which is corrected by any effective treatment. Whether this finding in rats has any relevance to the mode of action of antidepressants in man is an open question!

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The Viral Theory of Schizophrenia

SIR: I am grateful to Dr Crow (*Journal*, March 1988, **152**, 431) for updating me on the latest developments in genetic research, and I concede that I will never be in a position to refute his theories on genetic grounds for the reason I have already stated: that the parent science will keep throwing up new discoveries. The problem with the retrovirus theory, as I see it, is more philosophical than genetic.

Dr Crow asserts that there is no compelling evidence for the belief in an environmental contribution and offers in support evidence from population studies. These studies make certain predictions about the distribution of the disease, and Dr Crow infers that his causal theory is likely to be correct because it can be made to fit the predictions. Such an inference is untenable; there is no *a priori* reason to suppose a predictive model causally valid. An analogy can be made to the various theories of astronomy that have had, even at the time of Babylon, sufficient predictive validity to account for the ephemera and yet have been causally incorrect.

He circumvents the problem of monozygotic discordance by enlarging his theory to embrace the development of the central nervous system. The larger theory now consists, in pure terms, of three connected theories: (a) schizophrenia is caused by a genetic disorder, a retrovirus; (b) bilaterality is controlled by a gene; and (c) schizophrenia is a disorder of laterality. This has the appearance of logic, but the logic is unfortunately spurious. This is because all the above theories are of a class known as fictionalist: that is to say, they are not theories about observations but theories about ideas. For example, the first theory, that schizophrenia is caused by a retrovirus, is based on ideas about the hereditary nature of schizophrenia as shown by population studies and the idea that entities such as retroviruses may be important in schizophrenia. There is so far no evidence for schizophrenic retroviruses. Similar caveats operate on statements (b) and (c).

Fictionalist theories are inevitable in conditions when the number of ideas outweigh reliable evidence, such as currently obtain in schizophrenia research. They have a certain validity as conceptual guides to difficult territories, and it is difficult to see how science can proceed without them. They cannot, however, be combined to make larger theories, as Dr Crow does here, any more than works of fiction can be logically combined. Their relationship is entirely arbitrary.

Dr Crow also asserts that the (only) problem with the theory as it now stands is its lack of clarity, which when overcome may enable it to become testable. There are grave doubts about this. The only way that the theories could become clearer is with the emergence of new evidence. But if the criteria for acceptance of a theory are, as for Dr Crow's, logical rather than empirical then new evidence will result in further fictionalist hypotheses by a process of false syllogism whereby two false premises are joined to a true (empirical) conclusion. For example, if empirical research established pathology X as an important covariant of schizophrenia, a new syllogism might arise thus: (a) schizophrenics have retroviruses; (b) retroviruses cause pathology X; thus (c) schizophrenics have pathology X. The conclusion is empirically true, but not the premises. Although the second premise may appear, in this case, more testable, it must be remembered that the number of new syllogisms are limitless in the face of advances in collateral fields. The original theory remains unfalsifiable.

From meiosis onwards, gene and environment are inseparably linked and to tease out one half of the process as if it were acting *in vacuo* is absurd. It is also potentially damaging, as it creates a false determinism, analogous to the 'nurture only' determinism of the 1960s, which may distort the way the patient is perceived and managed. Although I cannot ascribe this to Dr Crow, it is nevertheless likely to be a problem with theories such as these.

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This letter was shown to Dr Crow, who suggested that those interested should refer to the preceding correspondence and the relevant original papers.

SIR: There has been discussion (*Journal*, March 1988, **152**, 429–431) regarding the retrovirus-transposon model for the causation of psychosis. As Dr Crow suggests, one of the good points of the theory is that it is more precise than others, and hence generates testable predictions. Some consequences of the theory are considered here and are drawn from fairly early observations of the mechanisms of viral transformation of normal cells to neoplastic cells.

