Stress-Associated Immune Modulation: Relevance to Viral Infections and Chronic Fatigue Syndrome

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The frequent association of an active viral infection with the symptoms of CFS led researchers to hypothesize that chronic fatigue syndrome (CFS) is induced by a virus. Results of these studies indicated that despite clinical support for this hypothesis, there were no clear data linking viruses to CFS. In this overview, we will explore the interrelation of the immune, endocrine, and central nervous systems, and the possibility that stress and/or the reactivation/replication of a latent virus (such as Epstein Barr virus) could modulate the immune system to induce CFS. Relevant research conducted in the developing field of psychoneuroimmunology will be reviewed, with a particular focus on cytokine synthesis, natural killer (NK) cell activity, and T-lymphocyte function, as they relate to CFS. Am J Med. 1998;105(3A):35S–42S. © 1998 by Excerpta Medica, Inc.

CFS is induced by a virus.2 For example, Jones et al3 and infection, studies have focused on the hypothesis that with CFS are often found associated with an active virus Strauss et al 4 provided evidence that Epstein-Barr virus 35S
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CFS is a syndrome in which the prevalent clinical symptoms are severe fatigue, myalgia, lymphadenopathy, sore throat, stress, and depression.1 Because symptoms associated with CFS are often found associated with an active virus infection, studies have focused on the hypothesis that CFS is induced by a virus.2 For example, Jones et al3 and Strauss et al4 provided evidence that Epstein-Barr virus (EBV) was the etiologic agent for a chronic illness that has now come to be called CFS. These early studies showed that patients with these symptoms had significantly higher antibody titers to EBV. Holmes et al5 also found higher EBV antibody titers in patients presumed to have CFS; antibody titers to other herpesviruses such as cytomegalovirus (CMV), Herpes simplex virus (HSV), and measles virus were also observed in these patients. Buchwald et al6 and Hellinger et al7 also found a relation between higher EBV antibody titers and CFS. Human herpesvirus 6 (HHV-6) has also been associated with CFS.8–11 Higher antibody titers to HHV-6 in CFS patients are consistent with reactivation of the latent virus.8,9 the presence of IgM antibodies to HHV-6 in a significant number of patients diagnosed with CFS would indicate a primary infection.10

However, over time, the association between EBV, HHV-6, other herpesviruses, and CFS has not produced a consensus on the etiology of CFS. In fact, in a recent study by Buchwald et al,12 antibody titers to 13 different viruses were measured in CFS patients; no relation was found between antibody titers to any of the 13 viruses, including latent herpesviruses, and CFS. The conclusion of these and other studies is that whereas the clinical evidence supports the hypothesis that CFS is caused by a virus, there are no clear data that link any particular virus(es) to CFS. Interestingly, individuals who are EBV seronegative have also been diagnosed as having CFS.

The term “syndrome” covers a broad range of symptoms and perhaps a varied etiology as well. It is possible that a subset of patients with clinical symptoms compatible with CFS may be infected with a viral agent that is responsible for inducing pathophysiologic/immunopathologic changes that cause these clinical symptoms. In this overview, we will explore the possibility that stress and/or the reactivation/replication of a latent virus such as EBV could modulate the immune system to induce CFS in patients.

It is now well established that the central nervous system (CNS), the endocrine system, and the immune systems interact with each other; psychological stress can downregulate the immune response by affecting the interplay of these systems. The interactions are complex, involving both the hypothalamic–pituitary–adrenal axis (HPA) and the autonomic nervous system.13

Psychoneuroimmunology is a rapidly developing field that is concerned with studying the interactions among these 3 body systems, how behavior modulates these interactions, and the implications for health. Whether the study of psychoneuroimmunology can help provide insight into the etiology and clinical course of CFS is an area of interest that has yet to be fully explored. However, in this report we will review the relevant psychoneuroimmunology literature focusing on changes in cytokine synthesis, natural killer (NK) cell activity, and T-lymphocyte function that may have implications for CFS. We will also review some of the health implications of stress-associated immune modulation and explore the possibility that stress-associated changes in immune regulation may result in changes in the steady-state expression of latent viruses.

