virus could attack and destroy neurons, perhaps during the second trimester of gestation, then disappear without leaving a viral RNA trace.

The Nature of the Poliovirus Receptor and Its Possible Relationship to Psychosis. Paralytic poliomyelitis is not usually associated with psychosis. One small epidemiological study, involving Connecticut and Massachusetts, found a statistically significant coherence between polio epidemics and excess schizophrenic births in Connecticut but not in Massachusetts (10). However, most instances of schizophrenia might be related exclusively to one of the 3 polio serotypes or even to certain strains of one of the serotypes. The virus in question could also be a related Coxsackie or ECHO enterovirus (4), although the coincidence of a decline in the incidence of schizophrenia with the initiation of polio vaccination suggests that the virus is one of the polioviruses. Poliovirus can be recovered from the motor cortex, deep cerebellar nuclei, brain stem and, especially, the motor neurons in the ventral part of the spinal cord in patients dying with paralytic poliomyelitis (11). Lesions are also observed in motor cortex, globus pallidus, and cerebellar vermis (11). It is interesting that the five brain regions exhibiting significantly reduced ^{3}H-flunitrazepam binding in a small sample of postmortem schizophrenic brains included motor cortex, globus pallidus, and cerebellar vermis (5). Neuronal cell loss from these three regions has also been described in schizophrenic brains. The neurotransmitters (other than acetylcholine) used by the neurons in the motor cortex, and other parts of the brain, that are susceptible to poliovirus are, apparently, not known at present.

It is well-known that during polio epidemics the ratio of paralytic to inapparent polio infection can be as high as 1:500 (12). The vast majority of those infected with poliovirus are unaware of it but are nevertheless able to infect others. An inapparently infected mother might be able to infect her unborn child. It is also well-known that not all cells that express the "poliovirus receptor" (PVR, which is a polio binding protein in the cell membrane) can be infected by poliovirus: the presence of the "poliovirus receptor" protein on the cell surface is not sufficient for the entry of viral RNA into the cell and its replication (13). Radiolabeled type 1 human poliovirus binds to synaptosomes prepared from virtually any region of the human brain (14), but only a few of these support viral replication that results in lesions (11). It is also known that certain cells, such as primate kidney and amnion cells, which are not normally infected in paralytic polio victims, become highly susceptible to poliovirus when the cells are grown in culture. Further, PVR is expressed in a wide range of human tissues, including those that are not sites of polio infection, suggesting that additional factors are required for poliovirus replication (13). It may be important that PVR expression in normal human placenta is restricted to specific cell types (13). These additional factors (co-receptors) could be other cell surface antigens, such as major histocompatibility complex (MHC) antigens (= HLAs), axonal path finding molecules, and cell adhesion molecules (CAM), as will be discussed below. The structure of functional poliovirus receptors could be somewhat analogous to the structure of the benzodiazepine binding sites, which are a subset of GABA-A receptor complexes containing α, β, and γ subunits in a pentameric structure. There are 6 types of α, 3 types of β, and 2 types of γ subunits. The α, β, and γ subunits, which are all required simultaneously, interact allosterically to induce high-affinity benzodiazepine binding sites on the subunits of the GABA-A receptor complex (15,16). In analogous fashion, the functional PVR complex might be made up of PVR together with (a) co-receptor(s), as is the case with HIV-1 receptors (17,18). According to this model, there may be several functional PVR complexes on neurons, containing, in addition to the binding protein, an axonal path finding or a cell ad-

hesion molecule serving as a co-receptor. Thus, there may be a family of functional PVR complexes, some located on T- or B-immunocytes, monocytes, and endothelial cells, others on well defined neuronal populations. The poliovirus binding protein (PVR), MHC antigens, as well as CAMs, and axonal path finding molecules, are all members of the immunoglobulin super family, the significance of which will be discussed below.

