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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.

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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

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