

# Chronic Fatigue Syndrome: Still a Long Way to Go

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Chronic fatigue syndrome is an enigmatic clinical entity defined by persistent, relapsing fatigue associated with substantial impairments of 6 months duration and beyond. An additional four (of eight) secondary symptoms, which cluster into the domains of flu-like pain and neurocognitive symptoms, are required for the diagnosis [1].

During the last three decades, a multitude of papers were published implying various etiologies for the disease. Of the many viruses considered to be the culprit, none was convicted. For example, in 1991, the prestigious journal *Proceedings of the National Academy of Sciences* published a study on the role of HTLV-2 in chronic fatigue syndrome [2], but subsequent studies failed to replicate the results. Almost two years ago, a publication in *Science* claimed that most cases of chronic fatigue syndrome were associated with a newly described gamma retrovirus, xenotropic murine leukemia virus-related virus [3]. This virus was previously detected in human prostate tumor tissue. Since retroviruses are known to affect both neurological and immunological function, Lombardi and colleagues [3] suggested that XMRV may be involved in the pathogenesis of chronic fatigue syndrome. They

XMRV = xenotropic murine leukemia virus-related virus

detected the virus in 67% of patients with the syndrome compared to only 3.7% of healthy controls. This *Science* paper was launched as a breakthrough with important implications for the prevention and treatment of the disorder. Indeed, in some patients antiretroviral treatment was requested for some patients, and the demand for a universal test for XMRV (at a cost of more than US \$500 per test) led to increased funding from several patient organizations. Soon after, several concerns about the study were raised. These included consideration of bias, reverse causality, and lack of generalization. The authors of the *Science* paper refuted all claims [4].

Two new papers published in the July issue of *Science* seem to reject a possible role for XMRV in chronic fatigue syndrome. The first study [5] could not find any evidence of XMRV infection in the same samples tested in the 2009 *Science* study. Furthermore, evidence was presented alluding that the Tag polymerase and other commercial laboratory reagents used in the 2009 study were contaminated by viral mouse DNA. The second study [6] showed that XMRV probably arose as the consequence of a recombination event between two mouse proviruses that occurred between 1993 and 1996, many years after the first description of chronic fatigue syndrome.

With these new data, the editor of *Science* approached Lombardi and colleagues to voluntarily retract their paper. The authors declared "it is premature to retract our paper" and thus the editor published an editorial expression of con-

cern attached to the original paper [7].

Despite the enormous pressure to find cause and cures for many common debilitating conditions, such as chronic fatigue syndrome, full scientific proof and validation remain paramount. Nonetheless, the story of XMRV and chronic fatigue syndrome should encourage basic and clinical research to continue at full strength to reconfirm results until the true cause of a disease, such as the one discussed here, is identified.

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**"When a man is wrapped up in himself he makes a pretty small package"**

John Ruskin (1819-1900), British author, art critic, and social reformer