

XMRV and CFS/ME

In light of the recent publication in Science regarding a new retrovirus discovered in patients with CFS and the attendant widespread publicity, the following is a scientific appraisal of this publication and the evidence so far. It has been adapted almost in full with permission from an article by Professor Andrew Lloyd, Director, Centre for Infection and Inflammation Research, University of New South Wales.

The first comment is that the findings are potentially important to our understanding of the illness. The paper describes the detection of genetic material of a virus known as xenotropic murine leukemia virus-related virus (XMRV) in 68 of 101 (67%) patients in the US, described as having illness "fulfilling the 1994 CDC Fukuda Criteria for Chronic Fatigue Syndrome and the 2003 Canadian Consensus Criteria for Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) and presenting with severe disability", compared to 8 of 218 (3.7%) healthy individuals. The significance of this finding was further supported by detection of XMRV proteins in the blood of 19 of 30 patients, but none of 5 healthy subjects. Antibodies against XMRV were found in the blood of 9 of 18 patients and none of 9 healthy individuals. The XMRV was shown to grow in cell culture in the laboratory.

As the retrovirus family also includes HIV, on face value this finding raises the suggestion that CFS may be caused in some cases by infection with XMRV which may affect both the immune system and the brain.

However, several strong notes of caution need to be applied:

1) Research into CFS has been plagued over several decades by studies using sophisticated molecular laboratory techniques to examine poorly characterised subjects and samples. In the recent study, the 101 patients are reported to have met diagnostic criteria for CFS, but perplexingly no details of their age, gender, or illness characteristics were provided - except the indication that the illness in these patients was causing "severe disability". This information is critical to allow the reader to understand how comparable the patients in the study were to 'typical' patients with CFS in the USA and worldwide. Disconcertingly, one of the authors of the study, Judy Mikovits has suggested during interviews with the Amy Dockser Marcus in the Wall Street Journal, that "20 patients of the 101 in the study have lymphoma" - if this statement is accurate the reliability of the designation of the 101 patients must be cast into serious doubt (as diagnosis of lymphoma precludes a diagnosis of CFS). Perplexingly, the paper also does not describe how the healthy control subjects were selected - for instance if the controls were family members of the cases, or individuals working in the laboratory where the studies were performed this would be inappropriate as they may have altered rates of contact with the XMRV.

2) the finding of a retrovirus in the blood would seem to be highly significant, however so called 'endogenous retroviruses' (ERVs) are actually found commonly in humans and generally cause no ill effects. These retroviruses are derived from ancient viral infections of germ cells in humans, mammals

and other vertebrates; and so are passed on through generations and now remain in the genome. Some research suggests that human ERVs may cause certain autoimmune diseases and cancers. XMRV has previously been associated with prostate cancer. Accordingly, the finding of XMRV in the recent study raises the possibility that infection with this virus may cause CFS in some patients - alternatively it may become active as a result of CFS - or it may have no role whatsoever in the illness (i.e it may be an epiphenomenon).

3) those of us who have been undertaking research into CFS for a long period will remember the remarkably comparable "discovery" of a retrovirus in patients with CFS made by Elaine Defreitas which was published in the similarly prestigious journal, *Proceedings of the National Academy of Sciences* in 1991. In brief, the initial report was of a retrovirus with both genetic material and viral proteins, as well as antibodies against the virus, identified in a significant proportion of patients and not in healthy individuals. A series of subsequent studies failed to confirm the findings - or find evidence for any known retroviral infection. This outcome is an important reminder that biomedical research is highly complex process and often uses new technologies to make discoveries - some are confirmed and found to have lasting significance - many are not. This process is a necessary element in the pathway to improved understanding of disease.

There can be no doubt that CFS is one of the most challenging on the list of unsolved medical conditions, hence the last two decades have witnessed many such 'discoveries' - time will tell whether this one stands the key test of independent replication, which is verification of the same finding in other laboratories and using other patient samples. A number of research groups will be undertaking this task over the next several months - until these results are in - there is no likelihood of a meaningful "diagnostic test". If the findings were confirmed the likelihood of an effective treatment would be several years away at the earliest.