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A starting point in understanding how the CNS can modulate the immune response and influence the expression of latent viruses is described in the following scenario: Psychological stress can upregulate the expression of corticotropin-releasing hormone (CRH) through the hypothalamus, which leads to the production of adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal cortex to increase levels of glucocorticoid hormones, which can downregulate several aspects of the immune response.\textsuperscript{13} It is also known that pharmacologic, and most importantly, physiologic levels of glucocorticoid hormones can reactivate latent EBV (and perhaps other latent viruses) from virus genome-positive cells in vitro;\textsuperscript{14–18} glucocorticoid hormones, ACTH, and CRH can enhance EBV-lytic replication in vitro.\textsuperscript{17} Other so-called “stress hormones” include epinephrine, norepinephrine, prolactin, and growth hormone; the latter 2 can act as immune enhancers.\textsuperscript{15} Data from these studies may provide clues in understanding the etiology of CFS.

Communication between the CNS and immune system is bidirectional. For example, interleukin 1 (IL-1) can influence the hypothalamus to modulate CRH production. There are now several reports that show that lymphocytes can synthesize hormones such as ACTH, prolactin, and growth hormone.\textsuperscript{13,19–21} These physiologic interactions have resulted in the reexamination of how the immune system is modulated in vivo and may also provide clues for the etiology of CFS.

Two central issues are being addressed by psychoneuroimmunology researchers: (1) the mechanisms underlying the complex interactions among the CNS and the endocrine and immune systems; and (2) the health implications of these interactions. As the mechanisms become clearer, the results may have implications for CFS, since neuroendocrine/immune function may be abnormal in patients with CFS and psychological stress may be one component underlying this state. There is considerable evidence that individuals who experience stressful negative life changes may be at greater risk for a variety of illnesses, particularly infectious disease. The association of stressful life events and illness has been well documented.\textsuperscript{22}

**THE INFLUENCE OF STRESS ON THE CELLULAR IMMUNE RESPONSE**

We have examined the impact of stress on different aspects of the cellular immune response. In a series of studies, we employed an academic stress model in first- and second-year medical students. Briefly, the curriculum at the Ohio State University College of Medicine for first- and second-year medical students was such that examinations occurred in several 2–3-day examination blocks across the academic year. Thus, the class cycled together over less stressful periods (baseline) and more stressful periods (examination blocks). Students completed questionnaires to provide data on anxiety and stress at the same time that blood samples were obtained, always between the hours of 10 AM and 12 noon, to control for diurnal variations. These longitudinal studies used a within-subject design, so that each medical student was his/her own control. Significant changes in the immune response were related to academic stress,\textsuperscript{23–32} as summarized in Table 1. The medical student academic stress studies provided information about the broad impact of an everyday psychological stressor across multiple aspects of the cellular immune response.

A second series of investigations evaluated the impact of aging and stress on immunity by studying individuals caring for a spouse (or a parent) with Alzheimer’s disease (AD) or other progressive dementias, a major hardship. Studies of spousal caregivers of AD patients explored the effect of this long-term stressor on the cellular immune response and the health implications of those effects. Differences between caregivers and well-matched control subjects were similar to the immune changes observed in the academic stress studies\textsuperscript{33–38} and are summarized in Table 2. The immunologic decrements associated with the stress of caregiving are a particular concern for this group, since older individuals have age-related reductions in their cellular immune response with important health consequences; spousal caregivers, therefore, have to contend with both aging and stress.

We believe that the stress-associated changes in the cell-

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**Table 1. Immune Changes Associated With Academic Stress in Medical Students**

- Decrement in NK cell activity
- Decrement in γ-interferon production by lymphocytes stimulated with ConA
- Decrement in cells expressing interleukin-2 receptor (IL-2R) and IL-2R mRNA
- Modulation of phorbol ester inhibition of radiation-induced apoptosis
- Decrement in proliferative responses of peripheral blood lymphocytes to mitogens (ConA, phytohemagglutinin)
- Decrement in T-cell proliferation to Epstein-Barr virus polypeptides (memory response)
- Decrement in T-cell killing of Epstein-Barr virus transformed autologous B-lymphocytes (memory response)
- Decrement in antibody and T-cell response to hepatitis B vaccination
- Evidence for reactivation of latent herpesviruses, e.g., Epstein-Barr virus, Herpes simplex virus-1
in vitro, suggesting an inhibition of the virus-specific T-cell response; peripheral blood leukocytes from the AD caregivers also produced less IL-1 than peripheral blood leukocytes obtained from the controls.\textsuperscript{40} Thus, the downregulation of the cellular immune response observed in the AD caregivers as compared with very well-matched control subjects is associated with the downregulation of the immune response to influenza virus vaccination. These results have implications for vulnerability to infection among stressed individuals. Subjects who do not respond well to vaccines experience higher rates of clinical illness, including influenza virus infections.\textsuperscript{41}

