Lack of Evidence for Retrovirus Infection in Schizophrenic Patients

DEAR SIR,

We read with interest the publication of Dr T. J. Crow's hypothesis associating retroviral infection with the development of schizophrenia (*Journal,* September 1984, **145,** 243–252). In view of the familial occurrence, indirect evidence for an infectious aetiology, and data suggesting immune dysfunction in some schizophrenic patients, we found this hypothesis plausible and worth investigating. No evidence exists, however, to suggest that retroviruses, rather than other classes of viruses, are involved. One of the unique properties common to all retroviruses is that they contain an enzyme, reverse transcriptase, which can transcribe DNA from RNA. The presence of this foreign enzyme in host cells may stimulate the production of antibodies directed against reverse transcriptase, which can be detected by standard immunological laboratory techniques. If an individual has, or previously had, an active retroviral infection, elevated titres of serum IgG specifically directed against reverse transcriptase may then be present, as has been recently reported in patients with the autoimmune disorder, systemic lupus erythematosus (Okamoto *et al,* 1983). We therefore examined sera from schizophrenic patients for the presence of antibodies to this protein, as well as others, that might provide evidence for Dr Crow's proposal.

Fifteen hospitalised DSM-III diagnosed chronic schizophrenics, all with evidence of active positive symptoms of psychosis, and 15 age-and gender-matched normal controls had serum samples drawn and blindly assayed for antibodies to reverse transcriptase. However, since reverse transcriptase is only weakly antigenic, and thus some individuals with retroviral infections may be missed if screening is limited to antibodies against this protein, we have also examined antibodies to Human T Cell Leukemia Virus antigens (HTLV I and III), the only class of retroviruses known to infect humans. The assay procedures have been described in detail elsewhere (Kalyanaraman *et al,* 1981; Saxinger and Gallo, 1983). At serum dilutions of 1:300 or greater no antibodies (IgG) to reverse transcriptase or any of the other viral proteins were found in either the schizophrenic or control groups. In contrast, almost 100 percent of human T cell leukemia patients have titres several fold greater to at least some of the viral proteins (Sarin & Gallo, 1983), as do patients with acquired immune deficiency syndrome (AIDS; Sarngadharan *et al,* 1984).

We, therefore have failed to find evidence that would be consistent with the presence of a retrovirus infection in schizophrenia. If schizophrenia is associated with periodic activation and reproduction of the retrovirus, particularly during an exacerbation of psychosis, then we would expect that at least a few of our 15 patients would have shown some antibody response to the enzyme, reverse transcriptase.

LYNN E. DELISI
PREM S. SARIN

National Institutes of Health, Bethesda, Maryland 20205

References

KALYANARAMAN, V. S., SARNGADHARAN, M. G., BUNN, P. A., MINNA, J. D. & GALLO, R. C. (1981) Antibodies in human sera reactive against an internal structural protein of human T-cell lymphoma virus. *Nature,* **294,** 271–273.

OKAMOTO, T., TAMURA, T. & TAKANO, T. (1983) Evidence in patients with systematic lupus erythematosus of the presence of antibodies against RNA-dependent DNA polymerase of baboon endogenous virus. *Clinical and Experimental Immunology,* **54,** 747–755.

SARIN, P. S. & GALLO, R. C. (1983) Human T-cell leukemia-lymphoma virus (HTLV). In *Progress in Hematology, volume XIII* (ed. E. B. Brown). New York: Grune & Stratton.

SARNGADHARAN, M., POPOVIC, M., BRUCH, L., SCHUPBACH, J. & GALLO, R. C. (1984) Antibodies reactive with human T-lymphotropic retroviruses HTLV-III. *Science,* **224,** 506–508.

SAXINGER, W. C. & GALLO, R. C. (1983) Application of the indirect enzyme linked immunoabsorbent assay microtest to the detection and surveillance of human T cell leukemia-lymphoma virus. *Laboratory Investigation,* **49,** 371–377.

Dr Crow replies

DEAR SIR,

The observations of DeLisi and Sarin, along with those of Robert Guroff and colleagues, (*Journal,* March 1985, **146,** 326), are obviously relevant to the retrovirus/transposon hypothesis of schizophrenia and are a welcome attempt to subject this theory to experimental test.

