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Editorial

Prenatal Exposure to Influenza as a Cause of Schizophrenia

There are inconsistencies and contradictions in the evidence

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In 1988 Mednick and colleagues made the original claim that people who were foetuses in the second trimester during the 1957 influenza epidemic

> "were at elevated risk of being admitted to a psychiatric hospital with a diagnosis of schizophrenia. This was true for both males and females and independently in several psychiatric hospitals."

Some subsequent investigators have supported this claim. Thus O'Callaghan *et al* (1991*a*) stated that five months after the peak of the 1957 A2 influenza epidemic,

> "the number of births of individuals who later developed schizophrenia was 88% higher than the average number of such births in the corresponding periods of the 2 previous and the next 2 years,"

and on the basis of a correlation study Sham *et al* (1992) concluded that

> "the hypothesis that maternal viral infection is an important cause of schizophrenia can explain many enigmatic aspects of the condition."

More recently Adams *et al* (1993) concluded that

> "Exposure to the 1957 epidemic of A2 influenza was associated with an increased incidence of schizophrenia . . . we conclude that these relationships are probably genuine and causal and that maternal influenza . . . or something closely associated with it, is implicated in the aetiology of some cases of schizophrenia."

The reader will find it difficult to resist the conclusion that an environmental cause of schizophrenic illness has been discovered.

But the apparent unanimity of these reports must be viewed not only in relation to other studies, but also with respect to their internal consistency. Are these the most incisive studies, and do they reinforce each other's findings?

From the start, the studies which claim positive findings have had odd features. As Kendell & Kemp (1989) pointed out, Mednick and colleagues compared the *proportion*, among all psychiatric admissions, of patients with schizophrenia in their index and control groups, and reported a difference significant at the 0.01 level. Had they used the actual *numbers* of patients with schizophrenia, the difference (according to Kendell & Kemp) would not have been significant at the 0.05 level. Nevertheless, the size of the effect (an 87% increase) is substantial and in apparent agreement with that reported by O'Callaghan *et al* (1991*a*) – an 88% increase in births of schizophrenic patients in March 1958 by comparison with the preceding and succeeding months (Fig. 1b).

O'Callaghan *et al* (1991*a*) and Sham *et al* (1992)

O'Callaghan *et al* (1991*a*) observed a spike in the relative births of schizophrenic people in a single month (their period 7) in February/March 1958 and concluded

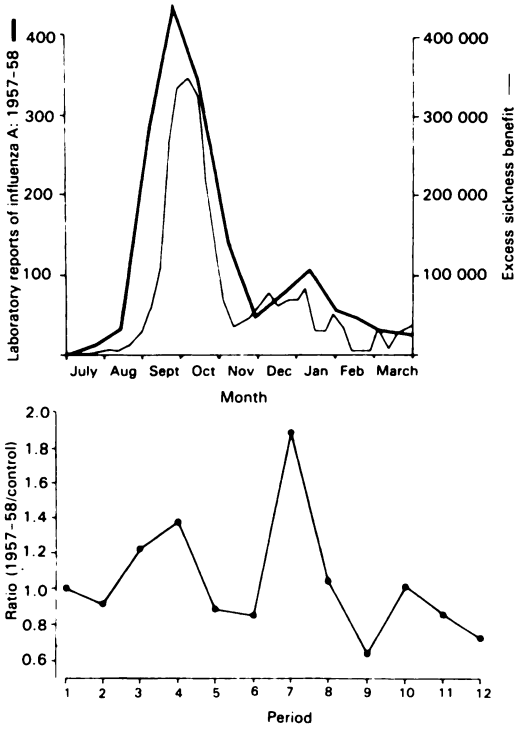

Fig. 1 (a) Monthly laboratory reports of influenza A, 1957/58, and excess claims for sickness benefit (1957/58–1953/54). (b) Ratio of affected births (study period/average for previous 2 and next 2 years). (Figures reproduced from O'Callaghan *et al*, 1991, courtesy of the *Lancet*.)

that this corresponded to the excess in Finland reported by Mednick *et al* (1988), and therefore could be related to the peak of the influenza epidemic five months earlier. The coincidence with the Finnish data was worth remarking upon, but it can be readily seen from Fig. 1(b) that had O'Callaghan *et al* analysed their findings by trimesters as Mednick and colleagues had done (i.e. periods 6, 7 and 8 versus 3, 4 and 5 and 9, 10 and 11) rather than on a monthly basis, the excess would have been much less impressive.