In another study with caregivers, we explored the possibility that caregiving stress would slow wound healing. Repair of a skin biopsy (3.5 mm in diameter) taken from female spousal caregivers and well-matched controls was assessed by photographing the wound to measure changes in the diameter of the wound, and also by assessing the response of the wound to hydrogen peroxide. A wound was defined as healed (epithelialized) when it no longer foamed after application of hydrogen peroxide. Wound healing took significantly longer in the caregiver subjects than in the matched controls, a mean of 48.7 days versus a mean of 39.3 days respectively, or an increase of 24%. The size of the wound over time was also related to caregiving stress, with control subjects healing more rapidly. In addition, peripheral blood leukocytes from the caregivers produced significantly less IL-1 messenger ribonucleic acid (mRNA) in response to lipopolysaccharide stimulation than peripheral blood leukocytes from the control subjects. These data raise important questions about the possibility of stress-related defects in wound repair that are important for individuals undergoing surgery.\textsuperscript{42}

There are several studies that support the hypothesis that stress can have a significant impact on the pathophysiology of a virus infection; e.g., a study by Cohen and coworkers\textsuperscript{43} demonstrated that human volunteers who were inoculated with 5 different strains of respiratory viruses showed a dose–response relation between stress and clinical symptoms observed after infection. Work from our group has demonstrated the influence of restraint stress on mice inoculated with both influenza type A virus and HSV-1. Data from a series of studies\textsuperscript{44–48} showed that restraint stress activated the HPA axis, resulting in an increase in corticosterone levels and a concomitant downregulation of the virus-specific T-cell response. The pathophysiology of the virus infection was also exacerbated in restraint-stressed animals. Both immune factors and endocrine factors were found to be important modulators of these effects.\textsuperscript{44–48}

**Table 2. Immune/Endocrine Changes Associated With Caregiving Compared to Well-Matched Controls**

Dementia caregivers show:

- Poorer blastogenic response of PBLs to mitogens (PHA, ConA)
- Poorer T-cell proliferative (memory) response of PBLs to HSV-1
- Poorer T-cell receptor-induced blastogenic response to a monoclonal antibody to the T-cell receptor
- Lower percentages of IL-2R-positive PBLs after mitogen stimulation
- Differences in the response of NK cells to cytokines:
  - Poorer response of NK cells to recombinant γ-interferon
  - Poorer response of NK cells to recombinant IL-2
- Evidence for reactivation of latent EBV
- Poorer response of PBLs to produce IL-1β after stimulation in vitro
- Poorer response to influenza virus vaccine, both antibody and T-cell responses
- Higher plasma ACTH levels
- Lower levels of growth hormone mRNA in PBLs
- More respiratory infections, more days ill

\textsuperscript{ACTH} = adrenocorticotrophic hormone; \textsuperscript{EBV} = Epstein-Barr virus; \textsuperscript{HSV} = Herpes simplex virus; \textsuperscript{IL-2} = interleukin-2; \textsuperscript{NK} = natural killer; \textsuperscript{PBL} = peripheral blood lymphocytes; \textsuperscript{PHA} = phytohemagglutinin.
STRESS CAN MODULATE THE STEADY-STATE EXPRESSION OF LATENT HERPES VIRUSES

There may not be a single etiologic agent for CFS. However, since it is possible that CFS is induced by an endogenous virus(es), it is useful to examine the impact of stress on the reactivation of latent herpesvirus. \(^{49}\) Psychological stressors have been linked to more frequent recurrences among individuals latently infected with HSV-1 or HSV-2—e.g., data from studies of nurses with recurrent HSV-1 lesions suggested that stress increased in the week before the appearance of a cold sore. \(^{50,51}\) Work from our laboratory has suggested that a latent virus such as EBV or HHV-6 could be involved in the etiology of CFS.