Essentially, cellular transformation is caused by two types of retroviruses. The first kind contains its own transforming gene or oncogene, which is usually a viral form of a normal host gene. Virally directed expression of this gene causes transformation of infected cells at high efficiencies and tumour production after short latencies. The second kind of virus possesses no oncogene as such, but transforms by integration into the host DNA next to a cellular oncogene. When this happens, viral DNA sequences designed to enhance transcription of the virus can also drive cellular transcription of the nearby cellular oncogene, causing its overexpression and hence cell transformation. For such viruses, since the site of integration is random with respect to the host genome, transformation is a rare event but is significant because transformed cells proliferate to form the cancer. An example of this type of virus is avian leukosis virus (ALV) whose major effect is cell kill, but which can (rarely) cause cell transformation leading to B-cell lymphomas after a long latency.

Transformation by this method is therefore random and secondary to other effects. Non-specificity also appears to be characteristic of mutation, due to mobile elements in drosophila (for extensive discussion see Georgiev, 1985).

Therefore it is conceptually possible that a retrovirus exists which contains a putative 'psychogene' which may be causative in psychosis (analogous to the oncogene-containing retroviruses). This could act via *de novo* infection or be passed through the germ-line when integrated into host DNA. Crow (1987) himself argues against this on observational grounds, and modifies the theory to include the concept that transpositions of a virus or mobile genetic element next to a critical site may account for the existence of apparently non-familial forms of psychosis or even an apparent increase in incidence of psychosis.

Considering mutation by insertion of mobile genetic elements, however, there are both conceptual as well as observational grounds against their importance to psychiatry. While there is indeed an embarrassment of candidate sequences in the human genome which must be or have been mobile, their present rate of mobility is difficult to assess. Nevertheless, it is highly improbable that the rate is high enough to make a substantial contribution to overall mutation rates in man. If so, one would expect to have detected abundant examples of germ-line insertion of mobile elements in the now large body of molecular analysis of human genetic disease. The example quoted by Crow of participation of Alu sequences in the mutation leading to familial hypercholesterolaemia involves recombination rather than transposition.

If we consider specific sequences rather than disease mutations, human endogenous retroviral sequences do not show detectable variation between individuals (Steele *et al*, 1984). In addition, hypervariable minisatellite sequences appear to gain most of their variability from recombination events rather than from transpositions. There is, however, an example of somatic cell mutation due to insertion of a LINE element in human breast carcinoma (Morse *et al*, 1988).

One may of course always propose the existence of novel transposable elements. For this reason, it is perhaps more significant to point out that there are strong theoretical problems for the viral/mobile element integration theory. Firstly, there is the low probability of random integrations occurring next to the causative cellular gene. This probability becomes vanishingly small when, as Crow (1987) rightly points out, to be significant to the brain this event must take place in the germ-line or very early in zygotic development. Secondly. such events would be associated with widespread other mutations.

Therefore, while insertional mutagenesis remains a clear candidate for causing disorders involving selection of affected cells, it does not appear to be conceptually relevant to psychotic aetiology.

What other possibilities are there? Crow has hinted that there may be a virogene/retroposon/transposon/hypervariable element next to the psychosis gene. Because of the unstable nature of this element, it is able to affect the psychosis gene at high frequencies. This is possible, but I would propose that at this point the theory starts to lose its value. It is equivalent to saying that the psychosis gene has a high rate of mutation because it is in a mutational hotspot.

There is one other permutation, which is that the unstable element and the psychosis gene are the same. This is a special case of the above concept. Here one has to consider virogenes, since other mobile elements do not generally encode useful genetic information. Instability of this virogene may affect its own transcription, and hence give rise to quantitative variations in genetic traits. Here we have come full circle back to the first concept of a 'psychogene'-containing retrovirus: i.e. a virogene which exerts positive effects in a manner which is independent of site of integration. To this is added the concept that quantitative variations occur in the readout of this virogene when integrated. The problem with this model is that it predicts the opposite to what is required of it. The vast majority of either normal mutation or transpositions result in degeneration of readout. Since the

virus would act in a positive manner, one would expect that its influence would decline rather than increase with time.