In addition, as already noted (Crow & Done, 1992), it is curious that the putative consequence of the epidemic (schizophrenic births assessed from selected health regions across England and Wales) should be more restricted in time (Fig. 1b) than the epidemic itself, which apparently spread over at least three months (Fig. 1a). But to draw their positive conclusions, O'Callaghan *et al* had to overlook an even greater problem – the prior publication of a similar investigation from the USA that included a sample of schizophrenic births that was 100 times that of the study from Finland and 26 times the size of their own. This study (Torrey *et al*, 1991) had revealed no trace of the effect that the protagonists of the influenza theory claimed to have discerned. The study is referred to in their introduction by O'Callaghan *et al*, but its sample size is not.

In this issue, Selten & Slaets (pp. 681–683) report a reinvestigation in Holland of the claims of O'Callaghan *et al* (1991*a*,*b*) and Mednick *et al* (1988) that exceptional numbers of patients with schizophrenia were born in the spring of 1958. As Selten & Slaets point out, their sample of the entire Dutch population exceeds in size those of the Finnish and UK samples. No unusual effects were observed.

A bold repetition of the claim for a causal relation was made by Sham *et al* (1992) on the basis of an analysis of birth dates of schizophrenic patients first admitted between 1970 and 1979 and influenza epidemics (assessed by influenza-related deaths) between 1939 and 1960. The conclusion – "that exposure to influenza epidemics between the third and seventh month of gestation is associated with schizophrenia in adult life" – is difficult for the reader to evaluate because it is based upon a complex statistical analysis, in the course of which the authors made a number of arbitrary assumptions (for example years are defined as beginning in November, and epidemic is defined as starting whenever influenza deaths exceed 100 in a month) and made no attempt to show whether the relationships they found were robust in the face of reasonable variations in their assumptions.

But one can ask whether the findings (the only data in the paper are as presented in Fig. 2) are consistent

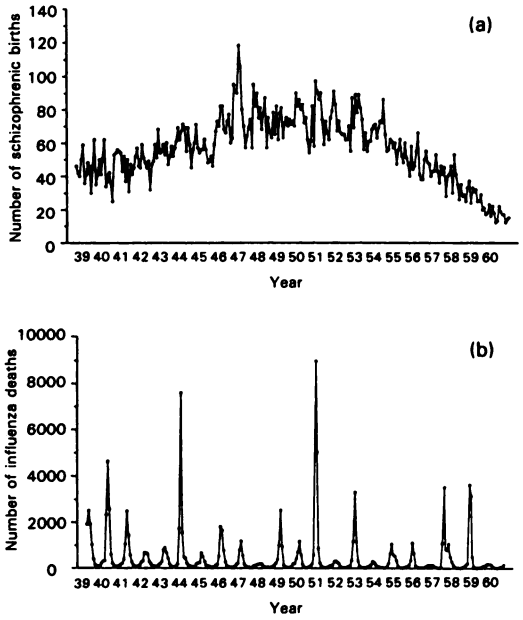

Fig. 2 (a) Average number of schizophrenic births in England and Wales per month, 1939–60. (b) Average number of deaths from influenza in England and Wales per month, 1939–60. (Figures reproduced from Sham *et al*, 1992.)

with the earlier conclusions of the same group (O'Callaghan *et al*, 1991*a*). Comparison of Fig. 2 (from Sham *et al*) with Fig. 1 (from O'Callaghan *et al*, 1991*a*) provokes the following questions:

(a) Why is the striking peak of schizophrenia births in a single month in February/March 1958 in Fig. 1(b) no longer apparent in Fig. 2(a)? Both figures relate to monthly birth rates of people with schizophrenia in England and Wales. Why has the peak now disappeared?

(b) Why, if there was an 88% increase in schizophrenia births in a single month in 1958 as a result of the influenza epidemic in the autumn of 1957, were there not much bigger peaks of schizophrenia births associated with the epidemics of 1940, 1944 and 1951?

On the basis of their erudite analysis, Sham *et al* conclude that

> "the effect of influenza, as indicated by parameter estimates in the final model, corresponds to a 1.4% increase in the number of schizophrenic births for every 1000 deaths attributable to influenza in the two to three months before birth."

This sounds inconsistent with the claim of O'Callaghan *et al* (1991*a*) that

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> "5 months after the peak infection prevalence, the number of individuals who later developed schizophrenia was 88% higher than the average number of such births in the corresponding periods of the 2 previous and the next 2 years."

