HYPOTHESIS

A Unified Theory of the Cause of Chronic Fatigue Syndrome

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AN ENIGMATIC, ILL-DEFINED malady of persisting overwhelming fatigue of sudden onset afflicts previously healthy, vigorous, productive, young or middle-aged adults. When this perplexing illness extends beyond 6 months and psychiatric disease is excluded, the syndrome is named the chronic fatigue syndrome (CFS) [1]. Although immunologic, neurologic, endocrine, and psychological associative abnormalities have been described, the cause(s) of CFS remain(s) unknown [2]. CFS is recognized throughout the world as a major public health problem.

The clinical symptoms and signs of CFS resemble those of infectious mononucleosis, but patients with CFS do not have the severe dysphagia and grey exudative pharyngitis often accompanied by submandibular adenopathy common to primary infection with the gamma subfamily herpesvirus, Epstein-Barr virus (EBV), the prototype virus of the lymphocryptovirus genus [3,4]. Acute primary EBV infection may be accompanied by hectic fevers and hepatitis (with or without jaundice). An association between EBV and African Burkitt's lymphoma, anaplastic nasopharyngeal carcinoma, post-bone marrow transplantation lymphoproliferative disease, and oral hairy leukoplakia in AIDS patients is also present [5]. Classically, an atypical mononucleosis in the peripheral blood depicts initial EBV infection within epithelial cells of the pharynx and B lymphocytes. Another "mononucleosis" syndrome, without the exudative pharyngitis, may be caused by the beta herpesvirus, human cytomegalovirus (HCMV) [6]. Primary EBV or HCMV mononucleosis is usually self-limited, and recovery is complete 12 weeks after onset. The similarity of symptoms of the mononucleosis syndrome and CFS suggests that the etiology of the two syndromes may be identical.

By definition, the persisting or relapsing fatigue of CFS reduces an affected person's activity level to below 50% of his/her normal activity level for a period of at least 6 months. Complaints include low-grade fevers, chills, sore throats, painful anterior or posterior cervical or axillary lymph nodes, muscle weakness, myalgias/arthralgias, generalized headaches, migratory arthralgias, vague neurocognitive abnormalities, and disturbances of sleep, all without any known medical or psychiatric cause [7,8]. These vague symptoms are, of course, shared by the well-characterized, self-limited mononucleosis syndrome. When CFS patients attempt to exercise at levels that would have been easily tolerated prior to the onset of illness, prolonged, generalized worsening fatigue regularly follows.

We now emphasize additional symptoms of CFS: (1) light-headedness (wooziness, nonrotational in type) of varying severity and duration without any known antecedent cause; (2) vague, dull, pressure-like chest ache (substernal, over the left breast and sometimes including the left shoulder) coming on with increasing fatigue at the end of the day, and not related to exertion; and (3) palpitations. There is also often (4) tachycardia with minimal or no exertion, which may persist for long periods of the day. The latter is easily seen at 24-h electrocardiogram (ECG) Holter monitoring. These important symptoms, we believe, are cardiac in origin and key to CFS. Clearly, the possibility of cardiac involvement must be carefully examined. Functional noncardiac chest pain of anxiety states has been described as Da Costa's syndrome, soldier's heart, effort syndrome, irritable heart, neurocirculatory asthenia, or functional cardiovascular disease. Principal symptoms of these latter conditions are chest pain and palpitations regarded as neuropsychiatric in origin. Likewise, the ECG in the "noncardiac" chest pain of anxiety may show minor depressions of the ST junction and inversions of T-waves, leading to a mistaken diagnosis of coronary artery disease [9]. Careful study has detected no heart disease in these anxiety states. On the other

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TABLE 1. A unified theory of the chronic fatigue syndrome (CFS)

Proposals	Research suggested
Epstein-Barr virus (EBV) or human cytomegalovirus (HCMV) continuing primary infection or reactivation, singly (EBV or HCMV) or, in combination (EBV and HCMV) are the major etiologic causes of the CFS.[a]	Appropriately designed seroepidemiologic studies taking into account possible single or combined persistent EBV or HCMV infection are indicated.
CFS is a nonpermissive, persistent herpesvirus (EBV or HCMV) infection of the heart. EBV and/or HCMV nucleic acids are predicted to be present in the hearts of CFS patients.	Endomyocardial biopsies with polymerase chain reaction or in situ hybridization assays for EBV and HCMV nucleic acids are indicated to prove/or disprove this hypothesis.
Specific antiviral therapy for CFS patients in controlled clinical trials is suggested.	Appropriately designed therapeutic trials with antiviral drugs are indicated.

