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The Viral Theory of Schizophrenia

SIR: Whatley (*Journal*, 1988, **153**, 259–261) has drawn attention to some strengths and weaknesses of the virogene (or retrovirus/transposon) hypothesis (Crow, 1984, 1987*a*) of psychosis. I agree with many of his points, and will attempt to clarify the theory. A number of questions are raised.

(a) *Is the agent exogenous or endogenous?* The virogene hypothesis arose from the failure of an earlier gene-environment interaction theory (Crow, 1983). According to the earlier view, the psychosis gene predisposes an individual to an environmental pathogen – in this case a virus. The hypothesis predicted that siblings would tend to be affected at the same point in time; the data shows on the contrary that there is a tendency for them to be affected at the same age (Crow & Done, 1986), a finding which restricts any hypothesis that includes an environmental factor. For this (and some other) reasons I now believe that the role of the postnatal environment in the aetiology of psychosis is negligible. While the data do not rule out a prenatal environmental influence, the scope for this also is restricted (see below). Causation of the disease is genetic and the problem is to understand the nature of the gene and the reasons for its survival.

According to the virogene hypothesis, the psychosis gene is an element with a degree of potential autonomy. That is to say that it is a genomic component with the capacity to replicate in defiance of normal regulatory controls and thus to disrupt cellular function. Animal models of disease caused by such a mechanism are available; for example, mammary tumours and leukemia in the mouse can both be caused by endogenous retroviruses that are inherited in a Mendelian manner (Teich, 1982). A type of motor neurone disease is also described which is caused by an interaction between an endogenous retrovirus and lactate dehydrogenase virus (Murphy *et al*, 1983). Besides demonstrating that disease can be caused by viral sequences that are part of the host genome, these animal models have two features of relevance to the psychoses: (i) the viruses are expressed in a tissue-specific manner; and (ii) the diseases that they cause are manifest at a characteristic point in the life span of the host. In two further respects, however, these diseases do not mirror the psychoses: (i) transmission conforms closely to a Mendelian dominant model, whereas in the psychoses the mode of genetic transmission is uncertain; and (ii) only certain mouse strains are affected, while psychotic illness is widely distributed in the human species.

I conclude that it is at least conceivable that the psychoses are caused by endogenous pathogens. Although the findings on age of onset in siblings do not rule out that such an agent is sometimes acquired *de novo* (e.g. *in utero*) it is more parsimonious to assume that the hypothetical virogene is a regular component of the human genome, i.e. that it is present (in some form) in everyone but is expressed as an autonomous pathogen only in affected individuals. High and culture-invariant prevalence is consistent with the possibility that the gene has a normal function. My suggestion is that this is to regulate the development of the asymmetries of structure which are present in the human brain – i.e. that the gene is the 'cerebral dominance gene' or 'right-shift factor' of Annett (Crow, 1984, 1986*a*). The challenge is to understand the nature of the variations in its form.

(b) *Are new mutations caused by transposition, unequal recombination or some other mechanism?* I have two reasons for supposing that psychosis is associated with a high rate of mutation: the disease persists even though it substantially reduces fertility,

and the form of psychosis not infrequently changes between generations (Crow, 1986*b*, 1987*b*). In the absence of a significant environmental contribution, a high rate of change in the psychosis gene must be postulated. As was previously appreciated, e.g. by Penrose, the rate of mutation required to compensate for diminished fertility is substantially above the mean rate for human genes. Therefore there must be a 'hot-spot' at the site of the psychosis gene.

Dr Whatley puts his finger on the problem of the nature of this 'hot-spot': is the variation due to transposition or unequal recombination? While high rates of germ-line acquisition of copies of endogenous leukemia-inducing viruses are reported in certain mouse hybrid strains (Jenkins & Copeland, 1985) it is difficult, as Dr Whatley emphasises, to see how such integration could be site-specific. Therefore, while the 'cerebral dominance gene' (i.e. the juxtaposition of mobile element and growth factor that has facilitated asymmetric brain growth) may have originated in a single transposition event a few million years ago, I suspect that the source of continuing variation in this gene complex is to be sought elsewhere, e.g. in unequal recombination. Another possibility is the type of heritable modification (e.g. due to methylation of cytosine residues) of the DNA sequence referred to as an 'epimutation' by Holliday (1987).