As discussed earlier, in a series of studies with medical students, examination stress was associated with changes in the steady-state expression of latent EBV. Higher antibody titers to EBV virus capsid antigen IgG were observed at the time of examinations as compared with baseline. \(^{28,49}\) Using the indirect immunofluorescence test (which was used in all our studies), a follow-up report to the academic stress studies confirmed that stress associated with caregiving for an AD patient can also affect the steady-state expression of latent EBV; caregivers had higher EBV viral capsid antigen IgG titers than well-matched controls. \(^{34}\) These differences were not linked to aging alone.

Other studies, with healthy geriatric subjects, have shown that aging results in some degree of reactivation of latent EBV \(^{52}\) and CMV \(^{53}\) perhaps associated with the decreases in the cellular immune response associated with aging. However, even after accounting for the aging effect, AD caregivers still had higher EBV viral capsid antigen IgG antibody titers than controls, and differences in antibody titers could not be explained by total serum levels of IgG or subclasses of IgG (unpublished data). Modulation of latent HSV-1 was also observed in AD caregivers, and caregivers had a poorer HSV-1 specific T-cell response. \(^{38}\)

In follow-up studies using the academic stress model with medical students, we examined the impact of stress on 2 different aspects of the EBV-specific memory T-cell response. In the first study, we found a significant decrease in the ability of EBV-specific cytotoxic T-cells (from EBV seropositive students) to kill EBV infected autologous B-lymphocytes associated with stress. In the second study, peripheral blood leukocytes obtained from EBV seropositive students also showed a decrease in proliferation when exposed to purified EBV polypeptides. \(^{28,54}\)

We also collected throat-washing samples to probe for the presence of EBV DNA in exfoliated cells found in the washings. We found no evidence for shedding of EBV in the nasopharynx. \(^{55}\) Thus, in this study, increases in viral capsid antigen IgG antibody titers to latent EBV at the time of academic examinations occurred in the absence of replication of complete virus (virions containing DNA) in the nasopharynx, as measured by dot-blot hybridization.

It was hypothesized that the changes in EBV viral capsid antigen IgG titers might be related to partial reactivation of the latent EBV genome. If this were the case, the increase in antibody titers observed by immunofluorescence and the absence of EBV DNA in throat-washing samples could be the result of incomplete reactivation of latent virus and the expression of only certain viral genes. The use of the immunofluorescence test to measure antibody titers would not have permitted the discrimination between complete and incomplete virus reactivation, since this assay measures essentially all EBV antibodies present in serum or plasma samples.

To test the above hypothesis, ELISA plates were separately coated with 2 different purified early viral proteins and 2 late viral proteins; each set of plates was coated with a single polypeptide. This allowed us to probe for 4 specific antibodies against these 4 viral proteins in each plasma sample. Plasma samples showing higher antibody titers at the time of examinations (determined by immunofluorescence) showed no changes in antibody titers to the 2 late viral proteins tested, the 125 kDa viral capsid antigen polypeptide and the glycoprotein 350/300 membrane protein. In addition, no evidence for changes in antibody titers against the 85 kDa early antigen (EA-R) protein was observed. However, antibody titers to the early antigen diffuse (EA-D) 52/50 kDa protein changed over the course of the study. \(^{55}\) In a recent study, similar results have been obtained with AD caregivers latently infected with varicella zoster virus (unpublished data) and HSV-1. \(^{38}\)

It is important to point out that these data are preliminary and measured a small number of viral proteins. To determine whether additional viral antibodies to EBV or other herpesviruses increased in these subjects would require studies measuring virtually all viral proteins. In addition, the issue of the sensitivity of the assays used must be kept in mind in interpreting the data. However, we believe that these data raise interesting questions on reactivation of latent viruses in vivo. It is possible that stress can modulate the steady-state expression of latent herpesviruses such as EBV, and that under certain circumstances, only some viral genes may be expressed, making it difficult to show a consistent relationship to patient groups using routine laboratory methods.
HYPOTHESIS: VIRAL PATHOLOGY AND/OR IMMUNOPATHOLOGY CAN RESULT FROM PARTIAL OR INCOMPLETE EXPRESSION OF A LATENT VIRUS IN A SUBGROUP OF CFS PATIENTS