[a] Herpesvirus 6 (HHV-6), or other viruses (e.g., enteroviruses) may also be involved in some cases.

hand, we believe a dynamic, ongoing, and, sometimes, progressive cardiomyopathy is fundamental to CFS. We offer the following hypothesis to guide research in gaining further understanding of CFS (Table 1).

Proposal Number One

CFS is, in the majority of cases, either a continuing primary infection with EBV or, in turn, a continuing primary infection with HCMV. Alternatively, a reactivation infection with prior latent EBV or prior HMCV, or both of these herpesviruses simultaneously, may be the etiology of the CFS. EBV, viral capsid antigen (VCA), IgM or EBV antibody to early antigen (EA), the latter, depicting EBV DNA polymerase activity, may be positive indicating current virus multiplication [10,11]. There may additionally or alternatively be a significant IgG enzyme immunoassay antibody (ELISA) to HCMV, with/without an IgM ELISA antibody titer to HCMV [12]. "Therefore, seroepidemiologic studies attempting to show a singular virologic causation to the CFS including singular searches for EBV or HCMV antibodies have yielded uniformly negative results" [14]. At least 15 different viruses, bacteria, and parasites have been previously suspected as "singular" etiologic agents to CFS, including EBV and HCMV, enteroviruses, and retroviruses. However, there has been, to date, no serologic association with any human virus [13–15]. We believe these studies have been designed in a way that actually masks the possibility of finding a major two-virus causality.

The two proposed major causative herpesviruses are characterized by latent, nonpermissive persistent infections [16,17]. In nonpermissive persistent herpesvirus infections, only a very low level of complete infectious virus is produced. Intracellular latent infection is characterized by a chronically infected virus-induced extrachromosomal intranuclear episome in a permanently metabolically altered host cell. However, this latently infected altered cell produces no progeny capable of infecting a new susceptible cell. The extrachromosomal herpesvirus episome persists for the life of the chronically infected cell [5]. The cellular sites of known latency for EBV are immunoglobulin-producing B lymphocytes and epithelial cells predominantly in the pharynx. EBV has been isolated from the cervix, but the nature of this infection (productive virus, latent virus, or both) has not yet been fully determined. EBV has also been recovered from breast milk and semen.

The cellular sites for latency for HCMV are the mononuclear phagocyte and its progenitor cells [18]. When the monocyte differentiates into the macrophage or histiocyte, infectious HCMV virus production ensues, with an associated irreversible destruction of the infected cell.

There is evidence that both HCMV an EBV are cardiotropic for the human myocyte [19,20]. We propose that the human cardiac myofiber, like the B lymphocyte for EBV and the mononuclear progenitor cell for HCMV, is a site of noninfectious, episome-mediated persistent infection. This is in contrast to the human epithelial cell of the pharynx, which produces mainly whole infectious EBV virus [21]. HCMV immediate-early gene transcripts have been detected in the heart by in situ hybridization techniques in patients with human immunodeficiency virus (HIV)-associated cardiomyopathy [19]. Likewise, the EBV genome was detected by polymerase chain reaction (PCR) amplification of DNA extracted from the heart at autopsy. PCRs for enteroviruses and cardiac viral cultures were negative. An intense mononuclear cell infiltrate in the myocardium consisted entirely of T cells without identifiable B cells.

