VAN BROEKHOVEN, C., DE BRUYN, A., RAEYMAEKERS, P., *et al* (1991) Molecular genetic analysis in bipolar illness. Proceedings of the 5th World Congress of Biological Psychiatry, Firenze, June 9–14. *Biological Psychiatry*, **2**, 452–454.

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AUTHOR'S REPLY: I want to point out that we have submitted an additional paper that extensively deals with statistical evaluations of clinical data (sex-dependent evaluations of reproduction rates, disease phenotypes, and mean ages of affected individuals) presented in eight studies favouring X-linkage of bipolar illness (Hebebrand & Hennighausen, 1992). Our study will statistically substantiate my previous criticism of the positive X-linkage studies (Hebebrand, *Journal*, January 1992, **160,** 7–11). We also show that out of the total of 43 pedigrees analysed in these eight linkage studies, 20 pedigrees were ascertained through male index cases. Thus ascertainment has not mainly occurred through doubly heterozygous females as Dr Mendlewicz presumes.

Because the reproductive status of affected males has not been clearly indicated in any X-linkage study, all statistical analyses (including segregation analyses) must deal with incompletely presented data. These missing data are of the utmost importance for substantiating the assumed X-linked dominant mode of inheritance. It is disappointing that Dr Mendlewicz has not addressed this core issue. My criticism could readily be rejected by the respective investigators by explaining whether the affected males have reproduced, how many offspring they have and what their sex and phenotype is.

I cannot agree more that twin, family and adoption studies do not support assumptions of "full or high penetrance of the genotype and complete expressivity of the phenotype". However, according to Mendlewicz *et al* (1979) this does not apply to X-linked bipolar illness, which is characterised by a "high density of affective disorders in the relatives and by a strong penetrance of the gene as suggested by the early age of onset in some relatives". High penetrance rates have been assumed in all positive X-linkage studies. Mendlewicz *et al* (1987) have shown that the load score drops upon assumption of reduced penetrance rates. Is Dr Mendlewicz now suggesting that the assumption of a high penetrance rate in the X-linkage studies was incorrect?

Concerning the elucidation of X-linked dominant disorders such as classic Alport syndrome, considerable efforts were spent on the demonstration of the characteristic segregation patterns in pedigrees analysed for X-linkage (Atkin *et al*, 1988). Unfortunately, this has not been the case for the allegedly X-linked dominant subgroup of bipolar illness. In historic terms, the assumption of X-linked dominant inheritance was merely based on early findings of a preponderance of affected females and a paucity of male to male transmissions in bipolar pedigrees. Both of these findings appear controversial, since they were not clearly substantiated in later studies. In addition, psychiatric research has not concentrated on other features that characteristically apply to X-linked dominant disorders. It appears as if formal genetics are not as important in psychiatry as in other medical fields.

It is quite surprising that Dr Mendlewicz considers unsystematic ascertainment. Were the ascertainment procedures in the X-linkage studies systematic as suggested in the respective publications or were they not?

In conclusion, the formal genetic aspects urgently need clarification. This work cannot be done by myself or anybody else who has not identified an X-linked bipolar pedigree.

ATKIN, C. L., HASSTEDT, S. J., MENLOVE, L., *et al* (1988) Mapping of Alport syndrome to the long arm of the X chromosome. *American Journal of Human Genetics*, **42**, 249–255.

HEBEBRAND, J. & HENNIGHAUSEN, K. (1992) A critical review of clinical data presented in 8 studies favoring X-linkage of bipolar illness with special emphasis on formal genetic aspects. *Human Genetics* (in press).

MENDLEWICZ, J., LINKOWSKI, P., GUROFF, J. J., *et al* (1979) Color blindness linkage to bipolar manic-depressive illness. *Archives of General Psychiatry*, **36**, 1442–1447.

—, SEVY, S., BROCAS, H., *et al* (1987) Polymorphic DNA marker on X chromosome and manic depression. *Lancet*, *i*, 1230–1232.

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Maternal viral infection hypothesis

SIR: The paper by Sham *et al* (*Journal*, April 1992, **160,** 461–466) concludes boldly that "our results indicate that exposure to influenza epidemics between the third and seventh months of gestation is associated with schizophrenia in adult life" and "The hypothesis that maternal viral infection is an important cause of schizophrenia can explain

many aspects of the enigmatic aetiology of the condition".