One of the reasons for the large number of inapparent polio infections may be the lack, or reduced numbers, of "functional" PVR complexes (FPVRC) on the neurons that are normally attacked and destroyed by polioviruses in cases of paralytic polio.

By the same token, other individuals, during development of the fetal brain, may express higher densities of FPVRCs on other types of neurons in the central nervous system, e.g. a restricted population of glutamatergic neurons (4,5). Thus, it seems possible that one (some) of the genetic elements determining susceptibility to schizophrenia may be a gene (or genes) that determine the expression of FPVR subunits in the relevant neurons.

In a transgenic mouse strain containing the human PVR gene, PVR RNA is expressed in neurons of the central and peripheral nervous system, developing T lymphocytes, epithelial cells of Bowman's capsule and tubules in the kidney, and endocrine cells in the adrenal cortex (13). Lower levels of PVR RNA are expressed in intestine, spleen and skeletal muscle. After infection with type 1 Mahoney poliovirus, replication was detected only in neurons in the brain and spinal cord, and in skeletal muscle of the transgenic mouse (13). In the transgenic mouse brain, poliovirus replication was detected in cerebral cortex, pyramidal layer of the hippocampus, olfactory bulb, thalamus, hypothalamus, and deep cerebellar nuclei. It is noteworthy that although the hippocampus is not affected in human cases of paralytic polio, it is in the transgenic mouse (13). This suggests that hippocampal pyramidal neurons of the normal mouse express a cell surface protein (a co-receptor) which, when combined with the human PVR protein, forms a FPVRC that allows the entry and replication of type 1 Mahoney poliovirus in these neurons. It can be expected that human hippocampal pyramidal neurons at some stage of development express an homologous cell surface protein (presently unidentified) which may exist in several allelic forms, one or more of which may combine with the PVR protein to yield a FPVRC. The presence of a FPVRCs on human hippocampal pyramidal neurons could represent a genetically determined susceptibility factor, contributing to schizophrenia after poliovirus infections in utero. Lesions have been reported in the hippocampi of schizophrenic brains, and significantly reduced levels of ^{3}H-flunitrazepam binding in the hippocampus were also found in a small sample of schizophrenic brains (5). We speculated that high densities of benzodiazepine binding sites may be expressed on excitatory glutamatergic and cholinergic neurons (4,5). This is known to be the case for glutamatergic hippocampal pyramidal neurons (5).

Could Histocompatibility Complex Antigens Play an Etiological Role in Schizophrenia and Affective Psychoses? An association between paralytic polio and HL-A3 and, especially, HL-A7 histocompatibility antigens has been reported, and there was speculation that these antigens might form part of a FPVR (19–21). Further, in one study (ref 22, Table 1.2, p 12), concordance for paralytic polio in identical (MZ) twins was 36%, while concordance in fraternal (DZ) twins was 6%, a pattern similar to that seen in schizophrenia (22), as well as in most "autoimmune" disorders (23) which are associated with specific HLAs. Specific histocompatibility antigens (HLAs) may also be associated with schizophrenia (24,25). This possibility has been much investigated, and there seems to be some association between HLA-A9 (26–28) and −B5 (24,26,27), as well as DRw8 (25), Aw 26 (29), B27 (27), and other histocompatibility antigens (29–31), and schizophrenia. There is also a highly significant negative association between schizophrenia and the "autoimmune" disease rheumatoid arthritis (32), which is strongly associated with HLA-DR1 or DR4 (33), as well as a positive association between schizophrenia and insulin-dependent diabetes mellitus (34). Recently, a negative association between the HLA DRBI*04 and schizophrenia has been reported. DRBI*04 is positively associated with rheumatoid arthritis (35). In general, schizophrenics with a schizophrenic first degree relative appear to be more likely to also have a parent or sibling with an autoimmune disease ($p = 0.0003$) (34). Like schizophrenia, rheumatoid arthritis and other "autoimmune" diseases exhibit low concordance rates among monozygotic twins (23). Further, several large linkage studies (36–38) found evidence for a vulnerability locus for schizophrenia in a region on human chromosome 6p near the HLA region. It is clear, however, that no *single* histocompatibility antigen is *consistently* associated with schizophrenia (39,40). The fact that MHC antigens (HLAs) are usually not expressed on neurons (41,42), and the finding that the HLAs reportedly associated with paralytic polio (19,20) are not among the several that have been reported to be associated with schizophrenia (see above) make it unlikely that MHC antigens participate in the