The latent, persistent infection and recrudescent infection characteristic of the herpesviruses, EBV and HCMV, is consistent with the chronic recrudescent illness of the CFS [21]. These two herpesviruses, EBV and HMCV, are the cardinal etiologic agents of the unified

hypothesis proposed here. Productive whole-virus herpesvirus, EBV or HCMV, infection is accompanied by lysis of infected cells. In latent infection, on the other hand, complete infectious virus is not produced, and host-cell survival continues. In persistent infection, varying low levels of infectious virus, latent virus, and intermittent reactivation may occur simultaneously. Productive infection is associated with cellular necrosis and a subsequent inflammatory response. Latent persistent infection may be associated with little inflammation or morphologic changes but may lead to only biochemical aberrations and degenerative cellular functions.

We have observed that *all* CFS patients have abnormal oscillating T-wave flattenings and T-wave inversions at Holter monitoring [22]. An initial 24-h ECG T-wave study compared CFS patients to random non-CFS patients from an internal medicine practice; both patient groups were restricted to an age of less than 50 years to minimize the occurrence of chronic diseases. Hypertensive vascular disease, electrolyte abnormalities, and coronary artery disease may produce similar oscillating abnormal T-waves, but CFS patients are young, formerly vigorous people who typically do not have these chronic diseases. The oscillating T-wave abnormalities we described also occur in about 5% of normal subjects upon their assumption of an upright posture. At resting 12-lead standard ECG, T-waves describing left ventricular electrical depolarization are upright, and the resultant ECG is normal. The 2-D echocardiogram is also usually normal, but 24-h ECG recordings (Holter monitoring) are abnormal; oscillating T-wave flattenings or T-wave inversions characteristically ensue with the onset of sinus tachycardias, and, subsequently, revert to normal T-wave configurations with the return of normal sinus rhythms. These abnormal T-waves are not specific to CFS. They also occur with diverse conditions, such as coronary artery disease, hypertensive vascular disease, and electrolyte abnormalities, but the abnormal T-waves at Holter monitoring were seen much more frequently in 24 random CFS patients than in 116 time-, place-, and age-matched random non-CFS subjects ($P < .01$) [22]. These studies indicate that the abnormal T-waves at 24-h ECG recordings in CFS patients are not artifacts and are associated with CFS.

Additionally, an initial group of CFS patients demonstrated abnormal left ventricular dynamics (decreased or falling ejection fractions, abnormal wall motion, or dilatation) by radionuclide stress multigaited acquisition studies [23]. Further, a consecutive case series of CFS patients from a single referral center in Birmingham, Michigan, during the years 1987–1993 demonstrated abnormal left ventricular dynamic function in 24.1% of 87 patients undergoing radionuclide ventriculography by the radioisotopic gated pool (MUGA) method (Lerner AM, Sayyeed T, Dworkin HJ, et al., unpublished observations). We have performed right ventricular endomyocardial biopsies in CFS patients. On electron microscopy, cardiomyopathic changes—including myofiber hypertrophy, myofiber disarray, and degenerative change in myofibers—have been seen [24]. (Rarely, inflammatory myocarditis is evident.) Infectious HCMV is not found in the heart, peripheral blood, or urine of this HCMV CFS subset of patients. The evidence appears conclusive that CFS is a major, newly discovered cardiomyopathy.

Proposal Number Two

CFS is a persistent nonpermissive herpesvirus infection of the heart (Table 1). CFS patients have abnormal Holter monitoring, reflecting their cardiomyopathy. Further, the majority of CFS patients have the appropriate serologic markers (as described above) of persistent EBV and/or HCMV infections. We hypothesize that EBV and/or HCMV nucleic acids are present in myofibers (myocytes) of cardiac tissues of these CFS patients and that they are detectable by PCR or in situ hybridization techniques. Further, we predict that EBV and/or HCMV nucleic acids will not be present in the myofibers of EBV- or HMCV-seropositive, non-CFS patients undergoing similar cardiac biopsies. In this regard, we have observed that patients with acute primary EBV infectious mononucleosis who recover rapidly have normal Holter monitoring throughout their illnesses. We propose that these EBV-infected patients have no cardiomyopathies. Conversely, patients with prolonged illnesses of acute primary EBV infectious mononucleosis have the abnormal Holter monitoring we describe.

