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Prenatal Factors in the Pathogenesis of Schizophrenia

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The excess of winter–spring births among individuals suffering from schizophrenia provides strong evidence for the existence of some prenatally occurring factors in the pathogenesis of schizophrenia. Recent epidemiological findings suggest that maternal viral infections during the second trimester of pregnancy may play a crucial role in the aetiology of adult schizophrenia. A 'two-hit window' hypothesis of the mechanism of action of prenatal factors in the pathogenesis of schizophrenia suggests at least two time-specific prenatal aetiological events. The observed association between prenatal viral infection and increased incidence of adult schizophrenia need not be a direct cytotoxic result of the viral infection, but may be caused indirectly, for example from foetal minor cerebral haemorrhages produced by the anticoagulant effects of aspirin.

Several lines of research suggest that some prenatal environmental factors play an important role in the aetiology of at least some forms of schizophrenia. The observed variations (Torrey, 1989) and the suggested recent decrease in the incidence of schizophrenia (Der *et al*, 1990) may be due to the varying or decreasing frequency of these prenatal schizophrenogenic factors. The identification of these prenatal aetiological factors and their mechanism of action is of primary interest in biological research into schizophrenia.

Seasonality of birth

Epidemiological research around the world has shown that persons who later develop schizophrenia as adults are born disproportionately more often during late winter and early spring (Machon *et al*, 1983; Torrey & Kaufmann, 1986; Hare, 1988). A similar although less marked season-of-birth effect has been reported for bipolar affective disorders, but not for neurotic or personality disorders.

It has been suggested that excessive winter–spring births among individuals suffering from schizophrenia result from a seasonal abnormality of parents' procreational habits, which might be due to hereditary factors, social class or age, but research has not been able to support any of these explanations. The possibility that this observed seasonality could be a statistical artefact or merely an accentuation of the seasonality observed for general births has been generally refuted (Torrey & Kaufmann, 1986; Sham *et al*, 1992).

On the whole, there seems to be a general consensus that some seasonally varying environmental cause damages either the developing foetus or the growing infant in such a way as to increase the risk for adult schizophrenia. Environmental factors that have been proposed to explain the seasonality of birth in schizophrenia include infectious agents, nutritional factors, temperature variations at the time of conception, environmental toxins, and an interaction of these factors with genetic traits. Of these, prenatal viral or other infections are currently the most favoured explanation. Many infectious diseases are seasonal, with typical peak incidences; this accounts for the peak incidence of congenital rubella in November–December, following maternal infection during the spring peak of adult rubella. The seasonality of anencephalic births, congenital abnormalities and mental retardation has been explained in the same way (Hare, 1988).

However, even if seasonally occurring infections or any other environmental events were to explain this effect in schizophrenia, such events need not necessarily occur prenatally. The central nervous system of the infant is immature at birth, and the developing brain during infancy and childhood may have critical periods of development at least several months, and possibly even years, after birth. In the Septembers of postnatal life, a child born in early spring is at a different developmental stage than with cousins born in late summer or fall.

Obstetric factors

There is fairly consistent evidence that some obstetric complications are a significant risk factor in the aetiology of at least some forms of schizophrenia (McNeil, 1988; Dykes *et al*, 1991). The concept of obstetric complications is, however, far too broad to permit any specific ideas of their exact role. Obstetric complications represent a variety of different somatic deviations, with probably highly varying consequences for the risk of developing schizophrenia or its subtypes.

Schizophrenic patients with high genetic risk and with a history of severe delivery complications are much more likely to have increased third-ventricle size and widening of cortical sulci, together with a predominantly negative symptom profile (Cannon *et al*, 1990). It has been suggested that in individuals with high genetic risk for schizophrenia, anoxia and/or haemorrhage secondary to delivery complications at birth may produce increased periventricular tissue damage (Cannon, 1991).

However, one has to remember that some of the obstetric complications reported at the time of birth probably have their origin earlier, during the prenatal period. The reports of low birth weight in some adult schizophrenics clearly point to some foetal developmental disturbance. Similarly, the findings of enlarged ventricles as well as those of abnormal size or cellular composition of various brain regions, including the grey matter of the thalamus, basal ganglia, and hippocampus, can be as well or more easily understood as prenatal developmental abnormalities in the formation, migration, or differentiation of cortical neurons (Nowakowski, 1987; Lyon & Barr, 1991; Bogerts & Falkai, 1991). These stages of development of neurons start in the late first trimester of gestation and extend to about 3–6 months after birth (Nowakowski, 1987).

Minor physical anomalies

Minor physical anomalies are thought to originate from damage to the foetus during the late first and early second trimester of gestation; these include low-set ears, relatively great distance between eyes, and a single transverse palmar crease. Several groups of patients with neurological diseases such as epilepsy, mental retardation, and learning disabilities have been reported to show more of these minor physical anomalies (Torrey & Kaufmann, 1986). A similar finding has been reported both in childhood schizophrenia and in a group of 40 patients with adult schizophrenia (Torrey & Kaufmann, 1986; Guy *et al*, 1983).