By applying Sham *et al*'s quotient to the data of O'Callaghan *et al*, one can see the extent of the discrepancy. If the 88% increase in schizophrenic births was really attributable to influenza, there should (according to Sham *et al*) have been 62 800 deaths in the corresponding month or months in 1957. But inspection of Fig. 2(b) indicates that there was less than one-tenth of this number in the whole of 1957 and 1958. A conservative conclusion to the analysis of Sham *et al* would appear to be that the authors (four of whom had contributed to the earlier paper) had failed to detect an effect of the magnitude reported by O'Callaghan *et al*.

Adams *et al* (1993)

A surprising conversion to the influenza school was announced by Adams *et al* (1993). Earlier, Kendell & Kemp (1989, 1990) had concluded from their studies in Scotland that "Overall, the hypothesis . . . is not supported," and "it is rather unlikely that maternal influenza contributes to the cause of schizophrenia," but now, on the basis of correlational studies in England, Scotland and Denmark, Adams *et al* declare themselves satisfied that the relationship is "both genuine and causal". But the grounds for their confidence are difficult to find. The authors state that

> "Using a variety of different statistical methods we examined the relationship between the monthly 'incidence' of schizophrenia and outbreaks of both influenza and measles. . . ."

Using a simple regression analysis (their Table 1), out of 110 comparisons five relationships significant at the 5% level were observed, without a consistent pattern. In a regression analysis of changes in incidence of schizophrenia and measles (their Table 2), out of 198 comparisons 15 significant relationships were observed, again without a consistent pattern. Five alternative definitions of an influenza or measles outbreak were adopted (the data are not presented) without consistent relationships being detected. Highest and lowest influenza incidence months were related to schizophrenia births (their Table 3), yielding 22 out of 198 associations significant at the 5% level, again without a consistent pattern. Birth dates of patients with schizophrenia in Denmark from 1916 to 1921 were examined in relation to the 1918 epidemic (their Table 5) without any relationship being demonstrated.

None of these negative findings is mentioned in the summary or influenced the conclusion implicit in the title. What the authors select as the basis for their positive conclusions are the findings in relation to the 1957 epidemic in which they discern meaning in the pattern of distribution of 14 significant comparisons (9 positive and 5 negative) out of a total of 132 in their Table 4. They draw particular attention (p. 529) to the facts that of nine statistically significant positive differences (i.e. those in which the incidence of schizophrenia is higher in the index than in the comparison months), "five . . . are in March 1958" (but only 2 of these are independent), "two of the others are in February 1958" (but these two are not independent, and one of the negative differences is also in February 1958), and "one is in April 1958" (as also are two, non-independent, negative differences). Only to the discerning eye of faith can the findings in their Table 4 be interpreted as favourable to the hypothesis; the results in Tables 1–3 and 5 and 6 reveal that influenza and schizophrenia are unrelated.

Even if the conclusions of Adams *et al* are taken at face value, they are inconsistent with other positive claims. Adams *et al* emphasise that their findings in relation to the 1957 epidemic were true particularly of females – but the original report of Mednick stressed that the excess applied to both males and females. Adams *et al* point to the sixth or seventh month of pregnancy as the vulnerable period – but if O'Callaghan *et al* had examined only the sixth and seventh months (their periods 8 and 9 in Fig. 1b), they would have reported nothing unusual.

Barr *et al* (1990)

The study by Barr *et al* (1990) of data on birth dates of patients with schizophrenia and influenza epidemics from 1911 to 1950 in Denmark that drew positive conclusions is subject to the same criticisms as the study of Sham *et al* (1992) – the methods of data handling and analysis are so complex that it is difficult for the reader to judge whether the relationships claimed would have held under different assumptions. The reader may ask how many analyses have been done and how were those that are presented selected? That there is a real difficulty is demonstrated: (a) by the fact that the most striking excess of influenza (their Table 1) was observed in 1918, but no analysis of schizophrenic births in relation to this epidemic is presented; and (b) by the comment (p. 873) that "we do not find a distinct upsurge of schizophrenic births following all epidemics". Thus the analyses that are presented have been selected from a larger set that included negative findings.

The problem of the complexity of analysis is illustrated by the fact that Adams *et al*, in their studies of the Danish population, examined a sample that included the same population that Barr *et al* had earlier studied, and Adams *et al* comment that

> "it is therefore somewhat disconcerting that we found no evidence of any relationship between the 'incidence' of schizophrenia and the incidence of influenza, whereas Barr *et al* found a highly significant relationship between the two in the sixth month of gestation."

Adams *et al* (p. 532) therefore repeated their analyses following the approach adopted by Barr *et al*, but again failed to replicate these workers' findings (Adams *et al*'s Table 6). Their failure to explain the discrepancies between their own and Barr *et al*'s findings is striking in view of the fact that the papers share an author (P. Munk-Jørgensen). If two sets of authors examine the same data with what they consider are the same analyses and, for reasons they are unable to explain, come up with different answers, the reader is bound to regard any positive conclusions with reserve.

