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Editor: Ian Pullen

New genetic model of schizophrenia

SIR: I enjoyed the provocative speculations of Roberts & Claridge about the genetics of schizophrenia (*Journal*, April 1991, **158**, 451–456). The notion that defects in different genes lead to similar phenotypes is plausible because of the known interactions between various neuronal systems in the brain. Such a possibility could be tested by investigating offspring of affected parents or affected half-siblings of ill individuals. In each instance, the proband would be likely to inherit defects in different genes. It would be predicted that the subject would either suffer from a more severe illness than his relatives or manifest a different phenotype. Indeed, it has been suggested that more severe illnesses emerge following matings between psychotic individuals (Penrose, 1968). Unfortunately, not all such studies are in agreement (Elsaaser, 1952). I am not aware of any studies involving half-siblings.

The concepts of 'leaky mutations' and threshold requirements of gene products for expression of phenotypes may explain the bewildering disagreement about the mode of inheritance of schizophrenia. The suggested continuum of severity linking schizotypy and schizophrenia also has considerable appeal. However, concepts of quantitative genetics may not be applicable here. Unlike clotting disorders or eye colour in *Drosophila*, the schizophrenic and schizotypal phenotypes are difficult to 'measure'. The difficulties arise not only because of disagreement about which features are specific to these disorders, but also because it is inherently difficult to quantify behaviour. Therefore, it may be difficult to demonstrate a gene dose–effect relationship for schizotypy and schizophrenia.

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PENROSE, L. S. (1968) Critical survey of schizophrenia genetics. In *Modern Perspectives in World Psychiatry* (ed. J. G. Howells). Edinburgh: Oliver and Boyd.

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SIR: The informative article of Roberts & Claridge (*Journal*, April 1991, **158**, 451–456) begs the question as to how we can conceptualise schizophrenia, and thus whether analogy with, for example, blood clotting mechanisms can be sustained.

It seems likely that the biological basis of schizophrenia is a vulnerable conformation of a part of the brain, established during brain development. What do we know about the likely involvement of genetically coded polypeptides in this?

Like other parts of the body, brain development is unlikely to be the consequence of a genetically coded series of events: rather, it will be a cascade of cellular differentiation mediated by peptide regulatory factors (Slack, 1989), whose (genetically coded) production will be switched on and off by the appearance of structures related in anatomy or in time. In addition, we know from the work of Hubel and Weisel that environmental factors can influence the final structure of neural pathways (Weisel, 1982). This is probably mediated by stimulating the development of certain neural buds, and not of others – again, a possible place for the activity of peptide growth activators.

In this model, 'the gene for schizophrenia' could code for a peptide associated with the migration of neural elements. But given the spreading network of interactions during growth and development of the brain, it is not possible to construct an explanation of