Dermatoglyphics

Although dermatoglyphics are determined mostly by genes, it has been shown that deleterious intra-uterine experiences, especially during the first two-thirds of the second trimester of pregnancy, can alter their form (Hamilton *et al*, 1973). Viral infections *in utero* have been shown to be capable of changing dermatoglyphics. Schizophrenic patients have been shown in studies from a number of countries to have significant deviations from normal in the epidermal ridge patterns of their fingers, palms, and soles (Torrey & Kaufmann, 1986; Bracha *et al*, 1991).

Bracha *et al* (1991, 1992) carried out an elegant study on the pattern of dermatoglyphics among 24 monozygotic pairs discordant for schizophrenia. The schizophrenic twins were found to have significantly more dysmorphological finger and palm epidermal ridge anomalies than their healthy identical co-twins. This finding is the first direct evidence of some deleterious environmental event during months 4–6 of gestation, in relation to the aetiology of schizophrenia.

Viral infections during gestation

The seasonal variation in the birth rate of individuals who develop adult schizophrenia, the findings of low birth weight, the increased frequency of minor physical anomalies, and the observed dysmorphological dermatoglyphics could all be explained by cytotoxic effects of maternal viral or other infections during pregnancy. Therefore, it is highly suggestive that several recent epidemiological studies have shown that maternal exposure to influenza or other respiratory viral epidemics during the second trimester of pregnancy seems to increase the incidence of adult schizophrenia in the child (Mednick *et al*, 1988; Barr *et al*, 1990; O'Callaghan *et al*, 1991; Sham *et al*, 1992). Such an effect, however, was not detected in two other studies (Kendell & Kemp, 1989; Bowler & Torrey, 1990). Also, in the former studies, the increased risk for schizophrenia was only related to second-trimester *exposure* to the epidemic (i.e. the temporal overlap of the second trimester of gestation with the height of the epidemic). None of the studies determined whether the mothers had actually contracted an infection.

We carried out a study in Helsinki to determine whether any of the mothers of the schizophrenic subjects born after the 1957 A2-influenza epidemic actually had experienced a viral infection. For this purpose, we examined the prenatal clinic files for each of the schizophrenics of our cohort. In this study, 86.7% (13 out of 15) of the mothers of the schizophrenics exposed to the influenza epidemic during the second trimester of pregnancy had had a definite influenza infection in that period. In contrast, only 20% (2 out of 10) of the mothers of the schizophrenics exposed to the influenza epidemic during the first or third trimester of pregnancy had had a definite influenza infection during those two trimesters. The differences are statistically significant (Fisher's exact test, $P = 0.003$). It is known that in the epidemic period 38% of the population experienced

a clinical viral infection and that about half of these cases were recorded in the prenatal clinical records (Hakosalo & Saxen, 1971). These results support the assertion that the increased rate of schizophrenia among the foetuses exposed to the Helsinki epidemic in their second trimester of gestation is associated with a significantly elevated rate of definite influenza infection (Mednick *et al*, 1994).

Discussion

On the whole, findings from epidemiological studies with a variety of viewpoints suggest fairly convincingly that some prenatal disturbance during the late first and/or second trimester of foetal neuronal development is of crucial importance in determining the risk of at least some subtypes of adult schizophrenia. There is also growing evidence that maternal viral infection during months 4–7 of gestation is associated with schizophrenia in adult life. The epidemiological fact of seasonal variation in the birth rate of patients with schizophrenia is most easily explained by maternal infections during critical periods of foetal development, since many infectious diseases are known to be seasonal, with virus-specific peak incidences.

Though current discussion is centred around the possible schizophrenogenic effects of maternal influenza infections during the second trimester of gestation, it must be pointed out that the recent findings of an association between gestational influenza epidemics and adult schizophrenia have somewhat erroneously been attributed only to influenza viruses. The findings of Mednick *et al* (1988) and of O'Callaghan *et al* (1991) were probably more specifically related to the 1957 A2-type influenza epidemic, although even they cannot exclude the possibility of overlapping by other epidemics (e.g. *Mycoplasma pneumoniae*). The findings of Barr *et al* (1990) are probably not related only to influenza epidemics, though the authors discuss their findings as related only to epidemics caused by influenza viruses. It is most probable that the cases under the heading influenza in official Danish statistics, especially some 30–40 years ago, consist of a variety of different epidemics including both influenza and other viral epidemics with flu-like respiratory symptoms and fever. The same criticism may be valid also for the findings of Sham *et al* (1992), as the only criterion for the definite diagnosis of an influenza epidemic in this study was the monthly numbers of deaths in the category of influenza in the official annual statistics of England and Wales for 1938–1960. Thus, quite possibly, it is not only influenza infections, but also other flu-like infections during the critical periods of foetal development that increase the risk of adult schizophrenia.