formation of FPVRs on neurons, although they could participate in their formation on lymphoid cells, or glia (41,42). For these reasons, cell surface antigens other than the MHC antigens, must also be considered as possible participants (co-receptors) in the formation of functional virus receptor complexes on neurons. But before leaving the discussion of a possible connection between specific histocompatibility complex antigens and schizophrenia, the relationship between narcolepsy, histocompatibility antigens and schizophrenia should be mentioned.

Narcolepsy and Schizophrenia. Narcolepsy is a "neurological" disorder characterized by recurrent daytime sleep attacks, sudden loss of muscle tone (cataplexy), sleep paralysis, disturbed nocturnal sleep, and hypnagogic hallucinations (43). Like schizophrenia and affective psychoses, narcolepsy has a strong genetic component, as well as a rather high discordance rate among monozygotic twins, again suggesting environmental factors in all three disorders (44,45). Narcolepsy has a very high (>98%) association with the HLA-DR2 histocompatibility antigen (46,47). Schizophreniform psychoses, perhaps representing an extension of hypnagogic hallucinations, are apparently more common among narcoleptic patients, than in the general population (48,49). Narcolepsy-related schizophreniform psychoses, therefore, may be part of the schizophrenia-manic depressive psychosis spectrum. Interestingly, narcolepsy-associated schizophreniform psychoses can be effectively treated with central stimulants, including d-amphetamine which often exacerbates "classical" schizophrenia (48). The mechanism through which the expression of HLA-DR2 antigen might lead to narcolepsy is, at present, entirely unknown.

Could Neural Cell Adhesion or Axonal Path-Finding Molecules Participate in the Formation of a "Functional" Virus Receptor? Neural cell adhesion and axonal path-finding molecules are especially attractive candidates for the virus co-receptor since they are restricted to the surface membranes of certain types of neurons possibly at specific times during development. Of these, the KAL gene product serves as a useful example (50,51). Kallmann's syndrome is characterized by secondary hypogonadism and infertility, inability to smell due to absence of olfactory bulbs and tracts, mental retardation, various midline defects of the body and brain, including defects in the hippocampus, cerebellum and other brain regions. Males are 5 to 7 times more frequently affected than females. The KAL gene, deleted or nonfunctional in Kallmann's syndrome, encodes a protein that exhibits amino acid sequence homology with neural cell adhesion and axonal path-finding molecules (50,51). Cowen and Green (52), have pointed out a number of similarities between schizophrenia and Kallmann's syndrome, including anosmia, reduced fertility, neuronal defects in hippocampus, temporal lobes, and cerebellar vermis. In the case of Kallmann's syndrome the deletion of the KAL gene results in the defective migration of several types of neurons. In schizophrenia, a variant KAL gene product might participate as a co-receptor, together with the (polio) virus binding protein (PVR), in the formation of a functional virus receptor permitting the entry of the virus into neurons expressing the variant KAL gene product, followed by neuronal destruction. Apparently, schizophrenia occurs less frequently in Kallmann's patients than in the general population (52), which is consistent with the hypothesis that a variant KAL gene (deleted in Kallmann's syndrome) might participate in the formation of FPVRs. KAL gene products may be transiently expressed during embryogenesis. Therefore, some of the genetic determinants in major psychoses could be variants of the KAL gene as well as the PVR gene. The HLAs, B-cell immunoglobulins, T-cell antigen receptors (TcR), cell adhesion molecules, axonal path-finding molecules (including the KAL gene product), as well as the "poliovirus receptor" are all members of the immunoglobulin superfamily. The significance of this fact will be discussed below.