However, the most direct test of this hypothesis – whether mothers who suffer from influenza during pregnancy actually have children who are at greater risk of schizophrenia – does not support it. Of the 945 mothers who had influenza in the second trimester of pregnancy, no more than the expected three children had by the age of 28 years developed schizophrenia by broad criteria (Crow *et al*, 1991). This leads one to inquire more closely about the somewhat indirect correlational approach that leads Dr Sham *et al* to their conclusions.

The first sentence of the results section states that "The average response curve [Fig. 2(a) of their paper] shows an obvious increase in the average number of schizophrenic births after the start of influenza epidemics" but what this actually shows (since epidemics generally start in the late autumn) is the well-known season-of-birth effect. Years are defined as from November to October, a definition that maximises the impression that there is a relationship between the season of birth effect (whatever this is due to) and the timing of influenza epidemics. Dr Sham *et al* counter this objection by Fig. 2(b) which shows that the "average season of birth" curve for high influenza years differs from that of low influenza years but no *P* value is given for the example of comparison between 'high' and 'low' influenza years.

If there is indeed a significant difference here one might ask how far this is dependent on the particular analysis adopted? For example, if the authors had matched schizophrenic births following each high influenza year with those in the succeeding low influenza year defined from the month in which influenza deaths exceeded 100, would the conclusions have been the same?

A curious feature of the findings reported in Fig. 1(b) is the absence of an excess of influenza deaths for the year 1957. The authors have previously presented the claim (O'Callaghan *et al*, 1991) that there was an 80% increase in schizophrenic births in the general population following the 1957 epidemic of Asian influenza. But if 1957 was a low influenza year the increase in schizophrenic births following high influenza years should have been correspondingly greater. But careful scrutiny of Fig. 1(a) (the only raw data that the reader is permitted to glimpse) reveals no evidence that this is the case.

The reader searches for, but does not find, a critical examination of the hypothesis to see whether it holds up in the face of different assumptions. The data on which the authors have based their analysis have not been presented in a way which others can examine and reanalyse them.

CROW, T. J., DONE, D. J. & JOHNSTONE, E. C. (1991) Schizophrenia and influenza. *Lancet*, **338**, 116–118.

O'CALLAGHAN, E., SHAM, P. C., TAKEI, N., *et al* (1991) Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet*, **337**, 1248–1250.

SHAM, P. C., O'CALLAGHAN, E., TAKEI, N., *et al* (1992) Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960. *British Journal of Psychiatry*, **160**, 461–466.

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AUTHOR'S REPLY: Dr Crow is right to be sceptical about the maternal viral infection hypothesis, for several recent hypotheses about the aetiology of schizophrenia have proved to be false (e.g. Crow & Done, 1986). However, his critique of our paper (*Journal*, April 1992, **160**, 461–466) is uncharitable, for we made clear in our final paragraph that the hypothesis was not yet firmly established, and that further research is necessary. What Dr Crow quoted was our attempt to state concisely the findings of the current analysis, according to the commonly accepted criteria for statistical significance. It is obvious that a degree of uncertainty is involved in the results of any single study. This applies also to the negative conclusion of Dr Crow's own study, the limitations of which have been discussed (e.g. Knight *et al*, 1990). Indeed, Mednick (unpublished) has presented findings which contradict those of Dr Crow's study. Dr Mednick and colleagues examined the antenatal records of all those schizophrenics born in Helsinki in Spring 1958, i.e. those who were exposed to the Asian influenza epidemic in the second trimester of gestation and who experienced an increased risk of schizophrenia (Mednick *et al*, 1988); the records showed that 87% of the mothers of these schizophrenics had suffered influenza during pregnancy, compared with 20% of controls. These data are likely to be more accurate than those quoted by Dr Crow, as they were recorded at the time of the infection, not several months later.

The statistical issues we encountered in our study were complex. Two previous investigations of the same question (Torrey *et al*, 1988; Barr *et al*, 1990) have employed two different approaches. Our preference was to combine graphical and modelling methods. An advantage of statistical modelling is the ability to examine several relationships simultaneously, while allowing for random fluctuations. However, the results of such a model, in terms of