discouraged, despite the obvious advantages of the drug for brief anaesthesia.

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Sex chromosomes and psychosis

SIR: The paper by Crow (*Journal*, November 1988, **153**, 675–683) raises many interesting points. He suggests that there is a pseudoautosomal locus on sex chromosomes for psychosis, but fails to mention whether the gene is dominant or recessive. We presume he has a dominant gene in mind, because one would not expect to find vertical concordance of sex with a recessive gene. The following possibilities occur to us for genes on the X or Y (underlining indicates presence of psychosis gene): paternal inheritance, (a) $\underline{XY} \times XX = XX, \underline{XY}, \underline{XY}$ ... (b) $\underline{XY} \times XX = \underline{XX}, \underline{XX}, XY$ ...; maternal inheritance, (c) $\underline{X}X \times X\underline{Y} = \underline{X}\underline{Y}, \underline{X}X$ ....

Dr Crow presents data to show same-sex concordance in sibs in schizophrenia, and has evidence for paternal transmission. This is consistent with (a) and (b). An excess of father-son over father-daughter transmission leads him to suggest a locus for schizophrenia with preferential mutation on the Y chromosome (situation (a)). Sib sex concordance is quoted for affective illnesses, as are excess of female-female sib pairs and a deficit of father-son transmission. These observations lead him to suggest preferential mutation on the X chromosome for affective illnesses (situation (b)). The lack of mother-daughter and mother-son difference is consistent with (c). We think it is an interesting hypothesis that explains certain cases of psychosis, but the model becomes strained if it attempts to account for all the epidemiological data. When Dr Crow tries to explain the greater severity in male schizophrenics he is referring to an X-linked semi-dominant model. We would also expect an excess of male schizophrenics and male-male pairs if we accept his model of preferential mutation on the Y chromosome for schizophrenia. He has attempted to explain these anomalies, but most importantly has failed to offer any evidence for paternal inheritance in affective illnesses which would be expected with a sex concordance in sibs. How does one explain the lack of same – sex concordance in the other sibling pairs? We would like to suggest that the reason may be genetic heterogeneity as well as variable penetrance.

A possible problem associated with genes in this region is the small size of the segment. Chromosomally, it cannot be larger than about 0.5% of the genome. Furthermore, the particular region that would give the exact concordance of sex must be a small segment on the border between the pseudoautosomal region and the region of the X- and Y-linked genes, because the obligatory crossover must occur proximally to the genes in question most of the time (>80%) for the concordance to be observed. Thus the total region in question must be less than 0.1% of the genome and possibly even smaller. This does not mean that the gene cannot be in this region, but it does mean that the possibility can be checked easily.

If we accept heterogeneity as a possibility, a case for X- and Y-linked genes can be made to give most types of concordance. Several types of sex-linked inheritance can be distinguished:

(a) X-linked lethals (often called sex-linked dominant): these are always passed on maternally, and would produce concordance of mother-daughter and sisters, as well as a deficiency of affected males, and a distorted sex ratio (2:1).
(b) X-linked true dominants: where male and female are similarly affected, would produce sister concordance from paternal transmission and no concordance from maternally affected individuals.
(c) X-linked semidominants: paternally passed on, genes would produce concordance of mild cases in the sisters and no affected sons. Maternally transmitted genes would show concordance of mild cases between the sisters and the mother, and concordance of severe cases between brothers.
(d) X-linked recessives: would produce, if passed on from the mother, concordant brothers; if passed on paternally, no affected individuals would be produced.
(e) Y-linked genes: always passed on paternally, and concordance is complete between all males.

We realise that no single hypothesis will account for all the data. However, it is possible that a gene or

some genes for psychosis could be controlled by sex-linked factors and produce various types of concordance. Muscular dystrophy in man not only has allelic types of varying severity located on Xp21, but also there are autosomal loci with similar phenotype (McKusick, 1988). So it is by no means impossible that one phenotype can be produced by several loci or a single locus with multiple alleles. Thus, the question of heterogeneity must not be forgotten. There is already experimental evidence for it (*Lancet*, 1987, 1988), but in a previous communication Dr Crow (1987) found it difficult to accept. We would suggest that pseudoautosomal or Y-linkage might be found if selected cases of father-son transmission were investigated, and that the X-linkage for the long arm already found in some families with affective disorders might be associated with those cases showing sex concordance.

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SIR: Certainly the possibility of heterogeneity must not be forgotten. Drs Schiwach & Crocker follow in the confident footsteps of the Lancet leader writer (1987) and Lander (1988) in concluding that it has already been established. But neither must it be too readily conceded. Occam's razor – that the simplest viable solution is to be preferred – is a powerful scientific principle.

The pseudoautosomal hypothesis arose from the counter-Kraepelinian notion that the psychoses are distributed along a continuum (Crow, 1986) rather than existing as two discrete entities. As the Lancet leader pointed out, if psychosis is sometimes sex-linked (e.g. in some affective disorders) and sometimes not, it appears that heterogeneity must be accepted. In resisting that conclusion I was forced to consider a pseudoautosomal locus (Crow, 1987), and having done so realised that it could account for same-sex concordance. This finding has been known, although neglected, in schizophrenia for many years. As far as I am aware it has not been commented on in the affective disorders; but it is present here also (Crow, 1988). The prediction of the pseudoautosomal theory is that it originates when the disease is inherited from the father. This has recently been confirmed in the case of schizophrenia (Crow *et al*, 1989), but not yet tested in the affective disorders.

Drs Shiwach & Crocker's explanation of same-sex concordance on the basis of pseudoautosomal inheritance is misleading in one respect. They are correct in supposing that it will arise when the gene is inherited from the father and not from the mother. The complexity arises from recombination between X and Y chromosomes in male meiosis. As a result of the single crossover that takes place somewhere within the pseudoautosomal region, a gradient of sex linkage exists from the pseudoautosomal limit (where there is sex linkage) to the short arm telomere where there is 50% crossover (i.e. sex linkage is absent). Same sex concordance will arise providing the crossover in either sibling has not occurred proximal to the putative locus. With a locus centromeric in the region (i.e. close to the limit) crossing over will generally be distal, and same-sex concordance will be prominent. With a locus at the telomere (with 50% crossover), concordance by sex will be absent. Therefore the size of the effect gives an indication of the location of the gene – the bigger the effect (assuming that it originates in paternal transmission), the closer the gene is likely to be to the border between pseudoautosomal and sex-specific regions.

But Drs Shiwach & Crocker state that "the obligatory crossover must occur proximally" (perhaps they mean distally) "to the genes in question most of the time (>80%) for the concordance to be observed". While it is true that same-sex concordance could arise as a result of proximal crossover in both siblings, because the rate of crossover in each male meiosis even at the telomere does not exceed 50% (only one of the two chromatids that make up each chromosome is subject to recombination) this will be an infrequent event. Whatever their meaning, Drs Shiwach & Crocker's conclusion is the same as mine – the locus should be close to the border between pseudoautosomal and sex-specific regions.

Drs Shiwach & Crocker draw attention to a number of other ways in which same-sex concordance might arise. Most if not all predict a sex difference such as is absent in schizophrenia and probably also in bipolar affective illness. Therefore, no one of these mechanisms provides a general explanation for transmission of psychosis; nor can they account for concordance by sex except in an unspecified subgroup of cases. A pseudoautosomal locus is compatible with equality of incidence in the two sexes, although it cannot readily explain certain other sex differences, e.g. earlier onset of schizophrenia in