British Journal of Psychiatry (1992), **160**, 598–600

Point of View

Are Polioviruses a Cause of Schizophrenia?

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Pre-natal infection with polioviruses could contribute to the subsequent development of schizophrenia. The hypothesis draws support from the declining incidence of schizophrenia, the excess of schizophrenic winter births, and the increased rates of schizophrenia among West Indian immigrants. There are parallels with other late sequelae of poliovirus infections. These postulations generate a testable hypothesis of a genetic link between schizophrenia and susceptibility to poliomyelitis.

There is little direct evidence on which to base suspicions that polioviruses play a part in the aetiology of schizophrenia. The only specific association is that of schizophrenics in Connecticut admitted to hospital in 1973–74, who were significantly more likely to have been born during those years when high rates of poliomyelitis infections were reported (Torrey *et al*, 1988). This paper links epidemiological aspects of schizophrenia with poliovirus infection, and espouses the view that polioviruses are the infectious agents that can be most plausibly related to the aetiology of schizophrenia.

Declining incidence of schizophrenia

Der *et al* (1990) have established that first admissions with schizophrenia in England and Wales have fallen by around 50% since the mid-1960s. This mirrors declines of a similar magnitude in Scotland (Eagles & Whalley, 1985), Denmark (Munk-Jorgensen, 1986), and New Zealand (Joyce, 1987). Although other possible explanations such as changes in diagnostic practices (Crow, 1990), the more widespread use of neuroleptics (Graham, 1990), and the move towards community care (Prince & Phelan, 1990) cannot be dismissed, present evidence suggests that these findings represent a genuine decline in the incidence of schizophrenia (Eagles *et al*, 1988; Der *et al*, 1990; Eagles, 1991).

Inactivated poliovirus vaccination was first used in the UK in 1956, with the subsequent introduction of oral polio vaccine (OPV) in 1962. Vaccination programmes resulted in a dramatic reduction in notifications for paralytic poliomyelitis between 1955 and 1960 (Miller & Galbraith, 1965), a decline which has continued after the introduction of OPV (Begg *et al*, 1987). Initially, the vaccination programmes concentrated on children, so that in the early 1960s, less than 20% of those vaccinated were adults (Miller & Galbraith, 1965). Ten years later, immunity levels in adults were more satisfactory, with 63% of pregnant women having antibodies to all three types of poliovirus (Mortimer & Cunningham, 1975).

Antibodies to poliovirus are passively transferred from mother to foetus. This transplacental transfer confers intra-uterine and neonatal immunity to poliovirus infection. While increasing maternal immunity in the population since the late 1950s could be linked to a decline in schizophrenia commencing 20 or more years later, this pattern alone does not accord with a decline commencing in the mid-1960s. It would be necessary to hypothesise that later reinfection is required, perhaps with a different poliovirus type, in an individual who may be sensitised and immunologically compromised by the initial infection. A similar mechanism has been proposed in multiple sclerosis (Alvord *et al*, 1987). If pre-natal and later reinfection with poliovirus were required to produce schizophrenia, then rising maternal (and hence foetal) and adult immunity through immunisation programmes could lead to the observed decline in incidence of schizophrenia. It should be acknowledged that a similar case could be made for other infectious agents such as rubella, measles, whooping cough, and diphtheria.

Winter excess of schizophrenic births

One of the most consistent findings in the epidemiology of schizophrenia is that of an excess of winter births between January and April in the northern hemisphere (Bradbury & Miller, 1985). While M. S. Lewis (1989) has suggested that this may constitute a statistical artefact, his contention has limited plausibility (Dalen, 1990; Torrey & Bowler, 1990; Watson, 1990). As Hare (1987) points out, such a pattern is strongly suggestive of a seasonal factor, most probably perinatal infections, in the aetiology of schizophrenia.

Although debate continues as to the timing of perinatal insults in schizophrenia (S. W. Lewis, 1989), the foetal brain is most sensitive to infective

damage within the first few months of gestation (Best & Banatvala, 1990), and gliosis would be expected in schizophrenic brains with infective damage after the second trimester (Roberts, 1991). It is thus difficult to reconcile the seasonal fluctuation of schizophrenic birthdates with the epidemiology of the common infectious agents, most of which exhibit a winter peak in incidence. In this respect, polioviruses (like other enteroviruses) are atypical, in that poliomyelitis peaks in the late summer and early autumn (Christie, 1987), that is, during the first and second trimesters of foetuses born during the first four months of the following year.

Immigration and schizophrenia

While it has been long established that many immigrant groups suffer increased rates of schizophrenia, attention has focused recently on West Indian immigrants to the UK, who have markedly increased rates of schizophrenia compared with the indigenous population (McGovern & Cope, 1987; Harrison *et al*, 1988). This excess is even more pronounced in second-generation than in first-generation immigrants from the Caribbean.

In Jamaica, polioviruses were endemic until the 1950s, the first epidemic occurring in 1954, with subsequent outbreaks in 1957, 1960, and 1964. Immunisation programmes covered less than half the children in Jamaica until after a further epidemic in 1982 (Ashley *et al*, 1985). Immunisation programmes are complicated in warmer countries, for unknown reasons, by the fact that seroconversion occurs less readily following vaccination than it does in more temperate countries (Chopra *et al*, 1989).

For these reasons, first-generation immigrants from the Caribbean are less likely to have immunity to polioviruses than are members of the native-born population. Their children (second-generation immigrants) are therefore more likely to acquire intra-uterine infections with poliovirus.

It is likely that poliomyelitis remained endemic in Jamaica until the advent of improvement in sanitation and hygiene in the 1950s. This endemic spread conferred immunity, by means of early natural infection, against the paralytic disease which occurs when infection is acquired at a later age (Ashley *et al*, 1985). This early infection may well have occurred pre-natally among first-generation West Indian immigrants.

Post-polio syndromes

Over the last few years a 'post-polio syndrome' has been identified. About 30 years after paralytic poliomyelitis, survivors suffer from severe fatigue, new neurological signs, generalised joint and muscle pain, and increased sensitivity to cold. The estimated frequency of such sequelae has varied between 25% (Raymond, 1986) and 78% (Howard *et al*, 1988). Postulated mechanisms of causation have included immunological dysfunction and recrudescence of latent poliovirus infection. A surprisingly high correlation has also been discovered between the development of motor neuron disease and death rates from poliomyelitis in English and Welsh counties 30–40 years earlier (Martyn *et al*, 1988). Since the mean age of onset of schizophrenia is close to 30 years of age, these data and similar models would accord with the concept of schizophrenia as a 'post-polio syndrome' which follows perinatal poliovirus infection.

Genetic considerations

It is widely accepted that there is a genetic component in the aetiology of schizophrenia. The search for the 'schizophrenia gene' has not, as yet, produced consistent or conclusive results. It is of interest that a poliovirus sensitivity gene has now been identified on chromosome 19 (Siddique *et al*, 1988). This gene encodes for sensitivity to non-modified poliovirus infection as an autosomal dominant trait.

Different types of interaction between genetic susceptibility and viral infection in the aetiology of schizophrenia have been postulated (e.g. Crow, 1983). It is possible that the inherited tendency to schizophrenia is a sensitivity to poliovirus infection. Even though sensitivity to pre-natal and post-natal infection may be dissimilar entities, it may prove productive to investigate the heritability of schizophrenia by scrutinising possible links with the poliovirus sensitivity area of chromosome 19.

Acknowledgements

I am grateful for the comments of Dr M. A. J. Moffat (Senior Lecturer in Virology, University of Aberdeen), and to Julie Bett and Anne Mutten for secretarial assistance.

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