The criticisms of obscurity of analysis and non-reporting of alternative analyses are not applicable to the paper of Adams *et al*: 764 comparisons or correlation coefficients are presented in tables and a further 792 are admitted. The problem is that only the positive correlations influence the conclusions and appear in the abstract. The perils of serial statistical assessments, continued until findings compatible with the hypothesis emerge, are well demonstrated by this paper and may (but one cannot tell) have been a factor in those of Sham *et al* and Barr *et al*.

Do mothers who suffer from influenza in pregnancy have more children with schizophrenia?

If there is a *prima facie* case that prenatal influenza and schizophrenia are related, then studies on the incidence of schizophrenia in the children of mothers who suffered from influenza in pregnancy are a more direct and incisive test of the hypothesis than temporal correlations in the general population. Two such studies have been reported.

Crow *et al* (1991) examined the numbers of children who, by the age of 28 years, had developed schizophrenia, born to mothers in the National Child Development Study (NCDS) cohort who had suffered from influenza in the 1957 epidemic. Of 945 mothers who were recorded as suffering from influenza in the second trimester, three children developed schizophrenia by broad criteria, a rate identical with that predicted from this cohort and from general population expectations. This study has been criticised by the protagonists of the influenza theory (O'Callaghan *et al*, 1991*b*; Adams *et al*, 1993, p. 533) on the grounds that the sample size is small. But these authors have overlooked that if O'Callaghan *et al* (1991*a*) had been right, 88 of 188 (47%) schizophrenics born in March 1958 would have been children of mothers who suffered from influenza in the second trimester. Applied to the NCDS cohort, 26.5 extra cases of schizophrenia by broad criteria would have been born to these 945 mothers (Crow & Done, 1992), in addition to three cases actually observed. A prospectively assessed sample of the general population in which mothers who suffered from influenza are identified thus has considerable power to detect an effect of the size claimed by O'Callaghan *et al* and Mednick *et al*. The findings are unequivocally negative.

In a follow-up study of 1218 people who were *in utero* during the 1957 epidemic, Cannon *et al* (1994) traced 238 whose mothers were described as having symptoms of influenza during pregnancy and 287 controls, and examined admission records in Dublin psychiatric hospitals. Two cases of schizophrenia by ICD-9 criteria were identified in each group. Because this study is not based upon a larger cohort of patients on whom independently assessed histories of influenza were available, it does not have the power of the NCDS cohort ($n = 16\,268$) to detect an effect. The findings with respect to schizophrenia are nevertheless negative. Three of the authors (P. C. Sham, R. M. Murray, E. O'Callaghan) have been among the most enthusiastic adherents of the influenza hypothesis; the full report of this study, if it includes a considered discussion, will be an illuminating addition to the literature.

Conclusions

It has been claimed that, as a result of exposure to the 1957 influenza epidemic, there was an increase of 87–88% in births of patients with schizophrenia in the spring of 1958. A number of subsequent correlational studies have revealed no evidence of an increase of such magnitude, but nevertheless have been interpreted by their authors as supporting a causal relation, but a small one. Thus Sham *et al* write that

> "Our results indicate that 1–2% of all schizophrenic births can be explained by the number of influenza deaths in the preceding months,"

Barr *et al* that

> "The association between influenza and schizophrenia is not strong. The percentage of variance accounted for is at most 4.0%,"

and Adams *et al*

> "it is unlikely that influenza is implicated in the aetiology of more than a small minority of cases."

But if the ambitions of the hypothesis have been scaled down from explaining 87% or 88% increases in incidence following epidemics to accounting for 1–2%, or "at most 4.0%" of the variance, why do not the authors consider that the original interpretations must have been in error and the true figure is 0%, that is, the null hypothesis is not disproved, schizophrenia and influenza are unrelated?

The only explanation is that at least three groups separately convinced themselves that there must be a causal connection between exposure to the influenza virus and some schizophrenic illnesses, and that the only problem was to unveil the evidence. In attempting to do this they have generated a literature rich in complex statistical methods, inconsistencies, and contradictions. Perhaps the lesson to be drawn is that straightforward hypotheses and simple analyses are to be preferred to their alternatives. The hypothesis that prenatal exposure to influenza is the cause of schizophrenia is easy to test and, if in error, to eliminate. The hypothesis that some (but not all) epidemics of influenza are responsible for a proportion (unspecified) of schizophrenic illnesses (of indeterminate type) is not. It has generated confusion.

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