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Maternal viral infection and schizophrenia

SIR: Sham *et al* (*Journal*, April 1992, **160**, 461–466) suggest that "maternal viral infection is an important cause of schizophrenia". They imply that the robust finding of a winter-birth excess among schizophrenics is due, in part at least, to a viral effect. They go on to state that this viral effect can help to explain the reported decline in the incidence of schizophrenia in countries in which there has been "an improvement in the living conditions in recent decades".

The explanatory hypothesis rests on the grounds that the viral infection of the mother adversely affects the developing brain of the foetus, predisposing it to later schizophrenia. This would be consistent with the neurodevelopmental theory of schizophrenia, but certain important factors remain unexplained.

Firstly, one of the hallmarks of neurodevelopmental schizophrenia is the early age of onset (Murray *et al*, 1992). In an extensive review of the literature, Bradbury & Miller (1985) found no consistent schizophrenic subtype to be more prone to the seasonality effect. However, Takei *et al* (1992) among others, have reported winter birth to be associated with schizophrenia of *later* onset. Additionally, in an epidemiologically-based study, Castle *et al* (1992) reported that later-onset 'paranoid' patients showed a winter-birth effect, while early-onset 'neurodevelopmental' patients did not.

Secondly, it is clear that it is males rather than females who show a particular vulnerability to the severe, early-onset "neurodevelopmental" form of schizophrenia (Castle & Murray, 1991). It is thus intriguing that, in an analysis of the "schizophrenogenic effect" of the 1957 influenza epidemic, O'Callaghan *et al* (1991) reported that such an effect was confined to females. Furthermore, in England and Wales, Der *et al* (1991) reported that the rates of schizophrenia for *both* sexes have declined, and that the sex-ratio has remained much the same over the years. In Ireland, Waddington & Youssef (1992) found the decline to be greatest for females and later-onset cases. Should the decline indeed be due to improved living conditions and less maternal viral infection, surely such an effect would be more emphatic in males?

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AUTHOR'S REPLY: The concept of 'neurodevelopmental' schizophrenia was proposed on the basis that early onset and male cases of schizophrenia have a high frequency of obstetric complications, childhood personality and cognitive problems, and dystrophic brain abnormalities. By proposing this concept (Murray & O'Callaghan, 1991), we hoped to promote a developmental perspective on schizophrenia, and yet draw attention to possible clinical and aetiological heterogeneity.

Drs Castle & Gill surmise that if prenatal exposure to influenza epidemics increases the risk of subsequent schizophrenia in the unborn child by impairing neurodevelopment, then the season-of-birth effect ought to be most obvious in early-onset and male cases of schizophrenia. They point out, however, that some reports suggest that the late winter/spring excess of births is most evident in later-onset and female (see Boyd *et al*, 1986) cases. It is also true that we regard 'neurodevelopmental' schizophrenia as having a poor prognosis, and yet two studies claim that the season-of-birth effect is greater

in acute than chronic schizophrenics (Dalen, 1975; Pulver *et al*, 1983). Even more telling, three investigations have found that the risk-increasing effect of influenza epidemics is more readily detected in female than male schizophrenics (Mednick *et al*, 1991; O'Callaghan *et al*, 1991; Takei *et al*, 1992).

How can we reconcile these seeming inconsistencies? We stand by the view that early-onset schizophrenia is a consequence of deviant brain development, and that, like other neurodevelopmental disorders, it is commoner in males. We have suggested elsewhere that it may result from an aberration in the genetic control of early brain growth or obstetric complications, or some combination of the two (Jones & Murray, 1991).

It remains uncertain whether the 'schizophrenogenic' effect of prenatal exposure to influenza operates preferentially in females, or whether it is simply easier to demonstrate this effect in female schizophrenics because of the smaller numbers of cases with a different aetiology. On the other hand, one can make a provisional case from the evidence reviewed above that prenatal exposure to influenza epidemics is more likely to be aetiologically implicated in later-onset milder schizophrenia, which is commoner in females. This form is associated with less premorbid dysfunction and gross structural abnormalities than the type which we have, perhaps confusingly, called the 'neurodevelopmental' type, but on such reasoning, would also have its origins very early in life. This tentative hypothesis is compatible with Castle's own finding that when schizophrenia is subtyped into 'neurodevelopmental' and later-onset forms, it is the later-onset paranoid form which shows a winter-birth excess. The decline in epidemic influenza and its complications since the 1930s is also a possible explanation for the report of Waddington & Youssef (1992) that the recent decline in rates of schizophrenia is greatest in later-onset female cases.

Such a simple heterogeneity model of schizophrenia is unlikely to be completely correct, and does not even begin to resolve the relative contributions of heredity to the different forms. However, it has the merit of being testable, and we shall look forward to Castle & Gill, among others, examining its strengths and weaknesses.

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Influenza and schizophrenia in Japan

SIR: Sham *et al* (*Journal*, April 1992, **160**, 461–466) show an effect of influenza on pre-schizophrenics *in utero*. This paper is a more sophisticated replication of the study by Barr *et al* (1990) showing a correlation between prenatal exposure to influenza epidemics and an increase of schizophrenic births in a longitudinal sample.

Although six studies have examined schizophrenic births following the 1957 influenza A2 pandemic, the results have not yet converged. Three studies, from Sweden (Mednick *et al*, 1988) and England (O'Callaghan *et al*, 1991; Fahy *et al*, 1992), demonstrated positive findings but two others, from Northwick Park (Crow *et al*, 1992) and the USA (Torrey *et al*, 1992), did not. The final study, from Scotland (Kendell & Kemp, 1989) is equivocal. This inconsistency requires more studies to clarify the aetiological role of influenza on schizophrenia.

In Japan, an increase in the reported number of deaths attributable to influenza epidemic began in June 1957, reaching a peak in July and a further greater peak in December (Statistics of Communicable disease and Food Poisoning, 1957/58: Ministry of Health and Welfare, Japan). We obtained information on all dates of birth of individuals born between 1955 and 1960, who were treated for schizophrenia during the study period, November to December 1991, at 12 mental hospitals around the