The KAL gene is located on the short arm of the X-chromosome (at X p22.3), outside the pseudoautosomal region. On the basis of considerations not dealt with in this paper, Crow (53) has suggested that a gene on the X chromosome, outside the pseudoautosomal region, may play a role in the development of the major psychoses.

It is noteworthy that cingulate cortex (a mid-line structure) exhibits both reduced ^{3}H-flunitrazepam binding (5) and neuronal loss in some schizophrenic brains (54).

The argument presented above, suggesting that a KAL gene product might function as a co-receptor for poliovirus, applies equally to one or more of the structurally related neuronal cell adhesion or axonal path-finding molecules (50).

Evidence for Motor Neuron Damage in Schizophrenia. An extensive investigation of neuromuscular dysfunction in "functional" psychoses by Meltzer and Crayton, has provided convincing evidence for denervation and reinervation of (cholinergic) motor neurons in both schizophrenia and affective psychoses (55,56). There is also some association between schizophrenia and amyotrophic lateral sclerosis, a progressive degenerative syndrome of unknown origin involving loss of

motor neuron systems (57). These findings are consistent with a limited destruction of some motor neurons in psychotic patients, by polio or other enterovirus. There is also evidence for the loss of some cholinergic neurons from the brains of schizophrenics. Karson et al. (58) reported a 46% reduction of the enzyme choline acetyl transferase (CAT, a marker for cholinergic neurons) in the pontine tegmentum of schizophrenic brains. Other lines of evidence are also consistent with the loss of certain cholinergic neurons from schizophrenic brains (2,4). A difference between these psychotic patients, and paralytic polio patients may be a relatively lower density of "functional" virus receptors on motor neurons and a higher density on, for example, some types of glutamatergic neurons in the former, during fetal development.

Influenza and Schizophrenia. Some epidemiological studies suggest a relationship between excess schizophrenic births and prenatal exposure to influenza during epidemics (59–62), while other studies indicate that this relationship does not uniformly exist (63–67). The balance of evidence now suggests that prenatal exposure to influenza is not a cause of schizophrenia. Fetal exposure to influenza virus during the second trimester as a cause of schizophrenia would seem difficult to reconcile with the observed excesses of schizophrenic births during the winter months, and the fact that most influenza epidemics also occur during the winter (typically December and January). Fetal exposure to an enterovirus during the second trimester would be in better agreement with the excesses of schizophrenic births during the winter, since enterovirus epidemics usually occur during the summer (1). Since several enteroviruses cause influenza-like symptoms, it seems possible that some "influenza" epidemics are, in reality, enterovirus epidemics, or mixed enterovirus-influenza epidemics, particularly those that start in the summer or fall (influenza virus was first isolated in 1933). The much studied A2 "influenza" pandemic of 1957 (e.g. 59, 61) is unusual in that it started in the UK in the summer of 1957 with a peak incidence of new infections occurring from mid-September to mid-October (61). The peak incidence in Helsinki occurred from October 8 to November 14, 1957 (59). This early appearance, especially in the UK, is more typical of an enterovirus epidemic, than an "influenza" epidemic. The severe "Spanish influenza" pandemic of 1918–1920 was unusual in at least two respects: 1) it was extremely virulent, killing more than 21 million people worldwide, many of them previously healthy young adults (68); 2) it began in the late summer of 1918, also suggesting the involvement of an enterovirus. It is striking that schizophreniform psychoses appeared in a number of previously healthy adults affected by the illness. Some of these psychoses were temporary, others (about one third) were permanent (69). These findings suggest that a virus can cause a schizophreniform psychosis in previously healthy adults. Thus, in addition to the psychoses that may result from viral infection of the fetus, there may be a spectrum of psychoses with sudden onset in adults of any age, caused by similar viruses. In his classic "A History of Poliomyelitis," John R. Paul (70) includes a chapter entitled "Other 'Virus' Diseases of the Central Nervous System," which, in addition to the "Spanish influenza," he also describes another epidemic which might have been caused by an enterovirus, and which displayed psychiatric symptoms: encephalitis lethargica, or von Economo's disease, which occurred almost simultaneously (1917–20) with the "Spanish influenza" (1918–20). Some experts thought there might be a relationship between the two diseases. For example, the "influenza" might render a person more susceptible to the encephalitis. Von Economo's encephalitis tended to be chronic with gradual mental and physical deterioration accompanied by personality changes and speech defects. The cause of von Economo's encephalitis remains unknown, and no new cases of it have been reported since 1927 (70).