Generally speaking, clinical symptoms associated with an infectious agent, e.g., a virus, are due to the combination of the pathology produced by the virus and the immunopathology produced as a result of the immune response to the virus. It is possible that latent viruses such as EBV, HHV-6, HSV-1, varicella zoster virus, CMV, or even HIV-1 may induce immunopathology in a more subtle way, by synthesizing viral protein(s) in latently infected cells or in cells in which the virus genome is only partially being expressed (incomplete replication). These proteins could modulate the response of a subpopulation(s) of peripheral blood leukocytes, with subsequent effects on cytokine and chemokine synthesis or on T-cell or NK cell function. Furthermore, if reactivation of the latent virus was incomplete, it might not be possible to detect significant changes in antibody titers in such groups of patients; antibody titers are routinely measured using Western blot, ELISA, or immunofluorescence assays employing either a whole viral preparation or a single viral polypeptide—e.g., one of the EBV viral capsid antigen proteins (p18) is commonly used in commercial kits as the test antigen.

There is evidence to support this hypothesis. For example, the 15 kDa polypeptide (p15) of the feline leukemia virus has been shown to significantly inhibit replication of mitogen-stimulated feline lymphocytes in vitro. In addition, capping of receptors for ConA on normal feline lymphocytes was also inhibited by the p15 protein.64 It has also been shown that a recombinant peptide, HIV-1 env-gag, suppressed the synthesis of IgG by pokeweed mitogen-treated human B-lymphocytes. The same recombinant peptide significantly increased the proliferative response of peripheral blood mononuclear cells as compared with control cultures.57 Putting these findings in the context of the preliminary data from our laboratory showing evidence for partial reactivation of latent EBV and HSV-1 (and perhaps varicella zoster virus), it is possible that ≥1 proteins of a latent virus (rather than infectious virions) could induce immunomodulation, e.g., an abnormal level of ≥1 cytokines, which could result in clinical symptoms associated with CFS in a subset of patients, and further, this link may not be detected using standard laboratory procedures already discussed.

Is there additional evidence to support this hypothesis in the literature? In earlier studies, work from our laboratory demonstrated that the EBV can code for a viral DNase and a DNA polymerase.58,59 Patients with nasopharyngeal carcinoma, when compared with patients with other diseases with which EBV is associated—e.g., infectious mononucleosis and Burkitt’s lymphoma—have an anti-EBV antibody profile that includes high levels of antibody to the viral DNase and polymerase in a high percentage of patients.60,61 In addition, it has long been known that patients with EBV-associated Burkitt’s lymphoma and nasopharyngeal carcinoma have high antibody titers to EBV viral capsid antigen. However, Burkitt’s lymphoma patients also have high antibody titers to the EA-R component of the early antigen complex of EBV proteins and not antibody to the EA-D component.62 In contrast, patients with EBV-associated nasopharyngeal carcinoma have high antibodies to EA-D, with little or no antibody titers to EA-R.63 In fact, there is evidence to suggest that antibody titers to EA-R correlate with prognosis of the Burkitt’s lymphoma patient.54

It is not understood why there are different antibody patterns to EBV in different groups of patients that have been infected with the virus. It is possible that under certain circumstances (e.g., stress) different viral genes are overexpressed (for unknown reasons), resulting in overexpression of selected viral proteins and, consequently, different antibody patterns. Little is known about the immunomodulating properties of individual herpesvirus proteins. If some of these proteins, alone or in combination with other viral proteins, can induce immune dysregulation (as attributed to some retrovirus protein already discussed),56,57 it is possible that the clinical symptoms of CFS could be the result of the immunopathology that is produced by these “more subtle” interactions. It is important to remember that, in this context, the term “interactions” includes changes in the HPA axis, autonomic nervous system, and neuropeptides. All of the above can modulate the immune system.