Whatley's further point that transposition is more likely to inactivate a gene than induce overexpression is well taken. In addition to the example he gives, an insertion of a LINE element into the factor VIII gene to cause haemophilia A has recently been reported (Kazazian *et al*, 1988). Overactivity is a more plausible explanation of the phenomena of episodes of psychosis than deletion. As in the case of neoplasia, activation can result from an interaction between a mobile element and a cellular regulatory component, i.e. a 'proto-oncogene'. If selective enhancement of brain growth has preserved the association between growth factor and mobile element that constitutes the cerebral dominance gene, it is conceivable that further modifications (whether attributable to unequal recombination or some other mechanism) at this variable locus sometimes lead to overexpression; this could be manifest as accumulation of virus particles.

(c) *What is the nature of the virogene?* A number of mobile elements have been described in the human genome – these include retroviral sequences, short and long-interspersed nuclear elements (SINEs and LINEs), and transposons apparently specific to man (Paulson *et al*, 1985). A feature of the virogene hypothesis is that by postulating an interaction between an endogenous viral sequence and a growth factor (or proto-oncogene) it provides a possible explanation for selectivity to the left hemisphere. Proto-oncogene/transposon interactions are described for retroviral sequences and for some other mobile elements (e.g. Katzir *et al*, 1985). Of particular interest are the sequences which give rise to intracisternal A-type particles (Kuff *et al*, 1983). These have homologies with retroviruses and are sometimes expressed, e.g. in the embryo, as intracellular virus-like particles; they may play a role in normal development. Such an element might have both a normal regulatory function and a capacity for uncontrolled replication.

It is not widely appreciated that there is already a strong case that one form of neuropsychiatric disease is caused by a virogene. The Gerstmann-Straussler syndrome is a dementing illness that is inherited as an autosomal dominant. We have demonstrated that the disease can be transmitted to the marmoset by intracerebral inoculation of brain material (Baker *et al*, 1985); it appears to be an inherited form of Creuzfeldt-Jakob disease. In our recent studies we have shown that some members (including those with the disease) of affected families have mutations (in one family an insertion) in the 'prion' gene (Owen *et al*, 1988). The prion gene is present in a single copy in all individuals and codes for the type of amyloid that accumulates in the brain in this and other transmissible encephalopathies. These mutations thus render pathogenic and transmissible a structure which originates in the host genome. The agent can justifiably be labelled a 'virogene', although in important respects it differs from the gene that causes psychosis.

I summarise the characteristics of the hypothetical psychosis virogene as follows.

(a) It comprises a genomic sequence with a degree of potential autonomy such as is possessed by the mobile elements (transposons) listed above.

(b) It is located close to, and may form a part of, a gene (the 'cerebral dominance gene' or 'right shift factor') responsible for the asymmetric development of the human brain. The symbiotic relationship between growth factor and virogene is assumed to have developed early in man's evolution from other primates; it may have resulted from a single transposition event.

(c) The gene complex (i.e. virogene plus right shift factor) includes a component which is subject to significant variation between individuals arising as a result of unequal recombination (or some other mechanism, e.g. epimutation). This component is responsible for variations in gene expression, including those which lead to psychosis. According to this concept, the psychosis virogene is no more than a labile and potentially deleterious variant of the cerebral

dominance gene which itself is highly variable between normal individuals.

A model for this last feature is the mouse LINE element described by Loeb *et al* (1986) that includes a variable number of tandem repeats. These authors consider that the tandem repeat sequence may regulate expression. Ono *et al* (1987) have reported a human retroviral sequence with similar repeats.

In addition to the above three postulates, I suggest that the new mutations required by the theory occur specifically in the course of male gametogenesis and are season-dependent (Crow, 1987*c*). In this way an environmental influence on the structure of the gene, and thereby on the occurrence of psychosis, is introduced.

The case that the psychosis gene indeed is closely related to the cerebral dominance gene has been strengthened by the finding that temporal horn enlargement in schizophrenia, by contrast with that in Alzheimer-type dementia, is highly selective to the left hemisphere (Crow *et al*, 1988*a*). A locus in the pseudoautosomal region of the sex chromosomes has been suggested (Crow, 1987*d*) and is supported by the observation that in a series of pairs of siblings with psychosis, concordance by sex is inherited from the paternal and not the maternal side (Crow *et al*, 1988*b*). These findings may facilitate a molecular approach to the nature of the psychosis gene.

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References

BAKER, H. F., RIDLEY, R. M. & CROW, T. J. (1985) Experimental transmission of an autosomal dominant spongiform encephalopathy: does the infectious agent originate in the human genome? *British Medical Journal*, **291**, 299–302.

CROW, T. J. (1983) Is schizophrenia an infectious disease? *The Lancet*, *i*, 173–175.

—— (1984) A re-evaluation of the viral hypothesis: is psychosis the result of retroviral integration at a site close to the cerebral dominance gene? *British Journal of Psychiatry*, **145**, 243–253.