The Los Angeles "polio" epidemic of spring 1934 also displayed psychiatric symptoms, mainly emotional lability with hysterical episodes, loss of concentration, lapses of memory and sleep disturbances, but surprisingly few paralytic cases (70,71). Later, there were speculations that some of the cases might have been caused by other members of the enterovirus family (Coxsackie or Echo viruses). Others thought that the Los Angeles epidemic of 1934 resembled the Akureyri, Iceland epidemic of winter 1948, or an epidemic in 1954, called "benign myalgic encephalomyelitis," or "epidemic neuromyasthenia" of which there were 13 outbreaks between 1954 and 1971 (70). After 1988 such outbreaks usually receive the designation "chronic fatigue syndrome," which has been associated with persistent enteroviral infections (72). Isolates from the spinal cords of fatal cases of the Los Angeles 1934 epidemic all contained the rare type II poliovirus (70).

The examples presented above serve to illustrate the probable ability of some enteroviruses, including poliovirus, to cause psychiatric disorders in humans.

Dichorionic (DC) Monozygotic (MZ) Twins Exhibit Larger Discordance Rates for Schizophrenia than Monochorionic (MC) Twins. About two-thirds of all monozygotic (MZ) twins share one placenta and one blood circulation system (monochorionic-MC), while one-third have separate placentas and blood circulation systems

(dichorionic-DC). A preliminary study indicated that DC-MZ twins may exhibit about 11% concordance, while MC-MZ twins may exhibit near 60% concordance rates for schizophrenia (73,74). To account for this large difference in concordance rates, the authors proposed that a "schizovirus" with a relatively low probability of passing across a placenta, would have a greater chance of infecting both MC-MZ twins (with one placenta and one blood circulation system), than both DC-MZ twins, each with its own placenta and blood circulation system. In this context the reported expression of PVR restricted to specific cell types in human placenta, is of great interest (13). The difference in concordance rates between MC- and DC-MZ twins, might also be accounted for by assuming 2 or 3 allelic exclusion events affecting "schizovirus" receptor subunits in blood cells (e.g. T-cells), and in the brain (specific neurons), even with a high probability of the virus passing from the maternal blood circulation, across the placenta, to the fetal blood circulation. For example, B-immunocyte immunoglobulin genes and T-cell antigen receptor genes (α/β or γ/δ) are among the few known genes not on the X-chromosome (X-inactivation) to be subject to allelic exclusion (the expression of only one allele at a given locus). It is known that MZ twins often have different T-cell repertoires (75–77), and it may be assumed that the differences will be greater for DC-MZ, than for MC-MZ twins due to selection of different immunoglobulin gene rearrangements during fetal development (this does not appear to have been investigated yet).

Since MC-MZ twins share a blood circulation system the T-cell antigen receptor gene rearrangements made by each twin will be mixed during fetal development. Such mixing will not occur in DC-MZ twins. Since maturation of T-cells requires contact (complexing) with HLAs, and since there seems to be some association between specific HLAs and schizophrenia, it seems possible that a specific T-cell-HLA complex could form a schizovirus receptor.