This hypothesis that the etiologic diagnosis of the cardiomyopathy of CFS requires cardiac biopsy with the recognition of the etiologic virus nucleic acid in the heart (e.g., EBV and/or HCMV) is not unique for the pathologic physiology of herpesvirus infections in humans. Like CFS, herpes simplex virus encephalitis (HSVE) defied etiologic identification by measures of rising serum antibodies, which might or might not be present. The diagnosis of HSVE required isolation of HSV type 1 from the brains of patients with encephalitis [25]. Rowe et al. [26] and Bou-Halaigah et al. [27] have recently described abnormal response to upright tilt in patients with CFS. They postulated an abnormal, neu-

TABLE 2. Proposed virologic cause of the chronic fatigue syndrome

Primary or recrudesecent *persisting infection*	Antibody titers					Nucleic acids in cardiac tissues	
	EBV			HCMV			
	Viral capsid antigen IgM		Early[a] antigen	IgM	IgG	EBV	HCMV
Epstein-Barr virus (EBV)	±	and/*or*	±	−	−	+	−
Cytomegalovirus (HCMV)	−		−	±	+	−	+
Combined EBV HCMV	±	and/*or*	±	±	+	+	+
(Other minor candidate viruses: e.g., several enteroviruses, herpesvirus-6)							

[a] In some cases of EBV CFS, *either* elevated antibody titers to EBV, VCA, IgM, *or* EBV, EA are present. In other cases of EBV CFS, both types of antibody titers are high simultaneously.

rally mediated hypotensive reflex or another as yet undescribed factor to explain their work. We do not believe the basis of CFS is an abnormal neural reflex; the evidence we present suggests that CFS is a cardiomyopathy inducing this abnormal cardiac response.

Proposal Number Three

In *appropriate* CFS patients, (e.g., corroborated by Holter monitoring, serologic studies, radionuclide stress multigaited acquisition studies and cardiac biopsy, as above), antiviral drugs, such as acyclovir or its derivatives, ganciclovir, foscarnet, and interferon, among other possible choices, deserve testing in controlled clinical trial (Tables 1 and 2) Previous therapeutic trials appear invalid because of the singular etiologies (e.g., EBV alone) presumed in the protocols of these efforts [28–33].

To be sure, no antiviral drug is active in vitro vs. any latent, nonpermissive persistent herpesvirus infection. However, implicit in this unified hypothesis is the assumption that low-level, continuing, infectious herpesvirus multiplication is occurring in susceptible B cells (EBV) and epithelial cells (EBV), and/or in tissue macrophages (HCMV) and cardiac myocytes (EBV and HCMV). Infectious EBV or HMCV might, we presume, intermittently be carried to the heart by the blood within productively infected B cells (EBV) or monocytes macrophages (HCMV). Eradication of productive virus infection by an effective antiviral drug might inhibit the slowly active, persisting pathologic process we hypothesize. For instance, new cardiac myofiber recruitment to nonpermissive persistent infection in the affected heart would stop. This should benefit the patient with CFS.

Substantive corollaries of this hypothesis include pursuing (1) further similar studies of the etiology of primary advanced idiopathic cardiomyopathic disease of unknown origin, and (2) an infectious mechanism (e.g., nonpermissive, persistent herpesvirus infection) for noninflammatory diseases, erstwhile considered other degenerative diseases. Thus, CFS in its simplest configuration, according to this hypothesis, is a persistent, nonpermissive EBV, HCMV, or combined EBV/HCMV cardiomyopathy [34].

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Correction

In the February issue (1997;6:110-7), the Editors regret that an error was made in the spelling of Dr. Steven M. Korotkin's name. The title of the article and authors should read:

NEW CARDIOMYOPATHY: PILOT STUDY OF INTRAVENOUS GANCICLOVIR IN A SUBSET OF THE CHRONIC FATIGUE SYNDROME

by A. Martin Lerner, Marcus Zervos, Howard J. Dworkin, Chung-ho Chang, James T. Fitzgerald, James Goldstein, Claudine Lawrie-Hoppen, Barry Franklin, Steven M. Korotkin, Marc Brodsky, Daniel Walsh, and William O'Neill