However while one might have interpreted a positive finding (i.e. an excess prevalence of antibodies to reverse transcriptase in a group of patients with psychosis by comparison with an appropriate control group) as support for the hypothesis, there are a number of reasons why a negative outcome may be less damaging than at first sight appears to be the case. One of these (alluded to indirectly by DeLisi and Sarin) is the antigenic variability of the class of retroviruses. Unless a virus very closely resembling HTLVI or III were postulated, antibodies to these viruses would not be expected. Therefore the force of the test relies heavily upon reverse transcriptase and, as DeLisi and Sarin note, this enzyme is only weakly antigenic. Moreover it is not entirely clear that if the virus were integrated in the genome that an antibody response would be elicited. For example retroviral sequences as detected by

https://doi.org/10.1192/S0007125000121713 Published online by Cambridge University Press

relaxed stringency hybridisation with mouse mammary tumour virus (Westley and May, 1984), murine leukemia virus and baboon endogenous virus (Martin *et al,* 1981; Steele *et al,* 1984) are present in human DNA, and reverse transcriptase activity has been detected in 80% of human placentae (Leong *et al,* 1984), yet antibodies to this enzyme apparently are not common in normal populations. One may also ask whether if viral antigens were expressed in an immunologically privileged site such as the brain, they would necessarily elicit an antibody response.

For these reasons I do not yet feel obliged to abandon the retrovirus theory. At the risk of being charged with constructing a hypothesis insusceptible to disproof I mention also the footnote which draws attention to the fact that retroviruses are but one member of the class of transposons or mobile genetic elements (Shapiro, 1983). The arguments which support a retroviral pathogen in psychosis do not exclude some other type of transposon. Some (e.g. Copia elements in Drosophila) but not all of these depend upon reverse transcriptase.

T. J. Crow

Clinical Research Centre,
Watford Road,
Middlesex HA1 3UJ

References

Leong, J. C., Nelson, J. A. & Levy, J. A. (1984) Optimal conditions for detection of reverse transcriptase activity in human placentas. *Biochimica et Biophysica Acta,* **782,** 441–445.

Martin, M. A., Bryan, T., Rasheed, S. and Khan, A. S. (1981) Identification and cloning of endogenous retroviral sequences present in human DNA. *Proceedings of the National Academy of Sciences,* **78,** 4892–4896.

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.

Westley, B. & May, F. E. B. (1984) The human genome contains multiple sequences of varying homology to mouse mammary tumour virus DNA. *Gene,* **28,** 221–227.

Shapiro, J. A. (1983) *Mobile Genetic Elements,* Orlando, Florida: Academic Press.

Is there Really a Schizophrenia?

Dear Sir,

While Dr L. Ciompi's attempt at a reformulation of the concept of schizophrenia (*Journal,* December 1984, **145,** 636–640) is admirable because of this obvious desire to integrate diverse theory into a biopsychosocial model, the result is neither new nor particularly illuminating.

If all the author wished to point out was that schizophrenia should be viewed as a *syndrome* rather than a *disease entity* (the former implying multifactorial causation and variable course), then he has certainly expended much effort rehashing what is probably already a prevalent idea in psychiatry.

Dr Ciompi's rejection of the prevailing concept of schizophrenia on the basis that it has no "common causes" nor a "uniform course" could just as well be applied, for example, to coronary artery disease. The latter, of course, remains a perfectly useful concept in medicine.

Atul C. Pande

Victoria Hospital,
375 South Street,
London,
Ontario, Canada

Eric and Erwin: Let's Get it Right

Dear Sir,

I had never thought, however belatedly, to discover Jove nodding in the person of Professor Anthony Clare in his fascinating account of the history of psychiatry at Bart's (*Journal,* February 1985, **146,** 120–126). Surely, Erwin was Stengel: Strauss was Eric?

Seymour Spencer

66 Old Road,
Headington,
Oxford OX3 7LW

[Yes, but surely it was Homer who occasionally nodded. *Corresp.Ed*]

CORRECTION

Journal, April 1985, 146, 341–347 'Understanding the Italian Experience'. The reference to Sarteschi, Cassano, Mauri & Petracca on page 347 should read (1985) Current status of psychiatric care in Italy. In *Psychiatry, Human Rights and the Law* (eds. M. Roth & R. Bluglass) Cambridge University Press.

https://doi.org/10.1192/S0007125000121713 Published online by Cambridge University Press