High frequency rearrangement of T-cell antigen receptor genes, as well as B-cell immunoglobulin genes, requires 2 gene products (recombinases), RAG-1 and RAG-2 (RAG = Recombination Activating Gene), although RAG-1 recombinase alone can rearrange immunoglobulin genes at a much lower frequency (~0.1%) (78). Using two different techniques, 2 groups have independently reported the expression of RAG-1 (or somatic DNA recombination) in neurons in mouse brain (78,80). Interestingly, both methods revealed RAG-1-like activity in cerebellar granule cells and hippocampal pyramidal cells, both glutamatergic (79,80). The more sensitive method of Matsuoka et al. (80) involves restoring to correct transcriptional orientation an inverted bacterial β-galactosidase gene flanked by two mouse recombination signal sequences (from a mouse Ig gene). This "recombination reporter gene" was injected into fertilized mouse oocytes to generate transgenic mice. More than 70 discrete areas of the adult transgenic mouse nervous system were β-galactosidase-positive. In addition to cerebellar granule cells and hippocampal pyramidal cells, β-galactosidase-positive neurons were also found in cingulate cortex, amygdala and globus pallidus, regions showing abnormalities in schizophrenic brains (5). In general, there was more prominent staining in sensory as opposed to motor regions of the brain (80). At present, it is not known which native genes (if any) in the β-galactosidase-positive neurons may be rearranged. Since neuronal cell adhesion molecules and axonal path-finding molecules are members of the immunoglobulin superfamily, it seems reasonable to speculate that at least some of the genes encoding these molecules may be substrates for DNA recombination enzymes. These genes should contain recombination signal sequences and be relatively easy to find. Since allelic exclusion is characteristic for immunoglobulin genes of B- and T-cells, it also seems reasonable to speculate that the genes which may be rearranged in neurons will exhibit allelic exclusion. This would represent an additional stage at which MZ twins might become discordant with respect to virus receptors on the surfaces of well-defined neuronal populations, and this discordance would be seen in both DC and MC twins, accounting for the ~40% discordance rate for schizophrenia in MC-MZ twins. Apparently, J. Singer-Sam was the first to suggest that at least one of the genes involved in schizophrenia will show allelic exclusion (81).

Synaptic Pruning as a Trigger for the Appearance of Schizophrenia After Adolescence. In humans, synaptic density in frontal cortex increases during infancy, reaching a maximum at age 1–2 years, which is at least 50% above adult values. After age 5, there is a decline in synaptic density which reaches adult values between the ages of 15 and 20 (82). P. Rakic and associates found similar patterns in rhesus (83) and macaque (84) monkeys: an increase in synaptic density until the second or third postnatal month, to about twice the adult levels, followed by a slow decline until sexual maturity is reached, at which time there is a more rapid decline to adult levels. Adult levels remain relatively constant for the rest of the animals' life. The elimination of synapses between childhood and puberty has been called "synaptic pruning" and there has been speculation that this reduction in synaptic density might contribute to the onset of schizophrenia (85,86). It is highly significant that

the elimination of synapses is selective: almost all of the synapses eliminated are excitatory (asymmetric synapses), while the density of inhibitory (symmetric) synapses remains relatively constant (83,84,86). Thus, the majority of synapses eliminated around puberty are glutamatergic and are located on dendritic spines of pyramidal neurons (83,84). According to the hypothesis presented so far, a virus selectively destroys a well-defined subpopulation of glutamatergic neurons during the second trimester of gestation, of individuals who will later become schizophrenic. The brain may be able to partly compensate for this lesion by increased branching of the remaining glutamatergic neurons. However, after the selective pruning of glutamatergic synapses around puberty, the brain will "decompensate" and symptoms of overt psychoses will start to appear. This interpretation is in accord with the proposal of Weinberger that the appearance of schizophrenia is linked to the normal maturation of a brain which had been damaged at a much earlier time (87). In addition to synaptic pruning other, sexually dimorphic, changes take place around puberty that affect the brain and behavior, most obviously hormonal status.