Even if the maternal viral infections during pregnancy do indeed play an important role in the pathogenesis of some forms of adult schizophrenia, the mechanism of this association is still unknown. If the viruses in the maternal blood are able to cross the placenta, the virus or a component of the virus such as neuraminidase (Conrad & Scheibel, 1987) could have a direct cytopathic effect or affect the proliferation, migration, or differentiation of developing cortical neurons. Several neurotropic viruses, such as influenza virus, Epstein–Barr virus, and cytomegalovirus, have a capsular neuraminidase that is able to alter the sialic acid moieties of neuronal cell adhesion molecules (NCAMs) regulating the migration of neurons during neuroembryogenesis (Conrad & Scheibel, 1987; Garver, 1989). It is also possible that the maternal antibodies for the viruses could act as foetal anti-brain auto-antibodies, provided that these maternal antibodies can cross the placenta.

The association between gestational viral infections and adult schizophrenia need not be in any way related to viruses or their antibodies, but could be connected with some factors related to the infection. Maternal stress during pregnancy has been shown to increase the incidence of psychiatric disorders, including schizophrenia, in the child and to affect negatively the child's temperament (Huttunen & Niskanen, 1978; Huttunen, 1989). Similarly, gestational radiation or stress caused by atomic explosion in Nagasaki was shown to increase the incidence of adult mental disturbance in the children (Otake & Schull, 1984). It is also possible that some non-specific effects of the infection, such as fever or anoxia, could be the mechanism for the observed association.

Maternal use of analgesics, and especially aspirin, during pregnancy has been shown to be associated with an increased risk of anencephaly and other inborn defects of the central nervous system (Granroth, 1978). Aspirin is known to be a strong anticoagulant and its use during gestational infections could probably increase the likelihood of minor cerebellar haemorrhages in the foetus. In this respect, it is interesting that the use of aspirin and other analgesics is reported to have decreased sharply in Finland and Scandinavia since the early 1960s (Kullander *et al*, 1976; Harjulehto *et al*, 1988). The question can be raised whether the suggested recent decrease in the incidence of schizophrenia (Der *et al*, 1990) could be related to the decreased use of analgesics during pregnancy.

The timing of gestational viral or other schizophrenogenic prenatal events seems to be quite crucial for their observed association with adult schizophrenia. The window of susceptibility is somewhere between the third and seventh months of gestation, but is probably much more narrow and possibly lies during the fifth and sixth months of gestation (Barr *et al*, 1990; LaFosse & Mednick, 1991; Sham *et al*, 1992).

It is interesting to speculate about the neurobiological mechanisms behind the possible tendency for paranoid ideation among schizophrenics who suffered a disturbance in the second trimester of gestation. It is possible that the relevant prenatal event might cause an inborn temperament of negative mood (Huttunen, 1989) or temporal lobe epilepsy, thus increasing the individual's tendency to "delusional atmosphere" (Berner, 1991) that is known to precede the formation of delusions, possibly as a way of coping with this uncanny and sinister pre-psychotic mood. It is equally possible that gestational infection directly affects the migration and differentiation of developing cortical neurons and synapses in the right hemisphere, thus creating a disordered wiring and an inborn tendency for misidentification and paranoid ideation (Cutting, 1991).

We have speculated that a true schizophrenogenic prenatal effect could involve two separate and time-specific windows – an earlier negative effect on temperament (late first trimester), and a later, second trimester, effect on the migration of cortical neurons. Foetal brain is constantly developing and thus probably has several critical periods during which a cytotoxic effect might be able to produce different and specific changes in the wiring of the cortical neurons, and thus different kinds of behaviour in adult life and symptoms in schizophrenia. In this respect, it is interesting that severe delivery complications have been shown to be associated with widened third ventricles and a predominantly negative symptom profile (Cannon *et al*, 1990). To the extent that the symptom profile of schizophrenic patients is determined by specifically timed prenatal and perinatal effects, one might describe these effects in terms of one-, two-, and three-hit-window hypotheses of the prenatal aetiology of schizophrenia.

It is not known whether some forms of adult schizophrenia could be caused by gestational factors alone, independently of genetic risk. We speculate that the symptom profile and subtype of schizophrenia could largely be determined by prenatal events in individuals with genetic risk for schizophrenia. The virus infection and its specific timing would thus explain both the symptom profile of the cases and the increased incidence of schizophrenia after a major epidemic. One could thus speak of one-, two-, or three-hit hypotheses depending on the requirement of genetic, prenatal, perinatal, or postnatal biological, psychological, or social aetiological factors in various subtypes of schizophrenia.

However, the mere statistical association with the prenatal viral or any other environmental factor does not yet provide any effective tools for the primary prevention of schizophrenia. Both the causal relationships between prenatal infections and schizophrenia and their mechanism of action require much further investigation.

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