—— (1986*a*) Left brain, retrotransposons and schizophrenia. *British Medical Journal*, **292**, 3–4.

—— (1986*b*) The continuum of psychosis and its implication for the structure of the gene. *British Journal of Psychiatry*, **149**, 419–429.

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

—— (1987*b*) Psychosis as a continuum and the virogene concept. *British Medical Bulletin*, **43**, 754–767.

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

—— (1987*d*) A pseudoautosomal locus for psychosis? *The Lancet*, *ii*, 1532.

—— COLTER, N., BROWN, R., BRUTON, C. J. & JOHNSTONE, E. C. (1988*a*) Schizophrenia as an anomaly of the cerebral dominance gene. (in press).

——, DELISI, L. E., JOHNSTONE, E. C. (1988*b*) Concordance by sex for psychosis is paternally inherited: evidence for a pseudoautosomal locus. (in press).

—— & DONE, D. J. (1986) Age of onset of schizophrenia in siblings: a test of the contagion hypothesis. *Psychiatric Research*, **18**, 107–117.

HOLLIDAY, R. (1987) The inheritance of epigenetic defects. *Science*, **238**, 163–170.

JENKINS, N. A. & COPELAND, N. G. (1985) High frequency germ-line acquisition of ecotropic MuLV proviruses in SWR/J–RF/J hybrid mice. *Cell*, **43**, 811–819.

KATZIR, N., RECHAVI, G., COHEN, J. B., UNGER, T., SIMONI, F., SEGUL, S., COHEN, D. & GIVOL, D. (1985) "Retroposon" insertion into the cellular oncogene c-myc in canine transmissible venereal tumor. *Proceedings of the National Academy of Sciences*, **82**, 1054–1058.

KAZAZIAN, H. H., WONG, C., YOUSSOUFIAN, H., SCOTT, A. F., PHILLIPS, D. G. & ANTONARAKIS, S. E. (1988) Haemophilia A resulting from *de novo* insertion of L1 sequences represents a novel mechanism for mutation in man. *Nature*, **332**, 164–166.

KUFF, E. L., FEENSTRA, A., LUEDERS, K., SMITH, L., HAWLEY, R., HOZUMI, N. & SHULMAN, M. (1983) Intracisternal A-particle genes as movable elements in the mouse genome. *Proceedings of the National Academy of Sciences*, **80**, 1992–1996.

LOEB, D. D., PADGETT, R. W., HARDIES, S. C., SHEHEE, W. R., COMER, M. B., EDGELL, M. H. & HUTCHISON, C. A. (1986) The sequence of a large L1Md element reveals a tandemly repeated 5′ end and several features found in retrotransposons. *Molecular Cell Biology*, **6**, 168–182.

MURPHY, W. H., NAWROCKI, J. F., & PEASE, L. R. (1983) Age-dependent paralytic viral infection in C58 mice: possible implications for human neurologic disease. *Progress in Brain Research*, **59**, 291–303.

ONO, M., KAWAKAMI, M. & TAKEZAWA, T. (1987) A novel human nonviral retroposon derived from an endogenous virus. *Nucleic Acids Research*, **15**, 8725–8737.

OWEN, F., POULTER, M., LOFTHOUSE, R., CROW, T. J., RISBY, D., BAKER, H. F. & RIDLEY, R. M. (1988) A rare MSP1 polymorphism in the human prion gene in a family with a history of early onset dementia. *Neuroscience Letters*, **Suppl. 32**, S53.

PAULSON, K. E., DOKA, N., SCHMID, G. W., MISRA, R., SCHINDLER, C. W., RUSH, M. G., KADYK, L. & LEINWAND, L. (1985) A transposon-like element in human DNA. *Nature*, **316**, 359–361.

TEICH, N. (1982) Endogenous viruses. In *RNA Tumour Viruses* (2nd edn) (eds R. Weiss, N. Teich, H. Varmus & J. Coffin) pp 1109–1203. New York: Cold Spring Harbor Laboratory.

Capgras Syndrome and the Amygdala

SIR: The patient described by Lipkin (*Journal*, July 1988, **153**, 117–118) demonstrates, as do several other cases reported by Dr Lipkin, that the Capgras syndrome may be an early symptom of dementia. This case report continues the debate as to whether this syndrome has an organic basis. It does occur in organic conditions with diffuse and focal cerebral lesions, but precise anatomical localisation of the lesion is not available. The localisation of lesions giving rise to an inability to distinguish one face from another, proposagnosia, is better established and seems to involve an area of the cerebral cortex at the occipito-temporal junction (Meadows, 1974).