CONCLUSION

According to the model presented here, a virus (probably a polio-like enterovirus) passes from the mother's blood, across the placenta, into the fetal brain where it very selectively infects and destroys a sub-set of well-defined neurons, probably during the second trimester of gestation (88,89). The genetic elements in schizophrenia determine the formation of several types of functional poliovirus receptors on certain cells of the placenta, monocytes, endothelial cells, T-immunocytes, and on certain neurons. Although the exact mechanisms by which poliovirus is transported from the intestinal lumen to the brain remains to be clarified, it appears that poliovirus particles are initially endocytosed by intestinal epithelial M cells of Peyers patches, which bring them into contact with T-cells and monocytes (90,91). Poliovirus replicates slowly in monocytes (the main reservoir of poliovirus in blood) which carry the virus into the brain by diapedesis (90). A small population of T-cells may also allow replication of poliovirus, and may also be required for the infection of monocytes and subsequent viral replication (90,91). It has been known since at least 1969 that poliovirus can replicate in endothelial and mononuclear cells (92).

Two or three allelic exclusion events are probably involved in virus receptor formation in several cell types and would explain the large discordance rates for schizophrenia in dichorionic monozygotic twins as well as monochorionic monozygotic twins. The allelic exclusion events may take place at the level of the T-cell antigen receptor as well as at the neuronal level in genes encoding neuronal cell adhesion and/or axonal pathfinding molecules.

Mothers may become inapparently infected with an enterovirus (poliovirus) during the second trimester of gestation and transplacentally infect the fetus at a time when functional poliovirus receptors are transiently expressed on the developing neurons in question. Mainly inapparent infections could account for both the basal level of schizophrenic births throughout the year as well as the excess births associated with (enterovirus) epidemics.

Children with virus-induced deficits of glutamatergic neurons can partially compensate for them until the age of puberty, because of a super abundance of glutamatergic synapses. These individuals become psychotic after the extensive and selective elimination of glutamatergic synapses around puberty together with hormonally induced changes in brain function.

The enterovirus itself is probably destroyed after it has destroyed the glutamatergic neurons in question. This would account for the failure to detect viruses, or viral RNA, in postmortem schizophrenic brains. Antipsychotic drugs act by blocking a sub-set of $GABA_A$ receptors and thus counterbalance deficits in glutamatergic neurotransmission.

Several of the hypotheses presented in this paper can be easily tested by: 1) determining the neurotransmitters used by the neurons that are lost in schizophrenia and affective psychoses. For example, slices of postmortem psychotic and nonpsychotic brains could be stained with antibodies to GABA, glutamate or other neurotransmitters, using immunohistochemical techniques, similar to the study of Kowall and Beal (93) who demonstrated a reduced number of glutamate-immunoreactive pyramidal neurons in the hippocampal cornu ammonis fields of postmortem brains from patients dying with Alzheimer's disease. Similar studies could be made using antibodies to GAD and CAT to selectively stain GABergic and cholinergic neurons, respectively; 2) the T-cell repertoires of MZ twin pairs, discordant for schizophrenia, should be compared, as has been done for several "autoimmune" diseases; 3) the T-cell repertoires of healthy dichorionic and monochorionic MZ twin pairs should be compared. It might be expected that dichorionic MZ twin pairs will be more discordant with respect to their T-cell repertoires than monochorionic twin pairs, as apparently is the case for schizophrenia,

and 4) using the PCR method of Taller et al. (9), "high risk" second trimester abortuses (from schizophrenic mothers) could be examined for the presence of poliovirus, and other viruses, in fetal brain, and 5) the genes for known axonal pathfinding and neural cell adhesion molecules should be searched for recombination signal sequences.

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