

Dear CFSAC Members,

My name is Dharam V. Ablashi. I am presently the Scientific Director of the HHV-6 Foundation which supports research on the role of virus in chronic diseases including Chronic Fatigue Syndrome. I am also the co-founder of AACFS and for many years, I served on the Board of Directors of AACFS. I was also the President of IACFS in 2003-2004. I served as a senior investigator at NIH/NCI for 22 years where I conducted research on establishing primate models for lymphomas induced by herpesviruses. In 1986, while at NCI, I co-discovered HHV-6.

The role of microbes in the pathogenesis of CFS has not been explored fully because of the lack of extramural funding from NIH and CDC. In my opinion, the etiology of CFS is multi-faceted. While infection may not trigger the illness in all cases, I have long believed that the evidence indicates infectious agents are involved in many cases. Indeed, the literature documents clearly that CFS can follow in the wake of infection with Epstein-Barr virus, human herpesvirus-6, Ross River virus, *B. burgdorferi* (the cause of Lyme disease), *C. burnetii* (the cause of Q fever), parvovirus B19, the enteroviruses and possibly mycoplasma organisms.

I am sorry to say that, over the years, several people in leadership positions both at the NIH and CDC have made it clear that they do not believe that studying infectious agents in CFS is important, and thus it has been neglected. This issue has become urgent with the recent report that a retrovirus (XMRV) is found in many patients with CFS, and in few healthy controls, published in Science from the Whittemore-Peterson Institute (2009). Given the known tropism of retroviruses, XMRV is an entirely plausible candidate to be producing the well-documented abnormalities of the central and autonomic nervous system, of the immune system, and of energy metabolism. Moreover, it is entirely plausible that XMRV may reactivate latent infectious agents—particularly the herpesviruses and endogenous retroviruses—which then contribute to producing pathology.

The CDC has made several assumptions that we believe will prove to be in error:

1. The CDC has assumed that if a pathogen exists, it can be found in the serum, and
2. The CDC assumed that if there is a pathogen, it is only one pathogen, not 8-12 pathogens that cause variations of the same syndrome.
3. The CDC has assumed that the timing of sample collection is unimportant

We think it is likely that CFS is a heterogeneous disorder and that there are multiple factors and pathogens that contribute to the condition. Even if XMRV is found in the majority of CFS patients, we expect that there are at least 8-12 other pathogens that act as co-factors to cause pathology. Unless you are looking for subsets, infections such as parvovirus B-19 or Q fever (which might represent a small fraction of the cases) will be completely overlooked as unimportant. Statistically, none of the subsets may be statistically significant, but when added together, these subsets could be very important.

Patient samples from newly diagnosed cases of CFS offer the best chance of finding evidence of an infectious agent. Studies should be organized to examine samples from these patients separately from those who have been ill for decades.

Much provocative work on infectious agents and CFS has languished for lack of funding. For example, Brigitte Huber at Tufts found that EBV could activate HERV-K18, an endogenous retrovirus. Danish

investigator Per Høllsberg from University of Aarhus found that HHV-6 activates HERV-K18 as well. Dr. Jose Montoya at Stanford University found marked clinical improvement when patients with CFS and active infection with EBV and/or HHV-6 were treated with an antiviral. Professors Ron Glaser and Nancy Klimas showed that EBV-DUTpase, a nonstructural protein, could activate NF-KB resulting in the production of proinflammatory cytokines which contribute to the pathophysiology associated with disease. Using biopsy specimens, Dr. John Chia at EB Medical Research in California has documented the presence of enterovirus in stomach antrum endothelium in 82% of stomach biopsies from patients with CFS compared to 20% of controls. Parvovirus B-19 has been implicated in a subset of CFS patients by several investigators, and new cardiac biopsy data from Europe suggests that the pathology may be due in part to chronic infection of myocardial tissues. Furthermore, Q-Fever is the cause of CFS in some cases and it is often missed by physicians outside of the US.

It is imperative that the CDC study biopsy samples from the gut, and brain as well as heart tissues, and that they look at spinal fluid. Most of the studies done by the CDC have been on serum. However, many pathogens cannot be found in the serum because they do not circulate in the peripheral blood after the initial infection. For example, Dr. Steven Jacobson's team at NIH has found a high viral load of HHV-6 in the brain tissue biopsies from mesial temporal lobe in epilepsy patients, even though serum and spinal fluid were negative for the virus. They also found that HHV-6 is barely detectable in the spinal fluid, even after full-blown HHV-6 encephalitis. A virus such as HHV-6 can persist in the brain tissue in spite of completely normal antibody levels in the peripheral blood. Of course it is far more convenient to look for virus in the serum. In this case, however, the only way to determine if these pathogens are responsible for central fatigue is dig deeper and start testing the brain tissue itself.

In summary, we propose that CDC should invest the majority of its research budget into exploring pathogens in CFS, with particular emphasis on examining spinal fluid, brain tissue, cardiac tissues and gut biopsies. I am confident this area of research would be beneficial to the health of CFS patients.

Thank you.