Where does this leave the retroviral/transposon theory of psychosis? Confusion has resulted because it has grown to become so complex – more a synthesis of several theories with a common thread. Perhaps it is time for Dr Crow to discard the parts which are not useful, thereby cutting a knot which both psychiatrists and geneticists find hard to unravel.

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References

CROW, T. J. (1987) Integrated viral genes as potential pathogens in the functional psychoses. *Journal of Psychiatric Research*, **21**, 479–485.

GEORGIEV, G. P. (1985) Mobile genetic elements in animal cells and their significance. *European Journal of Biochemistry*, **145**, 203–220.

MORSE, B., ROTHBERG, P. G., SOUTH, V. J., SPANDORFER, J. M. & ASTRIN, S. M. (1988) Insertional mutagenesis of the myc locus by a LINE-1 sequence in a human breast carcinoma. *Nature*, **333**, 87–90.

STEELE, P. E., RABSON, A. B., BRYAN, T. & MARTIN, M. A. (1984) Distinctive termini characterise two families of human endogenous retroviral sequences. *Science*, **225**, 943–947.

Dr Crow's detailed response will be published next month.

SIR: What else can be explained by this 'schizophrenic-mutagenic-virogene'? Dr Crow's account of schizophrenic aetiology via a virogene associated with a high rate of mutation (*Journal*, October 1987, **151**, 460–465) seems to resolve much of the contradictory data surrounding this baffling disease. Evidence such as the discordance in monozygotic pairs, age of onset uninfluenced by environment, seasonality of birth, adoption away from schizophrenic relatives not reducing risk of disease, relationship with paternal age, the apparent continuum of psychosis, constant incidence rates across populations, and even the increasing incidence in the 19th century can all, it seems, be drawn together with one explanation (Crow, 1987).

However, many of these features which are accounted for remain themselves controversial, and not everyone accepts them as part of the description of schizophrenia. What incontrovertible aspect of schizophrenia does this virogene hypothesis explain? There is some data that is accepted universally which may have been inadequately explained until now.

The evidence on life-time expectancy for schizophrenia in relatives of schizophrenic patients is well established. If one parent is affected, the average risk for a child is 12%. However, if a child is affected, the risk for parents is only 5%. This relatively low risk has been explained until now by the suggestion it is the more healthy parents who tend to reproduce.

A rapidly mutating gene might also predict this and perhaps account for the phenomenon more satisfactorily.

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Reference

CROW, T. J. (1987) Mutation and psychosis: a suggested explanation of seasonality of birth. *Psychological Medicine*, **17**, 821–828.

Psoriasis and Lithium

SIR: Humphreys & Waddell (*Journal*, March 1988, **152**, 437–438) suggest that lithium therapy led to an improvement in their patient's psoriasis. As their references reveal, the literature tends to show that lithium exacerbates psoriasis. There may be possibly an alternative explanation for this dermatological improvement, the clue to which lies in their patient's heavy drinking history.

Vincenti & Blunden (1987) reported a small series of regular alcohol abusers who had found a striking association between stopping drinking and improvement of their psoriasis. A much larger earlier study (Chaput *et al*, 1985) found a significant association, independent of alcohol liver damage, between alcohol abuse and psoriasis at the level of $P < 0.001$.

It would be interesting to ascertain whether the patient reported by the authors had successfully reduced his alcohol intake around the time he started lithium therapy.

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References

CHAPUT, J. C., POYNARD, T., NAVEAU, S., PENSO, D., DURRMEYER, O. & SUPLISSON, D. (1985) Psoriasis, alcohol and liver disease. *British Medical Journal*, **291**, 25.

VINCENTI, G. E. & BLUNDEN, S. M. (1987) Psoriasis and alcohol abuse. *Journal of the Royal Army Medical Corps*, **133**, 77–78.

SIR: We are grateful to Dr Vincenti for his remarks with regard to our report, the intention of which was