Is there evidence for a unique antibody pattern to EBV in some patients with CFS? In an earlier report65 we found that antibody to the EBV DNase and polymerase was preferentially observed in serum from a small group of CFS patients with severe clinical symptoms. These data were confirmed in a follow-up study by Natelson and co-workers.66 If individual feline leukemia virus and HIV-1 proteins can modulate different aspects of the T-cell response, then it is likely that cytokines and other cellular factors produced by subpopulations of leukocytes may also be affected by these viral proteins. As already discussed, it is not known whether purified EBV proteins can induce similar changes by themselves, but the hypothesis is testable. Based on this strategy, it should be possible to determine whether serum samples from CFS patients show unique antibody patterns to purified EBV, HHV-6, or other viral proteins. Illnesses such as CFS that have been historically difficult to link to a specific virus may be related to a latent virus in a more obscure way, i.e., a virus that is only being partially reactivated, resulting in the modulation of neuro-immuno-endocrine interactions and clinical symptoms of CFS.
IS THERE A CONNECTION BETWEEN STRESS-ASSOCIATED IMMUNE MODULATION AND CFS?

As already discussed, there is no consensus on the etiology of CFS. Some investigators believe that there may be a subset of patients who have clinical evidence for infection or reactivation of a virus. There is also some consensus that CFS is often precipitated by stress that might or might not be associated with an infectious agent. In regard to the immune response, particularly the cellular immune response, there is some consensus that NK cell lysis is downregulated in CFS patients.\(^{57-69}\) There is also some evidence for T-cell activation,\(^{68,70}\) evidence for downregulation of cellular immunity as suggested by anergy,\(^{71,72}\) a decrease in the response of peripheral blood lymphocytes to mitogens in vitro,\(^{70,72}\) alterations in cytokine synthesis by peripheral blood lymphocytes in vitro,\(^{68,69,73}\) and an increase in suppressor T-cell function.\(^{4,74}\) There is no consistent evidence for abnormal levels of plasma cytokines.\(^{75,77}\) Unfortunately, there is not a great deal of consistency with CFS patients in changes observed in immune function, making it difficult to use immune measures as clinical markers for CFS. The broad range in viruses historically implicated in CFS and the broad range of cellular immune changes observed in CFS patients could be explained by the heterogeneity of patients diagnosed with CFS.\(^{76}\)

Given the caveats discussed in this overview, one final point concerning the effects of cytokines on the CNS and behavior should be raised. Independent of the possibility of a viral etiology for CFS is the possibility that stress is inducing immunopathology, due to the modulation of cytokines, which may result in changes in behavior and produce clinical symptoms attributed to CFS. For example, it is thought that the immune system may be involved in changes in eating behavior associated with several clinical conditions.\(^{77}\) There is also evidence that stress can modulate proinflammatory cytokines, which could contribute to the pathogenesis of inflammatory disease and CFS.\(^{78,79}\) Of interest is the fact that decreased levels of IL-1 have been shown to depress social behavior in rats similar to changes observed in rats that have been adrenalectomized.\(^{80}\) For a detailed review on cytokine brain interactions and the implications for changes and behavior associated with these interactions, see Watkins et al.\(^{81}\) However, it is important to keep in mind that the interactions of the CNS and the endocrine and immune systems and the impact of psychological and physical stressors on these interactions, are still not well understood. There is a possibility that new cytokines yet to be discovered may play a role(s) in the modulation of the immune system and a role in the development of CFS. If this is the case, we are still missing pieces of the puzzle, which prevents us from totally understanding whether abnormalities in cytokine production are responsible for producing CFS clinical symptoms and whether neuroimmunomodulation induced by stress can trigger these symptoms. As already discussed, there are no clear cytokine markers that are consistently associated with CFS. Future studies will need to be performed to answer all of these questions.

In conclusion, data that we have reviewed show that stress can have significant impact on immune function, from antibody responses to downregulation of T-cell and NK cell functions, to effects on cytokine synthesis. The literature supports the conclusion that stress-associated immunomodulation can have implications for increased risk for infectious disease (and perhaps cancer). Many of the changes in the immune response described in CFS patients have been shown to be modulated by CNS–endocrine–immune interactions and stress. These interactions also have implications for control of the replication/reactivation of a variety of viruses, including latent herpesviruses and most likely involve both the immune and the endocrine systems; these 2 systems may play important roles in producing the symptoms associated with CFS. There are many pieces of this very complicated puzzle yet to be discovered, and the understanding of the interactions between body systems may elucidate the etiology of CFS and other similar syndromes.

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